Synthesis H. Kawakami et al. Special Topic

Nickel-Catalyzed C–F/N–H Annulation of 2-(2-Fluoroaryl) N-Heteroaromatic Compounds with Alkynes: Activation of C–F Bonds

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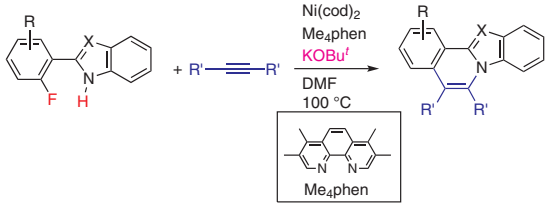
Dedicated to Professor Shinji Murai for his contribution to bond activation

Published as part of the Special Topic
Bond Activation – in Honor of Prof. Shinji Murai



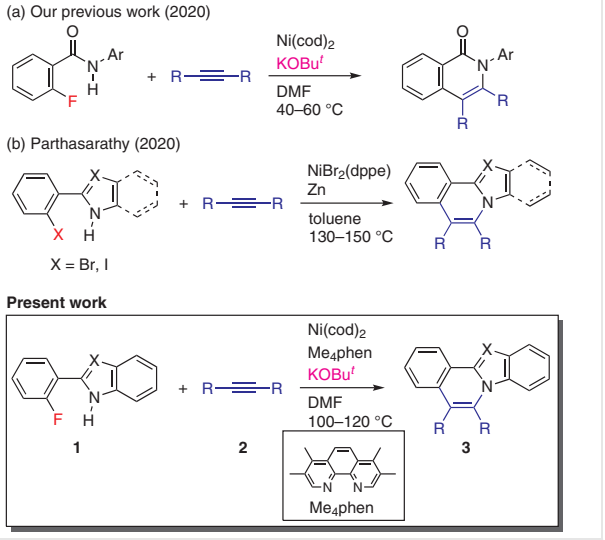
Received: 01.12.2020
Accepted after revision: 15.12.2020
Published online: 15.12.2020
DOI: 10.1055/a-1337-5504; Art ID: ss-2020-f0614-st

Abstract The reaction of 2-(2-fluoroaryl) N-heteroaromatic compounds, such as benzimidazole and indole derivatives, with internal alkynes in the presence of a catalytic amount of a nickel complex results in C–F/N–H annulation with alkynes. The reaction shows a high functional group compatibility. The presence of a strong base, such as KOBu^t or LiOBu^t, is required for the reaction to proceed.

Key words C–F bond activation, nickel, alkyne, annulation, N-heteroaromatic compounds

Transition-metal-catalyzed functionalization reactions of aryl halides (Ar–X) have revolutionized the way chemists approach the synthesis of a variety of molecules.[1] Compared with C–I, C–Br, and C–Cl bonds, the use of C–F bonds in organic transformation is significantly more challenging because of their inherent bond strength.[2] Indeed, C–F bonds are among the strongest bonds in organic compounds. Nickel complexes are known to show a high catalytic reactivity for activating C–F bonds.[3] We recently reported on a new Ni(0) system for the activation of C–F bonds using an amidate-promoted strategy. The reaction involves the Ni-catalyzed C–F/N–H annulation of *ortho*-fluoro-substituted aromatic amides with alkynes, leading to the production of isoquinolin-1(2*H*)-one derivatives (Scheme 1a).[4] The reaction proceeds under mild reaction conditions (most reactions can be carried out at 40–60 °C) and even under ligand-free conditions. A key to the success of the reaction is the use of a base, such as KOBu^t or even a weak base such as Cs_2CO_3, which functions to abstract a proton from an amide with the generation of an amidate anion. The amidate anion functions as a directing group to activate a C–F bond.

In 2020, Parthasarathy reported on the Ni-catalyzed synthesis of pyrroloquinolines, indoloquinolines, and indoloisoquinolines from the reaction of 2-iodo- or 2-bromoaryl N-heteroaromatic compounds with alkynes via C–C and C–N bond formation (Scheme 1b).[5] The reaction required higher reaction temperatures, frequently in the 130–150 °C range, even when 2-iodoaryl N-heteroaromatic compounds were used as the substrates. In contrast, we found that a similar transformation using 2-fluoroaryl N-heteroaromatic compounds proceeds even at 100 °C, by taking advantage of a base-promoted strategy (Scheme 1).



Scheme 1 Ni(0)-catalyzed C–X/N–H annulation with alkynes

The reaction of 2-(2-fluorophenyl)-1*H*-benzo[*d*]imidazole (**1a**) (0.25 mmol) with hex-3-yne (**2a**) (0.3 mmol) in the presence of Ni(cod)$_2$ (0.025 mmol) as the catalyst, PPh_3 (0.05 mmol) as the ligand, and KOBu^t (0.25 mmol) as the base in DMA (*N*,*N*-dimethylacetamide) (0.25 mL) at 120 °C for 18 hours gave 5,6-diethylbenzo[4,5]imidazo[2,1-*a*]iso-

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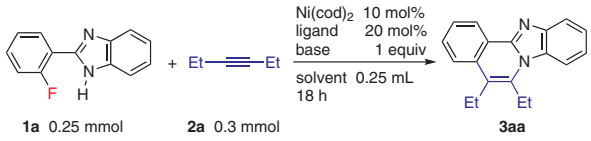
quinoline (**3aa**) in 18% NMR yield, along with 30% of **1a** being recovered (Table 1, entry 1). The use of other phosphines, such as dppe, dfppe, and DPEphos {bis[(2-diphenylphosphino)phenyl] ether} failed to improve the product yield, and when NHC ligands were used, the reaction failed to proceed. Gratifyingly, the use of 2,2′-dipyridine (bpy) and 1,10-phenanthroline (Phen) dramatically improved the product yield to 92% and 87% NMR yields, respectively (entries 2 and 3). Finally, 3,4,7,8-tetramethyl-1,10-phenanthroline (Me_4Phen) was found to be the ligand of choice (entry 4). The use of strong bases, such as LiOBu^t, NaOBu^t, and KOMe gave **3aa** in good yields (entries 5–7), while weak bases, such as NaOAc, KOAc, and K_2CO_3 gave only trace amounts of **3aa**. Although LiOBu^t gave a slightly higher product yield, KOBu^t was used for further optimization because it is less expensive. The solvent effects were examined using dtbbpy [4,4′-bis(di-*tert*-butyl)-2,2′-bipyridine] as a ligand. Polar solvents, such as DMF and DMSO gave higher product yields (entries 10 and 11). Finally, the optimal conditions for this reaction were established to be the following: **1a** (0.25 mmol) with hex-3-yne (**2a**; 0.3 mmol) in the presence of $Ni(cod)_2$ (0.025 mmol) as the catalyst, Me_4Phen (0.05 mmol) as the ligand, and KOBu^t (0.25 mmol) as the base in DMF (0.25 mL) at 100 °C for 18 hours (entry 13). We previously reported on the Ni-catalyzed synthesis of benzo[4,5]imidazo[2,1-*a*]isoquinoline derivatives via oxidative C–H/N–H coupling of 2-phenyl-1*H*-benzo[*d*]imidazole with alkynes, in which the *ortho* C–H bond participates in the reaction.[6] However, such a reaction did not proceed and the C–F bond was selectively activated under the conditions.

The results for the reaction of 2-(2-fluorophenyl)-1*H*-benzo[*d*]imidazole (**1a**) with various alkynes **2** are shown in Figure 1. Both aliphatic and aromatic internal alkynes were applicable to this annulation reaction. However, the reaction of **1a** with 1,2-bis[4-(trifluoromethyl)phenyl]ethyne gave the expected product, but in low yield (data not shown). Similar to our previous work,[4] an electron-deficient alkyne retarded the reaction. The reaction with 1-phenylpent-1-yne (**2f**) gave **3af** in a regioselective manner. A single crystal of **3af** was isolated and the structure was confirmed by X-ray crystallographic analysis.

The scope for the reaction with respect to the N-heteroaromatic substrate **1** is shown in Figure 2. Similar to our previous work,[4] the presence of an electron-withdrawing group on the phenyl ring retarded the reaction and a higher reaction temperature was required, as in **3ca–ea**. These results suggest that the activation of the C–F bond is not the rate-determining step. The reaction of **1h** which contains a methyl group on the benzimidazole ring gave **3ha** as a single product and the other isomer was not formed. The reaction was also applicable to 2-(2-fluorophenyl)-1*H*-indole (**1i**) to give 5,6-diethylindolo[2,1-*a*]isoquinoline (**3ia**) in 70% yield when LiOBu^t was used as a base instead of KOBu^t.

Table 1 Optimization of the Reaction Conditions



1a 0.25 mmol **2a** 0.3 mmol **3aa**

Entry	Base	Ligand	Solvent	Temp (°C)	NMR yield (%)[a] **3a**	**1a**
1	KOBu^t	PPh_3	DMA	120	18	30
2	KOBu^t	bpy	DMA	120	92	0
3	KOBu^t	Phen	DMA	120	87 (70)	0
4	KOBu^t	Me_4Phen	DMA	120	93 (78)	0
5	LiOBu^t	Me_4Phen	DMA	120	>99 (84)	0
6	NaOBu^t	Me_4Phen	DMA	120	70	0
7	KOMe	Me_4Phen	DMA	120	64	0
8	KOBu^t	dtbbpy	1,4-dioxane[b]	120	3	32
9	KOBu^t	dtbbpy	toluene	120	33	38
10	KOBu^t	dtbbpy	DMF	120	77	0
11	KOBu^t	dtbbpy	DMSO	120	>99	0
12	KOBu^t	Me_4Phen	DMA	100	53	45
13	**KOBu^t**	**Me_4Phen**	**DMF**	**100**	**99 (88)**	**0**

[a] Numbers in parentheses refer to isolated yields.
[b] 1,4-Dioxane (0.5 mL).

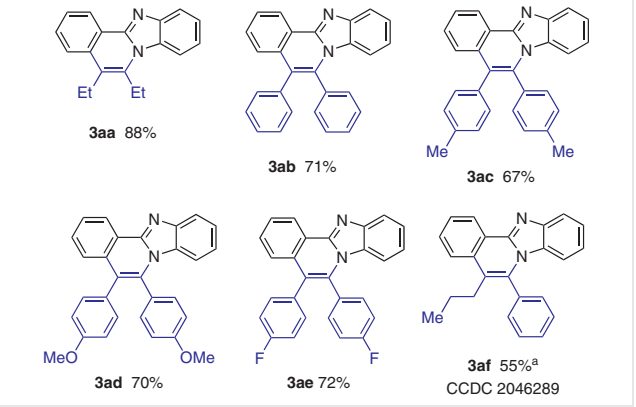


Figure 1 Alkyne scope. *Reagents and conditions*: **1a** (0.25 mmol), alkyne **2** (0.3 mmol), $Ni(cod)_2$ (0.025 mmol), Me_4phen (0.05 mmol), KOBu^t (0.25 mmol), DMF (0.25 mL), 100 °C, 18 h; yields shown are isolated yields. [a] At 120 °C.

Gratifyingly, it was found that an inexpensive and benchtop-stable $Ni(OAc)_2$/Zn system also gave a good yield of the corresponding product **3aa**. The method was applicable to a gram-scale reaction using the Ni(II)/Zn system (Scheme 2).

A proposed mechanism for the above annulation reaction is shown in Scheme 3. The base abstracts an NH proton in **1a** to generate the anion **A**, which is the actual substrate,

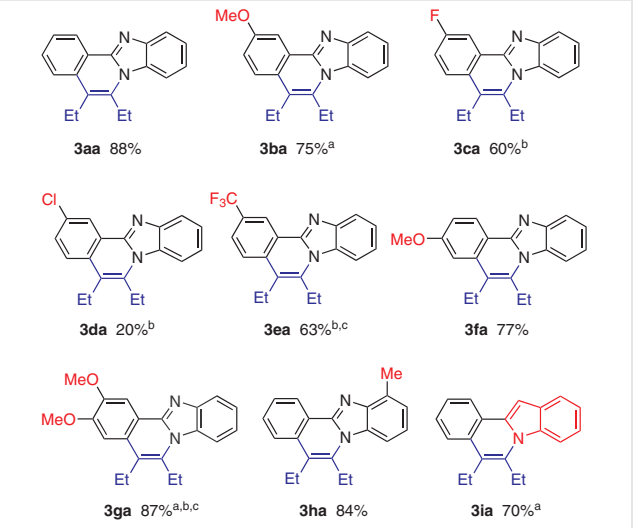
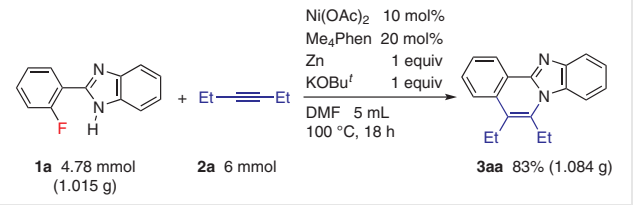


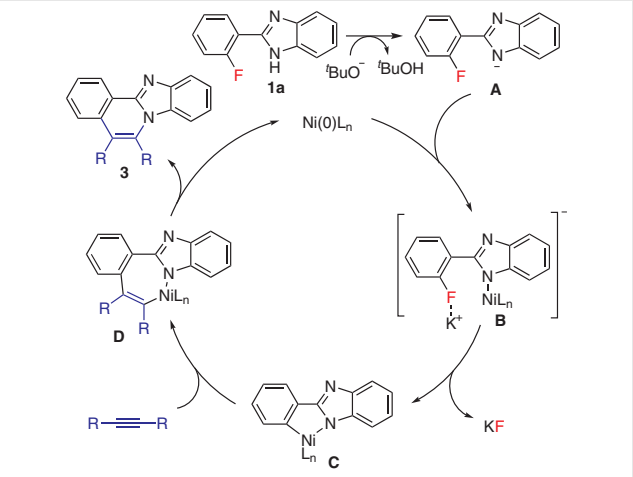
Figure 2 Substrate scope. *Reagents and conditions*: **1** (0.25 mmol), hex-3-yne (**2a**; 0.3 mmol), $Ni(cod)_2$ (0.025 mmol), Me_4Phen (0.05 mmol), $KOBu^t$ (0.25 mmol), DMF, 100 °C, 18 h. [a] $LiOBu^t$ was used as a base. [b] The reaction was carried out at 120 °C. [c] Bpy (2,2′-dipyridine) was used in place of Me_4Phen.



Scheme 2 Use of inexpensive and benchtop-stable $Ni(OAc)_2$/Zn as catalytic system (gram scale)

because one equivalent of base was used. The reaction of **A** with Ni(0) gives the nickelate complex **B**. Oxidative addition of the C–F bond gives the nickelacycle **C**, which is assisted by the coordination of the potassium cation to the F atom in **B**.[7] The coordination of an alkyne to complex **C**, followed by the insertion of an alkyne into the C–Ni bond gives the seven-membered nickalacycle **D**, which then undergoes reductive elimination to give the annulated product **3** with the regeneration of Ni(0).

In summary, we reported on the Ni(0)-catalyzed C–F/N–H annulation of 2-(2-fluoroaryl) N-heteroaromatic compounds with alkynes. The use of $KOBu^t$ or $LiOBu^t$ was essential for the reaction to proceed. This strategy is a promising method for the activation of C–F bonds[4] as well as other unreactive bonds, such as C–O, C–S, and C–CN.[8] Investigations on the further use of this methodology for the activation of unreactive bonds are currently underway and will be reported in due course.



Scheme 3 A proposed mechanism

^1H and ^{13}C NMR spectra were recorded on a JEOL ECZ-400 spectrometer; samples were dissolved in $CDCl_3$ with tetramethylsilane as an internal reference standard. IR spectra were recorded on a JASCO FT/IR-4200 spectrometer using the ATR method. Mass spectra were obtained using a SHIMDZU QP-2010 spectrometer with a quadrupole mass analyzer operating at 70 eV. HRMS was carried out on a JEOL JMS-T100LP spectrometer with a time-of-flight mass analyzer. Melting points were determined on a Stanford Research Systems MPA100 apparatus equipped with a digital thermometer. Column chromatography was performed on silica gel (Silicycle Siliaflash F60; 230–400 mesh).

2-(2-Fluoroaryl) N-Heteroaromatic Compounds 1a–i

2-Fluoroarylbenzimidazoles **1a–h** are all known compounds and were prepared by the reaction of 1,2-phenylenediamine derivatives with aldehydes in the presence of $MgCl_2$:[9] 2-(2-fluorophenyl)-1*H*-benzo[*d*]imidazole (**1a**) [CAS Reg. No. 321-51-7], 2-(2-fluoro-5-methoxyphenyl)-1*H*-benzimidazole (**1b**) [CAS Reg. No. 1508940-34-8], 2-(2,5-difluorophenyl)-1*H*-benzimidazole (**1c**) [CAS Reg. No. 1097793-36-6], 2-(5-chloro-2-fluorophenyl)-1*H*-benzimidazole (**1d**) [CAS Reg. No. 1094668-22-0], 2-[2-fluoro-5-(trifluoromethyl)phenyl]-1*H*-benzimidazole (**1e**) [CAS Reg. No. 1536220-29-7], 2-(2-fluoro-4-methoxyphenyl)-1*H*-benzimidazole (**1f**) [CAS Reg. No. 2620-81-7], 2-(2-fluoro-4,5-dimethoxyphenyl)-1*H*-benzimidazole (**1g**) [CAS Reg. No. 2443949-80-0], and 2-(2-fluorophenyl)-7-methyl-1*H*-benzimidazole (**1h**) [CAS Reg. No. 626606-16-4]. 2-(2-Fluorophenyl)-1*H*-indole (**1i**) [CAS Reg. No. 52765-22-7] was prepared by the Fischer indole synthesis by the reaction of 2-fluoroacetophenone and phenylhydrazine hydrochloride in the presence of polyphosphoric acid.[10]

5,6-Diethylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3aa); Typical Procedure

To an oven-dried 5 mL screw-capped vial in a glove box, $KOBu^t$ (28.1 mg, 0.25 mmol), Me_4Phen (11.8 mg, 0.05 mmol), $Ni(cod)_2$ (6.9 mg, 0.025 mmol), 2-(2-fluorophenyl)-1*H*-indole (**1a**, 53.1 mg, 0.25 mmol), hex-3-yne (**2a**, 24.6 mg, 0.3 mmol), and DMF (0.25 mL) were added in sequential order. The vial was then sealed and the mixture was stirred for 5 min at room temperature. The vial was then placed on a preheated aluminum heating block [Thermo Mighty Stirrer HHE-

19G-USIII (KPI)] and stirred for 18 h at 100 °C and then allowed to cool to room temperature. The resulting mixture was filtered through a Celite pad and the filtrate concentrated to dryness in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc, 10:1) to afford the desired product **3aa**.

Yield: 59.5 mg (88%); white solid; mp 123 °C; R_f = 0.26 (hexane/EtOAc, 3:1).

IR (ATR): 2970 m, 1630 w, 1523 m, 1450 s, 1368 s cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.6 Hz, 3 H), 1.48 (t, *J* = 7.6 Hz, 3 H), 2.99 (q, *J* = 7.6 Hz, 2 H), 3.40 (q, *J* = 7.6 Hz, 2 H), 7.33 (t, *J* = 7.6 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 7.60 (t, *J* = 7.2 Hz, 1 H), 7.66 (td, *J* = 8.4, 1.4 Hz, 1 H), 7.84 (d, *J* = 8.2 Hz, 1 H), 7.97 (d, *J* = 8.5 Hz, 1 H), 8.03 (d, *J* = 8.1 Hz, 1 H), 8.91 (d, *J* = 7.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.1, 15.1, 20.4, 22.3, 114.6, 119.6, 120.0, 121.6, 122.9, 123.4, 124.0, 125.6, 126.8, 130.0, 130.6, 131.3, 136.7, 144.4, 148.1.

MS (EI, 70 eV): *m*/*z* (%) = 275 (17), 274 [M^+] (76), 260 (21), 259 (100), 257 (13), 243 (21), 128 (10), 122 (15), 115 (10).

HRMS-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{19}N_2$: 275.1543; found: 275.1544.

5,6-Diphenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3ab)

[CAS Reg. No. 1037289-22-7]

Yield: 65.5 mg (71%); white solid; R_f = 0.36 (hexane/EtOAc, 3:1).

^1H NMR (400 MHz, $CDCl_3$): δ = 6.00 (d, *J* = 8.5 Hz, 1 H), 6.92 (t, *J* = 7.8 Hz, 1 H), 7.20–7.30 (m, 5 H), 7.33–7.42 (m, 7 H), 7.56 (t, *J* = 7.7 Hz, 1 H), 7.68 (t, *J* = 7.5 Hz, 1 H), 7.98 (d, *J* = 8.2 Hz, 1 H), 8.99 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 114.2, 119.7, 121.4, 123.0, 123.6, 124.2, 125.1, 126.5, 127.4, 127.9, 128.1, 128.9, 129.3, 130.0, 130.7, 131.3, 131.6, 132.7, 133.8, 135.2, 135.8, 144.4, 147.9.

5,6-Bis(4-methylphenyl)benzo[4,5]imidazo[2,1-*a*]isoquinoline (3ac)

[CAS Reg. No. 2281949-52-6]

Yield: 64.1 mg (67%); white solid; R_f = 0.37 (hexane/EtOAc, 3:1).

^1H NMR (400 MHz, $CDCl_3$): δ = 2.33 (s, 3 H), 2.42 (s, 3 H), 6.03 (d, *J* = 8.5 Hz, 1 H), 6.94 (t, *J* = 7.8 Hz, 1 H), 7.09 (s, 4 H), 7.18–7.23 (m, 4 H), 7.33–7.38 (m, 2 H), 7.56 (t, *J* = 7.0 Hz, 1 H), 7.67 (t, *J* = 7.0 Hz, 1 H), 7.98 (d, *J* = 8.2 Hz, 1 H), 8.97 (d, *J* = 7.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 21.7, 114.4, 119.6, 121.2, 123.0, 123.6, 124.1, 125.1, 126.5, 127.7, 128.9, 129.6, 129.9, 130.6, 131.0, 131.4, 132.8, 133.1, 135.4, 136.8, 139.1, 144.4, 147.9.

5,6-Bis(4-methoxyphenyl)benzo[4,5]imidazo[2,1-*a*]isoquinoline (3ad)

[CAS Reg. No. 2281949-53-7]

Yield: 79.3 mg (70%); white solid; R_f = 0.20 (hexane/EtOAc, 3:1).

^1H NMR ($CDCl_3$, 399.78 MHz): δ = 3.80 (s, 3 H), 3.85 (s, 3 H), 6.12 (d, *J* = 8.5 Hz, 1 H), 6.82 (d, *J* = 8.9 Hz, 2 H), 6.90 (d, *J* = 8.7 Hz, 2 H), 6.96 (t, *J* = 7.8 Hz, 1 H), 7.10 (d, *J* = 8.7 Hz, 2 H), 7.22 (d, *J* = 8.7 Hz, 2 H), 7.36 (t, *J* = 8.2 Hz, 2 H), 7.56 (t, *J* = 7.7 Hz, 1 H), 7.66 (t, *J* = 7.7 Hz, 1 H), 7.98 (d, *J* = 8.0 Hz, 1 H), 8.97 (dd, *J* = 8.0, 0.7 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100.53 MHz): δ = 55.3, 55.4, 113.6, 114.3, 114.4, 119.6, 121.3, 123.0, 123.6, 124.1, 125.1, 126.3, 126.5, 127.7, 128.1, 129.9, 131.4, 131.9, 132.6, 133.2, 135.4, 144.4, 147.9, 158.6, 160.0.

5,6-Bis(4-fluorophenyl)benzo[4,5]imidazo[2,1-*a*]isoquinoline (3ae)

[CAS Reg. No. 2281949-54-8]

Yield: 72.0 mg (72%); pale yellow solid; R_f = 0.26 (hexane/EtOAc, 3:1).

^1H NMR (400 MHz, $CDCl_3$): δ = 6.08 (d, *J* = 8.5 Hz, 1 H), 6.96–7.03 (m, 3 H), 7.09–7.19 (m, 4 H), 7.29–7.34 (m, 3 H), 7.39 (t, *J* = 7.7 Hz, 1 H), 7.59 (t, *J* = 7.7 Hz, 1 H), 7.70 (t, *J* = 7.5 Hz, 1 H), 7.99 (d, *J* = 8.0 Hz, 1 H), 8.98 (dd, *J* = 8.0, 0.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 113.9, 115.4 (d, *J* = 22.2 Hz), 116.3 (d, *J* = 22.2 Hz), 119.9, 121.6, 123.1, 124.4, 125.3, 126.3, 128.2, 129.8, 130.2, 131.2, 131.5, 132.5, 132.6 (d, *J* = 7.7 Hz), 133.2 (d, *J* = 7.6 Hz), 134.5, 144.4, 147.8, 162.1 (d, *J* = 247.6 Hz), 163.1 (d, *J* = 249.5 Hz).

5-Phenyl-6-propylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3af)[11]

Yield: 45.3 mg (55%); mp 181 °C; R_f = 0.38 (hexane/EtOAc, 3:1).

IR (ATR): 2959 m, 2930 w, 2871 w, 1630 w, 1608 w, 1595 w, 1525 m, 1479 m, 1445 s, 1373 m cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.3 Hz, 3 H), 1.63–1.65 (m, 2 H), 2.65–2.69 (m, 2 H), 5.85 (d, *J* = 8.5 Hz, 1 H), 6.89 (t, *J* = 7.3 Hz, 1 H), 7.32 (t, *J* = 7.6 Hz, 1 H), 7.47–7.50 (dd, *J* = 8.0, 1.6 Hz, 2 H), 7.62–7.76 (m, 5 H), 7.93 (t, *J* = 7.3 Hz, 2 H), 8.97 (d, *J* = 7.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 24.1, 30.3, 113.9, 119.5, 120.3, 121.1, 123.6, 123.9, 124.2, 125.7, 127.6, 129.5, 129.9, 130.0, 130.3, 131.3, 131.6, 134.5, 134.5, 144.2, 147.6.

MS (EI, 70 eV): *m*/*z* (%) = 337 (11), 336 [M^+] (49), 308 (22), 307 (100), 306 (24), 305 (19), 153 (10).

HRMS-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{21}N_2$: 337.1700; found: 337.1693.

5,6-Diethyl-2-methoxybenzo[4,5]imidazo[2,1-*a*]isoquinoline (3ba)

Yield: 55.5 mg (75%); white solid; mp 118 °C; R_f = 0.20 (hexane/EtOAc, 3:1).

IR (ATR): 2969 m, 2902 w, 2837 w, 1614 m, 1521 m, 1499 s, 1359 s, 1231 s cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.6 Hz, 3 H), 1.46 (t, *J* = 7.6 Hz, 3 H), 2.94 (q, *J* = 7.6 Hz, 2 H), 3.36 (q, *J* = 7.6 Hz, 2 H), 4.02 (s, 3 H), 7.25–7.28 (m, 1 H), 7.32 (t, *J* = 7.8 Hz, 1 H), 7.47 (t, *J* = 7.7 Hz, 1 H), 7.74 (d, *J* = 8.9 Hz, 1 H), 7.97 (d, *J* = 8.5 Hz, 1 H), 8.03 (d, *J* = 8.2 Hz, 1 H), 8.27 (d, *J* = 2.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.2, 15.2, 20.5, 22.1, 55.9, 105.6, 114.7, 119.6, 119.9, 120.7, 121.5, 124.0, 124.2, 125.2, 125.5, 130.8, 134.4, 144.4, 147.9, 158.5.

MS (EI, 70 eV): *m*/*z* (%) = 305 (24), 304 [M^+] (100), 290 (20), 274 (10), 246 (16), 245 (10).

HRMS-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{21}N_2O$: 305.1648; found: 305.1650.

5,6-Diethyl-2-fluorobenzo[4,5]imidazo[2,1-*a*]isoquinoline (3ca)

Yield: 43.4 mg (60%); white solid; mp 225 °C; R_f = 0.43 (hexane/EtOAc, 3:1).

IR (ATR): 2970 m, 1631 w, 1526 w, 1450 m, 1367 m, 1289 w cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.6 Hz, 3 H), 1.48 (t, *J* = 7.6 Hz, 3 H), 2.98 (q, *J* = 7.6 Hz, 2 H), 3.39 (q, *J* = 7.6 Hz, 2 H), 7.35–7.37 (m, 2 H), 7.48 (td, *J* = 8.0, 0.9 Hz, 1 H), 7.79–7.82 (m, 1 H), 7.97 (d, *J* = 8.5 Hz, 1 H), 8.01 (d, *J* = 8.2 Hz, 1 H), 8.52 (dd, *J* = 9.2, 2.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.1, 15.1, 20.7, 22.3, 110.8 (d, *J* = 23.1 Hz), 114.7, 118.5 (d, *J* = 24.1 Hz), 119.2, 120.2, 122.1, 124.2, 124.5 (d, *J* = 9.6 Hz), 125.9 (d, *J* = 8.7 Hz), 127.9, 130.7, 136.1, 144.4, 147.2, 161.3 (d, *J* = 247.6 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 293 (17), 292 [M$^+$] (72), 278 (21), 277 (100), 275 (13), 261 (20), 167 (17), 149 (47), 131 (14), 71 (19), 57 (25).

HRMS-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{18}N_2F$: 293.1449; found: 293.1451.

2-Chloro-5,6-diethylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3da)

Yield: 15.4 mg (20%); white solid; mp 190–191 °C; R_f = 0.50 (hexane/EtOAc, 3:1).

IR (ATR): 2970 m, 1629 w, 1525 m, 1452 m, 1368 s, 740 s cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.6 Hz, 3 H), 1.53 (t, *J* = 7.6 Hz, 3 H), 3.02 (q, *J* = 7.6 Hz, 2 H), 3.45 (q, *J* = 7.6 Hz, 2 H), 7.39 (t, *J* = 7.8 Hz, 1 H), 7.51 (t, *J* = 7.7 Hz, 1 H), 7.63 (dd, *J* = 8.9, 2.3 Hz, 1 H), 7.81 (d, *J* = 8.7 Hz, 1 H), 8.01–8.04 (m, 2 H), 8.91 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.1, 15.2, 20.6, 22.4, 114.7, 119.3, 120.3, 122.2, 124.2, 124.4, 125.1, 125.2, 129.7, 130.5, 130.7, 133.0, 137.1, 144.4, 147.0.

MS (EI, 70 eV): *m*/*z* (%) = 310 (28), 309 (19), 308 [M$^+$] (79), 295 (34), 294 (22), 293 (100), 291 (10), 277 (10), 243 (10), 128 (11), 122 (13).

HRMS-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{18}N_2Cl$: 309.1153; found: 309.1152.

5,6-Diethyl-2-(trifluoromethyl)benzo[4,5]imidazo[2,1-*a*]isoquinoline (3ea)

Yield: 53.2 mg (63%); white solid; mp 179–180 °C; R_f = 0.51 (hexane/EtOAc, 3:1).

IR (ATR): 2972 m, 1630 w, 1526 m, 1454 w, 1168 s cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (t, *J* = 7.6 Hz, 3 H), 1.52 (t, *J* = 7.6 Hz, 3 H), 3.03 (q, *J* = 7.6 Hz, 2 H), 3.43 (q, *J* = 7.6 Hz, 2 H), 7.39 (t, *J* = 7.8 Hz, 1 H), 7.51 (t, *J* = 7.7 Hz, 1 H), 7.86 (d, *J* = 8.7 Hz, 1 H), 7.93–8.04 (m, 3 H), 9.20 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.9, 15.0, 20.5, 22.5, 114.7, 119.1, 120.2, 122.4, 122.7, 123.2 (q, *J* = 4.8 Hz), 124.2 (q, *J* = 272.6 Hz), 124.2, 124.5, 125.9 (q, *J* = 2.9 Hz), 128.6 (q, *J* = 33.7 Hz), 130.5, 133.5, 139.0, 144.3, 147.2.

MS (EI, 70 eV): *m*/*z* (%) = 343 (20), 342 [M$^+$] (89), 328 (22), 327 (100), 325 (12), 311 (16).

HRMS-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{18}N_2F_3$: 343.1417; found: 343.1418.

5,6-Diethyl-3-methoxybenzo[4,5]imidazo[2,1-*a*]isoquinoline (3fa)

Yield: 56.8 mg (77%); white solid; mp 150–151 °C; R_f = 0.29 (hexane/EtOAc, 3:1).

IR (ATR): 2969 m, 2904 w, 2837 w, 1631 s, 1525 m, 1451 s, 1381 m, 1370 m, 1222 s cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.6 Hz, 3 H), 1.49 (t, *J* = 7.6 Hz, 3 H), 2.97 (q, *J* = 7.6 Hz, 2 H), 3.40 (q, *J* = 7.6 Hz, 2 H), 3.95 (s, 3 H), 7.21–7.26 (m, 2 H), 7.31 (t, *J* = 7.8 Hz, 1 H), 7.46 (t, *J* = 7.6 Hz, 1 H), 7.97 (t, *J* = 9.3 Hz, 2 H), 8.83 (d, *J* = 8.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.1, 14.9, 20.6, 22.4, 55.5, 106.1, 114.4, 115.2, 116.8, 119.2, 119.6, 121.2, 123.9, 127.5, 130.6, 133.2, 137.3, 144.6, 148.3, 161.2.

MS (EI, 70 eV): *m*/*z* (%) = 305 (24), 304 [M$^+$] (100), 290 (20), 289 (88), 246 (15), 245 (10).

HRMS-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{21}N_2O$: 305.1648; found: 305.1667.

5,6-Diethyl-2,3-dimethoxybenzo[4,5]imidazo[2,1-*a*]isoquinoline (3ga)

Yield: 70.0 mg (87%); yellow solid; mp 175–176 °C; R_f = 0.43 (hexane/EtOAc, 1:10).

IR (ATR): 2968 w, 2831 w, 1632 w, 1523 m, 1454 s, 1362 w, 1260 s, 1246 s cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (t, *J* = 7.4 Hz, 3 H), 1.51 (t, *J* = 7.4 Hz, 3 H), 3.01 (q, *J* = 7.6 Hz, 2 H), 3.44 (q, *J* = 7.6 Hz, 2 H), 4.05 (s, 3 H), 4.14 (s, 3 H), 7.22 (s, 1 H), 7.33 (t, *J* = 7.8 Hz, 1 H), 7.48 (t, *J* = 7.7 Hz, 1 H), 8.01 (d, *J* = 8.0 Hz, 2 H), 8.27 (s 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.2, 15.0, 20.8, 22.3, 56.1, 56.5, 104.3, 106.0, 114.6, 117.1, 119.2, 119.6, 121.1, 124.0, 126.5, 130.7, 135.4, 144.6, 147.9, 149.3, 151.8.

MS (EI, 70 eV): *m*/*z* (%) = 335 (25), 334 [M$^+$] (100), 320 (12), 319 (52), 303 (19).

HRMS-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{23}N_2O_2$: 335.1754; found: 335.1754.

5,6-Diethyl-11-methylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (3ha)

Yield 59.1 mg (84%); pale yellow solid; mp 123 °C; R_f = 0.59 (hexane/EtOAc, 3:1).

IR (ATR): 3022 w, 2970 m, 1629 m, 1525 s, 1451 s, 1367 m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ =1.32 (t, *J* = 7.6 Hz, 3 H), 1.48 (t, *J* = 7.6 Hz, 3 H), 2.86 (s, 3 H), 3.00 (q, *J* = 7.2 Hz, 2 H), 3.41 (q, *J* = 7.2 Hz, 2 H), 7.22–7.29 (m, 2 H), 7.59 (t, *J* = 7.5 Hz, 1 H), 7.66 (t, *J* = 7.5 Hz, 1 H), 7.82–7.85 (m, 2 H), 8.97 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.1, 15.1, 17.3, 20.4, 22.2, 112.1, 119.5, 121.5, 123.2, 123.3, 124.1, 125.8, 126.7, 129.8, 129.9, 130.3, 131.2, 136.8, 143.8, 147.5.

MS (EI, 70 eV): *m*/*z* (%) = 289 (24), 288 [M$^+$] (98), 274 (22), 273 (100), 271 (10), 258 (10), 257 (20), 128 (10), 122 (11).

HRMS-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{21}N_2$: 289.1699; found: 289.1701.

5,6-Diethylindolo[2,1-*a*]isoquinoline (3ia)

Yield: 46.7 mg (70%); pale yellow solid; mp 106 °C; R_f = 0.22 (hexane/Et_2O, 400:1).

IR (ATR): 2968 m, 1616 w, 1651 w, 1452 m, 1370 m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.6 Hz, 3 H), 1.54 (t, *J* = 7.8 Hz, 3 H), 2.97 (q, *J* = 7.6 Hz, 2 H), 3.45 (q, *J* = 7.6 Hz, 2 H), 7.25–7.34 (m, 3 H), 7.43–7.51 (m, 2 H), 7.74 (d, *J* = 7.6 Hz, 1 H), 7.83 (d, *J* = 7.6 Hz, 1 H), 8.07 (d, *J* = 8.7 Hz, 1 H), 8.23 (d, *J* = 7.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.3, 15.0, 20.5, 22.7, 94.0, 115.1, 117.3, 120.6, 120.6, 121.4, 123.3, 123.8, 125.5, 126.2, 127.5, 128.6, 129.9, 132.0, 136.2, 137.5.

MS (EI, 70 eV): *m*/*z* (%) = 274 (23), 273 [M$^+$] (100), 272 (13), 259 (19), 258 (88), 257 (12), 243 (18), 242 (18), 241 (14), 121 (11), 121 (18).

HRMS-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{20}N$: 274.1590; found: 274.15875.

Funding Information

This work was supported by a Grant-in-Aid for Specially Promoted Research by the Ministry of Education, Culture, Sports, Science and Technology, Japan (MEXT) (No. 17H06091).

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1337-5504.

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