Tetrahedron 65 (2009) 5062–5073

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of 1,3-diarylated imidazo[1,5-*a*]pyridines with a combinatorial approach: metal-catalyzed cross-coupling reactions of 1-halo-3-arylimidazo-[1,5-*a*]pyridines with arylmetal reagents

Fumitoshi Shibahara *, Eiji Yamaguchi, Asumi Kitagawa, Akio Imai, Toshiaki Murai *

Department of Chemistry, Faculty of Engineering, Gifu University, Yanagido, Gifu 501-1193, Japan

ARTICLE INFO

Article history:
Received 15 January 2009
Received in revised form 23 February 2009
Accepted 24 February 2009
Available online 3 March 2009

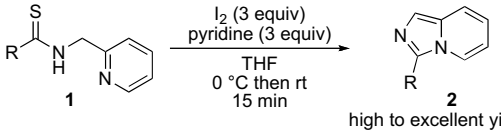
Keywords:
Halogenation
Cross-coupling
Imidazo[1,5-*a*]pyridine
Fluorescence

ABSTRACT

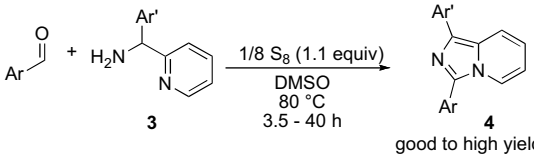
The halogenation of 3-arylimidazo[1,5-*a*]pyridines was carried out with iodine, bromine, *N*-chlorosuccinimide, and 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate as halogenating agents to give selectively halogenated products 1-halo-3-arylimidazo[1,5-*a*]pyridines in good to excellent yields. Kumada–Tamao–Corriu cross-coupling of the obtained 1-iodo-3-arylimidazo[1,5-*a*]pyridines and aryl Grignard reagents led to 1,3-diarylated imidazo[1,5-*a*]pyridines in good to excellent yields. Suzuki–Miyaura cross-coupling of the 1-bromo-3-phenylimidazo[1,5-*a*]pyridine and *p*- or *m*-methoxycarbonylphenylboronic acids furnished the coupling product in respective yields of 91% and 61%. The obtained 1,3-diarylated imidazo[1,5-*a*]pyridines showed a wide variety of fluorescent emissions in a wavelength range of 449–533 nm with improved quantum yields compared to monoarylated ones.

1. Introduction

Imidazo[1,5-*a*]pyridines are an important class of compounds due to their unique photophysical and biological properties.[1] As a part of our ongoing interest in the synthesis of this family to explore photo-functional materials, we were interested in methods for synthesizing a series of imidazopyridines involving π-conjugated systems such as aryl and alkynyl groups.[2,3] During our studies on the transformation of thioamides,[4] we developed two methods for forming imidazo[1,5-*a*]pyridine rings: (1) thioamides **1** that bear a 2-pyridylmethyl group at a thioamide nitrogen smoothly undergo oxidative desulfurization–cyclization in the presence of iodine and pyridine (Eq. 1).[5] The reaction gives a wide variety of 3-substituted imidazo[1,5-a]pyridines **2** in high to excellent yields. In addition, (2) oxidative condensation–cyclization of aldehyde and aryl-2-pyridylmethyl amine **3** using elemental sulfur as an oxidant gives 1,3-diarylated imidazopyridines **4** directly (Eq. 2),[6] but less commonly available **3** must be prepared by a multistep synthesis from 2-pyridylcarboaldehyde.[3a] Thus, a more straightforward and efficient method for synthesizing diverse 1,3-diarylated imidazo[1,5-*a*]pyridines is needed. Meanwhile, 3-arylated imidazo[1,5-*a*]pyridines **2**, which are readily obtained by the former method, were expected to be an expandable platform for 1,3-di arylated imidazo[1,5-*a*]pyridines by a selective halogenation–cross-coupling sequence.



(1)



(2)

The transition metal-catalyzed cross-coupling reaction of aryl halides and arylmetal reagents is one of the most straightforward synthetic strategies for obtaining a biaryl moiety, and many examples have been reported.[7–12] However, there are few reported examples in which electron-rich nitrogen-containing heteroaryls such as imidazopyridines are used as one or both of the coupling partners (e.g., heteroaryl halide and/or heteroaryl metal),[13] since the oxidative addition of electron-rich aryl halides to low-valence metals is usually sluggish, and an unprotected nitrogen moiety readily binds to metal catalysts to possibly inhibit the reaction (e.g., oxidative addition and transmetallation). In addition,

* Corresponding authors. Tel.: +81 58 293 2616; fax: +81 58 293 2794 (F.S.); tel.: +81 58 293 2614; fax +81 58 293 2794 (T.M.).
E-mail addresses: fshiba@gifu-u.ac.jp (F. Shibahara), mtoshi@gifu-u.ac.jp (T. Murai).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.02.062

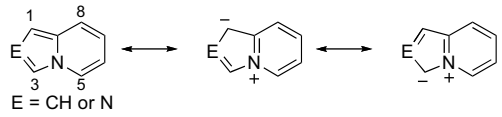


Figure 1. Three main mesomeric contributors of imidazopyridine family.

electron-rich heteroaryl metal species are usually unstable and readily undergo protodemetalation due to their high nucleophilic character.[14] In fact, in most previous reports on cross-coupling with such electron-rich nitrogen-containing heteroaryl substrates, the substrates were modified by attaching some electron-withdrawing groups directly to the heteroaryl moiety to reduce the electron density.[13] Therefore, it is important to investigate methods to achieve such a reaction with high efficiency but in the absence of electron-withdrawing groups. We report here the selective halogenation of 3-arylimidazo[1,5-*a*]pyridines and transition metal-catalyzed cross-coupling reactions, with Kumada–Tamao–Corriu (KTC) and Suzuki–Miyaura protocols, with electron-rich substrates. Under the optimal conditions, the cross-coupling reactions of the imidazopyridine substrates and arylmetal reagents proceeded with high efficiency in the absence of a protecting group on nitrogen moiety and an electron-withdrawing group.

2. Results and discussion

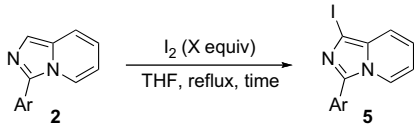
2.1. Halogenation

Electrophilic substitution of indolizine-related compounds and electrophiles is expected to occur at the C1 or C3 position of the ring due to the electron-rich character of the five-membered ring moiety and the main mesomeric contributors that are stabilized by the formation of pyridinium moiety, as shown in Figure 1.[1b] Thus, to obtain selective halogenated imidazopyridines **5**–**8**, we investigated conventional electrophilic halogenations.

2.1.1. Iodination

The iodination of imidazo[1,5-*a*]pyridines was investigated first. When 3-phenylimidazo[1,5-*a*]pyridine (**2a**) was treated with 3 equiv of iodine in THF under reflux conditions for 2 h, as expected, the iodination proceeded selectively at the 1-position of imidazopyridine **2a** to give the desired product **5a** in 87% yield (Table 1, entry 1). In the presence of Lewis acid or base such as $AlCl_3$ or pyridine, no reaction took place.[15] Under similar conditions, the C1-selective iodination of imidazopyridines **2** bearing an electron-donating or electron-withdrawing substituent at the 4-position of the phenyl group on C3 was carried out. The iodination proceeded smoothly to give the desired products **5** in high to excellent yields (entries 2–6). Meanwhile, the reaction of imidazopyridine bearing a highly electron-rich 4-dimethylaminophenyl group **2g** consumed the starting material within 30 min but resulted in the formation of a complex mixture, maybe due to competitive iodination at the dimethylaminophenyl group. Interestingly, an internal pyridyl group did not inhibit the iodination, and the reaction of imidazopyridine bearing a 2-pyridyl group **2h** gave the corresponding iodination product **5h** in 86% yield.

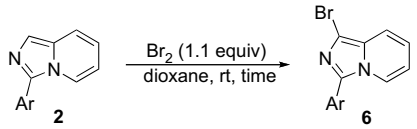
Table 1
Iodination of 3-arylimidazo[1,5-*a*]pyridines **2**



Entry	Ar		X (equiv)	Time (h)	Yield[a] (%)	
1	Ph–	**2a**	3	2	**5a**	87
2	4-$MeOC_6H_4$–	**2b**	2	1	**5b**	99
3	4-FC_6H_4–	**2c**	3	1.5	**5c**	96
4	4-$CF_3C_6H_4$–	**2d**	3	0.5	**5d**	98
5	4-MeC_6H_4–	**2e**	3	1	**5e**	82
6	4-BrC_6H_4–	**2f**	3	0.6	**5f**	81
7	4-$Me_2NC_6H_4$–	**2g**	3	0.5	**5g**	Complex mixture
8	2-pyridyl	**2h**	3	1	**5h**	86

[a] Isolated yields.

Table 2
Bromination of 3-arylimidazo[1,5-*a*]pyridines **2**



Entry	Ar	Time (h)	Yield[a] (%)	
1	**2a**	1.5	**6a**	82
2	**2b**	2	**6b**	97
3	**2c**	1.5	**6c**	93
4	**2d**	2	**6d**	99
5	**2e**	0.5	**6e**	56
6	**2f**	1	**6f**	92
7	**2h**	1.5	**6h**	89

[a] Isolated yields.

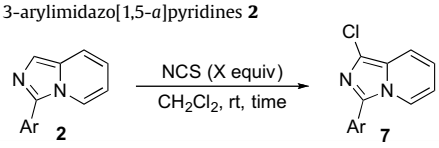
2.1.2. Bromination

We then turned to selective bromination with Br_2 as a bromine source.[16] Although the reactions in THF or dichloromethane did not proceed at all, the product **6a** was obtained in 82% yield in dioxane (Table 2, entry 1). Other imidazopyridines were treated with Br_2 in dioxane. Bromination took place with **2** having not only an electron-donating or -withdrawing group, but also a basic 2-pyridyl group to give the desired products **6** in excellent yields (entries 2–4, 6, and 7), except for 3-(4-tolyl)imidazopyridine **2e** (entry 5). The reaction of **2e** gave **6e** in a significantly lower yield (56%), probably due to the competitive radical bromination at the benzylic position of the tolyl group.[17]

2.1.3. Chlorination

Chlorination of **2** was also performed with *N*-chlorosuccinimide (NCS) in dichloromethane. The reactions of **2a**,**c**–**f** with a slight excess amount of NCS at room temperature afforded the desired products **7** in high yields (Table 3, entries 1 and 3–6). Although the reaction required an excess amount (3 equiv) of

Table 3
Chlorination of 3-arylimidazo[1,5-*a*]pyridines **2**



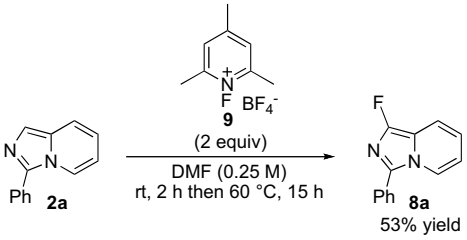
Entry	Ar	X (equiv)	Time (h)	Yield[a] (%)	
1	**2a**	1.3	1.5	**7a**	80
2	**2b**	3	1.5	**7b**	80
3	**2c**	1.3	1.5	**7c**	84
4	**2d**	1.5	2	**7d**	86
5	**2e**	1.3	1.5	**7e**	90
6	**2f**	1.5	2	**7f**	84
7	**2h**	3	2	**7h**	88

[a] Isolated yields.

NCS, 4-MeO-phenyl- and 2-pyridyl-substituted **2b** and **2h** were also chlorinated in isolated yields of 80% and 88%, respectively (entries 2 and 7).

2.1.4. Fluorination

Whereas a cross-coupling reaction rarely occurs on a carbon–fluorine bond, heterocycles bearing fluorine often play an important role in pharmaceutical, agrochemical, and material science.[18] Thus, we also investigated the fluorination of imidazopyridine **2a**. 1-Fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (**9**) was chosen as a fluoronium source for fluorination due to its ready availability. The reaction of **9** in dichloromethane or benzene gave a small amount of the desired product **8a** in 5.6% and 13% yields, respectively. After the optimization of the solvents, we found that DMF was a suitable solvent. Concentration of the solution also slightly affected the product yield and the reaction in 0.25 M DMF solution of **2a** gave the best result, with an isolated yield of 53% (Eq. 3).



(3)

2.2. Cross-coupling reactions

2.2.1. Nickel-catalyzed KTC cross-coupling using 1-iodoimidazopyridines

KTC cross-coupling was examined as the first choice for a cross-coupling reaction with iodoimidazopyridines **5** due to the ready availability of Grignard reagents.

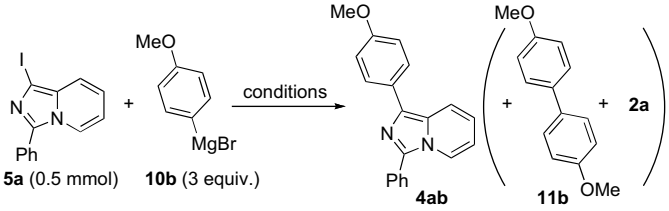
2.2.1.1. Optimization of reaction conditions. First, KTC cross-coupling of **5a** and 4-methoxyphenylmagnesium bromide (**10b**) under different typical conditions was examined (Table 4). A mixture of **5a** and $NiCl_2$ (10 mol %) was treated with **10b** at room temperature to give the coupling product **4ab** in 44% yield along with significant amounts of homocoupling product **11b** and reduced starting imidazopyridine **2a** (entry 1). A higher temperature did not affect the yield, and the reaction under reflux conditions furnished **4ab** in 40% yield along with similar byproducts (entry 2). Treatment with Grignard reagent at −78 °C followed by stirring at room temperature was not effective for the conversion of **5a** (entry 3). In this case, the reaction gave us a complex mixture after 19 h, though **5a** still remained. The use of $Ni(acac)_2$ as a catalyst and diisopropylaluminum hydride (DIBAL-H) as a reductant for catalyst to prepare Ni(0) species in situ did not give a good result (entry 4). Meanwhile, the use of diphenylphosphinopropane (dppp) as a ligand slightly improved the yield of **4ab** (entry 4 vs 5). Although the yield of **4ab** did not improve (44%), the use of $Ni(dppp)Cl_2$ suppressed the formation of **11b** (entry 6). Harsh conditions gave a complex mixture (entry 7). Finally, we found that immediate workup after complete conversion of the substrate **5a**, which was monitored by TLC analysis, was effective and the reaction at room temperature for 1 h gave **4ab** in 86% yield (entry 8). The results suggested that the product **4ab** is unstable under these reaction conditions.

2.2.1.2. Scope of substrates. With the optimum conditions in hand, the KTC cross-coupling of **5** and a variety of Grignard reagents **10** was examined with a combinatorial approach. The results are summarized in Table 5. The coupling with substituted aryl Grignard reagents **10** proceeded smoothly to give the products **4** in good to excellent NMR yields and moderate to high isolated yields. The use of tolyl Grignard **10e** tends to decrease the isolated yields of the products **4ae**–**4de**, maybe due to the instability of the product on silica gel. *p*-Trifluoromethyl imidazopyridine **5d** was a relatively sluggish substrate and the reaction required a slightly longer reaction time (**4da**–**4df**). Since the crystallization of **4bb** is quite fast and the product crystallized in a column under purification by column chromatography on silica gel, the isolated yield of **4bb** was significantly less than the NMR yield. The heteroaryl Grignard reagent 2-thienylmagnesium bromide (**10g**) also acted as a coupling partner of **5** to give the products **4ag**–**4dg** in moderate to high yields, though the reactions needed ca. 36 h for complete conversion. In addition, no reactions were observed in the reaction of pyridyl imidazopyridine **5h** and any of the Grignard reagents tested under these conditions.

2.2.2. Palladium-catalyzed Suzuki–Miyaura cross-coupling reaction

Although we succeeded in the KTC cross-coupling of **5** and aryl Grignard reagents **10**, the compatibility of the substituents (e.g., the use of ester, nitrile, and nitro groups) was still problematic under

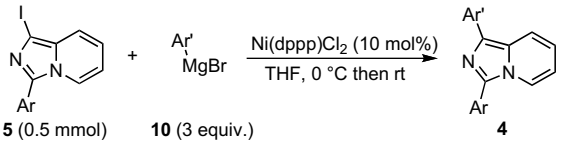
Table 4
Optimization of KTC cross-coupling of **5a** and 4-methoxyphenylmagnesium bromide

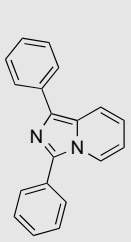


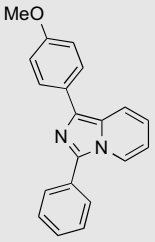
Entry	Conditions	Yield[a] (%)
1	$NiCl_2$ (10 mol %), rt, 3 h	44
2	$NiCl_2$ (10 mol %), 0 °C then reflux, 2.5 h	40
3	$NiCl_2$ (10 mol %), −78 °C then rt, 19 h	Complex mixture
4	$Ni(acac)_2$ (10 mol %), DIBAL-H(20 mol %), 0 °C then rt, 4 h	13
5	$Ni(acac)_2$ (10 mol %), DIBAL-H (20 mol %), dppp (20 mol %), 0 °C then rt, 3 h	40
6	$Ni(dppp)Cl_2$ (10 mol %), 0 °C then rt, 3 h	44
7	$Ni(dppp)Cl_2$ (10 mol %), 0 °C then reflux, 2.5 h	Complex mixture
8	$Ni(dppp)Cl_2$ (10 mol %), 0 °C then rt, 1 h	86

[a] Isolated yields.

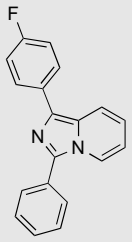
Table 5
Substrate scope of KTC cross-coupling[a]



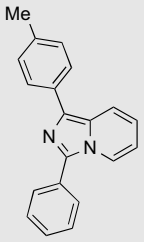

4aa
30 min, 99%(80%)



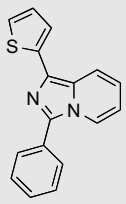
4ab
1 h, 90%(83%)



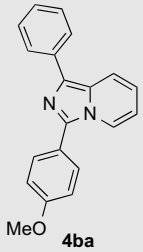
4ac
1 h, 83%(58%)



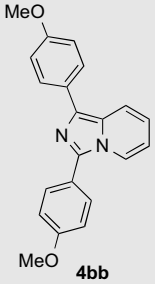
4ae
1 h, 85%(52%)



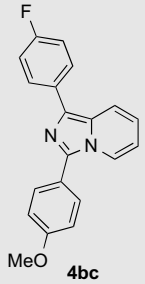
4ag
36 h, nd[b](52%)



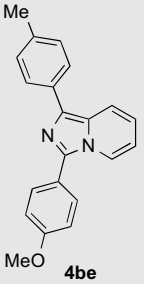
4ba
1 h, 93%(81%)



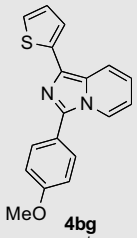
4bb
1 h, 83%(62%)



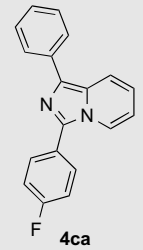
4bc
1 h, 98%(96%)



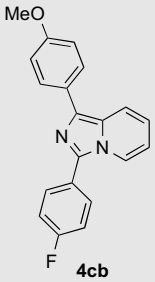
4be
1 h, 90%(58%)



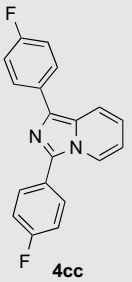
4bg
37 h, nd[b](68%)



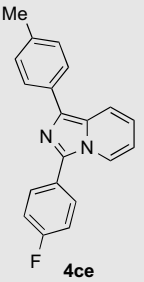
4ca
1 h, 95%(89%)



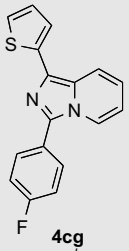
4cb
1 h, 88%(83%)



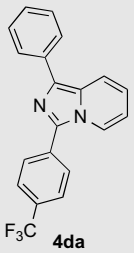
4cc
1 h, 83%(83%)



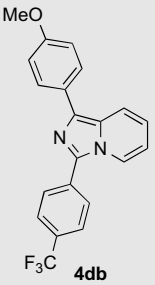
4ce
1 h, 80%(52%)



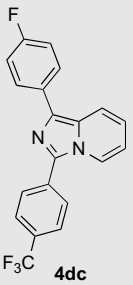
4cg
36 h, nd[b](81%)



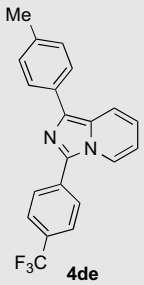
4da
1.5 h, 68%(37%)



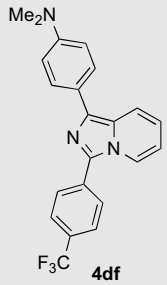
4db
1 h, 68%(66%)



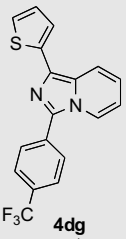
4dc
2 h, 83%(55%)



4de
1.5 h, 70%(58%)



4df
2 h, 98%(48%)



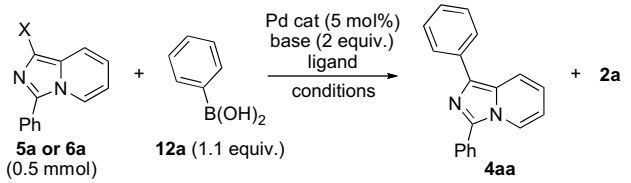
4dg
36 h, nd[b](93%)

[a] NMR yields are shown. Isolated yields are shown in parentheses.
[b]Not determined.

these conditions. Therefore, Suzuki–Miyaura cross-coupling was investigated next.

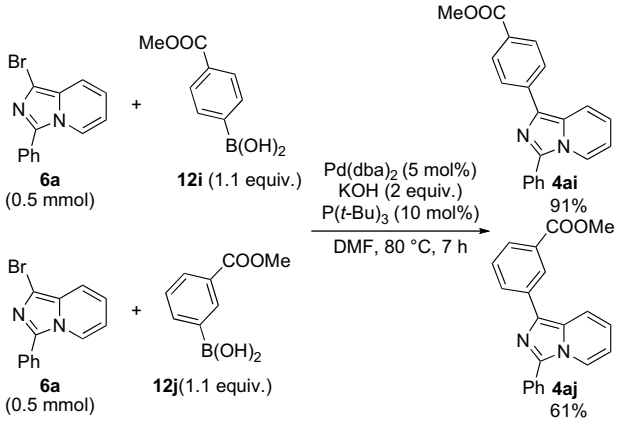
In our first unsuccessful attempts at Suzuki–Miyaura cross-coupling, iodinated imidazopyridine **5a** or **5d** was used in the reaction as a coupling partner. For example, the treatment of **5a** with a catalytic amount of $Pd(OAc)_2$ and a stoichiometric amount of Cs_2CO_3 and phenylboronic acid (**12a**) did not give the coupling product, and starting **5a** was recovered in 54% yield (Table 6, entry 1). The use of $Pd(PPh_3)_4$ instead of $Pd(OAc)_2$ in the reaction with **5d** led to the reduced product **2d** in quantitative yield (entry 2). On the other hand, the use of brominated imidazopyridine **6a** in the presence of $Pd(OAc)_2$ or $Pd(PPh_3)_2Cl_2$ gave the coupling product **4aa** in respective yields of 38% and 59% (entries 3 and 4). After several optimizations, we found that the treatment of **6a** with

Table 6
Optimization of Suzuki–Miyaura cross-coupling of **5** and phenylboronic acid (**12a**)



Entry	X	Pd cat	Base	Ligand	Conditions	Yield[a] (%)
1	I	$Pd(OAc)_2$	Cs_2CO_3	—	50 °C, 30 h	—[b]
2[c]	I	$Pd(PPh_3)_4$	Cs_2CO_3	—	90 °C, 27 h	—[d]
3	Br	$Pd(OAc)_2$	Cs_2CO_3	—	80 °C, 90 h	38
4	Br	$Pd(PPh_3)_2Cl_2$	Cs_2CO_3	—	80 °C, 90 h	59
5	Br	$Pd(dba)_2$	KOH	$P(t\text{-}Bu)_3$[e]	80 °C, 3 h	84

[a] Isolated yield.
[b] Starting **5a** was recovered in 54% yield.
[c] Compound **5d** was used as a substrate.
[d] Compound **2d** was obtained as a reduced product in 97% yield.
[e] 10 mol %.



Scheme 1. Suzuki–Miyaura cross-coupling of **6a** and **11h-i**.

$Pd(dba)_2$ and $P(t\text{-}Bu)_3$ as a catalyst and KOH as a base for 3 h gave the product in 84% yield (entry 5).

Subsequently, the reactions of *p*- or *m*-methoxycarbonyl phenylboronic acids **12i,j** were carried out under these conditions (Scheme 1). The reaction of **12i** afforded the product **4ai** in high yield. Although the yield was slightly decreased, the reaction of **12j** also gave the product **4aj** in 61% yield. In both cases, no hydrolysis of ester was observed.

2.3. Photophysical properties of imidazo[1,5-*a*]pyridines

The obtained products emitted a variety of fluorescence, as shown in Figure 2. To better understand the details of the photophysical properties, UV/vis and fluorescent spectra of the products are summarized in Table 7. As a result, trends in absorption, emission, and quantum yield are still unclear due to the complicated dual influences of two aryl groups, whereas the introduction of an aryl group into imidazo[1,5-*a*]pyridines obviously affected emission color and improved the quantum yield compared with those of parent **2a–h** (entries 1–8 vs 9–29). Nonetheless, the emissions of *p*-fluorophenyl substituted at C3 **4ca–4cg** were significantly influenced by the substituents at the C1 positions compared to other substrates (entries 19–23). Similarly, the emissions of a *p*-tolyl or 2-thienyl group at C1 **4ae–4de** (entries 12, 17, 22, and 27) and **4ag–4dg** (entries 13, 18, 23, and 28) were quite sensitive to the substituents on C3. The emission efficiencies for a strong electron-withdrawing carboxymethyl group-substituted **4ai** and **4aj** were significantly decreased as in the case of 3-(4-nitro-1,1′-biphen-4′-yl)imidazo[1,5-*a*]pyridine.[19]

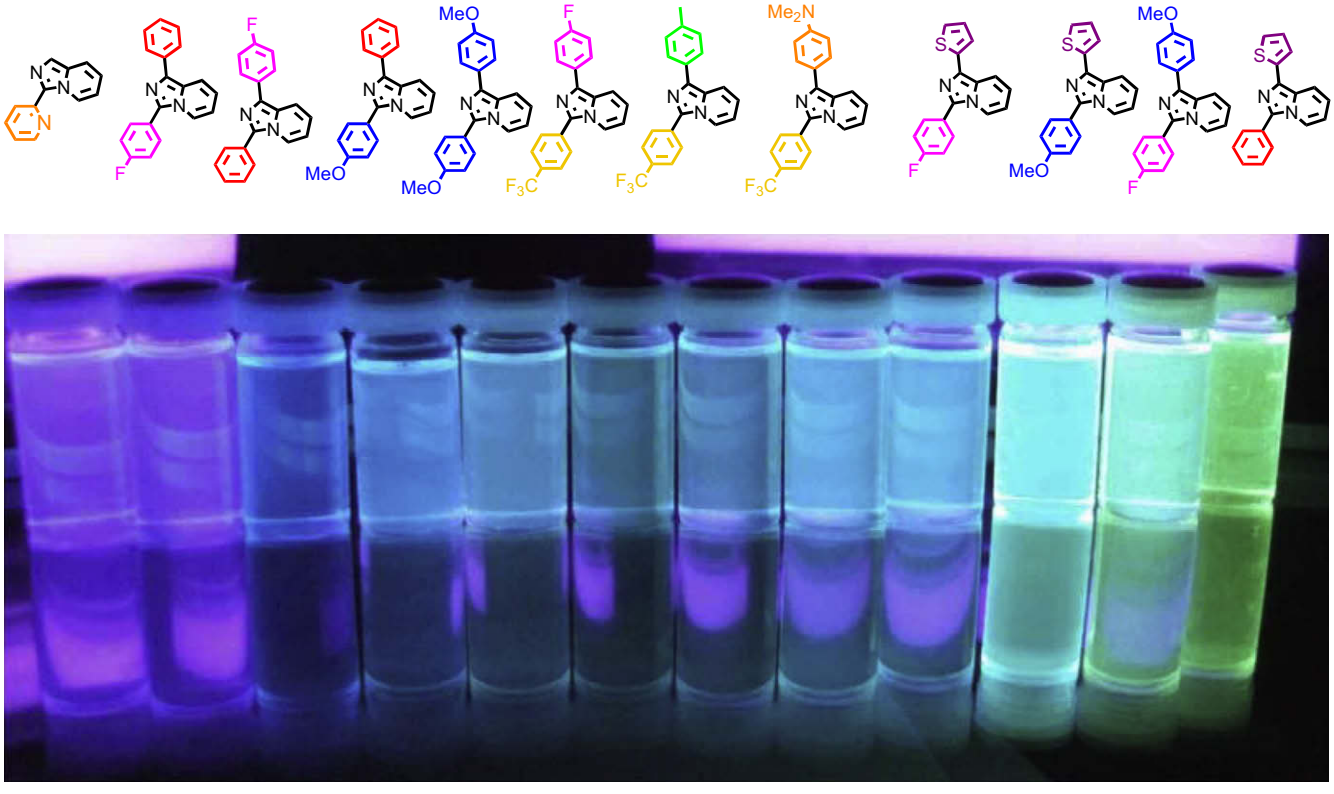


Figure 2. Selected emissions of obtained imidazo[1,5-*a*]pyridines in $CHCl_3$ under 365 nm irradiation.

Table 7
Photophysical studies on obtained imidazo[1,5-*a*]pyridines

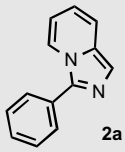
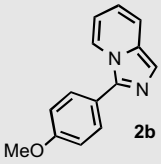
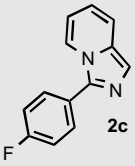
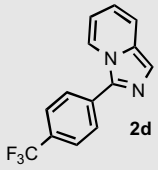
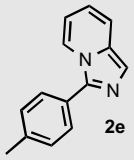
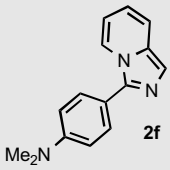
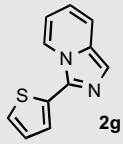
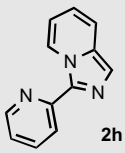
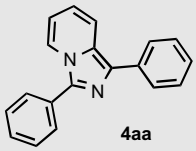
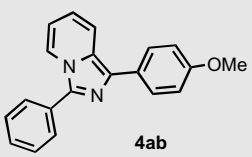
Entry	Compound	UV/vis[a]		Fluorescence[a]	
		λ_{max} (nm)	log ε	λ_{max} (nm)	Φ_F[b]
1	 **2a**	317	4.25	461	0.072
2	 **2b**	306	4.05	469	0.052
3	 **2c**	312	4.11	465	0.060
4	 **2d**	340	4.12	459	0.039
5	 **2e**	314	4.11	458	0.064
6	 **2f**	269, 322	4.14, 4.33	482	0.076
7	 **2g**	340	4.12	475	0.025
8	 **2h**	348	4.04	425	0.022
9	 **4aa**	308	4.18	454	0.14
10	 **4ab**	308	4.35	471	0.17

Table 7 (*continued*)

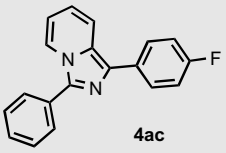
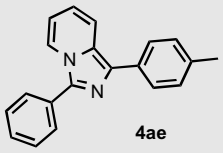
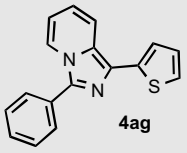
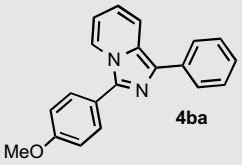
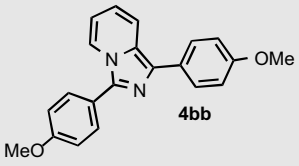
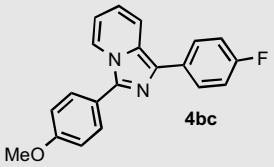
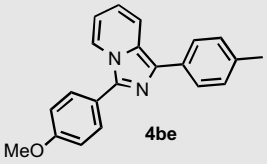
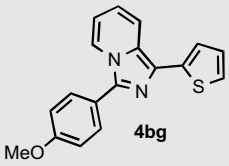
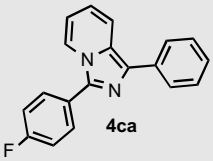
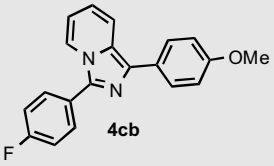
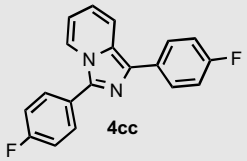
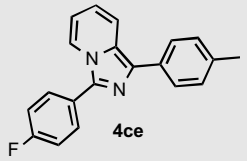
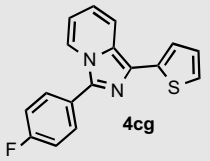
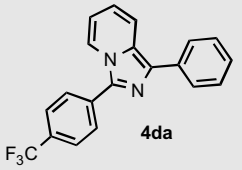
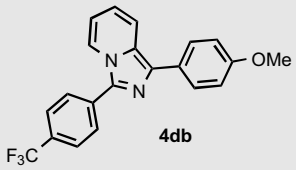
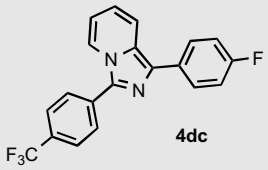
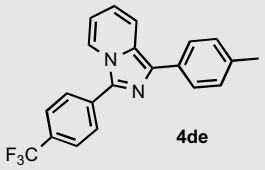
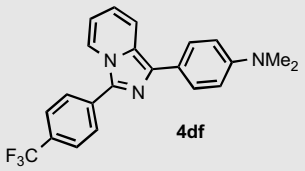
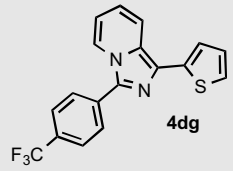
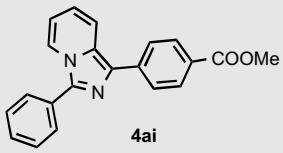
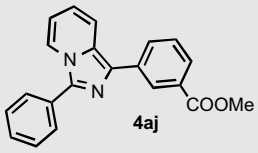
Entry	Compound	UV/vis[a]		Fluorescence[a]	
		λ_{max} (nm)	log ε	λ_{max} (nm)	Φ_F[b]
11	 **4ac**	308	4.30	461	0.14
12	 **4ae**	293	3.92	457	0.20
13	 **4ag**	322	4.16	533	0.087
14	 **4ba**	301	4.25	465	0.18
15	 **4bb**	303	4.31	479	0.22
16	 **4bc**	317	4.25	461	0.063
17	 **4be**	303	4.25	521	0.13
18	 **4bg**	316	4.05	483	0.14
19	 **4ca**	304	4.11	449	0.19
20	 **4cb**	268	4.12	526	0.17

Table 7 (*continued*)

Entry	Compound	UV/vis[a]		Fluorescence[a]	
		λ_{max} (nm)	log ε	λ_{max} (nm)	Φ_F[b]
21	 **4cc**	297	4.11	486	0.20
22	 **4ce**	293	4.10	523	0.16
23	 **4cg**	319	4.12	511	0.12
24	 **4da**	301, 343	3.85, 3.87	479	0.11
25	 **4db**	301, 353	4.02, 3.94	467	0.16
26	 **4dc**	291, 353	3.95, 3.90	478	0.15
27	 **4de**	296, 359	4.16, 4.08	487	0.11
28	 **4df**	313	4.12	508	0.12
29	 **4dg**	269, 309	4.00, 3.77	474	0.11
30	 **4ai**	339	4.38	477	0.080
31	 **4aj**	339	4.92	474	<0.01

[a] Measured in $CHCl_3$.
[b] Quantum yields (Φ_F) were determined with reference to quinine sulfate in 0.1 M aqueous sulfuric acid (excited at 350 nm).[20]

3. Conclusion

In conclusion, we have investigated a set of halogenations for imidazo[1,5-*a*]pyridines. The iodinated and brominated imidazopyridines obtained could be used in KTC or Suzuki–Miyaura cross-coupling. Although the trend in emission is still unclear, a series of imidazopyridines showed a wide variety of fluorescent emissions. Further investigations on introduction of some other π-system into imidazo[1,5-*a*]pyridines and the theoretical design of such compounds for functional materials are in progress in our laboratory.

4. Experimental

4.1. General

The IR spectra were obtained on a JASCO FT-IR spectrophotometer. The ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on a JEOL α-400 (400, 100, 376 MHz) in $CDCl_3$. Chemical shifts of ^{1}H and ^{13}C are reported in δ values referred to tetramethylsilane and $CDCl_3$ as an internal standard, respectively. The ^{19}F chemical shifts are expressed in δ value deshielded with respect to CF_3COOH as an external standard. The mass spectra (MS) and high resolution mass spectra (HRMS) were taken on a JEOL JNM 700 mass spectrometer. Elemental analyses were carried out by Elemental Analysis Center of Kyoto University. Melting points were determined using a Yanagimoto melting point apparatus and are uncorrected. UV/vis spectra were measured on a JAI Ubest-55 spectrophotometer. Fluorescence spectra were measured on a Hitachi F-4500 spectrophotometer. Preparative recycling gel permeation chromatography (GPC) was performed on a Japan Analytical Industry LC-908 recycling preparative HPLC equipped with JAIGEL-1H and -2H columns (chloroform as an eluent). Unless otherwise noted, reagents were commercially available and were used without purification. Imidazo[1,5-*a*]pyridines **2** were prepared according to our previously reported method.[5] Tetrahydrofuran (dehydrated) was purchased from Kanto Chemical Co., and used without further purification. DMF was distilled over calcium hydride under reduced pressure. Silica gel used for column chromatography was Silica gel 60 N (Spherical, Neutral, 100–210 mm) from Kanto Chemical Co., Inc.

4.2. General procedure for the iodination of 3-arylimidazo[1,5-*a*]pyridines 2

To a solution of 3-arylimidazo[1,5-*a*]pyridine **2** (2 mmol) in THF (4 mL) was added iodine (1.53 g, 6 mmol, 3 equiv) at room temperature under an Ar atmosphere. The resulting mixture was stirred at reflux temperature. The reaction mixture was quenched with saturated $Na_2S_2O_3$ aq, neutralized with $NaHCO_3$ aq, and extracted with CH_2Cl_2 (30 mL×3). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give 1-iodo-3-arylimidazo[1,5-*a*]pyridine **5**.

*4.2.1. 1-Iodo-3-phenylimidazo[1,5-a]pyridine (**5a**)*

Yield 87%, brownish solid, mp 118–119 °C, R_f=0.52 (hexane/AcOEt=4:1). IR (KBr): 1629.6, 1511.0, 1453.1, 1356.7, 1257.4, 1005.7, 942.1, 773.3, 740.5, 698.1, 682.7 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.52 (t, *J*=7.3 Hz, 1H), 6.72 (dd, *J*=7.3, 9.3 Hz, 1H), 7.27 (d, *J*=9.3 Hz, 1H), 7.36 (d, *J*=7.3 Hz, 1H), 7.43 (t, *J*=7.3 Hz, 2H), 7.68 (d, *J*=7.3 Hz, 2H), 8.13 (d, *J*=7.3 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 74.1, 113.9, 119.0, 120.2, 121.8, 128.0, 129.0, 129.1, 129.3, 133.4, 140.5. HRMS (EI) *m*/*z*: calcd for $C_{13}H_9IN_2$ (M^+), 319.9810; found 319.9820.

*4.2.2. 1-Iodo-3-(4-methoxyphenyl)imidazo[1,5-a]pyridine (**5b**)*

Yield 99%, green solid, mp 114.0–114.5 °C, R_f=0.23 (hexane/AcOEt=4:1). IR (KBr): 3009, 2935, 2835, 1606, 1525, 1505, 1455 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.80 (s, 3H, OMe), 6.51 (dd, *J*=6.3, 7.3 Hz, 1H, Ar), 6.70 (dd, *J*=6.3, 9.3 Hz, 1H, Ar), 6.93 (d, *J*=8.8 Hz, 2H, Ar), 7.27 (d, *J*=9.3 Hz, 1H, Ar), 7.61 (d, *J*=8.8 Hz, 2H, Ar), 8.07 (d, *J*=7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 55.4 (OMe), 113.7, 114.4, 114.7, 118.9, 119.9, 121.7, 129.5, 129.8, 133.0, 140.0, 160.1 (Ar). HRMS (EI) *m*/*z*: calcd for $C_{14}H_{11}IN_2O$ (M^+) 349.9916; found: 349.9911.

*4.2.3. 1-Iodo-3-(4-fluorophenyl)imidazo[1,5-a]pyridine (**5c**)*

Yield 96%, colorless solid, mp 125.0–125.5 °C, R_f=0.51 (hexane/AcOEt=4:1). IR (KBr): 3055, 3020, 1520, 1503, 1230 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.63 (t, *J*=6.8 Hz, 1H, Ar), 6.82 (dd, *J*=6.8, 9.1 Hz, 1H, Ar), 7.22 (t, *J*=8.8 Hz, 2H, Ar), 7.37 (d, *J*=9.1 Hz, 1H, Ar), 7.75 (q, *J*=8.8 Hz, 2H, Ar), 8.14 (d, *J*=6.8 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 114.1 (Ar), 116.2 (d, *J*=21.9 Hz, F–C–*C*), 119.1, 120.2, 121.5, 125.5, 126.0 (Ar), 130.0 (d, *J*=8.8 Hz, F–C–C=*C*), 133.4, 139.5, 162.2 (d, *J*=272 Hz, F–C). ^{19}F NMR ($CDCl_3$) δ −111.8 (F). HRMS (EI) *m*/*z*: calcd for $C_{13}H_8FIN_2$ (M^+) 337.9716; found: 337.9719.

*4.2.4. 1-Iodo-3-(4-trifluoromethylphenyl)imidazo-[1,5-a]pyridine (**5d**)*

Yield 98%, off-white solid, mp 91.0–91.5 °C, R_f=0.47 (hexane/AcOEt=4:1). IR (KBr): 3109, 3078, 1586, 1523, 1503, 1321 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.57 (dd, *J*=6.4, 5.6 Hz, 1H, Ar), 6.76 (dd, *J*=5.6, 8.6 Hz, 1H, Ar), 7.28 (d, *J*=8.6 Hz, 1H, Ar), 7.65 (d, *J*=7.6 Hz, 2H, Ar), 7.80 (d, *J*=7.6 Hz, 2H, Ar), 8.13 (d, *J*=6.4 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 114.7, 119.3, 120.8, 121.6, 123.9 (q, *J*=272.1 Hz, F_3C), 126.0 (q, *J*=4.1 Hz, F_3C–C=*C*), 128.0 (two carbon peaks were overlaped) (Ar), 130.7 (q, *J*=33.1 Hz, F_3C–*C*), 132.8, 134.0, 138.9 (Ar); ^{19}F NMR ($CDCl_3$) δ −63.4 (CF_3). HRMS (EI) *m*/*z*: calcd for $C_{14}H_{18}F_3IN_2$ (M^+) 387.9684; found: 387.9687.

*4.2.5. 1-Iodo-3-(4-methylphenyl)imidazo[1,5-a]pyridine (**5e**)*

Yield 82%, green solid, mp 80.5–82 °C, R_f=0.50 (hexane/AcOEt=4:1). IR (KBr): 2918, 2361, 1712, 1630, 1523, 1504, 1455, 1361, 1260, 1113, 1005, 741 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.34 (s, 3H, Me), 6.49 (dd, *J*=6.8, 7.3 Hz, 1H, Ar), 6.68 (dd, *J*=6.8, 8.7 Hz, 1H, Ar), 7.18–7.27 (m, 3H, Ar), 7.56 (d, *J*=7.8 Hz, 2H, Ar), 8.10 (d, *J*=7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 21.3 (Me), 113.6, 118.8, 119.9, 121.8, 126.4, 127.8 (two carbon atoms were overlapped.), 129.6, 133.1, 139.0, 140.5 (Ar). HRMS (EI) *m*/*z*: calcd for $C_{14}H_{11}IN_2$ (M^+) 333.9967; found: 333.9936.

*4.2.6. 1-Iodo-3-(4-bromophenyl)imidazo[1,5-a]pyridine (**5f**)*

Yield 81%, pale green solid, mp 134–135 °C, R_f=0.63 (hexane/AcOEt=4:1). IR (KBr): 2931, 1627, 1497, 1359, 1260, 1003, 833, 740 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.56 (dd, *J*=6.3, 7.3 Hz, 1H, Ar), 6.74 (dd, *J*=6.3, 8.2 Hz, 1H, Ar), 7.29 (d, *J*=9.3 Hz, 2H, Ar), 7.55–7.58 (m, 4H, Ar), 8.09 (d, *J*=7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 114.3, 119.1, 120.4, 121.6, 123.1, 128.2, 129.3, 132.2, 133.6, 139.3 (Ar). HRMS (EI) *m*/*z*: calcd for $C_{13}H_8{}^{79}BrIN2$ (M^+) 397.8916; found: 397.8905.

*4.2.7. 1-Iodo-3-(2-pyridyl)imidazo[1,5-a]pyridine (**5h**)*

Yield 86%, pale yellow solid, mp 157–158 °C, R_f=0.45 (hexane/AcOEt=4:1). IR (KBr): 2358, 1586, 1495, 1353, 1013, 754, 738 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.72 (dd, *J*=6.3, 7.3 Hz, 1H, Ar), 6.90 (dd, *J*=6.3, 8.7 Hz, 1H, Ar), 7.17 (ddd, *J*=1.5, 4.8, 6.3 Hz, 1H, Ar), 7.37 (d, *J*=8.3 Hz, 1H, Ar), 7.73 (ddd, *J*=1.5, 6.3, 8.3 Hz, 1H, Ar), 8.30 (d, *J*=8.7 Hz, 1H, Ar), 8.58 (d, *J*=4.8 Hz, 1H, Ar), 9.90 (d, *J*=7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 114.2, 118.2, 121.4, 121.8, 121.9, 126.5 (two carbon atoms were overlapped), 134.5, 136.5, 137.7, 148.0, 150.2 (Ar). HRMS (EI) *m*/*z*: calcd for $C_{12}H_8IN_3$ (M^+) 320.9763; found: 320.9780.

4.3. General procedure for the bromination of 3-arylimidazo[1,5-*a*]pyridines 2

To a solution of 3-arylimidazo[1,5-*a*]pyridine **2** (5.0 mmol) in dioxane (10 mL) was added a solution of bromine (0.27 mL, 5.5 mmol, 1.1 equiv) in dioxane (10 mL) at 0 °C under an air atmosphere. The resulting solution was stirred at room temperature for 1.5 h. The reaction mixture was quenched with saturated $Na_2S_2O_3$ aq, neutralized with NaOH aq, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give 1-bromo-3-arylimidazo[1,5-*a*]pyridine **6**.

*4.3.1. 1-Bromo-3-phenylimidazo[1,5-a]pyridine (**6a**)*

Yield 82%, brownish solid, mp 127–129 °C, R_f=0.53 (hexane/AcOEt=4:1). IR (KBr): 3390, 1632, 1513, 1264, 1010, 740 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.54 (dd, *J*=6.3, 7.3 Hz, 1H, Ar), 6.72 (dd, *J*=6.3, 8.8 Hz, 1H, Ar), 7.35–7.48 (m, 4H, Ar), 7.72 (d, *J*=8.3 Hz, 2H, Ar), 8.15 (d, *J*=7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 106.5, 113.2, 113.9, 118.0, 119.6, 121.5, 127.9, 128.9, 129.1, 129.3, 137.6 (Ar). HRMS (EI) *m*/*z*: calcd for $C_{13}H_9{}^{79}BrN_2$ (M^+) 271.9949; found: 271.9952.

*4.3.2. 1-Bromo-3-(4-methoxyphenyl)imidazo[1,5-a]pyridine (**6b**)*

Yield 97%, yellow solid, mp 89–89.5 °C, R_f=0.34 (hexane : AcOEt=4 : 1). IR (KBr): 2935, 1523, 1247 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.80 (s, 3H, OMe), 6.51 (dd, *J*=6.3, 7.3 Hz, 1H, Ar), 6.70 (dd, *J*=6.3, 9.3 Hz, 1H, Ar), 6.93 (d, *J*=8.8 Hz, 2H, Ar), 7.27 (d, *J*=9.3 Hz, 1H, Ar), 7.61 (d, *J*=8.8 Hz, 2H, Ar), 8.07 (d, *J*=7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 55.4 (OMe), 113.7, 114.4, 114.7, 118.9, 119.9, 121.7, 129.5, 129.8, 133.0, 140.0, 160.1 (Ar). HRMS (EI) *m*/*z*: calcd for $C_{14}H_{11}{}^{79}BrN_2O$ (M^+) 302.0055; found: 302.0059.

*4.3.3. 1-Bromo-3-(4-fluorophenyl)imidazo[1,5-a]pyridine (**6c**)*

Yield 93%, pale yellow solid, mp 82–83 °C, R_f=0.68 (hexane/AcOEt=2:1). IR (KBr): 3083, 1520, 1231, 1009 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.53 (dd, *J*=6.8, 7.4 Hz, 1H, Ar), 6.72 (dd, *J*=7.4, 9.2 Hz, 1H, Ar), 7.10–7.16 (m, 2H, Ar), 7.34 (d, *J*=9.2 Hz, 1H, Ar), 7.62–7.71 (m, 2H, Ar), 8.06 (d, *J*=6.8 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 106.2, 114.0 (Ar), 115.1 (d, *J*=21.8 Hz, F–C–*C*), 117.8, 119.6, 121.1, 125.3, 128.7 (Ar), 129.6 (d, *J*=8.3 Hz, F–C–C=*C*), 136.4 (Ar), 162.7 (d, *J*=250 Hz, F–C). ^{19}F NMR ($CDCl_3$): δ −111.8 (F). HRMS (EI) *m*/*z*: calcd for $C_{13}H_8F{}^{79}BrN_2$ (M^+) 289.9855; found: 289.9850.

*4.3.4. 1-Bromo-3-(4-trifluoromethylphenyl)imidazo-[1,5-a]pyridine (**6d**)*

Yield 99%, brownish solid, mp 111–113 °C, R_f=0.23 (hexane/AcOEt=4:1). IR (KBr): 2923, 1714, 1617, 1362, 1324, 1221, 1119, 1066,

1012 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.62 (dd, J=6.5, 7.3 Hz, 1H, Ar), 6.78 (dd, J=6.5, 9.3 Hz, 1H, Ar), 7.39 (d, J=9.3 Hz, 1H, Ar), 7.69 (d, J=8.3 Hz, 2H, Ar), 7.84 (d, J=8.3 Hz, 2H, Ar), 8.18 (d, J=7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 107.2, 114.6, 118.1, 120.2, 121.2 (Ar), 123.9 (q, J=272 Hz, F_3C), 125.9 (q, J=3.3 Hz, F_3C–C=*C*), 127.7, 129.5 (Ar), 130.4 (q, J=32.2 Hz, F_3C–*C*), 132.6, 135.8 (Ar). ^{19}F NMR ($CDCl_3$): δ −63.4 (CF_3). HRMS (EI) m/z: calcd for $C_{14}H_8^{79}BrF_3N_2$ (M^+) 339.9823; found: 339.9818.

*4.3.5. 1-Bromo-3-(4-methylphenyl)imidazo[1,5-a]pyridine (**6e**)*

Yield 56%, pale green solid, mp 107–109 °C, R_f=0.68 (hexane/AcOEt=2:1). IR (KBr): 3064, 1502, 1366 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.40 (s, 3H, Me), 6.49 (dd, J=7.3, 8.3 Hz, 1H, Ar), 6.68 (dd, J=8.3, 9.3 Hz, 1H, Ar), 7.22 (d, J=8.3 Hz, 2H, Ar), 7.32 (d, J=9.3 Hz, 1H, Ar), 7.56 (d, J=8.3 Hz, 2H, Ar), 8.10 (d, J=7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 21.45 (Me), 113.7, 118.0, 119.4, 121.5, 126.4, 127.8, 128.7, 129.6, 129.7, 131.7, 139.0 (Ar). HRMS (EI) m/z: calcd for $C_{14}H_{11}^{79}BrN_2$ (M^+) 286.0106; found: 286.0099.

*4.3.6. 1-Bromo-3-(4-bromophenyl)imidazo[1,5-a]pyridine (**6f**)*

Yield 92%, yellow solid, mp 132–133 °C, R_f=0.69 (hexane/AcOEt=3:1). IR (KBr): 3083, 1500, 1368 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.56 (dd, J=6.8, 7.3 Hz, 1H, Ar), 6.74 (dd, J=6.8, 9.1 Hz, 1H, Ar), 7.35 (dd, J=4.9, 7.6 Hz, 1H, Ar), 7.54–7.59 (m, 4H, Ar), 8.09 (d, J=7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): 106.7, 114.4, 118.2, 119.9, 121.3, 123.1, 128.2, 129.1, 129.2, 132.2, 136.4 (Ar). HRMS (EI) m/z: calcd for $C_{13}H_8^{79}Br_2N_2$ (M^+) 349.9054; found: 349.9050.

*4.3.7. 1-Bromo-3-(2-pyridyl)imidazo[1,5-a]pyridine (**6h**)*

Yield 89%, yellow solid, mp 126–127 °C, R_f=0.65 (hexane/AcOEt=3:1). IR (KBr): 3116, 1587, 1495, 1369 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.68 (dd, J=6.3, 7.3 Hz, 1H, Ar), 6.84 (dd, J=6.3, 9.3 Hz, 1H, Ar), 7.11 (dd, J=4.9, 7.6 Hz, 1H, Ar), 7.38 (d, J=9.3 Hz, 1H, Ar), 7.77 (dd, J=7.6, 8.2 Hz, 1H, Ar), 8.22 (d, J=7.3 Hz, 1H, Ar), 8.53 (d, J=4.9 Hz, 1H, Ar), 9.85 (d, J=7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): 106.9, 114.3, 117.2, 121.0, 121.7, 121.8, 126.2, 130.2, 134.7, 136.5, 148.1, 150.2 (Ar). HRMS (EI) m/z: calcd for $C_{12}H_8^{81}BrN_3$ (M^+) 274.9881; found: 274.9852.

4.4. General procedure for the chlorination of 3-arylimidazo[1,5-*a*]pyridines 2

To a solution of 3-arylimidazo[1,5-*a*]pyridine **2** (0.50 mmol) in CH_2Cl_2 (1 mL) was added NCS (0.09 g, 0.65 mmol, 1.3 equiv) at room temperature under an Ar atmosphere. The resulting solution was stirred at room temperature for 1.5 h. The reaction mixture was quenched with saturated $Na_2S_2O_3$ aq, neutralized with $NaHCO_3$ aq, and extracted with CH_2Cl_2 (30 mL×3). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give 1-chloro-3-arylimidazo[1,5-*a*]pyridine **7**.

*4.4.1. 1-Chloro-3-phenylimidazo[1,5-a]pyridine (**7a**)*

Yield 80%, colorless solid, mp 118–120 °C, R_f=0.51(hexane/AcOEt=4:1). IR (KBr) 2963, 1515, 1375 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.51 (dd, J=6.3, 7.3 Hz, 1H, Ar), 6.68 (dd, J=6.3, 8.3 Hz, 1H, Ar), 7.31–7.44 (m, 5H, Ar), 7.68 (d, J=8.3 Hz, 1H, Ar), 8.12 (d, J=7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 113.8, 117.5, 119.2, 119.7, 121.3, 126.3, 127.8, 128.9, 129.0, 129.3, 135.8 (Ar). HRMS (EI) m/z: calcd for $C_{13}H_9^{35}ClN_2$ (M^+) 228.0454; found: 228.0442.

*4.4.2. 1-Chloro-3-(4-methoxyphenyl)imidazo[1,5-a]pyridine (**7b**)*

Yield 80%, brownish solid, mp 85.5–86.5 °C, R_f=0.10 (hexane/AcOEt=10:1). IR (KBr): 2963, 1515, 1375 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.79 (s, 3H, OMe), 6.48 (dd, J=6.3, 7.3 Hz, 1H, Ar), 6.68 (dd, J=6.3, 9.1 Hz, 1H, Ar), 6.96 (d, J=8.8 Hz, 2H, Ar), 7.34 (d, J=9.1 Hz, 1H, Ar), 7.61 (d, J=8.8 Hz, 2H, Ar), 8.04 (d, J=7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 55.3 (OMe), 1113.6, 114.4, 117.5, 118.8, 119.4, 121.3, 121.7, 125.9, 129.3, 135.9, 160.9 (Ar). HRMS (EI) m/z: calcd for $C_{14}H_{11}^{35}ClN_2O$ (M^+) 258.0560; found: 258.0542.

*4.4.3. 1-Chloro-3-(4-fluorophenyl)imidazo[1,5-a]pyridine (**7c**)*

Yield 84%, brownish solid, mp 83–85 °C, R_f=0.55 (hexane/AcOEt=3:1). IR (KBr): 2922, 1524, 1232, 1023 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.65 (dd, J=6.4, 7.3 Hz, 1H, Ar), 6.81 (dd, J=6.4, 9.3 Hz, 1H, Ar), 7.22–7.30 (m, 2H, Ar), 7.49 (d, J=9.3 Hz, 1H, Ar), 7.76–7.80 (m, 2H, Ar), 8.16 (d, J=7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 114.0 (Ar), 116.1 (d, J=21.9 Hz, F–C–*C*), 117.6, 119.2, 121.0, 125.4, 125.5, 126.4 (Ar), 129.8 (d, J=7.7 Hz, F–C–C=*C*), 134.9 (Ar), 162.9 (d, J=249 Hz, F–C). ^{19}F NMR ($CDCl_3$): δ −111.8 (F). HRMS (EI) m/z: calcd for $C_{13}H_8^{35}ClFN_2$ (M^+) 246.0360; found: 246.0347.

*4.4.4. 1-Chloro-3-(4-trifluoromethylphenyl)imidazo[1,5-a]-pyridine (**7d**)*

Yield 86%, brownish solid, mp 104–105 °C, R_f=0.43 (hexane/AcOEt=4:1). IR (KBr): 2914, 1743, 1706, 1657, 1617, 1461, 1414, 1325, 1165, 1122, 1067 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.66 (dd, J=6.3, 7.3 Hz, 1H, Ar), 6.81 (dd, J=6.3, 9.0 Hz, 1H, Ar), 7.48 (d, J=9.0 Hz, 1H, Ar), 7.74 (d, J=8.2 Hz, 2H, Ar), 7.89 (d, J=8.2 Hz, 2H, Ar), 8.22 (d, J=7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 114.7, 117.8, 119.8, 120.7, 121.2 (Ar), 123.9 (q, J=272 Hz, F_3C), 126.0 (q, J=3.9 Hz, F_3C–C=*C*), 127.2, 127.9 (Ar), 130.5 (q, J=32.7 Hz, F_3C–*C*), 132.8, 134.3 (Ar). ^{19}F NMR ($CDCl_3$): δ −63.4 (CF_3). HRMS (EI) m/z: calcd for $C_{14}H_8^{35}ClF_3N_2$ (M^+) 296.0328; found: 296.0337.

*4.4.5. 1-Chloro-3-(4-methylphenyl)imidazo[1,5-a]pyridine (**7e**)*

Yield 90%, brownish solid, mp 68–69 °C, R_f=0.48 (hexane/AcOEt=3:1). IR (KBr): 3064, 1507, 1376, 1024 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.34 (s, 3H, Me), 6.49 (dd, J=6.3, 7.3 Hz, 1H, Ar), 6.66 (dd, J=6.3, 9.3 Hz, 1H, Ar), 7.22 (d, J=7.8 Hz, 2H, Ar), 7.35 (d, J=9.3 Hz, 1H, Ar), 7.58 (d, J=7.8 Hz, 2H, Ar), 8.09 (d, J=7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 21.3 (Me), 113.7, 117.4, 119.0, 119.5, 121.4, 126.1, 126.4, 127.7, 129.6, 136.0, 139.0 (Ar). HRMS (EI) m/z: calcd for $C_{14}H_{11}^{35}ClN_2$ (M^+) 242.7035; found: 242.0610.

*4.4.6. 1-Chloro-3-(4-bromophenyl)imidazo[1,5-a]pyridine (**7f**)*

Yield 84%, brownish solid, mp 124–126 °C, R_f=0.23 (hexane/AcOEt=10:1). IR (KBr): 2935, 1526, 1249, 1020 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.54 (dd, J=6.3, 6.8 Hz, 1H, Ar), 6.70 (dd, J=6.8, 9.3 Hz, 1H, Ar), 7.36 (d, J=9.3 Hz, 1H, Ar), 7.52–7.57 (m, 4H, Ar), 8.06 (d, J=6.8 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 114.3, 117.6, 119.4, 120.0, 121.1, 122.9, 126.6, 128.1, 129.1, 132.2, 134.6 (Ar). HRMS (EI) m/z: calcd for $C_{13}H_8^{81}Br^{37}ClFN_2$ (M^+) 309.9530; found: 309.9516.

*4.4.7. 1-Chloro-3-(2-pyridyl)imidazo[1,5-a]pyridine (**7h**)*

Yield 88%, colorless solid, mp 104–105 °C, R_f=0.50 (hexane/AcOEt=3:1). IR (KBr): 3118, 1590, 1495, 1377, 1031 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.68 (dd, J=6.3, 7.8 Hz, 1H, Ar), 6.84 (dd, J=6.3, 9.1 Hz, 1H, Ar), d 7.12 (dd, J=4.4, 7.3 Hz, 1H, Ar), 7.43 (d, J=9.1 Hz, 1H, Ar), 7.69 (dd, J=7.3, 7.5 Hz, 1H, Ar), 8.21 (d, J=7.8 Hz, 1H, Ar), 8.54 (d, J=4.4 Hz, 1H, Ar), 9.86 (d, J=7.5 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 106.7, 114.2, 117.1, 120.9, 121.6, 121.7, 126.1, 130.1, 134.5, 136.4, 148.0, 150.1 (Ar). HRMS (EI) m/z: calcd for $C_{12}H_8^{35}ClN_3$ (M^+) 229.0407; found: 229.0405.

4.5. Synthesis of 1-fluoro-3-phenylimidazo[1,5-*a*]-pyridine (8a)

To a solution of 3-phenylimidazo[1,5-*a*]pyridine (**2a**) (0.10 g, 0.50 mmol) in DMF (2 mL) was added 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (**9**) (0.23 g, 1.0 mmol, 2 equiv) at room temperature under an Ar atmosphere. The resulting solution was stirred at 60 °C for 2 h. The reaction mixture was quenched with 1 N NaOH aq and extracted with CH_2Cl_2. The organic layer was

dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/AcOEt=3:1) to give 1-fluoro-3-phenyl-2-azaindolizine (**8a**, 0.05 g, 0.27 mmol, 53%, R_f=0.47) as a pale yellow solid, mp 103–104 °C. IR (KBr): 2080, 3049, 2922, 1643, 1558, 1521, 1443, 1358, 1258, 1076 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.43–6.46 (m, 1H, Ar), 6.54 (dd, J=6.3, 9.3 Hz, 1H, Ar), 7.31–7.36 (m, 2H, Ar), 7.40–7.45 (m, 2H, Ar), 7.69 (d, J=8.3 Hz, 2H, Ar), 8.07 (d, J=7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 112.2 (J=38.5 Hz, F–C═*C*), 113.7 (Ar), 116.9 (J=5.9 Hz, F–C–N═*C*), 117.1 (J=2.9 Hz, F–C═C–*C*), 120.4, 127.7, 128.7, 129.0 (three carbon atoms were overlapped), 129.6 (Ar), 147.9 (J=233 Hz, F–*C*). ^{19}F NMR ($CDCl_3$): δ −140.1 (F). HRMS (EI) m/z: calcd for $C_{13}H_9FN_2$ (M^+) 212.0750; found: 212.0706.

4.6. General procedure for KTC cross-coupling of 3-arylimidazo[1,5-*a*]pyridines 5 and aryl Grignard reagents 10

To a solution of 1-iodo-3-arylimidazopyridine **5** (0.5 mmol) and Ni(dppp)Cl_2 (10 mol %, 27 mg) in THF (1 mL) in a flame-dried two-necked round-bottom flask was added dropwise aryl Grignard reagent **10** (1.5 mmol, 3 equiv) at 0 °C under an Ar atmosphere. After addition of Grignard reagent, the reaction mixture was stirred at room temperature. When the reaction was complete, the mixture was immediately quenched with satd NH_4Cl aq (1 mL), and extracted with CH_2Cl_2 (20 mL×3). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. Unless otherwise noted, the residue was purified by column chromatography on silica gel to give 1,3-diarylimidazo[1,5-*a*]pyridine **4**.

4.6.1. 1-Phenyl-3-phenylimidazo[1,5-a]pyridine (*4aa*)

Isolated yield 80% (99% NMR yield), yellow solid, mp 111–112 °C, R_f=0.38 (hexane/AcOEt=5:1). IR (KBr): 1598, 1516, 1457 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.50 (t, J=6.5 Hz, 1H, Ar), 6.73 (dd, J=6.5, 7.3 Hz, 1H, Ar), 7.23 (t, J=7.3 Hz, 1H, Ar), 7.37–7.50 (m, 5H, Ar), 7.78 (dd, J=1.7, 7.3 Hz, 3H, Ar), 7.87 (dd, J=1.0, 7.3 Hz, 2H, Ar), 8.18 (d, J=7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 113.3, 119.1, 119.7, 121.7, 126.5, 126.8, 127.6, 128.3, 128.7, 128.8, 129.0, 130.1, 131.9, 134.9, 138.1 (Ar). HRMS (EI) m/z: calcd for $C_{19}H_{14}N_2$ (M^+) 270.1157; found: 270.1149.

4.6.2. 1-(4-Methoxyphenyl)-3-phenylimidazo[1,5-a]pyridine (*4ab*)

Isolated yield 83% (90% NMR yield), yellow solid, mp 111.5–113.0 °C, R_f=0.33 (hexane/AcOEt=4:1). IR (KBr): 3063, 2990, 2959, 1600, 1573, 1541, 1502, 1458 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.72 (s, 3H, OMe), 6.37 (t, J=6.7 Hz, 1H, Ar), 6.57 (dd, J=6.7, 9.1 Hz, 1H, Ar), 6.90 (d, J=7.7 Hz, 2H, Ar), 7.30 (t, J=6.8 Hz, 1H, Ar), 7.39 (d, J=7.2 Hz, 2H, Ar), 7.62 (d, J=9.1 Hz, 1H, Ar), 7.69–7.80 (m, 4H, Ar), 8.05 (d, J=6.7 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 55.2 (OMe), 113.0, 113.3, 114.1, 119.1, 121.4, 123.6, 126.8, 127.5, 127.9, 128.1, 128.8, 130.0, 131.8, 137.5, 158.4 (Ar). HRMS (EI) m/z: calcd for $C_{20}H_{16}N_2O$ (M^+) 300.1262; found: 300.1264.

4.6.3. 1-(4-Fluorophenyl)-1-phenylimidazo[1,5-a]pyridine (*4ac*)

Isolated yield 58% (83% NMR yield), yellow solid, mp 134.5–135.0 °C, R_f=0.32 (hexane/AcOEt/Et_3N=4:1:1 vol %). IR (KBr): 1601, 1542, 1518, 1500, 1461, 1221 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.51 (t, J=7.0 Hz, 1H, Ar), 6.72 (dd, J=7.0, 9.2 Hz, 1H, Ar), 7.06–7.11 (m, 2H, Ar), 7.37–7.49 (m, 3H, Ar), 7.69–7.83 (m, 5H, Ar), 8.16 (d, J=7.0 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): 113.3 (Ar), 119.3 (d, J=21.0 Hz, F–C═*C*), 121.7, 126.8, 127.3, 128.3, 128.8, 129.0, 129.4 (Ar), 129.9 (d, J=8.3 Hz, F–C═C–*C*), 131.7, 131.9, 136.3, 137.8 (Ar), 161.5 (d, J=248.0 Hz, F–*C*). ^{19}F NMR ($CDCl_3$): δ −116.6 (F). HRMS (EI) m/z: calcd for $C_{29}H_{13}N_2F$ (M^+) 288.1063; found: 288.1058.

4.6.4. 1-(4-Methylphenyl)-3-phenylimidazo[1,5-a]pyridine (*4ae*)

Isolated yield 52% (85% NMR yield), yellow solid, mp 134.0–134.5 °C, R_f=0.41 (hexane/AcOEt=4:1). IR (KBr): 3054, 2915, 1601, 1542, 1518, 1500, 1459 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.32 (s, 3H, Me), 6.37 (t, J=6.5 Hz, 1H, Ar), 6.57 (t, J=7.6 Hz, 1H, Ar), 6.90 (d, J=7.8 Hz, 2H, Ar), 7.30 (t, J=6.8 Hz, 1H, Ar), 7.39 (t, J=7.1 Hz, 2H, Ar), 7.62 (d, J=9.2 Hz, 1H, Ar), 7.72 (dd, J=8.3, 17 Hz, 4H, Ar), 8.05 (d, J=6.5 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 21.3 (Me), 113.2, 113.4, 118.8, 118.9, 121.8, 126.8, 127.5, 128.4, 128.8, 129.1, 129.5, 130.3, 132.2, 136.6, 138.0 (Ar). HRMS (EI) m/z: calcd for $C_{20}H_{16}N_2$ (M^+) 284.1313; found: 288.1313.

4.6.5. 1-(2-Thienyl)-3-phenylimidazo[1,5-a]pyridine (*4ag*)

The product was isolated by GPC. 52% isolated yield, yellow solid, mp 115–116 °C. IR (KBr): 3060, 1600, 1559, 1522, 1442, 928 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.54 (t, J=6.3 Hz, 1H, Ar), 6.79 (dd, J=6.3, 9.2 Hz, 1H, Ar), 7.12 (dd, J=3.7, 5.6, 1H, Ar), 7.25 (dd, J=5.9, 8.0 Hz, 1H, Ar), 7. 41–7.53 (m, 4H, Ar), 7.78–7.81 (m, 3H, Ar), 8.18 (d, J=6.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): 113.4, 119.0, 119.9, 121.8, 122.2, 123.3, 124.3, 127.0, 127.6, 128.4, 128.9, 129.0, 129.8, 131.5, 137.9 (Ar). HRMS (EI) m/z: calcd for $C_{17}H_{12}N_2S$ (M^+) 276.0721; found: 276.0719.

4.6.6. 1-Phenyl-3-(4-methoxyphenyl)imidazo[1,5-a]-pyridine (*4ba*)[21]

Isolated yield 81% (93% NMR yield). ^1H NMR ($CDCl_3$) δ 3.29 (s, 3H, OMe), 6.50 (t, J=6.3 Hz, 1H, Ar), 6.71 (dd, J=6.3, 8.8 Hz, 1H, Ar), 7.01 (d, J=8.8 Hz, 2H, Ar), 7.24(dd, J=6.3, 7.8 Hz, 1H, Ar), 7.41 (d, J=7.5 Hz, 2H, Ar), 7.71(d, J=8.8 Hz, 2H, Ar), 7.77 (d, J=8.8 Hz, 1H, Ar), 7.89 (d, J=7.8 Hz, 2H, Ar), 8.11 (d, J=6.3 Hz, 1H, Ar).

4.6.7. 1-(4-Methoxyphenyl)-3-(4-methoxyphenyl)imidazo[1,5-a]-pyridine (*4bb*)

Isolated yield 62% (83% NMR yield), yellow solid, mp 175–176 °C, R_f=0.30 (hexane/AcOEt/Et_3N=3:1:1 vol %). IR (KBr): 2360, 1608, 1503, 1459, 1288, 1241, 1169, 1028 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.79 (s, 3H, OMe), 3.81 (s, 3H, OMe), 6.45 (t, J=6.5 Hz, 1H, Ar), 6.65 (m, 1H, Ar), 6.97 (q, J=9.3 Hz, 4H, Ar), 7.69 (d, J=8.3 Hz, 3H, Ar), 7.78 (d, J=8.3 Hz, 2H, Ar), 8.07 (d, J=6.5 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 55.3, 55.4 (OMe), 114.2, 114.5, 114.5, 119.1, 119.2, 119.5, 121.6, 121.7, 126.5, 126.8, 128.2, 128.7, 129.9, 160.1, 160.2 (Ar). HRMS (EI) m/z: calcd for $C_{21}H_{18}N_2O_2$ (M^+) 330.1367; found: 330.1367.

4.6.8. 1-(4-Fluorophenyl)-3-(4-methoxyphenyl)imidazo-[1,5-a]pyridine (*4bc*)

Isolated yield 96% (98% NMR yield), yellow solid, mp 171.5–171.2 °C, R_f=0.25 (hexane/AcOEt=4:1). IR (KBr): 1516, 1501, 1465, 1221, 1173 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.81 (s, 3H, OMe), 6.48 (t, J=6.3 Hz, 1H, Ar), 6.69 (dd, J=2.4, 6.3 Hz, 1H, Ar), 6.99 (dd, J=5.1, 8.8 Hz, 2H, Ar), 7.08 (t, J=8.8 Hz, 2H, Ar), 7.63–7.68 (m, 3H, Ar), 7.81 (t, J=8.8 Hz, 2H, Ar), 8.08 (d, J=6.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 55.4 (OMe), 113.1, 114.5 (Ar), 115.5 (d, J=21.5 Hz, F–C═*C*), 118.8, 119.6, 121.7, 122.3, 127.0, 128.3, 128.3, 129.7 (Ar), 130.8 (d, J=8.8 Hz, F–C═C–*C*), 138.5, 160.1 (Ar), 162.9 (d, J=248.8 Hz, F–*C*). ^{19}F NMR ($CDCl_3$): δ −116.8 (F). HRMS (EI) m/z: calcd for $C_{20}H_{15}FN_2O$ (M^+) 318.1168; found: 318.1159.

4.6.9. 1-(4-Methylphenyl)-3-(4-methoxyphenyl)imidazo-[1,5-a]pyridine (*4be*)

Isolated yield 58% (90% NMR yield), yellow solid, mp 151.0–151.5 °C, R_f=0.26 (hexane/AcOEt=4:1). IR (KBr): 3008, 2911, 1609, 1527, 1514, 1464, 1008 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.31 (s, 3H, Me), 3.82 (s, 3H, OMe), 6.49 (t, J=6.8 Hz, 1H, Ar), 6.69 (dd, J=6.8, 8.8 Hz, 1H, Ar), 7.00 (d, J=8.8 Hz, 2H, Ar), 7.21 (d, J=7.8 Hz, 2H, Ar), 7.69–7.77 (m, 5H, Ar), 8.08 (d, J=6.8 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 21.3 (Me), 55.5 (OMe), 113.0, 114.5, 119.1, 119.3, 121.6, 122.6, 126.7, 127.1, 129.4, 129.8, 131.7, 132.1, 136.1, 137.9, 160.0 (Ar). HRMS (EI) m/z: calcd for $C_{21}H_{18}N_2O$ (M^+) 314.1419; found: 314.1413.

*4.6.10. 1-(2-Thienyl)-3-(4-methoxyphenyl)imidazo[1,5-a]-pyridine (**4bg**)*

The product was isolated by GPC. Isolated yield 68%, yellow solid, mp 130.0–130.5 °C. IR (KBr): 1516, 1501, 1465, 1221, 1173 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.86 (s, 3H, OMe), 6.53 (t, J=6.5 Hz, 1H, Ar), 6.76 (dd, J=6.3, 9.2 Hz, 1H, Ar), 7.02 (d, J=7.8 Hz, 2H, Ar), 7.11 (dd, J=2.8, 3.6 Hz, 1H, Ar), 7.25 (t, J=2.8 Hz, 1H, Ar), 7.46 (d, J=3.6 Hz, 1H, Ar), 7.71 (d, J=7.8 Hz, 2H, Ar), 7.78 (d, J=9.2 Hz, 1H, Ar), 8.11 (d, J=6.5 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 55.4 (OMe), 113.1, 114.4, 118.9, 119.6, 121.7, 122.1, 122.2, 123.1, 126.7, 126.8, 127.5, 129.8, 137.9, 138.1, 160.1 (Ar). HRMS (EI) m/z: calcd for $C_{18}H_{14}N_2OS$ (M^+) 306.0827; found: 306.0829.

*4.6.11. 1-Phenyl-3-(4-fluorophenyl)-2-azaindolizine (**4ca**)[21]*

Isolated yield 89% (95% NMR yield). ^1H NMR ($CDCl_3$): δ 6.52 (t, J=6.3 Hz, 1H, Ar), 6.73 (dd, J=6.3, 8.8 Hz, 1H, Ar), 7.14–7.25 (m, 3H, Ar), 7.40 (t, J=7.8, 2H, Ar), 7.73–7.79 (m, 3H, Ar), 7.85 (d, J=8.3 Hz, 2H, Ar), 8.08 (d, J=6.5 Hz, 1H, Ar). ^{19}F NMR ($CDCl_3$): δ −112.2 (F).

*4.6.12. 1-(4-Methoxyphenyl)-3-(4-fluorophenyl)imidazo-[1,5-a]pyridine (**4cb**)*

Isolated yield 83% (88% NMR yield), yellow solid, mp 158.5–159.5 °C, R_f=0.37 (hexane/AcOEt/Et_3N=4:1:1 vol%). IR (KBr): 3076, 2952, 2841, 1609, 1573, 1221 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.84 (s, 3H, OMe), 6.53 (t, J=6.3 Hz, 1H, Ar), 6.72 (dd, J=6.3, 9.1 Hz, 1H, Ar), 6.95 (d, J=8.5 Hz, 2H, Ar), 7.20 (d, J=8.5 Hz, 2H, Ar), 7.73–7.83 (m, 5H, Ar), 8.10 (d, J=6.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 55.4 (OMe), 113.4, 114.2, 115.9 (Ar), 116.2 (d, J=21.8 Hz, F–C=*C*), 119.2, 121.3, 126.2, 126.9, 127.3, 128.0 (Ar), 130.2 (d, J=8.3 Hz, F–C=C–*C*), 131.8, 136.6, 158.5 (Ar), 162.89 (d, J=248.8 Hz, F–*C*). ^{19}F NMR ($CDCl_3$): δ −112.5 (F). HRMS (EI) m/z: calcd for $C_{20}H_{15}FN_2O$ (M^+) 318.01168; found: 318.1182.

*4.6.13. 1-(4-Fluorophenyl)-3-(4-fluorophenyl)imidazo-[1,5-a]pyridine (**4cc**)*

Isolated yield 83% (83% NMR yield), yellow solid, mp 180.0–180.5 °C, R_f=0.48 (hexane/AcOEt=4:1). IR (KBr): 1604, 1529, 1515, 1499, 1469, 1228, 1154 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.60 (t, J=6.3 Hz, 1H, Ar), 6.80 (dd, J=6.3, 9.3 Hz, 1H, Ar), 7.13–7.26 (m, 4H, Ar), 7.76–7.90 (m, 5H, Ar), 8.14 (d, J=6.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 113.6 (Ar), 115.7 (d, J=21.4 Hz, F–C=*C*), 116.2 (d, J=21.5 Hz, F–C=*C*), 119.0, 119.9, 121.5, 126.1, 127.4 (Ar), 128.4 (d, J=7.7 Hz, F–C=C–*C*), 130.3 (d, J=8.3 Hz, F–C=C–*C*), 130.9, 131.0, 137.0 (Ar), 161.9 (d, J=245.5 Hz, F–*C*), 163.1 (d, J=249.3 Hz, F–*C*). ^{19}F NMR ($CDCl_3$): δ −112.1, −116.4 (F). HRMS (EI) m/z: calcd for $C_{19}H_{12}F_2N_2$ (M^+) 306.0961; found: 306.0961.

*4.6.14. 1-(4-Methylphenyl)-3-(4-fluorophenyl)imidazo-[1,5-a]pyridine (**4ce**)*

Isolated yield 52% (80% NMR yield), yellow solid, mp 106.0–107.0 °C, R_f=0.45 (hexane/AcOEt=4:1). IR (KBr): 1524, 1459, 1223 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.59 (dd, J=6.4, 6.8 Hz, 1H, Ar), 6.82 (dd, J=6.4, 8.8 Hz, 1H, Ar), 7.01–7.26 (m, 4H, Ar), 7.50 (d, J=8.8 Hz, 1H, Ar), 8.20–8.39 (m, 4H, Ar), 8.11 (d, J=6.8 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 21.3 (Me), 113.4 (Ar), 116.1 (d, J=21.8 Hz, F–C=*C*), 119.3, 119.4, 121.4, 126.7, 126.9, 127.3, 127.4, 128.6 (Ar), 130.2 (d, J=8.2 Hz, F–C=C–*C*), 131.8, 132.1, 136.3 (Ar), 162.9 (d, J=248.3 Hz, F–*C*) (Ar). ^{19}F NMR ($CDCl_3$): δ −112.4 (F). HRMS (EI) m/z: calcd for $C_{20}H_{15}FN_2$ (M^+) 302.1219; found: 302.1222.

*4.6.15. 1-(2-Thienyl)-3-(4-fluorophenyl)imidazo[1,5-a]-pyridine (**4cg**)*

The product was isolated by GPC. Isolated yield 81%, yellow solid, mp 157.5–158.5 °C. IR (KBr): 1629, 1518, 1311, 1006 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.60 (t, J=6.3 Hz, 1H, Ar), 6.80 (dd, J=6.3, 9.2 Hz, 1H, Ar), 7.13–7.26 (m, 3H, Ar), 7.76–7.90 (m, 5H, Ar), 8.14 (d, J=6.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 113.6 (Ar), 116.1 (d, J=21.5 Hz, F–C=*C*), 118.9, 119.9, 120.2, 121.4, 122.2, 123.3, 125.9, 126.8, 127.0 (Ar), 130.2 (d, J=8.8 Hz, F–C=C–*C*), 136.9, 137.8 (Ar), 162.9 (d, J=248.8 Hz, F–*C*). ^{19}F NMR ($CDCl_3$) δ −112.1. HRMS (EI) m/z: calcd for $C_{17}H_{11}FN_2S$ (M^+) 294.0627; found: 294.0614.

*4.6.16. 1-Phenyl-3-(4-trifluoromethylphenyl)imidazo-[1,5-a]pyridine (**4da**)*

Isolated yield 37% (68% NMR yield), yellow solid, mp 149–151 °C, R_f=0.42 (hexane/AcOEt=4:1). IR (KBr) 2927, 1617, 1517, 1465, 1323 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.60 (t, J=6.3 Hz, 1H, Ar), 6.78 (dd, J=6.3, 7.8 Hz, 1H, Ar), 7.26 (t, J=7.8 Hz, 1H, Ar), 7.41 (t, J=7.8 Hz, 2H, Ar), 7.72 (d, J=8.3 Hz, 2H, Ar), 7.80–7.94 (m, 5H, Ar), 8.20 (d, J=6.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 113.9, 119.2, 120.2, 121.4 (Ar), 123.9 (q, J=272 Hz, F_3C), 125.9 (q, J=3.3 Hz, CF_3–C=*C*), 126.8, 128.1, 128.2 (Ar), 130.3 (q, J=33.1 Hz, F_3C–*C*), 132.7, 133.6, 134.5, 136.3 (Ar). ^{19}F NMR ($CDCl_3$) δ −63.4 (CF_3). HRMS (EI) m/z: calcd for $C_{20}H_{13}F_3N_2$ (M^+) 338.1031; found: 338.1008.

*4.6.17. 1-(4-Methoxyphenyl)-3-(4-trifluoromethylphenyl)-imidazo[1,5-a]pyridine (**4db**)*

Isolated yield 66% (68% NMR yield), yellow solid, mp 187.5–188.5 °C, R_f=0.31 (hexane/AcOEt=4:1). IR (KBr): 2951, 1614, 1542, 1518, 1502, 1323, 1066 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.85 (s, 3H, OMe), 6.61 (t, J=6.5 Hz, 1H, Ar), 6.79 (dd, J=6.5, 7.6 Hz, 1H, Ar), 7.01 (d, J=8.8 Hz, 2H, Ar), 7.75–7.98 (m, 5H, Ar), 7.97 (d, J=7.5 Hz, 2H, Ar), 8.22 (d, J=6.5 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 55.3 (OMe), 113.9, 114.3, 119.4, 119.7, 121.3 (Ar), 123.9 (q, J=272 Hz, $_3C$), 126.0 (q, J=3.3 Hz, F_3C–C=*C*), 126.9, 127.7, 128.1, 128.2 (Ar), 130.3 (q, J=33.1 Hz, F_3C–*C*), 132.6, 133.4, 136.1, 158.7 (Ar). ^{19}F NMR ($CDCl_3$): δ −63.4 (CF_3). HRMS (EI) m/z: calcd for $C_{21}H_{15}F_3N_2O$ (M^+) 368.1136; found: 368.1136.

*4.6.18. 1-(4-Fluorophenyl)-3-(4-trifluoromethylphenyl)-imidazo[1,5-a]pyridine (**4dc**)*

Isolated yield 55% (83% NMR yield), yellow solid, mp 209.0–209.5 °C, R_f=0.48 (hexane/AcOEt=4:1). IR (KBr): 2345, 1614, 1538, 1417, 1108 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.60 (t, J=6.8 Hz, 1H, Ar), 6.80 (dd, J=6.8, 8.3 Hz, 1H, Ar), 7.10 (d, J=8.3 Hz, 2H, Ar), 7.72–7.83 (m, 5H, Ar), 7.92 (d, J=8.3 Hz, 2H, Ar), 8.20 (d, J=6.8 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): 114.0 (Ar), 115.7 (d, J=21.5 Hz, F–C=*C*), 119.1, 120.3, 121.5 (Ar), 123.9 (d, J=272 Hz, F_3C), 126.0 (d, J=3.3 Hz, CF_3–C=C–*C*), 128.0, 128.2 (Ar), 128.5 (d, J=7.7 Hz, F–C=C–*C*), 130.3 (Ar), 130.8 (q, J=32.3 Hz, F_3C–*C*), 131.9, 133.5, 136.4 (Ar), 162.9 (d, J=248.9 Hz, F–*C*) (Ar). ^{19}F NMR ($CDCl_3$): δ −63.3 (CF_3), −116.1 (F). HRMS (EI) m/z: calcd for $C_{20}H_{12}F_4N_2$ (M^+) 356.0937; found: 356.0932.

*4.6.19. 1-(4-Methylphenyl)-3-(4-trifluoromethylphenyl)-imidazo[1,5-a]pyridine (**4de**)*

Isolated yield 58% (70% NMR yield), yellow solid, mp 120.0–120.5 °C, R_f=0.48 (hexane/AcOEt=4:1). IR (KBr): 2925, 1615, 1541, 1518, 1501, 1321 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.34 (s, 3H, Me), 6.56 (t, J=6.8 Hz, 1H, Ar), 6.75 (dd, J=6.8, 9.1 Hz, 1H, Ar), 7.22 (d, J=8.1 Hz, 2H, Ar), 7.70–7.79 (m, 5H, Ar), 7.92 (d, J=8.1 Hz, 2H, Ar), 8.18 (d, J=6.8 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 21.3 (Me), 113.8, 119.3, 119.8, 121.3 (Ar), 123.9 (q, J=272 Hz, F_3C), 125.8 (q, J=3.3 Hz, F_3C–C=*C*), 126.6, 128.0, 128.1, 129.4 (Ar), 130.2 (q, J=32.7 Hz, F_3C–*C*), 131.7, 132.8, 133.6, 136.1, 136.5 (Ar). ^{19}F NMR ($CDCl_3$): δ −63.3 (CF_3). HRMS (EI) m/z: calcd for $C_{21}H_{15}F_3N_2$ (M^+) 352.1187; found: 352.1180.

*4.6.20. 1-[4-(N,N-Dimethylamino)phenyl]-3-(4-trifluoromethylphenyl)imidazo[1,5-a]pyridine (**4df**)*

Isolated yield 48% (98% NMR yield), yellow solid, mp 174.0–174.5 °C, R_f=0.32 (hexane/AcOEt=4:1). IR (KBr): 2922, 1613, 1543, 1520, 1505, 1323 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.00 (s, 6H, NMe_2), 6.57 (t, J=6.5 Hz, 1H, Ar), 6.73 (dd, J=6.5, 9.2 Hz, 1H, Ar), 6.86 (d, J=8.8 Hz, 2H, Ar), 7.74–7.80 (m, 5H, Ar), 7.97 (d, J=7.5 Hz, 2H, Ar), 8.20 (d, J=6.5 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 40.7 (NMe_2), 112.9, 113.8, 119.0, 119.6, 121.2, 122.3 (Ar), 123.9 (q, J=271 Hz, F_3C), 125.8 (q, J=3.3 Hz,

F_3C–C═*C*), 127.4, 127.8, 128.1 (Ar), 129.8 (q, *J*=32.6 Hz, F_3C–*C*), 133.5, 133.8, 135.8, 149.5 (Ar). ^{19}F NMR ($CDCl_3$) δ −62.9. HRMS (EI) *m*/*z*: calcd for $C_{22}H_{18}F_3N_3$ (M^+) 381.1453; found: 381.1452.

*4.6.21. 1-(2-Thienyl)-3-(4-trifluoromethylphenyl)imidazo-[1,5-a]pyridine (**4dg**)*

The product was isolated by GPC. Isolated yield 93%, yellow solid, mp 152.0–152.5 °C. IR (KBr): 1614, 1505, 1323, 1123 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.64 (dd, *J*=6.5, 6.8 Hz, 1H, Ar), 6.86 (dd, *J*=6.8, 9.1 Hz, 1H, Ar), 7.12 (dd, *J*=3.1, 4.6 Hz, 1H, Ar), 7.28 (d, *J*=4.6 Hz, 1H, Ar), 7.48 (d, *J*=3.1 Hz, 1H, Ar), 7.76 (d, *J*=7.8 Hz, 2H, Ar), 7.85 (d, *J*=9.1 Hz, 1H, Ar), 7.96 (d, *J*=7.8 Hz, 2H, Ar), 8.22 (d, *J*=6.5 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 114.1, 119.3, 120.5, 121.5, 122.8, 123.7 (Ar), 123.9 (q, *J*=272 Hz, F_3C), 125.9 (q, *J*=3.3 Hz, F_3C–C═*C*), 127.5, 127.7, 127.8, 128.3 (Ar), 130.5 (q, *J*=32.6 Hz, F_3C–*C*), 133.1, 136.3, 137.5 (Ar). ^{19}F NMR ($CDCl_3$) δ −63.4 (CF_3). HRMS (EI) *m*/*z*: calcd for $C_{18}H_{11}F_3N_2S$ (M^+) 344.0595; found: 344.0531.

4.7. Suzuki–Miyaura cross-coupling reaction of 1-bromo-3-phenylimidazo[1,5-*a*]pyridine (6a) and methoxycarbonylphenylboronic acids 12

*4.7.1. 1-(4-Methoxycarbonylphenyl)-3-phenylimidazo-[1,5-a]pyridine (**4ai**)*

To a solution of 1-bromo-3-phenylimidazo[1,5-*a*]pyridine **6a** (0.08 g, 0.25 mmol) in DMF (2 mL) were added 4-methoxycarbonylphenylboronic acid **12i** (0.05 g, 0.28 mmol, 1.1 equiv), potassium hydroxide (0.03 g, 0.50 mmol, 2 equiv), tris(dibenzylideneacetone)dipalladium(0) (23 mg, 0.025 mmol), and tri-*tert*-butylphosphine (0.048 mL, 0.050 mmol) at room temperature under an Ar atmosphere, and mixture was heated at 80 °C for 7 h with stirring. The reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/AcOEt=4:1) to give 1-(4-methoxycarbonylphenyl)-3-phenylimidazo[1,5-*a*]pyridine (**4ai**, 0.075 g, 0.23 mmol, 91%, R_f=0.29) as a pale yellow solid: mp 118–120 °C. IR (KBr): 3053, 1716, 1608, 1276 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.86 (s, 3H, OMe), 6.51 (dd, *J*=6.3, 7.3 Hz, 1H, Ar), 6.70 (dd, *J*=6.3, 9.3 Hz, 1H, Ar), 6.93 (d, *J*=8.8 Hz, 2H, Ar), 7.27 (d, *J*=9.3 Hz, 1H, Ar), 7.61 (d, *J*=8.8 Hz, 1H, Ar), 8.07 (d, *J*=7.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 51.9 (Me), 113.4, 118.9, 120.8, 122.1, 126.0, 127.5, 128.3 (two carbon atoms are overlapped), 128.5, 129.0, 129.8, 130.0, 130.5, 138.7, 139.5 (Ar), 167.1 (C═O). HRMS (EI) *m*/*z*: calcd for $C_{21}H_{16}N_2O_2$ (M^+) 328.1212; found: 328.1174.

*4.7.2. 1-(3-Methoxycarbonylphenyl)-3-phenylimidazo-[1,5-a]pyridine (**4aj**)*

4-Methoxycarbonylphenylboronic acid **12j** was used as a coupling partner. The procedure of the reaction was the same as that of **4ai**. Pale yellow solid, mp 111–113 °C, R_f=0.33 (hexane/AcOEt=4:1). IR (KBr): 3066, 1719, 1602, 1263 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.87 (s, 3H, OMe), 6.52 (dd, *J*=6.3, 7.3 Hz, 1H, Ar), 6.76 (ddd, *J*=1.0, 6.3, 9.3 Hz, 1H, Ar), 7.36–7.48 (m, 4H, Ar), 7.75 (d, *J*=7.8 Hz, 2H, Ar), 7.79 (d, *J*=9.3 Hz, 1H, Ar), 7.88 (d, *J*=7.8 Hz, 1H, Ar), 8.09 (d, *J*=7.8 Hz, 1H, Ar), 8.17 (d, *J*=7.3 Hz, 1H, Ar), 8.51 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 52.1 (Me), 113.4, 118.9, 120.3, 121.9, 127.4, 127.5, 128.0, 128.3, 128.8, 128.9, 129.0, 129.9, 130.5, 130.7, 131.1, 135.3, 138.6 (Ar), 167.2 (C═O). HRMS (EI) *m*/*z*: calcd for $C_{21}H_{16}N_2O_2$ (M^+) 328.1212; found: 328.1190.

Acknowledgements

This work was supported by Grant-in-Aid for Scientific Research on Priority Areas (no. 19020020, 'Advanced Molecular Transformations of Carbon Resources') from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

References and notes

1. (a) Hajos, G.; Riedl, Z. *Sci. Synth.* **2002**, *12*, 613; (b) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell Science: Oxford, 2000; pp 489–503.
2. For recent advances in the synthesis of imidazo[1,5-*a*]pyridines via an acetic acid-mediated condensation pathway, see: (a) Wang, J.; Mason, R.; VanDerveer, K.; Feng, D.; Bu, X. R. *J. Org. Chem.* **2003**, *68*, 5415; (b) Dyers, J. W. L., Jr.; Mason, R., Jr.; Amoyaw, P.; Bu, X. R. *J. Org. Chem.* **2005**, *70*, 2353; (c) Siddiqui, S. A.; Potewar, T. M.; Lahoti, R. J.; Srinivasan, K. V. *Synthesis* **2006**, *17*, 2849 and references cited therein.
3. For recent advances in the synthesis of imidazo[1,5-*a*]pyridines via an oxidative pathway, see: (a) Bluhm, M. E.; Ciesielski, M.; Görls, H.; Döring, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 2962; (b) Bluhm, M. E.; Folli, C.; Pufky, D.; Kröer, M.; Walter, O.; Döring, M. *Organometallics* **2005**, *24*, 4139; (c) Ostermeier, M.; Limberg, C.; Ziemer, B.; Karunakaran, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 5329; (d) Moulin, A.; Garcia, S.; Martinez, J.; Fehrentz, J.-A. *Synthesis* **2007**, *17*, 2667 and references cited therein.
4. (a) Murai, T.; Niwa, H.; Kimura, T.; Shibahara, F. *Chem. Lett.* **2004**, *33*, 508; (b) Murai, T.; Mutoh, Y.; Ohta, Y.; Murakami, M. *J. Am. Chem. Soc.* **2004**, *126*, 5968; (c) Murai, T.; Sano, H.; Kawai, H.; Aso, H.; Shibahara, F. *J. Org. Chem.* **2005**, *70*, 8148; (d) Murai, T.; Toshio, R.; Mutoh, Y. *Tetrahedron* **2006**, *62*, 6312; (e) Shibahara, F.; Suenami, A.; Yoshida, A.; Murai, T. *Chem. Commun.* **2007**, 2354; (f) Murai, T.; Asai, F. *J. Am. Chem. Soc.* **2007**, *129*, 780; (g) Shibahara, F.; Yoshida, A.; Murai, T. *Chem. Lett.* **2008**, *37*, 646; (h) Murai, T.; Asai, F. *J. Org. Chem.* **2008**, *73*, 9518.
5. Shibahara, F.; Kitagawa, A.; Yamaguchi, E.; Murai, T. *Org. Lett.* **2006**, *8*, 5621.
6. Shibahara, F.; Sugiura, R.; Yamaguchi, E.; Kitagawa, A.; Murai. T. *J. Org. Chem.*, in press.
7. For reviews of Kumada–Tamao–Corriu cross-coupling (Mg), see: (a) Tamao, K. In *Comprehensive Organic Synthesis*; Torst, B., Ed.; Permagon: Oxford, 1991; Vol. 3, pp 435–480; (b) Corriu, R. J. P. *J. Organomet. Chem.* **2002**, *653*, 20; (c) Tamao, K. *J. Organomet. Chem.* **2002**, *653*, 23.
8. For a review of Negishi cross-coupling (Zn), see: Negishi, E. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 233.
9. For reviews of Migita–Kosugi–Stille cross-coupling (Sn), see: (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508; (b) Kosugi, M.; Fugami, K. *J. Organomet. Chem.* **2002**, *653*, 50.
10. For reviews of Suzuki–Miyaura cross-coupling (B), see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457; (b) Miyaura, N. *J. Organomet. Chem.* **2002**, *653*, 54.
11. For reviews of Hiyama-Hatanaka cross-coupling (Si), see: (a) Hiyama, T.; Hatanaka, Y. *Pure Appl. Chem.* **1994**, *66*, 1471; (b) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835.
12. For recent general reviews of cross-coupling reactions, see: (a) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359; (b) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VHC: Weinheim, 2004; (c) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651; (d) Fairlamb, I. J. S. *Chem. Soc. Rev.* **2007**, *36*, 1036.
13. For example, see: (a) Østby, O. B.; Dalhus, B.; Gundersen, L.-L.; Rise, F.; Bast, A.; Haenen, G. R. M. M. *Eur. J. Org. Chem.* **2000**, 3763; (b) Handy, S. T.; Zhang, Y.; Bregman, H. *J. Org. Chem.* **2004**, *69*, 2362; (c) Olsen, C. A.; Parera, N.; Albericio, F.; Álvarez, M. *Tetrahedron Lett.* **2005**, *46*, 2041; (d) Handy, S. T.; Sabatini, J. J. *Org. Lett.* **2006**, *8*, 1537.
14. For an example with arylboronic acid, see: Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028. Also see Ref. 13b.
15. In the electrophilic substitution of imidazo[1,5-*a*]pyridines with acetyl chloride, the course of the reaction is entirely different from usual electrophilic substitution. The imidazole nitrogen atom first attacks the electrophile. Next, the intermediate salt is deprotonated at the C1 (or C3) position. Finally, migration of the electrophile to this position gives the product. Therefore, Lewis acid or base additive may inhibit iodination. See: Hlasta, D. J. *Tetrahedron Lett.* **1990**, *31*, 5833.
16. The bromination of imidazopyridines has been noted, but no actual example has been reported. See: Paudler, W. W.; Kuder, J. E. *J. Org. Chem.* **1967**, *32*, 2430.
17. Shaw, H.; Perlmutter, H. D.; Gu, C.; Arco, S. D.; Quibuyen, T. O. *J. Org. Chem.* **1997**, *62*, 236.
18. (a) Hiyama, T. *Organofluorine Compounds: Chemistry and Applications*; Springer: Berlin, 2000; (b) Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, 2006.
19. 3-(4-Nitro-1,1′-biphen-4′-yl)imidazo[1,5-*a*]pyridine did not show fluorescence emission. See Ref. 5.
20. Demas, J. N.; Crosby, G. A. *J. Phys. Chem.* **1971**, *75*, 991.
21. Kovtun, P. Y.; Prostota, A. Y. *Chem. Heterocycl. Compd.* **2000**, *36*, 557.