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The $PdCl_2$-catalyzed sequential heterocyclization/Michael addition cascade in the synthesis of 2,3-disubstituted indoles

Donala Janreddy, Veerababurao Kavala, Chun-Wei Kuo, Ting-Shen Kuo, Chiu-Hui He, Ching-Fa Yao *

Department of Chemistry, National Taiwan Normal University, 88, Sec. 4, Tingchow Road, Taipei 116, Taiwan ROC

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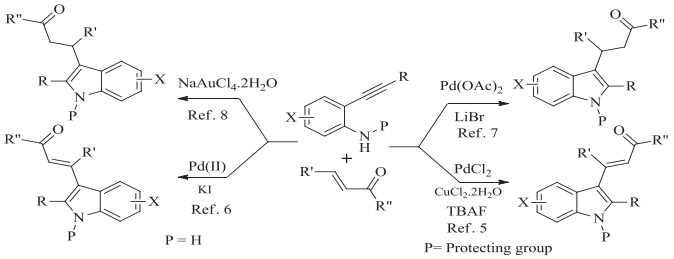
ABSTRACT

A cascade reaction of 2-*N*-unprotected-2-alkynylanilines and various electron-deficient alkenes in the presence of $PdCl_2$ provided 2,3-disubstituted indole derivatives, whereas, in the presence of $Pd(OAc)_2$, the same reaction resulted in the production of *N*-alkylated-2-alkynylaniline derivatives.

1. Introduction

Indole and its derivatives play a leading role in medicinal and synthetic chemistry due to the presence of this structure in a number of natural products and pharmaceutical agents.[1] A survey of the literature indicates that a wide variety of synthetic protocols exist for the construction of an indole moiety.[2] Among them, the transition metal-catalyzed intramolecular cyclization of 2-alkynylaniline is the most widely employed method for generating an indole moiety. The advantages of this method include a wide tolerance for functional groups, its simplicity and the fact that the yields of indole derivatives are acceptable.[3] A wide range of transition metal catalysts, including Cu, Au, In, Fe, Pd, Rh, Ag, Hg etc., can be used to generate indole derivatives via the annulation of 2-haloanilines with alkynes.[4]

On the other hand, the reaction of 2-alkynylanilines and electron-deficient alkenes in the presence of various transition metal catalyst results in the production of two different types of indole derivatives, namely, 3-substituted-2-alkenylindoles and 3-substituted-2-alkylindoles, depending on the conditions employed (Scheme 1). The formation of 3-substituted-2-alkenylindole derivatives involves a β-hydride elimination (the Heck reaction),[5,6] whereas the formation 3-substituted-2-alkyl substituted indole derivatives is the result of the protonolysis of metal–carbon bond and is achieved by controlling the extent of β-hydride elimination.[7,8]



Scheme 1. Previous reports on the differential reactivity of 2-alkynyl-anilines with various electron-deficient alkenes.

From all these reports, it is quite clear that both the reaction conditions and the additives used have an important impact on the reaction. The differential reactivity of 2-alkynylaniline with electron-deficient alkenes prompted us to further investigate this reaction. In fact, in recent years, we reported on some protocols for the synthesis of functionalized indole and quinoline derivatives.[9] In a continuation of these studies, we report herein on the reaction of 2-*N*-unprotected-2-alkynylanilines with electron-deficient alkenes in the presence of various metal catalysts.

2. Results and discussion

To study this reaction, we chose 2-(phenylethynyl) aniline and methyl vinyl ketone as model substrates. Lu and his co-worker

* Corresponding author. E-mail addresses: cheyaocf@ntnu.edu.tw, cheyaocf@yahoo.com.tw (C.-F. Yao).

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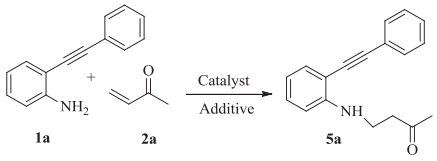
reported on the reaction of *N*-(2-(phenylethynyl) phenyl)methanesulfonamide derivatives and acrolein[7] in the presence of $Pd(OAc)_2$ and LiBr in which 3-(*N*-Mesyl-2′-phenylindol-3′-yl) propanal was produced as the major product. However, they did not investigate the use of 2-(phenylethynyl)aniline and methyl vinyl ketone substrates in their reaction. To determine whether these substrates could be employed in this process, we examined the reaction of 2-(phenylethynyl)aniline and methyl vinyl ketone in the presence of $Pd(OAc)_2$ and LiBr in THF or CH_3CN solvent at room temperature (Table 1, entry 2). Under these conditions, the final product of the reaction produced was the Michael adduct 4-((2-(phenylethynyl) phenyl)amino)butan-2-one. Even when the reaction was run at 60 °C, the outcome was the same, but a shorter reaction time was required (Table 1, entry 3). To further verify this result, we examined the reactions of a variety of 2-alkynylanilines with various α,β-unsaturated ketones. All of the substrates tested in this reaction, produced the corresponding Michael adduct in moderate to good yield (Table 2, entries 1–5). However, the desired product, the 2,3-disubstituted indole was not obtained under these reaction conditions (Table 1).

Table 1
The reactivity of 2-(phenylethynyl)aniline with methyl vinyl ketone catalyzed by $Pd(OAc)_2$

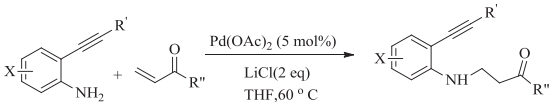


1a 2a 5a

Entry[a]	Catalyst (5 mol %)	Additive (2 equiv)	Temp (°C)	Time (h)	Yield (%)[b]
1	$Pd(OAc)_2$	LiCl	rt	24	60
2	$Pd(Oac)_2$	LiBr	rt	24	60
3	**$Pd(Oac)_2$**	**LiCl**	**60**	**24**	**80**

Bold values indicate optimum reaction conditions for this reaction.
[a] Unless otherwise noted, all reactions were carried out on a 0.25 mmol scale in THF solvent.
[b] NMR yields (CH_2Br_2 as internal standard).

Table 2
Reactions of 2-alkynylanilines with various Michael acceptors in the presence $Pd(OAc)_2$/LiCl



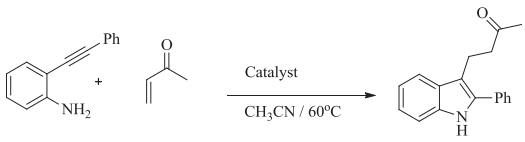
1 2 5a-e

Entry[a]	R′	R″	X	Product	Time (h)	Yield (%)[b]
1	Ph	Me	H	**5a**	24	65
2	Cyclopentyl	Me	4-Me	**5b**	30	68
3	*n*-Butyl	Me	4-Cl	**5c**	48	72
4	Ph	Et	H	**5d**	24	78
5	Ph	Ph	H	**5e**	24	62

[a] Unless otherwise noted, the reactions were carried out under the following conditions, 2-alkynylaniline (1.0 mmol), methyl vinyl ketone (1.5 mmol), $Pd(OAc)_2$ (5 mol %), LiCl (2 equiv) in THF solvent at 60 °C.
[b] Isolated yields.

In an attempt to examine the reaction using other palladium(II) catalysts, we performed the reaction using 5 mol % palladium chloride in the presence of lithium chloride in acetonitrile as the solvent at 60 °C. In this case, the reaction produced 4-(2-phenyl-1*H*-indol-3-yl)butan-2-one as the sole product and no trace of the *N*-alkylated product was observed (Table 3, entry 1) however, the starting material was not completely consumed. On the other hand, when $Pd(PPh_3)_2Cl_2$ was used as catalyst, two products, the 2,3-disubstituted indole derivative and the *N*-alkylated product were

Table 3
Investigation of reactivity of 2-(phenylethynyl) aniline with methyl vinyl ketone in the presence of various metal catalysts



1a 2a 3a

Entry[a]	Catalyst	Temp (°C)	Time (h)	Yield (%)[b]
1[c,d]	$PdCl_2$/LiCl	60	24	45
2[c,d]	$Pd(PPh_3)_2Cl_2$/LiCl	60	24	40
3[c,d]	$Pd(CH_3CN)_2Cl_2$/LiCl	60	24	42
4[d]	$PdCl_2$ (5 mol %)	60	24	33
5[d]	$PdCl_2$ (10 mol %)	60	6	65
6[d]	$Pd(PPh_3)_2Cl_2$(10 mol %)	60	24	50
7[d]	$Pd(CH_3CN)_2Cl_2$ (10 mol %)	60	4	65
8	**$PdCl_2$** (20 mol %)	**60**	**4**	**90**
9	$ZnCl_2$ (20 mol %)	60	4	Trace
10	$CuCl_2$ (20 mol %)	60	24	10
11	$CuBr_2$ (20 mol %)	60	24	9
12	CuI (20 mol %)	60	12	Trace
13	CuBr (20 mol %)	60	12	Trace
14	CuCl (20 mol %)	60	12	Trace
15	VCl_3 (20 mol %)	60	24	35
16	$InCl_3$ (10 mol %)	60	24	25
17	$FeCl_3$ (20 mol %)	60	4	27
18	$FeCl_2$ (20 mol %)	60	4	6
19	$In(OTf)_3$ (10 mol %)	60	9	62
20	$BF_3.Et_2O$ (30 mol %)	60	8.5	57
21	$TiCl_4$ (20 mol %)	60	2	54

Bold values indicate optimum reaction conditions for this reaction.
[a] Unless otherwise noted, all the reactions were carried out at 0.25 mmol scale in acetonitrile solvent.
[b] NMR yields (CH_2Br_2 as internal standard).
[c] 5 mol % of catalyst and 2 equiv of LiCl were used.
[d] Unreacted starting material **1a** was recovered.

produced, along with some unreacted starting material (Table 3, entry 2). Moreover, another palladium catalyst $Pd(CH_3CN)_2Cl_2$/LiCl gave the 2,3-disubstituted indole derivative but the reaction failed to reach completion, even after 24 h (Table 3, entry 3). On the other hand, when the same reaction was conducted with palladium chloride in the absence of lithium chloride, the yield of the desired product was similar (Table 3, entry 4). Based on these observations, we envisioned that $PdCl_2$ represents an ideal catalyst for this transformation. To evaluate this further, we carried out the reaction using increasing amounts of catalyst to 10 mo% at 60 °C. Under these conditions, the reaction afforded 65% of the desired product (Table 3, entry 5). However, an excellent yield was obtained when the reaction was performed using 20 mol % palladium chloride as catalyst (Table 3, entry 8). Further increases in catalyst loading failed to improve the product yield or the rate of the reaction. To compare the efficacy of the catalyst, we tested the reaction with various other transition metal catalysts such as, CuBr, $CuBr_2$, CuCl, CuI, $ZnCl_2$, $FeCl_3$, $FeCl_2$, $InCl_3$, VCl_3, $ZnBr_2$, $In(OTf)_3$, $BF_3{\cdot}OEt_2$, and $TiCl_4$ in acetonitrile at 60 °C (Table 3, entries 9–21). $In(OTf)_3$, $BF_3.OEt_2$, and $TiCl_4$ resulted in the production of the desired product in moderate yields, but the remaining catalysts were ineffective for this transformation (Table 3, entries 19–21).

We next investigated the effect of solvent; by carrying out the reaction in solvents such as DMF, DMSO, MeOH, THF and CH_2Cl_2. The use of polar solvents such as DMF, DMSO, and MeOH resulted in poor yields. The yield of product was comparable in case of CH_2Cl_2 but a longer time was needed for the reaction to reach completion. The best result was obtained when the reaction was performed in the presence of 20 mol % of $PdCl_2$ with acetonitrile as the solvent at 60 °C. The product, 4-(2-phenyl-1*H*-indol-3-yl)butan-2-one was well characterized by ^1H NMR, ^{13}C NMR, LRMS, and HRMS. In addition, the structure was confirmed by the single crystal X-RD analysis (Fig. 1).

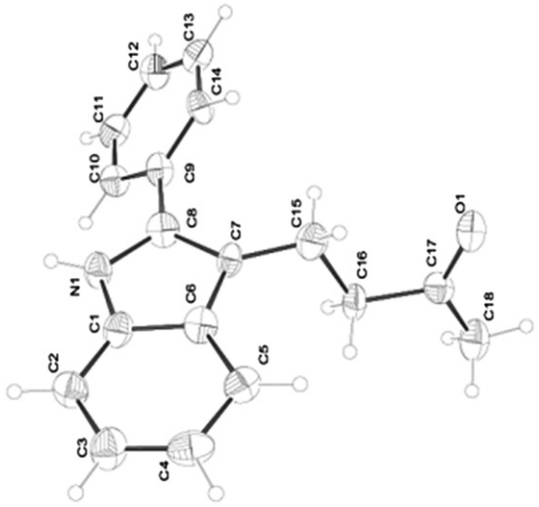
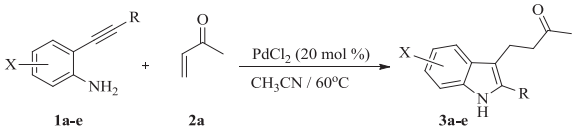


Fig. 1. ORTEP diagram of the single crystal X-ray diffraction structure of **3a**.[12]

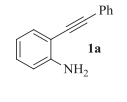
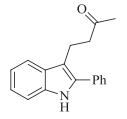
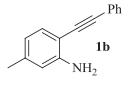
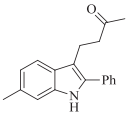
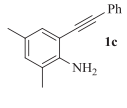
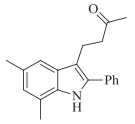
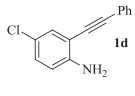
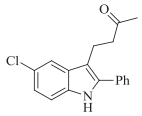
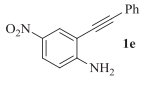
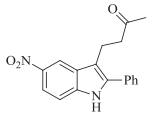
With optimized reaction conditions determined, we investigated the scope and limitations of the reaction using various substituted 2-(aryl/alkylethynyl)aniline and methyl vinyl ketone derivatives. In this regard, we first examined the reaction of various 2-(phenylethynyl)anilines with different substitutions on the phenyl ring (Table 4). The reaction of 2-(phenylethynyl)anilines containing electron releasing groups produced slightly higher yields of products than substrates with electron withdrawing groups (Table 4, entries 1–5). In order to check the effect of a lower catalyst loading, we conducted all these reactions using 10 mol % of $PdCl_2$. As shown in Table 3, in the presence of 10 mol % $PdCl_2$ catalyst, the reactions required a longer time to produce the corresponding product and the yields of the product were comparatively less.

Consequently, we examined the reaction with different substituted 2-cycloalkyl(alkylethynyl)anilines and 2-(alkylethynyl) anilines (Table 5). Reactions involving 2-cycloalkyl(alkylethynyl)anilines and 2-(alkylethynyl)anilines were much faster, compared to reactions using 2-(phenylethynyl)anilines (Tables 4 and 5). On the other hand, sensitive groups like ester, alcohol, and cyclopropyl functionalities tolerated the present reaction conditions. The yield of products was moderate to good in the case of cycloalkyl and long

Table 4
Synthesis of various 2,3-disubstituted indole derivatives

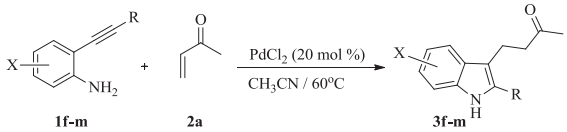


1a-e 2a 3a-e

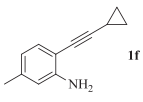
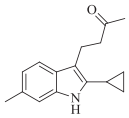
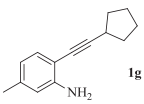
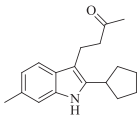
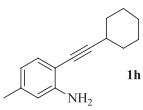
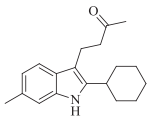
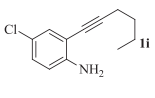
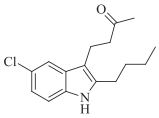
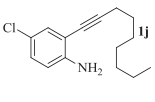
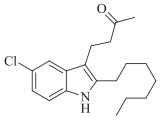
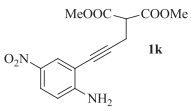
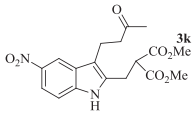
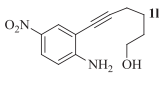
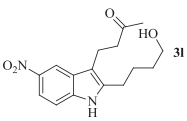
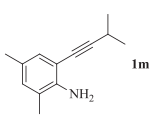
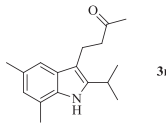
Entry[a]	Substrate	Product	Time (h)	Yield (%)[b]
1			4 (6)	70 (60)
2			5 (8)	69 (60)
3			1.5 (4)	70 (58)
4			2 (5)	65 (55)
5			6 (10)	50 (45)

[a] Unless otherwise noted, all reactions were carried out under the following conditions, 2-alkynylaniline (1.0 mmol), methyl vinyl ketone (1.5 mmol), $PdCl_2$ (20 mol %) in acetonitrile at 60 °C.
[b] Isolated yields. The yields and reaction times given in parentheses corresponds to the reactions using 10 mol % of $PdCl_2$.

Table 5
Synthesis of various 2,3-disubstituted indole derivatives



1f-m 2a 3f-m

Entry[a]	Substrate	Product	Time (h)	Yield (%)[b]
6			0.25	75
7			0.5	70
8			0.3	70
9			2	60
10			1	67
11			1	40
12			1	65
13			1	97

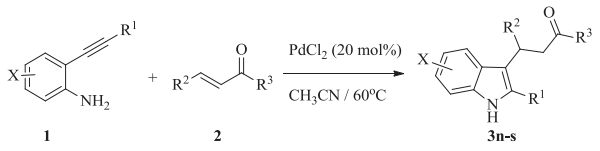
[a] Unless otherwise noted, all reactions were carried out under the following conditions, 2-alkynylaniline (1.0 mmol), methyl vinyl ketone (1.5 mmol), $PdCl_2$ (20 mol %) in acetonitrile at 60 °C.
[b] Isolated yields.

chain alkyl substituted 2-(alknylethynyl)anilines (Table 5, entries 6–12). However, the reaction of 2,4-dimethyl-6-(3-methylbut-1-ynyl)aniline gave the desired product in excellent yield (Table 5, entry 13).

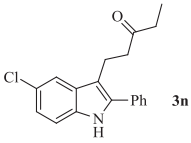
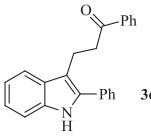
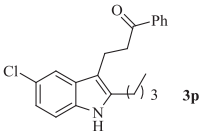
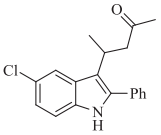
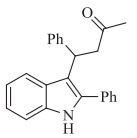
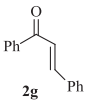
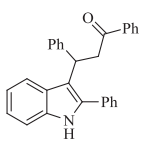
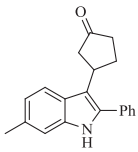
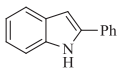
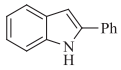
To explore the generality and scope of this protocol, further, we examined the reaction when various Michael acceptors were used (Table 6). The reaction of ethyl vinyl ketone with **1d** gave the desired product in excellent yield (Table 6, entry 1). Moreover, the reaction of phenyl vinyl ketone with **1a** and **1j** furnished the corresponding 2,3-disubstituted indole derivatives in good yields (Table 6, entries 2 and 3). However, the reactions required a long time compared to the ethyl vinyl ketone (Table 6, entries 1–3). The reactions of substituted vinyl ketones like *trans*-2-butenone, *trans*-1-phenyl-2-butenone and *trans*-chalcone took a longer time to produce the corresponding product in good yields (Table 6, entries 4–6). At the same time, sterically hindered and a less reactive enone[10] like cyclopentenone gave the desired product (51%) along with some 2-substituted indole (20%) (Table 6, entry 7). However, the reaction in the presence of weak Michael acceptors such as methyl acrylate and acrylonitrile resulted in the formation of 2-phenylindole as the final product. No trace of 2,3-disubstituted indole was obtained in both cases (Table 6, entries 8 and 9).

Finally, we tested the reaction of *N*-protected 2-alkynylaniline derivatives with methyl vinyl ketone under the present reaction conditions. Here, only the *N*-protected 2-phenylindole was obtained as a final product (Scheme 2, **4C**). We also examined the reaction of 2-ethynylaniline and 2-trimethylsillylethynylaniline. In this case, the expected product was not produced under the present reaction conditions (Scheme 2).

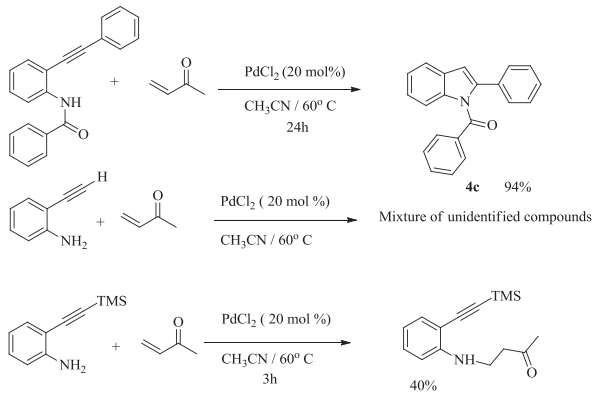
Table 6
Reactions of 2-alkynylanlines with various Michael acceptors



1 2 3n-s

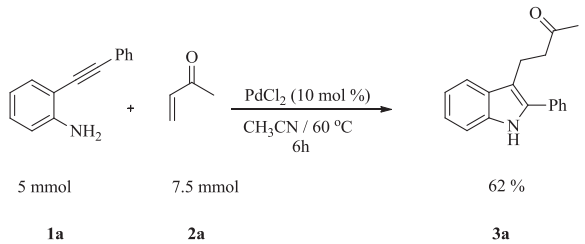
Entry[a]	Substrate	Enone	Product	Time (h)	Yield (%)[b]
1	**1d**	 **2b**	 **3n**	1.5	96
2	**1a**	 **2c**	 **3o**	8	75
3	**1j**	 **2d**	 **3p**	6	82
4	**1d**	 **2e**	 **3q**	48	70
5	**1a**	 **2f**	 **3r**	48	70
6	**1a**	 **2g**	 **3s**	48	75
7[c]	**1b**	 **2h**	 **3t**	24	51
8[d]	**1a**	 **2i**	 **4b**	24	54
9[d]	**1a**	 **2j**	 **4b**	24	77

[a] Unless otherwise noted, all the reactions were carried out under the following conditions, 2-alkynylaniline (1.0 mmol), methyl vinyl ketone (1.5 mmol), $PdCl_2$ (20 mol %) in acetonitrile solvent at 60 °C.
[b] Isolated yields.
[c] 20% of 6-methyl-2-phenylindole (**4a**) was formed as side product.
[d] Only 2-phenylindole was formed.



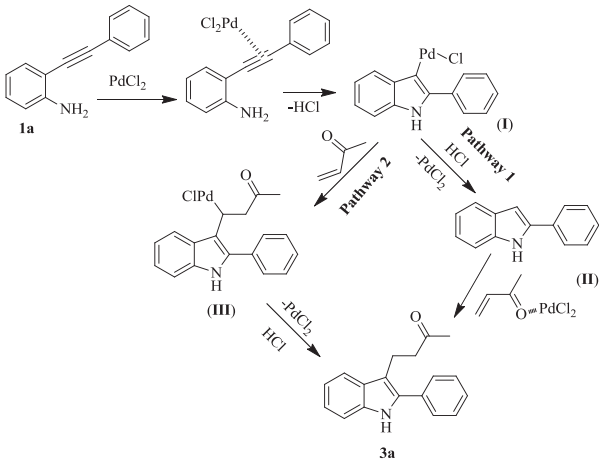
Scheme 2. Limitations of the protocol.

In order to extend the scope of the methodology, we carried out the reaction on a large scale using 5 mmol of 2-(phenylethynyl) aniline and 7.5 mmol of methyl vinyl ketone in presence of 10 mol % $PdCl_2$ in acetonitrile at 60 °C. The reaction proceeded without any difficulty and a good yield of the desired product was obtained (Scheme 3).



Scheme 3. 5 mmol scale reaction of 2-(phenylethynyl)aniline with methyl vinyl ketone.

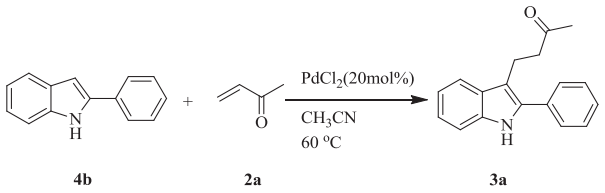
We speculate that the mechanism for this reaction is very similar to that proposed by Alfonsi et al.,[8] which involves the coordination of palladium chloride with the triple bond of a 2-akynylaniline and followed by aminopalladation to furnish an indole palladium intermediate (**I**) (Scheme 4), which then undergoes protonolysis in the presence of the strong acid HCl that was



Scheme 4. Plausible mechanistic pathways.

produced during the aminopalladation to afford the 2-substituted indole derivative (**II**). The resulting 2-substituted indole then reacts with the α,β-unsaturated ketone in the presence palladium chloride to give the corresponding 2,3-disubstituted indole derivative.[8] Alternatively the indole palladium intermediate (**I**) could react with the α,β-unsaturated ketone to produce intermediate (**III**), which then undergoes protonolysis to produce the desired product (Scheme 4).[7,11] The experimental results such as the formation of 2-phenylindole derivatives in the case of the reactions with methyl acrylate and acrylonitrile (Table 6, entries 8 and 9) as well as the reaction of *N*-(2-(phenylethynyl)phenyl)benzamide with methyl vinyl ketone (Scheme 2, **4C**) supports the **pathway 1** mechanism. As in both cases, after the formation of a 2-phenylindole derivative from the indole palladium intermediate (**I**), a Michael addition did not take place. In the former case both acrylonitrile and methyl acrylate are weak Michael acceptors whereas in the later case the presence of a benzoyl substituent on the indole moiety decreases the nucleophilicity.

Moreover when 2-phenylindole and methyl vinyl ketone was reacted in the presence of palladium chloride, the reaction produced 4-(2-phenyl-1*H*-indol-3-yl)butan-2-one in quantitative yield (Scheme 5). This reaction also supports the **Pathway 1** mechanism for the formation of 2,3-disubstituted indole derivative from the reaction of 2-alkynylanilines with various α,β-unsaturated ketones.



Scheme 5. Reaction of 2-phenylindole with methyl vinyl ketone.

3. Conclusion

In conclusion, we report on cascade reaction of 2-*N*-unprotected-2-alkynylanilines and various electron-deficient alkenes using palladium chloride and $Pd(OAc)_2$/LiCl catalytic systems. The presence of $PdCl_2$ resulted in the formation of 2,3-disubstituted indole derivatives whereas the $Pd(OAc)_2$/LiCl catalytic system produced *N*-alkylated-2-alkynylaniline derivatives. A mechanism was proposed for the formation of 2,3-disubstituted indole derivatives based on experimental outcome, which is consistent with related observations from the literature. This procedure offers a mild and easy method to access a variety of 2,3-disubstituted indole derivatives in moderate to good yields. A variety of functional groups readily tolerated under the reaction conditions employed.

4. Experimental section

4.1. General information

All reactions were performed at 60 °C. Analytical thin-layer chromatography was performed with E. Merck silica gel 60F glass plates and flash chromatography by using E. Merck silica gel 60 (230–400 mesh). MS or HRMS were measured by JEOL JMS-D300 or JEOL JMS-HX110 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance EX 400.

4.2. General experimental procedure for the synthesis of 2,3-disubstituted indoles

The substituted 2-alkynylaniline (1.0 mmol) was dissolved in acetonitrile (5.0 mL) and stirred until the solution became homogeneous. To this solution, methyl vinyl ketone (1.5 mmol) followed by 20 mol % of $PdCl_2$ (59–60%, 35 mg) was added under a nitrogen atmosphere, then heated to 60 °C and monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature and the acetonitrile was removed by vacuum evaporation. The resulting crude product was purified by column chromatography to afford the desired 2,3-disubstituted indoles.

4.3. Spectral data

*4.3.1. 4-(2-Phenyl-1H-indol-3-yl)butan-2-one (**3a**).* Yield: (184 mg, 70%); White solid; mp: 114–116 °C. FT-IR (KBr) (ν/cm^{-1}): 3343, 1708. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 8.12 (br s, 1H), 7.61 (d, *J*=7.92 Hz, 1H), 7.55–7.52 (m, 2H), 7.49–7.45 (m, 2H), 7.40–7.63 (m, 2H), 7.25–7.21 (m, 1H), 7.18–7.14 (m, 1H), 3.22–3.18 (m, 2H), 2.84–2.80 (m, 2H), 2.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 208.8, 136.0, 134.6, 133.2, 129.1, 128.9, 128.1, 127.9, 122.5, 119.8, 119.0, 111.9, 111.1, 44.6, 30.1, 18.9. LRMS (EI) (*m*/*z*) (relative intensity): 263 (M^+, 50), 221.4 (100), 205.5 (90), 179.1 (25); HRMS calcd for $C_{18}H_{17}O_1N_1$ (M^+): 263.1310, found 263.1314.

*4.3.2. 4-(6-Methyl-2-phenyl-1H-indol-3-yl)butan-2-one (**3b**).* Yield: (191 mg, 69%); White solid; mp: 170–172 °C. FT-IR (KBr) (ν/cm^{-1}): 3358, 1713. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 7.97 (br s, 1H), 7.53–7.44 (m, 5H), 7.38–7.34 (m, 1H), 7.16 (s, 1H), 6.99 (dd, *J*=8.0, 0.9 Hz, 1H), 3.20–3.16 (m, 2H), 2.83–2.79 (m, 2H), 2.48 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 208.9, 136.5, 133.9, 133.4, 132.4.9, 129.1, 128.0, 127.7, 126.8, 121.6, 118.7, 111.8, 111.1, 44.7, 30.4, 21.9, 19.0. LRMS (EI) (*m*/*z*) (relative intensity): 277 (M^+, 55), 220 (100), 234 (65), 236 (58); HRMS calcd for $C_{19}H_{19}O_1N_1$ (M^+): 277.1467, found 277.1460.

*4.3.3. 4-(5,7-Dimethyl-2-phenyl-1H-indol-3-yl)butan-2-one (**3c**).* Yield: (204 mg, 70%); White solid. Mp: 154–155 °C. FT-IR (KBr) (ν/cm^{-1}): 3358, 1715. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 7.94 (br s, 1H), 7.59–7.56 (m, 2H), 7.51–7.47 (m, 2H), 7.42–7.37 (m, 1H), 7.25 (s, 1H), 6.90 (s, 1H), 3.20–3.16 (m, 2H), 2.85–2.81 (m, 2H), 2.50 (s, 3H), 2.49 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 209.0, 134.6, 133.9, 133.5, 129.4, 129.0, 128.7, 128.1, 127.8, 124.9, 120.0, 116.3, 112.0, 44.8, 30.1, 21.7, 19.1, 16.7. LRMS (EI) (*m*/*z*) (relative intensity): 291 (M^+, 2), 249.0 (80), 105 (100); HRMS calcd for $C_{20}H_{21}O_1N_1$ (M^+): 291.1623, found 291.1627.

*4.3.4. 4-(5-Chloro-2-phenyl-1H-indol-3-yl)butan-2-one (**3d**).* Yield: (193 mg, 65%); White solid; mp: 170–171 °C. FT-IR (KBr) (ν/cm^{-1}):

3345, 1702. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 8.13 (br s, 1H), 6.95 (s, 1H), 7.54–7.45 (m, 5H), 7.41–7.36 (m, 1H), 7.28–7.26 (m, 1H), 7.15 (dd, J=8.5, 1.96 Hz, 1H), 3.14–3.10 (m, 2H), 2.79–2.75 (m, 2H), 2.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 208.5, 136.1, 134.4, 132.7, 130.1, 129.2, 128.3, 128.1, 125.5, 122.7, 118.5, 112.1, 111.6, 44.5, 30.1, 18.7. LRMS (EI) (m/z) (relative intensity): 297 (M^+, 42), 240 (100), 204 (40); HRMS calcd for $C_{18}H_{16}Cl_1O_1N_1$ (M^+): 297.0920, found 297.0912.

*4.3.5. 4-(5-Nitro-2-phenyl-1H-indol-3-yl)butan-2-one (**3e**).* Yield: (154 mg, 50%); Yellow solid. Mp: 172–173 °C. FT-IR (KBr) (ν/cm^{-1}): 3338, 1702. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 8.7 (br s, 1H), 8.54 (d, J=2.0 Hz, 1H), 8.09 (dd, J=8.9, 2.1 Hz, 1H), 7.55–7.53 (m, 2H), 7.50–7.47 (m, 2H), 7.44–7.38 (m, 2H) 3.21–3.17 (m, 2H), 2.80–2.79 (m, 2H), 2.12 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 208.1, 141.8, 139.0, 137.9, 131.9, 129.3, 128.8, 128.4, 128.1, 118.1, 116.3, 114.0, 110.0, 44.3, 30.1, 18.5. LRMS (EI) (m/z) (relative intensity): 308 (M^+, 55), 251 (100), 204 (40); HRMS calcd for $C_{18}H_{16}O_3N_2$ (M^+): 308.1161, found 308.1159.

*4.3.6. 4-(2-Cyclopropyl-6-methyl-1H-indol-3-yl)butan-2-one (**3f**).* Yield: (181 mg, 75%); Yellow Liquid. FT-IR (KBr) (ν/cm^{-1}): 3342, 1710. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 7.58 (br s, 1H), 7.35 (d, J=8.0 Hz, 1H), 7.04 (s, 1H) 6.92 (dd, J=8.0, 0.8 Hz, 1H), 3.07 (t, J=7.7 Hz, 2H), 2.82–2.78 (m, 2H), 2.44 (s, 3H), 2.25 (s, 3H), 2.07–2.00 (m, 1H), 1.00–0.95 (m, 2H), 0.74–0.700 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 209.5, 135.4, 135.3, 131.0, 126.4, 121.0, 117.6, 111.6, 110.7, 44.6, 30.3, 21.8, 18.7, 7.4, 6.4. LRMS (EI) (m/z) (relative intensity): 241.15 (M^+, 100); HRMS calcd for $C_{16}H_{19}O_1N_1$ (M^+): 241.1469, found 241.1467.

*4.3.7. 4-(2-Cyclopentyl-6-methyl-1H-indol-3-yl)butan-2-one (**3g**).* Yield: (188 mg, 70%); Thick red gummy liquid. FT-IR (KBr) (ν/cm^{-1}): 3350, 1715. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 7.65 (br s, 1H), 7.35 (d, J=8.0 Hz, 1H), 7.08 (s, 1H), 6.91 (d, J=7.9 Hz, 1H), 3.33–3.28 (m, 1H) 3.0–2.96 (m, 2H), 2.75 (t, J=7.66 Hz, 2H), 2.44 (s, 3H), 2.11 (s, 3H), 2.08–2.06 (m, 2H), 1.85–1.82 (m, 2H), 1.76–1.73 (m, 2H), 1.62–1.60 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 209.7, 138.1, 135.9, 131.0, 126.3, 121.0, 117.7, 110.7, 109.9, 45.0, 37.0, 33.6, 30.5, 25.9, 21.8, 18.8; LRMS (EI) (m/z) (relative intensity): 269.1 (M^+, 100); HRMS calcd for $C_{18}H_{23}O_1N_1$ (M^+): 269.1780, found 269.1779.

*4.3.8. 4-(2-Cyclohexyl-6-methyl-1H-indol-3-yl)butan-2-one (**3h**).* Yield: (198 mg, 70%); Pale brown liquid. FT-IR (KBr) (ν/cm^{-1}): 3356, 1725. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 7.74 (br s, 1H), 7.37 (d, J=8.0 Hz, 1H), 7.10 (s, 1H), 6.92 (dd, J=7.9, 0.9 Hz, 1H), 3.0–2.96 (m, 2H), 2.90–2.84 (m, 1H), 2.79–2.75 (m, 2H), 2.47 (s, 3H), 2.15 (s, 3H), 1.89–1.78 (m, 6H), 1.51–1.40 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 209.3, 139.8, 135.8, 130.9, 126.1, 120.9, 117.8110.7, 108.7, 45.0, 35.8, 33.6, 30.4, 26.8, 26.3, 21.8, 18.6. LRMS (EI) (m/z) (relative intensity): 283 (M^+, 100), 284 (22); HRMS calcd for $C_{19}H_{25}O_1N_1$ (M^+): 283.1936, found 283.1938.

*4.3.9. 4-(2-Butyl-5-chloro-1H-indol-3-yl)butan-2-one (**3i**).* Yield: (166 mg, 60%); Yellow Liquid. FT-IR (KBr) (ν/cm^{-1}): 3372, 1704. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 7.87 (br s, 1H), 7.42 (d, J=1.9 Hz, 1H), 7.16 (d, J=8.5 Hz, 1H), 7.05 (dd, J=8.5, 1.9 Hz, 1H), 2.94–2.90 (m, 2H), 2.75–2.70 (m, 4H), 2.1 (s, 3H) 1.65–1.57 (m, 2H), 1.42–1.33 (m, 2H), 0.92 (t, J=3.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 208.8, 137.6, 133.8, 129.6, 125.0, 121.3, 117.6, 111.5, 110.2, 44.5, 32.0, 30.0, 25.9, 22.7, 18.3, 14.0. LRMS (EI) (m/z) (relative intensity): 277 (M^+, 75), 220 (100), 177 (37); HRMS calcd for $C_{16}H_{20}Cl_1O_1N_1$ (M^+): 277.1233, found 277.1228.

*4.3.10. 4-(5-Chloro-2-heptyl-1H-indol-3-yl)butan-2-one (**3j**).* Yield: (214 mg, 67%); Colorless solid. Mp 88–89 °C. FT-IR (KBr) (ν/cm^{-1}): 3364, 1707. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 7.89 (br s, 1H), 7.43 (d, J=1.9 Hz, 1H), 7.16 (d, J=8.5 Hz, 1H), 7.05 (dd, J=8.5, 1.9 Hz, 1H), 2.94–2.90 (m, 2H), 2.76–2.70 (m, 4H), 2.12 (s, 3H), 1.66–1.59 (m, 2H), 1.36–1.27 (m, 8H), 0.88 (t, J=6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 208.8, 137.6, 133.8, 129.6, 125.0, 121.3, 117.6, 111.5, 110.2, 44.51, 31.9, 30.3, 29.9, 29.5, 29.3, 26.2, 22.8, 18.3, 14.2. LRMS (EI) (m/z) (relative intensity): 319 (M^+, 81), 262 (100), 177 (79); HRMS calcd for $C_{19}H_{26}Cl_1O_1N_1$ (M^+): 319.1703, found 319.1709.

*4.3.11. Dimethyl 2-((5-nitro-3-(3-oxobutyl)-1H-indol-2-yl)methyl) malonate (**3k**).* Yield: (150 mg, 40%); Yellow crystalline solid. Mp: 120–122 °C. FT-IR (KBr) (ν/cm^{-1}): 3449, 1735. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 8.44 (br s, 1H), 8.06 (m, 1H), 7.33–7.26 (m, 1H), 6.40 (s, 1H), 4.45 (t, J=7.1 Hz, 2H), 3.96–3.9 (m, 1H), 3.76 (s, 6H), 3.41–3.39 (m, 2H), 3.00–2.92 (m, 2H), 2.15 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 205.7, 168.8, 142.0, 140.2, 139.5, 127.3, 117.4, 117.3, 109.2, 102.3, 53.2, 50.7, 43.0, 38.1, 30.4, 26.0. LRMS (EI) (m/z) (relative intensity): 376 (M^+, 100), 285 (100); HRMS calcd for $C_{18}H_{20}O_7N_2$ (M^+): 376.1271, found 376.1279.

*4.3.12. (2-(4-Hydroxybutyl)-5-nitro-1H-indol-3-yl)butan-2-one (**3l**).* Yield: (197 mg, 65%); Yellow crystalline solid; mp: 160–161 °C. FT-IR (KBr) (ν/cm^{-1}): 3423, 1638. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 10.36 (br s, 1H), 8.25 (d, J=2.0 Hz, 1H), 7.81 (dd, J=8.8, 2.16 Hz, 1H), 7.14 (d, J=8.8 Hz, 1H), 3.50 (q, J=5.8 Hz, 2H), 3.40 (t, J=5.0 Hz, 1H), 2.83 (t, J=7.4 Hz, 2H), 2.60–2.60 (m, 4H), 1.97 (s, 3H), 1.66–1.59 (m, 2H), 1.50–1.43 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 208.1, 140.6, 139.9, 138.8, 127.3, 116.1, 114.7, 111.9, 110.2, 60.4, 44.2, 31.8, 30.0, 25.7, 25.3, 17.8. LRMS (EI) (m/z) (relative intensity): 304 (M^+, 100), 247 (80); HRMS calcd for $C_{16}H_{20}O_4N_2$ (M^+): 304.3142, found 304.1427.

*4.3.13. 4-(2-Isopropyl-5,7-dimethyl-1H-indol-3-yl)butan-2-one (**3m**).* Yield: (250 mg, 97%); Yellow solid. Mp: 109–110 °C. FT-IR (KBr) (ν/cm^{-1}): 3346, 1713. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 7.59 (br s, 1H), 7.13 (s, 1H), 6.79 (s, 1H), 3.34–3.27 (m, 1H), 2.99–2.95 (m, 2H), 2.79–2.76 (m, 2H), 2.45 (s, 3H), 2.43 (s, 3H), 2.15 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 209.2, 140.8, 133.0, 128.8, 128.1, 123.6, 119.5, 115.5, 108.9, 44.9, 30.3, 25.7, 23.0, 21.6, 18.6, 16.7. LRMS (EI) (m/z) (relative intensity): 257 (M^+, 50), 200 (100); HRMS calcd for $C_{17}H_{23}O_1N_1$ (M^+): 257.1780, found 257.1789.

*4.3.14. 1-(5-Chloro-2-phenyl-1H-indol-3-yl)pentan-3-one (**3n**).* Yield: (300 mg, 96%); Colorless solid. Mp: 138–140 °C. FT-IR (KBr) (ν/cm^{-1}): 3370, 1711. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 8.10 (br s, 1H), 7.55–7.53 (m, 3H), 7.47 (t, J=7.5 Hz, 2H), 7.40–7.36 (m, 1H), 7.27 (d, J=8.56 Hz, 1H), 7.15 (dd, J=8.5, 1.9 Hz, 1H), 3.15–3.11 (m, 2H), 2.77–2.73 (m, 2H), 2.39 (q, J=7.3 Hz, 2H), 1.03 (t, J=7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 211.1, 136.1, 134.4, 132.7, 130.1, 129.2, 128.3, 128.1, 125.5, 122.7, 118.6, 112.1, 111.9, 43.1, 36.2, 18.9, 7.9. LRMS (EI) (m/z) (relative intensity): 311 (M^+, 50), 328 (100); HRMS calcd for $C_{19}H_{18}Cl_1O_1N_1$ (M^+): 311.1077, found 311.1086.

*4.3.15. 1-Phenyl-3-(2-phenyl-1H-indol-3-yl)propan-1-one (**3o**).* Yield: (243 mg, 75%); Yellow Liquid. FT-IR (KBr) (ν/cm^{-1}): 3340, 1716. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 8.1 (br s, 1H), 7.92 (d, J=7.4 Hz, 1H), 7.64 (d, J=7.84 Hz, 1H), 7.58–7.52 (m, 3H), 7.49–7.36 (m, 6H) 7.23 (d, J=7.32 Hz, 1H), 7.17 (t, J=7.46 Hz, 1H), 3.37 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 200.0, 137.0, 136.1, 134.7, 133.2, 133.1, 129.1, 129.0, 128.7, 128.2, 128.1, 128.0, 122.6, 119.9, 119.1, 112.3, 111.1, 39.9, 19.4. LRMS (EI) (m/z) (relative intensity): 325 (M^+, 40), 206 (100); HRMS calcd for $C_{23}H_{19}O_1N_1$ (M^+): 325.1467, found 325.1469.

*4.3.16. 3-(2-Butyl-6-chloro-1H-indol-3-yl)-1-phenylpropan-1-one (**3p**).* Yield: (277 mg, 82%); Yellow gummy solid. FT-IR (KBr) (ν/cm^{-1}):

3358, 1710. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 7.94 (d, J=7.48 Hz, 2H), 7.82 (br s, 1H), 7.55 (t, J=7.34 Hz, 1H), 7.48–7.42 (m, 3H), 7.19 (d, J=8.48 Hz, 1H), 7.07 (dd, J=8.56, 1.8 Hz, 1H), 3.28 (t, J=7.62 Hz, 2H), 3.11 (t, J=7.58 Hz, 2H), 2.76 (t, J=7.68 Hz, 2H), 1.66–1.59 (m, 2H), 1.44–1.34 (m, 2H), 0.94 (t, J=7.32 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 200.0, 137.6, 137.7133.8, 133.8, 133.2, 129.7, 128.7, 128.2, 125.1, 121.4, 117.7, 111.5, 110.5, 39.7, 32.1, 26.0, 22.7, 18.8, 14.1. LRMS (EI) (m/z) (relative intensity): 339 (M^+, 100), 220 (86); HRMS calcd for $C_{21}H_{22}Cl_1O_1N_1$ (M^+): 339.1390, found 339.1390.

*4.3.17. 4-(5-Chloro-2-phenyl-1H-indol-3-yl)pentan-2-one (**3q**).* Yield: (218 mg, 70%); Colorless solid. Mp: 170–171 °C. FT-IR (KBr) (ν/cm^{-1}): 3423, 1638. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 8.08 (br s, 1H), 7.70 (d, J=1.9 Hz, 1H), 7.52–7.44 (m, 4H), 7.42–7.37 (m, 1H), 7.27–7.24 (m, 1H), 7.15–7.12 (m, 1H), 3.79–3.70 (m, 2H), 3.01–2.88 (m, 2H), 1.98 (s, 3H), 1.44 (d, J=7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 208.3, 135.9, 134.7, 132.8, 129.0, 128.9, 128.4, 128.3, 125.1, 122.3, 119.7, 116.3, 112.3, 50.5, 30.6, 27.0, 21.5. LRMS (EI) (m/z) (relative intensity): 311 (M^+, 38), 254 (100); HRMS calcd for $C_{19}H_{18}Cl_1O_1N_1$ (M^+): 311.1077, found 311.1080.

*4.3.18. 4-Phenyl-4-(2-phenyl-1H-indol-3-yl)butan-2-one (**3r**).* Colorless solid; Yield: (237 mg, 75%); mp: 123–125 °C; FT-IR (KBr): ν/cm^{-1} 3401, 1680; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 8.14 (br s, 1H), 7.61 (d, J=8 Hz, 1H), 7.54–7.52 (m, 2H), 7.47–7.33 (m, 6H), 7.29–7.26 (m, 2H), 7.21–7.17 (m, 2H), 7.12–7.09 (m, 1H), 5.08 (t, J=7.3 Hz, 1H), 3.49–3.34 (m, 2H),1.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 207.7, 144.6, 136.4, 135.9, 133.1, 129.0, 128.9, 128.6, 128.3, 127.8, 127.6, 126.2, 122.2, 120.8, 119.9, 114.1, 111.4, 49.5, 37.2, 30.5. LRMS (EI) (m/z) (relative intensity): 339 (M^+, 50), 282 (100), 204 (85), 78 (80); HRMS calcd for $C_{24}H_{21}O_1N_1$ (M^+): 339.1614, found 339.1623.

*4.3.19. 1,3-Diphenyl-3-(2-phenyl-1H-indol-3-yl)propan-1-one (**3s**).* Colorless solid; Yield: (307 mg, 70%); mp 98–100 °C; FT-IR (KBr): ν/cm^{-1} 3387, 1675; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 8.05 (br s, 1H), 7.83–7.81 (m, 2H), 7.61 (d, J=7.96 Hz, 1H) 7.52–7.50 (m, 3H), 7.48–7.41 (m, 2H), 7.40–7.33 (m, 6H), 7.27–7.24 (m, 2H), 7.21–7.15 (m, 2H), 7.11–7.07 (m, 1H), 5.32 (t, J=6.94 Hz, 1H), 4.01–3.87 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 198.8, 144.7, 137.2, 136.4, 135.7, 133.2, 133.0, 129.0, 128.9, 128.6, 128.5, 128.3, 128.2, 128.0, 127.8, 126.1, 122.2, 120.8, 119.9, 114.9, 111.3, 44.6, 37.0, LRMS (EI) (m/z) (relative intensity): 401 (M^+, 35), 282 (100), 105 (100), 77 (87); HRMS calcd for $C_{29}H_{23}O_1N_1$ (M^+): 401.1788, found 401.1780.

*4.3.20. 3-(6-Methyl-2-phenyl-1H-indol-3-yl)cyclopentanone (**3t**).* Yield: (147 mg, 51%); Colorless solid. Mp: 208–209 °C. FT-IR (KBr) (ν/cm^{-1}): 3336, 1737. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 8.00 (br s, 1H), 7.55 (d, J=8.1 Hz, 1H), 7.52–7.46 (m, 4H), 7.44–7.39 (m, 1H), 7.20 (s, 1H), 6.97 (dd, J=8.1, 0.9 Hz, 1H), 3.80–3.71 (m, 1H), 2.91–2.83 (m, 1H), 2.61–2.49 (m, 3H), 2.48 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 219.8, 137.0, 134.9, 133.3, 132.3, 129.0, 128.9, 128.2, 124.6, 121.5, 119.7, 113.2, 111.6, 44.8, 39.7, 34.8, 30.1, 21.8. LRMS (EI) (m/z) (relative intensity): 289 (M^+, 100), 231 (55); HRMS calcd for $C_{20}H_{19}O_1N_1$ (M^+): 289.1467, found 289.1472.

*4.3.21. 6-Methyl-2-phenyl-1H-indole (**4a**).* Yield: (41 mg, 20%); Colorless solid. Mp: 192–193 °C. FT-IR (KBr) (ν/cm^{-1}): 3430, 1453. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 8.20 (br s, 1H), 7.65–7.63 (m, 2H), 7.53 (d, J=8.0 Hz, 1H), 7.46–7.42 (m, 2H), 7.34–7.30 (m, 1H), 7.18 (s, 1H), 6.98 (d, J=8.04 Hz, 1H), 6.80–6.79 (m, 1H) 2.48 (s, 3H). ^{13}C NMR (100 MHz $CDCl_3$) δ_C (ppm): 137.5, 137.4, 132.7, 132.4, 129.1, 127.6, 127.2, 125.1, 122.2, 120.5, 111.0, 100.0, 22.0. LRMS (EI) (m/z) (relative intensity): 207 (M^+, 100), 178 (5); HRMS calcd for $C_{15}H_{13}N_1$ (M^+): 207.1048, found 207.1050.

*4.3.22. 2-Phenyl-1H-indole (**4b**).* White solid. Mp: 190–192 °C. FT-IR (KBr) (ν/cm^{-1}): 3430, 1457. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 8.31 (br s, 1H), 7.68–7.64 (m, 3H), 7.47–7.40 (m, 3H), 7.35–7.32 (m, 1H), 7.23–7.19 (m, 1H), 7.16–7.12 (m, 1H), 6.85 (d, J=1.9 Hz, 1H). ^{13}C NMR (100 MHz $CDCl_3$) δ_C (ppm): 138.1, 137.0, 132.6, 129.4, 129.2, 127.9, 125.3, 122.5, 120.8, 120.5, 111.1, 100.2. LRMS (EI) (m/z) (relative intensity): 193 (M^+, 100), 165 (19); HRMS calcd for $C_{14}H_{11}N_1$ (M^+): 193.0891, found 193.0895.

*4.3.23. Phenyl(2-phenyl-1H-indol-1-yl)methanone (**4c**).* Yield: (279 mg, 94%); White solid. Mp: 123–125 °C. FT-IR (KBr) (ν/cm^{-1}): 3059, 1686. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 7.71–7.69 (m, 1H), 7.67–7.61 (m, 3H), 7.41–7.37 (m, 1H), 7.32–7.24 (m, 6H), 7.20–7.16 (m, 2H), 7.15–7.11 (m, 1H), 6.78 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 170.2, 141.4, 138.4, 135.3, 133.2, 132.9, 130.4, 129.4, 128.5, 128.4, 128.3, 127.7, 124.4, 123.3, 120.9, 114.2, 109.6. LRMS (EI) (m/z) (relative intensity): 297 (M^+, 77), 105 (100), 250 (12); HRMS calcd for $C_{21}H_{15}O_1N_1$ (M^+): 297.1154, found 297.1155.

*4.3.24. 4-((2-(Phenylethynyl)phenyl)amino)butan-2-one (**5a**).* Yield: (170 mg, 65%); Yellow Liquid. FT-IR (KBr) (ν/cm^{-1}): 3348, 1710. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 7.54 (dd, J=7.78 Hz, 2H), 7.38–7.31 (m, 4H), 7.23–7.19 (m, 1H), 6.68–6.62 (m, 2H), 5.0 (br s, 1H), 3.52 (t, J=6.32 Hz, 2H), 2.79 (t, J=6.30 Hz, 2H), 2.18 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 207.7, 148.5, 132.4, 131.6, 130.1, 128.5, 128.3, 123.5, 116.8, 109.6, 108.2, 95.4, 85.9, 42.9, 38.2, 30.5. LRMS (EI) (m/z) (relative intensity): 263 (M^+, 58), 206.2 (100), 193 (25); HRMS calcd for $C_{20}H_{21}O_1N_1$ (M^+): 263.1310, found 263.1316.

*4.3.25. 4-((2-(Cyclopentylethynyl)-5-methylphenyl)amino)butan-2-one (**5b**).* Yield: (182 mg, 68%); Light Yellow Liquid. FT-IR (KBr) (ν/cm^{-1}): 3357, 1712. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 7.11 (d, J=7.63 Hz, 1H), 6.41 (t, J=7.74 Hz, 2H), 4.72 (br s, 1H), 3.46 (t, J=7.96 Hz, 2H), 2.89–2.85 (m, 1H), 2.75 (t, J=6.32 Hz 2H), 2.27 (s, 2H), 2.17 (s, 3H), 2.16 (s, 3H), 2.02–1.97 (m, 2H), 1.82–1.77 (m, 2H), 1.75–1.71 (m, 2H), 1.70–1.62 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 207.6, 148.2, 139.2, 131.9, 117.6, 110.2, 106.4, 100.0, 43.1, 38.2, 34.4, 31.2, 31.1, 30.5, 25.2, 22.1. LRMS (EI) (m/z) (relative intensity): 269.2 (M^+, 100), 199.2 (80), 170 (60); HRMS calcd for $C_{20}H_{21}O_1N_1$ (M^+): 269.1780, found 269.1786.

*4.3.26. 4-((4-Chloro-2-(hex-1-yn-1-yl)phenyl)amino)butan-2-one (**5c**).* Yield: (199 mg, 72%); Yellow gummy solid; FT-IR (KBr) (ν/cm^{-1}): 3335, 1702. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 7.19 (d, J=2.32 Hz, 2H), 7.07 (dd, J=8.74, 2.42 Hz 1H), 6.48 (d, J=8.8 Hz, 1H), 4.81 (br s, 1H), 3.44 (t, J=6.3 Hz, 2H), 2.74 (d, J=6.28 Hz, 2H), 2.46 (t, J=7.02 Hz, 2H), 2.16 (s, 3H), 1.62–1.56 (m, 2H), 1.50–1.45 (m, 2H), 0.95 (t, J=7.28 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 207.4, 147.0, 131.6, 129.0, 121.0, 110.6, 110.4, 97.6, 75.9, 42.8, 38.3, 31.0, 30.5, 22.2, 19.5, 13.8. LRMS (EI) (m/z) (relative intensity): 277 (M^+, 100), 279 (50), 220 (42); HRMS calcd for $C_{18}H_{16}Cl_1O_1N_1$ (M^+): 277.1233, found 277.1236.

*4.3.27. 1-((2-(Phenylethynyl)phenyl)amino)pentan-3-one (**5d**).* Yield: (216 mg, 78%); Yellow gummy solid. FT-IR (KBr) (ν/cm^{-1}): 3348, 1712. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 7.57 (dd, J=7.72, 1.48 Hz, 2H), 7.39–7.34 (m, 4H), 7.24–7.20 (m, 1H), 6.69–6.64 (m, 2H), 4.99 (t, J=5.76 Hz, 1H), 3.54 (q, J=6.34 Hz, 2H), 2.77 (t, J=6.34 Hz, 2H), 2.44 (q, J=7.34 Hz, 2H), 1.08 (t, J=7.32 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 210.4, 148.6, 132.4, 131.6, 130.1, 128.5, 128.3, 123.5, 116.7, 109.7, 108.2, 95.4, 85.9, 41.6, 38.3, 36.6, 7.8. LRMS (EI) (m/z) (relative intensity): 277 (M^+, 45), 206

(100); HRMS calcd for $C_{19}H_{19}O_1N_1$ (M^+): 277.1467, found 277.1462.

*4.3.28. 1-Phenyl-3-((2-(phenylethynyl)phenyl)amino)propan-1-one (**5e**).* Yield: (201 mg, 62%); Yellow Liquid. FT-IR (KBr) (ν/cm^{-1}): 3350, 1705. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 7.98–7.96 (m, 2H), 7.59–7.55 (m, 3H), 7.46 (t, J=7.6 Hz, 2H) 7.38–7.32 (m, 2H), 7.25–7.21 (m, 1H), 6.72–6.66 (m, 2H), 5.12 (br s, 1H), 3.74 (q, J=5.9 Hz, 2H), 3.34 (t, J=6.36 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 199.1, 148.6, 136.9, 133.5, 132.4, 131.7130.1, 128.8, 128.5, 128.3, 128.2, 123.5, 116.7, 109.6, 108.2, 95.4, 86.0, 38.6, 38.1. LRMS (EI) (m/z) (relative intensity): 325 (M^+, 52), 206 (100); HRMS calcd for $C_{23}H_{19}O_1N_1$ (M^+): 325.1467, found 325.1468.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.10.1016/j.tet.2013.01.081.

References and notes

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12. The CCDC number of **3a** is 857247. These data can be obtained free of charge from the Cambridge Crystallographic Data Center at the following website: www.ccdc.cam.ac.uk/datarequest/cif.