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Copper-Catalyzed Decarboxylative Three-Component Reactions for the Synthesis of Imidazo[1,2-*a*]pyridines

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Imidazo[1,2-*a*]pyridine derivatives were synthesized through multicomponent coupling reactions of 2-aminopyridines, aldehydes, and alkynecarboxylic acids in the presence of 10 mol-% CuI/Cu(OTf)$_2$. Both aryl- and alkyl-substituted alkynecarboxylic acids, including propiolic acid, were good alkyne sources and afforded the desired imidazo[1,2-*a*]pyridines in good yields through the decarboxylative coupling reactions. Arylalkynecarboxylic acids were synthesized through palladium-catalyzed coupling reactions between aryl iodides and propiolic acid and reacted with 2-aminopyridine and aldehydes, with or without a purification step. In both cases the desired imidazo[1,2-*a*]pyridines were obtained in good yields. Mechanistic studies suggested that in the case of propiolic acid the decarboxylative addition predominates over terminal alkyne addition.

Introduction

Heteroaromatic compounds containing nitrogen atoms are very important fragments in pharmacological and electromaterial molecules.[1] Among them, imidazopyridine derivatives have been widely used as core structures in drug discovery, their ring system being encountered in molecules showing bioactivity such as antiviral,[2] antibacterial,[3] anti-inflammatory,[4] and antiviral behavior.[5] In particular, imidazo[1,2-*a*]pyridine (Figure 1) is a key structure in anxiolytic agents (alpidem)[6] and in drugs used for the treatment of insomnia (zolpidem),[7] osteoporosis (minodronic acid),[8] and heart failure (olprinone).[9] In addition, imidazo[1,2-*a*]pyridine derivatives have received considerable attention as core ligands in the field of electronic devices.[10]

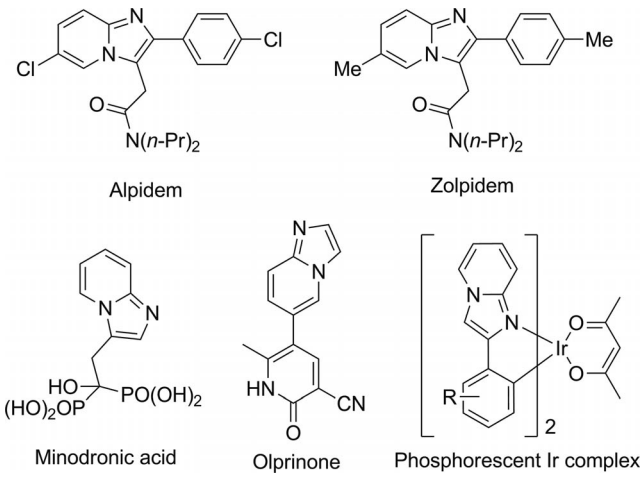

Figure 1. Imidazo[1,2-*a*]pyridine-based molecules.

The numerous synthetic methods for constructing the core ring system include condensation of 2-aminopyridine with carbonyl compounds and cyclization of the resulting intermediates (Scheme 1, a and b).[11] These methods, however, have some drawbacks, such as the need to prepare the carbonyl compounds. To address this problem, three-component reactions of 2-aminopyridine, aldehydes, and molecules containing triple bonds, such as isonitriles or alkynes, have been developed (Scheme 1, c)[12] Although this one-pot approach is a straightforward way to obtain the imidazo[1,2-*a*]pyridine derivative, it has some drawbacks in cases of low-molecular-weight alkynes and arylalkynes. Using low-molecular-weight alkynes is very difficult in a general organic laboratory.

Special equipment is required, for example, for the handling of acetylene gas in the synthesis of 3-methylimidazo[1,2-*a*]pyridine through a three-component reaction. Alternative methods such as the condensation of carbonyl compounds,[13] Suzuki coupling,[14] and hydroamination[15] have been reported, but all need multi-step procedures for the preparation of the starting materials. Even when arylalkynes have been used as starting materials they have also required multi-step reactions such as the Sonogashira reac-

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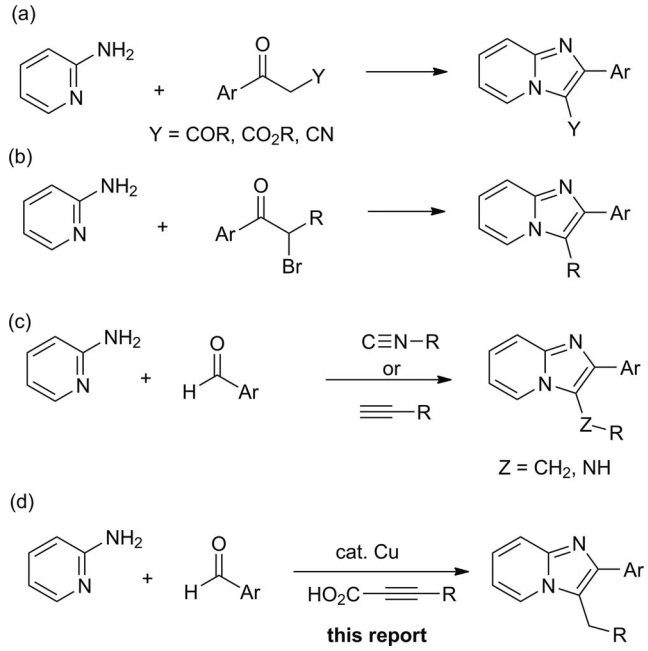


Scheme 1. Syntheses of imidazo[1,2-*a*]pyridines from 2-aminopyridine.

tion and deprotection for their preparation. A simpler and more general method therefore needs to be developed.

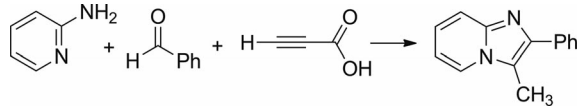
We have recently reported decarboxylative coupling reactions with aryl halides and alkynecarboxylic acids for the first time,[16] and have developed an efficient one-pot method for synthesizing arylalkynecarboxylic acids from aryl halides.[17]

To extend these reaction methods, we attempted to use alkynecarboxylic acids as alkyne sources in multicomponent coupling reactions. Alkynecarboxylic acids have three advantages as alkyne sources: 1) stable storage and ease of handling, 2) they are very good surrogates for alkynes of lower molecular weight, such as acetylene, propyne, and butyne, which are basically gases at room temperature,[18] and 3) in the case of arylalkynecarboxylic acids they are easily synthesized through coupling reactions of a variety of aryl iodides and propiolic acid.[17] Here we report one-pot syntheses leading to imidazo[1,2-*a*]pyridines through multicomponent couplings of 2-aminopyridines, aldehydes, and alkynecarboxylic acids.

Results and Discussion

To address the problems inherent in previously reported methods, we used propiolic acid as an alkyne source and coupled it with 2-aminopyridine and benzaldehyde. Our attempts to optimize the conditions for the synthesis of the imidazo[1,2-*a*]pyridine **4aa** are summarized in Table 1. As catalysts, palladium, nickel, and iron did not show any activity (Entries 1–3). Of the various copper(I) complexes, CuI showed the best yield (Entry 6).

Table 1. Optimized conditions for the synthesis of the imidazo[1,2-*a*]pyridine **4aa**.[a]



Entry	Catalyst	Additive[b]	Base	Solvent	Yield [%][d]
1	$Pd(OAc)_2$	–	–	DMSO	–
2	$Ni(OAc)_2$	–	–	DMSO	–
3	$FeCl_3$	–	–	DMSO	–
4	CuCl	–	–	DMSO	22
5	CuBr	–	–	DMSO	23
6	CuI	–	–		60
7	$Cu(OAc)_2$	–	–		46
8	$Cu(OTf)_2$	–	–		58
9	CuI	$Cu(OAc)_2$	–	DMSO	64
10	CuI	$Cu(OTf)_2$	–	DMSO	85
11	CuI	TMEDA	–	DMSO	15
12	CuI	phenanth[c]	–	DMSO	5
13	CuI	–	Cs_2CO_3	DMSO	80
14	CuI	–	K_3PO_4	DMSO	81
15	CuCl	$Cu(OTf)_2$	–	DMSO	80
16	CuI	$Cu(OTf)_2$	–	DMF	43
17	CuI	$Cu(OTf)_2$	–	NMP	34
18	CuI	$Cu(OTf)_2$	–	toluene	3
19	CuI	$Cu(OTf)_2$	–	diglyme	trace

[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.36 mmol), **3a** (0.36 mmol), and catalyst (0.03 mmol) were allowed to react in solvent (1.0 mL) at 110 °C for 16 h. [b] 0.03 mmol of additive was used. [c] 1,10-Phenanthroline. [d] Determined by GC with internal standard.

Use of copper(II) complexes such as $Cu(OAc)_2$ and $Cu(OTf)_2$ afforded the desired product in 46% and 58% yields, respectively (Entries 7 and 8). When combinations of CuI and the copper (II) complexes $Cu(OAc)_2$ and $Cu(OTf)_2$ were used, the yields were increased (Entries 9 and 10). The addition of chelating amines as ligands afforded lower product yields (Entries 11 and 12). However, the use of two inorganic bases – Cs_2CO_3 and K_3PO_4 – gave 80% and 81% yields, respectively (Entries 13 and 14). When the combination of CuCl and $Cu(OTf)_2$, previously reported by Gevorgyan,[12f] was used as a catalyst in this three-component reaction with propiolic acid the yield was similar to that obtained with CuI and $Cu(OTf)_2$ (Entry 15). Other solvents were tried instead of DMSO, but showed lower yields (Entries 16–19). Finally, we determined the following optimized conditions for the synthesis of imidazo[1,2-*a*]pyridine **4aa**: 2-aminopyridine (1.0 equiv.), benzaldehyde (1.2 equiv.), propiolic acid (1.2 equiv.), CuI (10 mol-%) and $Cu(OTf)_2$ (10 mol-%) in DMSO at 110 °C for 16 h.

To evaluate these optimized conditions further, we next used a variety of aldehydes in coupling reactions with 2-aminopyridine and propiolic acid. The results are summarized in Table 2. As expected, benzaldehyde produced an isolated yield of the desired product **4aa** of 81% (Entry 1). Alkyl-substituted benzaldehydes such as tolualdehydes and 4-*tert*-butylbenzaldehyde showed good yields (Entries 2–4). 2-Chlorobenzaldehyde, 4-chlorobenzaldehyde, and 3-fluorobenzaldehyde afforded the corresponding imidazo[1,2-*a*]-

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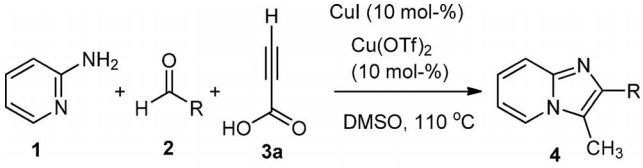
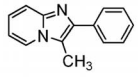
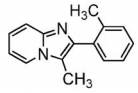
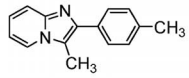
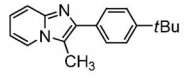
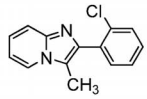
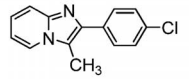
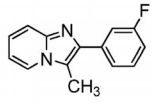
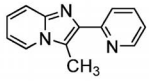
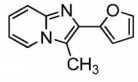
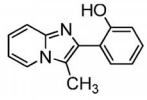
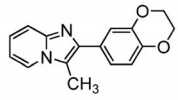
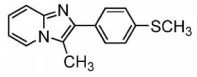
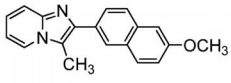
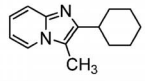
Table 2. Synthesis of imidazo[1,2-*a*]pyridines from 2-aminopyridine, different aldehydes, and propiolic acid.[a]



Entry	Product		Yield [%][b]
1		**4aa**	81
2		**4ba**	70
3		**4ca**	73
4		**4da**	64
5		**4ea**	60
6		**4fa**	71
7		**4ga**	63
8		**4ha**	65
9		**4ia**	68
10		**4ja**	55
11		**4ka**	64
12		**4la**	75
13		**4ma**	61
14		**4na**	70

[a] Reaction conditions: **1** (3.0 mmol), **2** (3.6 mmol), **3a** (3.6 mmol), CuI (0.3 mmol), and $Cu(OTf)_2$ (0.3 mmol) were allowed to react in DMSO (6.0 mL) at 110 °C for 16 h. [b] Isolated yield.

pyridines in 60%, 71%, and 63% yields, respectively (Entries 5–7). Heteroaromatic aldehydes such as pyridine-2-carboxaldehyde and furfural showed 65% and 68% yields, respectively (Entries 8 and 9). Salicylaldehyde, which contains a hydroxy group, also gave the desired product in 55% yield (Entry 10). Aldehydes bearing ether and thioether groups showed good yields (Entries 11 and 12). 6-Methoxy-2-naphthaldehyde produced a 61% yield of the product (Entry 13). In addition, cyclohexanecarboxaldehyde as a representative alkanecarbaldehyde successfully afforded the desired imidazo[1,2-*a*]pyridine in 70% yield (Entry 14).

We next expanded this reaction system to a variety of alkynecarboxylic acids; the results are summarized in Table 3. All of the alkynecarboxylic acids reacted as alkyne sources through decarboxylation to produce the corresponding imidazo[1,2-*a*]pyridines.

Phenylpropiolic acid produced 3-benzyl-2-phenylimidazo[1,2-*a*]pyridine (**4ab**) in 85% yield. 4-Substituted arylalkynecarboxylic acids afforded the corresponding products **4ac**, **4ad**, **4ae**, and **4af** in 80%, 71%, 65%, and 71% yields, respectively. 3-(Thiophen-2-yl)propiolic acid and 3-(2-naphthyl)propiolic acid afforded **4ag** and **4ah** in 61% and 63% yields, respectively. When alkyl alkynecarboxylic acids such as hept-2-ynoic acid and butynoic acid were used as the alkyne sources, the desired products **4ai** and **4aj** were obtained in 56% and 31% yields, respectively. When 4-tolualdehyde was used instead of benzaldehyde, similar yields were obtained (**4cc** and **4ci**). In addition, substituted 2-aminopyridines also produced the desired imidazo[1,2-*a*]pyridines **4aa-1** and **4aa-2** in moderate to good yields. In no case did we find the decarboxylative/carboxylative cyclized products recently reported by Van der Eycken.[19]

In view of the success of the decarboxylative couplings of alkynecarboxylic acids for the synthesis of imidazo[1,2-*a*]pyridines, we attempted to use in situ preparation of arylalkynecarboxylic acids through palladium-catalyzed coupling of aryl iodides and propiolic acid. Coupling of aryl iodides and propiolic acid was first conducted in the presence of DBU, $[Pd(PPh)_3]_2Cl_2$, and CuI at room temperature, and provided the desired arylalkynecarboxylic acids.[20]

Next, 2-aminopyridine, benzaldehyde, and $Cu(OTf)_2$ were added to the resulting reaction mixture without any isolation step and the reaction was allowed to proceed at 110 °C. The results are summarized in Table 4. As expected, all aryl iodides afforded the desired imidazo[1,2-*a*]pyridines in moderate to good yields. Phenyl iodide (**5a**) provided 3-benzyl-2-phenylimidazopyridine (**6a** = **4ab**) in 85% yield, which is almost the same as had been obtained from the reaction of phenylpropiolic acid (Entry 1). *ortho*-, *meta*-, and *para*-tolyl iodides afforded the corresponding imidazo[1,2-*a*]pyridines in 65%, 67%, and 82% yields, respectively (Entries 2–4). Iodoanisoles and 4-*tert*-butylphenyl iodide also produced the desired products (Entries 5–7). Aryl iodide **5h**, containing a keto group, gave the corresponding imidazo[1,2-*a*]pyridine in 45% yield (Entry 8). Halo-substituted, heteroaryl, and 1-naphthyl iodides showed 64%, 59%, and 57% yields, respectively (Entries 9–11). These yields were similar to those obtained from the reactions of the corresponding arylalkynecarboxylic acids.

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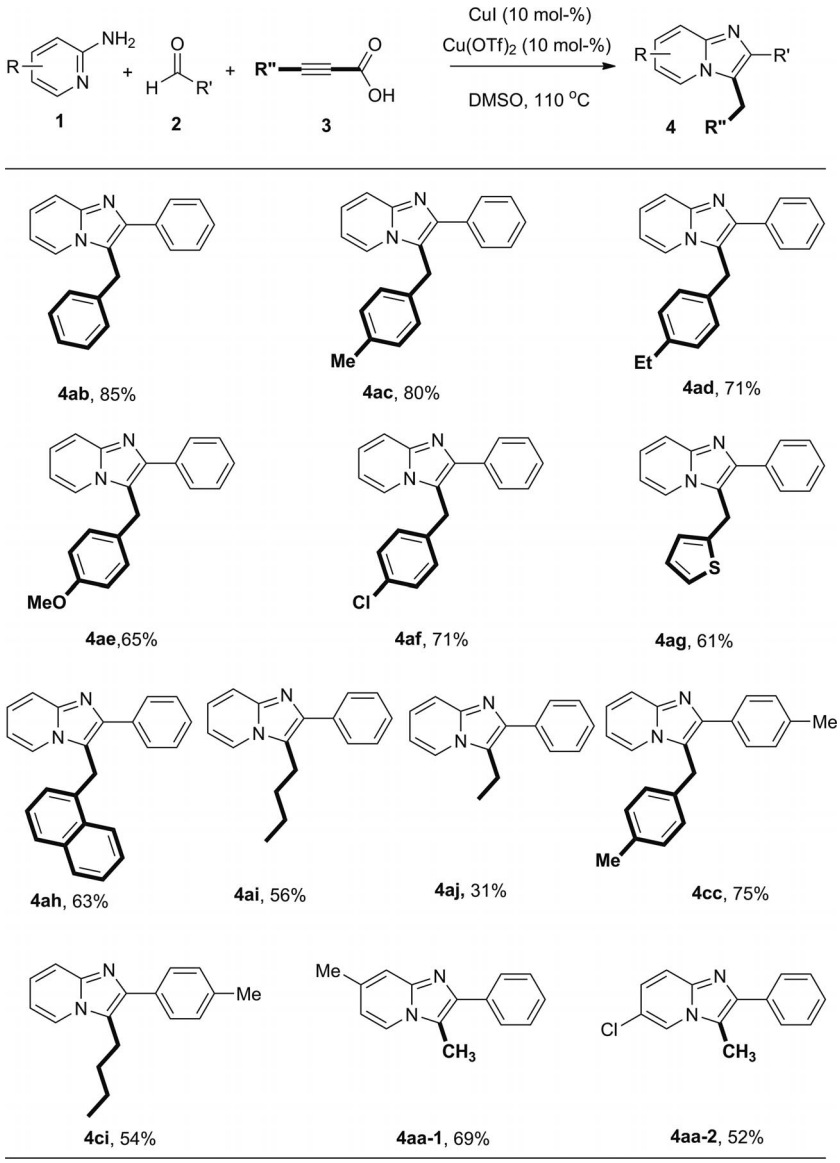
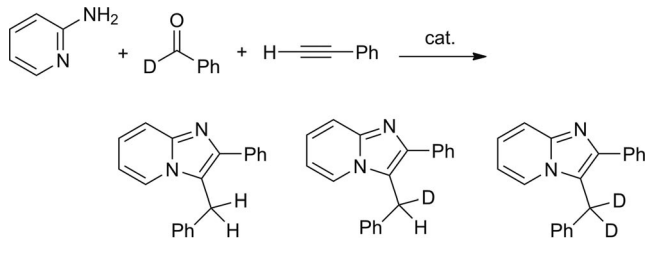
Table 3. Synthesis of imidazo[1,2-*a*]pyridines from 2-aminopyridines, aldehydes, and alkynecarboxylic acids.[a]



[a] Reaction conditions: **1** (3.0 mmol), **2** (3.6 mmol), **3a** (3.6 mmol), CuI (0.3 mmol) and $Cu(OTf)_2$ (0.3 mmol) were allowed to react in DMSO (6.0 mL) at 110 °C for 16 h.

The two potential reaction sites in propiolic acid are the terminal alkynyl carbon and the decarboxylative carbon. To investigate the main reaction site, we conducted several experiments in the presence of D_2O.[21,22] As shown in Scheme 2, when phenylacetylene was treated with 2-aminopyridine and C_6H_5CDO in the presence of D_2O, the dideuterated product **4ab-2D** was formed in 53% yield, whereas in the absence of D_2O the monodeuterated product **4ab-D** was formed in 65% yield.[22] These results suggest that one of the benzylic protons comes from the aldehyde and the other from water.

We next treated propiolic acid, C_6H_5CDO, and 2-aminopyridine in the presence of D_2O.[21] 3-Methyl-2-phenylimidazo[1,2-*a*]pyridine and deuterated analogues were isolated in 73% combined yield, as shown in Scheme 3. ^1H NMR



Scheme 2. Deuterium exchange experiments with phenylacetylene.

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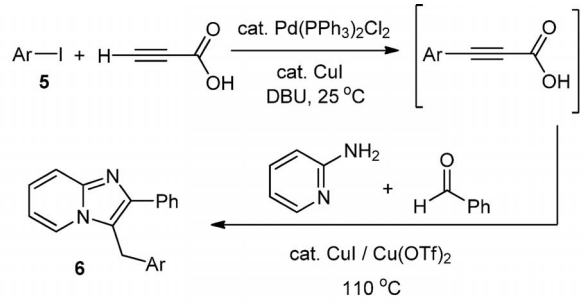
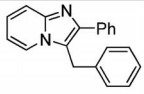
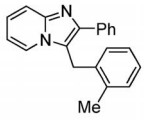
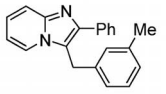
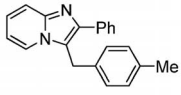
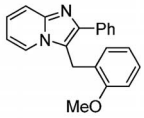
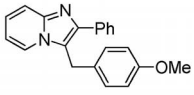
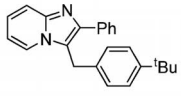
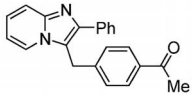
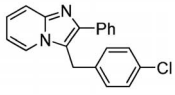
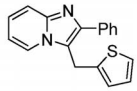
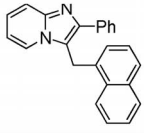
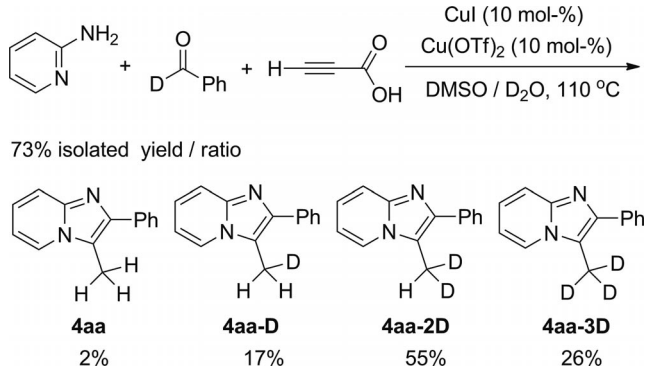
Table 4. Synthesis of imidazo[1,2-*a*]pyridines from 2-aminopyridines, aldehydes, aryl iodides, and propiolic acids.[a]



Entry	Ar		Product		Yield [%][b]
1	C_6H_5	**5a**		**6a (4ab)**	85
2	2-MeC_6H_4	**5b**		**6b**	65
3	3-MeC_6H_4	**5c**		**6c**	67
4	4-MeC_6H_4	**5d**		**6d (4ac)**	82
5	2-MeOC_6H_4	**5e**		**6e**	62
6	4-MeOC_6H_4	**5f**		**6f (4ae)**	79
7	4-*t*BuC_6H_4	**5g**		**6g**	75
8[c]	4-MeCOC_6H_4	**5h**		**6h**	45
9[c]	4-ClC_6H_4	**5i**		**6i (4af)**	64
10[c]	2-thiophenyl	**5j**		**6j (4ag)**	59
11[d]	1-naphthyl	**5k**		**6k (4ah)**	57

[a] Reaction conditions: **5** (4.5 mmol), propiolic acid (4.5 mmol), $Pd(PPh_3)_2Cl_2$, (0.225 mmol), CuI (0.45 mmol), and DBU (9.0 mmol) were allowed to react in DMSO at 25 °C for 8 h, and then 2-aminopyridine (3.0 mmol), benzaldehyde (3.6 mmol), CuI (0.3 mmol), and $Cu(OTf)_2$ (0.3 mmol) were added and allowed to react at 110 °C for 16 h. [b] Isolated yield. [c] DBU (22.5 mmol) was used. [d] DBU (13.5 mmol) was used.

deconvolution data analysis showed that the dideuterated product **4aa-2D** was formed in 55% proportion, along with 26% of the trideuterated **4aa-3D**.[22]



Scheme 3. Deuterium exchange experiments with propiolic acid.

We suggest a reaction pathway based on the H/D exchange experimental data and the previously reported proposed mechanism for the formation of imidazo[1,2-*a*]pyridines from propiolic acid in excess D_2O, as shown in Scheme 4.

The first step is the condensation of the 2-aminopyridine and deuterated benzaldehyde (C_6H_5CDO) to form the 2-iminopyridine **I**. In the next step, the 2-iminopyridine reacts with propiolic acid to form propargylamine **II-1** or **II-2**. Finally, the desired imidazo[1,2-*a*]pyridine is formed through a copper-catalyzed *5-exo-dig* cyclization.[12f,23]

With regard to the two reaction sites of propiolic acid, we proposed two pathways to form 3-methyl-2-phenylimidazo[1,2-*a*]pyridine (**4aa**): path A (Scheme 4), in which the decarboxylative coupling reaction occurs first and the intermediate **II-1** is produced, and path B, in which the reaction at the terminal alkynyl carbon occurs first and the intermediate **II-2** is produced. Intermediate **II-2** could be converted into **II-1** through decarboxylation. However, in excess D_2O the yield of **II-1** from the decarboxylation of **II-2** is much lower than that of **II-1-D** from **II-2**. Therefore, intermediate **III-1** with a terminal =C–H, is formed mainly through path A and converted into **4aa-2D** through rearrangement. Path B affords the formation of **4aa-3D** from intermediate **III-2**, which does not have a terminal alkyne carbon proton. The experimental results in Scheme 3 support the hypothesis that the two alternative pathways, A and B, are both involved in the reaction but that path A predominates over path B.

Conclusions

We have developed a three-component coupling reaction system for the synthesis of imidazo[1,2-*a*]pyridines from 2-aminopyridines, aldehydes, and alkynecarboxylic acids. The use of CuI and $Cu(OTf)_2$ as catalysts afforded the desired products in good yields. This reaction system demonstrated good applicability in the use of low-molecular-weight alkynes such as propiolic acid. In the case of propiolic acid, decarboxylative addition predominated over terminal al-

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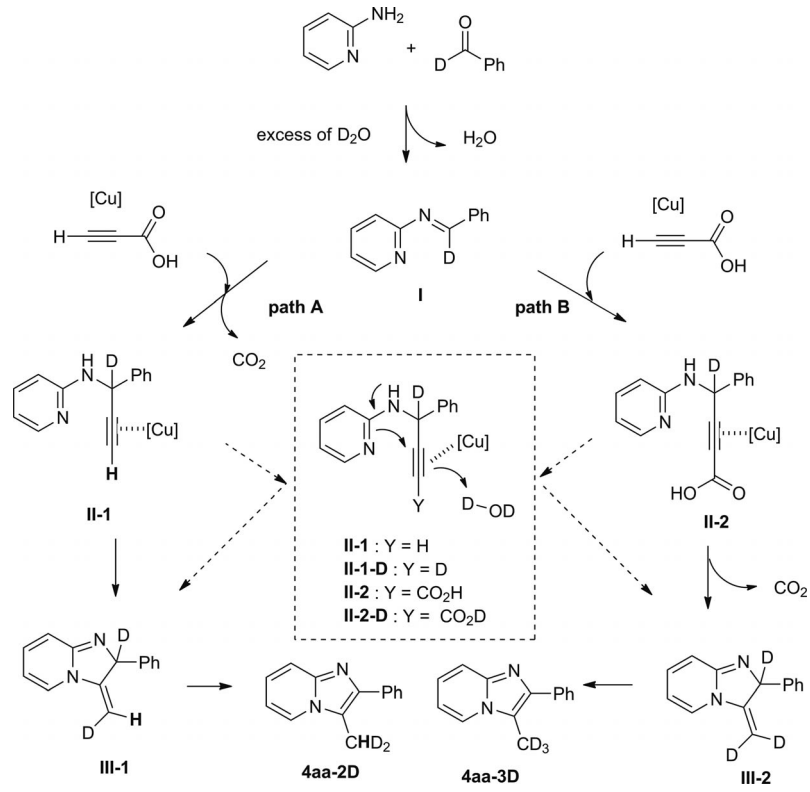

Scheme 4. Proposed mechanism.

kyne addition. In addition, arylalkynecarboxylic acids that had been prepared through palladium-catalyzed coupling of aryl iodides and propiolic acid were used in situ to produce the desired imidazo[1,2-*a*]pyridines in moderate to good yields by sequential reaction with 2-aminopyridine and benzaldehyde. This multicomponent reaction system is the first example of the use of alkynecarboxylic acids as alkyne sources in the synthesis of imidazo[1,2-*a*]pyridines.

Experimental Section

General Procedure for the Synthesis of Imidazo[1,2-*a*]pyridines from Arylalkynecarboxylic Acids: 2-Aminopyridine (282 mg, 3.0 mmol), the aldehyde (3.6 mmol, 1.2 equiv.), the alkyne carboxylic acid (3.6 mmol, 1.2 equiv.), CuI (57.1 mg, 0.3 mmol, 10 mol-%), $Cu(OTf)_2$ (108.4 mg, 0.3 mmol, 10 mol-%), and DMSO (6 mL) were placed in a 20 mL flask. The reaction mixture was tightly sealed and heated at 110 °C for 16 h. After cooling, the mixture was poured into EtOAc (50.0 mL), washed with water (3 × 25.0 mL) and brine (3 × 25.0 mL), and then dried with $MgSO_4$ and passed through a celite pad. Evaporation of the solvent under reduced pressure provided the crude product, which was purified by column chromatography (hexane/EtOAc 4:1) to afford the final product.

3-Methyl-2-phenylimidazo[1,2-*a*]pyridine (4aa):[15] 2-Aminopyridine (282 mg, 3.0 mmol), benzaldehyde (382 mg, 3.6 mmol), and propiolic acid (252 mg, 3.6 mmol) gave **4aa** (506 mg, 2.43 mmol, 81%) as a pale yellow solid after chromatography; m.p. 156–158 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 (d, J = 6.9 Hz, 1 H), 7.81 (d, J = 7.1 Hz, 2 H), 7.65 (d, J = 9.1 Hz, 1 H), 7.47 (t, J = 7.5 Hz, 2 H), 7.35 (t, J = 7.4 Hz, 1 H), 7.23 (m, 1 H), 6.85 (t, J = 6.8 Hz, 1 H), 2.65 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.4, 142.4, 134.8, 128.5, 128.3, 127.3, 123.5, 122.8, 117.5, 115.9, 112.00, 9.64 ppm. MS (EI): *m*/*z* (%) = 208 (100) $[M]^+$, 131 (10), 103 (20), 91 (10), 78 (35).

3-Methyl-2-*o*-tolylimidazo[1,2-*a*]pyridine (4ba): 2-Aminopyridine (282 mg, 3.0 mmol), *o*-tolualdehyde (432 mg, 3.6 mmol), and propiolic acid (252 mg, 3.6 mmol) gave **4ba** (470 mg, 2.11 mmol, 70%) as a pale yellow solid after chromatography; m.p. 122–125 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, J = 6.9, Hz, 1 H), 7.62 (dt, J = 9.1, 1.1 Hz, 1 H), 7.37 (m, 1 H), 7.26 (m, 3 H), 7.17 (m, 1 H), 6.85 (td, J = 6.8, 1.2 Hz, 1 H), 2.40 (s, 3 H), 2.33 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.0, 143.2, 137.36, 134.0, 130.7, 130.2, 127.8, 125.3, 123.1, 122.8, 117.4, 116.7, 111.8, 20.1, 9.1 ppm. HRMS (ESI): calcd. for $C_{15}H_{15}N_2$ $[M + H]^+$ 223.1235; found 223.1235.

3-Methyl-2-*p*-tolylimidazo[1,2-*a*]pyridine (4ca): 2-Aminopyridine (282 mg, 3.0 mmol), *p*-tolualdehyde (432 mg, 3.6 mmol), and propiolic acid (252 mg, 3.6 mmol) gave **4ca** (485 mg, 2.18 mmol, 73%) as a pale yellow solid after chromatography; m.p. 118–120 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, J = 6.9 Hz, 1 H), 7.77–7.66 (m, 2 H), 7.64 (d, J = 9.1 Hz, 1 H), 7.28 (dd, J = 8.5, 0.6 Hz, 2 H), 7.16 (m, 1 H), 6.84 (t, J = 6.8 Hz, 1 H), 2.63 (s, 3 H), 2.41 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.3, 142.5, 137.1, 131.9, 129.2, 128.2, 123.3, 122.7, 117.3, 115.6, 111.9, 21.2, 9.6 ppm. MS (EI): *m*/*z* (%) = 222 (100) $[M]^+$, 221 (22), 133 (8), 91 (32). $C_{15}H_{14}N_2$ (222.29): calcd. C 81.05, H 6.35, N 12.60; found C 80.96, H 6.37, N 12.42.

2-(4-*tert*-Butylphenyl)-3-methylimidazo[1,2-*a*]pyridine (4da): 2-Aminopyridine (282 mg, 3.0 mmol), 4-*tert*-butylbenzaldehyde (583 mg, 3.6 mmol), and propiolic acid (252 mg, 3.6 mmol) gave **4da** (510 mg, 1.93 mmol, 64%) as a pale yellow solid after chromatography; m.p. 153–155 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, J = 6.9 Hz, 1 H), 7.74 (d, J = 8.7 Hz, 2 H), 7.63 (dt, J = 9.0, 1.1 Hz,

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1 H), 7.48 (m, 2 H), 7.16 (m,1 H), 6.83 (m, 1 H), 2.65 (s, 3 H), 1.37 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.3, 144.3, 142.5, 132.0, 128.0, 125.4, 123.25, 122.7, 117.4, 115.6, 111.9, 34.6, 31.3, 9.7 ppm. MS (EI): *m*/*z* (%) = 264 (64) $[M]^+$, 249 (100), 234 (6), 166 (12). $C_{18}H_{20}N_2$ (264.37): calcd. C 81.78, H 7.63, N 10.60; found C 81.44, H 7.41, N 11.00.

2-(2-Chlorophenyl)-3-methylimidazo[1,2-*a*]pyridine (4ea): 2-Aminopyridine (282 mg, 3.0 mmol), *o*-chlorobenzaldehyde (505 mg, 3.6 mmol), and propiolic acid (252 mg, 3.6 mmol) gave **4ea** (440 mg, 1.81 mmol, 60%) as a pale yellow solid after chromatography; m.p. 105–107 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 6.9 Hz, 1 H), 7.64 (d, *J* = 9.1 Hz, 1 H), 7.56 (m, 1 H), 7.48 (m, 1 H), 7.35 (m, 2 H), 7.16 (m, 1 H), 6.87 (t, *J* = 6.8 Hz, 1 H), 2.43 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.2, 140.5, 133.8, 133.6, 132.6, 129.6, 129.2, 126.6, 123.5, 122.9, 117.8, 117.6, 112.1, 9.6 ppm. HRMS (ESI): calcd. for $C_{14}H_{12}ClN_2$ $[M + H]^+$ 243.0689; found 243.0683.

2-(4-Chlorophenyl)-3-methylimidazo[1,2-*a*]pyridine (4fa): 2-Aminopyridine (282 mg, 3.0 mmol), *p*-chlorobenzaldehyde (505 mg, 3.6 mmol), and propiolic acid (252 mg, 3.6 mmol) gave **4fa** (514 mg, 2.12 mmol, 71%) as a pale yellow solid after chromatography; m.p. 100–103 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 6.9 Hz, 1 H), 7.74 (d, *J* = 8.7 Hz, 2 H), 7.63 (d, *J* = 9.1 Hz, 1 H), 7.43 (d, *J* = 8.7 Hz, 2 H), 7.17 (m, 1 H), 6.86 (t, *J* = 6.8 Hz, 1 H), 2.62 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.4, 141.3, 133.3, 133.2, 129.5, 128.7, 123.8, 122.8, 117.4, 116.0, 112.2, 9.6 ppm. MS (EI): *m*/*z* (%) = 242 (100) $[M]^+$, 205 (30), 103 (25), 78 (40). $C_{14}H_{11}ClN_2$ (242.71): calcd. C 69.28, H 4.57, N 11.54; found C 68.92, H 4.69, N 11.14.

2-(3-Fluorophenyl)-3-methylimidazo[1,2-*a*]pyridine (4ga): 2-Aminopyridine (282 mg, 3.0 mmol), 3-fluorobenzaldehyde (446 mg, 3.6 mmol), and propiolic acid (252 mg, 3.6 mmol) gave **4ga** (430 mg, 1.90 mmol, 63%) as a pale yellow solid after chromatography; m.p. 152–155 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (dt, *J* = 6.9, 1.1 Hz, 1 H), 7.58 (m, 3 H), 7.42 (m, 1 H), 7.18 (m, 1 H), 7.03 (m, 1 H), 6.85 (td, *J* = 6.8, 1.2 Hz, 1 H), 2.63 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.9 (d, *J* = 245.0 Hz), 144.3, 141.2, 137.1 (d, *J* = 8.2 Hz), 129.9 (d, *J* = 8.4 Hz), 123.8 (d, *J* = 2.9 Hz), 123.8, 122.8, 117.5, 116.2, 115.0 (d, *J* = 22.4 Hz), 114.1 (d, *J* = 21.2 Hz), 112.2, 9.6 ppm. MS (EI): *m*/*z* (%) = 226 (91) $[M]^+$, 225 (100), 131 (5), 109 (21). $C_{14}H_{11}FN_2$ (226.25): calcd. C 74.32, H 4.90, N 12.38; found C 74.10, H 4.94, N 12.39.

3-Methyl-2-(pyridin-2-yl)imidazo[1,2-*a*]pyridine (4ha): 2-Aminopyridine (282 mg, 3.0 mmol), 2-pyridinecarboxaldehyde (385 mg, 3.6 mmol), and propiolic acid (252 mg, 3.6 mmol) gave **4ha** (410 mg, 1.96 mmol, 65%) as a pale yellow solid after chromatography; m.p. 92–95 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.66 (m, 1 H), 8.22 (d, *J* = 8.0 Hz, 1 H), 7.94 (dt, *J* = 6.0, 3.0 Hz, 1 H), 7.77 (m, 1 H), 7.64 (d, *J* = 9.1 Hz, 1 H), 7.18 (m, 2 H), 6.86 (t, *J* = 6.8 Hz, 1 H), 2.96 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.8, 148.9, 144.1, 140.2, 136.5, 124.0, 123.0, 122.1, 121.7, 119.4, 117.6, 112.3, 9.8 ppm. MS (EI): *m*/*z* (%) = 209 (100) $[M]^+$, 131 (40), 104 (15), 78 (50). $C_{13}H_{11}N_3$ (209.25): calcd. C 74.62, H 5.30, N 20.08; found C 74.65, H 5.51, N 20.94.

2-(Furan-2-yl)-3-methylimidazo[1,2-*a*]pyridine (4ia): 2-Aminopyridine (282 mg, 3.0 mmol), furfural (345 mg, 3.6 mmol), and propiolic acid (252 mg, 3.6 mmol) gave **4ia** (402 mg, 2.03 mmol, 68%) as a pale yellow solid after chromatography; m.p. 98–101 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 6.9 Hz, 1 H), 7.59 (d, *J* = 9.1 Hz, 1 H), 7.53 (dd, *J* = 1.8, 0.8 Hz, 1 H), 7.17 (m, 1 H), 6.87–6.81 (m, 2 H), 6.53 (m, 1 H), 2.72 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.4, 144.6, 141.9, 134.1, 123.9, 122.7, 117.2, 115.9, 112.1, 111.4, 107.2, 9.1 ppm. MS (EI): *m*/*z* (%) = 198 (100) $[M]^+$, 169 (50), 144 (10), 78 (35). $C_{12}H_{10}N_2O$ (198.22): calcd. C 72.71, H 5.08, N 14.13; found C 72.54, H 5.25, N 14.26.

2-(3-Methylimidazo[1,2-*a*]pyridin-2-yl)phenol (4ja): 2-Aminopyridine (282 mg, 3.0 mmol), 2-hydroxybenzaldehyde (439 mg, 3.6 mmol), and propiolic acid (252 mg, 3.6 mmol) gave **4ja** (368 mg, 1.64 mmol, 55%) as a pale yellow solid after chromatography; m.p. 98–100 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 6.9 Hz, 1 H), 7.96–7.90 (m, 2 H), 7.27–7.21 (m, 3 H), 7.07 (dd, *J* = 8.2, 1.2 Hz, 1 H), 6.93 (m, 2 H), 2.73 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.4, 142.3, 140.3, 129.1, 127.1, 124.2, 122.5, 118.8, 117.8, 117.5, 116.6, 115.3, 112.7, 10.3 ppm. MS (EI): *m*/*z* (%) = 224 (100) $[M]^+$, 207 (30), 131 (20), 78 (30). $C_{14}H_{12}N_2O$ (224.26): calcd. C 74.98, H 5.39, N 12.49; found C 74.84, H 5.33, N 12.65.

2-(2,3-Dihydrobenzo-1,4-dioxin-6-yl)-3-methylimidazo[1,2-*a*]pyridine (4ka): 2-Aminopyridine (282 mg, 3.0 mmol), 1,4-benzodioxan-6-carboxaldehyde (590 mg, 3.6 mmol), and propiolic acid (252 mg, 3.6 mmol) gave **4ka** (510 mg, 1.92 mmol, 64%) as a pale yellow oil after chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 6.9 Hz, 1 H), 7.62 (d, *J* = 9.1 Hz, 1 H), 7.33–7.27 (m, 2 H), 7.16 (m, 1 H), 6.97 (m, 1 H), 6.84 (td, *J* = 6.8, 1.1 Hz, 1 H), 4.32 (d, *J* = 6.8 Hz, 4 H), 2.62 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.2, 143.5, 143.1, 142.0, 137.8, 128.4, 123.3, 122.7, 121.6, 117.3, 117.3, 117.1, 111.9, 64.5, 64.4, 9.6 ppm. HRMS (ESI): calcd. for $C_{16}H_{15}N_2O_2$ $[M + H]^+$ 267.1134; found 267.1128.

3-Methyl-2-[4-(methylthio)phenyl]imidazo[1,2-*a*]pyridine (4la): 2-Aminopyridine (282 mg, 3.0 mmol), 4-(methylthio)benzaldehyde (547 mg, 3.6 mmol), and propiolic acid (252 mg, 3.6 mmol) gave **4la** (573 mg, 2.25 mmol, 75%) as a pale yellow solid after chromatography; m.p. 104–106 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 6.9 Hz, 1 H), 7.74 (m, 2 H), 7.63 (d, *J* = 9.0, Hz, 1 H), 7.34 (m, 2 H), 7.16 (m, 1 H), 6.83 (m, 1 H), 2.61 (s, 3 H), 2.52 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.3, 141.9, 137.5, 131.7, 128.6, 126.5, 123.5, 122.7, 117.3, 115.7, 112.0, 15.8, 9.6 ppm. MS (EI): *m*/*z* (%) = 254 (100) $[M]^+$, 239 (20), 205 (30), 78 (20). $C_{15}H_{14}N_2S$ (254.35): calcd. C 70.83, H 5.55, N 11.01; found C 70.67, H 5.33, N 11.23.

2-(6-Methoxynaphthalen-2-yl)-3-methylimidazo[1,2-*a*]pyridine (4ma): 2-Aminopyridine (282 mg, 3.0 mmol), 6-methoxy-2-naphthaldehyde (670 mg, 3.6 mmol), and propiolic acid (252 mg, 3.6 mmol) gave **4ma** (525 mg, 1.82 mmol, 61%) as a pale yellow solid after chromatography; m.p. 157–160 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 1.2 Hz, 1 H), 7.96–7.91 (m, 2 H), 7.85–7.80 (m, 2 H), 7.67 (d, *J* = 9.1 Hz, 1 H), 7.23–7.14 (m, 3 H), 6.86 (m, 1 H), 3.94 (s, 3 H), 2.71 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.7, 144.4, 142.5, 133.8, 130.1, 129.7, 129.0, 127.0, 126.9, 123.5, 122.8, 119.0, 117.3, 115.9, 112.0, 105.6, 55.3, 9.8 ppm. MS (EI): *m*/*z* (%) = 288 (100) $[M]^+$, 273 (15), 245 (20), 78 (20). $C_{19}H_{16}N_2O$ (288.35): calcd. C 79.14, H 5.59, N 9.72; found C 79.18, H 5.63, N 9.37.

2-Cyclohexyl-3-methylimidazo[1,2-*a*]pyridine (4na): 2-Aminopyridine (282 mg, 3.0 mmol), cyclohexanecarbaldehyde (403 mg, 3.6 mmol), and propiolic acid (252 mg, 3.6 mmol) gave **4na** (451 mg, 2.10 mmol, 70%) as a pale yellow oil after chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 (dt, *J* = 6.8, 1.1 Hz, 1 H), 7.56 (dt, *J* = 9.0, 1.1 Hz, 1 H), 7.07 (m, 1 H), 6.75 (m, 1 H), 2.77 (m, 1 H), 2.40 (s, 3 H), 1.84–1.77 (m, 6 H), 1.49–1.31 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.3, 143.8, 122.3 (2 C), 116.8, 114.0, 111.3, 36.8, 32.8, 26.7, 25.9, 8.2 ppm. HRMS (ESI): calcd. for $C_{14}H_{19}N_2$ $[M + H]^+$ 215.1548; found 215.1543.

3-Benzyl-2-phenylimidazo[1,2-*a*]pyridine (4ab):[12f] 2-Aminopyridine (282 mg, 3.0 mmol), benzaldehyde (382 mg, 3.6 mmol), and 3-

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phenylpropiolic acid (525 mg, 3.6 mmol) gave **4ab** (726 mg, 2.55 mmol, 85%) as a white solid after chromatography; m.p. 117–119 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (m, 2 H), 7.70 (m, 2 H), 7.43 (t, J = 6.5 Hz, 2 H), 7.34 (m, 3 H), 7.28 (m, 2 H), 7.18 (m, 2 H), 6.72 (m, 1 H), 4.51 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.8, 144.0, 136.7, 134.3, 129.0 (2 C), 128.6 (2 C), 128.2 (2 C), 127.8, 127.7 (2 C), 126.9, 124.3, 123.4, 117.7, 117.5, 112.3, 29.9 ppm. MS (EI): m/z (%) = 284 (100) $[M]^+$, 269 (10), 207 (95), 141 (10), 78 (45).

3-(4-Methylbenzyl)-2-phenylimidazo[1,2-*a*]pyridine (4ac):[12f] 2-Aminopyridine (282 mg, 3.0 mmol), benzaldehyde (382 mg, 3.6 mmol), and 3-*p*-tolylpropiolic acid (528 mg, 3.3 mmol) gave **4ac** (720 mg, 2.41 mmol, 80%) as a yellow solid after chromatography; m.p. 122–125 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79 (m, 2 H), 7.69 (m, 2 H), 7.44 (m, 2 H), 7.34 (m, 1 H), 7.18 (m, 1 H), 7.11 (d, J = 7.9 Hz, 2 H), 7.03 (d, J = 8.1 Hz, 2 H), 6.70 (m, 1 H), 4.46 (s, 2 H), 2.32 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.8, 144.0, 136.5, 134.5, 133.6, 129.7, 128.6, 128.2, 127.7, 127.5, 124.1, 123.4, 117.9, 117.5, 112.1, 29.5, 21.0 ppm. MS (EI): m/z (%) = 298 (100) $[M]^+$, 283 (15), 220 (10), 207 (70), 78 (30).

3-(4-Ethylbenzyl)-2-phenylimidazo[1,2-*a*]pyridine (4ad): 2-Aminopyridine (282 mg, 3.0 mmol), benzaldehyde (382 mg, 3.6 mmol), and 3-(4-ethylphenyl)propiolic acid (574 mg, 3.3 mmol) gave **4ad** (667 mg, 2.14 mmol, 71%) as a white solid after chromatography; m.p. 154–157 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (d, J = 6.9 Hz, 2 H), 7.69 (m, 2 H), 7.43 (m, 2 H), 7.34 (m, 1 H), 7.20–7.11 (m, 3 H), 7.05 (d, J = 8.3 Hz, 2 H), 6.69 (t, J = 6.8 Hz, 1 H), 4.46 (s, 2 H), 2.62 (q, J = 7.6 Hz, 2 H), 1.22 (t, J = 7.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.8, 144.1, 142.8, 134.6, 133.8, 128.6, 128.5, 128.2, 127.6, 127.6, 124.0, 123.4, 117.9, 117.5, 112.1, 29.47, 28.37, 15.5 ppm. HRMS (ESI): calcd. for $C_{22}H_{21}N_2$ $[M + H]^+$ 313.1705; found 313.1705.

3-(4-Methoxybenzyl)-2-phenylimidazo[1,2-*a*]pyridine (4ae):[12f] 2-Aminopyridine (282 mg, 3.0 mmol), benzaldehyde (382 mg, 3.6 mmol), and 3-(4-methoxyphenyl)propiolic acid (581 mg, 3.3 mmol) gave **4ae** (610 mg, 1.94 mmol, 65%) as a yellow solid after chromatography; m.p. 128–130 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (m, 2 H), 7.68 (m, 2 H), 7.43 (m, 2 H), 7.35 (m, 1 H), 7.18 (m, 1 H), 7.04 (m, 2 H), 6.84 (m, 2 H), 6.71 (m, 1 H), 4.44 (s, 2 H), 3.78 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.5, 144.8, 144.0, 134.5, 128.7, 128.6, 128.6, 128.2, 127.7, 124.1, 123.4, 118.0, 117.5, 114.4, 112.1, 55.3, 29.0 ppm. MS (EI): m/z (%) = 314 (100) $[M]^+$, 299 (40), 236 (10), 207 (60), 78 (30).

3-(4-Chlorobenzyl)-2-phenylimidazo[1,2-*a*]pyridine (4af): 2-Aminopyridine (282 mg, 3.0 mmol), benzaldehyde (382 mg, 3.6 mmol), and 3-(4-chlorophenyl)propiolic acid (595 mg, 3.3 mmol) gave **4af** (675 mg, 2.12 mmol, 71%) as a yellow oil after chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (m, 2 H), 7.69–7.66 (m, 2 H), 7.44 (m, 2 H), 7.38 (m, 1 H), 7.28 (m, 2 H), 7.21 (dd, J = 2.3, 1.3 Hz, 1 H), 7.07 (d, J = 8.7 Hz, 2 H), 6.74 (m, 1 H), 4.47 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.2, 144.6, 135.5, 134.5, 133.0, 129.5, 129.3, 129.0, 128.4, 128.1, 124.6, 123.5, 117.9, 117.3, 112.7, 29.6 ppm. HRMS (ESI): calcd. for $C_{20}H_{16}ClN_2$ $[M + H]^+$ 319.1002; found 319.1006.

2-Phenyl-3-(thiophen-2-ylmethyl)imidazo[1,2-*a*]pyridine (4ag): 2-Aminopyridine (282 mg, 3.0 mmol), benzaldehyde (382 mg, 3.6 mmol), and 3-(thiophen-2-yl)propiolic acid (502 mg, 3.3 mmol) gave **4ag** (532 mg, 1.83 mmol, 61%) as a yellow solid after chromatography; m.p. 127–130 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84–7.79 (m, 3 H), 7.68 (m, 1 H), 7.45 (m, 2 H), 7.37 (m, 1 H), 7.19 (m, 2 H), 6.94 (m, 1 H), 6.78–6.74 (m, 2 H), 4.60 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.5, 144.9, 143.8, 140.1, 134.3, 128.6, 128.3, 127.8, 127.2, 125.0, 124.3, 123.4, 117.6, 117.46, 112.3, 25.0 ppm. MS (EI): m/z (%) = 290 (100) $[M]^+$, 257 (40), 207 (20), 78 (50). $C_{18}H_{14}N_2S$ (290.38): calcd. C 74.45, H 4.86, N 9.65; found C 74.33, H 4.46, N 9.81.

3-(Naphthalen-1-ylmethyl)-2-phenylimidazo[1,2-*a*]pyridine (4ah): 2-Aminopyridine (282 mg, 3.0 mmol), benzaldehyde (382 mg, 3.6 mmol), and 3-(naphthalen-1-yl)propiolic acid (647 mg, 3.3 mmol) gave **4ah** (628 mg, 1.88 mmol, 58%) as a yellow solid after chromatography; m.p. 119–121 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.18 (m, 1 H), 7.96 (m, 1 H), 7.80 (d, J = 8.3 Hz, 1 H), 7.76–7.72 (m, 3 H), 7.65–7.56 (m, 3 H), 7.40–7.27 (m, 4 H), 7.20 (m, 1 H), 6.86 (dd, J = 7.1, 1.1 Hz, 1 H), 6.68 (m, 1 H), 4.87 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.1, 144.6, 134.4, 134.0, 131.8, 131.8, 129.0, 128.6, 128.0, 127.7, 127.8, 126.5, 126.0, 125.8, 124.3, 124.2, 123.1, 123.0, 117.6, 116.9, 112.2, 27.2 ppm. MS (EI): m/z (%) = 334 (100) $[M]^+$, 256 (25), 207 (65), 78 (60). $C_{24}H_{18}N_2$ (334.42): calcd. C 86.20, H 5.43, N 8.38; found C 85.90, H 5.46, N 8.57.

3-Butyl-2-phenylimidazo[1,2-*a*]pyridine (4ai): 2-Aminopyridine (282 mg, 3.0 mmol), benzaldehyde (382 mg, 3.6 mmol), and hept-2-ynoic acid (416 mg, 3.3 mmol) gave **4ai** (422 mg, 1.69 mmol, 56%) as a brown liquid after chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95 (d, J = 6.9 Hz, 1 H), 7.79 (m, 2 H), 7.64 (m, 1 H), 7.48 (m, 2 H), 7.35 (m, 1 H), 7.16 (m, 1 H), 6.82 (m, 1 H), 3.08 (t, J = 9.0 Hz, 2 H), 1.71 (m, 2 H), 1.47 (m, 2 H), 0.97 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.4, 142.2, 135.0, 128.5, 128.2, 127.4, 123.5, 122.9, 120.8, 117.7, 111.9, 29.8, 23.6, 22.7, 13.8 ppm. HRMS (ESI): calcd. for $C_{17}H_{19}N_2$ $[M + H]^+$ 251.1548; found 251.1561.

3-Ethyl-2-phenylimidazo[1,2-*a*]pyridine (4aj): 2-Aminopyridine (282 mg, 3.0 mmol), benzaldehyde (382 mg, 3.6 mmol), and but-2-ynoic acid (504 mg, 3.3 mmol) gave **4aj** (206 mg, 0.93 mmol, 31%) as a brown oil after chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97 (d, J = 6.9 Hz, 1 H), 7.79 (d, J = 7.0 Hz, 2 H), 7.65 (d, J = 9.1 Hz, 1 H), 7.52–7.43 (m, 2 H), 7.37 (d, J = 7.4 Hz, 1 H), 7.17 (m, 1 H), 6.84 (m, 1 H), 3.12 (q, J = 7.5 Hz, 2 H), 1.37 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.4, 143.7, 141.9, 134.9, 128.5, 128.2, 127.4, 123.5, 122.8, 117.7, 112.0, 17.1, 12.2 ppm. HRMS (ESI): calcd. for $C_{15}H_{15}N_2$ $[M + H]^+$ 223.1235; found 223.1231.

3-(4-Methylbenzyl)-2-*p*-tolylimidazo[1,2-*a*]pyridine (4cc): 2-Aminopyridine (282 mg, 3.0 mmol), *p*-tolualdehyde (432 mg, 3.6 mmol), and 3-*p*-tolylpropiolic acid (528 mg, 3.3 mmol) gave **4cc** (702 mg, 2.25 mmol, 75%) as a yellow oil after chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69–7.66 (m, 4 H), 7.23 (d, J = 7.8 Hz, 2 H), 7.18–7.09 (m, 3 H), 7.02 (d, J = 8.1 Hz, 2 H), 6.68 (m, 1 H), 4.43 (s, 2 H), 2.38 (s, 3 H), 2.32 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.7, 144.1, 137.4, 136.4, 133.7, 131.6, 129.6, 129.3, 128.0, 127.5, 123.9, 123.3, 117.6, 117.4, 112.0, 29.5, 21.2, 21.0 ppm. HRMS (ESI): calcd. for $C_{22}H_{21}N_2$ $[M + H]^+$ 313.1705; found 313.1707.

3-Butyl-2-*p*-tolylimidazo[1,2-*a*]pyridine (4ci): 2-Aminopyridine (282 mg, 3.0 mmol), *p*-tolualdehyde (432 mg, 3.6 mmol), and hept-2-ynoic acid (416 mg, 3.3 mmol) gave **4ci** (430 mg, 1.63 mmol, 39%) as a brown liquid after chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, J = 6.9 Hz, 1 H), 7.69–7.61 (m, 3 H), 7.29 (m, 2 H), 7.14 (m, 1 H), 6.81 (m, 1 H), 3.06 (m, 2 H), 2.41 (s, 3 H), 1.68 (m, 2 H), 1.47 (m, 2 H), 0.97 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.3, 142.2, 137.1, 132.0, 129.2, 128.0, 123.3, 122.9, 120.5, 117.5, 111.9, 29.8, 23.6, 22.7, 21.2, 13.8 ppm. HRMS (ESI): calcd. for $C_{18}H_{21}N_2$ $[M + H]^+$ 265.1705; found 265.1705.

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3,7-Dimethyl-2-phenylimidazo[1,2-*a*]pyridine (4aa-1): 2-Amino-4-picoline (324 mg, 3.0 mmol), benzaldehyde (382 mg, 3.6 mmol), and propiolic acid (252 mg, 3.3 mmol) gave **4aa-1** (463 mg, 2.08 mmol, 69%) as a yellow solid after chromatography; m.p. 155–158 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83–7.72 (m, 3 H), 7.49–7.41 (m, 2 H), 7.39 (m, 1 H), 7.33 (m, 1 H), 6.67 (dd, J = 7.0, 1.6 Hz, 1 H), 2.61 (s, 3 H), 2.41 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.8, 141.9, 135.0, 134.3, 128.4, 128.2, 127.1, 122.1, 115.8, 115.2, 114.6, 21.3, 9.6 ppm. HRMS (ESI): calcd. for $C_{15}H_{15}N_2$ [M + H]$^+$ 223.1235; found 223.1233.

6-Chloro-3-methyl-2-phenylimidazo[1,2-*a*]pyridine (4aa-2): 2-Amino-5-chloropyridine (385 mg, 3.0 mmol), benzaldehyde (381 mg, 3.6 mmol), and propiolic acid (252 mg, 3.3 mmol) gave **4aa-2** (380 mg, 1.57 mmol, 45%) as a yellow oil after chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (dd, J = 1.9, 0.6 Hz, 1 H), 7.77 (d, J = 7.0 Hz, 2 H), 7.62 (dd, J = 9.5, 0.8 Hz, 1 H), 7.50–7.43 (m, 2 H), 7.38 (m, 1 H), 7.14 (dd, J = 9.5, 2.0 Hz, 1 H), 2.62 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.5, 142.6, 134.2, 129.8, 128.6, 128.3, 127.7, 124.9, 120.8, 120.4, 117.7, 9.7 ppm. HRMS (ESI): calcd. for $C_{14}H_{12}ClN_2$ [M + H]$^+$ 243.0689; found 243.0689.

General Procedure for the Synthesis of Imidazo[1,2-a]pyridines from Arylalkynecarboxylic Acids: The aryl iodide (4.5 mmol), propiolic acid (918 mg, 4.5 mmol), $Pd(PPh_3)_2Cl_2$ (158 mg, 0.225 mmol), CuI (86 mg, 0.45 mmol), and DBU (1.37 g, 9.0 mmol) were allowed to react in DMSO at 25 °C for 8 h. 2-Aminopyridine (282 mg, 3.0 mmol), benzaldehyde (382 mg, 3.6 mmol), CuI (57.1 mg, 0.3 mmol), and $Cu(OTf)_2$ (108.4 mg, 0.3 mmol) were then added and allowed to react at 110 °C for 16 h. After cooling, the mixture was poured into EtOAc (50.0 mL), washed with water (3 × 25.0 mL) and brine (3 × 25.0 mL), and then dried with $MgSO_4$ and passed through a celite pad. Evaporation of the solvent under reduced pressure provided the crude product, which was purified by column chromatography (hexane/EtOAc 4:1) to afford the final product.

3-Benzyl-2-phenylimidazo[1,2-*a*]pyridine (6a = 4ab): Phenyl iodide (918 mg, 4.5 mmol) gave **6a** (726 mg, 2.55 mmol, 85%) after chromatography.

3-(2-Methylbenzyl)-2-phenylimidazo[1,2-*a*]pyridine (6b): 2-Iodotoluene (981 mg, 4.5 mol) gave **6b** (583 mg, 1.96 mmol, 65%) as a white solid after chromatography; m.p. 127–129 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73–7.69 (m, 3 H), 7.62 (d, J = 6.9 Hz, 1 H), 7.45–7.37 (m, 2 H), 7.37–7.26 (m, 2 H), 7.23–7.15 (m, 2 H), 7.05 (t, J = 7.5 Hz, 1 H), 6.75–7.67 (m, 2 H), 4.36 (s, 2 H), 2.44 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.9, 144.4, 136.3, 134.6, 134.5, 130.5, 128.6, 128.1, 127.6, 126.9, 126.6, 126.6, 124.1, 123.3, 117.6, 117.3, 112.2, 27.6, 19.8 ppm. HRMS (ESI): calcd. for $C_{21}H_{18}N_2$ [M + H]$^+$ 299.1548; found 299.1548.

3-(3-Methylbenzyl)-2-phenylimidazo[1,2-*a*]pyridine (6c): 3-Iodotoluene (981 mg, 4.5 mol) gave **6c** (597 mg, 2.00 mmol, 67%) as a yellow solid after chromatography; m.p. 129–130 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.80 (d, J = 7.1 Hz, 2 H), 7.69 (t, J = 8.0 Hz, 2 H), 7.43 (t, J = 7.5 Hz, 2 H), 7.35 (t, J = 7.4 Hz, 1 H), 7.23–7.14 (m, 2 H), 7.07 (d, J = 7.6 Hz, 1 H), 7.01–6.91 (m, 2 H), 6.72 (m, 1 H), 4.46 (s, 2 H), 2.29 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 144.8, 144.1, 138.7, 136.7, 134.5, 128.8, 128.6, 128.3, 128.2, 127.7, 124.7, 124.1, 123.4, 117.7, 117.5, 112.1, 29.8, 21.4 ppm. HRMS (ESI): calcd. for $C_{21}H_{18}N_2$ [M + H]$^+$ 299.1548; found 199.1548.

3-(4-Methylbenzyl)-2-phenylimidazo[1,2-*a*]pyridine (6d = 4ac): 4-Iodotoluene (981 mg, 4.5 mmol) gave **6d** (732 mg, 2.45 mmol, 82%) after chromatography.

3-(2-Methoxybenzyl)-2-phenylimidazo[1,2-*a*]pyridine (6e): 2-Iodoanisole (1.05 g, 4.5 mmol) gave **6e** (587 mg, 1.87 mmol, 62%) as a white solid after chromatography; m.p. 141–143 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.77 (d, J = 7.1 Hz, 2 H), 7.71 (d, J = 6.9 Hz, 1 H), 7.68 (d, J = 9.0 Hz, 1 H), 7.41 (t, J = 7.6 Hz, 2 H), 7.33 (m, 1 H), 7.24 (m, 1 H), 7.17 (m, 1 H), 6.95 (d, J = 7.7 Hz, 1 H), 6.80–6.66 (m, 3 H), 4.43 (s, 2 H), 3.92 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.3, 144.8, 144.2, 134.6, 128.5, 128.1, 127.9, 127.9, 127.5, 124.8, 123.9, 123.5, 120.7, 117.6, 117.4, 112.0, 110.1, 55.3, 23.9 ppm. HRMS (ESI): calcd. for $C_{21}H_{18}N_2O$ [M + H]$^+$ 315.1497; found 315.1563.

3-(4-Methoxybenzyl)-2-phenylimidazo[1,2-*a*]pyridine (6f = 4ae): 4-Iodoanisole (1.05 g, 4.5 mmol) gave **6f** (742 mg, 2.36 mmol, 79%) after chromatography.

3-(4-*tert*-Butylbenzyl)-2-phenylimidazo[1,2-*a*]pyridine (6g): 4-*tert*-Butyliodobenzene (1.17 g, 4.5 mol) gave **6g** (764 mg, 2.24 mmol, 75%) as a white solid after chromatography; m.p. 110–112 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (d, J = 7.0 Hz, 2 H), 7.72 (d, J = 6.8 Hz, 1 H), 7.68 (d, J = 9.0 Hz, 1 H), 7.43 (m, 2 H), 7.37–7.29 (m, 3 H), 7.17 (m, 1 H), 7.07 (d, J = 8.5 Hz, 2 H), 6.71 (m, 1 H), 4.46 (s, 2 H), 1.30 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.7, 144.8, 144.0, 134.5, 133.6, 128.6, 128.2, 127.6, 127.3, 125.9, 124.0, 123.5, 117.9, 117.5, 112.1, 34.4, 31.3, 29.4 ppm. HRMS (ESI): calcd. for $C_{24}H_{24}N_2$ [M + H]$^+$ 341.2018; found 341.2018.

3-(4-Acetylbenzyl)-2-phenylimidazo[1,2-*a*]pyridine (6h): In the presence of DBU (3.43 g, 22.5 mmol), 4′-iodoacetophenone (1.11 g, 4.5 mol) gave **6h** (440 mg, 1.35 mmol, 45%) as a yellow solid after chromatography; m.p. 132–134 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.91 (d, J = 8.3 Hz, 2 H), 7.77–7.73 (m, 2 H), 7.70 (d, J = 9.1 Hz, 1 H), 7.65 (t, J = 6.9 Hz, 1 H), 7.44 (t, J = 7.5 Hz, 2 H), 7.37 (d, J = 7.4 Hz, 1 H), 7.25–7.18 (m, 3 H), 6.73 (m, 1 H), 4.55 (s, 2 H), 2.57 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 197.5, 144.97, 144.5, 142.5, 136.0, 134.3, 129.1, 128.7, 128.1, 127.9, 127.8, 124.3, 123.1, 117.7, 116.7, 112.4, 29.9, 26.6 ppm. HRMS (ESI): calcd. for $C_{22}H_{18}N_2O$ [M + H]$^+$ 327.1497; found 327.1499.

3-(4-Chlorobenzyl)-2-phenylimidazo[1,2-*a*]pyridine (6i = 4af): In the presence of DBU (3.43 g, 22.5 mmol), 1-chloro-4-iodobenzene (1.07 g, 4.5 mol) gave **6i** (612 mg, 1.92 mmol, 64%) after chromatography.

2-Phenyl-3-(thiophen-2-ylmethyl)imidazo[1,2-*a*]pyridine (6j = 4ag): In the presence of DBU (3.43 g, 22.5 mmol), 2-iodothiophene (945 mg, 4.5 mol) gave **6j** (512 mg, 1.76 mmol, 59%) after chromatography.

3-(Naphthalen-1-ylmethyl)-2-phenylimidazo[1,2-*a*]pyridine (6k = 4ah): In the presence of DBU (2.06 g, 13.5 mmol), 1-iodonaphthalene (1.14 g, 4.5 mol) gave **6k** (795 mg, 2.38 mmol, 79%) after chromatography.

Supporting Information (see footnote on the first page of this article): Mechanistic experiments and copies of the ^{1}H NMR and ^{13}C NMR spectra.

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[23] For examples of *5-exo-dig* cyclizations, see: a) M. Durandetti, L. Hardou, R. Lhermet, M. Rouen, J. Maddaluno, *Chem. Eur. J.* **2011**, *17*, 12773–12783; b) R. Martin, M. R. Rivero, S. L. Buchwald, *Angew. Chem.* **2006**, *118*, 7237; *Angew. Chem. Int. Ed.* **2006**, *45*, 7079–7082; c) A. A. Tudjarian, T. G. Minehan, *J. Org. Chem.* **2011**, *76*, 3576–3581; d) T.-S. Jiang, R.-Y. Tang, X.-G. Zhang, X.-H. Li, J.-H. Li, *J. Org. Chem.* **2009**, *74*, 8834–8837.

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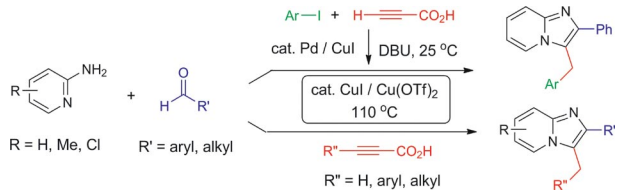
Multicomponent Reactions



Imidazo[1,2-*a*]pyridine derivatives were synthesized through three-component coupling reactions of 2-aminopyridines, aldehydes, and alkynecarboxylic acids in the presence of 10 mol-% $CuI/Cu(OTf)_2$

Keywords: Nitrogen heterocycles / Multicomponent reactions / Copper / Alkynes

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