Accepted Manuscript

Synthesis of pyrrolo-heterocycles via Pd-loaded zeolite catalyzed annulation of *o*-haloaromatic amine with terminal alkynes

Eul Kgun Yum, Ki Bum Hong

PII: S0040-4020(17)31010-4

DOI: 10.1016/j.tet.2017.10.002

Reference: TET 29005

To appear in: *Tetrahedron*

Received Date: 24 July 2017

Revised Date: 26 September 2017

Accepted Date: 2 October 2017

Please cite this article as: Yum EK, Hong KB, Synthesis of pyrrolo-heterocycles via Pd-loaded zeolite catalyzed annulation of *o*- haloaromatic amine with terminal alkynes, *Tetrahedron* (2017), doi: 10.1016/j.tet.2017.10.002.

Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

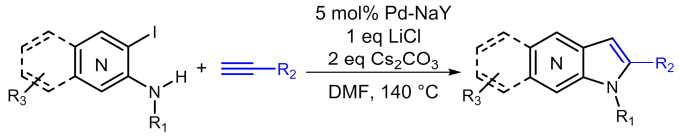
Synthesis of Pyrrolo-Heterocycles via Pd-loaded Zeolite Catalyzed Annulation of *o*-Haloaromatic Amine with Terminal Alkynes

Leave this area blank for abstract info.

Eul Kgun Yum[a] and Ki Bum Hong[b, *]

[a]*Department of Chemistry, Chungnam National University, Yusung, Daejon 34145, Korea*

[b]*New Drug Development Center (NDDC), Daegu-Gyeongbuk Medical Innovation Foundation (DGMIF), 80 Cheombok-ro, Dong-gu, Daegu, Korea*



Tetrahedron
journal homepage: www.elsevier.com

Synthesis of Pyrrolo-Heterocycles via Pd-loaded Zeolite Catalyzed Annulation of *o*-Haloaromatic Amine with Terminal Alkynes

Eul Kgun Yum[a] and Ki Bum Hong[b,*]

[a]*Department of Chemistry, Chungnam National University, Yusung, Daejon 34145, Korea*
[b]*New Drug Development Center (NDDC), Daegu-Gyeongbuk Medical Innovation Foundation (DGMIF), 80 Cheombok-ro, Dong-gu, Daegu, Korea*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Pd-zeolite
Heteroannulation
Pyrrolopyridine
Pyrroloquinoline
Terminal alkyne

ABSTRACT

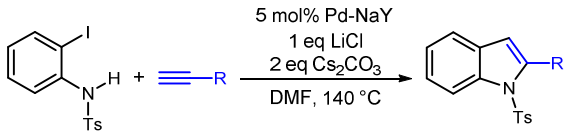
A Pd-loaded zeolite-catalyzed heteroannulation of various 2-iodopyridines and 2-iodoquinolines with terminal alkyne is demonstrated. This approach provides a rapid and convergent synthesis toward a diverse range of pyrrolo-pyridines (azaindoles) and pyrrolo-quinoline ring systems. The Pd-zeolite catalyst can be reused within the same reaction without reactivation of the Pd-zeolite catalyst. Furthermore, Pd-zeolite catalysis is an interesting alternative to homogeneous catalysis for the synthesis of heterocycles.

1. Introduction

Pd-catalyzed coupling reactions such as the Heck, Stille, Suzuki, Sonogashira, and Buchwald-Hartwig reactions are extensively used to form carbon–carbon, carbon–oxygen, and carbon–nitrogen bonds.[1-2] Palladium-catalyzed bond forming processes have proven to be a powerful and useful tool for the synthesis of heterocycles.[3] The increasing demands for the synthesis of heterocycle building blocks have prompted organic chemists to engage in studies directed towards the development of simple, novel, and more efficient methodologies.[4] Most palladium-catalyzed coupling reactions for the synthesis of various heterocycles have employed homogeneous palladium catalysts in the presence of base and ligand. Although homogeneous Pd catalysis has many advantages, one drawback is that it is difficult to recycle this type of catalyst. The development of low-cost and environmentally benign methodologies, a cornerstone of green chemistry, has shifted attention to immobilization processes due to their advantages in product isolation and catalyst reuse.[5] More specially, several catalyst immobilization methods use diverse solid supports such as metal oxide, silica, carbon, and zeolite. These supports were reported emphasizing the formation of nanoparticle catalysts. [6-9]

Zeolites have received great attention as a catalyst supporter due to the possible structural modification of their chemical and physical properties. These properties include acidity, basicity, hydrophobicity, hydrophilicity, size, shape selectivity, and thermal stability.[10-11] The use of zeolites and mesoporous materials in synthesis and industrial applications are extremely important due to their acidic properties and their ability to be reused. Several groups have reported the use of Pd-zeolite catalysts in Heck, Suzuki, and Sonogashira reactions as they minimize leaching and catalyst agglomeration.[11-15] Our research also describes a direct synthesis of 2-substituted indoles via a Sonogashira coupling and sequent cyclization of protected 2-iodoanilines with terminal alkynes using a heterogeneous Pd-zeolite catalyst system (Scheme 1).[16] One important finding within this study was that the Pd-zeolite catalyst could be used upwards of five times under the same reaction conditions without catalyst regeneration.

Scheme 1. 2-Substituted Indole Synthesis using Heterogeneous Pd Catalyst



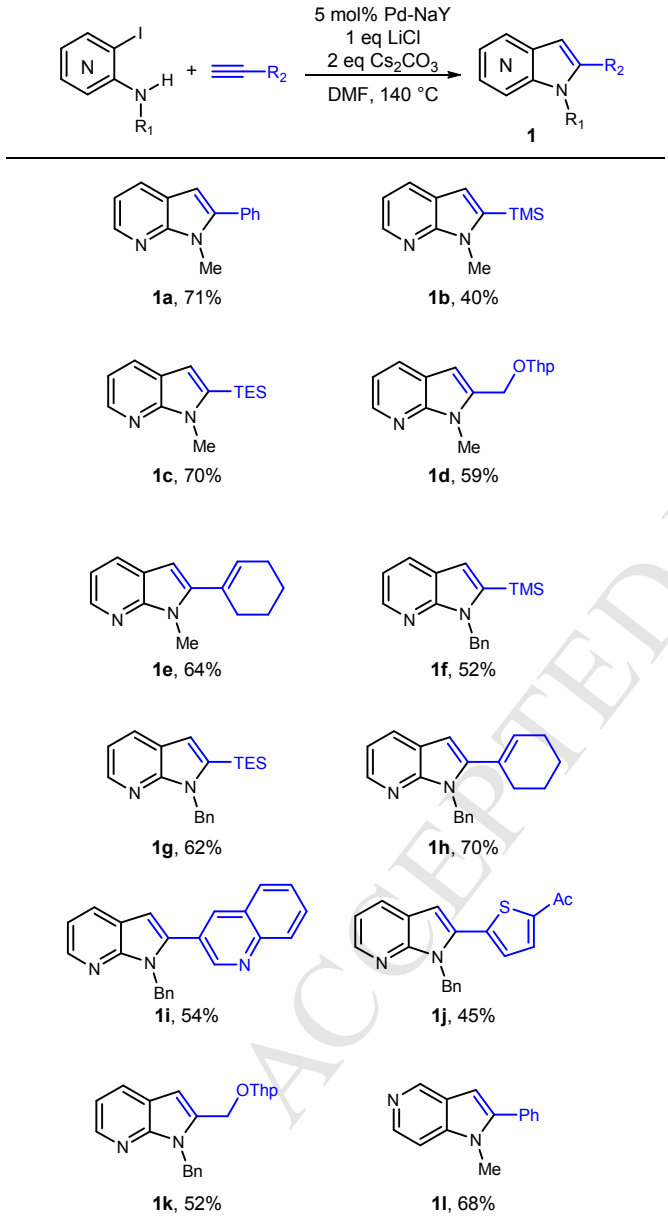
(1)

Many groups have previously reported Pd-zeolite catalysts as a means of carbon-carbon bond formations within Heck, Suzuki, and Sonogashira reactions.[11] However, the synthetic approach to heterocycles using Pd-zeolite catalysts were limited in literature.[16-19] As interests in developing metal-catalyzed synthetic methods for biologically active heterocycles such as indoles[16,20]azaindoles,[21] pyrrolo-quinoines,[22] carbazoles,[23] and thiazoles grew,[24] we further examined the synthesis of pyrrolo-pyridines and pyrrolo-quinolines under our established Pd-zeolite-catalyzed heteroannulation[16] using *o*-aminoazaarylhalides and terminal alkynes as coupling partners.

2. Results/Discussion

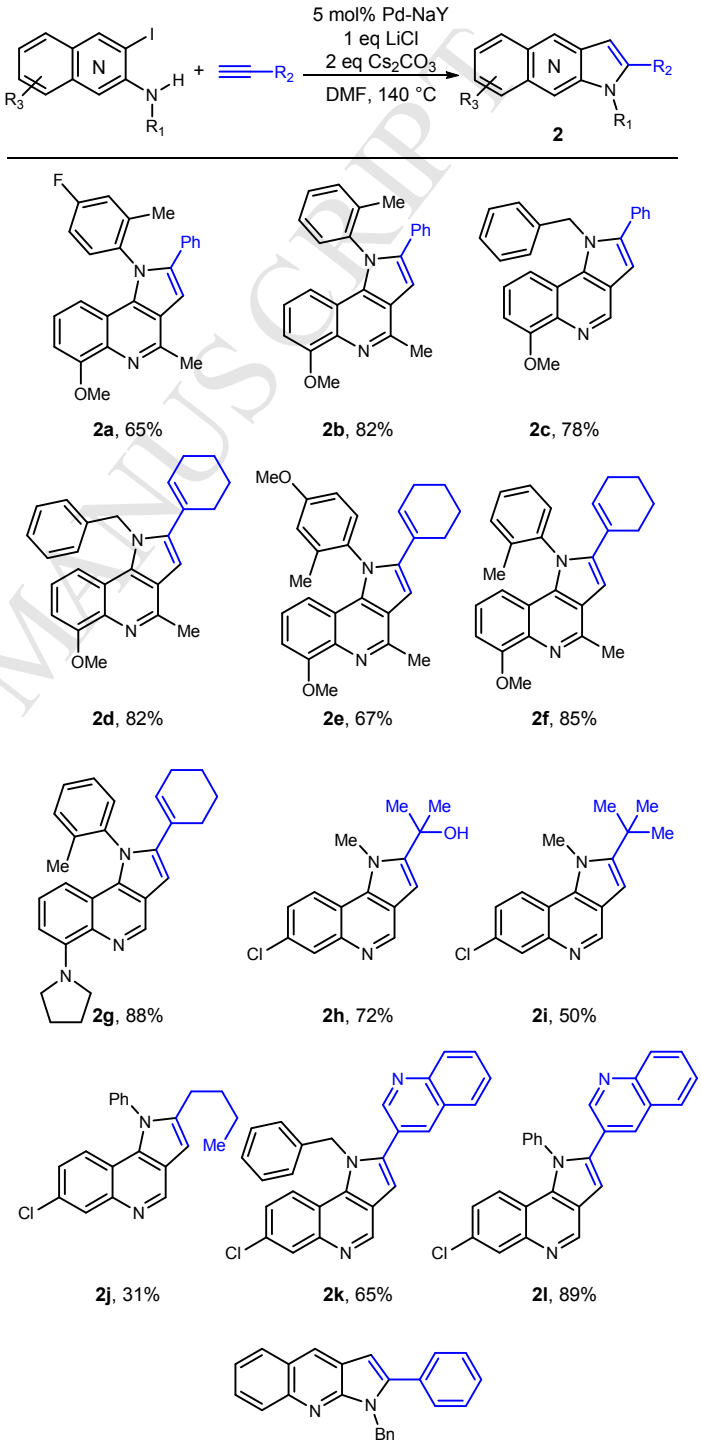
Initially, the Pd-zeolite catalyst was prepared according to reported methods.[25] Ion exchange of NaY zeolite (Aldrich No 33,444-8) with a 0.1 M aqueous solution of $[Pd(NH_3)_4]Cl_2$ at room temperature for 24 h produced $[Pd(NH_3)_4]^{2+}$–NaY. Calcination of the ion-exchanged $[Pd(NH_3)_4]^{2+}$–NaY zeolites at 500 °C for 4 h under O_2 gave the Pd(II)–NaY zeolite. Subsequent treatment at 300 °C for 4 h with 5% H_2 (N_2 balance) gave Pd(0)–NaY.[16] These Pd-containing zeolites had an SBET of 765 cm^2/g and an average pore diameter of 14.6 Å. When using AAS, the absolute palladium content of these catalysts was determined to be 1.0 ± 0.1 wt %..

Scheme 2. Substrate Scope: Pyrrolo-pyridines



Using our previously optimized reaction conditions, the general scope of pyrrolo-pyridine formation is described in Scheme 2. Reaction of *N*-methyl protected pyridine with phenylacetylene gave the desired protected pyrrolo[2,3-*b*]pyridine (**1a**) in 71% yield. The formation of compound (**1a**) was also examined with 3-bromo-2-*N*-methylaminopyridine instead of 3-iodo-2-*N*-methylaminopyridine, however, the reaction using bromo halide gave slightly lower yield of desired product than iodo halide even under slightly higher temperature (160 °C) with 12 h. The free NH of 2-phenyl pyrrolo[2,3-*b*]pyridine could be obtained from the heteroannulation of 2-*N*-acetyl amino-3-iodopyridine and phenylacetylene based on product formation and sequential deprotection of aceyl group.[16] However, the heteroanuulation reaction using internal alkyne did not provide the desired product under standard reaction conditions, probably the pore diameter of zeolite could not allow penetration of internal alkynes or product in this zeolite catalyst

Scheme 3. Substrate Scope: Pyrrolo-quinolines



system. Silyl acetylenes such as TMS and TES acetylenes provided the corresponding azaindoles in moderate (**1b**, 40%) to good (**1c**, 70%) yields. Thp-proteced alcohol and alkene functional groups also furnished pyrrolo[2,3-*b*]pyridine products

1d and **1e** in 59% and 64% yields, respectively. *N*-Benzyl protected pyridine engaged with the TMS and TES acetylenes, delivering pyrrolo[2,3-*b*]pyridines **1f** and **1g** in modest yields. Ethynylacetylene was also converted to pyrrolo[2,3-*b*]pyridine **1h** in 70% yield. Alkynes bearing heterocycles such as quinoline and thiophene were also tolerated under reaction conditions as pyrrolo[2,3-*b*]pyridines **1i** and **1j** were afforded in 54% and 45% yields, respectively. Finally,a thp-protected alcohol gave the desired product **1k** in 52% yield.

Additionally, pyrrolo[3,2-*c*]pyridine derivative was prepared under standard conditions using phenylacetylene (**1l**, 68%). The scope of pyrrolo-quinoline derivatives was suitable with a variety of *N*-protecting groups. A variety of substituted quinoline coupling partners proved sufficient as well (Scheme 4). Aniline protected 8-methoxy-2-methylquinoline derivatives gave the corresponding pyrrolo[3,2-*c*]quinolines in 65% (**2a**) and 82% (**2b**) yield, respectively. *N*-Benzyl protected quinolines also furnished the desired pyrrolo[3,2-*c*]quinolines with phenylacetylene (**2c**, 78%) and ethynylacetylene coupling partners (**2d**, 82%). Additionally, ethynylacetylene engaged with a variety of quinoline substrates as pyrrolo[3,2-*c*]quinolines **2e-2g** were furnished in moderate to good yields. Other alkynes with *tert*-alcohol and *tert*-butyl substituents also proved compatible under standard conditions, as pyrrolo[3,2-*c*]quinolines **2h** and **2i** were afforded in 72% and 50% yields, respectively. 1-Hexyne led to pyrrolo[3,2-*c*]quinolines **2j** (31%) in depressed yield. In contrast, quinoline-substituted alkynes gave moderate to good yield of pyrrolo[3,2-*c*]quinolines **2k** (65%) and **2l** (89%). Additionally, pyrrolo[2,3-*b*]quinoline **2m** was delivered in good yield (83%) when using phenylacetylene as the coupling partner under standard conditions.

Finally, we examined the resusability of the Pd-zeolite catalyst to heteroannulation for synthesizing compound (**1a**). The used Pd-zeolite catalyst was separated by a membrane filter and washed with CH_2Cl_2. The recycled catalyst was used for the same reaction with adding LiCl and Cs_2CO_3 to each reaction without any reactivation of the catalyst. The results are summarized in Scheme 4. Although the recycled catalyst did not provide the same catalyst activity as the fresh catalyst, the recycled catalyst showed good catalytic reusability with slightly longer reaction time.

Scheme 4. Reactivity of Recycled Pd-NaY Catalyst to Heteroannulation

Entry	Recycling	Reaction time (h)	Isolated yield (%)
1	fresh	6	71
2	1st	8	69
3	2nd	12	68
4	3rd	16	62
5	4th	24	60

3. Conclusion

We have described the synthesis of biologically relevant fused [5,6]-azaheterocyclic ring systems using a Pd-zeolite-catalyzed heteroannulation reaction. This approach provides a rapid and convergent access to a diverse range of pyrrolo[2,3-*b*]pyridines, pyrrolo[3,2-*c*]pyridine, pyrrolo[3,2-c]quinolines, and pyrrolo[2,3-*b*]quinoline. This method exhibits high reactivity toward heteroannulations with a high degree of functional group tolerance. Furthermore, Pd-zeolite catalysis could be an interesting alternative to homogeneous catalysis for the synthesis of heterocycles.

4. Experimental section

The ^{1}H NMR, and ^{13}C NMR spectra were recorded with a Verian Gemini 200 MHz NMR and Jeol JNM-400 MHz NMR, using TMS as internal standard. High-resolution mass spectra (HRMS) were obtained using a Thermo Scientific LTQ Orbitrap XL mass spectrometer, and recorded in positive ion mode with an electrospray (ESI) source. Elemental analysis data were obtained from EA 1110. Flash column chromatography was carried out with 230-400 mesh silica gel. Melting points were determined on a Mut-TEM apparatus and are uncorrected. All chemicals were used directly as obtained from commercial sources unless noted otherwise. If necessary, the chemicals were synthesized or purified by known methods and procedures.

4.1. General procedure for the synthesis of pyrrolo-heterocycles *via* heteroannulation using the Pd-loaded zeolite.

Pd-loaded zeolite (0.125 mmol), lithium chloride (0.5 mmol), cesium carbonate (1 mmol), the aryl iodide (0.5 mmol), the alkyne (1.0 mmol), and DMF (10 ml) were added to a sealed tube. After being heated for the appropriate time at 140 °C, the reaction mixture was diluted with saturated aqueous ammonium chloride. The product extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and the mixture was filtered and concentrated. The product was purified by silica gel column chromatography using a hexane/ethyl acetate gradient.

The following compounds were prepared via the above general procedures:

4.1.1. 2-Phenyl-1-methylpyrrolo[2,3-*b*]-pyridine (**1a**). Compound **1a** was obtained as a brown oil in 71% isolated yield from 3-iodo-2-(methylamino)pyridine and phenylacetylene after a 6 h reaction time: IR (KBr, cm^{-1}) 3054, 2946, 1587, 1402, 539; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 4.6, 1.6 Hz, 1H), 7.89 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.56-7.41 (m, 5H), 7.08 (dd, *J* = 7.8, 4.8 Hz, 1H), 6.52 (s, 1H), 3.88 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.57, 141.70, 132.24, 129.03, 128.50, 128.17, 128.00, 120.52, 115.98, 99.32, 29.77; HRMS (ESI) calcd for $C_{14}H_{12}N_2$ $[M]^+$ 208.1072, found 208.1069.

4.1.2. 2-Trimethylsilyl-1-methylpyrrolo[2,3-*b*]-pyridine (**1b**). Compound **1b** was obtained as a yellow oil in 40% isolated yield from 3-iodo-2-(methylamino)pyridine and trimethylsilylacetylene after a 6 h reaction time: IR (KBr, cm^{-1}) 3052, 2956, 1590, 1251, 844; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 4.6, 1.6 Hz, 1H), 7.45 (dd, *J* = 7.9, 1.6 Hz, 1H), 6.59 (dd, *J* = 7.8, 4.8 Hz, 1H), 6.23 (s, 1H), 3.56 (s, 3H), 0.00 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 150.63, 143.11, 141.61, 128.29, 120.23, 115.13, 109.12, 31.15, -0.870; HRMS (ESI) calcd for $C_{11}H_{16}N_2Si$ $[M]^+$ 204.1153, found 204.1150.

4.1.3. 2-Triethylsilyl-1-methylpyrrolo[2,3-*b*]-pyridine (**1c**). Compound **1c** was obtained as a brown oil in 70% isolated yield from 3-iodo-2-(methylamino)pyridine and trimethylsilylacetylene after a 6 h reaction time: IR (KBr, cm^{-1}) 3050, 2954, 2875, 1444, 733; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 4.6, 1.6 Hz, 1H), 7.84 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.98 (dd, *J* = 7.8, 4.8 Hz, 1H), 6.66 (s, 1H), 3.95 (s, 3H), 0.99 (m, 15H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 150.59, 142.90, 138.81, 128.08, 120.36, 115.00, 110.72, 31.15, 7.30, 3.55; HRMS (ESI) calcd for $C_{14}H_{23}N_2Si$ $[M+H]^+$ 247.1622, found 247.1618.

4.1.4. 1-Methyl-2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)-1H-pyrrolo[2,3-b]pyridine (**1d**). Compound **1d** was obtained as a brown oil in 59% isolated yield from 3-iodo-2-(methylamino)pyridine and tetrahydro-2-(2-propynyloxy)-2H-pyran after a 6 h reaction time: IR (KBr, cm^{-1}) 3039, 2940, 2869, 1735, 1457, 1405, 1024; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 4.4, 1.6 Hz, 1H), 7.84 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.02 (dd, *J* = 8.0, 4.4 Hz, 1H), 6.44 (s, 1H), 4.92 (d, J = 12.6 Hz, 1H), 4.73-4.69 (m, 2H), 3.91-3.89 (m, 1H), 3.89 (s, 3H), 3.59-3.54 (m, 1H), 1.81-1.55 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.74, 142.74, 136.48, 128.34, 119.78, 115.59, 100.39, 97.27, 62.19, 60.96, 30.35, 28.29, 25.26, 19.19; HRMS (ESI) calcd for $C_{15}H_{21}N_2O_2$ $[M+H]^+$ 261.1655, found 261.1613.

4.1.5. 2-Ethynylcyclohexenyl-1-methylpyrrolo[2,3-*b*]-pyridine (**1e**). Compound **1e** was obtained as a brown oil in 64% isolated yield from 3-iodo-2-(methylamino)pyridine and 1-ethynylcyclohexene after a 6 h reaction time IR (KBr, cm^{-1}) 3048, 2931, 1452, 1402, 800; 1H NMR (200 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.78 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.98 (dd, *J* = 7.6, 4.6 Hz, 1H), 6.27 (s, 1H), 6.00 (m, 1H), 3.82 (s, 3H), 2.36-2.23 (m, 4H), 1.76-1.71 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.59, 141.94, 129.75, 129.39, 127.50, 120.33, 115.57, 111.45, 97.13, 29.83, 28.84, 25.54, 22.68, 21.78; HRMS (ESI) calcd for $C_{14}H_{17}N_2$ $[M+H]^+$ 213.1383, found 213.1380.

4.1.6. 2-Trimethylsilyl-1-benzylpyrrolo[2,3-*b*]-pyridine (**1f**). Compound **1f** was obtained as a brown solid in 52% isolated yield from 3-iodo-2-(benzylamino)pyridine and trimethylsilylacetylene after a 6 h reaction time: mp 88-89 ℃; IR (KBr, cm^{-1}) 3031, 2950, 2368, 1438, 1419; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 4.6, 1.6 Hz, 1H), 7.72 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.06-6.96 (m, 3H), 6.91 (dd, *J* = 11.6, 4.8 Hz, 1H), 6.82-6.63 (m, 2H), 6.55 (s, 1H), 5.51 (s, 2H), 0.00 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 150.86, 143.58, 141.66, 138.68, 128.57, 126.87, 125.71, 120.11, 115.62, 110.37, 47.40, -0.72; HRMS (ESI) calcd for $C_{17}H_{21}N_2Si$ $[M+H]^+$ 281.1466, found 281.1460.

4.1.7. 2-Triethylsilyl-1-benzylpyrrolo[2,3-*b*]-pyridine (**1g**). Compound **1g** was obtained as a brown oil in 62% isolated yield from 3-iodo-2-(benzylamino)pyridine and triethylsilylacetylene after a 6 h reaction time: IR (KBr, cm^{-1}) 3027, 2954, 2875, 775; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.90 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.23-7.13 (m, 3H), 7.02 (dd, *J* = 7.8, 5.0 Hz, 1H), 6.85-6.8 (m, 2H), 6.67 (s, 1H), 5.56 (s, 2H), 0.96-0.63 (m, 15H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 150.94, 143.46, 138.68, 128.30, 128.20, 126.82, 125.61, 120.20, 115.52, 111.97, 45.50, 7.18, 3.36; HRMS (ESI) calcd for $C_{20}H_{27}N_2Si$ $[M+H]^+$ 323.1935, found 323.1930.

4.1.8. 1-Benzyl-2-(cyclohex-1-en-1-yl)-1H-pyrrolo[2,3-*b*]pyridine (**1h**). Compound **1h** was obtained as a yellow solid in 70% isolated yield from 3-iodo-2-(benzylamino)pyridine and 1-ethynylcyclohexene after a 6 h reaction time: mp 89-90 ℃; IR (KBr, cm^{-1}) 3027, 2931, 1450, 1425, 800; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.83 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.21-7.14 (m, 3H), 7.05-6.98 (m, 3H), 6.33 (s, 1H), 5.86-5.82 (m, 1H), 5.56 (s, 2H), 2.18-2.10 (m, 4H), 1.69-1.57 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.52, 142.42, 138.81, 129.86, 129.48, 128.47, 128.31, 127.65, 126.77, 126.45, 120.40, 116.06, 112.07, 98.25, 45.94, 29.29, 25.52, 22.69, 21.66; HRMS (ESI) calcd for $C_{20}H_{21}N_2$ $[M+H]^+$ 289.1696, found 289.1690.

4.1.9. 3-(1-Benzyl-1H-pyrrolo[2,3-*b*]pyridin-2-yl)-quinoline (**1i**). Compound **1i** was obtained as a yellow solid in 54% isolated yield from 3-iodo-2-(benzylamino)pyridine and 3-ethynyl-quinoline after a 6 h reaction time: mp 130-131 ℃; IR (KBr, cm^{-1}) 3048, 2929, 1448, 1415, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (d, *J* = 2.0 Hz, 1H), 8.41 (dd, *J* = 4.4, 1.2 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 8.03 (d, *J* = 2.0 Hz, 1H), 7.99 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.72 (t, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.54 (dd, *J* = 11.2, 7.2 Hz, 1H), 7.23-7.13 (m, 4H), 6.98 (m, 2H), 6.72 (s, 1H), 5.62 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 150.48, 149.47, 147.41, 143.72, 138.18, 138.14, 135.50, 129.99, 129.23, 128.63, 128.56, 127.96, 127.26, 127.19, 126.33, 125.43, 120.37, 116.76, 101.76, 46.10; HRMS (ESI) calcd for $C_{23}H_{18}N_3$ $[M+H]^+$ 335.1492, found 335.1490.

4.1.10. 1-[5-(1-Benzyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-4,5-dihydro-thiophen-2-yl]-ethanone (**1j**). Compound **1j** was obtained as a brown solid in 45% isolated yield from 3-iodo-2-(benzylamino)pyridine and 1-(5-ethynyl-thiophen-2-yl)-ethanone after a 6 h reaction time: mp 112-113 ℃; IR (KBr, cm^{-1}) 3026, 2362, 1735, 1648, 1276, 800, 727; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.92 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.52 (d, *J* = 4.0 Hz, 1H), 7.21-7.19 (m, 4H), 7.10 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.00-6.96 (m, 2H), 6.79 (s, 1H), 5.73 (s, 2H), 2.49 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 190.22, 149.43, 144.31, 144.13, 141.57, 137.71, 133.00, 132.76, 128.73, 128.58, 127.14, 126.88, 125.93, 119.95, 116.97, 102.50, 45.80, 26.46; HRMS (ESI) calcd for $C_{20}H_{17}N_2OS$ $[M+H]^+$ 333.1053, found 333.1055.

4.1.11. 1-Benzyl-4-(2-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)benzyl)-1H-pyrrolo[2,3-b]pyridine (**1k**). Compound **1k** was obtained as a brown oil in 52% isolated yield from 3-iodo-2-(benzylamino)pyridine and tetrahydro-2-(2-propynyloxy)-2H-pyran after a 6 h reaction time: IR (KBr, cm^{-1}) 3031, 2942, 2869, 1594, 1450, 1118, 1076, 727; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.33 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.89 (dd, *J* = 7.8, 1.6 H, 1H), 7.27-7.16 (m, 3H), 7.08-7.02 (m, 2H), 6.50 (s, 1H), 5.66 (s, 2H), 4.77 (d, *J* = 12.6 Hz, 1H), 4.63-4.51 (m, 2H), 3.87-3.77 (m, 1H), 3.55-3.44 (m, 1H), 1.76-1.41 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.93, 143.21, 138.22, 136.49, 128.43, 127.01, 126.45, 119.73, 116.04, 101.26, 97.17, 62.10, 61.03, 45.10, 30.23, 25.29, 19.14; HRMS (ESI) calcd for $C_{27}H_{29}N_2O_2$ $[M+H]^+$ 413.2228, found 413.2220.

4.1.12. 1-Methyl-2-phenyl-1H-pyrrolo[3,2-*c*]pyridine (**1l**). Compound **1l** was obtained as a brown solid in 68% isolated yield from 3-iodo-4-(methylamino)pyridine and phenylacetylene after a 6 h reaction time: mp 97-98 ℃; IR (KBr, cm^{-1}) 3024, 2358, 1477, 757, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.34 (d, *J* = 6.0 Hz, 1H), 7.49-7.40 (m, 5H), 7.24 (d, *J* = 5.6 Hz, 1H), 6.62 (d, *J* = 0.8 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.34, 140.66, 131.70, 129.30, 128.77, 128.60, 128.43, 127.27, 124.78, 104.88, 100.84, 31.04; HRMS (ESI) calcd for $C_{14}H_{13}N_2$ $[M+H]^+$ 209.1077, found 209.1070.

4.1.13. 1-(4-Fluoro-2-methyl-phenyl)-6-methoxy-4-methyl-2-phenyl-1H-pyrrolo[3,2-*c*]quinoline (**2a**). Compound **2a** was obtained as a brown solid in 65% isolated yield from 3-iodo-8-methoxy-2-methyl-4(4-fluoro-2-methylphenylamino)quinoline and phenylacetylene after a 6 h reaction time: mp 204-205 ℃; IR (KBr, cm^{-1}) 3023, 2991, 2960, 1733, 1587, 1504, 1484, 1226, 746; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 3.2 Hz, 1H),

7.24 (s, 5H), 7.10-6.98 (m, 4H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.55 (d, *J* = 8.4 Hz, 1H), 4.05 (s, 3H), 3.01 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.56 (J1 = 247.6 Hz), 154.15 (J1 = 242 Hz), 140.45, 139.90 (J3 = 8.5 Hz), 135.67, 134.92, 134.41, 134.39, 131.64, 131.38, 131.28, 128.92, 128.12, 127.73, 124.80, 121.14, 118.44, 117.77 (J2 = 23 Hz), 113.96 (J2 = 23 Hz), 111.52, 105.47, 103.38, 55.80, 22.863, 17.53; HRMS (ESI) calcd for $C_{26}H_{22}FN_2O$ $[M+H]^+$ 397.1715, found 397.1710.

4.1.14. 6-Methoxy-4-methyl-2-phenyl-1-*o*-tolyl- 1H-pyrrolo[3,2-*c*]quinoline (**2b**). Compound **2b** was obtained as a brown solid in 82% isolated yield from 3-iodo-8-methoxy-4-(2-methylphenylamino)quinoline and phenylacetylene after a 6 h reaction time: mp 209-210 ℃; IR (KBr, cm^{-1}) 2929, 1482, 1369, 1243, 744; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.44-7.30 (m, 9H), 7.24-6.87 (m, 3H), 6.54 (d, *J* = 8.0 Hz, 1H), 4.06 (s, 3H), 3.04 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.24, 152.96, 140.47, 138.40, 137.37, 135.50, 134.93, 131.17, 129.79, 129.55, 128.91, 128.06, 127.64, 127.04, 124.72, 121.14, 118.57, 111.83, 105.45, 103.26, 55.84, 22.85, 17.35; HRMS (ESI) calcd for $C_{26}H_{23}N_2O$ $[M+H]^+$ 379.1802, found 379.1812.

4.1.15. 1-Benzyl-6-methoxy-2-phenyl-1H-pyrrolo[3,2-*c*]quinoline (**2c**). Compound **2c** was obtained as a brown solid in 78% isolated yield from 3-iodo-8-methoxy-4-(benylamino)quinoline and phenylacetylene after a 6 h reaction time: mp 211-212 ℃; IR (KBr, cm^{-1}) 3446, 2948, 1735, 1513, 738; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.26 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.39-7.22 (m, 10H), 7.07-6.91 (m, 4H), 5.73 (s, 2H), 4.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.16, 144.78, 142.62, 137.70, 136.00, 135.31, 131.84, 129.63, 129.07, 128.57, 127.44, 125.69, 125.54, 121.97, 119.19, 112.97, 105.36, 103.34, 55.87, 50.40; HRMS (ESI) calcd for $C_{25}H_{21}N_2O$ $[M+H]^+$ 365.1646, found 365.1640.

4.1.16. 1-Benzyl-2-cyclohex-1-enyl-6-methoxy-1H-pyrrolo[3,2-*c*]quinoline (**2d**). Compound **2d** was obtained as a brown oil in 82% isolated yield from 3-iodo-8-methoxy-4(benylamino)quinoline and 1-ethynylcyclohexene after a 6 h reaction time; IR (KBr, cm^{-1}) 3342, 2925, 1735, 1513, 547; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.30-7.21 (m, 5H), 7.02 (d, 2H, J = 7.2 Hz), 6.92 (d, 1H, J = 7.6 Hz), 6.70 (s, 1H), 5.85 (s, 1H), 5.75 (s, 2H), 4.06 (s, 3H), 2.25-2.13 (m, 4H), 1.74-1.63 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.72, 145.04, 144.23, 137.78, 135.19, 131.27, 129.21, 129.04, 128.97, 127.35, 125.93, 125.69, 125.54, 121.77, 119.05, 112.91, 105.30, 101.41, 55.87, 50.38, 30.17, 25.58, 22.74, 21.66; HRMS (ESI) calcd for $C_{26}H_{27}N_2O$ $[M+H]^+$ 383.2115, found 383.2115.

4.1.17. 2-Cyclohex-1-enyl-6-methoxy-1-(4-methoxy-phenyl)-1H-pyrrolo[3,2-*c*]quinoline (**2e**). Compound **2e** was obtained as a brown oil in 67% isolated yield from 3-iodo-8-methoxy-4(4-methoxyphenylamino)quinoline and 1-ethynylcyclohexene after a 6 h reaction time; IR (KBr, cm^{-1}) 3737, 3444, 2923, 1511, 1247, 1091, 1029, 752; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 7.31 (d, *J* = 8.8 Hz, 2H), 7.13-7.04 (m, 3H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.73-6.70 (m, 2H), 5.78 (s, 1H), 4.06 (s, 3H), 3.94 (s, 3H), 2.04-1.98 (m, 4H), 1.55-1.50 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.86, 155.59, 144.87, 144.09, 144.08, 135.66, 132.50, 131.01, 130.16, 129.31, 125.31, 121.17, 119.09, 114.55, 112.67, 105.23, 101.37, 70.51, 55.87, 55.53, 29.64, 29.06, 25.65, 22.65, 21.61; HRMS (ESI) calcd for $C_{27}H_{29}N_2O_2$ $[M+H]^+$ 413.2221, found 413.2220.

4.1.18. 2-Cyclohex-1-enyl-6-methoxy-1-*o*-tolyl-1H-pyrrolo[3,2-c]quinoline (**2f**). Compound **2f** was obtained as a brown oil in 85% isolated yield from 3-iodo-8-methoxy-4-(2-methylphenylamino)quinoline and 1-ethynylcyclohexene after a 6 h reaction time; IR (KBr, cm^{-1}) 2925, 2360, 1735, 1511, 750; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 7.49-7.47 (m, 2H), 7.40-7.36 (m, 3H), 7.07 (t, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.77 (s, 1H), 5.70 (d, *J* = 1.6 Hz, 1H), 4.05 (s, 3H), 2.14-1.98 (m, 4H), 1.85 (s, 3H), 1.58-1.47 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.42, 144.00, 143.70, 138.99, 137.27, 134.92, 134.90, 131.12, 130.06, 129.52, 129.38, 128.87, 127.03, 125.63, 121.18, 119.09, 111.76, 105.35, 101.59, 55.80, 28.56, 25.59, 22.59, 21.51, 17.30; HRMS (ESI) calcd for $C_{26}H_{27}N_2O$ $[M+H]^+$ 383.2218, found 383.2220.

4.1.19. 2-Cyclohex-1-enyl-6-pyrrolidin-1-yl-1-*o*-tolyl-1H-pyrrolo[3,2-*c*]quinoline (**2g**). Compound **2g** was obtained as a brown oil in 88% isolated yield from 3-iodo- 8-pyrrolindinyl-(2-methylphenylamino)quinoline and 1-ethynylcyclohexene after a 6 h reaction time IR (KBr, cm^{-1}) 3052, 2933, 1650, 1494, 1434, 1357; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.55-7.34 (m, 3H), 7.21-7.13 (m, 2H), 6.84 (s, 1H), 6.66 (d, *J* = 8.8 Hz, 1H), 5.74 (d, *J* = 3.6Hz, 1H), 3.18 (s, 4H), 2.09-1.91 (m, 8H), 1.87 (s, 3H), 1.64-1.46 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.20, 138.38, 136.89, 136.19, 131.24, 130.80, 129.82, 129.03, 128.45, 127.18, 126.44, 120.12, 118.58, 116.74, 114.37, 102.24, 54.21, 28.41, 25.77, 25.49, 24.27, 22.41, 21.41, 21.32, 21.13, 17.24; HRMS (ESI) calcd for $C_{28}H_{30}N_3$ $[M+H]^+$ 408.2441, found 408.2440.

4.1.20. 2-(7-Chloro-1-methyl-1H-pyrrolo[3,2-*c*]quinolin-2-yl)propan-2-ol (**2h**). Compound **2h** was obtained as a brown oil in 72% isolated yield from 7-chloro-3-iodo-*N*-methylquinolin-4-amine and 2-methylbut-3-yn-2-ol after an 18 h reaction time; ^{1}H NMR (400 MHz, DMSO) δ 9.03 (s, ArH), 8.58 (d, *J* = 8.0 Hz, 1H), 8.08 (s, 1H), 7.59 (d, *J* = 9.2 Hz, 1H), 6.67 (s, 1H), 5.51 (brs, 1H), 4.48 (s, 3H), 3.38 (s, 6H); ^{13}C NMR (100 MHz, DMSO) δ 146.85, 146.70, 144.71, 134.24, 129.77, 128.41, 125.39, 123.17, 119.89, 117.00, 99.17, 67.99, 36.15, 30.61; Anal. Calcd. for $C_{15}H_{15}ClN_2O$: C, 65.57; H, 5.50; Cl, 12.90; N, 10.20; 0, 5.82. Found: C, 65.55; H, 5.51; Cl, 12.91; N, 10.22; 0, 5.80.

4.1.21. 2-(*tert*-Butyl)-7-chloro-1-methyl-1H-pyrrolo[3,2-*c*]quinoline (**2i**). Compound **2i** was obtained as a brown oil in 50% isolated yield from 7-chloro-3-iodo-*N*-methylquinolin-4-amine and 3,3-dimethylbut-1-yne after a 22 h reaction time; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.27 (dd, *J* = 8.0 Hz, 1H), 8.16 (d, *J* = 2.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 6.54 (s, 1H), 4.29 (s, 3H), 1.54 (s, 9H); ^{13}C NMR (100 MHz, CDCl3) δ 149.22, 146.65, 145.18, 135.29, 130.85, 129.46, 125.69, 121.75, 120.41, 117.18, 99.57, 36.79, 32.40, 30.41; Anal. calcd. for $C_{16}H_{17}ClN_2$: C, 70.45; H, 6.28; Cl, 13.00; N, 10.27. Found: C, 70.43; H, 6.27; Cl, 13.03; N, 10.27.

4.1.22. 2-Butyl-7-chloro-1-phenyl-1H-pyrrolo[3,2-*c*]quinoline (**2j**). Compound **2j** was obtained as a brown oil in 31% isolated yield from 7-chloro-*N*-phenylquinolin-4-amine and 1-hexyne after a 14 h reaction time^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 8.12 (d, *J* = 2.4 Hz, 1H), 7.64-7.62 (m, 3H), 7.40-7.37 (m, 2H), 7.08 (dd, *J* = 8.0, 2.4 Hz, 1H), 6.87 (d, *J* = 9.2 Hz, 1H), 6.62 (s, 1H), 2.51 (t, *J* = 8.0 Hz, 2), 1.61 (t, *J* = 8.0 Hz, 2H), 1.33 (q, 2H), 0.87 (t, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 146.45, 144.91, 142.71, 138.86, 134.72, 131.05, 130.09, 129.62, 129.08, 128.77, 125.66, 121.37, 121.22, 116.41, 100.53, 30.65, 26.54, 22.35, 13.83; Anal. calcd. for $C_{21}H_{19}ClN_2$: C, 75.33; H, 5.72; Cl, 10.59; N, 8.37. Found: C, 75.30; H, 5.75; Cl, 10.57; N, 8.39.

4.1.23. 1-Benzyl-7-chloro-2-(quinolin-3-yl)-1H-pyrrolo[3,2-c]quinoline (**2k**). Compound **2k** was obtained as a brown oil in 65% isolated yield from *N*-benzyl-7-chloro-3-iodoquinolin-4-amine and 3-ethynylquinoline after a 6 h reaction time; ^{1}H NMR (400 MHz, DMSO) δ 9.24 (s, 1H), 8.98 (d, *J* = 2.0 Hz, 1H), 8.21

(s, 1H), 8.14-8.11 (m, 2H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.78-7.74 (m, 1H), 7.69-7.67 (m, 1H), 7.59-7.55 (m, 1H), 7.39-7.30 (m, 4H), 7.09-7.07 (m, 3H), 5.75 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.47, 147.54, 147.10, 145.59, 138.92, 136.53, 136.08, 135.46, 131.93, 130.28, 129.54, 129.43, 129.24, 128.01, 127.98, 127.39, 127.17, 126.51, 125.92, 125.39, 124.69, 122.01, 121.51, 116.46, 105.02, 50.69; Anal. calcd. for $C_{27}H_{18}ClN_3$: C, 77.23; H, 4.32; Cl, 8.44; N, 10.01. Found: C, 77.22; H, 4.34; Cl, 8.43; N, 10.01.

4.1.24. 7-Chloro-1-phenyl-2-(quinolin-3-yl)-1H-pyrrolo[3,2-c]quinoline (**2l**). Compound **2l** was obtained as a brown oil in 89% isolated yield from 7-chloro-3-iodo-*N*-phenylquinolin-4-amine and 3-ethynylquinoline after a 6 h reaction time; ^{1}H NMR (400 MHz, DMSO) δ 9.30 (s, 1H), 8.82 (d, *J* = 1.6 Hz, 1H), 8.22 (s, 1H), 8.12 (d, *J* = 2.4 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.83-7.73 (m, 2H), 7.63-7.57 (m, 6H), 7.42 (s, 1H), 7.34 (dd, *J* = 8.0, 2.4 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 150.18, 147.27, 146.23, 144.97, 138.29, 138.16, 135.69, 134.98, 130.74, 130.18, 130.10, 129.36, 128.73, 128.51, 128.11, 127.22, 126.64, 125.84, 124.50, 121.71, 121.01, 116.23, 105.01, 94.04; Anal. calcd. for $C_{26}H_{16}ClN_3$: C, 76.94; H, 3.97; Cl, 8.73; N, 10.35. Found: C, 76.93; H, 3.94; Cl, 8.77; N, 10.35.

4.1.25. 1-Benzyl-2-phenyl-1H-pyrrolo[2,3-*b*]quinoline (**2m**). Compound **2m** was obtained as a brown solid in 83% isolated yield from 3-iodo-2-benzylaminoquinoline and phenylacetylene after a 6 h reaction time: mp 149-150 ℃; IR (KBr, cm^{-1}) 3056, 2364, 1428, 1402, 757; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.15 (d, *J* = 8.0 Hz, 1H), 7.97 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.69-7.50 (m, 10H), 7.48-7.00 (m, 2H), 6.67 (s, 1H), 5.70 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$)δ 151.16, 145.94, 145.14, 138.60, 132.24, 131.56, 129.15, 128.49, 128.29, 128.11, 127.93, 127.70, 127.42, 126.90, 125.27, 122.88, 122.10, 99.84, 46.04; HRMS (ESI) calcd for $C_{24}H_{19}N_2$ $[M+H]^+$ 335.1540, found 335.1545.

Acknowledgments

Financial support from DGMIF is gratefully acknowledged.

References and notes

1. Johansson Seechurn CCC, Kitching MO, Colacot TJ, Snieckus V. *Angew. Chem. Int. Ed.* 2012;51:5062-5085 and references therein. (Review)
2. Torborg C, Beller M. *Adv. Synth. Catal.* 2009;*351*:3027-3043 and reference therein.(Review)
3. Li JJ, Gribble GW. *Palladium in Heterocyclic Chemistry*: A guide for the synthetic Chemist, 2th Ed, ElSEVIER, Oxford, UK 2007.
4. Zeni G, Larock RC. *Chem. Rev*. 2006;*106*:4644-4680.
5. Yin L, Liebscher J. *Chem. Rev*. 2007;107:133-173.
6. Seki M. *Synthesis* 2006;2006:2975-2992.
7. Heitbaum M, Glorius F, Escher I. *Angew. Chem. Int. Ed.* 2006;*45*:4732-4762.
8. Astruc D, Lu F, Aranzaes JR. *Angew. Chem. Int. Ed.* 2005;44:7852-7872.
9. Sadjadi S, Heravi M M. *RSC Advances* 2016;6:88588-88624.
10. Cejka J, Corma A, Zones S, Zeolites and catalysis: synthesis, reactions and applications, 2010, Wiley, Weiheim.
11. Kumbhar A. *Top Curr Chem*, 2017;375:2.
12. Djakovitch L, Heise H, Köhler K. *J. Organometal. Chem.* 1999;584:16-26.
13. Bulut H, Artok L, Yilmazu S. *Tetrahedron. Lett.* 2003;44:289-291.
14. Artok L, Bulut H. *Tetrahedron. Lett*. 2004;45:3881-3884.
15. Djakovitch L, Koehler K. *J. Mol Cat A: Chem* 1999;142:275-284.
16. Hong KB, Lee CW, Yum EK. *Tetrahedron. Lett.* 2004;45:693-697.
17. Wegenhart B L, Yang L, Kwan SC, Harris R, Kenttämaa HI, Abu-Omar MM. *ChemSusChem* 2014;7:2742-2747.
18. Alam MN, Sarkar SM. *Reaction Kinetics, Mechanisms and Catalysis* 2011;103:493-500.
19. Sajiki H, Monguchi Y, Sawama Y, Takahashi T, Ito R. *Jpn. Kokai Tokkyo Koho*, 2013, JP 2013082637.
20. (a) Larock RC, Yum EK. *J. Am. Chem. Soc.* 1991;113:6689-6690. (b) Larock RC, Yum EK, Refvik MD. *J Org Chem* 1998;63:7652-7662.
21. (a) Park SS, Choi J-K, Yum EK, Ha D-C. *Tetrahedron. Lett.* 1998;39:627-630. (b) Chi SM, Choi J-K, Yum EK, Chi DY. *Tetrahedron. Lett.* 2000;41:919-922.
22. (a) Kang SK, Park SS, Kim SS, Choi J-K, Yum EK. *Tetrahedron. Lett.* 1999;40:4379-4382. (b) Strekowski L, Zegrocka O, Henary M, Say M, Mokrosz MJ, Kotecka BM, Manzel L, Macfarlane DE. *Bioorg. Med. Chem*. Lett. 1999;9:1819-1824.
23. Kwon JK, Cho JH, Ryu Y-S, Oh SH, Yum EK. *Tetrahedron* 2011;*67*:4820-4825.
24. Kim SK, Kim J-H, Park YC, Kim JW, Yum EK. *Tetrahedron* 2013;69:10990-10995.
25. Djakovitch L, Koehler K. *J. Am. Chem. Soc*. 2001;123:5990-5999.