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Synthesis of Indolo[2,1-*a*]isoquinolines via Copper-Catalyzed C–C Coupling and Cyclization of 2-(2-Bromoaryl)-1*H*-indoles with 1,3-Diketones

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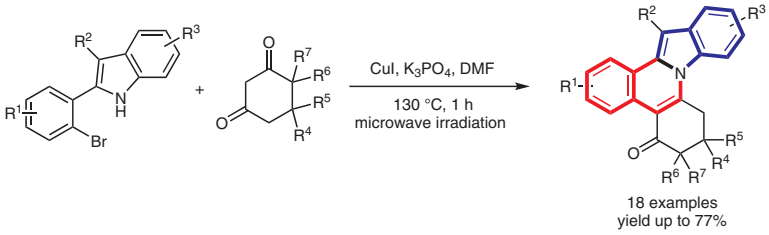

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Abstract 2-(2-Bromoaryl)-1*H*-indoles are coupled and cyclized with 1,3-diketones by microwave irradiation in DMF in the presence of a catalytic amount of copper(I) iodide along with a base to afford the corresponding indolo[2,1-*a*]isoquinolines in moderate to good yields.

Key words copper, coupling, cyclization, heterocycles, fused-ring systems

It is known that indole-fused isoquinolines, indolo[2,1-*a*]isoquinolines, and their reduced 5,6-dihydro analogues, are used as biologically active pharmaceuticals as well as solid-state fluorescent materials (Figure 1).[1,2] Besides conventional synthetic routes for indolo[2,1-*a*]isoquinoline scaffold,[1a,b,3] transition-metal-catalyzed versions also have been attempted as alternative methods due to the wide availability of substrates. It is reported that indoles undergo hydroamination and cyclization with 2-bromoarylalkynes in the presence of CuI along with benzotriazo-1-ylmethanol as ligand to give indolo[2,1-*a*]isoquinolines.[4] Such a similar cyclization is also exemplified with 2-(2-ethynylphenyl)indole catalyzed by platinum(II) chloride.[5] Miura and Huang have demonstrated that indolo[2,1-*a*]isoquinolines can be synthesized by rhodium-catalyzed oxidative coupling and cyclization of 2-arylindoles and aryltriazenes with alkynes via C–H and N–H bond activations.[2,6] Koning et al. have shown that 2-bromo-3-methylindole reacts with 2-acetylphenylboronic acid in the presence of a palladium catalyst to give Suzuki–Miyaura coupling product, which triggers subsequent cyclization and dehydration to afford indolo[2,1-*a*]isoquinoline scaffold.[7] During the course of our continuing studies directed towards copper-catalyzed coupling and cyclization reactions for the synthesis of N-fused hybrid scaffolds,[8,9] we have shown that 2-(2-bromovinyl)- and 2-(2-bromoaryl)benzimidazoles are coupled and cyclized with 1,3-diketones in the presence of a copper catalyst to give benzo[4,5]imidazo[1,2-*a*]pyridines and -isoquinolines.[10]

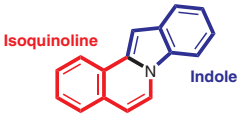


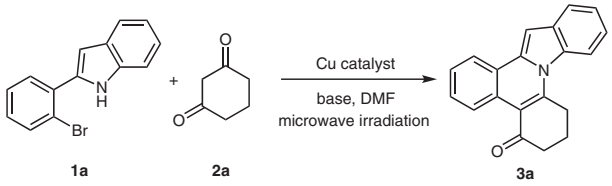
Figure 1 Indolo[2,1-*a*]isoquinoline

It is known that copper salts catalyze cross-coupling of aryl and vinyl halides with activated methylene compounds.[10–14] Such an intrinsic copper-catalyzed coupling and cyclization protocol using 1,3-diketones as building blocks led us to search for a new synthetic method for N-fused hybrid scaffolds.[15] This report describes a new synthetic method for indole-fused isoquinolines, indolo[2,1-*a*]isoquinolines from 2-(2-bromoaryl)-1*H*-indoles and 1,3-diketones via copper-catalyzed C–C coupling and cyclization under microwave irradiation conditions.

The results of several attempted coupling and cyclization of 2-(2-bromophenyl)-1*H*-indole (**1a**) with cyclohexane-1,3-dione (**2a**) for the optimization of reaction conditions are listed in Table 1. Treatment of **1a** with equimolar amount of **2a** in DMF at 130 °C for 1 hour in the presence of 10 mol% of CuI along with K_3PO_4 under microwave irradiation (100 W of initial power) afforded 7,8-dihydroindolo[1,2-*f*]phenanthridin-5(6*H*)-one (**3a**) in 35% isolated yield (Table 1, entry 1). The molar ratio of **2a** to **1a** affects the yield of **3a** with the yield increasing with an increase of the molar ratio up to 2.0 (entries 1–3). The yield of **3a** increases on prolonging the reaction time up to 1 hour with complete conversion of **1a**, which was monitored until **1a** had disappeared on TLC (entries 3 and 4). Lower reaction tempera-

ture resulted in a decreased yield of **3a** (entry 5). The amount of base is critical for the effective formation of **3a** (entry 6). No significant change of the yield of **3a** was observed with dilution of the reaction mixture (entry 7). The reaction also proceeded in the presence of other inorganic bases such as K_2CO_3, Cs_2CO_3, NaO*t*-Bu, and NaOAc, but the yields of **3a** were generally lower than that obtained in the presence of K_3PO_4 (entries 8–11). We recently reported that copper powder combined with microwave irradiation shows an efficient catalytic activity for the synthesis of several heterocycles by C–C or C–N bond coupling and cyclization protocol.[11,16] However, such a combined system was revealed to be ineffective for the present reaction (entry 12). The reaction proceeded using other copper(I) salts such as CuCl, CuBr, and Cu_2O but the yield of **3a** was lower than that by the use of CuI (entries 13–15). CuO exhibited the same catalytic activity as CuI (entry 16). Finally, lower yield was observed under usual heating conditions (screw-capped vial, 130 °C for 24 h) (entries 3 and 17). The best results in terms of the yield of product **3a** and complete conversion of **1a** were achieved by using the set of reaction conditions shown in entry 3 of Table 1.

Table 1 Optimization of Conditions for the Reaction of **1a** with **2a**[a]



1a **2a** **3a**

Entry	[**2a**]/[**1a**]	Cu catalyst	Base	Yield (%)[b]
1	1.0	CuI	K_3PO_4	35
2	1.5	CuI	K_3PO_4	63
3	2.0	CuI	K_3PO_4	74
4[c]	2.0	CuI	K_3PO_4	60
5[d]	2.0	CuI	K_3PO_4	19
6[e]	2.0	CuI	K_3PO_4	17
7[f]	2.0	CuI	K_3PO_4	67
8	2.0	CuI	K_2CO_3	35
9	2.0	CuI	Cs_2CO_3	41
10	2.0	CuI	NaO*t*-Bu	48
11	2.0	CuI	NaOAc	32
12	2.0	Cu powder	K_3PO_4	29
13	2.0	CuCl	K_3PO_4	64
14	2.0	CuBr	K_3PO_4	59
15	2.0	Cu_2O	K_3PO_4	68
16	2.0	CuO	K_3PO_4	74
17[g]	2.0	CuI	K_3PO_4	50

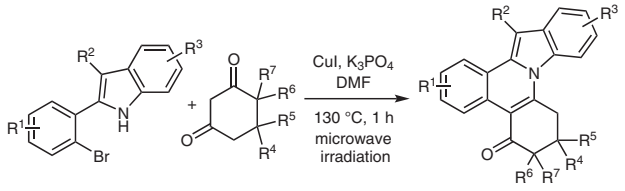
[a] Reaction conditions: **1a** (0.3 mmol), Cu catalyst (0.03 mmol), base (0.6 mmol), and DMF (3 mL), 130 °C, 1 h, microwave irradiation (100 W of initial power), unless otherwise stated.
[b] Isolated yield.
[c] Reaction time: 30 min.
[d] Reaction temperature: 100 °C.
[e] Base (0.3 mmol).
[f] DMF (5 mL).
[g] Under usual heating (screw-capped vial, 130 °C for 24 h).

After the reaction conditions had been established, various 2-(2-bromoaryl)-1*H*-indoles **1** were subjected to the reaction with 1,3-diketones **2** to investigate the scope of the reaction and several representative results are summarized in Table 2. The coupling and cyclization of 2-(2-bromoaryl)-1*H*-indoles **1a** and **1b** with cyclic 1,3-diketones **2a–d** afforded the corresponding indolo[2,1-*a*]isoquinolines **3a–g**) in 55–74% yields. Easily available 2-(2-bromoaryl)-1*H*-indoles **1c–f** having straight and branched alkyl chain and phenyl at position 3 (R^2) of indole moiety reacted with **2a** to give the corresponding indolo[2,1-*a*]isoquinolines **3h–k** in allowable yields irrespective of the identity of R^2. From the reaction of various 2-(2-bromoaryl)-1*H*-indoles **1g–k** having electron-donating and -withdrawing substituents (R^1 and R^3) on bromoaryl or indole moieties with **2a**, the corresponding indolo[2,1-*a*]isoquinolines **3l–p** were also formed in 49–75% yields.

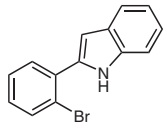
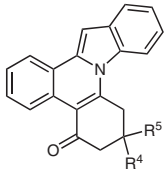
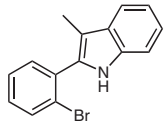
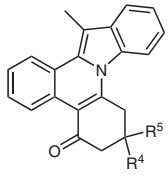
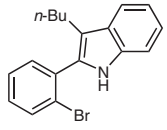
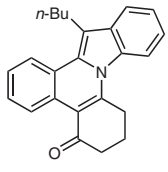
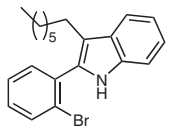
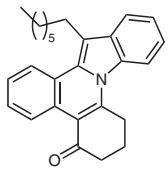
Not shown in Table 2 are the reactions of 2-(2-bromoaryl)-1*H*-indoles having R^1 (OMe) at *para*-position to Br and R^3 (Me, Cl) at *ortho*-position to N on indole moiety, which did not proceed at all toward the coupling and cyclization; several unidentified products were formed. It appears that the position of substituents (R^3) on the indole moiety of **1** had significant impact on the product formation. Benzo-fused 2-(2-bromophenyl)-1*H*-indole **1l** similarly coupled and cyclized with **2a** to give 9,10-dihydrobenzo[*i*]indolo[1,2-*f*]phenanthridin-7(8*H*)-one (**3q**) in 58% yield. Starting indole **1a** coupled and regioselectively cyclized with 4,4-dimethylcyclohexane-1,3-dione (**2e**) to afford 6,6-dimethyl-7,8-dihydroindolo[1,2-*f*]phenanthridin-5(6*H*)-one (**3r**) in 77% yield. Similar treatment of **1a** with acyclic 1,3-diketone, 1,3-diphenylpropane-1,3-dione (**2f**) under the employed conditions gave coupled and deacylative cyclized product **3s** in only 18% yield.[10] Slightly increased yield (26%) of **3s** was observed by the treatment of two-fold amount of CuI under the employed conditions. The reaction of **1a** with 2-methylcyclohexane-1,3-dione under the employed conditions did not proceed at all toward coupled and cyclized product, with 2-phenylindole by debromination of **1a** being formed in 83% yield.

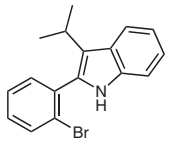
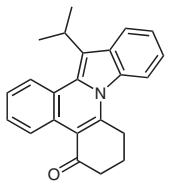
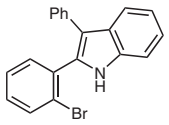
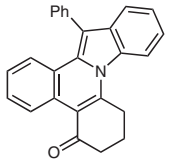
Indole-fused isoquinolines **3a–c** can be converted into N-fused trinuclear hybrid scaffolds **4a–c** by a one-pot procedure (Scheme 1). Sequential reduction of **3a–c** to alcohols with $NaBH_4$ in MeOH, dehydration of the alcohols with *p*-TsOH in benzene, and oxidation with DDQ in benzene afforded **4a–c** in 60–73% yields.[17]

Table 2 CuI-Calatyzed Synthesis of Indolo[2,1-*a*]isoquinolines **3** from **1** and **2**[a]



1 **2a** $R^4 = R^5 = R^6 = R^7 = H$
2b $R^4 = R^6 = R^7 = H$; $R^5 = Me$
2c $R^4 = R^6 = R^7 = H$; $R^5 = Ph$
2d $R^4 = R^5 = Me$; $R^6 = R^7 = H$
2e $R^4 = R^5 = H$; $R^6 = R^7 = Me$ **3**

1	2	3	Yield (%)
			
1a	**2a**	**3a**	74
	2b	**3b**	67
	2c	**3c**	63
	2d	**3d**	59
			
1b	**2a**	**3e**	64
	2c	**3f**	55
	2d	**3g**	72
			
1c	**2a**	**3h**	51
			
1d	**2a**	**3i**	54

1	2	3	Yield (%)
			
1e	**2a**	**3j**	72
			
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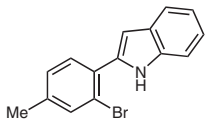		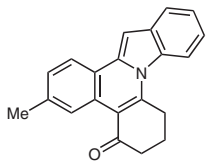	
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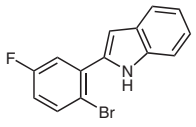		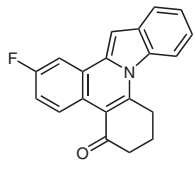	
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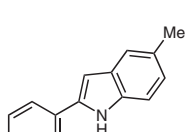		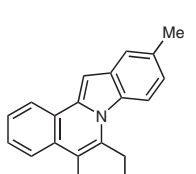	
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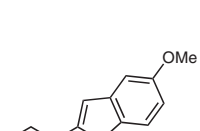
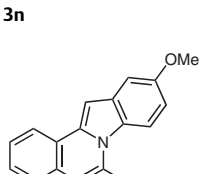
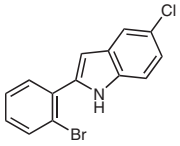
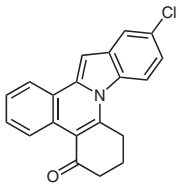
			
1j	**2a**	**3o**	54

1	2	3	Yield (%)
			
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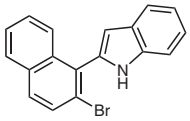		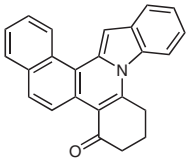	
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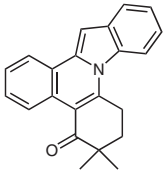
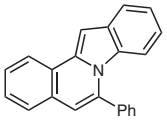
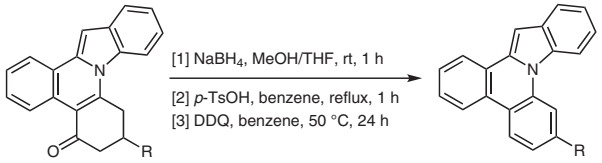
			
1a	**2e**	**3r**	77
			
1a	**2f**	**3s**	26[b]

[a] Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol), CuI (0.03 mmol), K_3PO_4 (0.6 mmol), DMF (3 mL), 130 °C, 1 h, microwave irradiation (100 W of initial power), unless otherwise stated.
[b] CuI used: 0.06 mmol.

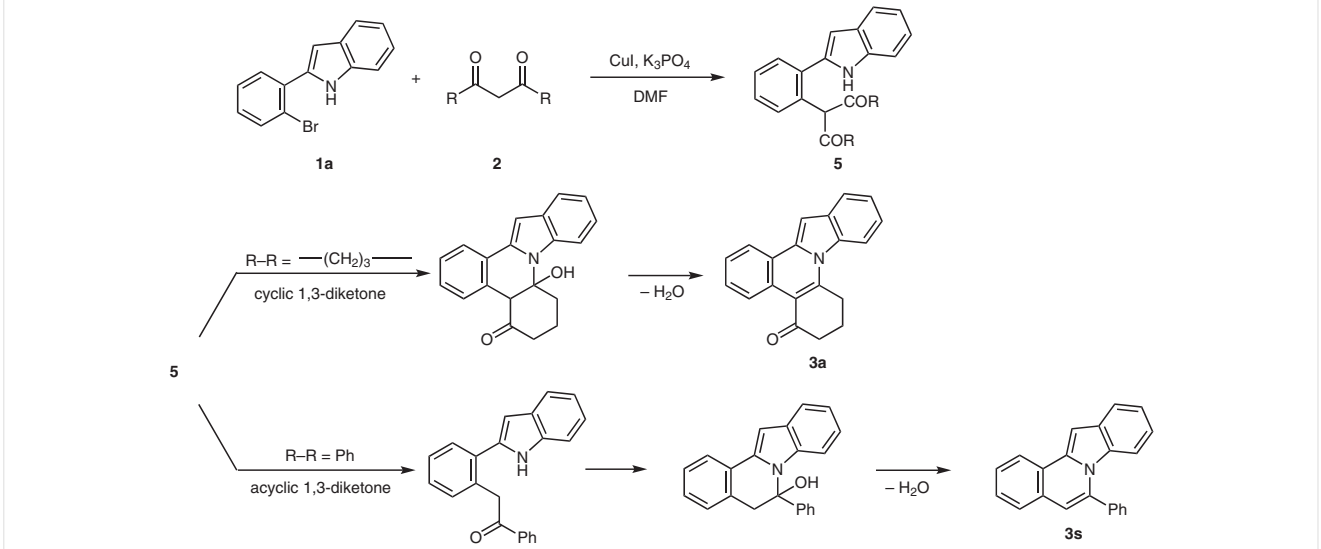


Scheme 1 One-pot reduction–dehydration–oxidation of **3** to **4**

As to the reaction pathway, this seems to proceed via an initial formation of C–C coupled intermediate **5** by copper-catalyzed C–C coupling between **1a** and **2** (Scheme 2). It is reported that aryl and vinyl halides are found to couple with 1,3-dicarbonyl compounds in the presence of a copper salt to give 2-aryl- and 2-vinyl-1,3-dicarbonyl intermediates or products.[10–14] This is followed by cyclocondensation (cyclic 1,3-diketone) to give **3a** or deacylative cyclocondensation (acyclic 1,3-diketone) to give **3s**.[10,13a,18]

In summary, we have shown that 2-(2-bromoaryl)-1*H*-indoles react with 1,3-diketones by microwave irradiation in the presence of copper(I) iodide and K_3PO_4 to give indole-fused isoquinolines and indolo[2,1-*a*]isoquinolines via coupling and cyclization process. The present reaction provides a new method for the synthesis of such scaffolds. Further attempts on the syntheses of N-fused hybrid scaffolds using copper-catalyzed coupling and cyclization reaction are underway.

^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Bruker Avance III 500 spectrometer using TMS as an internal standard. Melting points were determined on a Standford Research Inc. MPA100 automated melting point apparatus. High-resolution mass



Scheme 2 Reaction pathway

data were recorded using electronic ionization (HRMS-EI, magnetic sector-electric sector double focusing mass analyzer) at the Korea Basic Science Center, Daegu, Korea. All microwave reactions (CEM, Discover LabMate) were carried out in sealed tube (5 mL) and maintenance of the reaction temperature was monitored by an external infrared sensor. The isolation of pure products was carried out via TLC (silica gel 60 GF_{254}, Merck). The starting 2-(2-bromoaryl)-1*H*-indoles were prepared from the corresponding bromoketones and arylhydrazines according to literature procedures.[19] Commercially available organic and inorganic compounds were used without further purification.

Indolo[2,1-*a*]isoquinolines 3; General Procedure

A 5 mL microwave reaction tube was charged with 2-(2-bromoaryl)-1*H*-indole **1** (0.3 mmol), 1,3-diketone **2** (0.6 mmol), K_3PO_4 (0.127 g, 0.6 mmol), CuI (0.006 g, 0.03 mmol), and DMF (3 mL). After stirring at r.t. for 5 min, the reaction mixture was heated at 130 °C for 1 h under microwave irradiation at 100 W of initial power. The mixture was then cooled to r.t., and filtered through a short silica gel column (CH_2Cl_2–MeOH) to remove inorganic salts. Evaporation of the solvent gave a crude mixture that was purified by TLC [silica gel 60 GF_{254} (Merck), CH_2Cl_2–MeOH] to give **3**.

Except for known **3s**,[4] all new products were characterized spectroscopically.

7,8-Dihydroindolo[1,2-*f*]phenanthridin-5(6*H*)-one (3a)

Yellow solid; yield: 63 mg (74%); mp 161–163 °C (hexane).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.23–2.28 (m, 2 H), 2.71–2.73 (m, 2 H), 3.57 (t, *J* = 6.2 Hz, 2 H), 7.16 (s, 1 H), 7.28–7.31 (m, 1 H), 7.37–7.40 (m, 1 H), 7.42–7.45 (m, 1 H), 7.47–7.51 (m, 1 H), 7.77 (d, *J* = 7.4 Hz, 1 H), 8.01–8.05 (m, 2 H), 9.20–9.22 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.55, 30.74, 38.98, 97.12, 113.64, 116.35, 121.21, 121.81, 123.17, 123.53, 124.64, 126.14, 127.06, 127.36, 128.48, 131.64, 133.68, 136.33, 151.07, 197.69.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{20}H_{15}NO$: 285.1154; found: 285.1155.

7-Methyl-7,8-dihydroindolo[1,2-*f*]phenanthridin-5(6*H*)-one (3b)

Yellow solid; yield: 60 mg (67%); mp 158–160 °C (hexane).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.28 (d, *J* = 6.2 Hz, 3 H), 2.36–2.48 (m, 2 H), 2.73–2.76 (m, 1 H), 3.08–3.13 (m, 1 H), 3.70–3.74 (m, 1 H), 7.16 (s, 1 H), 7.29–7.32 (m, 1 H), 7.38–7.41 (m, 1 H), 7.42–7.45 (m, 1 H), 7.47–7.50 (m, 1 H), 7.77 (dd, *J* = 7.8, 0.4 Hz, 1 H), 8.01–8.05 (m, 2 H), 9.22 (dd, *J* = 8.3, 1.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.22, 28.72, 38.51, 46.82, 96.89, 113.05, 116.20, 121.01, 121.58, 122.96, 123.33, 124.41, 125.87, 126.74, 127.16, 128.29, 131.44, 133.46, 136.16, 150.26, 197.64.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{21}H_{17}NO$: 299.1310; found: 299.1312.

7-Phenyl-7,8-dihydroindolo[1,2-*f*]phenanthridin-5(6*H*)-one (3c)

Yellow solid; yield: 68 mg (63%); mp 242–244 °C (hexane).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.96–3.06 (m, 2 H), 3.53–3.63 (m, 2 H), 4.00–4.03 (m, 1 H), 7.23–7.26 (m, 2 H), 7.35–7.40 (m, 4 H), 7.44–7.55 (m, 4 H), 7.79 (d, *J* = 7.8 Hz, 1 H), 7.95 (d, *J* = 8.7 Hz, 1 H), 8.07–8.09 (m, 1 H), 9.28 (d, *J* = 8.1 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 38.44, 39.43, 45.30, 97.15, 113.23, 116.18, 121.08, 121.80, 123.04, 123.49, 124.53, 125.81, 126.83, 126.87, 127.39, 127.48, 128.42, 129.12, 131.47, 133.44, 136.22, 142.39, 150.01, 196.75.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{26}H_{19}NO$: 361.1467; found: 361.1468.

7,7-Dimethyl-7,8-dihydroindolo[1,2-*f*]phenanthridin-5(6*H*)-one (3d)

Yellow solid; yield: 55 mg (59%); mp 228–229 °C (hexane).

^{1}H NMR (500 MHz, $CDCl_3$): δ =1.22 (s, 6 H), 2.60 (s, 2 H), 3.44 (s, 2 H), 7.20 (s, 1 H), 7.30–7.33 (m. 1 H), 7.39–7.42 (m, 1 H), 7.44–7.47 (m, 1 H), 7.49–7.52 (m, 1 H), 7.79 (d, *J* = 7.8 Hz, 1 H), 8.06 (d, *J* = 8.2 Hz, 2 H), 9.25–9.27 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.54, 32.32, 44.14, 52.32, 96.90, 112.36, 116.39, 121.05, 121.57, 122.98, 123.35, 124.46, 125.70, 126.75, 127.20, 128.34, 131.48, 133.51, 136.37, 149.00, 197.75.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{22}H_{19}NO$: 313.1467; found: 313.1468.

14-Methyl-7,8-dihydroindolo[1,2-*f*]phenanthridin-5(6*H*)-one (3e)

Yellow solid; yield: 57 mg (64%); mp 157–158 °C (hexane).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.12–2.17 (m, 2 H), 2.55 (s, 3 H), 2.64–2.66 (m, 2 H), 3.36 (t, *J* = 6.1 Hz, 2 H), 7.26–7.29 (m, 1 H), 7.38–7.42 (m, 2 H), 7.43–7.46 (m, 1 H), 7.70 (d, *J* = 7.9 Hz, 1 H), 7.90 (d, *J* = 8.6 Hz, 1 H), 8.07 (d, *J* = 7.7 Hz, 1 H), 9.19–9.20 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.69, 21.35, 30.65, 38.68, 107.69, 112.87, 116.11, 118.64, 121.80, 122.74, 124.15, 126.12, 126.39, 126.57, 126.74, 127.21, 130.78, 132.00, 132.50, 151.10, 197.12.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{21}H_{17}NO$: 299.1310; found: 299.1313.

14-Methyl-7-phenyl-7,8-dihydroindolo[1,2-*f*]phenanthridin-5(6*H*)-one (3f)

Yellow solid; yield: 62 mg (55%); mp 166–168 °C (hexane).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.59 (s, 3H), 2.90–2.92 (m, 2 H), 3.32–3.46 (m, 2 H), 3.78–3.82 (m, 1 H), 7.22–7.25 (m, 1 H), 7.33–7.36 (m, 3 H) , 7.38–7.49 (m, 5 H), 7.72–7.74 (m, 1 H), 7.81 (d, *J* = 8.6 Hz, 1 H), 8.11–8.13 (m, 1 H), 9.27–9.29 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.75, 38.42, 39.42, 45.23, 107.95, 112.57, 116.17, 118.72, 122.01, 122.92, 124.21, 126.17, 126.35, 126.58, 126.78, 126.87, 127.35, 129.03, 130.86, 131.94, 132.57, 142.50, 150.23, 196.40.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{27}H_{21}NO$: 375.1623; found: 375.1625.

7,7,14-Trimethyl-7,8-dihydroindolo[1,2-*f*]phenanthridin-5(6*H*)-one (3g)

Yellow solid; yield: 71 mg (72%); mp 70–73 °C (hexane).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.16 (s, 6 H), 2.55 (s, 2 H), 2.65 (s, 3 H), 3.31 (s, 2 H), 7.31–7.34 (m, 1 H), 7.41–7.50 (m, 3 H), 7.75–7.77 (m, 1 H), 7.96 (d, *J* = 8.6 Hz, 1 H), 8.17–8.19 (m, 1 H), 9.27–9.28 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.85, 28.49, 32.37, 44.33, 52.28, 107.71, 111.86, 116.41, 118.76, 121.82, 122.84, 124.18, 126.27, 126.38, 126.53, 126.68, 127.36, 131.15, 132.11, 132.67, 149.20, 197.44.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{23}H_{21}NO$: 327.1623; found: 327.1624.

14-Butyl-7,8-dihydroindolo[1,2-*f*]phenanthridin-5(6*H*)-one (3h)

Yellow solid; yield: 52 mg (51%); mp 124–127 °C (hexane).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.01 (t, *J* = 7.4 Hz, 3 H), 1.51–1.59 (m, 2 H), 1.73–1.80 (m, 2 H), 2.22–2.27 (m, 2 H), 2.71–2.74 (m, 2 H), 3.19–3.23 (m, 2 H), 3.60 (t, *J* = 6.1 Hz, 2 H), 7.31–7.34 (m, 1 H), 7.42 (t, *J* = 7.4 Hz, 1 H), 7.46–7.51 (m, 2 H), 7.80 (d, *J* = 7.7 Hz, 1 H), 8.06 (d, *J* = 8.6 Hz, 1 H), 8.19–8.21 (m, 1 H), 9.21–9.24 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.05, 21.58, 23.10, 25.33, 31.05, 31.31, 38.78, 113.17, 113.47, 116.16, 118.85, 122.01, 122.91, 123.88, 126.01, 126.66, 126.87, 126.91, 127.43, 130.56, 132.27, 132.48, 151.18, 197.10.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{24}H_{23}NO$: 341.1780; found: 341.1781.

14-Heptyl-7,8-dihydroindolo[1,2-*f*]phenanthridin-5(6*H*)-one (3i)

Yellow solid; yield: 62 mg (54%); mp 88–89 °C (hexane).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.9 Hz, 3 H), 1.27–1.35 (m, 4 H), 1.35–1.42 (m, 2 H), 1.48–4.54 (m, 2 H), 1.72–7.78 (m, 2 H), 2.19–2.24 (m, 2 H), 2.69–2.72 (m, 2 H), 3.14–.3.17 (m, 2 H), 3.55 (t, *J* = 6.1 Hz, 2 H), 7.29–7.32 (m, 1 H), 7.41 (t, *J* = 7.4 Hz, 1 H), 7.44–7.49 (m, 2 H), 7.78 (d, *J* = 7.8 Hz, 1 H), 8.02 (d, *J* = 8.6 Hz, 1 H), 8.14–8.16 (m, 1 H), 9.20–9.23 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.12, 21.52, 22.69, 25.57, 29.08, 29.19, 29.96, 30.97, 31.86, 38.73, 113.08, 113.48, 116.16, 118.79, 121.97, 122.87, 123.84, 125.94, 126.59, 126.83, 126.85, 127.37, 130.45, 132.21, 132.40, 151.21, 197.13.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{27}H_{29}NO$: 383.2249; found: 383.2248.

14-Isopropyl-7,8-dihydroindolo[1,2-*f*]phenanthridin-5(6*H*)-one (3j)

Yellow solid; yield: 71 mg (72%); mp 153–154 °C (hexane).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.63 (d, *J* = 7.1 Hz, 6 H), 2.20–2.26 (m, 2 H), 2.68–2.71 (m, 2 H), 3.57 (t, *J* = 6.1 Hz, 2 H), 4.08 (sept, *J* = 7.1 Hz, 1 H), 7.27–7.30 (m, 1 H), 7.35–7.38 (m, 1 H), 7.42–7.49 (m, 2 H), 8.02–8.05 (m, 2 H), 8.11 (dd, *J* = 1.4, 7.9 Hz, 1 H), 9.12–9.14 (m. 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.66, 22.19, 26.68, 30.89, 38.70, 113.03, 116.52, 119.46, 121.26, 121.71, 122.50, 124.78, 125.62, 126.54, 126.56, 127.45, 127.68, 130.49, 130.82, 133.23, 150.92, 196.91.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{23}H_{21}NO$: 327.1623; found: 327.1624.

14-Phenyl-7,8-dihydroindolo[1,2-*f*]phenanthridin-5(6*H*)-one (3k)

Yellow solid; yield: 72 mg (66%); mp 227–229 °C (hexane).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.23–2.28 (m, 2 H), 2.71–2.73 (m, 2 H), 3.56–3.58 (m, 2 H), 7.27–7.31 (m, 1 H), 7.37–7.40 (m, 1 H), 7.41–7.45 (m, 1 H), 7.47–7.51 (m, 1 H), 7.54–7.56 (m, 2 H), 7.68–7.73 (m, 3 H), 7.77 (d, *J* = 7.5 Hz, 1 H), 8.01–8.05 (m, 2 H), 9.20–9.21 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.03, 30.22, 38.46, 110.21, 113.25, 116.19, 121.10, 121.82, 123.05, 123.51, 124.54, 125.83, 126.85, 126.89, 127.40, 127.49, 128.44, 129.13, 131.49, 133.45, 136.24, 142.41, 150.03, 196.77.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{26}H_{19}NO$: 361.1467; found: 361.1469.

3-Methyl-7,8-dihydroindolo[1,2-*f*]phenanthridin-5(6*H*)-one (3l)

Yellow solid; yield: 53 mg (59%); mp 161–163 °C (hexane).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.04–2.09 (m, 2 H), 2.46 (s, 3 H), 2.55–2.58 (m, 2 H), 3.27–3.29 (m, 2 H), 7.02 (s, 1 H), 7.18–7.21 (m, 1 H), 7.29–7.33 (m, 2 H), 7.34–7.38 (m, 1 H), 7.81 (d, *J* = 8.6 Hz, 1 H), 7.99 (d, *J* = 7.7 Hz, 1 H), 9.12 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.31, 22.61, 30.61, 38.63, 97.65, 112.83, 116.06, 118.60, 121.76, 122.70, 124.11, 126.35, 126.52, 126.70, 127.17, 129.47, 130.74, 131.96, 132.46, 151.06, 197.08.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{22}H_{17}NO$: 299.1310; found: 299.1311.

2-Fluoro-7,8-dihydroindolo[1,2-*f*]phenanthridin-5(6*H*)-one (3m)

Yellow solid; yield: 45 mg (49%); mp 177–178 °C (hexane).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.29–2.34 (m, 2 H), 2.75–2.78 (m, 2 H), 3.59–3.61 (m, 2 H), 7.15 (s, 1 H), 7.27–7.31 (m, 1 H), 7.37–7.40 (m, 1 H), 7.41–7.45 (m, 1 H), 7.47–7.50 (m, 1 H), 7.60–7.64 (m, 2 H), 9.45 (dd, *J* = 10.4, 4.4 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.34, 30.52, 38.77, 96.91, 113.36 (d, *J* = 19.8 Hz), 116.11 (d, *J* = 8.6 Hz), 121.01, 121.52 (d, *J* = 19.8 Hz), 122.94 (d, *J* = 8.6 Hz), 123.33, 124.44, 125.94, 126.86, 127.16, 128.27, 131.42 (d, *J* = 3.0 Hz), 133.48, 136.13, 158.91 (d, *J* = 233.6 Hz), 197.50.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{20}H_{14}FNO$: 303.1059; found: 303.1058.

12-Methyl-7,8-dihydroindolo[1,2-*f*]phenanthridin-5(6*H*)-one (3n)

Yellow solid; yield: 50 mg (56%); mp 167–170 °C (hexane).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.24–2.29 (m, 2 H), 2.52 (s, 3 H), 2.71–2.74 (m, 2 H), 3.58 (t, *J* = 6.2 Hz, 2 H), 7.09–7.11 (m, 1 H), 7.13 (s, 1 H), 7.42–7.45 (m, 1 H), 7.47–7.50 (m, 1 H), 7.54–7.55 (m, 1 H), 7.92 (t, *J* = 8.8 Hz, 1 H), 8.03–8.05 (m, 1 H), 9.21–9.23 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.26, 21.36, 30.39, 38.75, 96.55, 113.04, 115.76, 120.65, 122.88, 123.21, 124.40, 125.95, 126.80, 127.01, 128.12, 131.73, 131.77, 132.98, 136.18, 150.85, 197.44.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{21}H_{17}NO$: 299.1310; found: 299.1313.

12-Methoxy-7,8-dihydroindolo[1,2-*f*]phenanthridin-5(6*H*)-one (3o)

Yellow solid; yield: 51 mg (54%); mp 119–121 °C (hexane).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.23–2.28 (m, 2 H), 2.71–2.73 (m, 2 H), 3.56–3.59 (m, 2 H), 3.82 (s, 3 H), 6.93 (dd, *J* =8.9, 2.8 Hz, 1 H), 7.00 (d, *J* = 2.8 Hz, 1 H), 7.13 (s, 1 H), 7.28–7.31 (m, 1 H), 7.42 (d, *J* = 8.9 Hz, 1 H), 7.47–7.51 (m, 1 H), 7.77 (d, *J* = 7.5 Hz, 1 H), 9.20–9.22 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.73, 22.35, 30.75, 55.77, 97.30, 103.57, 113.55, 115.49, 121.26, 121.42, 122.13, 123.71, 127.12, 127.25, 129.52, 131.44, 133.64, 136.04, 158.45, 170.14, 199.26.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{21}H_{17}NO_2$: 315.1259; found: 315.1256.

12-Chloro-7,8-dihydroindolo[1,2-*f*]phenanthridin-5(6*H*)-one (3p)

Yellow solid; yield: 72 mg (75%); mp 203–206 °C (hexane).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.29–2.34 (m, 2 H), 2.75–2.78 (m, 2 H), 3.60 (t, *J* = 6.1 Hz, 2 H), 7.16 (s, 1 H), 7.24–7.26 (m, 1 H), 7.47–7.50 (m, 1 H), 7.52–7.56 (m, 1 H), 7.74 (d, *J* = 2.2 Hz, 1 H), 7.99 (d, *J* = 9.1 Hz, 1 H), 8.06–8.08 (m, 1 H), 9.22–9.23 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.33, 30.49, 38.76, 96.22, 113.91, 117.00, 120.20, 121.66, 123.15, 124.16, 126.03, 126.99, 127.42, 128.76, 129.12, 131.80, 132.60, 137.45, 150.16, 197.42.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{20}H_{14}ClNO$: 319.0764; found: 319.0761.

9,10-Dihydrobenzo[*i*]indolo[1,2-*f*]phenanthridin-7(8*H*)-one (3q)

Yellow solid; yield: 58 mg (58%); mp 210–211 °C (hexane).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.23–2.28 (m, 2 H), 2.71–2.73 (m, 2 H), 3.56–3.59 (m, 2 H), 7.16 (s, 1 H), 7.28–7.31 (m, 1 H), 7.37–7.40 (m, 1 H), 7.42–7.45 (m, 1 H), 7.47–7.51 (m, 1 H), 7.90–7.92 (m, 1 H), 8.15–8.23 (m, 3 H), 9.20–9.22 (m, 1 H), 9.80 (d, *J* = 8.3 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.34, 30.53, 38.77, 96.92, 113.44, 116.15, 117.01, 117.61, 122.98, 123.33, 124.44, 125.95, 126.33, 126.52, 126.86, 127.16, 128.28, 129.57, 130.14, 131.44, 133.49, 136.13, 150.88, 197.50.

HRMS (EI): *m*/*z* [M⁺] calcd for $C_{24}H_{17}NO$: 335.1310; found: 335.1312.

6,6-Dimethyl-7,8-dihydroindolo[1,2-*f*]phenanthridin-5(6*H*)-one (3r)

Yellow solid; yield: 72 mg (77%); mp 152–154 °C (hexane).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.33 (s, 6 H), 2.17 (t, *J* = 6.3 Hz, 2 H), 3.70 (t, *J* = 6.3 Hz, 2 H), 7.30–7.33 (m, 2 H), 7.39–7.42 (m, 1 H), 7.47–7.51 (m, 2 H), 7.82 (d, *J* = 7.8 Hz, 1 H), 8.12–8.14 (m, 1 H), 8.18 (d, *J* = 8.6 Hz, 1 H), 9.14–9.16 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.81, 27.14, 34.47, 41.31, 96.76, 116.16, 121.06, 121.61, 123.08, 123.28, 124.86, 126.35, 127.00, 127.17, 128.24, 129.01, 131.48, 133.55, 136.28, 148.93, 202.64.

HRMS (EI): *m*/*z* [M⁺] calcd for $C_{22}H_{19}NO$: 313.1467; found: 313.1465.

Indolo[1,2-*f*]phenanthridines 4; General Procedure

A 25 mL round-bottomed flask was charged with **3** (0.2 mmol), $NaBH_4$ (0.045 g, 1.2 mmol), and THF–MeOH (5 mL, 1:4). The reaction mixture was stirred at r.t. for 1 h. After removing the solvent under reduced pressure followed by the addition of *p*-TsOH·H_2O (0.006 g, 0.03 mmol) in benzene (5 mL) to the crude alcohol, the reaction mixture was heated to 90 °C for 1 h. After cooling to 50 °C, DDQ (0.050 g, 0.22 mmol) was added and the mixture was stirred for 24 h. Removal of the solvent under reduced pressure left a crude mixture that was separated by TLC (CH_2Cl_2) to give the desired product **4**.

Compound **4a** is known.[20]

2-Methylindolo[1,2-*f*]phenanthridine (4b)

Yellow solid; yield: 41 mg (73%); mp 173–175 °C (hexane).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.35 (s, 3 H), 7.19 (s, 1 H), 7.31–7.34 (m, 1 H), 7.39–7.43 (m, 2 H), 7.44–7.47 (m, 1 H), 7.49–7.53 (m, 1 H), 7.76 (d, *J* = 7.8 Hz, 1 H), 7.79–7.80 (m, 1 H), 7.88 (dd, *J* = 7.9, 1.2 Hz, 1 H), 8.04–8.07 (m, 2 H), 8.44–8.46 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 38.65, 94.33, 115.32, 115.51, 115.68, 120.51, 120.67, 121.79, 121.84, 122.92, 123.52, 124.55, 125.43, 126.58, 127.52, 127.81, 128.08, 130.08, 132.86, 135.93, 136.81.

HRMS (EI): *m*/*z* [M⁺] calcd for $C_{21}H_{15}N$: 281.1204; found: 281.1205.

2-Phenylindolo[1,2-*f*]phenanthridine (4c)

Yellow solid; yield: 41 mg (60%); mp 140–142 °C (hexane).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25 (s, 1 H), 7.26–7.29 (m, 1 H), 7.38–7.43 (m, 4 H), 7.46–7.52 (m, 3 H), 7.54–7.57 (m, 2 H), 7.81 (d, *J* = 7.8 Hz, 1 H), 7.92 (d, *J* = 8.8 Hz, 1 H), 7.98 (d, *J* = 8.7 Hz, 1 H), 8.03–8.05 (m, 1 H), 8.09–8.11 (m, 1 H), 8.61 (d, *J* = 8.1 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 97.18, 113.26, 115.07, 116.21, 119.47, 120.79, 121.11, 121.83, 123.07, 123.52, 124.56, 125.84, 126.87, 126.90, 127.42, 127.51, 128.45, 129.15, 130.82, 131.50, 133.47, 136.26, 139.72, 142.42.

HRMS (EI): *m*/*z* [M⁺] calcd for $C_{26}H_{17}N$: 343.1361; found: 343.1362.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591589.

References

(1) (a) Ambros, R.; von Angerer, S.; Wiegrebe, W. *Arch. Pharm. (Weinheim)* **1988**, *321*, 481. (b) Ambros, R.; von Angerer, S.; Wiegrebe, W. *Arch. Pharm. (Weinheim)* **1988**, *321*, 743. (c) Ambros, R.; Schneider, M. R. von Angerer S. *J. Med. Chem.* **1990**, *33*, 153. (d) Goldbrunner, M.; Loidl, G.; Polossek, T.; Mannschreck, A.; von Angerer, E. *J. Med. Chem.* **1997**, *40*, 3524.
(2) Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 2068.
(3) (a) Harley-Mason, J. *J. Chem. Soc.* **1953**, 1465. (b) Kametani, T.; Ogasawara, K. *J. Chem. Soc. C* **1967**, 2208. (c) Boente, J. M.; Castedo, L.; Rodriguez de Lera, A.; Saá, J. M.; Suau, R.; Vidal, M. C. *Tetrahedron Lett.* **1983**, *24*, 2295. (d) Orito, K.; Harada, R.; Uchiito, S.; Tokuda, M. *Org. Lett.* **2000**, *2*, 1799. (e) Kraus, G. A.; Beasley, J. *Tetrahedron Lett.* **2013**, *54*, 5597.
(4) Verma, A. K.; Kesharwani, T.; Singh, J.; Tandon, V.; Larock, R. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 1138.
(5) Mamane, V.; Hannen, P.; Fürstner, A. *Chem. Eur. J.* **2004**, *10*, 4556.
(6) Sun, H.; Wang, C.; Yang, Y.-F.; Chen, P.; Wu, Y. D.; Zhang, X.; Huang, Y. *J. Org. Chem.* **2014**, *79*, 11863.
(7) (a) de Koning, C. B.; Michael, J. P.; Pathak, R.; van Otterlo, W. A. L. *Tetrahedron Lett.* **2004**, *45*, 1117. (b) Lötter, A. N. C.; Pathak, R.; Sello, T. S.; Fernandes, M. A.; van Otterlo, W. A. L.; de Koning, C. B. *Tetrahedron* **2007**, *63*, 2263.
(8) (a) Dao, P. D. Q.; Lee, H. K.; Sohn, H.-S.; Yoon, N. S.; Cho, C. S. *ACS Omega* **2017**, *2*, 2953. (b) Ho, S. L.; Dao, P. D. Q.; Cho, C. S. *Synlett* **2017**, *28*, 1811.
(9) (a) For palladium-catalyzed synthesis of N-fused hybrid scaffolds, see: Yoo, J. M.; Ho, S. L.; Cho, C. S. *Synlett* **2016**, *27*, 1383. (b) Yang, B. W.; Ho, S. L.; Lim, H.-J.; Cho, C. S. *J. Organomet. Chem.* **2016**, *806*, 83.
(10) Yang, B. W.; Dao, P. D. Q.; Yoon, N. S.; Cho, C. S. *J. Organomet. Chem.* **2017**, *851*, 136.
(11) Ho, S. L.; Cho, C. S.; Sohn, H.-S. *Synthesis* **2015**, *47*, 216.
(12) Xie, X.; Cai, G.; Ma, D. *Org. Lett.* **2005**, *7*, 4693.
(13) (a) Fan, X.; He, Y.; Cui, L.; Guo, S.; Wang, J.; Zhang, X. *Eur. J. Org. Chem.* **2012**, 673. (b) Kavala, V.; Wang, C.-C.; Barange, D. K.; Kuo, C.-W.; Lei, P.-O.; Yao, C.-F. *J. Org. Chem.* **2012**, *77*, 5022.
(14) (a) Cai, S.; Wang, F.; Xi, C. *J. Org. Chem.* **2012**, *77*, 2331. (b) Yip, S. F.; Cheung, H. Y.; Zhou, Z.; Kwong, F. Y. *Org. Lett.* **2007**, *9*, 3469. (c) Wang, F.; Liu, H.; Fu, H.; Jiang, Y.; Zhao, Y. *Org. Lett.* **2009**, *11*, 2469. (d) Kálai, T.; Bognár, B.; Zsolnai, D.; Berente, Z.; Hideg, K. *Synthesis* **2012**, *44*, 3655. (e) Malakar, C. C.; Schmidt, D.; Conrad, J.; Beifuss, U. *Org. Lett.* **2011**, *13*, 1972.
(15) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Hidai, M.; Uemura, S. *J. Org. Chem.* **2004**, *69*, 3408.
(16) (a) Jiao, Y.; Cho, C. S. *Appl. Organomet. Chem.* **2015**, *29*, 372. (b) Ho, S. L.; Cho, C. S. *Synlett* **2013**, *24*, 2705.
(17) Utermoehlen, C. M.; Singh, M.; Lehr, R. E. *J. Org. Chem.* **1987**, *52*, 5574.
(18) Zeevaart, J. G.; Parkinsown, C. J.; de Koning, C. B. *Tetrahedron Lett.* **2004**, *45*, 4261.
(19) (a) Xie, R.; Ling, Y.; Fu, H. *Chem. Commun.* **2012**, *48*, 12210. (b) Bhunia, S. K.; Polley, A.; Natarajan, R.; Jana, R. *Chem. Eur. J.* **2015**, *21*, 16786.
(20) Xie, C.; Zhang, Y.; Huang, Z.; Xu, P. *J. Org. Chem.* **2007**, *72*, 5431.