JOC The Journal of Organic Chemistry

pubs.acs.org/joc Note

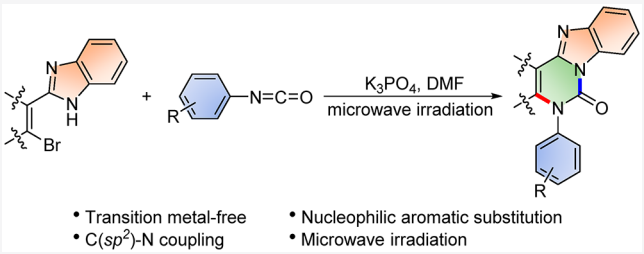
Construction of Binuclear Benzimidazole-Fused Quinazolinones and Pyrimidinones Using Aryl Isocyanates as Building Blocks by Transition-Metal-Free C(sp^2)−N Coupling

Pham Duy Quang Dao and Chan Sik Cho*

Cite This: https://dx.doi.org/10.1021/acs.joc.0c02067 Read Online

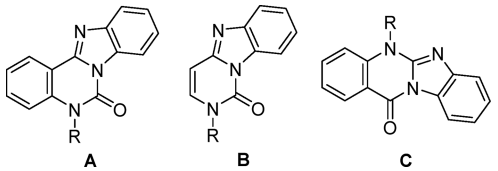
ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A class of binuclear N-fused hybrid scaffolds was constructed by the reaction of 2-(2-bromoaryl)- and 2-(2-bromovinyl)benzimidazoles with aryl isocyanates as building blocks in the presence of a base under microwave irradiation. A nucleophilic addition followed by an unprecedented transition-metal-free C(sp^2)−N coupling is proposed as a reaction pathway of this green process.



Many synthetic methods of polynuclear N-fused hybrid scaffolds have been achieved due to their intrinsic biological activities and optical properties that are not shown in each homonuclear scaffold.[1] In contrast to well-known synthetic methods and biological activities of each homonuclear scaffold (benzimidazole and quinazolinone) of scaffold **A**,[2,3] several synthetic examples are only found for N-fused hybrid scaffold **A** (Schemes 1 and 2).[4−8] Even though the

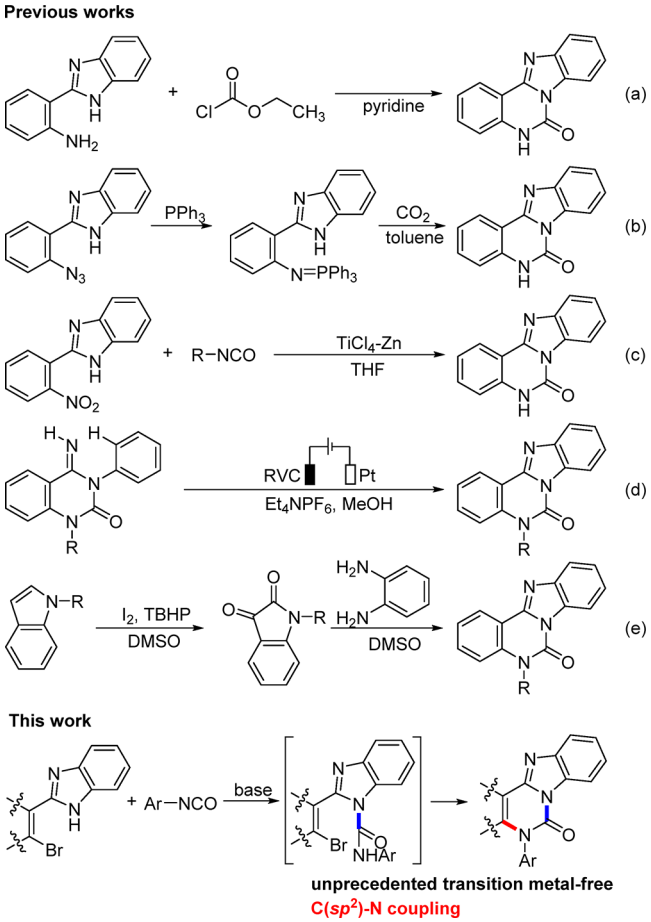
Scheme 1. Binuclear N-Fused Hybrid Scaffolds Containing Benzimidazole



biological activities of scaffold **A** were not explored yet, scaffold **C**, analogue of scaffold **A**, has been tested for their biological activities (Scheme 1).[9] Sharma et al. reported that 2-(2-aminophenyl)benzimidazole reacts with ethyl chloroformate in pyridine to give binuclear N-fused hybrid scaffold **A** via double nucleophilic acyl substitution (Scheme 2a).[4] Molina and coworkers also demonstrated that iminophosphoranes derived from 2-(2-azidophenyl)benzimidazole and triphenylphosphine with carbon dioxide trigger aza-Wittig reaction to produce scaffold **A** (Scheme 2b).[5] It is reported that 2-(2-nitrophenyl)-benzimidazoles are found to be reductively cyclized with aryl isocyanates in the presence of $TiCl_4$/Zn to give scaffold **A** irrespective of aryl isocyanates (Scheme 2c).[6] Such a scaffold **A** also can be constructed by the electrochemical C−H/N−H cross-coupling of 4-imino-3-phenyl-3,4-dihydroquinazolin-2(1*H*)-ones via an amidinyl radical (Scheme 2d).[7] Ma et al. recently have shown that scaffolds **A** can be accessed by subsequent treatment of I_2/TBHP and *o*-benzenediamines starting from indoles (Scheme 2e).[8] Despite advancing synthetic methods for scaffold **A**, these precedents still have some drawbacks such as multistep process, limitation of scope, and expensive reagents or catalysts. In connection with this report, it is known that a C(sp^2)−N bond forming reaction is of great importance in developing new, mild, and cheap synthetic methodologies.[1] Thus, many traditional transition-metal-catalyzed versions as well as recent transition-metal-free versions have been developed for such a C(sp^2)−N coupling.[10,11] As part of our ongoing studies on copper-catalyzed and transition-metal-free synthesis of polynuclear N-fused hybrid scaffolds via a C(sp^2)−N coupling, we recently reported that 2-(2-bromoaryl)- and 2-(2-bromovinyl)-benzimidazoles reacted with 2-aminoazoles in the presence of a base to form trinuclear N-fused hybrid scaffolds via a transition-metal-free double C(sp^2)−N coupling involving nucleophilic aromatic substitution (S_NAr).[12−14] The present work started during the course of the extension of such a transition-metal-free C(sp^2)−N coupling to synthesize polynuclear N-fused hybrid scaffolds. This work shows the construction of benzimidazole-fused quinazolinones, 5-arylbenzo[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-ones (Scheme 1, **A**) from 2-(2-bromoaryl)benzimidazoles and aryl isocya-

Received: August 27, 2020

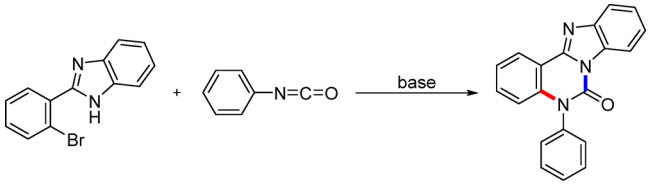
Scheme 2. Synthetic Routes for Scaffold A



nates as building blocks via such a transition-metal-free C(sp^2)−N coupling as a key step (Scheme 2). To the best of our knowledge, this is the first example for transition-metal-free coupling of C(sp^2) and N of a urea.[15] This protocol can also be extended to the reaction of 2-(2-bromovinyl)-benzimidazoles with aryl isocyanates to form binuclear N-fused hybrid scaffolds **B** (Scheme 1).

Treatment of 2-(2-bromophenyl)-1*H*-benzo[*d*]imidazole (**1a**) with equimolar amount of phenyl isocyanate (**2a**) in DMF in the presence of K_3PO_4 (2 equiv) at 130 °C for 1 h under microwave irradiation (100 W of initial power) afforded binuclear N-fused hybrid scaffold, 5-phenylbenzo[4,5]imidazo-[1,2-*c*]quinazolin-6(5*H*)-one (**3a**) in 37% isolated yield with 68% conversion of **1a** (Table 1, entry 1). The yield of **3a** increased with the increase in the molar ratio of **2a** to **1a** up to 2 equiv with complete conversion of **1a** (Table 1, entries 2 and 3). No significant change of the yield of **3a** was observed with prolonging the reaction time or higher reaction temperature (Table 1, entries 4 and 5). However, lower reaction temperature resulted in lower yield of **3a** with incomplete conversion of **1a** (Table 1, entry 6). Performing the reaction under the increased amount of K_3PO_4 (3 equiv to **1a**) also resulted in no significant change of the yield of **3a** (Table 1, entry 7).[13a] The reaction also proceeded in the presence of other bases such as K_2CO_3, KO^{t}Bu, and Cs_2CO_3 under the employed conditions, but the yields of **3a** were generally lower than that obtained with K_3PO_4 except for KO^{t}Bu, which showed a similar activity as K_3PO_4 with complete conversion of **1a** (Table 1, entries 8−10). However, other bases such as

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



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

entry	[**2a**]/[**1a**]	base	solvent	temp (°C)	time (h)	conv. of **1a** (%)	yield (%)
1	1.0	K_3PO_4	DMF	130	1	68	37
2	1.5	K_3PO_4	DMF	130	1	81	53
3	2.0	K_3PO_4	DMF	130	1	100	71
4	2.0	K_3PO_4	DMF	130	2	100	69
5	2.0	K_3PO_4	DMF	150	1	100	70
6	2.0	K_3PO_4	DMF	110	1	86	49
7[b]	2.0	K_3PO_4	DMF	130	1	100	70
8	2.0	K_2CO_3	DMF	130	1	71	42
9	2.0	KO^{t}Bu	DMF	130	1	100	70
10	2.0	Cs_2CO_3	DMF	130	1	31	12
11	2.0	KOH	DMF	130	1	29	0
12	2.0	CsF	DMF	130	1	0	0
13	2.0	K_3PO_4	DMSO	130	1	41	trace
14	2.0	K_3PO_4	xylene	130	1	66	27
15[c]	2.0	K_3PO_4	DMF	130	24	84	42

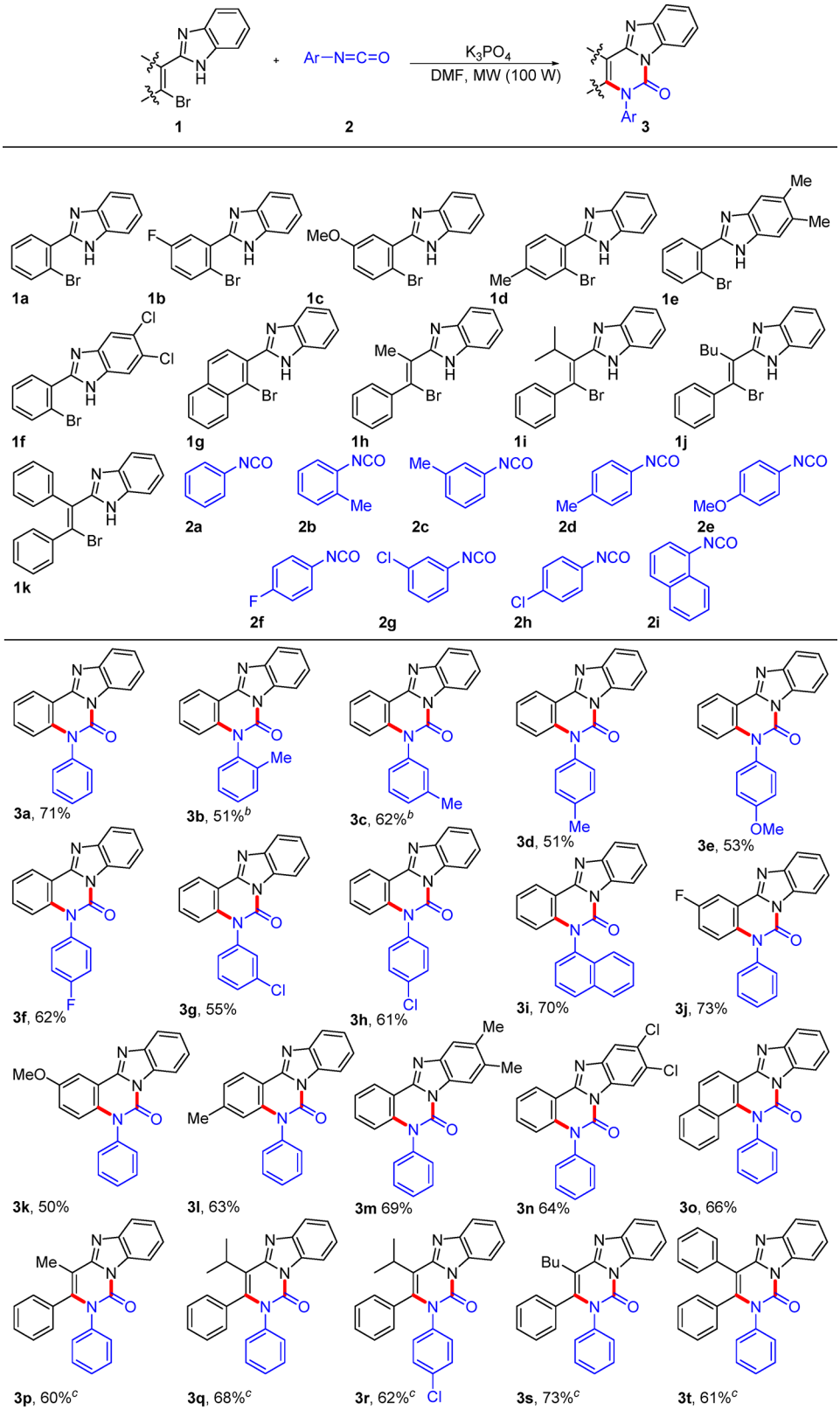
[a]Reaction conditions: **1a** (0.3 mmol), base (0.6 mmol), DMF (3 mL), under microwave irradiation (100 W of initial power). [b]K_3PO_4(0.9 mmol). [c]Usual heating (screw-capped vial, 130 °C, 24 h).

KOH and CsF were not effective at all for the formation of **3a** (Table 1, entries 11 and 12). Among solvents examined under the employed conditions, DMF was shown to be the solvent of choice in terms of the yield of **3a** and complete conversion of **1a** (Table 1, entries 3, 13, and 14). On the other hand, performing the reaction under usual heating conditions produced **3a** in only 42% yield with incomplete conversion of **1a** (Table 1, entry 15). The best result in terms of both product yield and complete conversion of **1a** was obtained using the reaction conditions shown in entry 3 of Table 1. Not shown in Table 1, similar treatment of triflate analogue of **1a**, 2-(1*H*-benzo[*d*]imidazol-2-yl)phenyl trifluoromethanesulfonate with **2a** under the conditions of entry 3 of Table 1 also afforded **3a** in 72% yield with complete conversion of **1a**.

After obtaining the optimized conditions, the reaction scope was investigated by subjecting many 2-(2-bromoaryl)- and 2-(2-bromovinyl)benzimidazoles **1** with aryl isocyanates **2**, and the representative results are shown in Table 2.[16] 2-(2-Bromophenyl)benzimidazole **1a** was successfully coupled and cyclized with various aryl isocyanates **2a−h** which have electron-donating and -withdrawing substituents to yield the corresponding benzimidazole-fused quinazolinones **3a−h** in moderate to good yields. With **2b** and **2c**, higher molar ratio of **2** to **1a** and prolonging reaction time were needed for the allowable formation of such scaffolds (**3b** and **3c**). Scaffolds **3b** and **3c** were formed in 21 and 34% yields, respectively, under [**2**]/[**1a**] = 2.0. 2-(2-Bromophenyl)benzimidazole **1a** also reacted with 1-naphthyl isocyanate (**2i**) to give the corresponding N-fused hybrid scaffold **3i** in similar yield. From the reaction of several 2-(2-bromoaryl)benzimidazoles **1b−f** having electron-donating and -withdrawing substituents on the bromoaryl or benzimidazole moiety with **2a**, the

https://dx.doi.org/10.1021/acs.joc.0c02067
J. Org. Chem. XXXX, XXX, XXX−XXX

Table 2. Scope of Reaction[a]



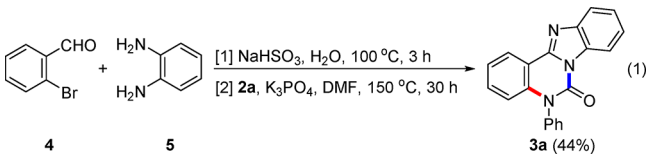
[a]Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol), K_3PO_4 (0.6 mmol), DMF (3 mL), under microwave irradiation (100 W of initial power), 130 °C, 1 h. [b][**2**]/[**1**] = 3, 2 h. [c][**2**]/[**1**] = 3, 150 °C, 2 h.

corresponding binuclear N-fused hybrid scaffolds **3j−n** were also formed in 50−73% yields. Benzo-fused 2-(2-bromophenyl)benzimidazole **1g** was also readily coupled and cyclized with **2a** to give the corresponding scaffold **3o** in 66% yield. Similar treatment of 2-(2-bromovinyl)benzimidazoles **1h−k** having alkyl and phenyl substituents on the vinyl moiety

https://dx.doi.org/10.1021/acs.joc.0c02067
J. Org. Chem. XXXX, XXX, XXX−XXX

with aryl isocyanates **2** under modified reaction conditions (molar ratio [**2**]/[**1**] = 3.0, 150 °C, 2 h) invariably afforded the corresponding benzimidazole-fused pyrimidinones **3p−t** irrespective of the identity of such substituents. Scaffolds **3p−t** were formed in 25−36% yields under [**2**]/[**1**] = 2.0.

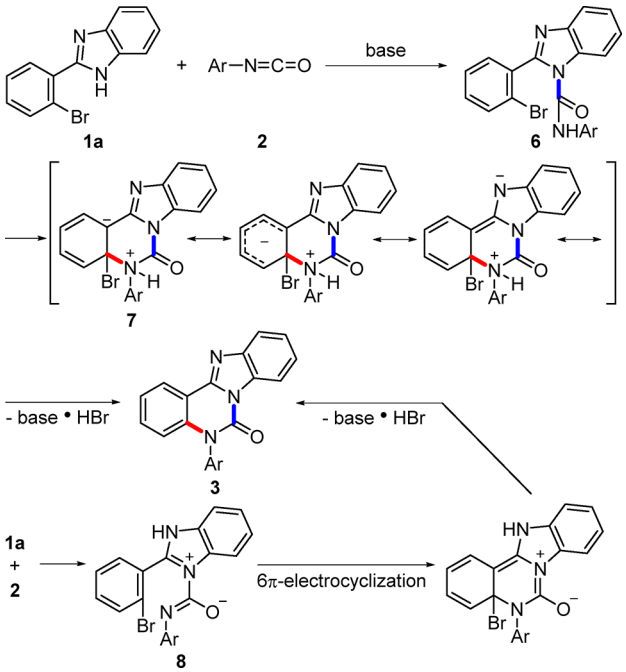
On the other hand, a one-pot step by step gram scale procedure starting from 2-bromobenzaldehyde (**4**) and benzene-1,2-diamine (**5**) renders the synthesis of **3a** practical. Initial treatment of **4** with equimolar amount of **5** in the presence of $NaHSO_3$ in H_2O at 100 °C followed by removal of H_2O and inorganic components by decantation afforded a yellow solid.[16] Further addition of **2a**, K_3PO_4 and DMF to the flask containing a yellow solid and stirring at 150 °C for 30 h gave **3a** in 44% yield (eq 1).

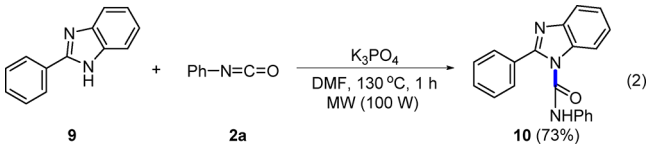


4 **5** **3a** (44%) (1)

Based on additional experiments to delineate the mechanism and literature, the reaction pathway seems to proceed via an initial formation of a urea **6** by nucleophilic addition of the N−H of **1a** to isocyanate **2** (Scheme 3).[17] Subsequent intramolecular nucleophilic attack of the carbamoyl NH to the carbon attached to Br in **6** forms a resonance-stabilized carbanion, Meisenheimer complex **7**.[18] This is followed by the loss of the leaving group to complete an addition−elimination nucleophilic aromatic substitution for the production of **3**. The *ortho*-substituted benzimidazole ring in **6** lowers the energy of the transition state that forms such a Meisenheimer complex **7** by further electron delocalization.[18,19] The following additional experimental observations are worth noting as evidence for the formation of such a nucleophilic addition intermediate **6**. Treatment of 2-phenyl-1*H*-benzo[*d*]imidazole (**9**) with **2a** under the employed conditions gave a nucleophilic addition product **10** in 73% yield (eq 2). Fortunately, we also confirmed

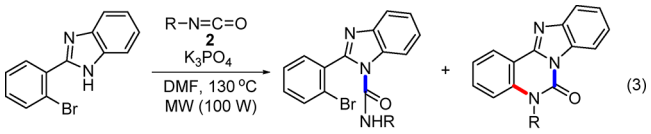
Scheme 3. Reaction Pathway





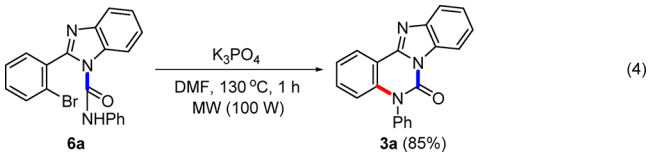
9 **2a** **10** (73%) (2)

that a similar treatment of **1a** with **2a** for a shorter reaction time (30 min) under the employed conditions afforded the nucleophilic addition intermediate **6a** and the cyclized product **3a** in 28 and 37% yields, respectively, with 81% conversion of **1a** (eq 3). The intermediate **6a** thus isolated was readily



1a **2a** R = Ph, **2j** R = cyclohexyl **6a** R = Ph (28%), **6b** R = cyclohexyl (63%) **3a** R = Ph (37%), **3u** R = cyclohexyl (0%) (3)

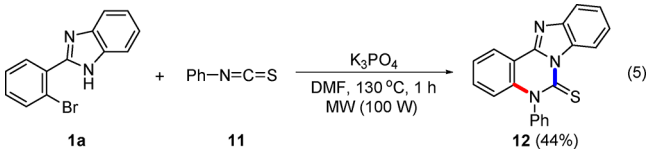
cyclized under the optimized conditions to give the desired product **3a** in 85% yield (eq 4). This results clearly support the



6a **3a** (85%) (4)

formation of intermediate **6** during the course of the reaction. Furthermore, although not yet elucidated, in contrast to the reaction with aryl isocyanate, performing the reaction of **1a** with cyclohexyl isocyanate (**2j**) under the employed conditions only afforded the nucleophilic addition intermediate **6b** in 63% yield without the formation of the expected cyclized product **3u** (eq 3). A reviewer also suggested that product **3** would be formed by an alternative mechanism through 6π-electrocyclization of an intermediate **8** derived from **1a** and **2** (Scheme 3).[20]

Finally, the substrate scope of the present reaction was expanded with several readily available compounds. Treatment of **1a** with phenyl isothiocyanate (**11**) under the employed conditions afforded the corresponding N-fused hybrid scaffold **12** in 44% yield along with several unidentifiable side products (eq 5). Performing the reaction of 2-(2-bromophenyl)indole

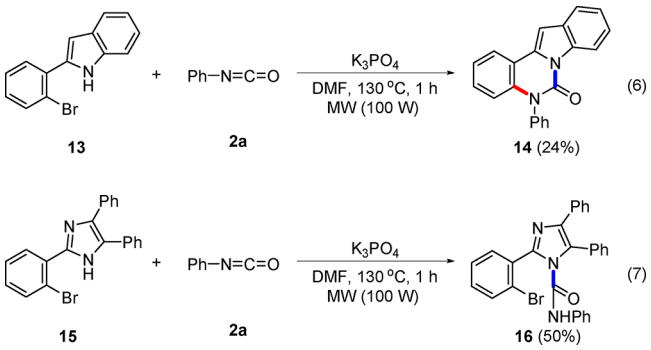


1a **11** **12** (44%) (5)

13 with **2a** under the employed conditions afforded the coupling and cyclized product **14** in only 24% yield with 46% conversion of **13** (eq 6). However, similar reaction of 2-(2-bromophenyl)imidazole **15** with **2a** resulted in the formation of nucleophilic addition product **16** in 50% yield with 68% conversion of **15** (eq 7).

In summary, we developed a transition-metal-free construction of binuclear N-fused hybrid scaffolds by the treatment of 2-(2-bromoaryl)- and 2-(2-bromovinyl)-benzimidazoles with aryl isocyanates as building blocks in

https://dx.doi.org/10.1021/acs.joc.0c02067
J. Org. Chem. XXXX, XXX, XXX−XXX



the presence of a base under microwave irradiation. This process involves an unprecedented example of transition-metal-free C(sp^2)−N coupling as a key step. Further challenges on the green construction of polynuclear N-fused hybrid scaffolds using this protocol are under way.

EXPERIMENTAL SECTION

General Information. ^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded in $CDCl_3$ or DMSO-d_6. High-resolution mass data were obtained using electronic ionization (HRMS, magnetic sector-electric sector double focusing mass analyzer) at the Korea Basic Science Center (Daegu). Melting points were measured on a microscopic melting point apparatus (Stanford Research Inc. MPA100 automated melting point apparatus). All reactions were carried out in a sealed tube under microwave irradiation (CEM, Discover LabMate), and the reaction temperature was maintained by an external infrared sensor. The products were isolated by TLC (a glass plate coated with Kieselgel 60 GF_{254}, Merck). The starting compounds **1** and **9** were prepared by a known method from the corresponding aldehydes and *o*-phenylenediamine.[12d,14,16] 2-(2-Bromophenyl)indole **13** and 2-(2-bromophenyl)imidazole **15** were synthesized by reported methods, respectively.[21,22] Other commercially available organic and inorganic reagents were used without further purification.

General Procedure for the Synthesis of 3, 12, 14, and 16. To a 10 mL microwave reaction tube, **1** (0.3 mmol), **2** (0.6 mmol for **3a** and **3d**−**o**; 0.9 mmol for **3b**, **3c**, and **3p**−**t**), K_3PO_4 (0.128 g, 0.6 mmol), and DMF (3 mL) were added. After stirring the reaction mixture at room temperature for 5 min, it was heated at 130−150 °C for 1−2 h under microwave irradiation (100 W of initial power). The reaction mixture was cooled to room temperature and filtered through a short silica gel column to eliminate inorganic salts using ethyl acetate. Removal of the eluent under reduced pressure left a crude mixture, which was purified by TLC to give **3**. All new products were characterized spectroscopically, as shown below. The reactions for the synthesis of **12**, **14**, and **16** were similarly carried out with experimental procedure for the synthesis of **3**.

5-Phenylbenzo[4,5]imidazo[1,2-c]quinazolin-6(5H)-one (***3a***). **3a** was purified by TLC (dichloromethane/MeOH = 200/1, 2 times) as a white solid (0.066 g, 71%); mp 263−265 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (dd, J = 7.8 and 1.5 Hz, 1H), 8.43 (d, J = 8.0 Hz, 1H), 7.94 (d, J = 8.1 Hz, 1H), 7.69−7.66 (m, 2H), 7.63−7.60 (m, 1H), 7.54−7.50 (m, 1H), 7.46−7.43 (m, 4H), 7.40−7.37 (m, 1H), 6.71 (d, J = 8.4 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 147.0, 146.8, 144.0, 139.3, 136.2, 131.9, 131.3, 130.5, 129.7, 129.3, 125.7, 125.4, 124.5, 124.0, 119.5, 116.4, 115.5, 113.1. HRMS (EI) m/z: [M]$^+$ Calcd for $C_{20}H_{13}N_3O$ 311.1059; Found 311.1057.

5-(o-Tolyl)benzo[4,5]imidazo[1,2-c]quinazolin-6(5H)-one (***3b***). **3b** was purified by TLC (dichloromethane/MeOH = 200/1, 2 times) as a white solid (0.050 g, 51%); mp 230−233 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (dd, J = 7.8 and 1.4 Hz, 1H), 8.45 (d, J = 8.1 Hz, 1H), 7.95 (d, J = 8.1 Hz, 1H), 7.55−7.44 (m, 6H), 7.41−7.38 (m, 1H), 7.33 (d, J = 7.5 Hz, 1H), 6.62 (d, J = 8.2 Hz, 1H), 2.15 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 147.1, 146.3, 144.0, 138.6, 137.0, 134.9, 132.2, 132.0, 131.3, 130.0, 129.2, 128.1, 125.7, 125.5, 124.4, 124.1, 119.5, 115.8, 115.5, 113.1, 17.4. HRMS (EI) m/z: [M]$^+$ Calcd for $C_{21}H_{15}N_3O$ 325.1215; Found 325.1217.

5-(m-Tolyl)benzo[4,5]imidazo[1,2-c]quinazolin-6(5H)-one (***3c***). **3c** was purified by TLC (dichloromethane/MeOH = 200/1, 2 times) as a pale yellow solid (0.061 g, 62%); mp 218−221 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (dd, J = 7.8 and 1.5 Hz, 1H), 8.44 (d, J = 8.0 Hz, 1H), 7.94 (d, J = 8.1 Hz, 1H), 7.56−7.50 (m, 2H), 7.47−7.36 (m, 4H), 7.25−7.23 (m, 2H), 6.73 (d, J = 8.2 Hz, 1H), 2.48 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 147.0, 146.9, 144.0, 140.8, 139.3, 136.0, 131.9, 131.3, 130.5, 130.3, 129.7, 126.1, 125.6, 125.4, 124.0, 119.5, 116.5, 115.5, 113.0, 21.4. HRMS (EI) m/z: [M]$^+$ Calcd for $C_{21}H_{15}N_3O$ 325.1215; Found 325.1212.

5-(p-Tolyl)benzo[4,5]imidazo[1,2-c]quinazolin-6(5H)-one (***3d***). **3d** was purified by TLC (dichloromethane/MeOH = 200/1, 2 times) as a white solid (0.050 g, 51%); mp 263−266 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (dd, J = 7.8 and 1.4 Hz, 1H), 8.43 (d, J = 8.1 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.53−7.49 (m, 1H), 7.46−7.41 (m, 4H), 7.38−7.35 (m, 1H), 7.32 (d, J = 8.2 Hz, 2H), 6.74 (d, J = 8.4 Hz, 1H), 2.50 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 147.0, 146.9, 143.9, 139.8, 139.4, 131.9, 131.3, 131.1, 128.9, 125.6, 125.3, 124.4, 123.9, 116.4, 115.5, 113.0, 21.4. HRMS (EI) m/z: [M]$^+$ Calcd for $C_{21}H_{15}N_3O$ 325.1215; Found 325.1213.

5-(4-Methoxyphenyl)benzo[4,5]imidazo[1,2-c]quinazolin-6(5H)-one (***3e***). **3e** was purified by TLC (dichloromethane/MeOH = 200/1, 2 times) as a pale yellow solid (0.054 g, 53%); mp 271−273 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60−8.58 (m, 1H), 8.45−8.43 (m, 1H), 7.95−7.93 (m, 1H), 7.54−7.50 (m, 1H), 7.48−7.43 (m, 2H), 7.40−7.33 (m, 3H), 7.17−7.14 (m, 2H), 6.77 (d, J = 8.4 Hz, 1H), 3.92 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 160.3, 147.1, 147.0, 144.0, 139.6, 131.9, 131.3, 130.2, 128.6, 125.6, 125.4, 124.4, 124.0, 119.5, 116.5, 115.7, 115.5, 113.1, 55.7. HRMS (EI) m/z: [M]$^+$ Calcd for $C_{21}H_{15}N_3O_2$ 341.1164; Found 341.1166.

5-(4-Fluorophenyl)benzo[4,5]imidazo[1,2-c]quinazolin-6(5H)-one (***3f***). **3f** was purified by TLC (dichloromethane/MeOH = 200/1, 2 times) as a pale yellow solid (0.062 g, 62%); mp 266−269 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (d, J = 7.7 Hz, 1H), 8.41 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.54−7.51 (m, 1H), 7.48−7.39 (m, 5H), 7.37−7.34 (m, 2H), 6.71 (d, J = 8.4 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.0 (d, $^1J_{C-F}$ = 248.9 Hz), 146.9 (d, $^4J_{C-F}$ = 1.8 Hz), 144.0, 139.2, 132.0 (132.00), 132.0 (131.99), 131.2 (d, $^3J_{C-F}$ = 9 Hz), 125.7, 125.5, 124.2, 119.6, 117.6 (d, $^2J_{C-F}$ = 23.2 Hz) 116.2, 115.4, 113.2. HRMS (EI) m/z: [M]$^+$ Calcd for $C_{20}H_{12}FN_3O$ 329.0964; Found 329.0965.

5-(3-Chlorophenyl)benzo[4,5]imidazo[1,2-c]quinazolin-6(5H)-one (***3g***). **3g** was purified by TLC (dichloromethane/MeOH = 200/1) as a white solid (0.057 g, 55%); mp 260−263 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (dd, J = 7.8 and 1.1 Hz, 1H), 8.41 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.63−7.61 (m, 2H), 7.54−7.51 (m, 1H), 7.49−7.44 (m, 3H), 7.41−7.36 (m, 2H), 6.70 (d, J = 8.4 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 146.8, 146.6, 143.9, 138.8, 137.2, 136.1, 132.0, 131.4, 131.2, 130.1, 129.8, 127.7, 125.8, 125.6, 124.6, 124.3, 119.6, 116.1, 115.4, 113.1. HRMS (EI) m/z: [M]$^+$ Calcd for $C_{20}H_{12}ClN_3O$ 345.0669; Found 345.0668.

5-(4-Chlorophenyl)benzo[4,5]imidazo[1,2-c]quinazolin-6(5H)-one (***3h***). **3h** was purified by TLC (dichloromethane/MeOH = 200/1) as a white solid (0.063 g, 61%); mp 243−246 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60−8.58 (m, 1H), 8.40 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.65−7.63 (m, 2H), 7.54−7.51 (m, 1H), 7.46−7.44 (m, 2H), 7.41−7.38 (m, 3H), 6.71 (d, J = 8.3 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 146.8, 146.6, 143.9, 138.9, 135.8, 134.6, 132.0, 131.2, 130.8, 130.7, 125.8, 125.5, 124.6, 124.3, 119.6, 116.1, 115.4, 113.1. HRMS (EI) m/z: [M]$^+$ Calcd for $C_{20}H_{12}ClN_3O$ 345.0669; Found 345.0669.

5-(Naphthalen-1-yl)benzo[4,5]imidazo[1,2-c]quinazolin-6(5H)-one (***3i***). **3i** was purified by TLC (dichloromethane/MeOH = 200/1) as a white solid (0.076 g, 70%); mp 267−269 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66−8.65 (m, 1H), 8.43 (d, J = 8.0 Hz, 1H), 8.12 (d, J = 8.3 Hz, 1H), 8.04 (d, J = 8.3 Hz, 1H), 7.98 (d, J = 8.1 Hz, 1H), 7.74−7.71 (m, 1H), 7.64 (dd, J = 7.2 and 1.1 Hz, 1H), 7.59−7.52 (m, 3H), 7.47−7.43 (m, 2H), 7.40−7.34 (m, 2H), 6.53−6.51 (m, 1H).

https://dx.doi.org/10.1021/acs.joc.0c02067
J. Org. Chem. XXXX, XXX, XXX−XXX

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 147.1, 146.8, 144.0, 139.3, 135.0, 132.5, 132.1, 131.4, 130.4, 130.3, 128.9, 127.9, 127.7, 127.1, 126.1, 125.7, 125.5, 124.5, 124.2, 131.9, 119.6, 116.6, 115.6, 113.1. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{24}H_{15}N_3O$ 361.1215; Found 361.1213.

*2-Fluoro-5-phenylbenzo[4,5]imidazo[1,2-c]quinazolin-6(5H)-one (**3j**).* **3j** was purified by TLC (dichloromethane/MeOH = 200/1) as a white solid (0.072 g, 73%); mp 331−333 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.44 (d, J = 8.1 Hz, 1H), 8.27 (dd, J = 8.2 and 3.0 Hz, 1H), 7.95 (d, J = 8.1 Hz, 1H), 7.69−7.66 (m, 2H), 7.63−7.60 (m, 1H), 7.57−7.52 (m, 1H), 7.49−7.43 (m, 3H), 7.18−7.14 (m, 1H), 6.69 (dd, J = 9.3 and 4.3 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 159.0 (d, $^1J_{C-F}$ = 244.0 Hz), 146.5, 146.0 (d, $^4J_{C-F}$ = 3.4 Hz), 143.9, 136.1, 135.7, 131.3, 130.6, 129.9, 129.2, 125.9, 124.9, 119.7, 119.5 (d, $^2J_{C-F}$ = 24.1 Hz), 118.3 (d, $^3J_{C-F}$ = 8.1 Hz), 115.5, 114.3 (d, $^3J_{C-F}$ = 8.9 Hz), 111.1 (d, $^2J_{C-F}$ = 25.1 Hz). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{20}H_{12}FN_3O$ 329.0964; Found 329.0963.

*2-Methoxy-5-phenylbenzo[4,5]imidazo[1,2-c]quinazolin-6(5H)-one (**3k**).* **3k** was purified by TLC (dichloromethane/MeOH = 200/1, 2 times) as a pale yellow solid (0.051 g, 50%); mp 337−339 °C. ^1H NMR (500 MHz, DMSO-d_6) δ 8.32 (d, J = 7.9 Hz, 1H), 7.92−7.90 (m, 1H), 7.70−7.67 (m, 2H), 7.64−7.61 (m, 1H), 7.58−7.56 (m, 2H), 7.54−7.51 (m, 1H), 7.48−7.45 (m, 1H), 7.19 (dd, J = 9.2 and 3.0 Hz, 1H), 6.52 (d, J = 9.2 Hz, 1H), 3.90 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 156.3, 147.0, 146.6, 143.9, 136.3, 133.5, 131.4, 130.5, 129.6, 129.3, 125.7, 124.5, 121.2, 119.4, 118.0, 115.6, 113.7, 106.4, 56.1. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{21}H_{15}N_3O_2$ 341.1164; Found 341.1167.

*3-Methyl-5-phenylbenzo[4,5]imidazo[1,2-c]quinazolin-6(5H)-one (**3l**).* **3l** was purified by TLC (dichloromethane/MeOH = 200/1, 2 times) as a white solid (0.062 g, 63%); mp 310−312 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.47 (d, J = 8.1 Hz, 1H), 8.42 (d, J = 8.1 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.70−7.66 (m, 2H), 7.64−7.61 (m, 1H), 7.53−7.49 (m, 1H), 7.45−7.41 (m, 3H), 7.21 (dd, J = 8.1 and 0.7 Hz, 1H), 6.48 (s, 1H), 2.34 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 147.2, 147.0, 144.0, 143.0, 139.3, 136.2, 131.3, 130.5, 129.6, 129.3, 125.6, 125.4, 125.3, 124.2, 119.3, 116.5, 115.4, 110.7, 22.1. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{21}H_{15}N_3O$ 325.1215; Found 325.1217.

*9,10-Dimethyl-5-phenylbenzo[4,5]imidazo[1,2-c]quinazolin-6(5H)-one (**3m**).* **3m** was purified by TLC (dichloromethane/MeOH = 200/1) as a white solid (0.070 g, 69%); mp 277−279 °C. ^1H NMR (500 MHz, DMSO-d_6) δ 8.67 (s, 1H), 7.80 (dd, J = 8.0 and 1.1 Hz, 1H), 7.74 (dd, J = 7.7 and 1.7 Hz, 1H), 7.55−7.52 (m, 1H), 7.47−7.42 (m, 4H), 7.30−7.26 (m, 2H), 6.98−6.95 (m, 1H), 2.34 (s, 3H), 2.32 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 142.1, 140.8, 140.7, 133.8, 133.0, 132.3, 130.4, 130.3, 129.4, 129.1, 128.9, 128.4, 128.2, 128.1, 127.6, 125.6, 125.1, 121.1, 114.8, 113.4, 21.0, 20.2. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{22}H_{17}N_3O$ 339.1372; Found 339.1374.

*9,10-Dichloro-5-phenylbenzo[4,5]imidazo[1,2-c]quinazolin-6(5H)-one (**3n**).* **3n** was purified by TLC (dichloromethane/MeOH = 200/1) as a white solid (0.073 g, 64%); mp 249−252 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.26 (dd, J = 7.9 and 1.7 Hz, 1H), 7.89 (s, 1H), 7.70 (dd, J = 8.1 and 1.1 Hz, 1H), 7.62 (s, 1H), 7.50−7.47 (m, 1H), 7.37−7.30 (m, 3H), 7.21−7.17 (m, 1H), 7.10−7.08 (m, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 151.7, 142.5, 134.1, 133.5, 132.9, 132.8, 131.7, 129.8, 129.6, 128.2, 127.6, 127.0, 125.7, 124.7, 121.6, 121.1, 120.3, 112.4. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{20}H_{11}Cl_2N_3O$ 379.0279; Found 379.0283.

*7-Phenylbenzo[h]benzo[4,5]imidazo[1,2-c]quinazolin-8(7H)-one (**3o**).* **3o** was purified by TLC (dichloromethane/MeOH = 200/1) as a white solid (0.072 g, 66%); mp 258−261 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.63 (d, J = 8.6 Hz, 1H), 8.46 (d, J = 8.1 Hz, 1H), 7.96 (d, J = 8.1 Hz, 1H), 7.90−7.88 (m, 2H), 7.56−7.43 (m, 8H), 7.30−7.27 (m, 1H), 7.12−7.09 (m, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 147.6, 146.0, 136.7, 135.4, 129.7, 129.2, 128.9, 128.7, 127.3, 126.8, 125.9, 125.4, 124.5, 121.9, 121.2, 119.5, 115.6. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{24}H_{15}N_3O$ 361.1215; Found 361.1213.

*4-Methyl-2,3-diphenylbenzo[4,5]imidazo[1,2-c]pyrimidin-1(2H)-one (**3p**).* **3p** was purified by TLC (dichloromethane/MeOH = 200/1, 2 times) as a white solid (0.063 g, 60%); mp 211−214 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.89−8.87 (m, 1H), 8.04−8.00 (m, 1H), 7.88 (d, J = 8.1 Hz, 1H), 7.74−7.68 (m, 3H), 7.61−7.53 (m, 4H), 7.37−7.32 (m, 2H), 6.96−6.93 (m, 1H), 5.94 (d, J = 8.4 Hz, 1H), 2.41 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 147.1, 144.2, 142.4, 137.6, 131.8, 130.5, 129.7 (129.72), 129.7 (129.66), 129.4, 125.5, 124.2, 124.0, 121.9, 121.3, 119.7, 119.4, 115.0, 112.9, 12.8. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{23}H_{17}N_3O$ 351.1372; Found 351.1375.

*4-Isopropyl-2,3-diphenylbenzo[4,5]imidazo[1,2-c]pyrimidin-1(2H)-one (**3q**).* **3q** was purified by TLC (dichloromethane/MeOH = 200/1, 2 times) as a white solid (0.077 g, 68%); mp 219−223 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.91−8.88 (m, 1H), 8.04−8.00 (m, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.73−7.67 (m, 3H), 7.59−7.52 (m, 5*H*), 7.32−7.29 (m, 1H), 6.91−6.88 (m, 1H), 5.71 (d, J = 8.4 Hz, 1H), 3.09 (sept, J = 7.1 Hz, 2H), 1.55 (d, J = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 145.3, 144.2, 142.5, 136.5, 132.3, 130.4, 129.7 (129.68), 129.7 (129.66), 129.2, 125.3, 124.1, 123.8, 121.7, 119.7, 119.3, 118.7, 114.9, 112.8, 29.3, 21.1. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{25}H_{21}N_3O$ 379.1685; Found 379.1686.

*2-(4-Chlorophenyl)-4-isopropyl-3-phenylbenzo[4,5]imidazo[1,2-c]pyrimidin-1(2H)-one (**3r**).* **3r** was purified by TLC (dichloromethane/MeOH = 200/1, 2 times) as a pale yellow solid (0.061 g, 62%); mp 206−209 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, J = 8.1 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.52−7.48 (m, 1H), 7.41−7.38 (m, 1H), 7.25−7.17 (m, 5*H*), 7.11−7.08 (m, 4H), 2.80 (sept, J = 7.1 Hz, 2H), 1.48 (d, J = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 147.7, 144.5, 142.5, 137.7, 133.4, 130.2, 129.9, 129.8, 128.9, 128.6, 128.3, 128.1, 125.5, 123.5, 119.3, 115.8, 115.5, 29.9, 21.1. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{25}H_{20}ClN_3O$ 413.1295; Found 413.1293.

*4-Butyl-2,3-diphenylbenzo[4,5]imidazo[1,2-c]pyrimidin-1(2H)-one (**3s**).* **3s** was purified by TLC (dichloromethane/MeOH = 200/1, 2 times) as a white solid (0.094 g, 73%); mp 227−230 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.89−8.86 (m, 1H), 8.04−8.01 (m, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.74−7.66 (m, 3H), 7.59−7.54 (m, 5*H*), 7.33−7.29 (m, 1H), 6.92−6.89 (m, 1H), 5.84 (d, J = 8.4 Hz, 1H), 2.80−2.77 (m, 2H), 1.76−1.70 (m, 2H), 1.37−1.30 (m, 2H), 0.81 (t, J = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 146.6, 144.3, 142.4, 142.2, 137.4, 130.5, 129.9, 129.5, 125.4, 124.1, 123.8, 121.8, 119.7, 119.4, 115.0, 114.3, 112.9, 31.8, 26.9, 22.7, 13.8. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{26}H_{23}N_3O$ 393.1841; Found 393.1842.

*2,3,4-Triphenylbenzo[4,5]imidazo[1,2-c]pyrimidin-1(2H)-one (**3t**).* **3t** was purified by TLC (dichloromethane/MeOH = 200/1, 2 times) as a white solid (0.082 g, 61%); mp 318−320 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.93−8.91 (m, 1H), 7.99−7.97 (m, 1H), 7.92−7.90 (m, 1H), 7.61−7.27 (m, 14H), 6.96−6.93 (m, 1H), 5.94−5.96 (m, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 146.6, 144.5, 142.6, 142.4, 138.5, 132.1, 130.4, 130.1, 129.8, 129.0, 128.2, 128.1, 125.4, 124.4, 124.1, 122.0, 120.2, 119.5, 115.5, 114.9, 113.3. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{28}H_{19}N_3O$ 413.1528; Found 413.1530.

*2-(2-Bromophenyl)-N-cyclohexyl-1H-benzo[d]imidazole-1-carboxamide (**6b**).* **6b** was purified by TLC (dichloromethane/MeOH = 99/1) as a pale yellow solid (0.077 g, 64%); mp 248−250 °C. ^1H NMR (500 MHz, DMSO-d_6) δ 12.72 (s, 1H), 9.26 (d, J = 7.7 Hz, 1H), 7.91 (dd, J = 7.9 and 1.5 Hz, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.52 (d, J = 7.7 Hz, 1H), 7.28−7.18 (m, 2H), 6.83 (d, J = 8.3 Hz, 1H), 6.68−6.65 (m, 1H), 3.59−3.53 (m, 1H), 2.02−2.00 (m, 2H), 1.79−1.76 (m, 2H), 1.62−1.59 (m, 1H), 1.50−1.34 (m, 5*H*). $^{13}C\{^1H\}$ NMR (125NHz, DMSO-d_6) δ 152.5, 146.7, 142.6, 133.4, 130.9, 127.7, 122.5, 121.4, 118.1, 114.0, 110.7, 110.2, 49.5, 32.3, 25.5, 23.8. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{20}H_{20}BrN_3O$ 397.0790; Found 397.0788.

*5-Phenylbenzo[4,5]imidazo[1,2-c]quinazoline-6(5H)-thione (**12**).* **12** was purified by TLC (dichloromethane/MeOH = 99/1) as a white solid (0.043 g, 44%); mp 275−277 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 9.44 (d, J = 8.4 Hz, 1H), 8.68−8.64 (m, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.70−7.67 (m, 2H), 7.64−7.56 (m, 2H), 7.48−7.41 (m, 3H), 7.37−7.35 (m, 2H), 6.60−6.56) (m, 1H). $^{13}C\{^1H\}$ NMR (125 MHz,

https://dx.doi.org/10.1021/acs.joc.0c02067
J. Org. Chem. XXXX, XXX, XXX−XXX

$CDCl_3$) δ 171.8, 144.7, 144.5, 140.4, 138.8, 133.4, 131.9, 130.6, 129.4, 129.3, 126.4, 125.4, 125.1, 123.9, 119.5, 118.1, 117.3, 114.5. HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{20}H_{13}N_3S$ 327.0830; Found 327.0828.

*5-Phenylindolo[1,2-c]quinazolin-6(5H)-one (**14**).* **14** was purified by TLC (dichloromethane/hexane = 1/1) as a white solid (0.022 g, 24%); mp 269−271 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.66−8.62 (m, 1H), 8.03−7.99 (m, 1H), 7.76−7.71 (m, 1H), 7.65−7.62 (m, 2H), 7.59−7.55 (m, 1H), 7.44−7.42 (m, 2H), 7.41−7.35 (m, 2H), 7.25−7.21 (m, 2H), 7.17 (s, 1H), 6.59−6.55 (m, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 147.7, 137.0, 136.9, 134.5, 133.3, 130.3, 130.0, 129.5, 129.2, 128.8, 123.9, 123.8, 123.6, 123.4, 120.1, 116.4, 116.2, 115.1, 98.7. HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{21}H_{14}N_2O$ 310.1106; Found 310.1102.

*2-(2-Bromophenyl)-N,4,5-triphenyl-1H-imidazole-1-carboxamide (**16**).* **16** was purified by TLC (dichloromethane/MeOH = 99/1, 2 times) as a white solid (0.074 g, 50%); mp 220−222 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 9.28 (br s, 1H), 7.67 (d, *J* = 7.2 Hz, 2H), 7.51−7.45 (m, 4H), 7.42−7.29 (m, 9H), 7.26−7.20 (m, 2H), 7.03−6.99 (m, 1H), 6.86−6.83 (m, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 145.8, 143.0, 142.3, 136.6, 134.4, 130.9, 129.5, 129.3, 129.0, 128.3, 128.2, 128.1, 127.3, 126.9, 126.4, 125.5, 122.0, 120.6, 118.2, 115.4, 114.0. HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{28}H_{20}BrN_3O$ 493.0790; Found 493.0792.

Larger Scale Synthesis of 3a. To a 10 mL microwave reaction tube, **1a** (1.093 g, 4 mmol), **2a** (0.953 g, 8 mmol), K_3PO_4 (1.698 g, 8 mmol), and DMF (6 mL) were added. After stirring the reaction mixture at room temperature for 5 min, it was heated at 130 °C for 1 h under microwave irradiation (100 W of initial power). The workup procedure was similar to that described above except for eluent (dichloromethane/MeOH = 99/1) in purifying crude mixture using TLC to produce **3a** (0.735 g, 59%).

One-Pot Step by Step Procedure for the Synthesis of 3a. To a 50 mL round bottomed flask, 2-bromobenzaldehyde (**4**) (1.112 g, 6 mmol), benzene-1,2-diamine (**5**) (0.649 g, 6 mmol), $NaHSO_3$ (6.868 g, 66 mmol), and H_2O (20 mL) were charged. After the reaction mixture was stirred at 100 °C for 3 h, H_2O and inorganic components were removed by decantation using H_2O several times. To the flask containing a yellow solid dried under a reduced pressure for several hours, **2a** (1.429 g, 12 mmol), K_3PO_4 (2.547 g, 12 mmol), and DMF (10 mL) were added. The reaction mixture was stirred at 150 °C for 30 h, cooled to room temperature, and filtered through a short silica gel column to eliminate inorganic salts using ethyl acetate. Removal of the eluent under reduced pressure left a crude mixture, which was purified by TLC (dichloromethane/MeOH = 200/1, 2 times) to give **3a** (0.822 g, 44%).

Procedure for the Reaction of 9 with 2a. To a 10 mL microwave reaction tube, **9** (0.058 g, 0.3 mmol), **2a** (0.071 g, 0.6 mmol), K_3PO_4 (0.128 g, 0.6 mmol), and DMF (3 mL) were added. After stirring the reaction mixture at room temperature for 5 min, it was heated at 130 °C for 1 h under microwave irradiation (100 W of initial power). A workup procedure similar to that described above afforded **10**.

*N,2-Diphenyl-1H-benzo[d]imidazole-1-carboxamide (**10**).* **10** was purified by TLC (dichloromethane/MeOH = 97/3) as a white solid (0.069 g, 73%); mp 261−263 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 10.27 (br s, 1H), 8.38 (dd, *J* = 8.0 and 1.7 Hz, 1H), 7.68 (d, *J* = 7.2 Hz, 2H), 7.64 (dd, *J* = 8.1 and 1.2 Hz, 1H), 7.49 (d, *J* = 7.2 Hz, 2H), 7.45−7.31 (m, 6H), 7.27−7.20 (m, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 143.9, 138.0, 134.6, 133.8, 131.6, 130.9, 130.0, 129.9, 129.0, 128.3, 128.04, 127.98, 127.8, 127.7, 127.1, 119.0. HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{20}H_{15}N_3O$ 313.1215; Found 313.1218.

Experimental Procedure for Mechanism Study. To a 10 mL microwave reaction tube, **1a** (0.082 g, 0.3 mmol), **2a** (0.071 g, 0.6 mmol), K_3PO_4 (0.128 g, 0.6 mmol), and DMF (3 mL) were added. After stirring the reaction mixture at room temperature for 5 min, it was heated at 130 °C for 30 min under microwave irradiation (100 W of initial power). A workup procedure similar to that described above afforded **6a** and **3a**.

*2-(2-Bromophenyl)-N-phenyl-1H-benzo[d]imidazole-1-carboxamide (**6a**).* **6a** was purified by TLC (dichloromethane/MeOH = 200/1, 2 times) as a white solid (0.033 g, 28%); mp 225−227 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.17−8.15 (m, 1H), 7.61−7.57 (m, 5*H*), 7.39−7.36 (m, 4H), 7.33−7.31 (m, 2H), 6.98−6.94 (m, 1H), 5.96 (br s, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 152.5, 150.4, 148.6, 139.7, 133.4, 132.4, 132.2, 131.3, 128.8, 127.8, 122.6, 121.8, 121.5, 119.1, 118.2, 115.6, 113.9, 111.6. HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{20}H_{14}BrN_3O$ 391.0320; Found 391.0318.

Cyclization of 6a to 3a. To a 10 mL microwave reaction tube, **6a** (0.078 g, 0.2 mmol), K_3PO_4 (0.079 g, 0.4 mmol), and DMF (3 mL) were added. After stirring the reaction mixture at room temperature for 5 min, it was heated at 130 °C for 1 h under microwave irradiation (100 W of initial power). A workup procedure similar to that described above afforded **3a** (0.053 g, 85%).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02067.

Copies of ^1H and ^{13}C NMR spectra of all products (PDF)

FAIR data file, including the primary NMR FID files, for compounds **3a**−**3t**, **6a**, **6b**, **10**, **12**, **14**, and **16** (ZIP)

■ AUTHOR INFORMATION

Corresponding Author

Chan Sik Cho − *Department of Applied Chemistry, Kyungpook National University, Bukgu, Daegu 41566, Republic of Korea;* orcid.org/0000-0001-6416-1741; Email: cscho@knu.ac.kr

Author

Pham Duy Quang Dao − *Department of Applied Chemistry, Kyungpook National University, Bukgu, Daegu 41566, Republic of Korea;* orcid.org/0000-0002-2537-1874

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c02067

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (Ministry of Science and ICT) (2020R1F1A1054806).

■ REFERENCES

(1) For reviews, see: (a) Katritzky, A. R.; Ramsden, C. A.; Joule, J. A.; Zhdankin, V. V. *Handbook of Heterocyclic Chemistry*; Elsevier, 2010. (b) Alvarez-Builla, J.; Vaquero, J. J. In *Modern Heterocyclic Chemistry*; Alvarez-Builla, J., Vaquero, J. J., Barluenga, J., Eds.; Wiley-VCH: Weinheim, 2011; Vol. 4, Chapter 22, pp 1989−2070. (c) Guo, X.-X.; Gu, D.-W.; Wu, Z.; Zhang, W. Copper-catalyzed C-H functionalization reactions: Efficient synthesis of heterocycles. *Chem. Rev.* **2015**, *115*, 1622−1651. (d) Manna, S. K.; Das, T.; Samanta, S. Polycyclic benzimidazole: Synthesis and photophysical properties. *ChemistrySelect* **2019**, *4*, 8781−8790.

(2) For recent reviews on benzimidazoles, see: (a) Song, D.; Ma, S. Recent development of benzimidazole-containing antibacterial agents. *ChemMedChem* **2016**, *11*, 646−659. (b) Yadav, G.; Ganguly, S. Structure activity relationship (SAR) study of benzimidazole scaffold for different biological activities: A mini-review. *Eur. J. Med. Chem.* **2015**, *97*, 419−443. (c) Keri, R. S.; Hiremathad, A.; Budagumpi, S.; Nagaraja, B. M. Comprehensive review in current developments of benzimidazole-based medicinal chemistry. *Chem. Biol. Drug Des.* **2015**, *86*, 19−65. (d) Gaba, M.; Singh, S.; Mohan, C. Benzimidazole: An

emerging scaffold for analgesic and anti-inflammatory agents. *Eur. J. Med. Chem.* **2014**, *76*, 494−505. (e) Bansal, Y.; Silakari, O. The therapeutic journey of benzimidazoles: A review. *Bioorg. Med. Chem.* **2012**, *20*, 6208−6236.

(3) For recent reports on quinazolinones, see: (a) Gatadi, S.; Lakshmi, T. V.; Nanduri, S. 4(3*H*)-Quinazolinone derivatives: Promising antibacterial drug leads. *Eur. J. Med. Chem.* **2019**, *170*, 157−172. (b) He, D.; Wang, M.; Zhao, S.; Shu, Y.; Zeng, H.; Xiao, C.; Lu, C.; Liu, Y. Pharmaceutical prospects of naturally occurring quinazolinone and its derivatives. *Fitoterapia* **2017**, *119*, 136−149. (c) Dhiman, S.; Nandwana, N. K.; Dhayal, S.; Saini, H. K.; Kumar, D.; Kumar, A. A Facile synthesis of quinazolin-4(3*H*)-ones via copper-catalyzed one-pot, three-component tandem reaction. *ChemistrySelect* **2017**, *2*, 8016−8019. (d) Nandwana, N. K.; Dhiman, S.; Saini, H. K.; Kumar, I.; Kumar, A. Synthesis of quinazolinones, imidazo[1,2-*c*]quinazolines and imidazo[4,5-*c*]quinolines through tandem reductive amination of aryl halides and oxidative amination of C(sp^3)-H bonds. *Eur. J. Org. Chem.* **2017**, *2017*, 514−522. (e) Maiden, T. M. M.; Harrity, J. P. A. Recent developments in transition metal catalysis for quinazolinone synthesis. *Org. Biomol. Chem.* **2016**, *14*, 8014−8025. (f) Khan, I.; Zaib, S.; Batool, S.; Abbas, N.; Ashraf, Z.; Iqbal, J. Quinazolines and quinazolinones as ubiquitous structural fragments in medicinal chemistry: An update on the development of synthetic methods and pharmacological diversification. *Bioorg. Med. Chem.* **2016**, *24*, 2361−2381.

(4) Abuzar, S.; Sharma, S. Synthesis of substituted benzimidazoles as potential anthelminthics. *Arch. Pharm.* **1982**, *315*, 866−871.

(5) (a) Molina, P.; Alajarín, M.; Vidal, A. Heterocyclic synthesis via a tandem aza-Wittig reaction/heterocumulene-mediated annulation reaction. New methodology for the preparation of quinazoline derivatives. *Tetrahedron Lett.* **1988**, *29*, 3849−3852. (b) Molina, P.; Alajarín, M.; Vidal, A. New methodology for the preparation of quinazoline derivatives via tandem aza-wittig/heterocumulene-mediated annulation. Synthesis of 4(3*H*)-quinazolinones, benzimidazo-[1,2-*c*] quinazolines, quinazolino[3,2-*a*]quinazolines and benzothiazolo[3,2-*c*]quinazolines. *Tetrahedron* **1989**, *45*, 4263−4286.

(6) Zhao, X.; Shi, D.-Q. Synthesis of imidazo[1,2-*c*]quinazolin-5(6*H*)-ones and benzimidazo[1,2-*c*]quinazolin-6(5*H*)-ones with the aid of low-valent titanium reagent. *J. Heterocycl. Chem.* **2010**, *47*, 524−527.

(7) Zhao, H.-B.; Hou, Z.-W.; Liu, Z.-J.; Zhou, Z.-F.; Song, J.; Xu, H.-C. Amidinyl radical formation through anodic N-H bond cleavage and its application in aromatic C-H bond functionalization. *Angew. Chem., Int. Ed.* **2017**, *56*, 587−590.

(8) (a) Li, P.-G.; Yan, C.; Zhu, S.; Liu, S.-H.; Zou, L.-H. Direct construction of benzimidazo[1,2-*c*]quinazolin-6-ones via metal-free oxidative C-C bond cleavage. *Org. Chem. Front.* **2018**, *5*, 3464−3468. (b) Dai, Z.; Li, S.; Li, Y.; Feng, L.; Ma, C. Metal-free synthesis of benzimidazo[1,2-*c*]quinazolin-6-ones with indole and benzenediamine oxidized by I_2/TBHP. *Tetrahedron* **2019**, *75*, 2012−2017.

(9) (a) Dalla Via, L.; Gia, O.; Marciani Magno, S.; Da Settimo, A.; Marini, A. M.; Primofiore, G.; Da Settimo, F.; Salerno, S. Synthesis, in vitro antiproliferative activity and DNA-interaction of benzimidazo-quinazoline derivatives as potential anti-tumor agents. *Farmaco* **2001**, *56*, 159−167. (b) Carpenter, R. D.; Lam, K. S.; Kurth, M. J. Microwave-mediated heterocyclization to benzimidazo[2,1-*b*]-quinazolin-12(5*H*)-ones. *J. Org. Chem.* **2007**, *72*, 284−287. (c) Yang, D.; Wang, Y.; Yang, H.; Liu, T.; Fu, H. Copper-catalyzed domino synthesis of benzimidazo[2,1-*b*]quinazolin-12(6*H*)-ones using cyanamide as a building block. *Adv. Synth. Catal.* **2012**, *354*, 477−482. (d) Gnanasekaran, K. K.; Muddala, N. P.; Bunce, R. A. Benzo[4,5]imidazo[2,1-*b*]quinazolin-12-ones and benzo[4,5]imidazo-[1,2-*a*]pyrido[2,3-*d*]pyrimidin-5-ones by a sequential N-acylation-S_NAr reaction. *Tetrahedron Lett.* **2015**, *56*, 7180−7183. (e) Liu, J.; You, J.; Zhang, S.; Song, C.; Ji, Z.; Zhuang, J.; Yu, Y. New fluorescent labeling reagent Benzimidazo[2,1-*b*]quinazoline-12(6*H*) -one-5-ethyl-imidazole ester and its application in the analysis of endocrine disrupting compounds in milk by high performance liquid chromatography with fluorescence detection. *Microchem. J.* **2018**, *138*, 309−315.

(10) For reviews on transition-metal-catalyzed C(sp^2)−N bond formation, see: (a) Bariwal, J.; Van der Eycken, E. C-N bond forming cross-coupling reactions: an overview. *Chem. Soc. Rev.* **2013**, *42*, 9283−9303. (b) Sambiagio, C.; Marsden, S. P.; Blacker, A. J.; McGowan, P. C. Copper catalysed Ullmann type chemistry: from mechanistic aspects to modern development. *Chem. Soc. Rev.* **2014**, *43*, 3525−3550. (c) Ruiz-Castillo, P.; Buchwald, S. L. Applications of Palladium-catalyzed C-N cross-coupling reactions. *Chem. Rev.* **2016**, *116*, 12564−12649. (d) Heravi, M. M.; Kheilkordi, Z.; Zadsirjan, V.; Heydari, M. Buchwald-Hartwig reaction: An overview. *J. Organomet. Chem.* **2018**, *861*, 17−104. (e) Forero-Cortés, P. A.; Haydl, A. M. The 25th Anniversary of the Buchwald-Hartwig amination: Development, applications, and outlook. *Org. Process Res. Dev.* **2019**, *23*, 1478−1483. (f) Dorel, R.; Grugel, C. P.; Haydl, A. M. The Buchwald-Hartwig amination after 25 years. *Angew. Chem., Int. Ed.* **2019**, *58*, 17118−17129.

(11) For recent reports on transition-metal-free C(sp^2)−N bond formation, see: (a) Sun, C.-L.; Shi, Z.-J. Transition-metal-free coupling reactions. *Chem. Rev.* **2014**, *114*, 9219−9280. (b) Liu, W.; Li, J.; Querard, P.; Li, C.-J. Transition-metal-free C-C, C-O, and C-N cross-couplings enabled by light. *J. Am. Chem. Soc.* **2019**, *141*, 6755−6764. (c) Diness, F.; Fairlie, D. P. Catalyst-free N-arylation using unactivated fluorobenzenes. *Angew. Chem., Int. Ed.* **2012**, *51*, 8012−8016. (d) Diness, F.; Begtrup, M. Sequential direct S_NAr reactions of pentafluorobenzenes with azole or indole derivatives. *Org. Lett.* **2014**, *16*, 3130−3133. (e) Sandtorv, A. H.; Stuart, D. R. Metal-free synthesis of aryl amines: Beyond nucleophilic aromatic substitution. *Angew. Chem., Int. Ed.* **2016**, *55*, 15812−15815. (f) Jacobson, C. B.; Meldal, M.; Diness, F. Mechanism and scope of base-controlled catalyst-free N-arylation of amines with unactivated fluorobenzenes. *Chem. - Eur. J.* **2017**, *23*, 846−851.

(12) For our recent reports on the synthesis of polynuclear N-fused hybrid scaffolds via a C(sp^2)−N coupling, see: (a) Dao, P. D. Q.; Lee, H. K.; Sohn, H.-S.; Yoon, N. S.; Cho, C. S. Synthesis of benzo[4,5]imidazo[1,2-*c*]pyrimidin-1-amines and their analogs via copper-catalyzed C-N coupling and cyclization. *ACS Omega* **2017**, *2*, 2953−2958. (b) Dao, P. D. Q.; Ho, S. L.; Cho, C. S. Synthesis of N-fused benzimidazole-4,7-diones via sequential copper-catalyzed C-N coupling/cyclization and oxidation. *ACS Omega* **2018**, *3*, 5643−5653. (c) Kim, D. Y.; Dao, P. D. Q.; Cho, C. S. Synthesis of pyrimidine- and quinazoline-fused benzimidazole-4,7-diones using combinatorial cyclocondensation and oxidation. *ACS Omega* **2018**, *3*, 17456−17465. (d) Dao, P. D. Q.; Cho, C. S. Copper-catalyzed construction of trinuclear N-fused hybrid scaffolds using cyclic ureas as new building blocks. *Eur. J. Org. Chem.* **2020**, *2020*, 330−338. (e) Diep, T. D.; Dao, P. D. Q.; Ho, S. L.; Cho, C. S. Copper-catalyzed synthesis of trinuclear N-fused hybrid scaffolds by double C(sp^2)−N bond formation between 2-(2-bromoaryl)indoles and 2-aminoazoles. *Eur. J. Org. Chem.* **2020**, *2020*, 2807−2812. (f) Kwak, J. P.; Dao, P. D. Q.; Cho, C. S. Synthesis of 2-aminoquinazoline- and 2-aminopyrimidine-fused hybrid scaffolds by copper-catalyzed C(sp^2)−N coupling and cyclization followed by oxidation. *Eur. J. Org. Chem.* **2020**, *2020*, 3468−3474.

(13) For our recent reports on transition-metal-free cyclizations via homolytic aromatic substitution (HAS) type pathway, see: (a) Dao, P. D. Q.; Ho, S. L.; Lim, H.-J.; Cho, C. S. Microwave-assisted cyclization under mildly basic conditions: Synthesis of 6*H*-benzo[*c*]chromen-6-ones and their 7,8,9,10-tetrahydro analogues. *J. Org. Chem.* **2018**, *83*, 4140−4146. (b) Dao, P. D. Q.; Lim, H.-J.; Cho, C. S. Weak base-promoted lactamization under microwave irradiation: Synthesis of quinolin-2(1*H*)-ones and phenanthridin-6(5*H*)-ones. *ACS Omega* **2018**, *3*, 12114−12121.

(14) Dao, P. D. Q.; Lim, H.-J.; Cho, C. S. Transition metal-free construction of trinuclear N-fused hybrid scaffolds by double nucleophilic aromatic substitution under microwave irradiation. *Green Chem.* **2019**, *21*, 6590−6593.

https://dx.doi.org/10.1021/acs.joc.0c02067
J. Org. Chem. XXXX, XXX, XXX−XXX

(15) For reports on transition-metal-catalyzed coupling of C(sp^2) and N of ureas, see: (a) Sharma, D. K.; Adams, S. T., Jr; Liebmann, K. L.; Miller, S. C. Rapid access to a broad range of 6′-substituted firefly luciferin analogues reveals surprising emitters and inhibitors. *Org. Lett.* **2017**, *19*, 5836−5839. (b) Tetlow, D. J.; Hennecke, U.; Raftery, J.; Waring, M. J.; Clarke, D. S.; Clayden, J. Sequential double α-arylation of N-allylureas by asymmetric deprotonation and N→C aryl migration. *Org. Lett.* **2010**, *12*, 5442−5445. (c) Clayden, J.; Hennecke, U. α-Pyridylation of chiral amines via urea coupling, lithiation and rearrangement. *Org. Lett.* **2008**, *10*, 3567−3570. (d) Stelmach, J. E.; Liu, L.; Patel, S. B.; Pivnichny, J. V.; Scapin, G.; Singh, S.; Hop, C. E. C. A.; Wang, Z.; Strauss, J. R.; Cameron, P. M.; Nichols, E. A.; O'Keefe, S. J.; O'Neill, E. A.; Schmatz, D. M.; Schwartz, C. D.; Thompson, C. M.; Zaller, D. M.; Doherty, J. B. Design and synthesis of potent, orally bioavailable dihydroquinazolinone inhibitors of p38 MAP kinase. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 277−280.

(16) Jiang, Y.; Jia, S.; Li, X.; Sun, Y.; Li, W.; Zhang, W.; Xu, G. An efficient $NaHSO_3$-promoted protocol for chemoselective synthesis of 2-substituted benzimidazoles in water. *Chem. Pap.* **2018**, *72*, 1265−1276.

(17) Molina, P.; Lorenzo, A.; Aller, E. Iminophosphorane-mediated annulation of 1,3,5-triazine to benzimidazole: Synthesis of 1,3,5-triazino[1,2-*a*]benzimidazoles. *Synthesis* **1992**, *1992*, 297−298.

(18) (a) March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*; Wiley: New York, 1992; pp 641−676. (b) Terrier, F. *Modern Nucleophilic Aromatic Substitution*; Wiley-VCH: Weinheim, 2013. (c) Chupakhin, O. N.; Charushin, V. N. Recent advances in the field of nucleophilic aromatic substitution of hydrogen. *Tetrahedron Lett.* **2016**, *57*, 2665−2672.

(19) Smith, J. G. *Organic Chemistry*, 6th ed.; McGraw-Hill: New York, 2020; p 283.

(20) Thomé, I.; Besson, C.; Kleine, T.; Bolm, C. Base-catalyzed synthesis of substituted indazoles under mild, transition-metal-free conditions. *Angew. Chem., Int. Ed.* **2013**, *52*, 7509−7513.

(21) Xie, R.; Ling, Y.; Fu, H. Copper-catalyzed synthesis of benzocarbazoles via a-C-arylation of ketones. *Chem. Commun.* **2012**, *48*, 12210−12212.

(22) Gang, M.-Y.; Liu, J.-Q.; Wang, X.-S. CuI-catalyzed Sonogashira reaction for the efficient synthesis of 1*H*-imidazo[2,1-*a*]isoquinoline derivatives. *Tetrahedron* **2017**, *73*, 4698−4705.

https://dx.doi.org/10.1021/acs.joc.0c02067
J. Org. Chem. XXXX, XXX, XXX−XXX