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Recyclable Magnetic Cu-MOF-74-Catalyzed C(sp^2)-N Coupling and Cyclization under Microwave Irradiation: Synthesis of Imidazo[1,2-*c*]quinazolines and Their Analogues

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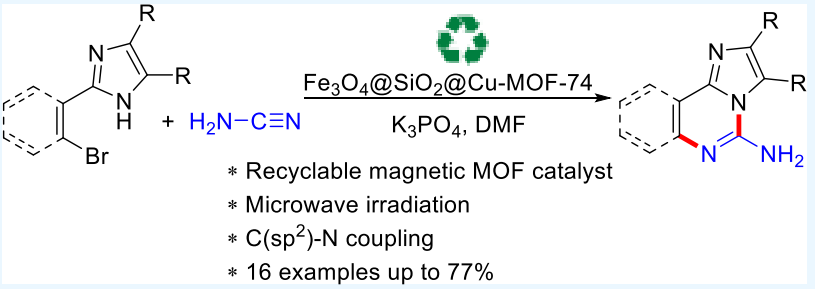

ABSTRACT: Magnetic Cu-MOF-74 (Fe_3O_4@SiO_2@Cu-MOF-74) was synthesized for the first time by grafting MOF-74 (copper as the metal center) on the surface of core-shell magnetic carboxyl-functionalized silica gel (Fe_3O_4@SiO_2-COOH), which was prepared by coating core Fe_3O_4 nanoparticles with hydrolyzed 2-(3-(triethoxysilyl)propyl)succinic anhydride and tetraethyl orthosilicate. The structure of Fe_3O_4@SiO_2@Cu-MOF-74 nanoparticles was characterized by Fourier transform infrared (FT-IR) spectroscopy, scanning electron microscopy (SEM), energy-dispersive X-ray spectroscopy (EDS), and transmission electron microscopy (TEM). The prepared Fe_3O_4@SiO_2@Cu-MOF-74 nanoparticles could be applied as a recyclable catalyst to the synthesis of N-fused hybrid scaffolds. 2-(2-Bromoaryl)imidazoles and 2-(2-bromovinyl)imidazoles were coupled and cyclized with cyanamide in DMF in the presence of a catalytic amount of Fe_3O_4@SiO_2@Cu-MOF-74 along with a base to give imidazo[1,2-*c*]quinazolines and imidazo[1,2-*c*]pyrimidines, respectively, in good yields. The Fe_3O_4@SiO_2@Cu-MOF-74 catalyst could be easily recovered by a super magnetic bar and recycled more than four times while almost maintaining catalytic activity.

INTRODUCTION

Various synthetic methods of N-fused heterocyclic compounds have been attempted and developed due to their intrinsic biological activities and photoelectronic properties.[1] It is known that imidazole-fused quinazolines, imidazo[1,2-*c*]-quinazolines, also exhibit such biological activities and photoelectronic properties.[2−4] However, unlike well-known synthetic methods of each homonuclear component (imidazole and quinazoline) that makes up imidazo[1,2-*c*]-quinazoline, several synthetic methods have been reported for their binuclear N-fused hybrid scaffolds with a limited substrate scope.[5,6] Kumar et al. reported that 2-(2-bromoaryl)-imidazoles react with formamide in the presence of CuI to produce imidazo[1,2-*c*]quinazolines via tandem Ullmann-type C−N coupling and intramolecular dehydrative cyclization (Scheme 1, route a).[7] They also demonstrated that imidazo-[1,2-*c*]quinazolines can be formed by an initial copper-catalyzed reductive amination of 2-(2-bromoaryl)imidazoles with sodium azide followed by oxidative amination with *N*,*N*-dimethylacetamide (DMA) and oxidation in the presence of *t*-butyl hydroperoxide (TBHP) (Scheme 1, route b).[8] Imidazo-[1,2-*c*]quinazoline itself can be formed by coupling and cyclization of 2-(2-aminophenyl)imidazole with cyanogen bromide (Scheme 1, route c).[2] Two-step processes, initial cyclizations of 2-(2-aminophenyl)-4,5-dihydroimidazole with trimethyl orthoformate (or orthoacetate), methyl acetimidate (or benzimidate) hydrochlorides and aldehydes followed by oxidative dehydrogenations using Pd/C or $KMnO_4$ were also shown to produce imidazo[1,2-*c*]quinazolines (Scheme 1, route d).[9] It is known that 2-(2-nitroaryl)imidazoles are reductively cyclized with C-1 components such as alkyl/arylisothiocyanates and triethyl orthoformate under reduction systems ($SnCl_2$·H_2O/MeOH, Zn dust/AcOH, $TiCl_4$/Zn) (Scheme 1, route e).[10] Imidazo[1,2-*c*]quinazolines also can be synthesized by a cyclization of 4-aminoquinazoline with bromoacetaldehyde diethyl acetal and 4′-methoxyphenacyl

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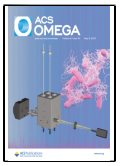

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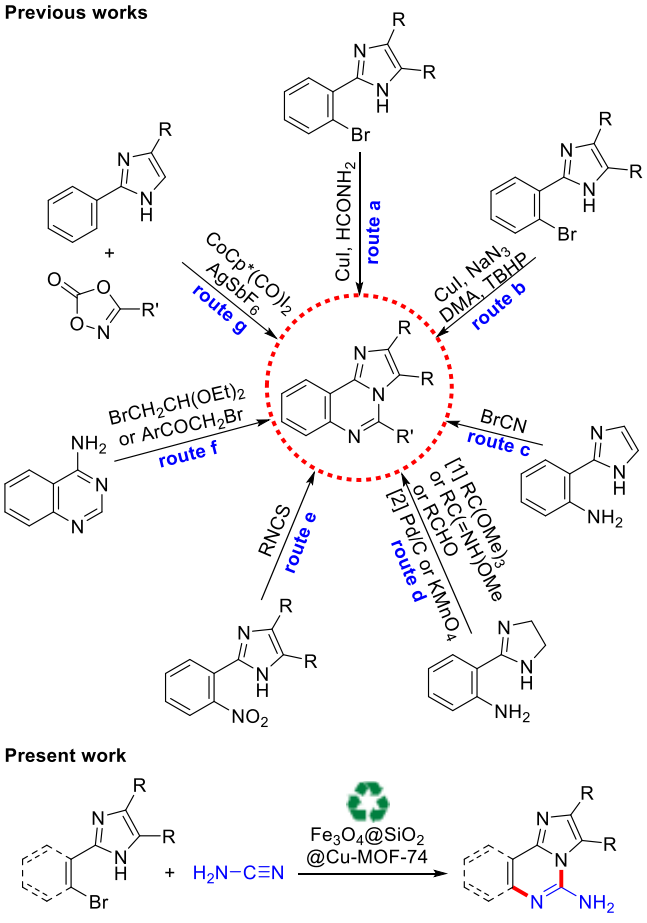
Scheme 1. Synthetic Methods for Imidazo[1,2-*c*]quinazolines



bromide (Scheme 1, route f).[11] Recently, Dong and Xu group reported that 2-arylimidazoles reacted with 1,4,2-dioxazo-5-ones to produce imidazo[1,2-*c*]quinazolines by cobalt-catalyzed C(sp^2)-H amidation and cyclocondensation (Scheme 1, route g).[12] In a series of studies on the synthesis of heterocyclic compounds, we have recently developed novel copper-catalyzed and transition-metal-free synthetic methods for polynuclear N-fused hybrid scaffolds.[13,14] This work describes synthesis of imidazo[1,2-*c*]quinazolines and their analogues by recyclable magnetic Cu-MOF-74-catalyzed C-(sp^2)-N coupling and cyclization of 2-(2-bromoaryl)- and 2-(2-bromovinyl)imidazoles with cyanamide (Scheme 1).[15]

RESULTS AND DISCUSSION

Heterogeneous magnetic Cu-MOF-74 (Fe_3O_4@SiO_2@Cu-MOF-74) was synthesized by grafting Cu-MOF-74 on the surface of core−shell magnetic carboxyl-functionalized silica gel (Fe_3O_4@SiO_2-COOH), which was prepared by coating core Fe_3O_4 nanoparticles with hydrolyzed 2-(3-(triethoxysilyl)-propyl)succinic anhydride (Hyd-TESPSA) and tetraethyl orthosilicate (TEOS) (Figure 1).[16,17] The FT-IR absorption bands at 795, 900, 1205, 1250, 1425, and 1530 cm^{-1} of Fe_3O_4@SiO_2@Cu-MOF-74 were observed to be almost identical to those of known Cu-MOF-74 (Figure 2b−d).[17] The band at 1080 cm^{-1} assigned to the presence of Si−O−Si bond was observed from both carboxyl-functionalized silica gel (Fe_3O_4@SiO_2-COOH) and Fe_3O_4@SiO_2@Cu-MOF-74 (Figure 2a,b). The catalyst was further analyzed by using energy-

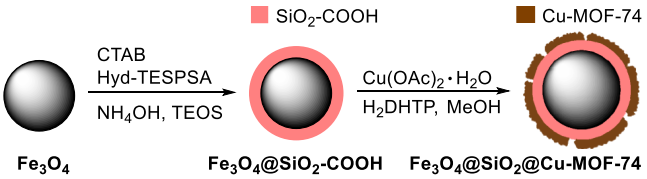


Figure 1. Synthetic route of Fe_3O_4@SiO_2@Cu-MOF-74.

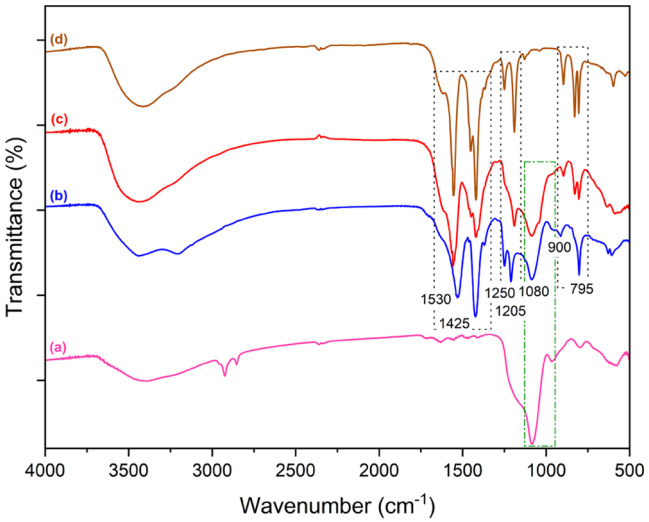
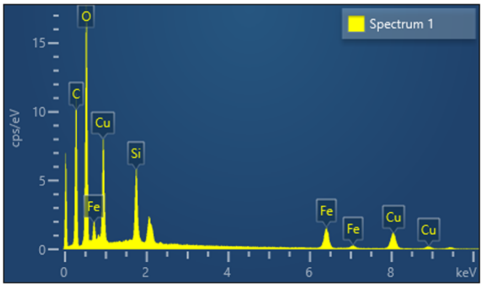


Figure 2. FT-IR spectra of (a) Fe_3O_4@SiO_2-COOH, (b) Fresh Fe_3O_4@SiO_2@Cu-MOF-74, (c) Fe_3O_4@SiO_2@Cu-MOF-74 after 4th reuse, and (d) Cu-MOF-74.

dispersive X-ray spectroscopy (EDS). The EDS spectrum showed that the catalyst contains C (35.22 wt %), O (31.12 wt %), Fe (9.93 wt %), Si (4.56 wt %), and Cu (19.17 wt %) elements (Figure 3). The morphology of the magnetic catalyst



Element	Wt%	Atomic %
C	35.22	53.13
O	31.12	35.24
Si	4.56	2.94
Fe	9.93	3.22
Cu	19.17	5.47
Total:	100.00	100.00

Figure 3. EDS spectrum of Fe_3O_4@SiO_2@Cu-MOF-74.

was characterized by FE-SEM and TEM. The FE-SEM micrographs showed that Fe_3O_4@SiO_2@Cu-MOF-74 nanoparticles are aggregated and composed of a network structure with a crystal size ranging from 10 to 20 nm (Figure 4a). The TEM images also showed the aggregate structure and typical core-shell nanoparticles (Figure 4b). These results indicated that Fe_3O_4@SiO_2@Cu-MOF-74 was successfully synthesized

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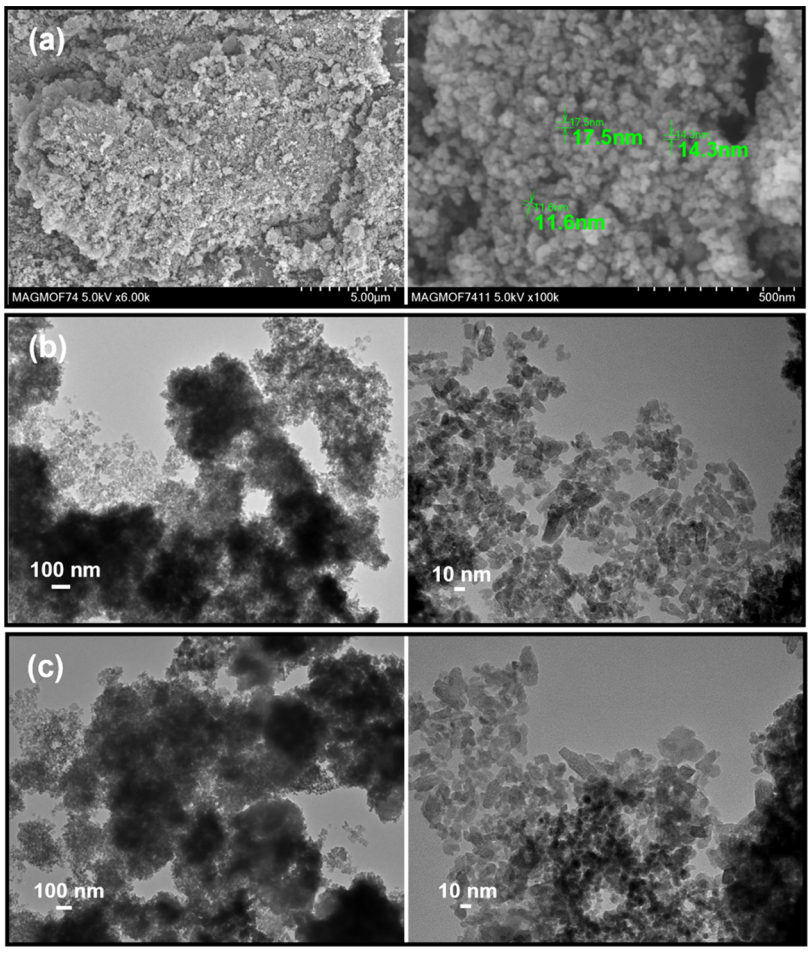

Figure 4. (a) FE-SEM images of Fe_3O_4@SiO_2@Cu-MOF-74, (b) TEM images of fresh Fe_3O_4@SiO_2@Cu-MOF-74, and (c) TEM images of Fe_3O_4@SiO_2@Cu-MOF-74 after 4th reuse.

by grafting Cu-MOF-74 onto the core shell of Fe_3O_4@SiO_2-COOH.

The prepared Fe_3O_4@SiO_2@Cu-MOF-74 could be applied as an effective recyclable catalyst to the synthesis of N-fused hybrid scaffolds accompanied by C(sp^2)-N coupling. As shown in Table 1, 2-(2-bromophenyl)-4,5-diphenyl-1*H*-imidazole (**1a**) and cyanamide (**2**) were chosen as model substrates to investigate the suitable reaction conditions for the effective formation of binuclear N-fused hybrid scaffold, 2,3-diphenylimidazo[1,2-*c*]quinazolin-5-amine (**3a**). Treatment of **1a** with an equimolar amount of **2** in DMF in the presence of a catalytic amount of Fe_3O_4@SiO_2@Cu-MOF-74 (10 mol %) along with K_3PO_4 (2 equiv) at 150 °C for 1 h under microwave irradiation (100 W of initial power) afforded **3a** in 38% isolated yield with 100% conversion of **1a** (Table 1, entry 1). The yield of **3a** was significantly affected by the molar ratio of **2** to **1a**, [**2**]/[**1a**] and increased with the increase in the molar ratio up to 2 (Table 1, entries 1−3). Even though the coupling and cyclization also proceeded with other bases such as K_2CO_3, Cs_2CO_3, KO^{t}Bu, CsF, and KOH with complete conversion of **1a**, K_3PO_4 was most effective for the formation of **3a** (Table 1, entries 2 and 4−8). However, performing the reaction in the absence of a base under the employed conditions resulted in a lower yield of **3a** (27%) with incomplete conversion of **1a** (Table 1, entry 9). Lower yield of **3a** and incomplete conversion of **1a** were observed with lower reaction temperature (Table 1, entries 10 and 11). Reaction time also affected the product formation, and the yield of **3a** increased to the reaction time up to 1 h (Table 1, entries 2, 12, and 13). When the reaction was carried out in the presence of core−shell Fe_3O_4@SiO_2-COOH, precursor of Fe_3O_4@SiO_2@Cu-MOF-74, no product was formed and the starting **1a** was recovered intact (Table 1, entry 14). However, similar catalytic activity was observed with Cu-MOF-74 (Table 1, entry 15).[17] The reaction using Fe_3O_4@SiO_2@MOF-199 in place of Fe_3O_4@SiO_2@Cu-MOF-74 also produced **3a** in 57% yield (Table 1, entry 16).[18] Performing the present reaction under conventional heating for 20 h using a screw-capped vial resulted in **3a** in 50% yield with complete conversion of **1a** (Table 1, entry 17). Not shown in Table 1, the reactions using other solvents such as DMSO, DMA, and HMPA under the employed condition afforded **3a** in 55%, 45%, and 51% yields, respectively.

Diverse 2-(2-bromoaryl)imidazoles and their analogues **1** were subjected to the reaction with cyanamide **2** under the optimized reaction conditions to investigate the substrate scope of the reaction, and the representative results are shown in Table 2.[19,20] 2-(2-Bromophenyl)imidazoles **1b-d** having electron-donating and -withdrawing substituents on the two phenyl moieties attached to the imidazole ring were similarly coupled and cyclized with **2** to afford the corresponding imidazole-fused quinazolines **3b-d** irrespective of the identity of such substituents in **1b-d**. The coupling and cyclization of 2-(2-bromoaryl)imidazoles **1e-i** with **2** also produced the

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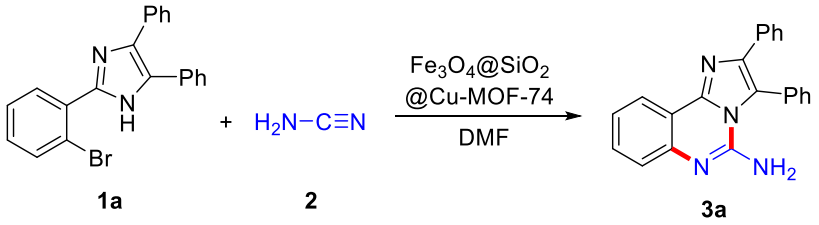
Table 1. Optimized Reaction Conditions[a]



1a 2 3a

entry	[2]/[1a]	base	temp. (°C)	time (h)	conv (%) of 1a	yield[b] (%)
1	1	K_3PO_4	150	1	100	38
2	2	K_3PO_4	150	1	100	68
3	3	K_3PO_4	150	1	100	69
4	2	K_2CO_3	150	1	100	58
5	2	Cs_2CO_3	150	1	100	60
6	2	KO^{t}Bu	150	1	100	50
7	2	CsF	150	1	100	55
8	2	KOH	150	1	100	42
9	2		150	1	60	27
10	2	K_3PO_4	110	1	73	21
11	2	K_3PO_4	130	1	100	51
12	2	K_3PO_4	150	0.5	100	60
13	2	K_3PO_4	150	2	100	69
14[c]	2	K_3PO_4	150	1	0	0
15[d]	2	K_3PO_4	150	1	100	65
16[e]	2	K_3PO_4	130	1	100	57
17[f]	2	K_3PO_4	130	20	100	50

[a]Reaction conditions: **1a** (0.3 mmol), base (0.6 mmol), Fe_3O_4@SiO_2@Cu-MOF-74 (0.03 mmol), DMF (3 mL), under microwave irradiation (100 W of initial power). [b]Isolated yields. [c]Fe_3O_4@SiO_2-COOH was used in the place of Fe_3O_4@SiO_2@Cu-MOF-74. [d]Cu-MOF-74 was used in the place of Fe_3O_4@SiO_2@Cu-MOF-74. [e]Fe_3O_4@SiO_2@MOF-199 was used in the place of Fe_3O_4@SiO_2@Cu-MOF-74. [f]Conventional heating (screw-capped vial).

corresponding coupled and cyclized binuclear scaffolds **3e-i** in 50−63% yields. The electronic nature and position of substituents (Me, OMe, OCH_2O, F) on the bromophenyl moiety of 2-(2-bromoaryl)imidazoles had some relevance with product yield. In the cases of **1e** and **1f**, prolonging the reaction time (2 h) was needed for an allowable yield of imidazo[1,2-*c*]quinazolines (**3e** and **3f**). The reaction also took place with 2-(2-bromophenyl)imidazoles **1j-l**, which have no aryl substituents or one phenyl group on imidazole moiety to give the corresponding imidazo[1,2-*c*]quinazolines **3j-l** in 53−77% yields. The present reaction can also be extended to the reaction with cyclic and acyclic 2-(2- bromovinyl)-imidazoles.[19,21] Treatment of such cyclic and acyclic 2-(2-bromovinyl)imidazoles (**1m-o**) with **2** under the employed conditions afforded binuclear imidazole-fused pyrimidines (**3m-o**) in 47−64% yields. Here again, an extension of the reaction time up to 2 h was also needed to obtain an allowable yield of **3n** and **3o**. It is known that such imidazole-fused pyrimidines, imidazo[1,2-*c*]pyrimidines exhibit diverse biological activities.[22]

Similar treatment of 5-(2-bromophenyl)triazole **1p** with **2** under the optimized conditions also produced triazole-fused quinazoline [1,2,4]triazolo[1,5-*c*]quinazoline **3p** in 66% yield.[23] In contrast to well-documented synthetic methods and biological activities of 1,2,4-triazole-containing compounds, limited synthetic methods and biological activities are known for its binuclear N-fused hybrid scaffolds with quinazoline, [1,2,4]triazolo[1,5-*c*]quinazolines.[24] The Fe_3O_4@SiO_2@Cu-MOF-74 catalyst could be easily recovered from a reaction tube using a super magnetic bar and recycled four times while almost maintaining catalytic activity (Figure 5). The yield of **3a** by the coupling and cyclization between **1a** and **2** under the employed reaction conditions was observed from 67% (first recycle), 65% (second recycle), and 64% (third recycle) to 64% (fourth recycle). The reaction proceeded with complete conversion of **1a**, and the catalyst was recovered almost completely in each run (Figure 6).

To confirm the sustainability of the catalyst after reuse, the recovered catalyst after fourth reuse was analyzed with FT-IR and TEM. The FT-IR spectra of the recovered catalyst after fourth reuse showed almost the same absorption bands as those of the fresh catalyst (Figure 1b,c). The TEM images of the recovered catalyst after fourth reuse catalyst also showed the similarity of structure and particle size to fresh catalyst (Figure 4b,c).

The reaction pathway seems to proceed with an initial production of intermediate **4** by magnetic Cu-MOF-74-catalyzed Ullmann-type C-N bond formation between **1a** and **2** (Scheme 2).[25] This is followed by an intramolecular 6-exo-dig closure by the addition of N−H to CN to form a guanidine intermediate **5**, which is tautomerized to scaffold **3**. It is known that metal−organic frameworks were used as an efficient heterogeneous catalyst for C(sp^2)−C and C(sp^2)−N bond-forming reactions.[26]

CONCLUSIONS

In summary, we have synthesized heterogeneous magnetic Cu-MOF-74 (Fe_3O_4@SiO_2@Cu-MOF-74) for the first time by grafting MOF-74 on the surface of core−shell magnetic carboxyl-functionalized silica gel (Fe_3O_4@SiO_2-COOH),

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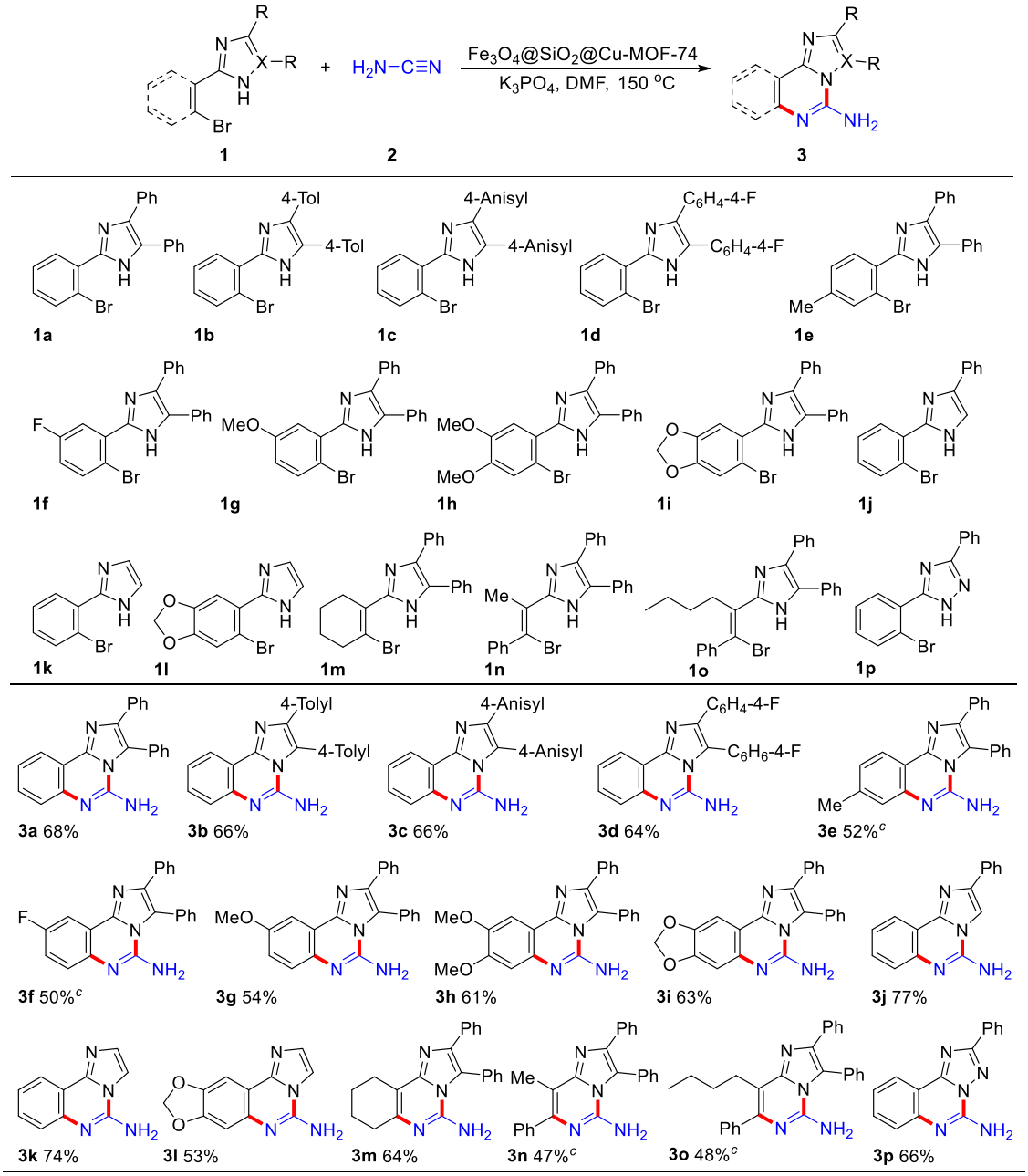
Table 2. Scope of Reaction[a,b]



[a]Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol), K_3PO_4 (0.6 mmol), Fe_3O_4@SiO_2@Cu-MOF-74 (0.03 mmol), DMF (3 mL), under microwave irradiation (100 W of initial power), for 1 h. [b]Isolated yields are shown. [c]For 2 h.

which was prepared by coating core Fe_3O_4 nanoparticles with hydrolyzed 2-(3-(triethoxysilyl)propyl)succinic anhydride and tetraethyl orthosilicate. The prepared Fe_3O_4@SiO_2@Cu-MOF-74 was characterized with several instruments such as Fourier transform infrared (FT-IR) spectroscopy, scanning electron microscopy (SEM), energy-dispersive X-ray spectroscopy (EDS), and transmission electron microscopy (TEM). We have developed an alternative synthetic method of a class of binuclear N-fused hybrid scaffolds, imidazo[1,2-*c*]-quinazolines and imidazo[1,2-*c*]pyrimidines, by magnetic Cu-MOF-74-catalyzed C(sp^2)−N coupling and cyclization of 2-(2-bromoaryl)imidazoles and 2-(2-bromovinyl)imidazoles with cyanamide as a building block. The heterogeneous catalyst could be easily recovered with a super magnetic bar and recycled more than four times while almost maintaining catalytic activity. Further applications of the recyclable Fe_3O_4@SiO_2@Cu-MOF-74 catalyst to C−C and C−N bond-forming reactions are expected.

EXPERIMENTAL SECTION

General Experimental Details. ^1H (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Bruker Avance Digital 500 spectrometer using TMS as an internal standard in DMSO-d_6. High-resolution mass data were obtained using electronic ionization (HRMS-EI and FAB, magnetic sector-electric sector double-focusing mass analyzer) at the Korea Basic Science Center (Daegu). Transmission electron microscopy (TEM) images were obtained by a Hitachi HT 7700

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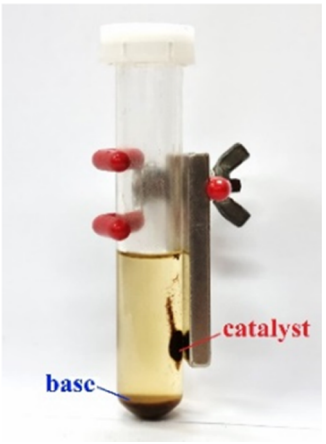


Figure 5. Recovery of Fe_3O_4@SiO_2@Cu-MOF-74 by a super magnetic bar.

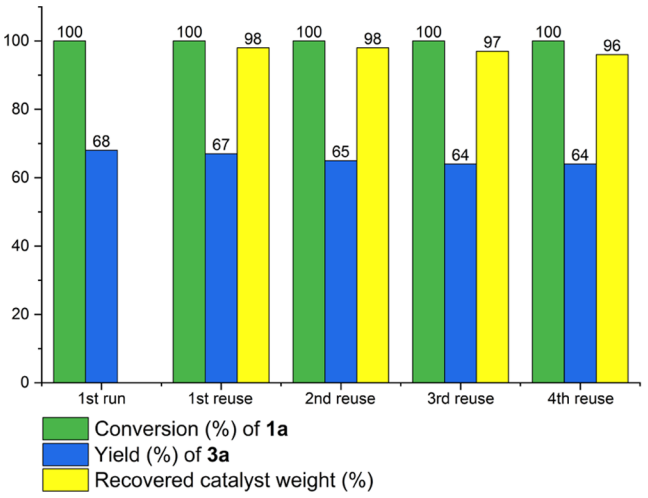


Figure 6. Catalytic activity of recovered Fe_3O_4@SiO_2@Cu-MOF-74.

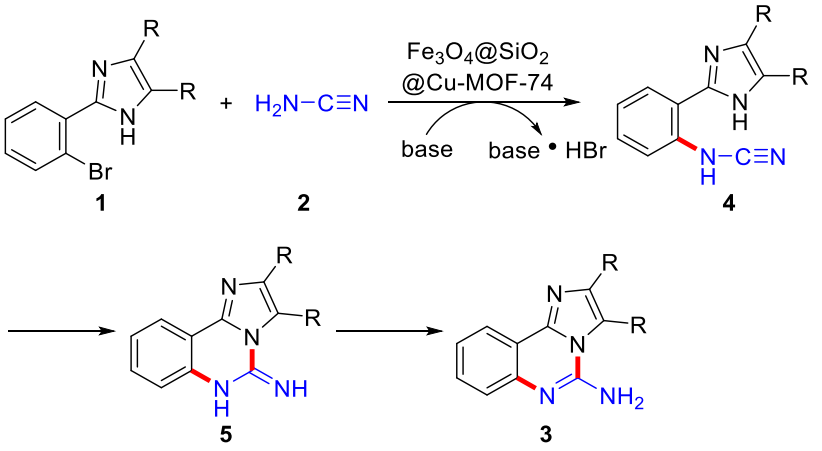
operated at an acceleration voltage of 100 kV. Field emission scanning electron microscopy (FE-SEM) and energy-dispersive X-ray spectroscopy (EDS) were carried out on a Hitachi SU8230. Melting points were measured on a microscopic melting point apparatus (Stanford Research, Inc. MPA100 automated melting point apparatus). The products were isolated by TLC (a glass plate coated with Kieselgel 60 GF_{254}, Merck). The starting compounds **1** were prepared from the corresponding aldehydes and benzils according to the reported methods.[14e,f,19] Other commercially available organic and inorganic reagents were used without further purification.

Preparation of Magnetic Carboxyl-Functionalized Silica Gel (Fe_3O_4@SiO_2-COOH).[16] 1.0 g of Fe_3O_4 nanoparticles and 1.6 g of cetyltrimethylammonium bromide (CTAB) were dispersed in the mixture of distilled water (200 mL) and ethanol (60 mL) in an ultrasonic bath for 30 min. Simultaneously, [(3-triethoxysilyl)propyl]succinic anhydride (TESPSA) (1.4 mL) was hydrolyzed by adding distilled water (1 mL) and conc. HCl (0.27 mL). After stirring the dispersed mixture for 1 h at room temperature, hydrolyzed TESPSA (Hyd-TESPSA) was added into the strongly stirred mixture. Then, ammoniac water (6 mL) was added to the mixture and the resulting mixture was stirred for 15 min at room temperature. Finally, tetraethyl orthosilicate (TEOS) (5 mL) was dropped into the mixture and stirred for 24 h at room temperature. The magnetic carboxyl-functionalized silica gel (Fe_3O_4@SiO_2-COOH) separated by a super magnetic bar was stirred in ethanol (100 mL)/acetic acid (50 mL)/acetone (100 mL) for 4 h to remove CTAB. The collected Fe_3O_4@SiO_2-COOH was washed with distilled water and ethanol several times and dried at 50 °C for 6 h in a vacuum oven.

Preparation of Magnetic Cu-MOF-74 (Fe_3O_4@SiO_2@Cu-MOF-74).[17] 1.0 g of Fe_3O_4@SiO_2-COOH was dispersed in distilled water (50 mL) and MeOH (50 mL). After 4.0 g of $Cu(OAc)_2{\cdot}H_2O$ was added to the dispersed mixture, the mixture was stirred for 20 min at room temperature. To the mixture was added 2.0 g of 2,5-dihydroxyterephthalic acid (H_2DHTP) dissolved in MeOH and the resulting mixture was further stirred for 20 h at room temperature. The precipitates separated by a super magnetic bar were washed with distilled water (30 mL × 3) and MeOH (30 mL × 3). The precipitates were immersed in MeOH (100 mL) for 4 days and exchanged with the same amount of fresh MeOH every 24 h. The collected Fe_3O_4@SiO_2@Cu-MOF-74 was dried at 100 °C for 12 h.

General Procedure for the Synthesis of 3 and Catalyst Recyclability. In a 10 mL microwave reaction tube were placed **1** (0.3 mmol), **2** (0.025 g, 0.6 mmol), Fe_3O_4@SiO_2@Cu-MOF-74 (0.018 g, 0.03 mmol), K_3PO_4 (0.128 g, 0.6 mmol), and DMF (3 mL). After stirring the

Scheme 2. Reaction Pathway



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reaction mixture at an ambient temperature for 5−10 min and at 150 °C for 1 h under microwave irradiation (100 W of initial power), it was cooled to an ambient temperature. The resulting mixture except for Fe_3O_4@SiO_2@Cu-MOF-74, which was fixed with a super magnetic bar, was filtered through a short silica gel column (chloroform/MeOH = 7/3) to remove inorganic precipitates. Evaporation of the filtrate under reduced pressure left a crude mixture, which was purified by TLC (hexane/ethyl acetate = 2/1) to produce **3**. The catalyst that remained in the microwave reaction tube was washed with MeOH (20 mL × 3) and water (30 mL × 2) and dried at 100 °C for 12 h under vacuum. The recovered Fe_3O_4@SiO_2@Cu-MOF-74 was subjected to next run by charging **1**, **2**, K_3PO_4, and DMF.

*2,3-Diphenylimidazo[1,2-c]quinazolin-5-amine (**3a**).*[15] **3a** was purified by TLC (hexane/ethyl acetate = 2/1) as a white solid (0.069 g, 68%); mp 236−238 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.37 (dd, J = 7.9 and 1.0 Hz, 1H), 7.70−7.56 (m, 6H), 7.52−7.47 (m, 3H), 7.39−7.36 (m, 1H), 7.30−7.23 (m, 3H), 6.04 (brs, 2H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 144.7, 143.8, 142.5, 140.4, 133.6, 132.2, 130.4, 130.2, 130.1, 129.3, 128.3, 127.5, 127.3, 124.3, 123.4, 122.4, 121.2, 115.5.

*2,3-Di-p-tolylimidazo[1,2-c]quinazolin-5-amine (**3b**).* **3b** was purified by TLC (hexane/ethyl acetate = 2/1) as a white solid (0.072 g, 66%); mp 270−273 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.33 (dd, J = 7.9 and 1.1 Hz, 1H), 7.57−7.53 (m, 3H), 7.46−7.33 (m, 6H), 7.08 (d, J = 8.0 Hz, 2H), 6.03 (brs, 2H), 2.45 (s, 3H), 2.25 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 144.7, 143.6, 142.5, 140.6, 140.0, 136.8, 132.0, 130.8, 130.1, 129.8, 128.9, 127.2, 127.1, 124.2, 123.3, 122.3, 120.8, 115.5, 21.1, 20.7. HRMS (EI) m/z: [M]$^+$ calcd for $C_{24}H_{20}N_4$ 364.1688; found: 364.1686.

*2,3-Bis(4-methoxyphenyl)imidazo[1,2-c]quinazolin-5-amine (**3c**).* **3c** was purified by TLC (hexane/ethyl acetate = 2/1) as a white solid (0.078 g, 66%); mp 223−226 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.35 (dd, J = 7.9 and 1.2 Hz, 1H), 7.60−7.54 (m, 3H), 7.49−7.46 (m, 3H), 7.36−7.33 (m, 1H), 7.18−7.15 (m, 2H), 6.87−6.84 (m, 2H), 6.08 (brs, 2H), 3.88 (s, 3H), 3.73 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 160.4, 158.6, 144.8, 143.4, 142.4, 140.5, 133.5, 130.0, 128.4, 126.1, 124.2, 123.2, 122.3, 121.8, 119.9, 115.5, 114.7, 113.7, 55.4, 55.0. HRMS (FAB) m/z: [M + H]$^+$ calcd for $C_{24}H_{21}N_4O_2$ 397.1665; found: 397.1662.

*2,3-Bis(4-fluorophenyl)imidazo[1,2-c]quinazolin-5-amine (**3d**).* **3d** was purified by TLC (hexane/ethyl acetate = 2/1) as a white solid (0.071 g, 64%); mp 240−243 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.34 (dd, J = 7.0 and 1.2 Hz, 1H), 7.74−7.71 (m, 2H), 7.57−7.54 (m, 1H), 7.50−7.42 (m, 5H), 7.36−7.33 (m, 1H), 7.13−7.09 (m, 2H), 6.04 (brs, 2H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 163.1 (d, $^1J_{C\text{-}F}$ = 247.1 Hz), 161.6 (d, $^1J_{C\text{-}F}$ = 243.7 Hz), 144.7, 144.0, 142.5, 140.0, 134.6 (d, $^3J_{C\text{-}F}$ = 8.6 Hz), 130.3, 130.0 (d, $^4J_{C\text{-}F}$ = 3.2 Hz), 129.3 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 126.1 (d, $^4J_{C\text{-}F}$ = 3.0 Hz), 124.3, 123.4, 122.4, 120.0, 116.4 (d, $^2J_{C\text{-}F}$ = 21.6 Hz), 115.4, 115.2 (d, $^2J_{C\text{-}F}$ = 21.5 Hz). HRMS (EI) m/z: [M]$^+$ calcd for $C_{22}H_{14}F_2N_4$ 372.1187; found: 372.1183.

*8-Methyl-2,3-diphenylimidazo[1,2-c]quinazolin-5-amine (**3e**).* **3e** was purified by TLC (hexane/ethyl acetate = 2/1) as a white solid (0.055 g, 52%); mp 280−283 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.24 (d, J = 8.0 Hz, 1H), 7.68−7.59 (m, 5H), 7.50−7.48 (m, 2H), 7.28−7.19 (m, 5H), 5.99 (brs, 2H), 2.44 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 144.7, 144.0, 142.7, 140.3, 140.1, 133.6, 132.2, 130.3, 130.2, 129.3, 128.3, 127.5, 127.3, 124.9, 124.0, 122.3, 120.9, 113.1, 21.4. HRMS (EI) m/z: [M]$^+$ calcd for $C_{23}H_{18}N_4$ 350.1531; Found: 350.1529.

*9-Fluoro-2,3-diphenylimidazo[1,2-c]quinazolin-5-amine (**3f**).* **3f** was purified by TLC (hexane/ethyl acetate = 2/1) as a white solid (0.053 g, 50%); mp 267−270 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.01 (dd, J = 8.9 and 2.9 Hz, 1H), 7.69−7.60 (m, 5H), 7.52−7.48 (m, 3H), 7.43 (td, J = 8.8 and 3.0 Hz, 1H), 7.29−7.22 (m, 3H), 6.01 (brs, 2H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 158.2 (d, $^1J_{C\text{-}F}$ = 238.8 Hz), 144.3, 143.1 (d, $^4J_{C\text{-}F}$ = 4.3 Hz), 140.7, 139.2, 133.4, 132.1, 130.5, 129.9, 129.3, 128.3, 127.6, 127.3, 126.6 (d, $^3J_{C\text{-}F}$ = 8.4 Hz), 121.6, 118.4 (d, $^2J_{C\text{-}F}$ = 23.7 Hz), 116.1 (d, $^3J_{C\text{-}F}$ = 9.8 Hz), 107.1 (d, $^2J_{C\text{-}F}$ = 23.9 Hz). HRMS (FAB) m/z: [M + H]$^+$ calcd for $C_{22}H_{16}FN_4$ 355.1359; found: 355.1361.

*9-Methoxy-2,3-diphenylimidazo[1,2-c]quinazolin-5-amine (**3g**).* **3g** was purified by TLC (hexane/ethyl acetate = 2/1) as a white solid (0.059 g, 54%); mp 193−196 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.78 (d, J = 2.9 Hz, 1H), 7.69−7.60 (m, 5H), 7.52−7.49 (m, 2H), 7.43 (d, J = 8.9 Hz, 1H), 7.30−7.24 (m, 3H), 7.21 (dd, J = 8.5 and 3.0 Hz, 1H), 5.84 (brs, 2H), 3.92 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 155.6, 143.7, 143.4, 140.5, 136.8, 133.6, 132.2, 130.4, 130.2, 129.2, 128.3, 127.6, 127.4, 126.0, 121.3, 119.9, 115.9, 103.1, 55.6. HRMS (FAB) m/z: [M + H]$^+$ calcd for $C_{23}H_{19}N_4O$ 367.1559; found: 367.1561.

*8,9-Dimethoxy-2,3-diphenylimidazo[1,2-c]quinazolin-5-amine (**3h**).* **3h** was purified by TLC (hexane/ethyl acetate = 2/1) as a white solid (0.073 g, 61%); mp 234−237 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.70 (s, 1H), 7.68−7.59 (m, 5H), 7.51−7.49 (m, 2H), 7.28−7.21 (m, 3H), 6.96 (s, 1H), 5.79 (brs, 2H), 3.93 (s, 3H), 3.88 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 151.8, 146.5, 143.9, 140.3, 137.9, 133.7, 132.2, 130.4, 130.2, 129.1, 128.2, 127.4, 127.3, 120.4, 108.2, 106.1, 102.7, 55.8, 55.6. HRMS (FAB) m/z: [M + H]$^+$ calcd for $C_{24}H_{21}N_4O_2$ 397.1665; found: 397.1667.

*2,3-Diphenyl-[1,3]dioxolo[4,5-g]imidazo[1,2-c]-quinazolin-5-amine (**3i**).* **3i** was purified by TLC (hexane/ethyl acetate = 2/1) as a white solid (0.072 g, 63%); mp 256−260 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.69 (s, 1H), 7.67−7.58 (m, 5H), 7.50−7.48 (m, 2H), 7.28−7.21 (m, 3H), 6.95 (s, 1H), 6.15 (s, 2H), 5.87 (brs, 2H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 150.0, 144.5, 144.0, 143.9, 140.3, 139.1, 133.6, 132.2, 130.3, 130.2, 129.1, 128.2, 127.4, 127.3, 120.3, 109.4, 103.4, 101.6, 99.7. HRMS (FAB) m/z: [M + H]$^+$ calcd for $C_{23}H_{17}N_4O_2$ 381.1352; found: 381.1355.

*2-Phenylimidazo[1,2-c]quinazolin-5-amine (**3j**).* **3j** was purified by TLC (hexane/ethyl acetate = 2/1) as a pale yellow solid (0.060 g, 77%); mp 180−184 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.57 (s, 1H), 8.30 (dd, J = 7.9 and 1.1 Hz, 1H), 8.00−7.98 (m, 2H), 7.64 (brs, 2H), 7.58−7.50 (m, 4H), 7.39−7.33 (m, 2H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 144.3, 144.2, 143.2 (143.24), 143.2 (143.23), 133.4, 130.0, 128.9, 127.9, 125.4, 124.6, 122.9, 122.3, 114.8, 107.0. HRMS (FAB) m/z: [M + H]$^+$ calcd for $C_{16}H_{13}N_4$ 261.1140; found: 261.1143.

*Imidazo[1,2-c]quinazolin-5-amine (**3k**).* **3k** was purified by TLC (hexane/ethyl acetate = 2/1) as a pale yellow solid (0.041 g, 74%); mp 210−212 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.23 (dd, J = 8.0 and 1.2 Hz, 1H), 8.13 (d, J = 1.5 Hz, 1H), 7.64 (brs, 2H), 7.58 (d, J = 1.5 Hz, 1H), 7.56−7.53 (m, 1H), 7.50 (dd, J = 8.2 and 0.8 Hz, 1H), 7.34−7.30 (m, 1H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 144.5, 143.9,

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143.0, 131.8, 129.8, 124.4, 122.8, 122.1, 115.0, 111.3. HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{10}H_9N_4$ 185.0827; found: 185.0825.

*[1,3]Dioxolo[4,5-g]imidazo[1,2-c]quinazolin-5-amine (**3l**).* **3l** was purified by TLC (hexane/ethyl acetate = 2/1) as a white solid (0.036 g, 53%); mp 236−240 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.99 (d, J = 1.5 Hz, 1H), 7.54 (s, 1H), 7.48 (d, J = 1.5 Hz, 1H), 7.41 (brs, 2H), 6.95 (s, 1H), 6.11 (s, 2H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 149.6, 144.1 (144.14), 144.1 (144.11), 143.7, 139.6, 131.6, 110.4, 108.9, 103.6, 101.4, 99.6. HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{11}H_9N_4O_2$ 229.0726; found: 229.0723.

*2,3-Diphenyl-7,8,9,10-tetrahydroimidazo[1,2-c]-quinazolin-5-amine (**3m**).* **3m** was purified by TLC (hexane/ethyl acetate = 2/1) as a white solid (0.065 g, 64%); mp 248−251 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.63−7.55 (m, 5H), 7.45−7.42 (m, 2H), 7.25−7.18 (m, 3H), 5.72 (brs, 2H), 2.82−2.80 (m, 2H), 2.57−2.55 (m, 2H), 1.83−1.79 (m, 4H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 146.7, 146.6, 144.7, 141.0, 134.0, 132.2, 130.6, 129.9, 128.9, 128.1, 127.3 (127.34), 127.3 (127.28), 118.5, 108.1, 30.3, 22.6, 22.3, 21.9. HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{22}H_{21}N_4$ 341.1766; found: 341.1769.

*8-Methyl-2,3,7-triphenylimidazo[1,2-c]pyrimidin-5-amine (**3n**).* **3n** was purified by TLC (hexane/ethyl acetate = 2/1) as a pale yellow solid (0.053 g, 47%); mp 251−254 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.66−7.58 (m, 7H), 7.50−7.45 (m, 4H), 7.42−7.38 (m, 1H), 7.28−7.21 (m, 3H), 5.84 (brs, 2H), 2.46 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 147.7, 146.5, 144.7, 141.7, 138.9, 133.9, 132.2, 130.3, 130.1, 129.2, 129.0, 128.2, 127.8 (127.84), 127.8 (127.75), 127.5, 127.4, 118.8, 107.0, 13.1. HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{25}H_{21}N_4$ 377.1766; found: 377.1763.

*8-Butyl-2,3,7-triphenylimidazo[1,2-c]pyrimidin-5-amine (**3o**).* **3o** was purified by TLC (hexane/ethyl acetate = 2/1) as a pale yellow solid (0.060 g, 48%); mp 242−245 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.67−7.57 (m, 5H), 7.52−7.45 (m, 6H), 7.41−7.38 (m, 1H), 7.28−7.21 (m, 3H), 5.86 (brs, 2H), 2.87−2.84 (m, 2H), 1.75−1.69 (m, 2H), 1.32−1.26 (m, 2H), 0.83 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 147.2, 147.0, 144.7, 141.6, 139.3, 133.9, 132.2, 130.4, 130.0, 128.9, 128.8, 128.1, 127.9, 127.7, 127.4, 118.5, 112.0, 31.3, 26.2, 22.2, 13.6. HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{28}H_{27}N_4$ 419.2236; found: 419.2239.

*2-Phenyl-[1,2,4]triazolo[1,5-c]quinazolin-5-amine (**3p**).* **3p** was purified by TLC (hexane/ethyl acetate = 2/1) as a white solid (0.052 g, 66%); mp 277−279 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.31−8.28 (m, 3H), 7.86 (brs, 2H), 7.73−7.70 (m, 1H), 7.62−7.54 (m, 4H), 7.43−7.40 (m, 1H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 162.4, 151.9, 145.0, 144.7, 132.1, 130.5, 130.1, 129.0, 127.0, 125.0, 123.4, 123.1, 113.3. HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{15}H_{12}N_5$ 262.1093; found: 262.1091.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c00680.

Copies of ^{1}H and ^{13}C NMR spectra of **3a**-**3p** (PDF)

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Notes

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