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ARTICLE

Synthesis of topologically constrained naphthalimide appended Palladium(II)-N-Heterocyclic carbene complexes- Insights into additive controlled product selectivity

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Topologically constrained naphthalimide appended Pd-NHCs were synthesized and characterized. These structurally related complexes were catalytically compared with the previously synthesized Pd-NHC in the regioselective heteroannulation of *o*-haloanilines and arylethynyl-trimethylsilane. The unique effect of the additive on the product selectivity has been clearly demonstrated. The scope of the reaction with respect to different TMS protected alkynes and *o*-haloanilines are presented. Importantly, the step- economic regioselective synthesis of *N*-alkyl-3-aryl-indoles from *o*-haloanilines and arylethynyl-trimethylsilane assisted by Pd(II)-NHC has been clearly demonstrated *via* one-pot heteroannulation, TMS deprotection and *N*-alkylation. In addition, synthetic utility was demonstrated with several derivatizations.

Introduction

The indole scaffolds are recurring heterocycles in many biologically active natural products, pharmaceuticals, agrochemical and functional materials.[1] In that event, its supremacy is further validated by 3-arylindoles *viz.* dragmacidin D, meridianins, nortosentins, hemacanthins B which are bestowed with a multitude of medicinal properties such as antitumor, antifungal, antiviral, antibacterial and antagonists to progesterone receptor (PR).[2] Recently, the efficacy of transition-metal-catalyzed annulation to produce a plethora of heterocycles have been recognized and its constant development in organic synthesis is highly demanded.[3] Traditionally, 3-arylindoles were synthesized by Fischer indole synthesis involving arylhydrazines and aldehydes.[4] Recent reports show Pd-catalyzed reductive amination of nitroalkenes in the presence of carbon monoxide, reductive cyclization of 2-(2-nitroaryl)acetonitriles (Rh & Pt),[5] annulation of *o*-haloanilines with aldehydes or alkynes,[6] and direct arylation of indoles.[7] Besides, 3-arylindoles were synthesized by gold-catalyzed annulation of nitrosoarenes and alkynes.[8] Helleday *et al* reported two-step synthesis: vinylation of *ortho*-nitrohaloarenes using MIDA and subsequent cyclization under phosphite-mediated conditions.[9] However, the reported reactions demand harsh reaction conditions, high H_2 pressure, involving CO, long reaction time, assembling multi-components and demanding pre-functionalized substrates. To oust such challenges, heteroannulation of *o*-haloanilines and arylethynyl-trimethylsilane with apropos additives and catalyst yields 3-aryl-2-(trimethylsilyl)-1*H*-indoles **23** and *N*-butyl-3-phenyl-indoles **25**. Moreover, heteroarylsilanes proved to be important synthon in organic synthesis and find applications in medicinal chemistry, advanced materials and polymer synthesis. Common strategies to facilitate the C-Si bond construction entail the intervention of heteroaryl lithium or magnesium reagents with silicon electrophiles or cross-dehydrogenative coupling of aromatic heterocycles with hydrosilanes catalyzed by KO*t*-Bu.[10]

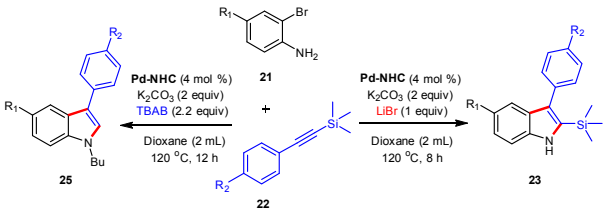

Figure 1. Outline of the present work

Remarkably strong σ-binding and steric tunability of NHCs, makes them versatile ligands in the area of homogenous catalysis.[11] Lately, our research group have effectively harnessed the π-stacking approach in enhancing the catalytic properties – synthesis of 2-alkenylindoles catalyzed by Pd-NHC appended with naphthalimide or bisnaphthalimide moieties from *o*-haloanilines and tertiary propargyl alcohols.[12] We have reasoned that enhanced catalytic efficiency of these complexes is attributed to the π-stacking nature of naphthalimide coupled with the flexible alkyl linker. In this

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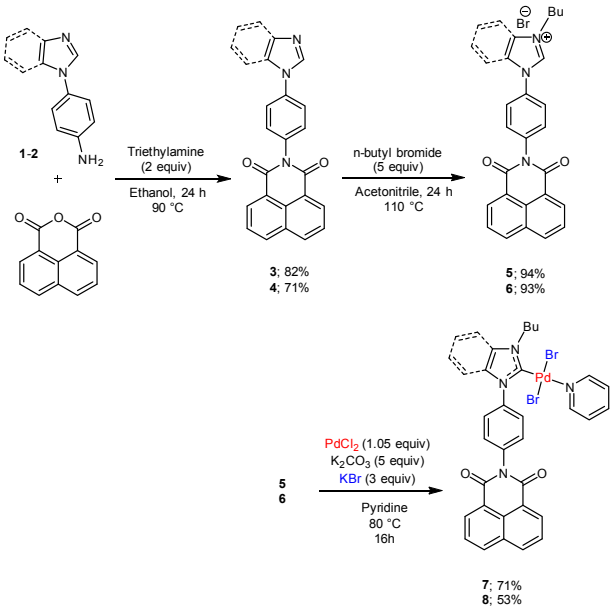
regard, we have decided to further study the structure and catalytic activity of various palladium complexes with topologically constrained naphthalimide carbenes. Herein, we report a direct, convenient, and one-pot synthesis of 3-aryl-2-(trimethylsilyl)-1*H*-indoles **23** and *N*-butyl-3-phenyl-indoles **25** employing decorated Pd-NHC precatalyst (Figure 1).

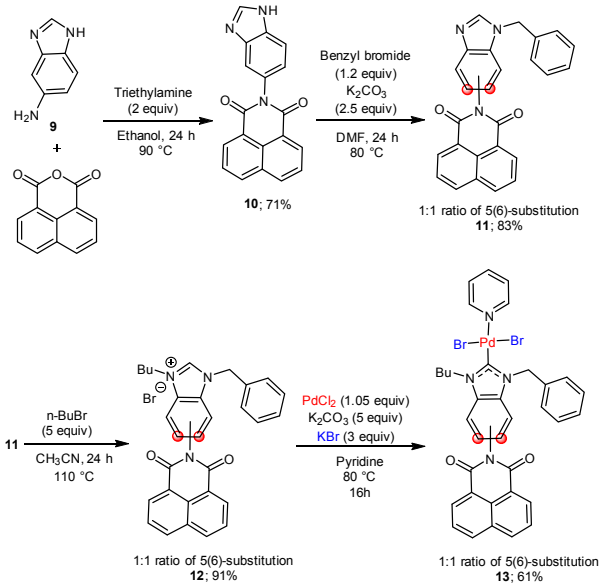
Results and Discussion

Initially compounds **3**, **4** & **10** were synthesized by the condensation of amino derivatives of heterocycles (**1**, **2** & **9**) with 1,8-naphthalic anhydride respectively (Scheme 1 & 2). Compound **10** was then subjected to *N*-benzylation employing the standard protocol of DMF/K_2CO_3 to afford the designed compound **11**. However, we observed only the 1:1 mixture of 5(6)-substituted derivative due to tautomer effect of NH in benzimidazole ring. Despite numerous efforts, isolation of a single isomer was not achieved. Compounds **3**, **4** & **11** were subjected to treatment with n-butyl bromide affording desired imidazolium salts **5**, **6** & **12** respectively in excellent yields (91-94% yields).



Scheme 1. Synthesis of Pd-PEPPSI NHC complexes **7** & **8**

Finally, Pd-PEPPSI NHC complexes **7**, **8** & **13** were conveniently synthesized by palladation of corresponding imidazolium salts in 71%, 53% and 61% yields respectively (Scheme 1 & 2). The synthesized complexes are stable in air and moisture in both solid and solution state. The chemical structure of the complexes was confirmed by the multinuclear NMR and mass spectroscopy. The resonances of Pd-$C_{carbene}$ of complexes **7**, **8** & **13** appear in the range of 149.50 to 165.72 ppm. In contrast to previously synthesized complexes **14**-**20** (Structures of **14**-**20** are shown in table 1), the movement of the naphthalimide moiety is restricted in **7**, **8** & **13** which is parted by benzene spacer. In case of **7** and **8**, the naphthalimide moiety is a wingtip substituent to imidazole, whereas, in **13** it is a part of benzimidazole backbone.



Scheme 2. Synthesis of Pd-PEPPSI NHC complex **13**

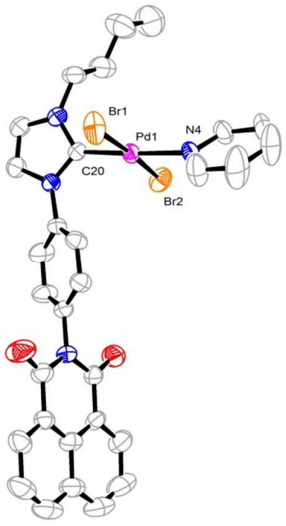


Figure 2. ORTEP representation of **7** (CCDC1584103, 50% probability ellipsoids and hydrogens are omitted for clarity)

Yellow crystals of **7** suitable for single-crystal X-ray diffraction analysis were obtained by slow evaporation of its concentrated dichloromethane solution at RT. As shown in the Fig.2, **7** adopts square planar geometry with the carbene and pyridine *trans* to each other. The Pd-$C_{carbene}$ bond length in **7** is 1.950 Å. However, the lower yield of **8** was ascribed to the formation of cyclic urea derivative (confirmed by single-crystal X-ray analysis & ORTEP representation in supporting information) *via* sequential deprotonation and oxidation of NHC as observed previously by other authors.[13]

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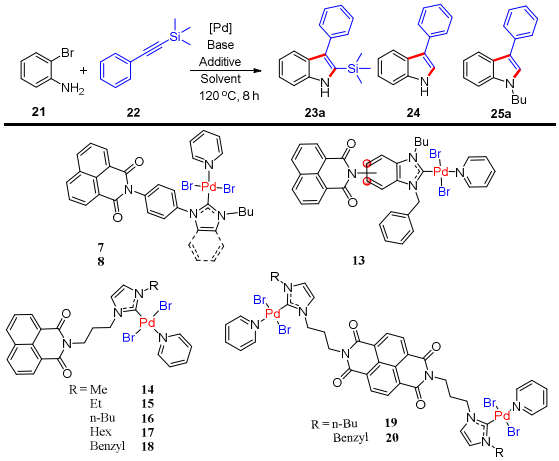
Table 1. Optimization details[a,b]

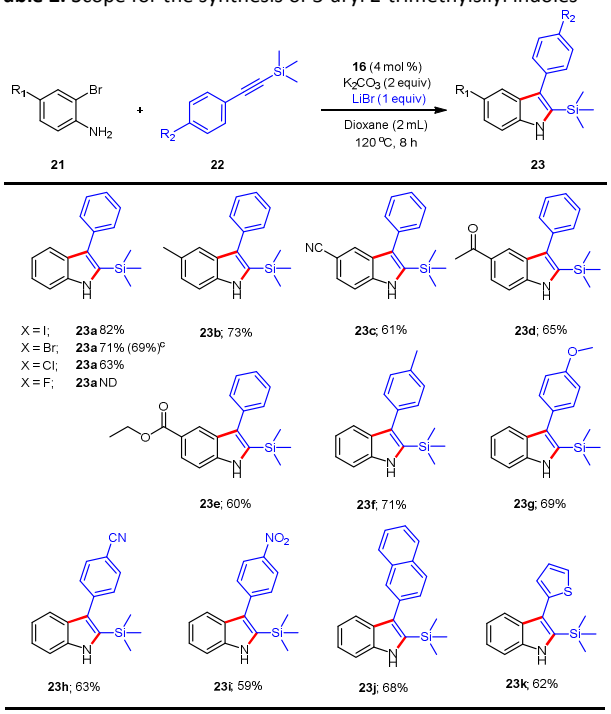


Entry	[Pd]	Base	Additive	Yield (%) 23a	25a
1[c, d]	**16**	K_2CO_3	TBAB	17	-
2	**16**	K_2CO_3	NaBr	63	-
3	**16**	**K_2CO_3**	**LiBr**	**71**	**-**
4	**16**	K_2CO_3	KBr	55	-
5	**16**	Na_2CO_3	LiBr	65	-
6	**16**	Cs_2CO_3	LiBr	71	-
7	**16**	KO*t*-Bu	LiBr	50	-
8	**16**	NaOH	LiBr	52	-
9	**16**	TEA	LiBr	11[c]	-
10	**16**	DIPEA	LiBr	14[c]	-
11	**16**	KOH	LiBr	50	-
12[e]	**16**	K_2CO_3	LiBr	64	-
13[f]	**16**	K_2CO_3	LiBr	31	-
14[g]	**16**	K_2CO_3	LiBr	52	-
15[h]	**16**	K_2CO_3	LiBr	60	-
16	**14**	K_2CO_3	LiBr	63	-
17	**15**	K_2CO_3	LiBr	65	-
18	**17**	K_2CO_3	LiBr	70	-
19	**18**	K_2CO_3	LiBr	70	-
20	**19**	K_2CO_3	LiBr	70	-
21	**20**	K_2CO_3	LiBr	68	-
22	**7**	K_2CO_3	LiBr	64	-
23	**8**	K_2CO_3	LiBr	67	-
24	**13**	K_2CO_3	LiBr	70	-
25	**16**	K_2CO_3	TBAB[i]	-	58
26	**16**	**K_2CO_3**	**TBAB[j]**	**-**	**65**
27	**16**	K_2CO_3	-	46	-

[a] **21** (1 mmol), **22** (2 mmol), [Pd] (4 mol %), base (2 mmol), additive (1 mmol), 1,4-dioxane (2 mL), 120 °C, 8 h. [b] Isolated yields. [c] GC yields determined using n-decane as internal standard. [d] **24** was observed in 50% yield. [e] DMF as solvent. [f] DMSO as solvent. [g] Ethanol as solvent. [h] NMP as solvent. [i] 2 mmol of TBAB was used. [j] 2.2 mmol of TBAB was used.

In pursuit of 3-phenyl-2-(trimethylsilyl)-1*H*-indoles **23a**, we reacted the **22** with **21** by adopting our previously reported optimized conditions[12], **16** as a catalyst, K_2CO_3 as a base, TBAB as an additive with 1,4-dioxane as solvent at 120 °C. Surprisingly, we obtained mixture of annulated products 3-phenyl-2-(trimethylsilyl)-1*H*-indoles **23a** (17%) and 3-phenyl-1*H*-indole **24** (50%) (Table 1 entry-1). Intention to obtain selectively **23a** was realized by replacing TBAB with various salts *viz.* NaBr, LiBr and KBr, (entries 2-4) among these LiBr found to be best (71%, entry 3). Replacement of K_2CO_3 with other bases such as Na_2CO_3, KO*t*-Bu, NaOH, triethylamine, DIPEA & KOH proved less effective or not effective (entries 5-11). The temperature of above 120 °C failed to improve yield further. Among a variety of solvents, which includes DMF, DMSO, ethanol, dioxane and NMP, we found out that dioxane is very effective (entries 12-15). Extending the optimized reaction condition to other Pd-NHC's **14**, **15**, **17**-**20**, **7**, **8** & **13** could not furnish profound increment in the yield of **23a** (entries 16-24). However, modest catalytic performance has been observed with **7** & **8** (entries 22-23) which could be attributed to restricted movement of naphthalimide moiety appended to the Pd-NHC. Having realized the selective formation of **23a**, we turned our attention to investigate the formation of **24a** & **25a**. To our delight, an increment in the loading of TBAB from 1 to 2 equivalents (entry 25) leads to the generation of **25a**, and it was further furnished that 2.2 equivalents are the best (entry 26). Thus it is conceived that TBAB plays multiple roles as an additive, deprotecting and an alkylating agent.

Table 2. Scope for the synthesis of 3-aryl 2-trimethylsilyl indoles[a,b]



[a] **21** (1 mmol), **22** (2 mmol), **16** (4 mol %), K_2CO_3 (2 mmol), LiBr (1 mmol), dioxane (2 mL), 120 °C, 8 h. [b] Isolated yields. [c] Gram-scale reaction

Having established the set of optimized reaction conditions, first, we set out to evaluate the substrate scope with respect to different *o*-haloanilines and arylethynyl-trimethylsilane to

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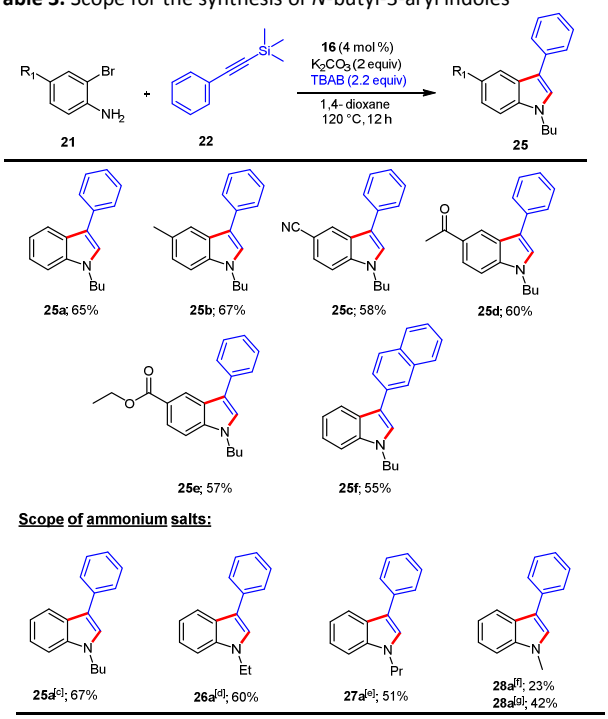
yield 3-aryl-2-(trimethylsilyl)-1*H*-indoles **23** (Table 2). Heteroannulation reaction was compatible with different *o*-haloanilines namely iodo, bromo, chloro whereas *o*-fluoroaniline was non-reactive. It is noteworthy that gram scale reaction of **21** with **22** afforded the **23a** without erosion in yield, which is highly significant in scalability. Henceforth, by employing *o*-bromoaniline derivatives, a wide variety of 3-aryl-2-(trimethylsilyl)-1*H*-indoles **23a**-**23e** were synthesized. Reactive functional groups such as cyano, acetyl and ester were well tolerated furnishing the desired products in synthetically useful yields **23c**-**23e**. Incongruent to the literature, *N*-acetyl bromoanilines failed to react with **22** to the afford desired indole. Subsequently, we examined the scope of arylethynyl-trimethylsilane. Both electron-donating **23f** & **23g** and electron-withdrawing substituents **23h** & **23i** on the aryl moiety were found to proceed smoothly under the optimized conditions. Likewise, this protocol was amenable to substrates containing naphthalene **23j** and thiophene **23k**.

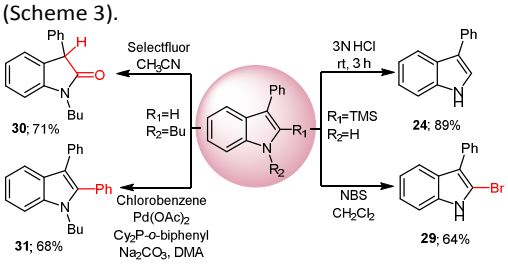
Table 3. Scope for the synthesis of *N*-butyl-3-aryl indoles [a,b]



[a] **21** (1 mmol), **22** (2 mmol), **16** (4 mol %), K_2CO_3 (2 mmol), TBAB (2.2 mmol), dioxane (2 mL), 120 °C, 12 h. [b] Isolated yields. [c] Tetrabutylammonium fluoride (TBAF) [d] Tetraethylammonium bromide as additive. [e] Tetrapropylammonium bromide as additive. [f] Aliquat 336 (Methyltrioctylammonium chloride) as additive. [g] tetramethylammonium chloride as additive.

Using the second set of conditions, the *N*-butyl-3-aryl indoles **25** were obtained with excellent regioselectivity (Table 3). *o*-bromoanilines bearing electron-donating (-CH_3) **25b** was successfully employed without any detrimental effect on the reactivity and they are well tolerated. This strategy was employed for aniline substrates bearing various reactive functional groups such as cyano, acetyl and ester **25c**-**25e**, which can undergo subsequent transformation *via* transition metal catalysis. Even the sterically encumbered naphthyl group were well tolerated affording the corresponding indole derivative in synthetically useful yields **25f**. It should be noted that broad functional group tolerance highlights the synthetic potential of the protocol in late-stage derivatization. Even the reaction proceeded exceedingly well when TBAB was replaced with TBAF affording **25a** in good yields (67%). It is noteworthy that, when the reaction of **21** and **22** was performed under the optimized conditions in the presence of different ammonium salts, the corresponding desired products **26a**-**28a** were successfully obtained. However, the yield of **28a** was low when aliquat 336 was employed.

The synthetic utility of the current protocol was further demonstrated through different derivatizations as evident from scheme 3. TMS-deprotection from **23a** enables the formation of 3-phenylindoles **24** in good yield. Furthermore, bromination[14] of **23a** assisted by NBS to affords **29**, indicating the potential for further synthetic elaboration. Likewise, **25a** was transformed into synthetically useful products **30** and **31** employing suitable reaction conditions as reported earlier[15] (Scheme 3).



Scheme 3. Derivatizations.

To gain more insights into the mechanism involving the formation of **25a**, the reaction of **21** with **22** under the optimized conditions was carefully monitored by GC-MS analysis. As assumed, tributylamine was detected by GC-MS along with **25a** (Scheme 4) which suggested the thermal decomposition of tetrabutylammonium bromide to yield n-butyl bromide and tributylamine which thereby assists in the N-alkylation of the *in situ* formed **24**. Even the reaction of isolated **24** with TBAB under the optimized conditions yielded **25a** as the sole product which corroborates the *in situ* formation of **24** followed by alkylation. In addition, reaction of **23a** with TBAB under the optimized conditions to yield **25a**.

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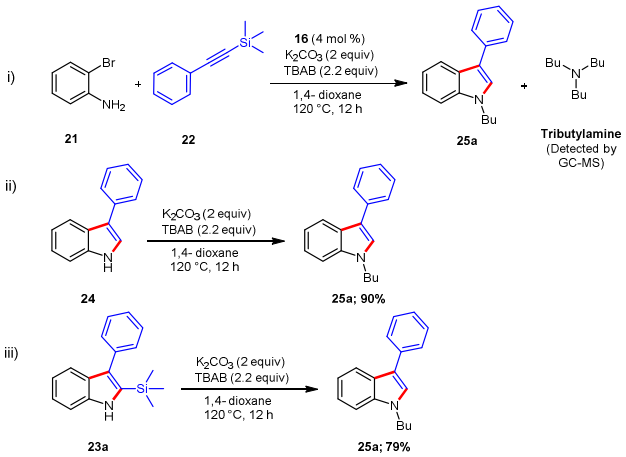
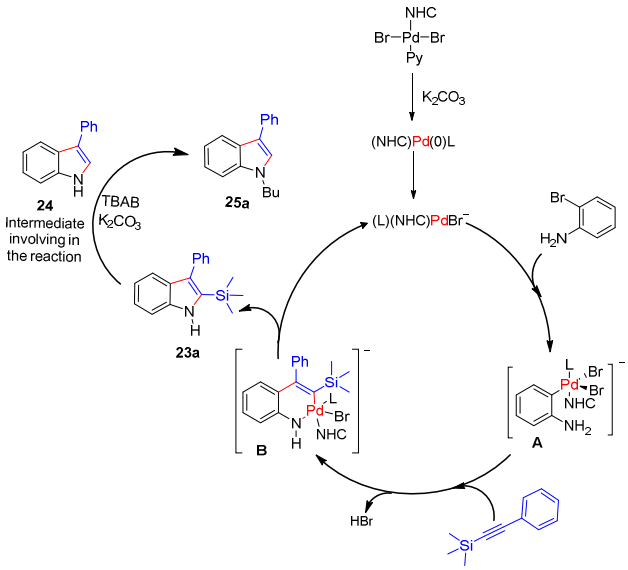


Scheme 4. Control studies

Based on the control experiments discussed above and the earlier works,[12,16] we envision the pathway involved in the heteroannulation reaction (Scheme 5). Initial oxidative addition to Pd(0) complex forms NHC-Pd(II)-aryl complex **A** followed by sequential coordination and selective insertion of trimethyl(phenylethynyl)silane resulting in intermediate **B** with the release of HBr which eventually lead to **23a**. The halide ligation step is believed to stabilize the intermediate.[16,17]



Scheme 5. Plausible Mechanism

Experimental Section

Unless otherwise mentioned, all the reactions were carried out in screw cap reaction tubes and all the chemicals were purchased commercially and used without purification. Different palladium salts and the reagents were purchased at the highest commercial quality and used without purification. Flash chromatographic technique on silica gel (100-200 mesh) was used for the purification of the products. Thin layer chromatography was conducted with 0.25mm silica plates ($60F_{254}$) and visualized by exposure to UV light (254 nm). ^{1}H NMR spectra were recorded on Bruker spectrometer (400 MHz) and are reported in units ppm (parts per million) relative to the signals for residual chloroform (7.26 ppm) and DMSO (2.54 ppm) in the deuterated solvent. ^{13}C NMR spectra were recorded on Bruker spectrometer (100 MHz) and are reported in ppm relative to deuterated chloroform (77.23 ppm) and DMSO (39.52 ppm). Coupling constants (*J*) are reported in Hz; splitting patterns are assigned s = singlet, d = doublet, t = triplet, q = quartet, br = broad signal. High-resolution mass spectra (HRMS) and ESI mass were performed on TOF-Q analyser.

Typical Procedure for the Synthesis of Precursors (3, 4 & 10)

To a stirred suspension of 1,8-naphthalic anhydride and amine derivatives of heterocycles (**1**, **2** & **9**) in ethanol, triethylamine (2 equiv) was charged. After stirring for 24 h at 90 °C, the mass was cooled to room temperature and the solids formed were filtered and washed with a minimum quantity of ethanol to washout the unwanted impurities. The solids were dried under vacuum and used without further purification.

Synthesis of 11: To a stirred suspension of **10** (1 equiv), K_2CO_3 (2.5 equiv) and DMF (5 mL), benzyl bromide (1.2 equiv) was added and the resulting mixture was stirred at 80 °C for 24 h. The reaction mass was then poured into ice-cold water and extracted with 3 × 25 mL ethyl acetate. The combined organic layers were washed with water, dried over Na_2SO_4 and the solvent was concentrated under reduced pressure. The crude was purified using column chromatography to afford **11**. 1:1 inseparable mixture of 5(6)-substituted derivatives were observed due to tautomer effect of NH in benzimidazole ring. Yield: 83%; White coloured solid. R_f=0.60 (MeOH/DCM 1:49). Purified by column chromatography on silica gel (DCM/Methanol = 97/3). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 – 8.54 (m, 10H), 7.97 – 7.93 (t, *J* = 7.74 Hz, 4H), 7.84 (d, *J* = 8.48 Hz, 1H), 7.76 (dd, *J* = 1.56, 11.36 Hz, 2H), 7.69 (d, *J* = 8.52 Hz, 1H), 7.47 – 7.41 (m, 4H), 7.39 – 7.37 (m, 6H), 7.28 (dd, *J* = 1.8, 8.48 Hz, 2H), 5.63 (s, 2H), 5.54 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) 164.50, 164.47, 137.33, 137.28, 134.90, 134.81, 131.92, 131.29, 131.22, 131.18, 130.51, 129.25, 129.20, 128.33, 128.28, 128.03, 127.91, 127.70, 123.96, 123.42, 123.23, 123.13, 120.65, 119.93, 111.86, 111.17, 48.33, 48.13; HRMS [M+H$^+$] Calcd. for $C_{26}H_{18}N_3O_2$: 404.1399, found: 404.1406.

General Procedure for the Synthesis of Imidazolium salts (5, 6 & 12)

To a suspension of **3**, **4** & **11** in acetonitrile solution, 5 equivalents of n-butyl bromide were added and stirred at 100 °C until completion of starting material as indicated by thin layer chromatography. The reaction mixture was cooled and concentrated under reduced pressure. Ethylacetate was then added, stirred for 30 min and the solids formed are filtered, dried under vacuum.

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Compound 5: Yield: 94%; White coloured solid. R_f=0.40 (MeOH/DCM 4:46). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (s, 1H), 8.57 – 8.53 (t, *J* = 8.00 Hz, 4H), 8.45 (s, 1H), 8.13 (s, 1H), 7.99 – 7.92 (m, 4H), 7.76 (d, *J* = 8.68 Hz, 2H), 4.32 – 4.29 (t, *J* = 7.2 Hz, 2H), 1.96 – 1.88 (m, 2H), 1.42 – 1.33 (m, 2H), 0.98 – 0.95 (t, *J* = 7.36 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) 164.16, 137.74, 136.10, 135.15, 134.94, 131.97, 131.51, 131.31, 128.37, 127.78, 123.87, 123.04, 122.99, 121.81, 49.66, 31.62, 19.35, 13.84; HRMS (ESI) m/z: [M–Br+H]$^+$ Calcd for $C_{25}H_{23}N_3O$ 397.1790; Found, 397.1805.

Compound 6: Yield: 93%; White coloured solid. R_f=0.40 (MeOH/DCM 4:46). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.42 (s, 1H), 8.64 – 8.61 (m, 4H), 8.35 (d, *J* = 7.84 Hz, 1H), 8.12 (d, *J* = 8.12 Hz, 2H), 8.06 – 7.99 (m, 3H), 7.91 – 7.82 (m, 4H), 4.70 – 4.67 (t, *J* = 6.94 Hz, 2H), 2.11 – 2.05 (m, 2H), 1.56 – 1.49 (m, 2H), 1.07 – 1.03 (t, *J* = 7.18 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) 164.20, 143.20, 138.32, 135.16, 133.44, 131.99, 131.85, 131.78, 131.42, 131.32, 128.41, 128.03, 127.79, 127.50, 126.11, 123.04, 114.61, 114.11, 47.37, 30.98, 19.67, 13.96; HRMS (ESI) m/z: [M–Br]$^+$ Calcd for $C_{29}H_{24}N_3O_2$ 446.1863; Found, 446.1885.

Compound 12: 1:1 mixture of 5(6)-substituted derivatives were observed. Yield: 91%; White coloured solid. R_f=0.35 (MeOH/DCM 4:46). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 2H), 8.58 – 8.52 (m, 8H), 8.33 (d, *J* = 0.96 Hz, 1H), 8.31 (d, *J* = 8.84 Hz, 1H), 8.22 (d, *J* = 0.96 Hz, 1H), 8.13 (d, *J* = 8.84 Hz, 1H), 7.96 – 7.92 (m, 4H), 7.80 (dd, *J* = 1.4, 8.76 Hz, 1H), 7.76 – 7.73 (dd, *J* = 1.36, 8.76 Hz, 1H), 7.63 (d, *J* = 7.04 Hz, 2H), 7.55 (d, *J* = 6.64 Hz, 2H), 7.49 – 7.38 (m, 6H), 5.85 (s, 2H), 5.77 (s, 2H), 4.61 – 4.58 (t, *J* = 7.20 Hz, 2H), 4.51 – 4.47 (t, *J* = 7.34 Hz, 2H), 2.03 – 1.89 (m, 4H), 1.49 – 1.34 (m, 4H), 1.01 – 0.97 (t, *J* = 7.34 Hz, 3H), 0.96 – 0.92 (t, *J* = 7.36 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) 164.35, 143.92, 135.28, 135.22, 134.39, 134.27, 132.16, 131.98, 131.74, 131.53, 131.38, 131.35, 131.05, 129.52, 129.46, 129.31, 129.25, 128.95, 128.77, 128.62, 128.35, 127.82, 122.96, 122.89, 115.35, 115.19, 114.83, 114.77, 50.64, 50.50, 47.36, 30.94, 30.82, 19.67, 19.60, 13.92, 13.84; HRMS (ESI) m/z: [M – Br]$^+$ Calcd for $C_{30}H_{26}N_3O_2$ 460.2020; Found, 460.2006.

General Procedure for the Synthesis of PEPPSI complexes (7, 8 & 13)

To an oven-dried screw cap reaction tube equipped with magnetic stir bar, **5**, **6** & **12** (1 equiv), $PdCl_2$ (1.05 equiv), K_2CO_3 (5 equiv), KBr (3 equiv) and pyridine (5 mL) were charged. The tube was then capped and placed in a preheated oil bath at 80 °C for 16 h under vigorous stirring. After completion, the reaction mass was filtered over a short plug of celite using dichloromethane as washing solvent. The combined organic layers were concentrated under reduced pressure and the crude was purified by column chromatography using DCM/Methanol as eluents to afford pure complexes.

Complex 7: Yield: 71%; Yellow coloured solid. R_f=0.30 (MeOH/DCM 2:98). Purified by column chromatography on silica gel (DCM/Methanol = 97/3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (dd, *J* = 1.44, 6.4 Hz, 2H), 8.69 (d, *J* = 7.24 Hz, 2H), 8.31 (d, *J* = 7.84 Hz, 2H), 8.19 (d, *J* = 8.56 Hz, 2H), 7.84 – 7.80 (t, *J* = 7.74 Hz, 2H), 7.73 – 7.69 (m, 1H), 7.55 (d, *J* = 8.56 Hz, 2H), 7.32 – 7.29 (m, 2H), 7.27 (s, 1H), 7.13 (d, *J* = 1.96 Hz, 1H), 4.69 – 4.65 (t, *J* = 7.74 Hz, 2H), 2.21 – 2.13 (m, 2H), 1.62 – 1.53 (m, 2H), 1.10 – 1.06 (t, *J* = 7.36 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 164.18, 152.64, 149.50, 139.63, 137.64, 135.65, 134.47, 131.81, 131.75, 129.78, 128.58, 127.53, 127.12, 124.52, 123.40, 122.73, 122.14, 51.49, 32.03, 20.09, 13.84; Anal. Calcd for $C_{30}H_{26}Br_2N_4O_2Pd$: C, 48.64; H, 3.54; N, 7.56. Found: C, 48.62; H, 3.57; N, 7.51. HRMS (ESI) m/z: [M–2Br-Py] Calcd for $C_{25}H_{21}N_3O_2Pd$ 503.0673; Found, 503.0743.

Complex 8: Yield: 53%; Yellow coloured solid. R_f=0.25 (MeOH/DCM 2:98). Purified by column chromatography on silica gel (DCM/Methanol = 97/3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, *J* = 5.8 Hz, 2H), 8.71 (d, *J* = 7.24 Hz, 2H), 8.32 (d, *J* = 8.2 Hz, 2H), 8.16 (d, *J* = 8.4 Hz, 2H), 7.85 – 7.81 (t, *J* = 7.74 Hz, 2H), 7.74 – 7.70 (t, *J* = 7.7 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 7.96 Hz, 1H), 7.39 – 7.29 (m, 5H), 4.94 – 4.90 (t, *J* = 8.02 Hz, 2H), 2.36 – 2.28 (m, 2H), 1.71 – 1.63 (m, 2H), 1.15 – 1.11 (t, *J* = 7.34 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 164.16, 154.37, 152.56, 138.37, 137.65, 137.28, 136.22, 136.04, 134.45, 134.40, 131.85, 131.70, 130.10, 129.62, 128.63, 127.13, 125.00, 124.58, 123.55, 123.50, 122.81, 111.22, 110.46, 48.93, 31.04, 20.48, 13.87; Anal. Calcd for $C_{34}H_{28}Br_2N_4O_2Pd$: C, 51.64; H, 3.57; N, 7.08. Found: C, 51.67; H, 3.55; N, 7.10. HRMS (ESI) m/z: [M–2Br–Py-H] Calcd for $C_{29}H_{23}N_3O_2Pd$ 550.0747; Found, 550.0748;.

Complex 13: Yield: 61%; Yellow coloured solid. R_f=0.45 (MeOH/DCM 3:97). Purified by column chromatography on silica gel (DCM/Methanol = 97/3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 – 8.96 (m, 4H), 8.58 – 8.55 (dd, *J* = 0.88, 7.24 Hz, 2H), 8.53 – 8.51 (dd, *J* = 0.88, 7.28 Hz, 2H), 8.21 – 8.17 (m, 4H), 7.73 – 7.66 (m, 6H), 7.56 (d, *J* = 7.16 Hz, 2H), 7.50 – 7.48 (m, 2H), 7.33 – 7.31 (m, 3H), 7.29 – 7.19 (m, 8H), 7.17 – 7.09 (m, 3H), 6.99 – 6.97 (m, 2H), 6.14 (s, 2H), 6.09 (s, 2H), 4.88 – 4.78 (m, 4H), 2.28 – 2.16 (m, 4H), 1.62 – 1.55 (m, 2H), 1.51 – 1.47 (m, 2H), 1.07 – 1.04 (t, *J* = 7.36 Hz, 3H), 1.02 – 0.98 (t, *J* = 7.34 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 165.72, 165.55, 164.52, 164.36, 152.67, 137.97, 135.58, 135.08, 134.95, 134.69, 134.58, 134.52, 134.49, 134.40, 131.86, 131.79, 131.74, 130.83, 130.67, 128.97, 128.89, 128.53, 128.49, 128.28, 128.22, 128.08, 127.11, 127.06, 124.62, 124.60, 124.04, 123.83, 122.58, 112.25, 112.18, 111.10, 111.00, 54.01, 53.73, 49.07, 31.19, 31.04, 20.45, 20.41, 13.92, 13.83; Anal. Calcd for $C_{35}H_{30}Br_2N_4O_2Pd$: C, 52.23; H, 3.76; N, 6.96. Found: C, 52.34; H, 3.69; N, 7.05. HRMS (ESI) m/z: [M–Br]$^+$ Calcd for $C_{35}H_{30}BrN_4O_2Pd$ 725.0567; Found, 725.0560; [M–Br-Py] Calcd for $C_{30}H_{25}BrN_3O_2Pd$ 646.0145; Found, 646.0148.

General Procedure for the Synthesis of 3-aryl-2-trimethylsilyl indoles (23)

A flame dried reaction tube was charged with *o*-haloaniline (1 mmol), **16** (0.04 mmol), LiBr (1 mmol), anhydrous K_2CO_3 (2 mmol), TMS protected alkynes (2 mmol) and 1,4-dioxane (2 mL). The tube was capped and stirred at 120 °C for 8 h. On completion of the reaction, the mixture was cooled to room temperature, diluted with 15 mL of ethyl acetate and filtered through a short plug of celite. The organic layers were washed with water, dried over sodium sulphate and concentrated in *vacuo*. The crude mixture was then purified by column chromatography to afford the desired products.

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General Procedure for the Synthesis of *N*-alkyl-3-arylindoles (25)

The aforementioned procedure was applied with *o*-bromoaniline (1 mmol), **16** (0.04 mmol), TBAB (2.2 mmol), anhydrous K_2CO_3 (2 mmol), TMS protected alkynes (2 mmol) and 1,4-dioxane (2 mL) to yield the desired products in excellent yields.

Conclusions

In conclusion, topologically different Pd-NHCs appended with naphthalimides have been synthesized, characterized and evaluated for their catalytic activity. In addition, a unique effect of the additive on the product selectivity was observed for the Pd(II)-NHC catalyzed regioselective heteroannulation of *o*-haloaniline and TMS protected acetylenes. Electronically and sterically varied alkynes and *o*-haloanilines proved to be competent and the reaction is readily scalable. Late-stage derivatizations of both the silylated and the alkylated entities were carried to demonstrate the synthetic applicability.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

‡ Footnotes relating to the main text should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

1 a) A. Brancale, R. Silvestri, *Med Res Rev,* 2007, **27**, 209-238; b) A. Fernando Rodrigues de Sa, J. B. Eliezer, F. Carlos Alberto Manssour, *Mini. Rev. Med. Chem.* 2009, **9**, 782-793.

2 a) T. C. Leboho, J. P. Michael, W. A. L. van Otterlo, S. F. van Vuuren, C. B. de Koning, *Bioorg. Med. Chem. Lett.* 2009, **19**, 4948-4951; b) T. I. Richardson, C. A. Clarke, K.-L. Yu, Y. K. Yee, T. J. Bleisch, J. E. Lopez, S. A. Jones, N. E. Hughes, B. S. Muehl, C. W. Lugar, T. L. Moore, P. K. Shetler, R. W. Zink, J. J. Osborne, C. Montrose-Rafizadeh, N. Patel, A. G. Geiser, R. J. S. Galvin, J. A. Dodge, *ACS Med. Chem. Lett.* 2011, **2**, 148-153; c) S. Süzen, in *Bioactive Heterocycles V* (Ed.: M. T. H. Khan), Springer Berlin Heidelberg, Berlin, Heidelberg, 2007, pp. 145-178; d) S. Fatma, D. Singh, P. Mishra, P. K. Singh, P. Ankit, M. Singh, J. Singh, *RSC Adv.* 2013, **3**, 22527-22531.

3 a) T. Guo, F. Huang, L. Yu, Z. Yu, *Tetrahedron Lett.* 2015, **56**, 296-302. b) R. C. Larock, E. K. Yum, *J. Am. Chem. Soc.* 1991, **113**, 6689-6690; c) R. C. Larock, E. K. Yum, M. D. Refvik, *J. Org. Chem.* 1998, **63**, 7652-7662.

4 a) E. Siddalingamurthy, K. M. Mahadevan, J. N. Masagalli, H. N. Harishkumar, *Tetrahedron Lett.* 2013, **54**, 5591-5596; b) G. Bartoli, R. Dalpozzo, M. Nardi, *Chem. Soc. Rev.* 2014, **43**, 4728-4750.

5 a) T. H. H. Hsieh, V. M. Dong, *Tetrahedron,* 2009, **65**, 3062-3068; b) R. Yang, J.-T. Yu, S. Sun, Q. Zheng, J. Cheng, *Tetrahedron Lett.* 2017, **58**, 445-448; c) F. Zhou, D.-S. Wang, T. G. Driver, *Adv. Synth. Catal.* 2015, **357**, 3463-3468; d) S. Tong, Z. Xu, M. Mamboury, Q. Wang, J. Zhu, *Angew. Chem. Int. Ed.* 2015, **54**, 11809-11812; e) F. Ferretti, M. A. El-Atawy, S. Muto, M. Hagar, E. Gallo, F. Ragaini, *Eur. J. Org. Chem.* 2015, **2015**, 5712-5715; f) I. Choi, H. Chung, J. W. Park, Y. K. Chung, *Org. Lett.* 2016, **18**, 5508-5511.

6 Y. Jia, J. Zhu, *J. Org. Chem.* 2006, **71**, 7826-7834.

7 a) Y.-P. Zhang, X.-L. Feng, Y.-S. Yang, B.-X. Cao, *Tetrahedron Lett.* 2016, **57**, 2298-2302; b)Y. Chen, S. Guo, K. Li, J. Qu, H. Yuan, Q. Hua, B. Chen, *Adv. Synth. Catal.* 2013, **355**, 711-715; c) R. J. Phipps, N. P. Grimster, M. J. Gaunt, *J. Am. Chem. Soc.* 2008, **130**, 8172-8174; d) F. Bellina, F. Benelli, R. Rossi, *J. Org. Chem.* 2008, **73**, 5529-5535.

8 S. Murru, A. A. Gallo, R. S. Srivastava, *ACS Catal.* 2011, **1**, 29-31.

9 S. Llona-Minguez, M. Desroses, A. Ghassemian, S. A. Jacques, L. Eriksson, R. Isacksson, T. Koolmeister, P. Stenmark, M. Scobie, T. Helleday, *Chem. Eur. J.* 2015, **21**, 7394-7398.

10 a) B. Lu, J. R. Falck, *Angew. Chem. Int. Ed.* 2008, **47**, 7508-7510; b) L. Zhang, Z. Hang, Z.-Q. Liu, *Angew. Chem. Int. Ed.* 2016, **55**, 236-239; c) L. Guo, A. Chatupheeraphat, M. Rueping, *Angew. Chem. Int. Ed.* 2016, **55**, 11810-11813; d) A. K. Franz, S. O. Wilson, *J. Med. Chem.* 2013, **56**, 388-405; e) K. Devaraj, C. Sollert, C. Juds, P. J. Gates, L. T. Pilarski, *Chem. Commun.* 2016, **52**, 5868-5871.

11 a) W. A. Herrmann, *Angew. Chem. Int. Ed.* 2002, **41**, 1290-1309; b) M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, *Nature* 2014, **510**, 485-496; c) G. C. Fortman, S. P. Nolan, *Chem. Soc. Rev.* 2011, **40**, 5151-5169; d) C. J. O'Brien, E. A. B. Kantchev, C. Valente, N. Hadei, G. A. Chass, A. Lough, A. C. Hopkinson, M. G. Organ, Chem. Eur. J 2006, **12**, 4743-4748; e) M. G. Organ, S. Çalimsiz, M. Sayah, K. H. Hoi, A. J. Lough, *Angew. Chem. Int. Ed*. 2009, **121**, 2419-2423; f) M. G. Organ, G. A. Chass, D.-C. Fang, A. C. Hopkinson, C. Valente, *Synthesis* 2008, **2008**, 2776-2797.

12 P. K. R. Panyam, T. Gandhi, *Adv. Synth. Catal.* 2017, **359**, 1144-1151.

13 S. Ibanez, M. Poyatos, E. Peris, *Chem. Commun.* 2017, **53**, 3733-3736.

14 P. Tao, J. Liang, Y. Jia, *Eur. J. Org. Chem.* 2014, **2014**, 5735-5748.

15 a) X. Jiang, J. Yang, F. Zhang, P. Yu, P. Yi, Y. Sun, Y. Wang, *Org. Lett.* 2016, **18**, 3154-3157; b) E. T. Nadres, A. Lazareva, O. Daugulis, *J. Org. Chem.* 2011, **76**, 471-483.

16 R. C. Larock, E. K. Yum, M. D. Refvik, *J. Org. Chem.* 1998, **63**, 7652-7662.

17 C. Amatore, A. Jutand and A. Suarez, *J. Am. Chem. Soc.*, 1993, **115**, 9531-9541

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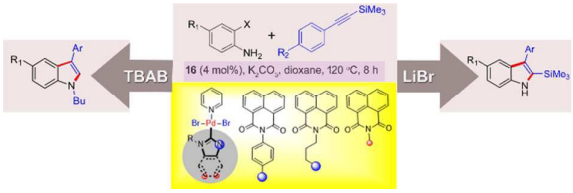

Pd(II)-NHC catalyzed regioselective heteroannulation of *o*-haloanilines and arylethynyl-trimethylsilane to yield indoles and additive controlled switchable product selectivity has been demonstrated.