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Palladium-Catalyzed Regioselective Arylation of Pyrazolo[1,5-*a*]pyridines via C−H Activation and Synthetic Applications on P38 Kinase Inhibitors

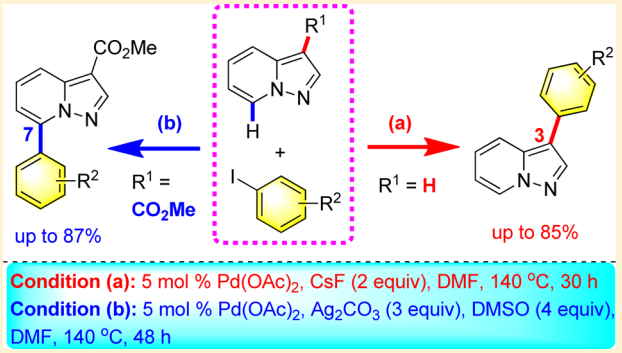
Hung-Chou Wu,[†,§] Jean-Ho Chu,[*,‡] Chin-Wei Li,[‡,§] Long-Chih Hwang,[†] and Ming-Jung Wu[*,†,‡]

[†]Department of Medicinal and Applied Chemistry, Kaohsiung Medical University, Kaohsiung, Taiwan 804

[‡]Department of Chemistry, National Sun Yat-sen University, Kaohsiung, Taiwan 804

Supporting Information

ABSTRACT: A direct arylation of pyrazolo[1,5-*a*]pyridines with aryl iodides selectively occurring at the C-3 and C-7 positions via palladium-catalyzed C−H activation is described. In these reactions, (a) cesium(I) fluoride and (b) silver(I) carbonate were employed as the additive to afford 3- and 7-arylated pyrazolo[1,5-*a*]pyridines, respectively, in modest to good yields. These reactions showed good compatibility with functional groups, and the catalytic mechanisms of these reactions were proposed. Finally, the synthetic application on the potent p38 kinase inhibitors was demonstrated.



INTRODUCTION

Heterocycles containing nitrogen atoms are key motifs in natural products and pharmaceutical compounds because of their potent bioactivities.[1] Among them, pyridines and their derivatives are recognized as the most important family of compounds.[2] Therefore, developing more efficient and convenient strategies to approach these molecular architectures is becoming highly critical for organic chemists.

Pyrazolo[1,5-*a*]pyridine has been known as an important skeleton in a class of biologically active compounds, such as p38 kinase inhibitors,[3] $5HT_3$-antagonists,[4] dopamine D_4,[5] and MT_1/MT_2 melatonin receptor ligands.[6] In 2011 and 2012, we reported the copper-mediated and gold(I)-catalyzed cyclizations of enediynones and enynylpyrazoles, respectively, to afford pyrazolo[1,5-*a*]pyridines.[7] After that, we went onto the development of more efficient and convenient methodologies for the synthesis of pyrazolo[1,5-*a*]pyridine derivatives, especially in the aryl-substituted pyrazolo[1,5-*a*]pyridines.

In the literature, the arylation of pyrazolo[1,5-*a*]pyridines is usually achieved by the conventional methods, such as halogenation and subsequent C−C coupling,[8] but this is still not good enough in terms of synthetic efficiency. Recently, the direct C−H functionalization has received great attention due to its remarkable efficiency in organic synthesis.[9,10] To date, the synthetic strategy via C−H activation has been widely applied to synthesize various organic compounds, especially in the aryl-substituted heterocycles.[11] However, only rare studies on the direct arylation of pyrazolo[1,5-*a*]pyridine analogues were reported.[12,13] For instance, in 2013, Berteina-Raboin and co-workers demonstrated the direct C-3 arylation of 5,7-dimethyl-2-phenylpyrazolo[1,5-*a*]pyrimidines,[12] in which aryl bromides, $Pd(OAc)_2$, $PtBu_3{\cdot}HBF_4$, and K_2CO_3 were employed as reaction reagents and toluene was the solvent that eventually provided 3-arylated-5,7-dimethyl-2-phenylpyrazolo[1,5-*a*]pyrimidines. Meanwhile, the use of PPh_3 and Cs_2CO_3 instead of $PtBu_3{\cdot}HBF_4$ and K_2CO_3 was able to generate 7-diarylated-5-methyl-2-phenylpyrazolo[1,5-*a*]pyrimidines as major products. On the other hand, in 2015, Bedford and co-workers reported the palladium(II)-catalyzed direct regioselective C-3 and C-7 arylation of pyrazolo[1,5-*a*]pyrimidines.[13] In the study, the authors found that a phosphine ligand, 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (SPhos, 20 mol %), is very critical for the formation of 7-arylated-pyrazolo[1,5-*a*]pyrimidines, whereas 3-arylated-pyrazolo[1,5-*a*]pyrimidines are easy to synthesize without the use of an SPhos ligand.

In this article, we present a palladium-catalyzed direct C-3/C-7 arylation of pyrazolo[1,5-*a*]pyridines with aryl iodides via C−H activation and finally demonstrate the simple synthesis of potent p38 kinase inhibitors based on the developed methodology.

RESULTS AND DISCUSSION

For the direct C-3 arylation of pyrazolo[1,5-*a*]pyridines **1**, it was examined by the reaction of **1a** with **2a** (phenyl iodide) in the presence of 5 mol % palladium(II) acetate (see Table 1). In the beginning, triphenylphosphine (Ph_3P) was employed as the ligand without any additives, and the reaction was heated in

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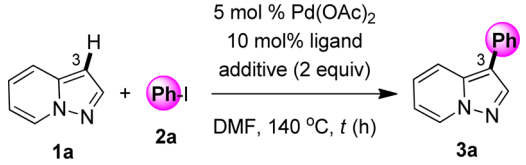
Table 1. Optimization of the Direct C-3 Arylation of Pyrazolo[1,5-*a*]pyridines 1



entry	ligand	additive	Ph-I (**2a**) (equiv)	*t* (h)	yield (%)[a]
1	Ph_3P		2	72	trace
2	Ph_3P	Cs_2CO_3	2	72	47
3	Ph_3P	CsF	2	72	40
4	Ph_3P	K_2CO_3	2	72	32
5	Ph_3P	K_3PO_4	2	72	27
6	Ph_3P	KOAc	2	72	24
7	Ph_3P	Na_2CO_3	2	72	20
8	Ph_3P	NaOAc	2	72	25
9	Ph_3P	KF	2	72	8
10	Ph_3P	K_2HPO_4	2	72	trace
11	Ph_3P	Cs_2CO_3	4	48	40
12	Ph_3P	CsF	4	48	54
13	Ph_3P	CsF	4	48	trace[b]
14	Ph_3P	CsF	4	48	8[c]
15	Ph_3P	CsF	4	48	15[c]
16	**L1**	CsF	4	48	43
17	**L2**	CsF	4	48	40
18	**L3**	CsF	4	48	39
19	**L4**	CsF	4	48	36
20	**L5**	CsF	4	48	32
21	**L6**	CsF	4	48	29
22		**CsF**	**4**	**30**	**68**
23		KF	4	30	35
24		AgF	4	30	34
25		TBAF[e]	4	30	26
26		CuF_2	4	30	19
27		Cs_2CO_3	4	30	38
28		K_2CO_3	4	30	30
29		Na_2CO_3	4	30	24
30		KOAc	4	30	18
31		NaOAc	4	30	26

[a]Product yields were determined as an average of three runs by isolation. [b,c,d]1,4-Dioxane, toluene, and dimethylacetamide were used as the solvent, respectively. [e]TBAF = tetrabutylammonium fluoride. **L1** = $(o\text{-tolyl})_3P$, **L2** = Ph_2PCl, **L3** = $(4\text{-MeO-}C_6H_4)_3P$, **L4** = $(2\text{-furyl})_3P$, **L5** = Ph_2PSiMe_3, **L6** = $(C_6F_5)_3P$.

dimethylformamide (DMF) at 140 °C for 72 h. The experimental results showed that only a trace amount of 3-phenylpyrazolo[1,5-*a*]pyridine (**3a**) was detected (entry 1, Table 1). Subsequently, various additives were added to the above reaction (entries 2−10, Table 1), and we found that both cesium carbonate (Cs_2CO_3) and cesium fluoride (CsF) were able to increase the product yield of **3a** to 40−47% yields (entries 2 and 3, Table 1). On the basis of these results, we attempted to increase the used amount of phenyl iodide (**2a**) (up to 4 equiv) and concurrently reduce the reaction time (down to 48 h) toward the two cases of Cs_2CO_3 and CsF to optimize the reaction conditions. According to the experimental results, product **3a** was eventually generated in 40% and 54% yield, respectively (entries 11 and 12, Table 1). In the above tuning of reaction conditions, we found that the product yield of **3a** was slightly decreased when Cs_2CO_3 was used, but increased when Cs_2CO_3 was replaced by CsF.

In view of this, we then concentrated on the use of CsF as the additive and further studied the solvent effects of the reaction on the influence of reactivity (entries 13−15, Table 1). However, the product yield of **3a** was not obviously improved in the variation of solvents; oppositely, poor results were observed (trace−15%). Thus, we turned to examine other phosphine ligands, but unfortunately the product yield of **3a** was still not improved as anticipated (entries 16−21, Table 1).

Nevertheless, these above results drove us to remove the phosphine ligand from the reaction and to only use CsF as the additive. Delightfully, the product yield of **3a** was potentially increased to 68% yield (from 54% yield) with a reduction of reaction time (30 h, entry 22, Table 1). Finally, we screened a series of fluoride salts (entries 23−26, Table 1) and other additives (entries 27−31, Table 1), but the experimental results showed that CsF was still the best additive for the reaction.

With the optimized reaction conditions in hand (5 mol % $Pd(OAc)_2$, 4 equiv of aryl iodide,[14a] 2 equiv of CsF in DMF at 140 °C[14b] for 30 h), we subsequently carried out the direct C-3 arylation of **1a** with a variety of aryl iodides **2** to afford 3-arylpyrazolo[1,5-*a*]pyridines **3** in modest to good yields. The experimental results are summarized in Table 2. In addition to the reaction of **1a** with **2a** leading to product **3a** (68%, entry 1, Table 2), we also carried out the reaction of **1a** with **2b−g**, bearing a methoxy or methyl substituent at the *para*-, *meta*-, and *ortho*-position, respectively, to provide the anticipated products **3b−g** in 50−85% yields (entries 2−7, Table 2). In the above reactions, we found that the reaction of **1a** with *meta*-methylphenyl iodide (**2c**)/*meta*-methoxyphenyl iodide (**2f**) usually gave higher product yields (85% for **3c** and 65% for **3f**, entries 3 and 6, Table 2) than that of *ortho*- and *para*-substituted cases (51% for **3b** and 50% for **3d**, entries 2 and 4, Table 2; 68% for **3g** and 72% for **3i**, entries 5 and 7, Table 2). Moreover, dimethoxy-substituted aryl iodides, such as 2,4-dimethoxyphenyl iodide (**2h**) and 2,6-dimethoxyphenyl iodide (**2i**), were also explored in the reaction, and that gave products **3h** and **3i** in 40% and 51% yield, respectively (entries 8 and 9, Table 2). When aryl iodides **2j−l**, bearing a nitro group at the *para*-, *meta*-, and *ortho*-position, respectively, were employed as the coupling reagents, products **3j−l** were isolated in 68−82% yields (entries 10−12, Table 2). Among these, the product yield of **3k** (68%) was found to be lower than that of product **3j** (74%) and **3l** (82%). These results seem to indicate that the substituent position (i.e., inductive effects) potentially influences the direct C-3 arylation of pyrazolo[1,5-*a*]pyridine (**1a**).

Furthemore, the reaction of **1a** with halogen-substituted phenyl iodides **2m−o** could afford the anticipated products **3m−o** in 61−81% yields (entries 13−15, Table 2). Interestingly, an unexpected product, **3o-I** (23%), was isolated in the reaction of **1a** with *para*-bromophenyl iodide (**2o**) (entry 15, Table 2). This indicates that the reaction can also take place when aryl bromides are employed as the coupling reagents under the reaction conditions, although its reactivity is relatively poorer than that of aryl iodides.[15] Herein, the structure of **3n** was secured by X-ray crystallography as shown in Figure 1.[16] Finally, we explored the reaction of **1a** with pyridinyl iodides **2p−r**, and it smoothly gave the corresponding products **3p−r** in 44−60% yields (entries 16−18, Table 2).

Proposed Mechanism for the Direct C-3 Arylation of Pyrazolo[1,5-*a*]pyridine (1a). In order to gain insight into the reaction, we presented a possible mechanism as shown in Figure 2. First, palladium(II) ion is reduced to palladium(0) in

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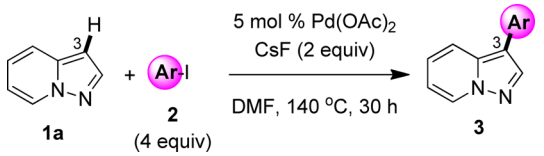
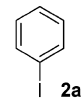
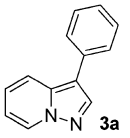
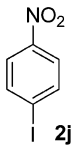
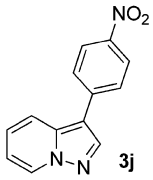
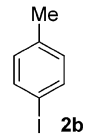
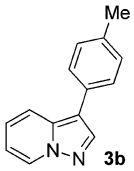
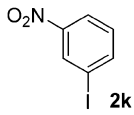
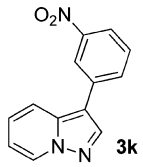
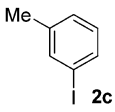
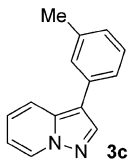
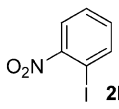
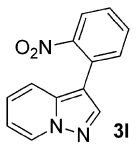
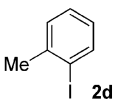
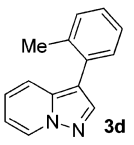
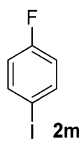
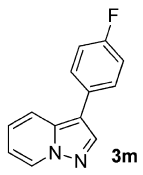
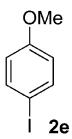
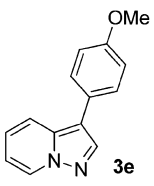
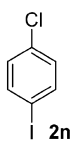
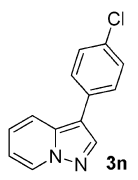
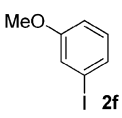
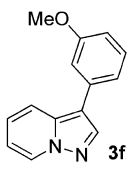
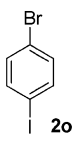
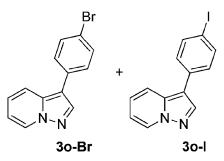
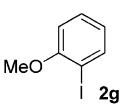
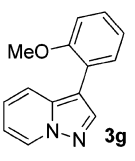
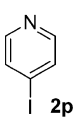
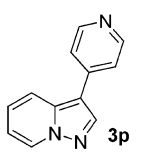
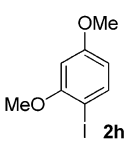
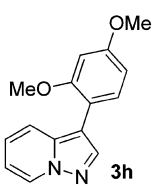
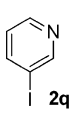
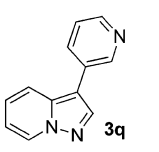
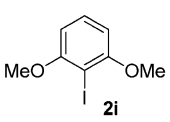
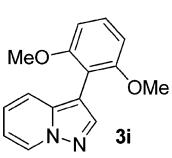
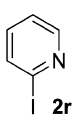
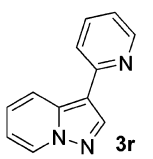
Table 2. Direct C-3 Arylation of 1a with 2



entry	Ar-I (2)	product 3	yield (%)[a]	entry	Ar-I (2)	product 3	yield (%)[a]
1	 2a	 3a	68	10	 2j	 3j	74
2	 2b	 3b	68	11	 2k	 3k	68
3	 2c	 3c	85	12	 2l	 3l	82
4	 2d	 3d	72	13	 2m	 3m	75
5	 2e	 3e	51	14	 2n	 3n	61
6	 2f	 3f	65	15	 2o	 3o-Br 3o-I	81
7	 2g	 3g	50	16	 2p	 3p	50
8	 2h	 3h	40	17	 2q	 3q	60
9	 2i	 3i	51	18	 2r	 3r	44

[a]Product yields were determined as an average of three runs by isolation.

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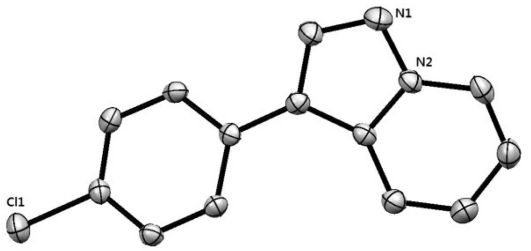


Figure 1. ORTEP drawings of compound **3n**.[16] All hydrogen atoms are omitted for clarity.

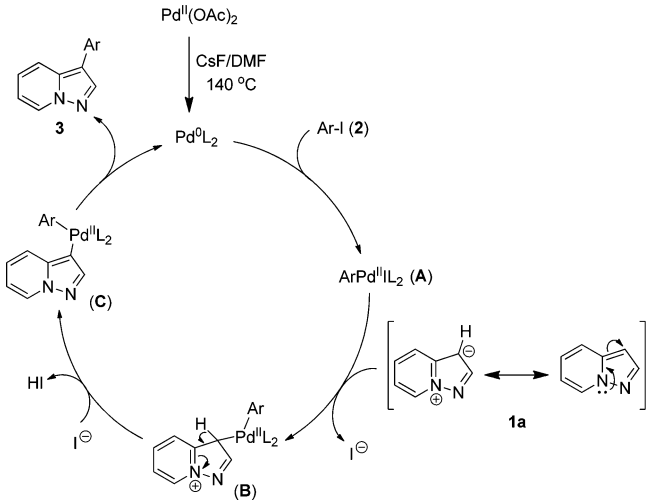
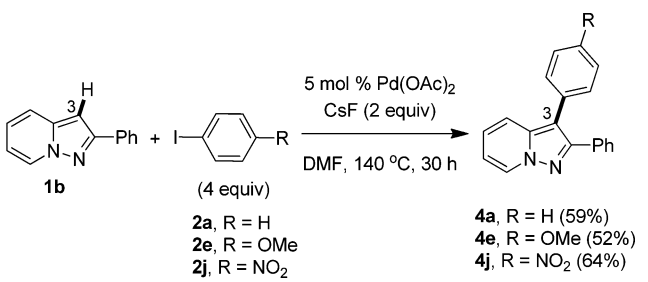


Figure 2. Proposed mechanism for the direct C-3 arylation of **1a**.

the presence of cesium(I) fluoride at 140 °C.[17] Subsequently, palladium(0) ion insertion into the carbon(sp^2)−iodine bond of aryl iodides **2** led to the formation of aryl palladium(II) complex (**A**), and then complex **A** reacts with the zwitterion form of **1a** to generate intermediate **B** by a release of an iodine anion.[18] Intermediate **B** is rapidly transformed into intermediate **C** through intramolecular electron transfer by a release of hydrogen iodide. Eventually, the desired product **3** is given through reductive elimination of intermediate **C**, and the released palladium(II) ion is reduced to palladium(0) ion and continues the catalytic cycle.

In addition to **1a**, the direct C-3 arylation of another starting substrate, 2-phenylpyrazolo[1,5-*a*]pyridine (**1b**), was also explored under the aforementioned reaction conditions. Three aryl iodides, **2a**, **2e**, and **2j**, were introduced to the above reaction and eventually provided the anticipated products, 2,3-diarylpyrazolo[1,5-*a*]pyridines **4a**,**e**,**j**, in 59%, 52%, and 64% yields, respectively (see Scheme 1).

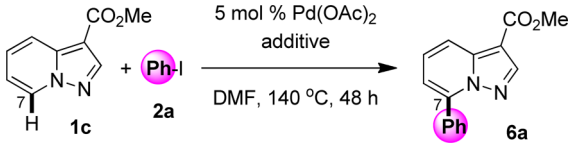
Scheme 1. Direct C-3 Arylation of Substrate 1b



During the course of the investigation, we serendipitously isolated 12% yield of 3,7-diphenylpyrazolo[1,5-*a*]pyridine (**5**) from the reaction of **1a** with **2a**, whereas the anticipated product **3a** was isolated in 36% yield when the reaction additive, cesium(I) fluoride, was replaced by silver(I) carbonate.

In view of the findings, we subsequently turned to evaluate the possibility of the direct C-7 selective arylation of **1a** through the screening of other additives, but the C-3-arylated compound (i.e., **3a**) was still generated as a major product accompanying a few C-7 arylated products (i.e., **6a**). This result indicated that the reactivity of the C-3 position of pyrazolo[1,5-*a*]pyridine (**1a**) is still prior to that of the C-7 position in terms of structural consideration. Thus, we turned to tagging a CO_2Me group at the C-3 position of **1a** to prevent the formation of 3-phenylpyrazolo[1,5-*a*]pyridine (**3a**). Preliminarily, the reaction of methyl pyrazolo[1,5-*a*]pyridine-3-carboxylate (**1c**) with phenyl iodides (**2a**) was carried out with 5 mol % $Pd(OAc)_2$ and 1.5 equiv of Ag_2CO_3 in DMF at 140 °C for 48 h and gave 7-phenylpyrazolo[1,5-*a*]pyridine (**6a**) in 20% yield (entry 1, Table 3). The structure of **6a** was further

Table 3. Optimization for the Direct C-7 Arylation of Methyl Pyrozolo[1,5-*a*]pyridine-3-carboxylate (1c)



entry	Ph-I (**2a**) (equiv)	additive (equiv)	yield (%)[a]
1	2	Ag_2CO_3 (1.5)	20
2	2	Ag_2CO_3 (1.5) + $BnBu_3NCl$ (0.1)	33
3	3	Ag_2CO_3 (2) + $BnBu_3NCl$ (0.1)	31
4	3	Ag_2CO_3 (3) + $BnBu_3NCl$ (0.2)	25
5	3	Ag_2CO_3 (2) + DMSO (4)	43
6	**3**	**Ag_2CO_3 (3) + DMSO (4)**	**75**
7	3	AgOAc (2) + DMSO (4)	43
8	3	AgOAc (3) + DMSO (4)	29
9	3	AgOAc (3) + $BnBu_3NCl$ (0.2)	17

[a]Product yields were determined as an average of three runs by isolation.

secured by X-ray crystallography as shown in Figure 3.[16] Subsequently, the reaction conditions were optimized as shown in Table 3. Initially, 0.1 and 0.2 equiv of an ammonium salt, benzyltributylammonium chloride ($BnBu_3NCl$), was added to the above reaction. However, the product yield of **6a** was not obviously improved (only 25−33% yields were observed) even

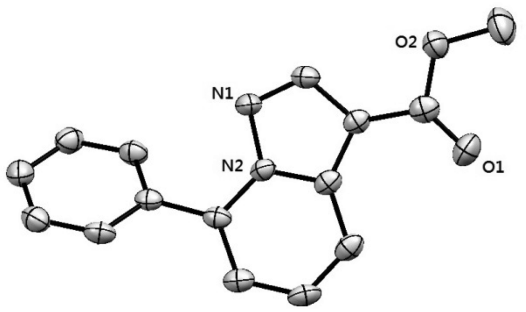


Figure 3. ORTEP drawing of compound **6a**.[16] All hydrogen atoms were omitted for clarity.

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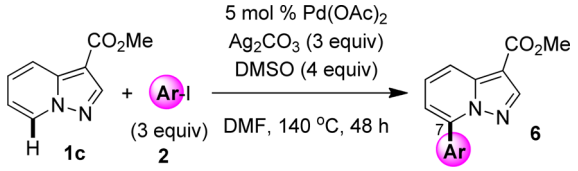
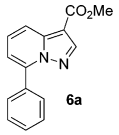
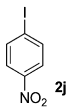
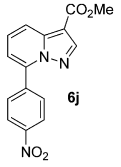
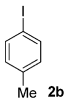
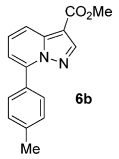
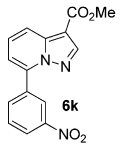
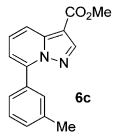
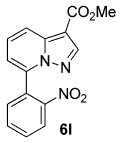
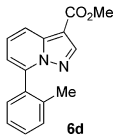
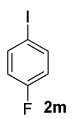
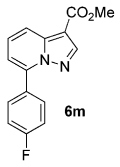
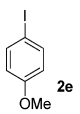
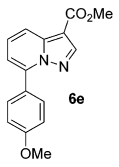
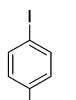
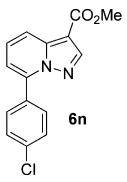
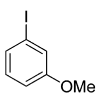
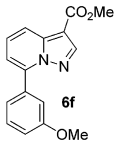
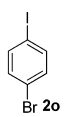
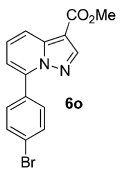
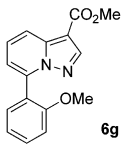
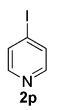
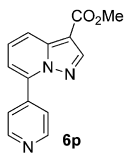
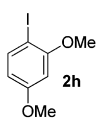
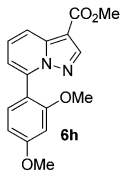
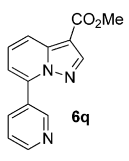
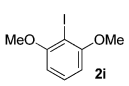
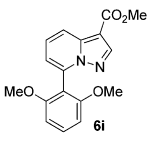
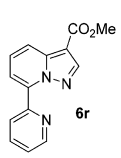
Table 4. Direct C-7 Arylation of 1c



entry	Ar-I (2)	product 3	yield (%)[a]	entry	Ar-I (2)	product 3	yield (%)[a]
1	 2a	 6a	75	10	 2j	 6j	20
2	 Me 2b	 6b	82	11	 2k	 6k	trace
3	 2c	 6c	80	12	 2l	 6l	trace
4	 2d	 6d	87	13	 F 2m	 6m	68
5	 2e	 6e	72	14	 Cl 2n	 6n	70
6	 2f	 6f	67	15	 Br 2o	 6o	68
7	 2g	 6g	60	16	 2p	 6p	52
8	 2h	 6h	40	17	 2q	 6q	63
9	 2i	 6i	25	18	 2r	 6r	52

[a]Product yields were determined as an average of three runs by isolation.

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when the used amount of silver(I) carbonate and phenyl iodide (**2a**) were increased to 3 equiv (entries 2−4, Table 3). Finally, we found that the addition of DMSO[19] was able to increase the product yield of **6a** (43%, entry 5, Table 3), especially combining both 3 equiv of Ag_2CO_3 and 4 equiv of DMSO, where 75% yield of **6a** was obtained (entry 6, Table 3). On the other hand, we also used AgOAc with either DMSO or $BnBu_3NCl$ in the reaction, but the product yield of **6a** was not improved (entries 7−9, Table 3).

With the optimized reaction conditions in hand (5 mol % $Pd(OAc)_2$, 3 equiv of Ag_2CO_3, and 4 equiv of DMSO in DMF at 140 °C for 48 h), we subsequently carried out the direct C-7 arylation of **1c** with a variety of aryl iodides **2** to afford the desired products **6**.[20] The experimental results are summarized in Table 4. In addition to the reaction of **1c** with **2a** leading to product **6a** (75%, entry 1, Table 4), the reaction of **1c** with **2b−r** was subsequently carried out to give products **6b−r** in 20−87% yields (entries 2−18, Table 4). Among these, the reaction of **1c** with **2b−d**, bearing a methyl substituent on the phenyl ring at the *para*-, *meta*-, and *ortho*-position, produced the anticipated compounds **6b−d** in 82%, 80%, and 87% yield, respectively (entries 2−4, Table 4). Then, the reaction of **1c** with **2e−g**, bearing a methoxy substituent on the phenyl ring at the *para*-, *meta*-, and *ortho*-position, gave the anticipated products **6e−g** in 72%, 62%, and 60% yield, respectively (entries 5−7, Table 4). On the other hand, dimethoxy-substituted aryl iodides **2h** and **2i** were also involved in the reaction, which led to products **6h** and **6i** in 45% and 20% yield, respectively (entries 8 and 9, Table 4).

In order to evaluate the substituent electronic effects on the influence of this reaction, we further carried out the reaction of **1c** with **2j−l**, bearing a nitro substituent on the phenyl ring at the *para*-, *meta*-, and *ortho*-position. The experimental results showed that products **6j**, **6k**, and **6l** were generated in 20% and trace yields, repectively (entries 10−12, Table 4).[21] In view of the above results, we believe that the substituent electronic effects indeed influence the reactivity for the direct C-7 arylation of **1c**. In other words, the aryl iodide **2**, bearing an electron-withdrawing group (e.g., $-NO_2$), usually resulted in a lower product yield of **6** than that of an electron-donating group (e.g., −OMe). Meanwhile, the steric hindrance caused from the *ortho*-substituent seems to slightly influence the reactivity of the reaction, especially in the methoxy-substituted cases. Moreover, the substituent position seems not to show obvious influence on the *para*-, *meta*-, and *ortho*-substituted aryl iodides **2** in the reaction.

On the other hand, halogen-substituted aryl iodides **2m−o** were also employed into the reaction, and the anticipated products **6m−o** were generated in moderate yields (63−76%, entries 13−15, Table 4). Finally, the reaction of **1c** with 4-, 3-, and 2-iodopyridines **2p−r** were carried out to afford products **6p−r** in 50−70% yields (entries 16−18, Table 4).

In order to gain insight into the direct C-7 arylation of **1c** with **2**, we attempted to synthesize and isolate the possible palladium intermediate. Herein, a stoichiometric reaction of **1c** with $Pd(OAc)_2$ in dichloromethane was carried out, and eventually a bis(3-methylcarboxylpyrazolo[1,5-*a*]pyridine)-palladium(II) intermediate (**D**) was isolated and secured by X-ray crystallography as shown in Figure 4.[16]

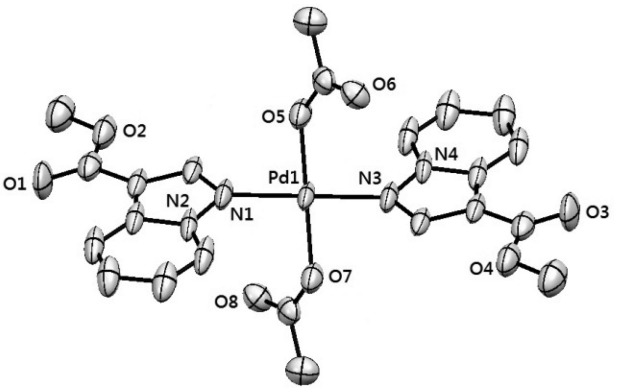

Figure 4. ORTEP drawing of complex **D**.[16] All hydrogen atoms were omitted for clarity.

Proposed Mechanism for the Direct C-7 Arylation of 3-Methylcarboxylpyrazolo[1,5-*a*]pyridine (1c). Based on the isolation of complex **D**, a possible reaction mechanism for the direct C-7 arylation of **1c** was presented as shown in Figure 5. First, palladium(II) ion is reduced to palladium(0) ion in the

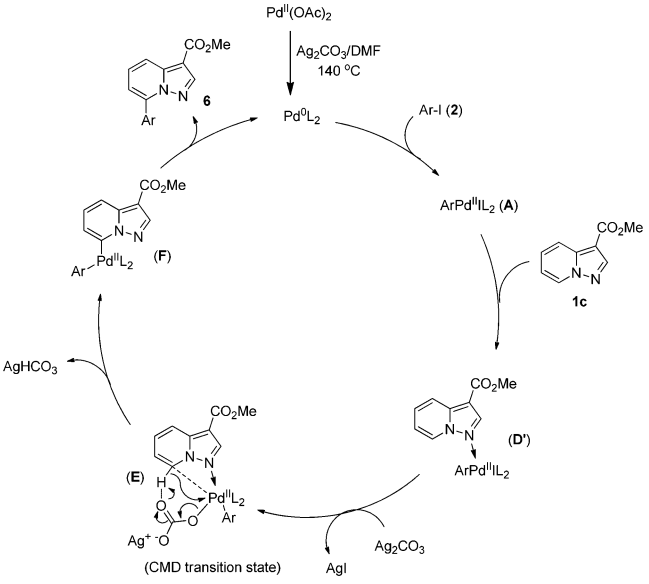

Figure 5. Proposed mechanism for the direct C-7 arylation of **1c**.

presence of silver(I) carbonate at 140 °C.[17] Subsequently, the palladium(0) ion inserts into the carbon(sp^2)−iodine bond of aryl iodide **2** and generates aryl palladium(II) intermediate **A**. Intermediate **A** is then coordinated with the nitrogen atom located at the N-1 position of **1c** and generates complex **D′**.[22] Furthermore, complex **D′** is transformed to intermediate **E** (a concerted-metalation-deprotonation transition state)[23] in the presence of silver(I) carbonate, whereas silver(I) iodide is released. Intermediate **E** is eventually converted to intermediate **F** by a release of silver(I) hydrogen carbonate, and product **6** is produced through reductive elimination of intermediate **E**, which releases a palladium(0) ion and continues the next catalytic cycle.

With 7-aryl-pyrazolo[1,5-*a*]pyridines **6** in hand, we subsequently removed the CO_2Me group by the treatment of an

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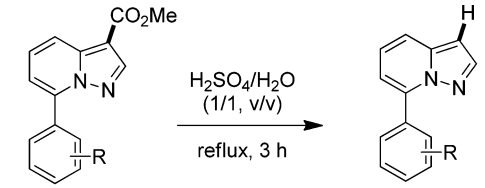
acidic solution, sulfonic acid/water (1/1, v/v), under reflux conditions. Finally, 7-arylpyrazolo[1,5-*a*]pyridines **7** were obtained in 44−81% yields (see Scheme 2).

Scheme 2. Removal of the CO_2Me Group of Compound 6



6a, R = H
6c, R = *m*-Me
6d, R = *o*-Me
6e, R = *p*-OMe
6g, R = *o*-OMe
6j, R = *p*-NO_2
6o, R = *p*-Br
6r, R-C_6H_4- = 2-pyridinyl

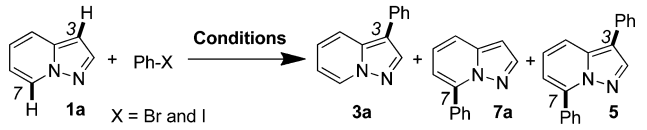
7a, R = H (76%)
7c, R = *m*-Me (81%)
7d, R = *o*-Me (80%)
7e, R = *p*-OMe (78%)
7g, R = *o*-OMe (77%)
7j, R = *p*-NO_2 (64%)
7o, R = *p*-Br (70%)
7r, R-C_6H_4- = 2-pyridinyl (44%)

On the other hand, in order to evaluate Bedford's reaction conditions[13] on the direct C-3 and C-7 arylation of pyrazolo[1,5-*a*]pyridines **1**, we carried out the reaction of pyrazolo[1,5-*a*]pyridine (**1a**) with 3 and 1 equiv of phenyl bromide/iodide, respectively, under their conditions A (10 mol % $Pd(OAc)_2$, 20 mol % SPhos, 1 equiv of Cs_2CO_3, and 1 equiv of LiCl heated at 150 °C for 18 h in toluene) to synthesize 7-phenylpyrazolo[1,5-*a*]pyridines **7a** and conditions B (10 mol % $Pd(OAc)_2$, 1 equiv of K_2CO_3, and 1 equiv of LiCl heated at 120 °C for 18 h in 1,4-dioxane) to synthesize 3-phenylpyrazolo[1,5-*a*]pyridines **3a**.

According to the experimental results (see Scheme 3), only a 5% product ratio of **7a** was observed in the reaction of **1a** with phenyl bromide under conditions A, whereas 76% and 19% product ratios of **3a** and **5** (3,7-diphenylpyrazolo[1,5-*a*]-pyridine) were determined, respectively, and the reaction total yield was determined to be 85%. Moreover, we found that

Scheme 3. Evaluation of Bedford's Reaction Conditions[13] on the Direct C-3/C-7 Arylation of 1

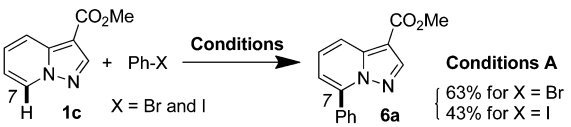
(a) The reaction of **1a** with phenyl bromide/iodide employing **Conditions A** (for C-7 arylation) and **B** (for C-3 arylation)



Conditions A { 76:5:19 (85% total yield) for X = Br
86:8:6 (37% total yield) for X = I

Conditions B { 91:3:6 (70% total yield) for X = Br
88:1:11 (57% total yield) for X = I

(b) The reaction of **1c** with phenyl bromide/iodide employing **Conditions A** (for C-7 arylation)



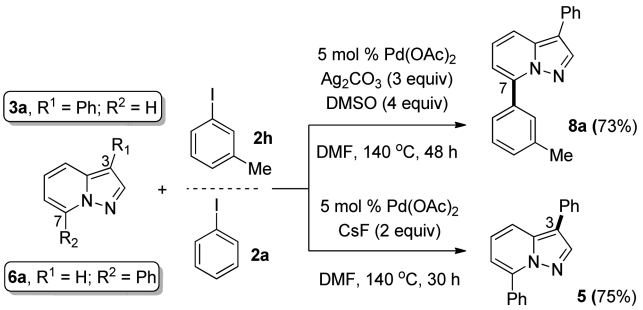
Conditions A { 63% for X = Br
43% for X = I

Conditions A: 10 mol % $Pd(OAc)_2$, 20 mol % SPhos, 1 equiv Cs_2CO_3 and 1 equiv LiCl heated at 150 °C for 18 hours in toluene.
Conditions B: 10 mol % $Pd(OAc)_2$, 1 equiv K_2CO_3 and 1 equiv LiCl heated at 120 °C for 18 hours in 1,4-dioxane

91% product ratio of **3a** accompaning 3% and 6% product ratios of **7a** and **5** (70% total yield) was observed in the same reaction under conditions B. When phenyl iodide instead of phenyl bromide was employed as the coupling reagent in the above reactions, a similar product distribution to that of phenyl bromide was observed, and the product ratio of **3a**, **7a**, and **5** was determined to be 86:8:6 (37% total yield) for conditions A and 88:1:11 (57% total yield) for conditions B (see Scheme 3a). Finally, we carried out the reaction of methyl pyrozolo[1,5-*a*]pyridine-3-carboxylate (**1c**) with Ph−X (X = Br and I) under conditions A, and that smoothly gives a single product, **6a**, in 63% yield (X = Br) and 43% yield (X = I), respectively (see Scheme 3b).

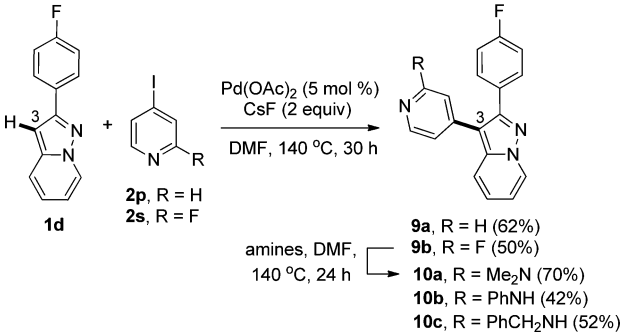
In addition, we are able to selectively synthesize 3,7-diaryl-substituted pyrazolo[1,5-*a*]pyridines **8a** and **5** by the reaction of **3a** with **2h**/**6a** with **2a** in 73% and 75% yield, respectively, based on the developed methodologies (see Scheme 4).

Scheme 4. Direct C-3/C-7 Arylation of Substrates 3a and 6a



Finally, in order to demonstrate the synthetic applications of the presented methodology, the syntheses of p38 kinase inhibitor **9a**[24] and its analogue **9b** were then carried out through the direct C-3 arylation of **1d** with **2p** and **2s**, respectively. The experimental results showed that 62% yield of **9a** and 50% yield of **9b** were eventually obtained (see Scheme 5). Moreover, other potent p38 kinase inhibitors, such as **10a**−**c**, can be easily prepared by the reaction of **9b** with various amines in 42−70% yields based on the reported reaction conditions.[3a]

Scheme 5. Synthesis of p38 Kinase Inhibitors 9 and 10 Directed from the Reaction of 1d with 2p,s



CONCLUSION

We have successfully developed a convenient and efficient strategy for the synthesis of 3- and 7-aryl-substituted pyrazolo-[1,5-*a*]pyridines via palladium-catalyzed C−H bond activation

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and C−C bond coupling. Possible catalytic mechanisms were presented to give an insightful understanding on these reactions. The synthesis of potent p38 kinase inhibitors based on the developed methodologies was demonstrated. Finally, we believe that the developed methodologies can further be used as useful synthetic tools in the field of pharmaceutical synthesis.

EXPERIMENTAL SECTION

General Procedures. Solvents and reagents were purchased from commercial suppliers and used without purification. ^{1}H NMR spectra were measured on 300, 400, 500, and 600 MHz NMR spectrometers. Natural abundance ^{13}C NMR spectra were measured by using 300, 400, 500, and 600 MHz NMR spectrometers operating at 75, 100, 125, and 150 MHz, respectively. Chemical shifts are given in parts per million (ppm) and coupling constant J in hertz (Hz) for both nuclei, with the solvent (usually $CDCl_3$) peak as an internal standard. The reference peak for ^{1}H is δ 7.26 of chloroform and for ^{13}C it is the central peak at δ 77.0. Low- and high-resolution mass spectrometry was majorly obtained by the following ionization method and mass analyzer type: EI-magnetic sector. Melting points were measured by using open capillary tubes and are uncorrected.

General Procedure for the Syntheses of 3 and 4. $Pd(OAc)_2$ (4.7 mg, 0.021 mmol) and CsF (127 mg. 0.840 mmol) were added to a well-stirred solution of pyrazolo[1,5-*a*]pyridines **1** (**1a**: 50 mg, 0.42 mmol; **1b**: 81 mg, 0.42 mmol) and aryl iodides **2** (4 equiv) in *N*,*N*-dimethylformamide (5 mL), and then the reaction was heated at 140 °C for 30 h. After cooling to room temperature, the reaction mixture was quenched with water (20 mL). The resulting solution was extracted with ethyl acetate (2 × 5 mL). Finally, the organic layers were combined, dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by flash chromatography on silica gel using *n*-hexane/ethyl acetate (20/1 to 5/1) as the eluent to give products **3** and **4**. All product yields are listed as follows. **3a**: 68% (55 mg, 0.29 mmol); **3b**: 68% (60 mg, 0.29 mmol); **3c**: 85% (74 mg, 0.36 mmol); **3d**: 72% (62 mg, 0.30 mmol); **3e**: 51% (48 mg, 0.21 mmol); **3f**: 65% (60 mg, 0.27 mmol); **3g**: 50% (47 mg, 0.21 mmol); **3h**: 40% (43 mg, 0.17 mmol); **3i**: 51% (53 mg, 0.21 mmol); **3j**: 74% (74 mg, 0.31 mmol); **3k**: 68% (68 mg, 0.28 mmol); **3l**: 82% (81 mg, 0.34 mmol); **3m**: 75% (68 mg, 0.32 mmol); **3n**: 61% (59 mg, 0.26 mmol); **3o-Br**: 58% (66 mg, 0.24 mmol); **3o-I**: 23% (32 mg, 0.10 mmol); **3p**: 50% (41 mg, 0.21 mmol); **3q**: 60% (49 mg, 0.25 mmol); **3r**: 44% (35 mg, 0.18 mmol); **4a**: 59% (68 mg, 0.25 mmol); **4e**: 52% (66 mg, 0.22 mmol); **4j**: 64% (85 mg, 0.27 mmol).

General Procedure for the Syntheses of 6. $Pd(OAc)_2$ (3.1 mg, 0.014 mmol) and Ag_2CO_3 (154 mg, 0.560 mmol) were added to a mixture of 3-methylcarboxylpyrazolo[1,5-*a*]pyridine **1c** (50 mg, 0.28 mmol) and aryl iodides **2** (3 equiv) in *N*,*N*-dimethylformamide (5 mL), 4 equiv of dimethyl sulfoxide (79 μL, 1.1 mmol) was injected into the above solution, and the reaction was then well-stirred and heated at 140 °C for 48 h. After cooling to room temperature, the reaction mixture was quenched with water (20 mL). The resulting solution was extracted with ethyl acetate (2 × 5 mL). Finally, the organic layers were combined, dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by the flash chromatography on silica gel using *n*-hexane/ethyl acetate (30/1 to 5/1) as the eluent to give product **6**. All product yields are listed as follows. **6a**: 75% (53 mg, 0.21 mmol); **6b**: 82% (61 mg, 0.23 mmol); **6c**: 80% (59 mg, 0.22 mmol); **6d**: 87% (69 mg, 0.24 mmol); **6e**: 72% (56 mg, 0.20 mmol); **6f**: 67% (52 mg, 0.18 mmol); **6g**: 60% (48 mg, 0.17 mmol); **6h**: 40% (36 mg, 0.12 mmol); **6i**: 25% (22 mg, 0.07 mmol); **6j**: 20% (18 mg, 0.06 mmol); **6k**: trace; **6l**: trace; **6m**: 68% (53 mg, 0.19 mmol); **6n**: 70% (55 mg, 0.19 mmol); **6o**: 68% (63 mg, 0.19 mmol); **6p**: 52% (36 mg, 0.15 mmol); **6q**: 63% (46 mg, 0.18 mmol); **6r**: 52% (38 mg, 0.15 mmol).

General Procedure for the Syntheses of 7.[25] Sulfuric acid (50% v/v in water; 2.0 mL, 4.1 mmol) was added to 7-aryl-3-methylcarboxylpyrazolo[1,5-*a*]pyridine **6** (**6a**: 50 mg, 0.20 mmol; **6c**: 50 mg, 0.19 mmol; **6d**: 50 mg, 0.19 mmol; **6e**: 50 mg, 0.18 mmol; **6g**: 50 mg, 0.18 mmol; **6j**: 50 mg, 0.17 mmol; **6o**: 50 mg, 0.15 mmol; **6r**: 50 mg, 0.20 mmol), and the reaction was heated under reflux for 3 h. After cooling to room temperature, sodium hydroxide solution (50% w/w in water) was added to the reaction while maintaining the temperature below 35 °C using an ice bath and until the solution was basic, as determined by litmus paper. Finally, the basic solution was extracted by ethyl acetate (5 mL × 3). The organic layers were combined, dried over Mg_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography on silica gel using *n*-hexane/ethyl acetate (20/1 to 5/1) as the eluent to give product **7**. All product yields are listed as follows. **7a**: 76% (29 mg, 0.15 mmol); **7c**: 81% (31 mg, 0.15 mmol); **7d**: 80% (31 mg, 0.15 mmol); **7e**: 78% (31 mg, 0.14 mmol); **7g**: 77% (31 mg, 0.14 mmol); **7j**: 64% (26 mg, 0.11 mmol); **7o**: 70% (30 mg, 0.11 mmol); **7r**: 44% (18 mg, 0.09 mmol).

Characterization Data of Compounds 3−10. *3-Phenylpyrazolo[1,5-a]pyridine (**3a**):* pale yellow solid; mp 120−122 °C; R_f = 0.55 (*n*-hexane/ethyl acetate = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.50 (d, J = 7.0 Hz, 1 H), 8.15 (s, 1 H), 7.83 (d, J = 9.0 Hz, 1 H), 7.61 (dd, J = 8.0, 1.0 Hz, 2 H), 7.46 (t, J = 7.5 Hz, 2 H), 7.30 (t, J = 7.5 Hz, 1 H), 7.18 (t, J = 8.0 Hz, 1 H), 6.80 (td, J = 7.0, 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.3, 136.9, 133.1, 129.0, 128.9, 127.0, 126.2, 123.9, 117.4, 112.8, 112.0; HRMS (EI-magnetic sector) m/z [M$^+$] calcd for $C_{13}H_{10}N_2$ 194.0844, found 194.0847.

*3-(p-Tolyl)pyrazolo[1,5-a]pyridine (**3b**):* yellow solid; mp 100−102 °C; R_f = 0.54 (*n*-hexane/ethyl acetate = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.48 (d, J = 7.0 Hz, 1 H), 8.12 (s, 1 H), 7.79 (d, J = 8.5 Hz, 1 H), 7.49 (d, J = 8.0 Hz, 2 H), 7.27 (d, J = 8.5 Hz, 2 H), 7.15 (m, 1 H), 6.77 (t, J = 7.0 Hz, 1 H), 2.40 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.2, 136.8, 135.9, 130.1, 129.6, 128.9, 126.9, 123.6, 117.5, 112.8, 111.8, 21.1; HRMS (EI-magnetic sector) m/z [M$^+$] calcd for $C_{14}H_{12}N_2$ 208.1000, found 208.1003.

*3-(m-Tolyl)pyrazolo[1,5-a]pyridine (**3c**):* brown oil; R_f = 0.58 (*n*-hexane/ethyl acetate = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.49 (d, J = 7.0 Hz, 1 H), 8.15 (s, 1 H), 7.82 (d, J = 9.0 Hz, 1 H), 7.42 (d, J = 9.5 Hz, 2 H), 7.35 (t, J = 7.5 Hz, 1 H), 7.16−7.11 (m, 2 H), 6.76 (td, J = 7.0, 1.0 Hz, 1 H), 2.43 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.2, 138.4, 136.8, 132.9, 128.8, 128.7, 127.6, 126.9, 124.0, 123.6, 117.4, 112.8, 111.8, 21.4; HRMS (EI-magnetic sector) m/z [M$^+$] calcd for $C_{14}H_{12}N_2$ 208.1000, found 208.0997.

*3-(o-Tolyl)pyrazolo[1,5-a]pyridine (**3d**):* brown oil; R_f = 0.56 (*n*-hexane/ethyl acetate = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.50 (d, J = 7.0 Hz, 1 H), 8.01 (s, 1 H), 7.44 (d, J = 9.0 Hz, 1 H), 7.37−7.27 (m, 4 H), 7.09 (m, 1 H), 6.76 (td, J = 6.5, 1.0 Hz, 1 H), 2.33 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.4, 137.6, 136.5, 131.8, 130.4, 130.3, 128.6, 127.0, 125.7, 123.2, 117.4, 111.9, 111.7, 20.4; HRMS (EI-magnetic sector) m/z [M$^+$] calcd for $C_{14}H_{12}N_2$ 208.1000, found 208.0997.

*3-(4-Methoxyphenyl)pyrazolo[1,5-a]pyridine (**3e**):* yellow solid; mp 76−78 °C; R_f = 0.52 (*n*-hexane/ethyl acetate = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.48 (d, J = 7.0 Hz, 1 H), 8.08 (s, 1 H), 7.75 (d, J = 9.0 Hz, 1 H), 7.51 (dt, J = 9.0, 2.0 Hz, 2 H), 7.13 (m, 1 H), 7.01 (dt, J = 9.0, 2.0 Hz, 2 H), 6.76 (td, J = 7.0, 1.0 Hz, 1 H), 3.85 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.2, 140.0, 136.7, 128.8, 128.2, 125.5, 123.5, 117.3, 114.4, 112.6, 111.8, 55.3; HRMS (EI-magnetic sector) m/z [M$^+$] calcd for $C_{14}H_{12}N_2O$ 224.0950, found 224.0953.

*3-(3-Methoxyphenyl)pyrazolo[1,5-a]pyridine (**3f**):* brown oil; R_f = 0.55 (*n*-hexane/ethyl acetate = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.50, (d, J = 7.0 Hz, 1 H), 8.14 (s, 1 H), 7.83 (d, J = 9.0 Hz, 1 H), 7.37 (t, J = 8.0 Hz, 1 H), 7.20−7.13 (m, 3 H), 6.86 (m, 1 H), 6.79 (td, J = 7.0, 1.0 Hz, 1 H), 3.88 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.0, 140.4, 136.9, 134.5, 129.9, 129.0, 123.9, 119.5, 117.5, 112.8, 112.7, 112.0, 111.4, 55.2; HRMS (EI-magnetic sector) m/z [M$^+$] calcd for $C_{14}H_{12}N_2O$ 224.0950, found 224.0949.

*3-(2-Methoxyphenyl)pyrazolo[1,5-a]pyridine (**3g**):* brown oil; R_f = 0.54 (*n*-hexane/ethyl acetate = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.49 (d, J = 7.0 Hz, 1 H), 8.20 (s, 1 H), 7.65 (d, J = 9.0 Hz, 1 H), 7.49 (dd, J = 7.5, 1.5 Hz, 1 H), 7.32 (td, J = 8.0, 1.5 Hz, 1 H), 7.14−7.02 (m, 3 H), 6.77 (td, J = 7.0, 1.0 Hz, 1 H), 3.87 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.3, 142.1, 137.6, 129.9, 128.7, 127.7, 123.2, 121.8, 120.8, 118.4, 111.7, 111.1, 108.7, 55.3; HRMS (EI-magnetic sector) m/z [M$^+$] calcd for $C_{14}H_{12}N_2O$ 224.0950, found 224.0951.

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*3-(2,4-Dimethoxyphenyl)pyrazolo[1,5-a]pyridine (**3h**):* brown oil; R_f = 0.48 (*n*-hexane/ethyl acetate = 5/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.47 (d, J = 7.0 Hz, 1 H), 8.12 (s, 1 H), 7.60 (d, J = 9.0 Hz, 1 H), 7.37 (d, J = 8.5 Hz, 1 H), 7.09 (dd, J = 9.0, 9.0 Hz, 1 H), 6.74 (td, J = 6.5, 1.0 Hz, 1 H), 6.61−6.58 (m, 2 H), 3.87 (s, 3 H), 3.84 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.8, 157.4, 141.8, 137.4, 130.4, 128.6, 122.9, 118.3, 114.5, 111.5, 108.5, 104.6, 99.0, 55.4; HRMS (EI-magnetic sector) m/z [M$^+$] calcd for $C_{15}H_{14}N_2O_2$ 254.1055, found 254.1057.

*3-(2,6-Dimethoxyphenyl)pyrazolo[1,5-a]pyridine (**3i**):* yellow oil; R_f = 0.54 (*n*-hexane/ethyl acetate = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.46 (d, J = 7.0 Hz, 1 H), 8.11 (s, 1 H), 7.34 (d, J = 9.0 Hz, 1 H), 7.29 (t, J = 8.5 Hz, 1 H), 7.05 (m, 1 H), 6.73 (td, J = 6.5, 1.0 Hz, 1 H), 6.70 (d, J = 8.5 Hz, 2 H), 3.79 (s, 6 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.2, 140.0, 136.7, 128.8, 128.2, 125.5, 123.5, 117.3, 114.4, 112.6, 111.8, 55.3; HRMS (EI-magnetic sector) m/z [M$^+$] calcd for $C_{15}H_{14}N_2O_2$ 254.1055, found 254.1055.

*3-(4-Nitrophenyl)pyrazolo[1,5-a]pyridine (**3j**):* orange solid; mp 188−190 °C; R_f = 0.42 (*n*-hexane/ethyl acetate = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.56 (d, J = 7.0 Hz, 1 H), 8.32 (d, J = 7.0 Hz, 2 H), 8.25 (s, 1 H), 7.88 (d, J = 9.0 Hz, 1 H), 7.75 (dt, J = 9.0, 2.0 Hz, 2 H), 7.33 (m, 1 H), 6.91 (td, J = 6.5, 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.5, 141.0, 140.2, 137.3, 129.5, 126.6, 125,.7, 124.5, 117.1, 112.9, 110.4; HRMS (EI-magnetic sector) m/z [M+] calcd for $C_{13}H_9N_3O_2$ 239.0695, found 239.0696.

*3-(3-Nitrophenyl)pyrazolo[1,5-a]pyridine (**3k**):* yellow solid; mp 131−132 °C; R_f = 0.44 (*n*-hexane/ethyl acetate = 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.55 (d, J = 6.8 Hz, 1 H), 8.46 (dd, J = 2.0, 2.0 Hz, 1 H), 8.23 (s, 1 H), 8.13 (dd, J = 8.4, 2.0, 0.8 Hz, 1 H), 7.92 (d, J = 9.2 Hz, 1 H), 7.86 (d, J = 9.2 Hz, 1 H), 7.62 (dd, J = 8.0, 8.0 Hz, 1 H), 7.30 (ddd, J = 8.8, 6.8, 0.8 Hz, 1 H), 6.89 (ddd, J = 6.8, 6.8, 0.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.9 (Cq), 140.6 (CH), 137.2 (Cq), 135.1 (Cq), 132.6 (CH), 129.9 (CH), 129.4 (CH), 125.2 (CH), 121.2 (CH), 120.8 (CH), 116.9 (CH), 112.7 (CH), 110.5 (Cq); HRMS (EI-magnetic sector) m/z [M$^+$] calcd for $C_{13}H_9N_3O_2$ 239.0695, found 239.0695.

*3-(2-Nitrophenyl)pyrazolo[1,5-a]pyridine (**3l**):* orange solid; mp 78−80 °C; R_f = 0.44 (*n*-hexane/ethyl acetate = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.47 (d, J = 7.0 Hz, 1 H), 8.02 (s, 1 H), 7.88 (dd, J = 8.5, 1.0 Hz, 1 H), 7.60 (td, J = 7.5, 1.0 Hz, 1 H), 7.52 (dd, J = 7.5, 1.0 Hz, 1 H), 7.43 (td, J = 8.5, 1.5 Hz, 1 H), 7.37 (d, J = 9.0 Hz, 1 H), 7.14 (m, 1 H), 6.79 (td, J = 6.5, 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.1, 141.1, 137.7, 132.3, 132.2, 128.9, 127.5, 126.8, 124.6, 124.4, 116.5, 112.3, 107.2; HRMS (EI-magnetic sector) m/z [M$^+$] calcd for $C_{13}H_9N_3O_2$ 239.0695, found 239.0695.

*3-(4-Fluorophenyl)pyrazolo[1,5-a]pyridine (**3m**):* yellow, viscous liquid; R_f = 0.45 (*n*-hexane/ethyl acetate = 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.50 (d, J = 7.2 Hz, 1 H), 8.10 (s, 1 H), 7.76 (d, J = 9.2 Hz, 1 H), 7.52−7.57 (m, 2 H), 7.12−7.21 (m, 3 H), 6.80 (ddd, J = 6.8, 6.8, 1.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.5 (d, J_{C-F} = 159.6 Hz, Cq), 140.1 (CH), 136.9 (Cq), 129.1 (d, J_{C-F} = 2.5 Hz, Cq), 128.6 (d, J_{C-F} = 6.3 Hz, CH × 2), 124.1 (CH), 117.2 (CH), 115.9 (d, J_{C-F} = 16.8 Hz, CH × 2), 112.0 (CH), 112.0 (Cq); HRMS (EI-magnetic sector) m/z [M$^+$] calcd for $C_{13}H_9N_2F$ 212.0750, found 212.0748.

*3-(4-Chlorophenyl)pyrazolo[1,5-a]pyridine (**3n**):* white solid; mp 144−146 °C; R_f = 0.51 (*n*-hexane/ethyl acetate = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.50 (d, J = 7.0 Hz, 1 H), 8.12 (s, 1 H), 7.77 (d, J = 9.0 Hz, 1 H), 7.52 (d, J = 9.0 Hz, 2 H), 7.42 (d, J = 8.5 Hz, 2 H), 7.20 (t, J = 8.0 Hz, 1 H), 6.81 (td, J = 7.0, 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.3, 136.9, 131.9, 131.6, 129.1, 128.1, 124.2, 117.2, 112.1, 111.7; HRMS (EI-magnetic sector) m/z [M$^+$] calcd for $C_{13}H_9N_2{}^{35}Cl$ 228.0454, found 228.0454.

*3-(4-Bromophenyl)pyrazolo[1,5-a]pyridine (**3o-Br**):* white solid; mp 150−152 °C; R_f = 0.56 (*n*-hexane/ethyl acetate = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.50 (d, J = 7.0 Hz, 1 H), 8.12 (s, 1 H), 7.77 (d, J = 9.0 Hz, 1 H), 7.54 (d, J = 8.5 Hz, 2 H), 7.43 (d, J = 8.5 Hz, 2 H), 7.20 (t, J = 8.0 Hz, 1 H), 6.81 (td, J = 6.5, 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.2, 137.9, 136.8, 132.1, 129.6, 128.9, 126.9, 123.6, 117.5, 112.1, 111.6; HRMS (EI-magnetic sector) m/z [M$^+$] calcd for $C_{13}H_9N_2Br$ 271.9949, found 271.9950.

*3-(4-Iodophenyl)pyrazolo[1,5-a]pyridine (**3o-I**):* white solid; mp 156−158 °C; R_f = 0.54 (*n*-hexane/ethyl acetate = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.50 (d, J = 7.0 Hz, 1 H), 8.12 (s, 1 H), 7.76 (d, J = 9.0 Hz, 1 H), 7.56 (d, J = 8.5 Hz, 2 H), 7.46 (d, J = 8.5 Hz, 2 H), 7.20 (t, J = 8.0 Hz, 1 H), 6.81 (td, J = 6.5, 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.2, 137.9, 136.8, 132.0, 129.1, 128.4, 124.3, 119.8, 117.1, 112.1, 111.6; HRMS (EI-magnetic sector) m/z [M+] calcd for $C_{13}H_9N_2I$ 319.9810, found 319.9810.

*3-(Pyridin-4-yl)pyrazolo[1,5-a]pyridine (**3p**):* brown solid; mp 71−72 °C; R_f = 0.60 (*n*-hexane/ethyl acetate = 1/1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.63 (d, J = 6.0 Hz, 2 H), 8.55 (ddd, J = 7.2, 1.2, 1.2 Hz, 1 H), 8.27 (s, 1 H), 7.89 (ddd, J = 9.0, 1.2, 1.2 Hz, 1 H), 7.53 (dd, J = 4.8, 1.5 Hz, 2 H), 7.31 (ddd, J = 7.2, 7.2, 1.2 Hz, 1 H), 6.89 (ddd, J = 6.6, 6.6, 1.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.1 (CH), 141.2 (Cq), 141.0 (CH), 135.5 (Cq), 129.6 (CH), 125.5 (CH), 121.0 (CH), 117.3 (CH), 112.8 (CH), 109.9 (Cq); HRMS (EI-magnetic sector) m/z [M$^+$] calcd for $C_{12}H_9N_3$ 195.0796, found 195.0798.

*3-(Pyridin-3-yl)pyrazolo[1,5-a]pyridine (**3q**):* brown oil; R_f = 0.46 (*n*-hexane/ethyl acetate = 5/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.88 (d, J = 2.0 Hz, 1 H), 8.52−8.51 (m, 2 H), 8.16 (s, 1 H), 7.87 (dt, J = 8.0, 1.5 Hz, 1 H), 7.79 (d, J = 9.0 Hz, 1 H), 7.36 (dd, J = 8.0, 5.0 Hz, 1 H), 7.23 (m, 1 H), 6.84 (td, J = 7.5, 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.9, 147.2, 140.3, 137.1, 134.0, 129.3, 129.2, 124.7, 123.7, 116.9, 109.1; HRMS (EI-magnetic sector) m/z [M$^+$] calcd for $C_{12}H_9N_3$ 195.0796, found 195.0799.

*3-(Pyridin-2-yl)pyrazolo[1,5-a]pyridine (**3r**):* yellow solid; mp 58−60 °C; R_f = 0.46 (*n*-hexane/ethyl acetate = 5/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.64 (dd, J = 4.5, 0.5 Hz, 1 H), 8.54 (d, J = 9.0 Hz, 1 H), 8.50 (d, J = 7.0 Hz, 1 H), 8.38 (s, 1 H), 7.69 (td, J = 8.0, 1.5 Hz, 1 H), 7.63 (d, J = 8.0 Hz, 1 H), 7.27 (m, 1 H), 7.09 (m, 1 H), 6.85 (td, J = 7.0, 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.2, 149.5, 138.1, 136.3, 128.8, 124.9, 120.1, 120.0, 119.7, 112.7, 112.0; HRMS (EI-magnetic sector) m/z [M$^+$] calcd for $C_{12}H_9N_3$ 195.0796, found 195.0797.

*2,3-Diphenylpyrazolo[1,5-a]pyridine (**4a**):* yellow solid; mp 134−136 °C; R_f = 0.53 (*n*-hexane/ethyl acetate = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.51 (d, J = 7.0 Hz, 1 H), 7.63−7.61 (m, 2 H), 7.57 (d, J = 9.0 Hz, 1 H), 7.41−7.28 (m, 8 H), 7.11 (m, 1 H), 6.78 (td, J = 6.5, 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.9, 139.5, 133.1, 33.0, 129.8, 128.8, 128.6, 128.4, 128.3, 128.0, 126.5, 123.6, 117.1, 112.1, 110.2; HRMS (EI-magnetic sector) m/z [M$^+$] calcd for $C_{19}H_{14}N_2$ 270.1157, found 270.1154.

*3-(4-Methoxyphenyl)-2-phenylpyrazolo[1,5-a]pyridine (**4e**):* white solid; mp 118−120 °C; R_f = 0.55 (*n*-hexane/ethyl acetate = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.49 (d, J = 7.0 Hz, 1 H), 7.64 (dd, J = 7.5, 2.0 Hz, 2 H), 7.52 (d, J = 8.5 Hz, 1 H), 7.35−7.28 (m, 5 H), 7.09 (t, J = 7.5 Hz, 1 H), 6.95 (d, J = 8.5, Hz, 2 H), 6.77 (td, J = 6.5, 1.0 Hz, 1 H), 3.85 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.4, 150.7, 139.6, 133.1, 131.0, 128.8, 128.4, 128.3, 127.9, 125.2, 123.4, 117.2, 114.1, 112.0, 109.8, 55.2; HRMS (EI-magnetic sector) m/z [M$^+$] calcd for $C_{20}H_{16}N_2O$ 300.1263, found 300.1260.

*3-(4-Nitrophenyl)-2-phenylpyrazolo[1,5-a]pyridine (**4j**):* yellow solid; mp 190−192 °C; R_f = 0.43 (*n*-hexane/ethyl acetate = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.55 (d, J = 7.0 Hz, 1 H), 8.23 (d, J = 9.0 Hz, 2 H), 7.63 (d, J = 9.0 Hz, 1 H), 7.56−7.50 (m, 4 H), 7.38−7.36 (m, 3 H), 7.25 (m, 1 H), 6.88 (td, J = 6.5, 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.9, 146.0, 140.4, 139.4, 132.2, 129.9, 129.0, 128.8, 128.6, 128.2, 125.2, 124.0, 116.5, 112.9, 108.0; HRMS (EI-magnetic sector) m/z [M$^+$] calcd for $C_{19}H_{13}N_3O_2$ 315.1008, found 315.1010.

*3,7-Diphenylpyrazolo[1,5-a]pyridine (**5**):* colorless solid; mp 136−138 °C; R_f = 0.53 (*n*-hexane/ethyl acetate = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.19 (s, 1 H), 7.91 (d, J = 8.0 Hz, 2 H), 7.85 (dd, J = 9.0, 1.5 Hz, 1 H) 7.64 (d, J = 8.0 Hz, 2 H), 7.57−7.47 (m, 5 H), 7.34−7.25 (m, 2 H), 6.87 (dd, J = 7.0, 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.8, 140.1, 137.9, 133.6, 133.3, 129.4, 129.1, 128.9, 128.4, 127.2, 126.2, 124.1, 116.3, 113.1, 112.8; HRMS (EI-magnetic sector) m/z [M$^+$] calcd for $C_{19}H_{14}N_2$ 270.1157, found 270.1158.

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Methyl-7-phenylpyrazolo[1,5-a]pyridine-3-carboxylate (**6a**): colorless solid; mp 120−122 °C; R_f = 0.51 (*n*-hexane/ethyl acetate = 5/1); ^{1}H NMR (CDCl3, 500 MHz) δ 8.42 (s, 1 H), 8.21 (dd, J = 9.0, 1.5 Hz, 1 H), 7.85 (dd, J = 8.0, 1.5 Hz, 2 H), 7.55−7.46 (m, 4 H), 6.99 (dd, J = 7.0, 1.5 Hz, 1 H), 3.93 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.8, 144.2, 141.8, 141.3, 132.7, 129.7, 129.2, 128.4, 127.5, 117.7, 114.4, 103.6, 51.1; HRMS (EI-magnetic sector) m/z [M^+] calcd for $C_{15}H_{12}N_2O_2$ 252.0899, found 252.0900.

Methyl-7-(p-tolyl)pyrazolo[1,5-a]pyridine-3-carboxylate (**6b**): white solid; mp 134−135 °C; R_f = 0.63 (*n*-hexane/ethyl acetate = 3/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.41 (s, 1 H), 8.19 (dd, J = 9.0, 1.0 Hz, 1 H), 7.74 (d, J = 8.0 Hz, 2 H), 7.48 (dd, J = 8.5, 8.5 Hz, 1 H), 7.35 (d, J = 8.0 Hz, 2 H), 7.00 (dd, J = 7.0, 1.0 Hz, 1 H), 3.93 (s, 3 H), 2.44 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.0 (Cq), 144.4 (CH), 141.9 (Cq), 141.6 (Cq), 140.1 (Cq), 130.0 (Cq), 129.2 (CH × 4), 127.6 (CH), 117.6 (CH), 114.2 (CH), 103.6 (Cq), 51.2 (CH_3), 21.4 (CH_3); HRMS (EI-magnetic sector) m/z [M^+] calcd for $C_{16}H_{14}N_2O_2$ 266.1055, found 266.1053.

Methyl-7-(m-tolyl)pyrazolo[1,5-a]pyridine-3-carboxylate (**6c**): white solid; mp 108−110 °C; R_f = 0.51 (*n*-hexane/ethyl acetate = 5/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.40 (s, 1 H), 8.15 (d, J = 9.0 Hz, 1 H), 7.61−7.60 (m, 2 H), 7.43−7.37 (m, 2 H), 7.29 (d, J = 7.5 Hz, 1 H), 6.94 (d, J = 6.5 Hz, 1 H), 3.91 (s, 3 H), 2.42 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.3, 144.0, 141.6, 137.9, 132.5, 130.3, 129.6, 128.1, 127.3, 126.2, 117.3, 114.2, 103.3, 50.9, 21.2; HRMS (EI-magnetic sector) m/z [M^+] calcd for $C_{16}H_{14}N_2O_2$ 266.1055, found 266.1056.

Methyl-7-(o-tolyl)pyrazolo[1,5-a]pyridine-3-carboxylate (**6d**): yellow oil; R_f = 0.52 (*n*-hexane/ethyl acetate = 5/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.39 (s, 1 H), 8.24 (dd, J = 9.0, 1.5 Hz, 1 H), 7.50 (dd, J = 9.0, 7.0 Hz, 1 H), 7.45−7.32 (m, 4 H), 6.89 (dd, J = 7.0, 1.0 Hz, 1 H), 3.93 (s, 3 H), 2.08 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.8, 144.6, 141.6, 141.3, 137.3, 132.8, 130.2, 129.8, 129.6, 127.2, 125.9, 117.8, 114.7, 103.5, 51.1, 19.4; HRMS (EI-magnetic sector) m/z [M^+] calcd for $C_{16}H_{14}N_2O_2$ 266.1055, found 266.1052.

Methyl-7-(4-methoxyphenyl)pyrazolo[1,5-a]pyridine-3-carboxylate (**6e**): white solid; mp 130−132 °C; R_f = 0.51 (*n*-hexane/ethyl acetate = 5/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.40 (s, 1 H), 8.15 (dd, J = 9.0, 1.0 Hz, 1 H), 7.80 (d, J = 9.0 Hz, 2 H), 7.45 (dd, J = 9.0, 7.0 Hz, 1 H), 7.05 (d, J = 9.0 Hz, 2 H), 6.96 (dd, J = 7.0, 1.0 Hz, 1 H), 3.92 (s, 3 H), 3.87 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.9, 160.6, 144.2, 141.8, 141.2, 130.7, 127.5, 125.0, 117.1, 113.9, 113.8, 103.4, 55.3, 51.1; HRMS (EI-magnetic sector) m/z [M^+] calcd for $C_{16}H_{14}N_2O_3$ 282.1004, found 282.1003.

Methyl-7-(3-methoxyphenyl)pyrazolo[1,5-a]pyridine-3-carboxylate (**6f**): white solid; mp 95−96 °C; R_f = 0.48 (*n*-hexane/ethyl acetate = 3/1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.42 (s, 1 H), 8.21 (dd, J = 9.0, 1.0 Hz, 1 H), 7.39−7.51 (m, 4 H), 7.06 (ddd, J = 9.0, 2.5, 1.0 Hz, 1 H), 7.02 (dd, J = 7.0, 1.0 Hz, 1 H), 3.94 (s, 3 H), 3.87 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.0 (Cq), 159.5 (Cq), 144.4 (CH), 141.9 (Cq), 141.3 (Cq), 134.1 (Cq), 129.6 (CH), 127.5 (CH), 121.7 (CH), 117.9 (CH), 115.4 (CH), 114.5 (CH), 114.0 (CH), 103.7 (Cq), 55.4 (CH_3), 51.2 (CH_3); HRMS (EI-magnetic sector) m/z [M^+] calcd for $C_{16}H_{14}N_2O_3$ 282.1004, found 282.1003.

Methyl-7-(2-methoxyphenyl)pyrazolo[1,5-a]pyridine-3-carboxylate (**6g**): white solid; mp 98−100 °C; R_f = 0.58 (*n*-hexane/ethyl acetate = 5/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.37 (s, 1 H), 8.21 (dd, J = 8.5, 1.0 Hz, 1 H), 7.49−7.42 (m, 3 H), 7.11 (td, J = 7.5, 1.0 Hz, 1 H), 7.07 (d, J = 8.0 Hz, 1 H), 6.96 (dd, J = 7.0, 1.0 Hz, 1 H), 3.92 (s, 3 H), 3.75 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.0, 157.4, 144.2, 141.4, 139.2, 131.3, 130.8, 127.2, 122.3, 120.6, 117.8, 115.2, 111.4, 103.3, 55.6, 51.1; HRMS (EI-magnetic sector) m/z [M+] calcd for $C_{16}H_{14}N_2O_3$ 282.1004, found 282.1006.

Methyl-7-(2,4-dimethoxyphenyl)pyrazolo[1,5-a]pyridine-3-carboxylate (**6h**): pale yellow solid; mp 114−115 °C; R_f = 0.44 (*n*-hexane/ethyl acetate = 2/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.36 (s, 1 H), 8.18 (dd, J = 9.0, 1.0 Hz, 1 H), 7.46 (dd, J = 9.0, 7.0 Hz, 1 H), 7.37 (d, J = 8.0 Hz, 1 H), 6.94 (dd, J = 7.0, 1.0 Hz, 1 H), 6.62−6.64 (m, 2 H), 3.92 (s, 3 H), 3.88 (s, 3 H), 3.73 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.1 (Cq), 162.4 (Cq), 158.6 (Cq), 144.2 (CH), 141.5 (Cq), 139.1 (Cq), 131.6 (CH), 127.3 (CH), 117.6 (CH), 115.4 (CH), 115.0 (Cq), 104.8 (CH), 103.3 (Cq), 99.1 (CH), 55.7 (CH_3), 55.5 (CH_3), 51.1 (CH_3); HRMS (EI-magnetic sector) m/z [M^+] calcd for $C_{17}H_{16}N_2O_4$ 312.1110, found 312.1111.

Methyl-7-(2,6-dimethoxyphenyl)pyrazolo[1,5-a]pyridine-3-carboxylate (**6i**): pale yellow solid; mp 133−134 °C; R_f = 0.39 (*n*-hexane/ethyl acetate = 1/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.34 (s, 1 H), 8.19 (dd, J = 9.0, 1.0 Hz, 1 H), 7.43−7.50 (m, 2 H), 6.92 (dd, J = 7.0, 1.0 Hz, 1 H), 6.70 (d, J = 8.5 Hz, 2 H), 3.91 (s, 3 H), 3.69 (s, 6 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.2 (Cq), 158.5 (CH), 144.2 (CH), 141.6 (Cq), 135.6 (CH), 131.6 (CH), 127.3 (CH), 117.6 (CH), 116.4 (CH), 110.9 (Cq), 104.2 (CH × 2), 103.2 (Cq), 55.9 (CH_3), 51.1 (CH_3); HRMS (EI-magnetic sector) m/z [M^+] calcd for $C_{17}H_{16}N_2O_4$ 312.1110, found 312.1111.

Methyl-7-(4-nitrophenyl)pyrazolo[1,5-a]pyridine-3-carboxylate (**6j**): yellow solid; mp 128−130 °C; R_f = 0.44 (*n*-hexane/ethyl acetate = 5/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.42−8.39 (m, 3 H), 8.30 (dd, J = 9.0, 1.5 Hz, 1 H), 8.09 (d, J = 9.0 Hz, 2 H), 7.54 (dd, J = 9.0, 7.0 Hz, 1 H), 7.10 (dd, J = 7.0, 1.5 Hz, 1 H), 3.95 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.7, 148.3, 144.4, 141.8, 138.9, 138.8, 130.4, 127.3, 123.7, 119.4, 115.2, 104.3, 51.3; HRMS (EI-magnetic sector) m/z [M^+] calcd for $C_{15}H_{11}N_3O_4$ 297.0750, found 297.0748.

Methyl-7-(4-fluorophenyl)pyrazolo[1,5-a]pyridine-3-carboxylate (**6m**): pale yellow solid; mp 201−202 °C; R_f = 0.53 (*n*-hexane/ethyl acetate = 3/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.41 (s, 1 H), 8.22 (d, J = 9.0 Hz, 1 H), 7.86 (dd, J = 8.5, 5.5 Hz, 2 H), 7.49 (dd, J = 7.5, 7.5 Hz, 1 H), 7.22−7.27 (m, 2 H), 6.99 (d, J = 7.0 Hz, 1 H), 3.94 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.9 (Cq), 163.5 (d, J_{C-F} = 249.1 Hz, Cq), 144.4 (CH), 141.9 (Cq), 140.4 (Cq), 131.4 (d, J_{C-F} = 8.8 Hz, CH), 128.9 (d, J_{C-F} = 3.3 Hz, Cq), 127.5 (CH), 118.0 (CH), 115.7 (d, J_{C-F} = 21.5 Hz, CH), 114.4 (CH), 103.9 (Cq), 51.2 (CH_3); HRMS (EI-magnetic sector) m/z [M+] calcd for $C_{15}H_{11}N_2O_2F$ 270.0805, found 270.0807.

Methyl-7-(4-chlorophenyl)pyrazolo[1,5-a]pyridine-3-carboxylate (**6n**): white solid; mp 169−170 °C; R_f = 0.55 (*n*-hexane/ethyl acetate = 3/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.41 (s, 1 H), 8.23 (dd, J = 9.0, 1.5 Hz, 1 H), 7.82 (d, J = 8.5 Hz, 2 H), 7.48−7.53 (m, 3 H), 7.01 (dd, J = 7.0, 1.0 Hz, 1 H), 3.94 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.9 (Cq), 144.4 (CH), 141.9 (Cq), 140.3 (Cq), 136.0 (Cq), 131.2 (Cq), 130.7 (CH × 2), 128.8 (CH × 2), 127.5 (CH), 118.2 (CH), 114.5 (CH), 103.9 (Cq), 51.3 (CH_3); HRMS (EI-magnetic sector) m/z [M^+] calcd for $C_{15}H_{11}N_2O_2{}^{35}Cl$ 286.0509, found 286.0510.

Methyl-7-(4-bromophenyl)pyrazolo[1,5-a]pyridine-3-carboxylate (**6o**): yellow solid; mp 186−188 °C; R_f = 0.50 (*n*-hexane/ethyl acetate = 5/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.41 (s, 1 H), 8.23 (dd, J = 9.0, 1.0 Hz, 1 H), 7.75−7.47 (m, 5 H), 7.01 (dd, J = 7.0, 1.0 Hz, 1 H), 3.93 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.8, 144.3, 141.8, 140.2, 131.7, 131.6, 130.9, 127.5, 124.2, 118.2, 114.4, 103.9, 51.2; HRMS (EI-magnetic sector) m/z [M^+] calcd for $C_{15}H_{11}N_2O_2{}^{79}Br$ 330.0004, found 330.0006.

Methyl-7-(pyridin-4-yl)pyrazolo[1,5-a]pyridine-3-carboxylate (**6p**): white solid; mp 163−164 °C; R_f = 0.39 (*n*-hexane/ethyl acetate = 1/2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.82 (bs, 2 H), 8.44 (s, 1 H), 8.30 (dd, J = 9.0, 1.0 Hz, 1 H), 7.84 (d, J = 6.0 Hz, 2 H), 7.53 (dd, J = 9.0, 9.0 Hz, 1 H), 7.11 (dd, J = 7.0, 1.0 Hz, 1 H), 3.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.7 (Cq), 150.2 (CH), 144.4 (CH), 141.9 (Cq), 140.3 (Cq), 138.6 (Cq), 127.3 (CH), 123.5 (CH), 119.5 (CH), 115.1 (CH), 104.3 (Cq), 51.4 (CH_3); HRMS (EI-magnetic sector) m/z [M^+] calcd for $C_{14}H_{11}N_3O_2$ 253.0851, found 253.0850.

Methyl-7-(pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carboxylate (**6q**): white solid; mp 159−160 °C; R_f = 0.42 (*n*-hexane/ethyl acetate = 1/2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.03 (s, 1 H), 8.75 (d, J = 3.5 Hz, 1 H), 8.41 (s, 1 H), 8.35 (d, J = 8.0 Hz, 1 H), 8.26 (d, J = 9.0 Hz, 1 H), 7.48−7.54 (m, 2 H), 7.07 (d, J = 7.0 Hz, 1 H), 3.94 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.8 (Cq), 150.6 (CH), 149.6 (CH), 144.4 (CH), 141.8 (Cq), 138.1 (Cq), 137.1 (CH), 129.0 (Cq), 127.4 (CH), 123.1 (Cq), 118.8 (CH), 114.7 (CH), 104.2 (Cq), 51.3 (CH_3); HRMS (EI-magnetic sector) m/z [M^+] calcd for $C_{14}H_{11}N_3O_2$ 253.0851, found 253.0850.

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*Methyl-7-(pyridin-2-yl)pyrazolo[1,5-a]pyridine-3-carboxylate (**6r**):* white solid; mp 132−134 °C; R_f = 0.44 (*n*-hexane/ethyl acetate = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.80 (m, 1 H), 8.58 (d, J = 8.0 Hz, 1 H), 8.46 (s, 1 H), 8.29 (dd, J = 9.0, 1.5 Hz, 1 H), 7.90 (td, J = 7.5, 1.5 Hz, 1 H), 7.65 (dd, J = 7.0, 1.5 Hz, 1 H), 7.56 (dd, J = 9.0, 7.5 Hz, 1 H), 7.41 (ddd, J = 7.5, 5.0, 1.0 Hz, 1 H), 3.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.9, 150.3, 149.8, 144.2, 142.0, 139.5, 136.4, 127.5, 125.2, 124.2, 119.0, 115.7, 103.8, 51.2; HRMS (EI-magnetic sector) m/z [M^+] calcd for $C_{14}H_{11}N_3O_2$ 253.0851, found 253.0849.

*Dimethyl [7,7′-bipyrazolo[1,5-a]pyridine]-3,3′-dicarboxylate (**6s**):* white solid; mp >250 °C (dec); R_f = 0.45 (*n*-hexane/ethyl acetate = 1/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.40 (dd, J = 9.0, 1.5 Hz, 2 H), 8.34 (s, 2 H), 7.57 (dd, J = 9.0, 7.0 Hz, 2 H), 7.30 (dd, J = 7.0, 1.0 Hz, 2 H), 3.93 (s, 6 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.7 (Cq × 2), 144.6 (CH × 2), 141.3 (Cq × 2), 133.0 (Cq × 2), 126.7 (CH × 2), 120.8 (CH × 2), 116.5 (CH × 2), 104.6 (Cq × 2), 51.6 (CH_3 × 2); HRMS (ESI-positive) m/z [MH^+] calcd for $C_{18}H_{15}N_4O_4$ 351.1093, found 351.1089.

*7-Phenylpyrazolo[1,5-a]pyridine (**7a**):* yellow oil; R_f = 0.55 (*n*-hexane/ethyl acetate = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.00 (d, J = 2.5 Hz, 1 H), 7.90 (dt, J = 8.5, 2.0 Hz, 2 H), 7.57−7.47 (m, 4 H), 7.19 (dd, J = 9.0, 7.0 Hz, 1 H), 6.82 (dd, J = 7.0, 1.0 Hz, 1 H), 6.62 (d, J = 2.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.3, 141.1, 140.5, 133.7, 129.3, 129.0, 128.3, 123.3, 117.0, 112.4, 97.1; HRMS (EI-magnetic sector) m/z [M^+] calcd for $C_{13}H_{10}N_2$ 194.0844; found 194.0841.

*7-(m-Tolyl)pyrazolo[1,5-a]pyridine (**7c**):* brown oil; R_f = 0.58 (*n*-hexane/ethyl acetate = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.99 (d, J = 2.0 Hz, 1 H), 7.68 (m, 2 H), 7.55 (dd, J = 9.0, 1.0 Hz, 1 H), 7.42 (t, J = 8.0 Hz, 1 H), 7.30 (d, J = 7.5 Hz, 1 H), 7.18 (dd, J = 9.0, 7.0 Hz, 1 H), 6.80 (dd, J = 7.0, 1.0 Hz, 1 H), 6.61 (d, J = 2.0 Hz, 1 H), 2.45 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.3, 141.1, 140.7, 138.0, 133.7, 130.1, 129.6, 128.3, 126.2, 123.3, 116.9, 112.3, 97.0, 21.5; HRMS (EI-magnetic sector) m/z [M^+] calcd for $C_{14}H_{12}N_2$ 208.1000, found 208.1002.

*7-(o-Tolyl)pyrazolo[1,5-a]pyridine (**7d**):* brown oil; R_f = 0.56 (*n*-hexane/ethyl acetate = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.97 (d, J = 2.0 Hz, 1 H), 7.60 (dd, J = 9.0, 1.0 Hz, 1 H), 7.44−7.32 (m, 4 H), 7.20 (dd, J = 9.0, 7.0 Hz, 1 H), 6.71 (dd, J = 6.5, 1.0 Hz, 1 H), 6.61 (d, J = 2.5 Hz, 1 H), 2.12 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.7, 140.7, 140.5, 137.4, 133.8, 130.1, 129.6, 129.4, 125.8, 123.0, 117.0, 112.6, 96.9, 19.4; HRMS (EI-magnetic sector) m/z [M^+] calcd for $C_{14}H_{12}N_2$ 208.1000, found 208.1002.

*7-(4-Methoxyphenyl)pyrazolo[1,5-a]pyridine (**7e**):* brown oil; R_f = 0.52 (*n*-hexane/ethyl acetate = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.99 (d, J = 2.5 Hz, 1 H), 7.87 (d, J = 9.0 Hz, 2 H), 7.52 (dd, J = 9.0, 1.0 Hz, 1 H), 7.16 (dd, J = 8.5, 7.0 Hz, 1 H), 7.05 (d, J = 9.0 Hz, 2 H), 6.78 (dd, J = 7.0, 1.0 Hz, 1 H), 6.60 (d, J = 2.0 Hz, 1 H), 3.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.3, 141.2, 141.1, 140.3, 130.4, 126.1, 123.3, 116.5, 113.8, 111.8, 96.9, 55.3; HRMS (EI-magnetic sector) m/z [M^+] calcd for $C_{14}H_{12}N_2O$ 224.0950, found 224.0952.

*7-(2-Methoxyphenyl)pyrazolo[1,5-a]pyridine (**7g**):* yellow solid; mp 124−126 °C; R_f = 0.50 (*n*-hexane/ethyl acetate = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.94 (d, J = 2.5 Hz, 1 H), 7.57 (dd, J = 8.5, 1.0 Hz, 1 H), 7.50−7.45 (m, 2 H), 7.19−7.06 (m, 3 H), 6.76 (dd, J = 7.0, 1.0 Hz, 1 H), 6.58 (d, J = 2.0 Hz, 1 H), 3.76 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.4, 141.3, 140.6, 138.1, 130.9, 130.8, 123.2, 122.9, 120.6, 117.0, 113.1, 111.4, 96.7, 55.7; HRMS (EI-magnetic sector) m/z [M^+] calcd for $C_{14}H_{12}N_2O$ 224.0950, found 224.0951.

*7-(4-Nitrophenyl)pyrazolo[1,5-a]pyridine (**7j**):* orange solid; mp 138−140 °C; R_f = 0.45 (*n*-hexane/ethyl acetate = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.38−8.35 (m, 2 H), 8.14 (d, J = 9.0 Hz, 2 H), 7.99 (d, J = 2.0 Hz, 1 H), 7.65 (dd, J = 9.0, 1.0 Hz, 1 H), 7.23 (dd, J = 9.0, 7.0 Hz, 1 H), 6.91 (dd, J = 7.0, 1.0 Hz, 1 H), 6.67 (d, J = 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.0, 141.6, 139.8, 138.0, 130.0, 128.3, 124.3, 123.6, 123.1, 118.7, 113.4, 97.8; HRMS (EI-magnetic sector) m/z [M^+] calcd for $C_{13}H_9N_3O_2$ 239.0695, found 239.0697.

*7-(4-Bromophenyl)pyrazolo[1,5-a]pyridine (**7o**):* yellow solid; mp 68−70 °C; R_f = 0.54 (*n*-hexane/ethyl acetate = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.98 (d, J = 2.0 Hz, 1 H), 7.80−7.78 (m, 2 H), 7.66−7.64 (m, 2 H), 7.58 (dd, J = 8.5, 1.0 Hz, 1 H), 7.18 (dd, J = 9.0, 7.0 Hz, 1 H), 6.80), dd, J = 7.0, 1.0 Hz, 1 H), 6.62 (d, J = 2.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.4, 141.1, 139.3, 132.5, 131.6, 130.7, 123.5, 123.2, 117.5, 112.3, 97.3; HRMS (EI-magnetic sector) m/z [M^+] calcd for $C_{13}H_9N_2Br$ 271.9949, found 271.9951.

*7-(Pyridin-2-yl)pyrazolo[1,5-a]pyridine (**7r**):* orange oil; R_f = 0.48 (*n*-hexane/ethyl acetate = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.73 (d, J = 4.5 Hz, 1 H), 8.63 (d, J = 8.0 Hz, 1 H), 7.99 (d, J = 2.0 Hz, 1 H), 7.80 (td, J = 7.5, 2.0 Hz, 1 H), 7.56 (dd, J = 9.0, 1.0 Hz, 1 H), 7.44 (dd, J = 7.0, 1.0 Hz, 1 H), 7.30−7.27 (m, 1 H), 7.18 (dd, J = 9.0, 7.0 Hz, 1 H), 6.59 (d, J = 2.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.8, 149.4, 141.2, 140.9, 138.4, 136.0, 124.5, 123.5, 123.0, 118.2, 113.6, 97.1; HRMS (EI-magnetic sector) m/z [M^+] calcd for $C_{12}H_9N_3$ 195.0796, found 195.0795.

*3-Phenyl-7-(m-tolyl)pyrazolo[1,5-a]pyridine (**8a**):* yellow solid; mp 140−142 °C; R_f = 0.53 (*n*-hexane/ethyl acetate = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.19 (s, 1 H), 7.84 (dd, J = 9.0, 1.0 Hz, 1 H), 7.71−7.64 (m, 4 H), 7.49 (t, J = 7.5 Hz, 2 H), 7.45 (t, J = 8.0 Hz, 1 H), 7.34−7.24 (m, 3 H), 6.85 (dd, J = 6.5, 1.0 Hz, 1 H), 2.48 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.0, 140.0, 138.0, 137.9, 133.5, 133.3, 130.2, 129.7, 128.9(2C),128.3, 127.2(2C), 126.2, 126.1, 124.1, 116.1, 113.0, 112.8, 21.5; HRMS (EI-magnetic sector) m/z [M^+] calcd for $C_{20}H_{16}N_2$ 284.1313, found 284.1312.

*2-(4-Fluorophenyl)-3-(pyridin-4-yl)pyrazolo[1,5-a]pyridine (**9a**):* characterization data were consistent with those reported in the literature;[7b] white solid; mp 136−138 °C; R_f = 0.48 (*n*-hexane/ethyl acetate = 5/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.57 (bs, 2 H), 8.50 (d, J = 7.0 Hz, 1 H), 7.62 (d, J = 9.0 Hz, 1 H), 7.53 (m, 2 H), 7.26−7.19 (m, 3 H), 7.05 (t, J = 8.5 Hz, 2 H), 6.85 (dt, J = 7.0, 1.0 Hz, 1 H).

*2-(4-Fluorophenyl)-3-(2-fluoropyridin-4-yl)pyrazolo[1,5-a]-pyridine (**9b**):* characterization data were consistent with those reported in the literature;[3a] brown solid; mp 168−170 °C; R_f = 0.52 (*n*-hexane/ethyl acetate = 5/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (d, J = 6.9 Hz, 1 H), 8.18 (d, J = 5.4 Hz, 1 H), 7.66 (d, J = 9.3 Hz, 1 H), 7.56−7.51 (m, 2 H), 7.30−7.26 (m, 1 H), 7.15−7.06 (m, 3 H), 6.91 (m, 2 H).

*4-(2-(4-Fluorophenyl)pyrazolo[1,5-a]pyridin-3-yl)-N,N-dimethyl-pyridin-2-amine (**10a**):* characterization data were consistent with those reported in the literature;[3a] brown solid; mp 158−160 °C; R_f = 0.60 (*n*-hexane/ethyl acetate = 5/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (d, J = 7.2 Hz, 1 H), 8.17 (d, J = 5.4 Hz, 1 H), 7.65−7.59 (m, 3 H), 7.20−7.15 (m, 1 H), 7.05 (t, J = 9.0 Hz, 2 H), 6.83 (t, J = 6.9 Hz, 1 H), 6.55 (d, J = 5.1 Hz, 1 H), 6.46 (s, 1 H), 3.03 (s, 6 H).

*4-(2-(4-Fluorophenyl)pyrazolo[1,5-a]pyridin-3-yl)-N-phenyl-pyridin-2-amine (**10b**):* characterization data were consistent with those reported in the literature;[3a] brown solid; mp 177−178 °C; R_f = 0.46 (*n*-hexane/ethyl acetate = 5/1); ^{1}H NMR (300 MHz, acetone-d_6) δ 8.66 (d, J = 7.2 Hz, 1 H), 8.22 (m, 2 H), 7.78−7.62 (m, 5 H), 7.36 (m, 1 H), 7.27−7.19 (m, 4 H), 7.02 (td, J = 6.9, 1.2 Hz, 1 H), 6.87 (t, J = 7.5 Hz, 1 H), 6.87 (s, 1 H), 6.79 (dd, J = 5.4, 1.5 Hz, 1 H).

*4-(2-(4-Fluorophenyl)pyrazolo[1,5-a]pyridin-3-yl)-N-benzyl-pyridin-2-amine (**10c**):* characterization data were consistent with those reported in the literature;[3a] brown solid; mp 158−160 °C; R_f = 0.55 (*n*-hexane/ethyl acetate = 5/1); ^{1}H NMR (300 Mz, acetone-d_6) δ 8.60 (d, J = 6.9 Hz, 1 H), 8.01 (d, J = 5.1 Hz, 1 H), 7.66 (m, 2 H), 7.50 (d, J = 9.0 Hz, 1 H), 7.39- 7.13 (m, 7 H), 6.96 (t, J = 6.9 Hz, 1 H), 6.53 (s, 1 H), 6.46 (d, J = 5.1 Hz, 1 H), 6.32 (m, 1 H), 4.58 (d, J = 6.0 Hz, 2 H).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.5b00988.

^{1}H and ^{13}C NMR spectra of new compounds and ^{1}H NMR of known compounds (PDF)

CIF file giving X-ray crystallographic data for compound **3n** (CIF)

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CIF file giving X-ray crystallographic data for compound **6a** (CIF)

CIF file giving X-ray crystallographic data for complex **D** (CIF)

Text file of all computed molecule Cartesian coordinates in a format for convenient visualization (XYZ)

AUTHOR INFORMATION

Corresponding Authors

*E-mail: j_hchu@yahoo.com.tw.

*E-mail: mijuwu@faculty.nsysu.edu.tw.

Author Contributions

§H.-C. Wu and C.-W. Li equally contributed to this work.

Notes

The authors declare no competing financial interest.

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(14) (a) The amount of aryl iodide can be reduced to 3 equivalents for the reaction, but the product yield of **3** is usually decreased by 10−15% compared to 4 equivalents used of aryl iodide. (b) The reaction can be carried out at lower reaction temperatures (e.g., 100−130 °C), but that would prolong the reaction time (up to 3 days) while lowering product yields of **3**..

(15) In addition to aryl iodides/bromides, we also carried out the direct C-3 and C-7 arylation of **1a,c** with phenyl tosylates/mesylates, respectively, under our optimal reaction conditions. However, according to the experimental results, only a trace amount of desired C-3-arylated product **3a** was detected by GC-MS, but no C-7-arylated product **6a** was found. Moreover, most of the starting materials (e.g., **1a,c** and phenyl tosylates/mesylates) were recovered in the above reactions. Regarding the employment of aryl tosylates/mesylates as the coupling reagent in the direct arylation of heteroarenes, see: (a) Ackermann, L.; Althammer, A.; Fenner, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 201−204. (b) Ackermann, L.; Fenner, S. *Chem. Commun.* **2011**, *47*, 430−432.

(16) Copies of the deposited crystallographic data CCDC-1439753 (**3n**), CCDC-1439754 (**6a**), and CCDC-1439755 (**D**) can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(17) Palladium(II) ions can be reduced to palladium(0) ions at a higher reaction temperature in the presence of salt additives; see: Oestreich, M. *The Mizororki-Heck Reaction*; John-Wiley & Sons, Ltd: Chichester, 2009; pp 1−43.

(18) The mechanistic proposal for the reaction of intermediate **A** with the zwitterionic form of **1a** leading to intermediate **B** is supported

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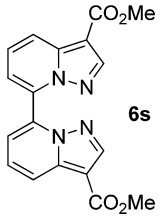
by the substituent electronic effects of the direct C-3 arylation of **1a**; see entries 2−7 and 10−12 in Table 2.

(19) DMSO was found to prohibit the catalyst decomposition and metal aggregation; see: (a) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904−11905. (b) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 9651−9653 and ref 10e.

(20) When the reaction conditions of direct C-3 arylation of **1a** (i.e., the catalytic system of $Pd(OAc)_2$/CsF) was applied to the direct C-7 arylation of **1c**, the experimental results showed that no product **6** was formed, whereas most of starting materials were recovered.

(21) In the reaction of **1c** with an alternative of 3-nitrophenyl iodide (**2k**) and 2-nitrophenyl iodide (**2l**), we serendipitously isolated an approximately 10−20% yield of dimethyl [7,7′-bipyrazolo[1,5-*a*] pyridine]-3,3′-dicarboxylate (**6s**), in which only trace amounts of products **6k** and **6l** were detected by GC-MS. Most of the starting substrate **1c** was recovered after the reaction.



6s

(22) Based on the findings of compound **6s** (refer to ref 21), we suspect that the poor reactivity of palladium(0) ion and nitro-substituted phenyl iodides (e.g., **2k** and **2l**) might provide the opportunity to form complex **D** in the course of the reaction and eventually transform it to the dimeric product (i.e., **6s**) via a concerted metalation−deprotonation process in the presence of silver(I) carbonate. Moreover, this result also supports the proposal of intermediate **D′**, **E**, and **F** for the direct C-7 aryaltion of **1c** with aryl iodide **2**.

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(25) The experimental procedure was operated by the literature reported; see: Bethel, P. A.; Campbell, A. D.; Goldberg, F. W.; Kemmitt, P. D.; Lamont, G. M.; Suleman, A. *Tetrahedron* **2012**, *68*, 5434−5444.

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