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Advanced Synthesis & Catalysis

Palladium-Nanoparticles-Catalyzed Oxidative Annulation of Benzamides with Alkynes for the Synthesis of Isoquinolones

Nidhi Sharma,[a] Rajib Saha,[a] Naziya Parveen,[a] and Govindasamy Sekar[a,*]

[a] Department of Chemistry, Indian Institute of Technology Madras, Chennai, Tamil Nadu – 600036, India
Fax: (+) 91 44 2257 4202; e-mail: gsekar@iitm.ac.in

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Abstract: A novel method to synthesize isoquinolones *via* oxidative annulation of *N*-alkoxy benzamides and alkynes using binaphthyl-stabilized palladium nanoparticles (Pd-BNP) as catalyst has been developed. This methodology affords various isoquinolone derivatives in good to excellent yields with high regioselectivities in the presence of air as oxidant. *N*-Methoxybenzothioamide was also found to undergo oxidative annulation with alkyne successfully and provided a sulfur analogue of isoquinolones in moderate yields. The Pd-BNP catalyst was easily recovered and reused up to four times without any apparent agglomeration.

Keywords: Palladium-nanoparticles; Oxidative annulation; Benzamides; Alkynes; Isoquinolones

The importance of nitrogen-containing heterocycles in medicinal chemistry has motivated many research groups to develop new and efficient protocols for their synthesis.[1–3] The conventional methods for the synthesis of these molecules involve prior fabrication of the coupling partners.[3,4] In this context, direct C–N bond formation through C–H functionalization has emerged as an efficient and alternative pathway towards their synthesis.[5] The main advantage of the C–H activation approach lies in its step- and atom-economical process.[6]

Isoquinolone is an important *N*-containing scaffold, present in many alkaloids and pharmacologically important molecules (Figure 1).[7,8] Among the reported synthetic protocols for its synthesis, chelation-assisted direct C–H bond activation through metal catalyzed cyclization of aromatic amides with alkynes is widely used.[9]

In recent years, the substantial growth has been made by utilizing metal nanoparticles for the synthesis of fine-chemicals and currently, a large number of synthetic protocols using nanocatalysts have been developed.[10] Though the nanocatalyst owns various properties[11] such as high surface area, easy recovery and reusability etc., most of the earlier methods to synthesize isoquinolones are homogeneous in nature. Development of new synthetic approaches where catalyst can be recovered and reused is still in demand. Li and Wang recently showed Pd/C catalyzed synthesis of isoquinolones through C–H functionalization of benzamides and alkynes.[12]

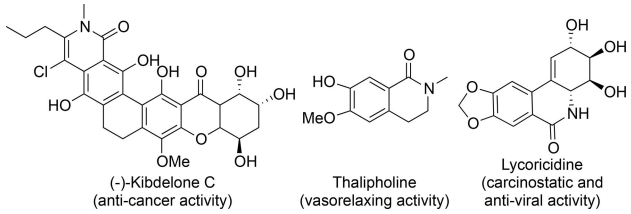


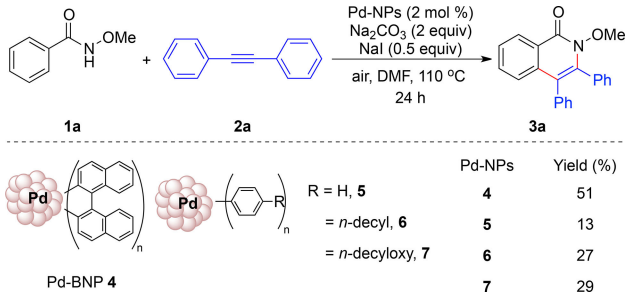
Figure 1. Representative example of biologically active molecules containing the isoquinolin-1(2*H*)-one skeleton.

As a part of our ongoing research towards the application of our Pd-BNP in organic transformations,[13] herein we report Pd-BNP (stabilized by Pd-$C_{(sp2)}$ covalent bond)[13a,14] catalyzed synthesis of isoquinolones through direct annulation of *N*-alkoxy benzamides and alkynes *via* C–H functionalization (Scheme 1).

Scheme 1. General representation of Pd-BNP catalyzed direct annulation reaction.

The preliminary investigation was started by choosing *N*-methoxy benzamide **1a** and diphenylethyne **2a** as model substrates with Pd-BNP **4** catalyst (2 mol%), Na_2CO_3 (2 equiv.) at 110 °C under air. The desired

annulated product **3a** was isolated in 23% yield after 24 h. Using NaI (0.5 equiv.) as an additive, the yield of **3a** was improved to 51% (Scheme 2). When, Pd-nanoparticles stabilized with other aryl backbones (**5**–**7**) were examined, inferior results than **4** were obtained.



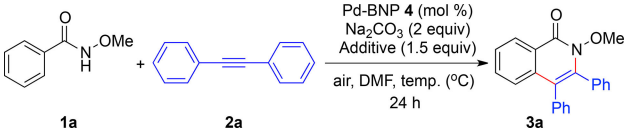
Scheme 2. Pd-nanoparticles catalyzed annulation reaction.

Further, various reaction parameters were examined to improve the yield using Pd-BNP **4** as catalyst and results are summarized in Table 1. Increasing the quantity of NaI, the yield of the product **3a** was increased to 65% (Table 1, entry 2). Then, various additives were screened and KI was found to be the best, yielding 70% of **3a** (entry 6). Then, various bases were screened, except Na_2CO_3 none of them given good yield (entries 7 to 11). Surprisingly, when the reaction was conducted in the absence of Na_2CO_3, **3a** was obtained in 86% yield, which shows that KI alone with Pd-BNP is effective to catalyze this reaction (entry 12).

Then the reaction was carried out in presence of various ligands such as triphenylphosphine and 1,10-phenanthroline; however, they were unable to improve the yield of product (entries 13 and 14). In the case of 1,10-phenanthroline not even a trace amount of product formation was observed which could be due to the strong co-ordination of N atoms present in the ligands to the active sites of palladium-BNP. When the reaction was carried out in the presence of KF instead of KI or without KI, no product formation was observed (entries 15 to 16) which could be due the iodide ion acting as a soft ligand. When the reaction was conducted with KBr, the reaction gave only 39% yield of product (entry 17). To find out the actual role of KI in the annulation reaction, various oxidizing agents as well as a reducing agent were screened. In presence of an oxidizing agent, the reaction is unable to give the corresponding annulation product; however, the reducing agent Ph_3SiH gave only 43% yield of product (entries 19 to 22).

Solvents such as dioxane, dicholoroethane and toluene suppressed the product formation, but polar aprotic solvents like dimethyl acetamide (DMA) and

Table 1. Optimization of reaction parameters[a].



Entry	Base	Additive	Temp (°C)	Yield (%)[b]
1	Na_2CO_3	NaI	110	53[c]
2	Na_2CO_3	NaI	110	65
3	Na_2CO_3	I_2	110	trace
4	Na_2CO_3	TBAI	110	10
5	Na_2CO_3	NIS	110	00
6	Na_2CO_3	KI	110	70
7	K_2CO_3	KI	110	41
8	KOH	KI	110	12
9	NaOH	KI	110	15
10	KO^{t}Bu	KI	110	00
11	Et_3N	KI	110	40
12	–	KI	110	86
13	–	KI	110	33[d]
14	–	KI	110	00[e]
15	–	KF	110	00
16	–	–	110	00
17	–	KBr	110	39
18	–	KI	100	00[f]
19	–	KI	100	00[g]
20	–	KI	100	00[h]
21	–	KI	100	00[i]
22		KI	100	43[j]
23	–	KI	100	93
24	–	KI	90	70
25	–	KI	100	71[k]
26	–	KI	100	94[l]
27	–	KI	100	90[l,m]
28	–	KI	100	11[l,n]
29	–	KI	100	90[l,o]
30	–	KI	100	77[p]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (3 equiv.), 10.6 mg of Pd-BNP (2 mol%, 10 wt% by ICP-OES analysis) in 2 mL DMF.
[b] Isolated yield.
[c] 1 equiv. of NaI was used.
[d] 10 mol% of PPh_3 was used.
[e] 10 mol% of 1,10-phenanthroline was used.
[f] Without Pd-BNP.
[g] 1.5 equiv. of TBHP(10% in water) was used.
[h] 1.5 equiv. of $K_2S_2O_8$ was used.
[i] 1.5 equiv. of oxone was used.
[j] 1.5 equiv. of Ph_3SiH was used
[k] 1.5 mol% of Pd-BNP was used.
[l] 2.5 equiv. of **2a** was used.
[m] O_2 balloon was used.
[n] Under N_2 atmosphere
[o] **1a** (7.0 mmol, 1 g) was used.
[p] 2 mol% of Palladium nanopowder (Pd, 99%, < 12 nm) was used.

DMSO gave good yield, however, the yield was less than the DMF.[15] Lowering the temperature to 100 °C, led to an increase in the yield (93%) (entry 23) and further reduction in temperature resulted in decrease of yield (entry 18). The progress of the reaction was also hindered when less quantity of Pd-BNP **4** was used (entry 19) and without **4**, formation of **3a** was not observed (entry 20).

Product **3a** was obtained in 94% yield when 2.5 equiv. of **2a** was used (entry 26). When the reaction was carried out under O_2 atmosphere (O_2 balloon), the result is similar to open air conditions (entries 26 and 27). Reaction under N_2 atmosphere gave 11% yield of **3a** which suggests that air is necessary for the annulation reaction (entry 28). To probe the practical utility and efficacy of the Pd-BNP catalyzed annulation reaction, a gram scale reaction was conducted under the optimized condition and product **3a** was isolated with 90% yield within 24 h (entry 29). Then the reaction was conducted with commercially available palladium nanopowder (Pd, 99%, <12 nm), and the reaction gave only 73% yield of product (entry 30).

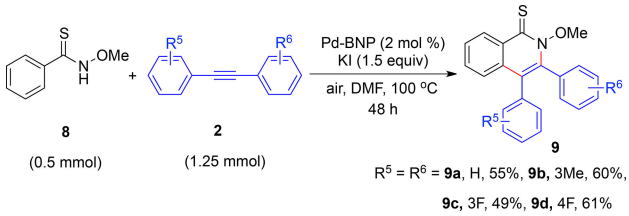
After establishing the optimized reaction conditions, the efforts toward the scope of the annulation reaction were established and the results are summarized in Table 2. Initially *N*-methoxybenzamides **1** containing various substituents such as alkyl-, aryl-, nitro- and halide- on the phenyl ring were reacted with 1,2-diphenylethyne **2a** for the synthesis of various isoquinolone derivatives (**3a–r**). It was observed that annulation reaction for electron-rich *N*-methoxybenzamides with **2a**, provided corresponding products in good yields (**3a–f** and **3l–n**) whereas electron-withdrawing substituents such as *para*-nitro group was present on phenyl ring of *N*-methoxybenzamide, even trace amount of product formation was not observed and *para*-chloro-substituted *N*-methoxybenzamide gave only 22% yield for the product **3g**.

This Pd-BNP catalyzed annulation protocol was found to be highly regioselective when *meta*-substituted *N*-methoxybenzamide and 3,4-disubsituted *N*-methoxybenzamides were employed. Annulation progressed toward the less sterically hindered side of the phenyl ring of *N*-methoxybenzamides and exclusively, single regioisomeric products (**3h–k**) with excellent yields were isolated. Interestingly, *ortho*-substitution on phenyl ring of *N*-methoxybenzamides had no adverse effect on this reaction and afforded various products (**3l–n**) in good yields. When *N*-ethoxy and *N*-benzyloxy benzamides were utilized, corresponding isoquinolone **3o** and **3p** were obtained in 93% and 76% yields, respectively. Employing *N*-substituted benzamides such as *N*-methyl, *N*-COOEt, *N*-benzyl and free-*N*H as substrates, even trace amount of corresponding isoquinolone derivatives formation was not observed. These results show that *N*-alkoxy group is necessary for this transformation.

N-(Benzyloxy)-4-methylbenzamide and *N*-(benzyloxy)-3,4-dimethoxybenzamide were also provided good yields of their corresponding products (**3q–r**). The heteroaromatic amides *viz*. *N*-methoxythiophene-2-carboxamide, *N*-benzyloxythiophene-2-carboxamide and *N*-methoxyfuran-2-carboxamide were also underwent annulation with **2a** and gave **3s**, **3t** and **3ae** in 78%, 73% and 68% yields, respectively. However, the annulation of nitrogen containing heteroaromatic amides such as *N*-methoxypyrol-2-carboxamide, *N*-methoxypyridine-2-carboxamide, *N*-methoxyindole-2-carboxamide and 1-methyl-1,4-dihydro-*N*-methoxy-4-oxo-3-quinolinecarboxamide, with **2a** under the optimized reaction conditions did not succeed.

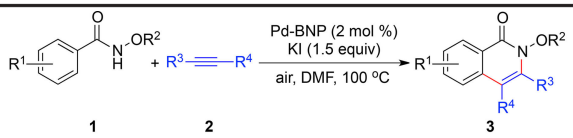
Subsequently, the scope of the annulation reaction with respect to symmetrical tolane derivatives **2** was studied. When methyl-, methoxy- and fluoro-substituted tolanes were treated with **1a**, moderate to good yields of various isoquinolones (**3u–y**) were obtained. Also, *N*-(benzyloxy)benzamide on reaction with 1,2-bis(4-fluorophenyl)ethyne yielded 69% of the product **3z**. Aliphatic alkyne such as 4-octyne on treatment with **1a** provided 49% yield of the isoquinolone **3aa**. Employing unsymmetrical tolanes such as *para*-anisylphenylacetylene and *para*-tolylphenylacetylene as precursors for annulation with **1a**, regioisomeric mixture with combined yield of 51% and 45% for **3ab** and **3ac** was obtained, respectively.[16] Isoquinolone **3ad** was formed in 45% yield on reaction of 1-phenyl-1-propyne with **1a**.[17] When the annulation of *N*-(benzyloxy)-4-methoxybenzamide was carried out with 2-butyne, it gave 32% the product **3af**. The annulation reaction of others alkynes, such as phenylacetylene, trimethylsilylacetylene, di-*tert*-butylethyne and di-isopropylethyne, with **1a** under the optimized reaction conditions failed to give the corresponding products.

Further, the study towards the Pd-BNP catalyzed direct annulation was extended by exploring the reactivity of *N*-methoxybenzothioamide **8** with symmetrical tolanes **2** (Scheme 3). The C–H/N–H bond functionalization progressed smoothly and provided



Scheme 3. Pd-BNP catalyzed direct annulation reaction of **8** with alkynes.

Table 2. Pd-BNP catalyzed oxidative annulation of benzamides and alkynes[a,b].



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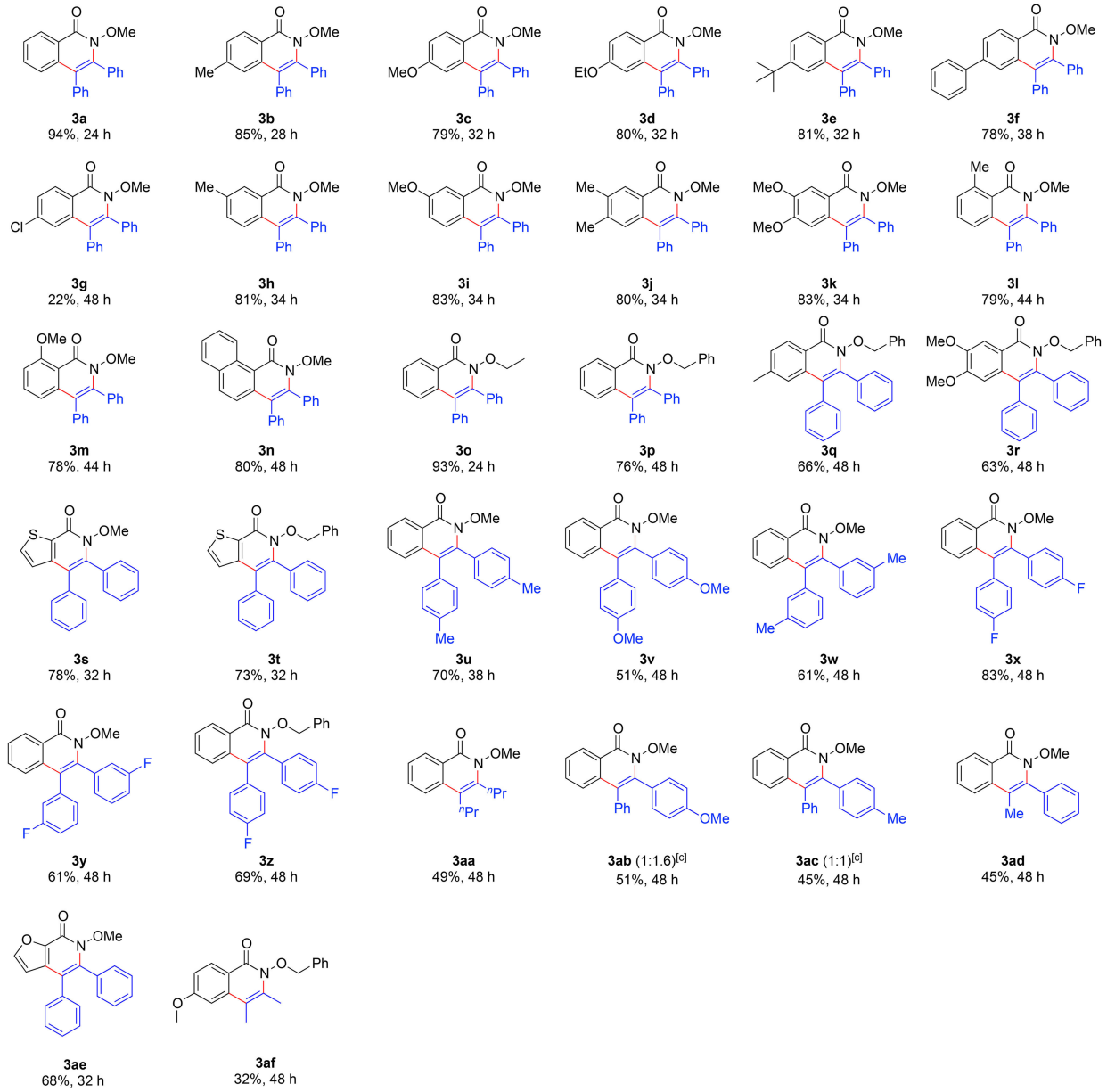
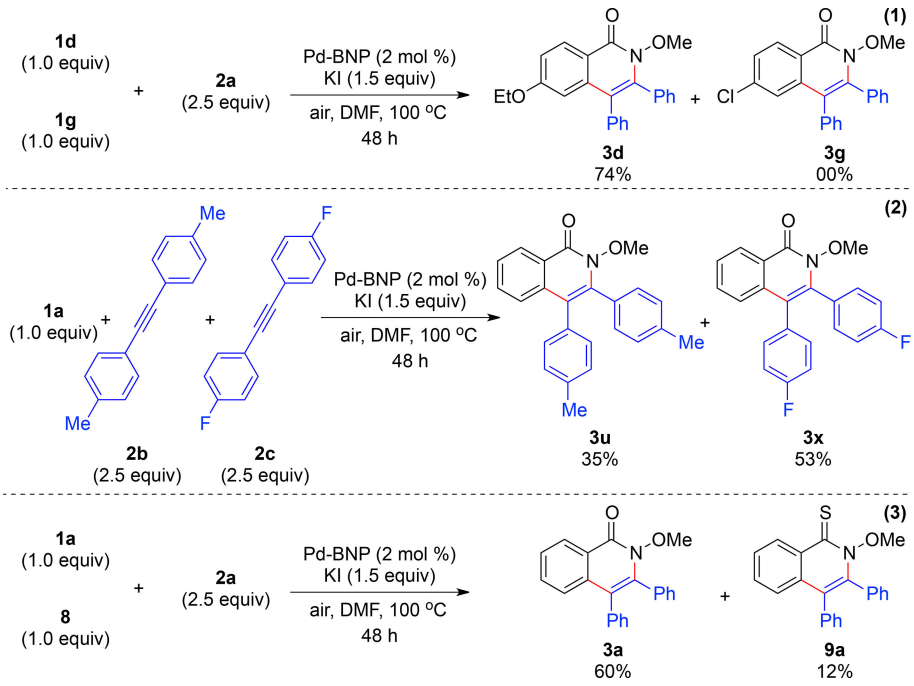


[a] Reaction conditions: 0.5 mmol of **1**, 2.5 equiv. of **2**, 10.6 mg of Pd-BNP and 2 mL DMF were used. [b] Isolated yield. [c] Two regioisomers were separated in a mixture and the regiosiomeric ratio of these compounds was determined using ^{1}H-NMR analysis.[15–17]

moderate yields for the desired sulfur analogue of isoquinolones (**9a–d**).

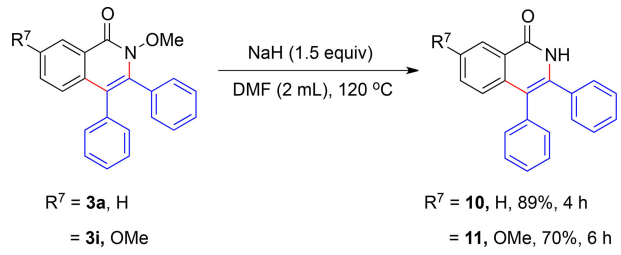
Intermolecular competitive reactions were conducted to study the mode of reactivity of *N*-methoxybenzamides and tolanes (Scheme 4). Reaction of 4-ethoxy-*N*-methoxybenzamide **1d** and 4-chloro-*N*-methoxybenzamide **1g** under the optimized conditions gave exclusively **3d** with 74% yield and even trace amount of **3g** was not observed (Scheme 4, eq. 1). This result implies that electron-donating ethoxy-substituted benzamide **1d** is more reactive towards the annulation reaction. Furthermore, when **1a** was



Scheme 4. Intermolecular competitive reactions.

treated with **2b** and **2c**, the corresponding products **3u** and **3x** were isolated in 35% and 53% yield, indicating that **2c** is more reactive than **2b** (Scheme 4, eq. 2). Similarly, treatment of *N*-methoxybenzamide **1a** and *N*-methoxybenzothioamide **8** with **2a** under the standard conditions provided products **3a** and **9a** in 60% and 12% yields (Scheme 4, eq. 3). This result clearly connotes that **1a** greatly favors the annulation reaction.

In addition, a one-pot annulation-*N*-demethoxylation[9h] reaction was carried out employing NaH as demethoxylating agent. NaH (1.5 equiv.) was added after the completion of the annulation and this resulted in 35% and 23% yields for **10** and **11**, respectively. When only *N*-demethoxylation reaction was conducted on isoquinolones **3a** and **3i**, good yields for the products **10** and **11** were obtained (Scheme 5).[18]



Scheme 5. *N*-Demethoxylation of **3a** and **3i**.

Attempts were made to investigate the reusability and recoverability of the Pd-BNP catalyst. The annulation reaction of **1a** was carried out at 2 mmol scale under the standard conditions. The catalyst was recovered and reused up to four catalytic cycles and the desired product **3a** was isolated in yields of 92%, 90%, 87% and 84% in successive runs. HR-TEM image of recovered Pd-BNP catalyst shows that there was no major change in the size of the nanoparticles. The average size of Pd-BNP was consistently around 5–6 nm (Figure 2).[19] ICP-OES analysis revealed that the very less Pd (0.48 wt%) was present in the solution withdrawn from filtrate after performing the hot filtration test. Hg poisoning test[14d] suggested that the reaction is catalyzed by both soluble Pd and Pd-BNP catalyst, but the main catalyst responsible for accel-

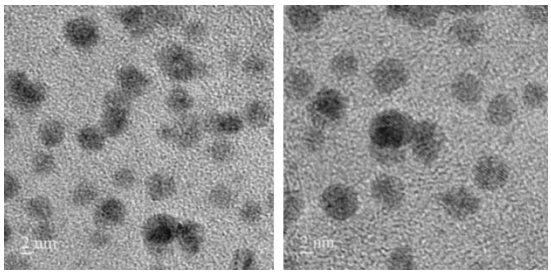


Figure 2. HR-TEM images of Pd-BNP catalyst: before (left) and after fourth (right) catalytic cycle.

erating the annulation reaction is the heterogeneous Pd-BNP.

In conclusion, an efficient method for the synthesis of isoquinolones employing Pd-BNP as catalyst through oxidative annulation of benzamides and alkynes has been developed. Electron-donating group substituted benzamides and alkynes produced various isoquinolones in good to excellent yield. For the first time, *N*-methoxybenzothioamide was utilized for the cyclization with tolanes and various sulfur analogues of isoquinolones were isolated in moderate yield. The Pd-BNP was easily recovered and reused up to four times without any apparent agglomeration. Filtration test and mercury poisoning experiments confirmed that the active catalyst for the annulation reaction is heterogeneous Pd-BNP.

Experimental Section

General Consideration

All reactions were carried out in reaction tubes under open to air atmosphere. All the solvents used to carry out the reactions were obtained from Fischer Scientific, India Pvt. Ltd. The reactions were monitored by thin-layer chromatography (TLC) using Merck silica gel 60 F_{254} precoated plates (0.25 mm) and visualized by UV fluorescence quenching using appropriate mixture of ethyl acetate and hexanes. Silica gel (particle size: 100–200 mesh) was purchased from Avra and used for column chromatography using hexanes and ethyl acetate mixture as eluent. K_2PdCl_4 (98%), aryl iodides, diphenylacetylene, 4-octyne, 1-phenyl-1-propyne, and 2-butyne were purchased from Sigma-Aldrich Company and Alfa-aesar. Palladium nanopowder (Pd, 99%, <12 nm) was purchased from NANOSHEL LLC. Other chemicals like $NaBH_4$, KI, NaI, TBAI and iodine were purchased from Avra and Spectrochem Pvt. Ltd., India. *Rec.*-BINAM was purchased from Gerchem Pvt. Ltd, Hyderabad, India and used as received. 1,1′-Binaphthyl,-2,2′ bis(diazoniumtetrafluoroborate) was prepared using literature reported procedure.[20] Calcium carbide was purchased from Merck Pvt. Ltd. Nanopure water was obtained from Barnstead nanopure water system. All the reactions were carried out in temperature controlled IKA magnetic stirrers. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 and 500 instruments. ^{1}H NMR spectra were reported relative to Me_4Si (δ 0.0 ppm) or residual $CDCl_3$ (δ 7.26 ppm) and ^{13}C NMR were reported relative to $CDCl_3$ (δ 77.16 ppm). FTIR spectra were recorded on a Nicolet 6700 spectrometer and were reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were recorded on Q-Tof Micro mass spectrometer.

Experimental procedure for the synthesis of isoquinolones 3

N-alkoxy benzamide **1** (0.5 mmol, 1 equiv.), alkyne **2** (1.25 mmol, 2.5 equiv.), Pd-BNP (10.6 mg, 2 mol%) and KI (0.75 mmol, 1.5 equiv.) were taken in a dry reaction tube equipped with a magnetic pellet. To this reaction mixture, 2 mL DMF was added and stirred at 100 °C in open to air until completion. The reaction was monitored using TLC and after completion, the reaction mixture was then allowed to cool to room temperature and extracted with ethyl acetate (3×10 mL), followed by brine solution. Then the organic phase was dried over Na_2SO_4 and concentrated in vacuum. The resulting reaction mixture was purified by column chromatography on silica gel (hexanes: ethyl acetate) to get isoquinolone as a desired product **3**.

2-Methoxy-3,4-diphenylisoquinolin-1(2*H*)-one (3a):[12a] Yield 94%; 154 mg; white solid; mp. 186–188 °C [lit. 188–190 °C];[9k] R_f 0.20 (20% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.59 (dd, J=8.0 Hz, 1.6 Hz, 1H), 7.59–7.49 (m, 2H), 7.28–7.19 (m, 9H), 7.10 (dd, J=8.0 Hz, 2.0 Hz, 2H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 158.3, 136.7, 135.6, 132.4, 131.81, 131.77, 130.8, 128.4, 128.2, 128.0, 127.6, 127.3, 126.9, 125.9, 118.5, 63.6; FTIR (KBr) 3010, 2978, 1662, 1560, 1508, 1073, 766, 727, 700, 679 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{22}H_{17}NO_2$ 328.1333; found: 328.1334.

2-Methoxy-6-methyl-3,4-diphenylisoquinolin-1(2*H*)-one (3b):[12a] Yield 85%; 145 mg; white solid; mp. 194–196 °C [lit. 196–198 °C];[9k] R_f 0.35 (20% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.47 (d, J=7.2 Hz, 1H), 7.34 (d, J=8.0 Hz, 1H), 7.27–7.17 (m, 8H), 7.12–7.06 (m, 2H), 7.02 (s, 1H), 3.72 (s, 3H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 158.3, 143.1, 140.1, 136.7, 135.7, 131.9, 131.8, 130.8, 128.6, 128.3, 128.2, 127.9, 127.6, 127.2, 125.5, 124.3, 118.3, 63.6, 22.1; FTIR (KBr) 3079, 3052, 2752, 1655, 1610, 1560, 1443, 1330, 1298, 1164, 875, 766, 721 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{23}H_{20}NO_2$ 342.1505; found: 342.1494.

2,6-Dimethoxy-3,4-diphenylisoquinolin-1(2*H*)-one (3c):[9i] Yield 79%; 141 mg; white solid; mp. 218–220 °C [lit. 220–221 °C];[9i] R_f 0.50 (30% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.59 (d, J=8.0 Hz, 1H), 7.25–7.17 (m, 8H), 7.12–7.06 (m, 3H), 6.61 (d, J=2.4 Hz, 1H), 3.72–3.69 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 162.9, 158.1, 140.7, 138.7, 135.6, 131.9, 131.7, 130.7, 130.0, 128.4, 128.3, 127.6, 127.3, 120.3, 118.0, 115.8, 107.7, 63.6, 55.4; FTIR (KBr) 3079, 3058, 2957, 1657, 1609, 1561, 1485, 1443, 1378, 1282, 1229, 1170, 1101, 763, 726, 694 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{23}H_{20}NO_3$ 358.1443; found: 358.1439.

6-Ethoxy-2-methoxy-3,4-diphenylisoquinolin-1(2*H*)-one (3d): Yield 80%; 149 mg; white solid; mp. 220–222 °C; R_f 0.60 (30% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.49 (d, J=8.8 Hz, 1H), 7.25–7.17 (m, 8H), 7.11–7.05 (m, 3H), 6.59 (d, J=2.4 Hz, 1H), 3.92 (q, J=7.2 Hz, 2H), 3.71 (s, 3H), 1.34 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 162.3, 158.1, 140.6, 138.7, 135.7, 131.9, 131.7, 130.7, 130.0, 128.4, 128.3, 127.6, 127.3, 120.2, 118.0, 108.4, 63.7, 63.6, 14.7; FTIR (KBr) 3058, 3020, 2983, 2817, 1662, 1606, 1555, 1469, 1443, 1282, 1212, 1111, 1042, 763, 694 cm^{-1}; HRMS (*m*/*z*): $[M+Na]^+$ calcd. for $C_{24}H_{21}NO_3Na$ 394.1419; found: 394.1395.

6-(Tert–butyl)-2-methoxy-3,4-diphenylisoquinolin-1(2*H*)-one (3e): Yield 81%; 155.3 mg; white solid; mp. 206–208 °C [lit. 203–205 °C];[10k] R_f 0.43 (20% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.50 (d, J=8.4 Hz, 1H),

7.59 (dd, $J=8.4$ Hz, 1.6 Hz,1H), 7.25–7.17 (m, 9H), 7.13–7.08 (m, 2H), 3.71 (s, 3H), 1.23 (s, 9H),; ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 158.2, 156.0, 140.0, 136.5, 135.6, 131.9, 131.7, 130.9, 128.3, 128.1, 127.7, 127.6, 127.2, 125.1, 124.2, 121.9, 118.8, 63.6, 35.4, 31.1; FTIR (KBr) 3064, 2962, 2862, 1662, 1614, 1582, 1480, 1443, 1314, 1181, 1095 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{26}H_{26}NO_2$ 384.1960; found: 384.1940.

2-Methoxy-3,4,6-triphenylisoquinolin-1(2*H*)-one (3f): Yield 78%; 157.3 mg; white solid; mp. 196–198 °C [lit. 195–197 °C];[9k] R_f 0.50 (40% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.71 (d, $J=8.4$ Hz, 1H), 7.82 (dd, $J=8.4$ Hz, 1.6 Hz, 1H), 7.58–7.53 (m, 2H), 7.51 (d, $J=1.2$ Hz, 1H), 7.49–7.44 (m, 2H), 7.43–7.37 (m, 1H), 7.35–7.25 (m, 8H), 7.23–7.17 (m, 2H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 158.2, 145.2, 140.5, 140.3, 137.1, 135.5, 131.78, 131.75, 130.8, 129.0, 128.6, 128.4, 128.30, 128.25, 127.7, 127.6, 127.4, 126.2, 125.4, 124.1, 118.6, 63.7; FTIR (KBr) 3056, 3026, 2926, 1663, 1560, 1528, 1496, 1478, 1379, 1265,1176, 1075, 759 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{28}H_{22}NO_2$ 404.1653; found: 404.1643.

6-Chloro-2-methoxy-3,4-diphenylisoquinolin-1(2*H*)-one (3g): Yield 22%; 39.8 mg; yellow solid; mp. 216–214 °C [lit. 216–218 °C];[9i] R_f 0.50 (20% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.55 (d, $J=2.4$ Hz, 1H), 7.50 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 7.25–7.20 (m, 9H), 7.10–7.05 (m, 2H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 157.3, 140.4, 135.2, 135.1, 133.1, 132.8, 131.6, 131.4, 130.7, 128.6, 128.4, 127.7, 127.6, 127.5, 127.3, 118.0, 63.7; FTIR (KBr) 3052, 2924, 1662,1604, 1479, 1325, 1255, 1159, 1038 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{22}H_{17}NClO_2$ 362.0947; found: 362.0949.

2-Methoxy-7-methyl-3,4-diphenylisoquinolin-1(2*H*)-one (3h): Yield 81%; 138.3 mg; white solid; mp. 192–194 °C; R_f 0.32 (20% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.38 (s, 1H), 7.38 (dd, $J=8.4$ Hz, 1.6 Hz, 1H), 7.25–7.19 (m, 8H), 7.15 (d, $J=8.4$ Hz, 1H), 7.11–7.07 (m, 2H), 3.72 (s, 3H), 2.50 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 158.3, 139.1, 137.1, 135.7, 134.4, 133.9, 131.8, 131.7, 130.9, 128.3, 128.2, 127.6, 127.5, 127.2, 126.4, 125.9, 118.5, 63.5, 21.4; FTIR (KBr) 3064, 2993, 2928, 1659, 1491, 1448, 1329, 1213, 1111 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{23}H_{19}NO_2$ 342.1448; found: 342.1453.

2,7-Dimethoxy-3,4-diphenylisoquinolin-1(2*H*)-one (3i):[9i] Yield 83%; 148.3 mg; white solid; mp. 190–192 °C [lit. 189–190 °C];[9i] R_f 0.36 (30% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.97 (d, $J=2.0$ Hz, 1H), 7.25–7.15 (m, 10H), 7.12–7.06 (m, 2H), 3.96 (s, 3H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 158.8, 157.9, 137.7, 135.8, 131.8, 131.7, 131.0, 128.3, 128.2, 127.8, 127.63, 127.59, 127.3, 122.9, 118.8, 107.6, 63.5, 55.9; FTIR (KBr) 3074, 3026, 2926, 1641, 1582, 1508, 1260, 1119, 778, 691 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{23}H_{20}NO_3$ 358.1445; found: 358.1457.

2-Methoxy-6,7-dimethyl-3,4-diphenylisoquinolin-1(2*H*)-one (3j):[9i] Yield 80%; 142.2 mg; light brown solid; mp. 220–222 [lit. 220–222 °C];[9i] R_f 0.32 (20% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.33 (s, 1H), 7.25–7.18 (m, 8H), 7.11–7.06 (m, 2H), 6.99 (s, 1H), 3.71 (s, 3H), 2.42 (s, 3H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 158.2, 142.4, 139.2, 136.6, 135.9, 134.8, 132.0, 131.8, 130.9,, 128.2, 128.1, 128.0, 127.5, 127.1, 126.1, 124.6, 118.2, 63.5, 20.5, 19.9; FTIR (KBr) 3100, 3064, 2963, 1661, 1589, 1488, 1216, 1090, 770 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{24}H_{22}NO_2$ 356.1651; found: 356.1663.

2,6,7-Trimethoxy-3,4-diphenylisoquinolin-1(2*H*)-one (3k):[9i] Yield 83%; 160.7 mg; light brown solid; mp. 196–198 °C; R_f 0.36 (40% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.94 (s, 1H), 7.25–7.18 (m, 8H), 7.13–7.07 (m, 2H), 6.60 (s, 1H), 4.05 (s, 3H), 3.72 (s, 3H), 3.70 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 157.6, 153.4, 149.4, 138.6, 135.9, 132.0, 131.9, 131.6, 130.9, 128.3, 127.6, 127.3, 120.5, 118.0, 107.7, 106.2, 63.6, 56.6, 55.9; FTIR (KBr) 3111, 3052, 2924, 1657, 1614, 1587, 1137, 1116, 726 cm^{-1}; HRMS (*m*/*z*): $[M+K]^+$ calcd. for $C_{24}H_{21}NO_4K$ 426.1090; found: 426.1108.

2-Methoxy-8-methyl-3,4-diphenylisoquinolin-1(2*H*)-one (3l): Yield 79%; 134.8 mg; white solid; mp. 190–192 °C [lit. 187–189 °C];[9k] R_f 0.54 (20% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.37 (d, $J=7.6$ Hz, 1H), 7.29–7.17 (m, 9H), 7.12–7.03 (m, 3H), 3.71 (s, 3H), 3.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 158.3, 139.1, 137.1, 135.7, 134.3, 133.9, 131.8, 131.7, 130.9, 128.3, 128.2, 127.6, 127.5, 127.2, 126.4, 125.9, 118.5, 63.5, 21.4; FTIR (KBr) 3074, 3016, 2978, 1646, 1593, 1560, 1489, 1443, 1325, 1165 cm^{-1}; HRMS (*m*/*z*): $[M+Na]^+$ calcd. for $C_{23}H_{20}NO_2Na$ 364.1313; found: 364.1296.

2,8-Dimethoxy-3,4-diphenylisoquinolin-1(2*H*)-one (3m): Yield 78%; 139.4 mg; white solid; mp. 194–196 °C; R_f 0.30 (60% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.42 (t, $J=8.0$ Hz, 1H), 7.24–7.15 (m, 8H), 7.10–7.04 (m, 2H), 6.93 (d, $J=8.0$ Hz, 1H), 6.76 (dd, $J=8.0$ Hz, 0.8 Hz, 1H), 4.04 (s, 3H), 3.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 161.3, 156.9, 141.0, 139.7, 136.2, 132.8, 132.0, 131.9, 130.5, 128.3, 128.2, 127.5, 127.2, 118.2, 117.4, 116.0, 108.5, 63.5, 56.6; FTIR (KBr) 3064, 3020, 2930, 1662, 1587, 1558, 1457, 1265, 1154, 1096 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{23}H_{20}NO_3$ 358.1443; found: 358.1459.

2-Methoxy-3,4-diphenylbenzo[h]isoquinolin-1(2*H*)-one (3n): Yield 80%; 150.9 mg; light black solid; mp. 160–162 °C [lit. 165–167 °C];[9k] R_f 0.45 (20% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 10.30 (d, $J=8.8$ Hz, 1H), 7.88–7.81 (m, 2H), 7.78–7.72 (m, 1H), 7.63–7.57 (m, 1H), 7.25–7.16 (m, 9H), 7.14–7.06 (m, 2H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 158.7, 141.6, 137.8, 136.1, 133.6, 132.2, 132.1, 132.0, 131.8, 130.6, 128.7, 128.5, 128.32, 128.26, 127.8, 127.7, 127.4, 126.8, 123.6, 120.1, 118.4, 63.7; FTIR (KBr) 3047, 3020, 2957, 1652, 1610, 1582, 1541, 1502, 1441, 1362, 1261, 1074, 767, 734, 698 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{26}H_{20}NO_2$ 378.1496; found: 378.1488.

2-Ethoxy-3,4-diphenylisoquinolin-1(2*H*)-one (3o): Yield 93%; 158.7 mg; white solid; mp. 190–192 °C; R_f 0.67 (30% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.60–8.55 (m, 1H), 7.59–7.49 (m, 2H), 7.29–7.17 (m, 9H), 7.14–7.08 (m, 2H), 4.02 (q, $J=6.8$ Hz, 2H), 0.91 (t, $J=6.8$ Hz, 3H)); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 158.5, 140.4, 136.6, 135.6, 132.3, 131.9, 131.8, 130.9, 128.3, 128.2, 127.9,

127.5, 127.3, 126.8, 126.5, 125.8, 118.2, 72.0, 13.0; FTIR (KBr) 3099, 3062, 2985, 2865, 1662, 1608, 1552, 1477, 1386, 1322, 1180, 1020 cm^{-1}.

2-(Benzyloxy)-3,4-diphenylisoquinolin-1(2*H*)-one (3p): Yield 76%; 153.3 mg; white solid; mp. 208–210 °C; R_f 0.46 (15% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.64–8.60 (m, 1H), 7.62–7.51 (m, 2H), 7.32–7.16 (m, 13H), 7.15–7.10 (m, 2H), 6.89–6.82 (m, 2H), 4.95 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 158.5, 140.5, 136.7, 135.6, 133.6, 132.4, 132.0, 131.8, 131.2, 130.0, 129.0, 128.4, 128.3, 127.9, 127.7, 127.3, 127.0, 126.6, 126.0, 118.4, 77.7; FTIR (KBr) 3117, 3057, 2957, 2865, 1663, 1604, 1560, 1508, 1477, 1457, 1375, 1170, 1105 cm^{-1}; HRMS (*m*/*z*): $[M+Na]^+$ calcd. for $C_{28}H_{21}NO_2Na$ 426.1470; found: 426..1467.

2-(Benzyloxy)-6-methyl-3,4-diphenylisoquinolin-1(2*H*)-one (3q): Yield 66%; 137.6 mg; white solid; mp. 208–210 °C; R_f 0.46 (15% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.51 (d, *J* = 6.8 Hz, 1H), 7.37 (dd, *J* = 6.4 Hz, 1.2 Hz, 1H), 7.29–7.21 (m, 9H), 7.20–7.17 (m, 2H), 7.15–7.11 (m. 2H), 6.87–6.82 (m, 2H), 4.93 (s, 2H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 158.5, 143.1, 140.4, 136.8, 135.7, 133.6, 132.1, 131.8, 129.4, 128.9, 128.6, 128.4, 128.3, 128.2, 127.9, 127.6, 127.2, 125.6, 124.3, 118.2, 77.2, 22.2; FTIR (KBr) 3073, 3060, 2982, 2853, 1662, 1614, 1554, 1481, 1441, 1330, 1170, 1076 cm^{-1}.

2-(Benzyloxy)-6,7-dimethoxy-3,4-diphenylisoquinolin-1(2*H*)-one (3r): Yield 63%; 146 mg; white solid; mp. 200–202 °C; R_f 0.36 (30% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.98 (s, 1H), 7.30–7.11 (m, 13H), 6.90–6.83 (m, 2H), 6.86 (s, 1H), 4.93 (s, 2H), 4.06 (s, 3H), 3.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 157.8, 153.4, 149.4, 139.0, 135.9, 133.7, 132.12, 132.08, 131.7, 131.3, 130.0, 129.0, 128.4, 128.3, 127.6, 127.3, 120.5, 117.8, 107.7, 106.2, 77.7, 56.4, 56.0; FTIR (KBr) 3106, 3072, 3025, 2990, 2843, 1668, 1608, 1583, 1481, 1332, 1170, 1118 cm^{-1}.

6-Methoxy-4,5-diphenylthieno[2,3-c]pyridin-7(6*H*)-one (3s):[9i] Yield 78%; 130 mg; white solid; mp. 202–204 °C [lit. 205–207 °C];[9i] R_f 0.47 (30% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.65 (d, *J* = 5.6 Hz, 1H), 7.30–7.17 (m, 8H), 7.13–7.06 (m, 2H), 6.97 (d, *J* = 5.2 Hz, 2H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 154.6, 145.1, 141.1, 136.1, 133.3, 131.3, 131.1, 130.9, 129.8, 128.6, 128.3, 127.8, 127.3, 125.0, 116.8, 63.9; FTIR (KBr) 3057, 3026, 2733, 1662, 1600, 1578, 1518, 1166 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{20}H_{15}NSO_2$ 334.0902; found: 334.0899.

6-(Benzyloxy)-4,5-diphenylthieno[2,3-c]pyridin-7(6*H*)-one (3t): Yield 73%; 149.5 mg; white solid; mp. 176–178; R_f 0.48 (20% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.76 (d, *J* = 5.2 Hz, 1H), 7.39–7.15 (m, 13H), 7.09 (d, J = 5.2 Hz, 1H), 6.96 (d, *J* = 7.2 Hz, 2H), 5.02 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 154.8, '45.1, 141.4, '36.1, 133.4, 133.3, 131.6, 131.4, 130.9, 130.1, 129.9, 129.0, 128.6, 128.4, 128.3, 127.8, 127.3, 125.1, 116.6, 78.1; FTIR (KBr) 3059, 3036, 2831, 1664, 1598, 1573, 1522, 1176, 1126 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{26}H_{20}NSO_2$ 410.1215; found: 410.1219.

2-Methoxy-3,4-di-*p*-tolylisoquinolin-1(2*H*)-one (3u): Yield 70%; 124.4 mg; white solid; mp. 150–152 °C [lit. 152–154 °C];[9k] R_f 0.53 (20% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.73 (d, *J* = 8.0 Hz, 1H), 7.74–7.62 (m, 2H), 7.41 (d, *J* = 8.8 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 2H), 7.23–7.17 (m, 4H), 7.14 (d, *J* = 8.0 Hz, 2H), 3.88 (s, 3H), 2.48–2.44 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 158.3, 140.1, 138.1, 136.9, 136.8, 132.6, 132.3, 131.5, 130.6, 128.94, 128.85, 128.3, 127.8, 126.7, 126.4, 125.9, 118.4, 63.5, 21.4, 21.3; FTIR (KBr) 3047, 3020, 2972, 1657, 1605, 1542, 1509, 1476, 1323, 1261, 1175, 1101, 817 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{24}H_{22}NO_2$ 356.1652; found: 356.1642.

2-Methoxy-3,4-bis(4-methoxyphenyl)isoquinolin-1(2*H*)-one (3v):[12a] Yield 51%; 98.8 mg; white solid; mp. 196–198 °C [lit. 193–195 °C];[9k] R_f 0. 30 (40% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.55 (dd, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.58–7.46 (m, 2H), 7.30–7.25 (m, 1H), 7.15 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.83–6.72 (m, 4H), 3.81–3.75 (m, 6H), 3.70 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 159.3, 158.6, 158.4, 140.0, 137.0, 132.8, 132.3, 132.2, 127.94, 127.86, 127.2, 126.7, 125.9, 124.1, 118.2, 113.1, 63.5, 55.28, 55.25; FTIR (KBr) 3078, 3046, 2972, 2924, 1642, 1602, 1575, 1559, 1522, 1485, 1383, 1260, 1209, 1135, 1096, 853, 803 cm^{-1}; HRMS (*m*/*z*): $[M+Na]^+$ calcd. for $C_{24}H_{21}NO_4Na$ 410.1395; found: 410.1396.

2-Methoxy-3,4-di–*m*-tolylisoquinolin-1(2*H*)-one (3w): Yield 61%; 108.4 mg; white solid; mp. 186–188 °C; R_f 0.30 (20% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.50 (d, *J* = 7.6 Hz, 1H), 7.25–7.14 (m, 2H), 7.10–6.90 (m, 7H), 6.87–6.76 (m, 2H), 3.67 (s, 3H), 2.30–2.15 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 158.3, 137.7, 137.1, 135.5, 132.4, 132.3, 131.7, 131.5, 129.1, 128.8, 127.99, 127.95, 127.9, 127.8, 127.4, 126.8, 126.4, 118.5, 63.6, 21.4; FTIR (KBr) 3020, 2925, 1657, 1600, 1519, 1481, 1164, 766, 705 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{24}H_{22}NO_2$ 356.1640; found: 356.1651.

3,4-Bis(4-fluorophenyl)-2-methoxyisoquinolin-1(2*H*)-one (3x): Yield 83%; 150.8 mg; white solid; mp. 206–208 °C [lit. 205–207 °C];[9i] R_f 0. 30 (20% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.57 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.62–7.50 (m, 2H), 7.25–7.17 (m, 3H), 7.10–7.02 (m, 2H), 7.00–6.91 (m, 4H), 3.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 162.5 (d, $J_{c\text{-}f}$ = 248.0 Hz), 162.0 (d, $J_{c\text{-}f}$ = 245.0 Hz), 158.2, 139.9, 136.4, 133.2 (d, $J_{c\text{-}f}$ = 8.0 Hz), 132.61 (d, $J_{c\text{-}f}$ = 8.0 Hz), 132.62, 131.3 (d, $J_{c\text{-}f}$ = 3.0 Hz), 128.0, 127.5 (d, $J_{c\text{-}f}$ = 4.0 Hz), 127.2, 126.5, 125.7, 117.7, 115.5 (d, $J_{c\text{-}f}$ = 21.0 Hz), 115.0 (d, $J_{c\text{-}f}$ = 22.0 Hz), 63.6; FTIR (KBr) 3069, 3052, 2983, 1657, 1609, 1544, 1507, 1485, 1223, 1154, 1101, 833, 780 cm^{-1}; HRMS (*m*/*z*): $[M+Na]^+$ calcd. for $C_{22}H_{15}NO_2F_2Na$ 386.0969; found: 386.0966.

3,4-Bis(3-fluorophenyl)-2-methoxyisoquinolin-1(2*H*)-one (3y): Yield 61%; 110.8 mg; white solid; mp. 198–200 °C; R_f 0. 48 (30% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.57 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.66–7.50 (m, 2H), 7.28–7.17 (m, 3H), 7.08–6.78 (m, 6H), 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 162.6 (d, $J_{c\text{-}f}$ = 246.0 Hz), 162.0 (d, $J_{c\text{-}f}$ = 246.0 Hz), 158.1, 138.9, 137.4 (d, $J_{c\text{-}f}$ = 8.0 Hz), 136.0, 133.4 (d, $J_{c\text{-}f}$ = 8.0 Hz), 132.7, 130.0, 129.5 (d, $J_{c\text{-}f}$ = 9.0 Hz), 128.1, 127.5 (d, $J_{c\text{-}f}$ = 3.0 Hz), 126.3, 126.62, 126.56 (d, $J_{c\text{-}f}$ = 4.0 Hz),, 125.6, 118.6 (d, $J_{c\text{-}f}$ = 21.0 Hz), 117.8 (d, $J_{c\text{-}f}$ = 23.0 Hz), 117.4, 115.9 (d, $J_{c\text{-}f}$ = 21.0 Hz), 114.7 (d, $J_{c\text{-}f}$ =

20.0 Hz), 63.8; FTIR (KBr) 3085, 3068, 2933, 1660, 1687, 1473, 132.6, 1228, 1160, 1054 cm^{-1}.

2-(Benzyloxy)-3,4-bis(4-fluorophenyl)isoquinolin-1(2*H*)-one (3z): Yield 69%; 151.6 mg; white solid; mp. 210–212 °C; R_f 0.30 (15% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.89 (d, J = 7.6 Hz, 1H), 7.92–7.80 (m, 2H), 7.59–7.41 (m, 6H), 7.38–7.31 (m, 2H), 7.28–7.16 (m, 6H), 5.22 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 162.6 (d, J_{c-f} = 247.0 Hz), 162.0 (d, J_{c-f} = 246.0 Hz), 158.4, 139.8, 136.5, 133.5, 133.3 (d, J_{c-f} = 8.0 Hz), 133.0 (d, J_{c-f} = 8.0 Hz), 132.6, 131.4 (d, J_{c-f} = 4.0 Hz), 129.9, 129.1, 128.5, 128.0, 127.9 (d, J_{c-f} = 4.0 Hz), 127.2, 126.6, 125.7, 117.5, 115.5 (d, J_{c-f} = 21.0 Hz), 114.9 (d, J_{c-f} = 22.0 Hz), 77.8; FTIR (KBr) 3074, 3031, 2854, 1655, 1609,1578, 1508, 1479, 1326,, 1223, 1158, 1095, 775, 750, 731 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{28}H_{20}NO_2F_2Na$ 440.1462; found: 440.1441.

2-Methoxy-3,4-dipropylisoquinolin-1(2*H*)-one (3aa): Yield 49%; 63.5 mg; yellow liquid; R_f 0.30 (10% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.47 (d, J = 8.0 Hz, 1H), 7.72–7.68 (m, 2H), 7.48–7.39 (m, 1H), 4.08 (s, 2H), 2.80–2.65 (m, 4H), 1.77–1.55 (m, 4H), 1.06 (q, J = 7.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 158.4, 140.0, 136.1, 132.2, 128.1, 126.4, 125.9, 123.2, 113.4, 63.9, 29.9, 29.7, 23.8, 23.2, 14.5, 14.4; FTIR (DCM) 3089, 2958, 2981, 2854, 1661, 1564, 1461, 1182, 1002 cm^{-1}.

2-Methoxy-3-(4-methoxyphenyl)-4-phenyl isoquinolin-1(2*H*)-one and 2-methoxy-4-(4-methoxyphenyl)-3-phenylisoquinolin-1(2*H*)-one (1:1.6)[15] (3ab): Yield 45%; 91.1 mg; white solid; mp. 174–176 °C; R_f 0. 37 (30% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.54 (d, J = 8.0 Hz, 2H), 7.57–7.43 (m, 4H), 7.28–7.18 (m, 10H), 7.13 (d, J = 8.4 Hz, 3H), 7.07 (d, J = 6.8 Hz, 2H), 6.97 (d, J = 8.4 Hz, 1H), 6.72 (t, J = 8.4 Hz, 4H), 3.73 (s, 6H), 3.71–3.66 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 159.4, 158.6, 158.4, 136.7, 135.8, 132.8, 132.4, 132.2, 131.8, 130.8, 128.33, 128.29, 127.9, 127.7, 127.2, 126.9, 126.8, 126.5, 126.4, 125.9, 125.8, 123.9, 118.6, 113.7, 113.0, 63.6, 63.5, 55.2; FTIR (KBr) 3178, 3172, 3062, 2933, 1664, 1610, 1511, 1442, 1324, 1290, 1247, 1176 cm^{-1}.

2-Methoxy-4-phenyl-3-(*p*–tolyl) isoquinolin-1(2*H*)-one and 2-methoxy-3-phenyl-4-(*p*–tolyl)isoquinolin-1(2*H*)-one (1:1)[15] (3ac): Yield 51%; 76.8 mg; light brown solid; mp. 152–154 °C; R_f 0. 28 (20% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.60–8.55 (m, 2H), 7.58–7.48 (m, 4H), 7.29–7.21 (m, 10H), 7.15–7.07 (m, 4H), 7.05–6.95 (m, 6H), 3.73 (s, 6H), 2.31–2.27 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 158.4, 158.3, 140.2, 140.1, 138.2, 136.9, 136.7, 135.8, 132.4, 132.3, 131.9, 131.8, 131.5, 130.8, 130.7, 129.0, 128.7, 128.4, 128.2, 127.9, 127.6, 127.2, 126.83, 126.78, 126.51, 126.45, 126.0, 125.8, 118.4, 63.6, 21.4, 21.3; FTIR (KBr) 3120, 3079, 2985, 2954, 1650, 1594, 1509, 1440, 1359, 1278, 1182, 1120, 1070 cm^{-1}.

2-Methoxy-4-methyl-3-phenylisoquinolin-1(2*H*)-one (3ad): Yield 45%; 59.7 mg; light brown solid; mp. 176–178 °C; R_f 0. 45 (20% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.58–8.25 (m, 1H), 7.77–7.68 (m, 2H), 7.57–7.52 (m, 1H), 7.51–7.46 (m, 3H), 7.42–7.38 (m, 2H), 3.68 (s, 3H), 2.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 158.2, 139.3, 136.6, 132.5, 132.4, 131.2, 130.3, 128.9, 128.3, 128.2, 126.8, 123.7, 110.5, 63.5, 14.5; FTIR (KBr) 3147, 3049, 2937, 1648, 1569, 1509, 1440, 1186, 1105 cm^{-1}.

6-Methoxy-4,5-diphenylfurano[2,3-c]pyridin-7(6*H*)-one (3ae):[9i] Yield 68%; 108 mg; white solid; mp. 140–141 °C R_f 0.37 (30% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 500 MHz, ppm) δ 7.78 (s, 1H), 7.35–7.25 (m, 5H), 7.24- 7.16 (m, 3H), 7.07 (d, J = 7.5 Hz, 2H), 6.57 (d, J = 1.5 Hz, 1H), 3.71 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz, ppm) δ 149.9, 148.7, 142.6, 140.4, 135.2, 133.2, 131.2, 131.1, 130.3, 128.7, 128.3, 127.8, 127.2, 113.4, 107.6, 64.0; FTIR (KBr) 3401, 2968, 2927, 1684, 1625, 1586, 1440, 1194, 1128 cm^{-1}. HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{20}H_{15}NO_3$ 317.3440; found: 318.1147.

2-(benzyloxy)-6-methoxy-3,4-dimethylisoquinolin-1(2*H*)-one (3af): Yield 32%; 50.0 mg; white solid; mp. 100–102 °C; R_f 0.56 (30% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.43 (d, J = 8.8 Hz, 1H), 7.59–7.53 (m, 2H), 7.43–7.37 (m, 3H), 7.06 (dd, J = 2.4 Hz, J = 9.2 Hz,1H), 6.97 (d, J = 2.4 Hz, 1H), 5.23 (s, 2H), 3.93 (s, 3H), 2.39 (s, 3H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 162.9, 158.4, 138.7, 136.7, 134.4, 130.1, 129.9, 1129.2, 128.8, 119.8, 114.7, 107.7, 104.9, 55.6, 14.2, 13.8; FTIR (KBr) 3019, 2922, 2791, 2373, 2347, 1589, 1528, 1429, 1170 cm^{-1}; HRMS (*m*/*z*): $[M+Na]^+$ calcd. for $C_{19}H_{19}NO_3Na$ 332.3650; found: 332.1262.

Experimental procedure for the annulation of *N*-Methoxybenzothioamide 8 with alkyne 2

N-Methoxybenzothioamide **8** (0.5 mmol, 1 equiv.), alkyne **2** (1.25 mmol, 2.5 equiv.), Pd-BNP (10.6 mg, 2 mol %) and KI (0.75 mmol, 1.5 equiv.) were taken in a dry reaction tube equipped with a magnetic pellet. To this reaction mixture, 2 mL of DMF was added and stirred at 100 °C in open to air until completion. The reaction was monitored using TLC. After completion, the reaction mixture was then allowed to cool to room temperature and extracted with ethyl acetate (3 × 10 mL), followed by brine solution. Then the organic phase was dried over Na_2SO_4 and concentrated in vacuum. The resulting reaction mixture was purified by column chromatography on silica gel (hexanes: ethyl acetate) to get isoquinolone as a desired product **9**.

2-Methoxy-3,4-diphenylisoquinoline-1(2*H*)-thione (9a): Yield 55%; 94.4 mg; white solid; mp. 188–190 °C; R_f 0.27 (20% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.58 (d, J = 7.2 Hz, 1H), 7.60–7.47 (m, 2H), 7.30–7.18 (m, 9H), 7.10 (d, J = 6.4 Hz, 2H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 158.3, 140.1, 136.6, 135.6, 132.4, 131.7, 130.8, 128.4, 128.2, 127.9, 127.6, 127.3, 126.9, 126.5, 125.9, 118.5, 63.6; FTIR (KBr) 3100, 3031, 1662, 1603, 1576, 1550, 1475, 1368, 1320, 1175, 1122, 967, 694 cm^{-1}; HRMS (*m*/*z*): $[M+Na]^+$ calcd. for $C_{22}H_{17}NSONa$ 366.0929; found: 366.0941.

2-Methoxy-3,4-di-*m*-tolylisoquinoline-1(2*H*)-thione (9b): Yield 60%; 111.3 mg; light brown solid; mp. 194–196 °C; R_f 0.35 (20% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.59–8.55 (m, 1H), 7.59–7.47 (m, 2H), 7.28–7.24 (m, 1H), 7.14–6.98 (m, 6H), 6.95–6.86 (m, 2H), 3.74 (s, 3H), 2.28–2.21 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz,

ppm) δ 158.3, 140.2, 137.7, 137.1, 136.8, 135.5, 132.4, 132.3, 131.7, 131.5, 129.1, 128.8, 127.99, 127.95, 127.9, 127.8, 127.4, 126.8, 126.5, 126.0, 118.5, 63.6, 21.4; FTIR (KBr) 3096, 3047, 2983, 1665, 1605, 1552, 11691036, 999, 773, 756 cm^{-1}; HRMS (*m*/*z*): $[M+Na]^+$ calcd. for $C_{24}H_{21}NSONa$ 394.1242; found: 394.1260.

3,4-Bis(3-fluorophenyl)-2-methoxyisoquinoline-1(2*H*)-thione (9c): Yield 49%; 92.9 mg; white solid; mp. 166–168 °C; R_f 0. 48 (30% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.64–8.54 (m, 1H), 7.70–7.45 (m, 2H), 7.28–7.17 (m, 3H), 7.10–6.75 (m, 6H), 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 163.9 (d, $J_{c\text{-}f}$=246.0 Hz), 163.5 (d, $J_{c\text{-}f}$=246.0 Hz), 158.2, 138.9, 137.4 (d, $J_{c\text{-}f}$=8.0 Hz), 136.0, 133.4 (d, $J_{c\text{-}f}$=8.0 Hz), 132.7, 130.0, 129.5, 129.4, 128.1, 127.5 (d, $J_{c\text{-}f}$=3.0 Hz), 127.4, 126.64, 126.57 (d, $J_{c\text{-}f}$=4.0 Hz), 118.6 (d, $J_{c\text{-}f}$=21.0 Hz), 117.8 (d, $J_{c\text{-}f}$=22.0 Hz), 117.4, 115.9 (d, $J_{c\text{-}f}$=21.0 Hz), 114.7 (d, $J_{c\text{-}f}$=21.0 Hz), 63.8; FTIR (KBr) 3064, 2931, 1668, 1633, 1596, 1475, 1438, 1336, 1197, 1091 cm^{-1}.

3,4-Bis(4-fluorophenyl)-2-methoxyisoquinoline-1(2*H*)-thione (9d): Yield 61%; 115.7 mg; white solid; mp. 198–200 °C; R_f 0.35 (20% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.59–8.55 (m, 1H), 7.61–7.50 (m, 2H), 7.24–7.18 (m, 3H), 7.09–7.02 (m, 2H), 6.99–6.91 (m, 4H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 162.6 (d, $J_{c\text{-}f}$=247.0 Hz), 162.0 (d, $J_{c\text{-}f}$=246.0 Hz), 158.2, 139.4, 136.5, 133.3 (d, $J_{c\text{-}f}$=8.0 Hz), 132.63 (d, $J_{c\text{-}f}$=8.0 Hz), 132.61, 131.3 (d, $J_{c\text{-}f}$=3.0 Hz), 128.1, 127.6 (d, $J_{c\text{-}f}$=4.0 Hz), 127.2, 126.6, 125.5, 117.7, 115.5 (d, $J_{c\text{-}f}$=22.0 Hz), 115.1 (d, $J_{c\text{-}f}$=21.0 Hz), 63.6; FTIR (KBr) 3065, 3026, 2925, 1663, 1609, 1560, 1508, 1477, 1326, 1159, 1095, 929, 836, 775 cm^{-1}; HRMS (*m*/*z*): $[M+Na]^+$ calcd. for $C_{22}H_{15}NSOF_2Na$ 402.0740; found: 402.0738.

Experimental procedure for *N*-demethoxylation of 3a and 3i

To a stirred solution of *N*-methoxyisoquinolone **3a** or **3i** (0.25 mmol, 1 equiv.) in 2 mL DMF, NaH (0.375 mmol, 60% in mineral oil, 1.5 equiv.) was added and resulted reaction mixture was stirred at 120 °C until completion and monitored by TLC. After completion, the reaction mixture was allowed to cool to room temperature and extracted with ethyl acetate (3×10 mL), followed by brine solution. Then the organic phase was dried over Na_2SO_4 and concentrated in vacuum. The resulting reaction mixture was purified by column chromatography on silica gel (hexanes: ethyl acetate) to get the desired product.

3,4-Diphenylisoquinolin-1(2*H*)-one (10): Yield 89%; 66.1 mg; white solid; mp. 240–242 °C [lit. 242–246 °C];[21] R_f 0.45 (50% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 9.31 (s, 1H), 8.54 (dd, *J*=8.0 Hz, 1.2 Hz, 1H), 7.70–7.62 (m, 1H), 7.60–7.53 (m, 1H), 7.44–7.28 (m, 10H), 7.27–7.23 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 162.9, 138.8, 137.2, 135.9, 135.2, 132.8, 132.0, 129.3, 128.8, 128.5, 127.6, 127.5, 126.8, 125.8, 125.3, 117.4; FTIR (KBr) 3038, 3010, 2972, 1643, 1583, 1563, 1548, 1498, 1418, 1259 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{21}H_{16}NO$ 298.1239; found: 298.1235.

7-Methoxy-3,4-diphenylisoquinolin-1(2*H*)-one (11): Yield 70%; 62.5 mg; white solid; mp. 248–250 °C [lit. 246–248 °C];[22] R_f 0.36 (40% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ 9.31 (s, 1H), 7.88 (d, *J*=2.8 Hz, 1H), 7.32–7.27 (m, 4H), 7.25–7.20 (m, 6H), 7.19–7.15 (m, 2H), 3.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 162.5, 158.7, 136.0, 135.3, 134.8, 132.8, 131.9, 129.4, 128.54, 128.49, 128.5, 127.6, 127.4, 126.4, 123.2, 117.4, 55.8; FTIR (KBr) 3058, 3026, 2967, 1638, 1578, 1560, 1524, 1484, 1445, 1260, 1121, 1031 cm^{-1}; HRMS (*m*/*z*): $[M+Na]^+$ calcd. for $C_{22}H_{17}NO_2Na$ 350.1156; found: 350.1144.

Experimental procedure for recovery of the Pd-BNP catalyst

For recyclability of Pd-BNP, the reaction was repeated with *N*-methoxybenzamide **1a** as substrate in 2.0 mmol scale retaining the same conditions such as 1,2-diphenylethyne **2a** (2.5 equiv.), KI (1.5 equiv.), and 3 mL DMF under open to air condition at 100 °C, except using the recovered Pd-BNP catalyst rather than fresh catalyst. After completion of the annulation reaction, the reaction mixture was allowed to cool to room temperature. Ethyl acetate (5 mL) was added to the reaction mixture and centrifuged. The liquid then decanted to a 50 mL conical flask. Again ethyl acetate (5 mL) was added and centrifuged and decanted to the same conical flask, this procedure was repeated up to two to three times. After that the catalyst was washed with nano pure water (5 mL) and ethanol (5 mL) two to three times. Finally, the resulting solid black coloured particles (Pd-BNP) dried under vacuum. The dried catalyst was reused for further catalytic cycle. The collected liquid was extracted with ethyl acetate (3×10 mL), followed by brine solution. Then the organic phase was dried over Na_2SO_4 and concentrated in vacuum. The resulting reaction mixture was purified by column chromatography on silica gel (hexanes: ethyl acetate) to afford 2-methoxy-3,4-diphenylisoquinolin-1(2*H*)-one **3a** as desired product.

Filtration Test

To determine the leaching of Pd-BNP catalyst in the Pd-BNP catalyzed annulation reaction, a filtration test was carried out under the standard reaction condition.

N-methoxybenzamide **1a** (1.0 mmol, 1.0 equiv.)), 1,2-diphenylethyne **2a** (2.5 equiv.), Pd-BNP catalyst (21.2 mg, 2 mol%), KI (1.5 equiv.) and 1,2,4,5-tetramethylbenzene (internal standard) (1 equiv.) in 4 mL DMF were taken in oven dried reaction tube equipped with magnetic pellet and stirred at 100 °C in open to air conditions. After 4 h of reaction, reaction mixture was centrifuged; filtered and Pd-BNP catalyst was separated from the reaction mixture. From the mother liquid (filtrate), 1.5 mL of filtrate was taken and extracted with ethylacetate and ^1H NMR showed that 28% yield of **3a** was obtained. From the remaining mother liquid i.e., Pd-BNP free-reaction mixture, a small amount of aliquot was withdrawn for ICP-OES analysis and rest amount of filtrate was then used for annulation reaction under the similar conditions and continued up to 24 h and 35% yield of **3a** was obtained (yield was determined by ^1H NMR).

Mercury Poisoning Experiment

Mercury poisoning experiment was performed to support that the annulation reaction of *N*-methoxybenzamides and alkynes was accelerated by Pd-BNP catalyst not by the leached Pd. Three sets of reactions were conducted:

In first set of reaction, Hg (30 equiv.) and Pd-BNP (2 mol%) in DMF in presence of air were stirred at room temperature for 2 h, then other reagents: **1a** (2 mmol, 1.0 equiv.), **2a** (2.5 equiv.), Pd-BNP (2 mol%), KI (1.5 equiv.) and 1,2,4,5-tetramethylbenzene (internal standard) (1.0 equiv.) were added and stirred at 100 °C. Even trace amount of product **3a** was not detected in the reaction, even continue the reaction for 48 h.

In second set of reaction, Hg (30 equiv.) was added at a time with all other reagents: **1a** (2 mmol, 1.0 equiv.), **2a** (2.5 equiv.), Pd-BNP (2 mol%), KI (1.5 equiv.) and 1,2,4,5-tetramethylbenzene (internal standard) (1.0 equiv.) in presence of air in DMF solvent and stirred at 100 °C up to 48 h. Complete inhibition in the product **3a** formation was observed.

In third set of reaction, Hg (30 equiv.) was added after continuing the standard reaction for 4 h at 29% yield for **3a**, slight progress in the reaction was observed and 38% yield of **3a** was obtained and yield was determined by ^{1}H-NMR spectra.These results displayed that leached Pd and Pd-BNP catalyst catalyzed the annulation reaction. But heterogeneous Pd-BNP is more effective toward this reaction.

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[15] See the supporting information for details.

[16] Due to very less polarity difference, regioisomeric mixtures of **3ab** and **3ac** were inseparable. Regioisomeric ratio of these compounds was determined by using deconvolution technique. Resolving the ^{1}H-NMR peaks at range between 367–3.62 ppm for **3ab** and 2.32–2.27 ppm for **3ac**, shows that the presence of 1:1.6 and 1:1 ratio for regioisomers in these compounds.

[17] The structure of **3ad** was determined by single crystal XRD analysis. CCDC-1503957 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[18] To examine the effect of KI and Pd-BNP, demethoxylation was carried out using pure **3a** with the addition of NaH (1.5 equiv.), KI (1.5 equiv.) and Pd-BNP (2 mol%). The reaction gave only a trace amount of product **3a**. Then the reaction was carried out in the presence of 3 equiv. of NaH, KI (1.5 equiv.) and Pd-BNP (2 mol%). Surprisingly, the yield of the demethoxylation product was 47%. This result shows that KI and Pd-BNP play a role in reducing the yield of demethoxylation product in the one-pot reaction.

[19] After the annulation reaction, the Pd-BNP has similar particle size, shapes and reactivity. It shows that Pd does not disconnect from the aryl back bond.

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UPDATES

Palladium-Nanoparticles-Catalyzed Oxidative Annulation of Benzamides with Alkynes for the Synthesis of Isoquinolones

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N. Sharma, R. Saha, N. Parveen, G. Sekar*