JOC The Journal of Organic Chemistry

Article

Copper-catalyzed anti-Markovnikov hydroindolation of terminal alkynes: Regioselective synthesis of bis(indolyl)alkanes

Ananya Srivastava, Shyam Sunder Patel, Nisha Chandna, and Nidhi Jain

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.6b02058 • Publication Date (Web): 27 Oct 2016

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

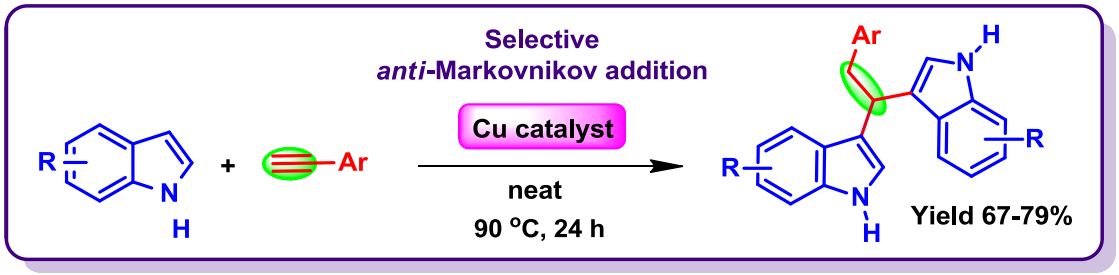
Copper-catalyzed *anti*-Markovnikov hydroindolation of terminal alkynes: Regioselective synthesis of bis(indolyl)alkanes

*Ananya Srivastava, Shyam Sunder Patel, Nisha Chandna and Nidhi Jain**

Department of Chemistry, Indian Institute of Technology, Delhi

Email: njain@chemistry.iitd.ac.in

TABLE OF CONTENTS



ABSTRACT

An efficient copper-catalyzed intermolecular hydroindolation reaction of terminal aryl alkynes to expeditiously synthesize bis(indolyl)alkanes in moderate to high yields is described. The double nucleophilic addition of two molecules of indole to one molecule of alkyne occurs in a tandem manner through an *anti*-Markovnikov pathway. Various arenes and alkynes allow for this transformation. Preliminary mechanistic study sheds light on the observed regioselectivity involving a Cu-vinylidene complex, and 3-styryl-1H-indole as probable intermediates.

Key words: copper catalyst, *anti*-Markovnikov addition, bis(indolyl)alkanes

INTRODUCTION

Bis(indolyl)alkanes are structurally important compounds, and are key synthetic intermediates for many natural products and pharmaceutical drugs (Figure 1).[1] In view of their immense biological significance, numerous methods for their preparation have developed over the years. In general, the synthesis of bis(indolyl)alkane derivatives has been reported using Lewis or protic acid mediated reaction of indoles with aldehydes,[2] ketones,[3] amino acids,[4] tertiary enamides,[5] and phenylacetaldehyde[6] as the alkyl source. The use of amino acids for installation of alkyl group involves an iron catalyzed decarboxylative-deaminative protocol, making the process expensive, and non-atom-economic. Further, preparation of enamides or substituted aryl acetaldehydes requires elaborate synthetic procedures.

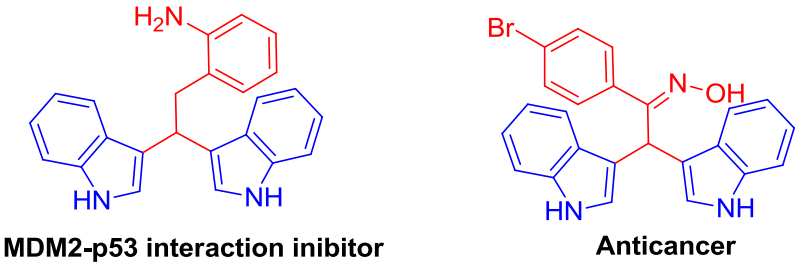
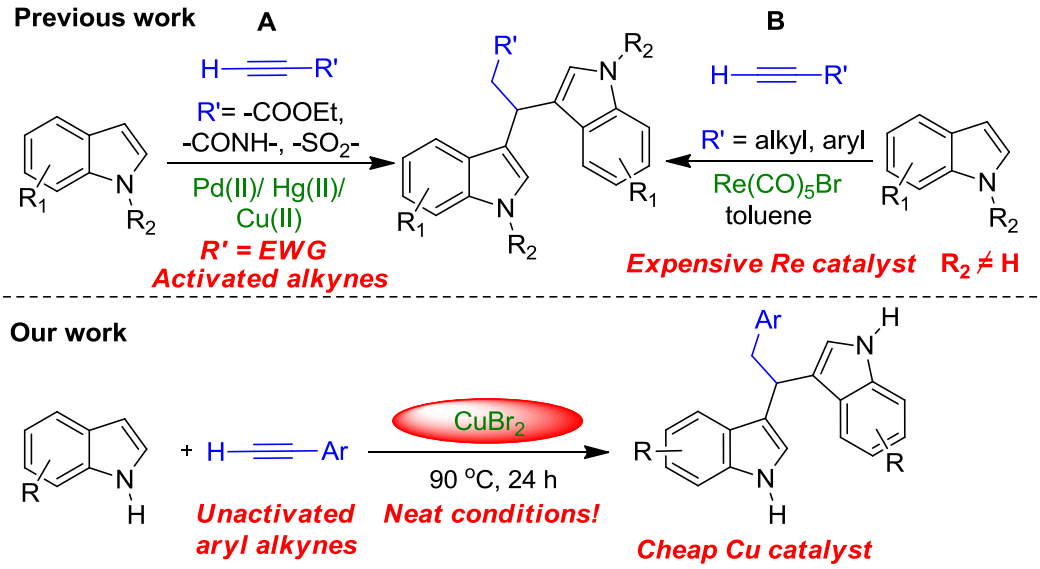


Figure 1. Examples of biologically active bisindoles.

In this context, catalytic hydroindolation using alkynes as cheap and easily available substrates constitutes a potentially powerful, direct atom-economic approach for bis(indolyl)alkane synthesis. Although progress has been made in the hydroindolation processes, the control of regioselectivity during addition of indoles to terminal alkynes still poses a challenge. The electronic imbalance of the triple bond in transition metal-alkyne complex is ascribed to govern the specificity of the attack of indoles on to internal C-atom of unactivated terminal alkynes,

resulting in Markovnikov's adducts. Thus, while the Markovnikov addition of indoles on both activated and unactivated terminal alkynes has been extensively studied *via* a variety of transition metal catalysts such as Pt,[7] Ag,[8] Au,[9] Ga,[10] In[11] and Ru[12]; a general protocol for *anti*-Markovnikov hydroindolation on unactivated alkynes is less investigated. To create an electronic bias in the C-C triple bond, and facilitate indole addition at the terminal carbon of the alkyne; alkynes are activated with electron withdrawing groups such as ester,[13] amide,[14] sulfone[15] etc. and Pd, Hg, or Cu salts are used as catalysts (Scheme 1A). In two separate reports from the groups of Echavarren[16] and Barluenga,[17] Au catalysis has been used for achieving intramolecular hydroindolation or a hydroxyl "directing group" assisted strategy has been employed for intermolecular hydroindolation of terminal alkynes through an *anti*-Markovnikov route.



Scheme 1. An overview of previous methods for *anti*-Markovnikov hydroindolation vs. our approach.

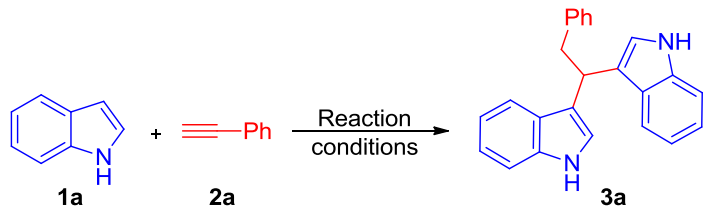
With unactivated terminal alkynes, however, the only report on a direct intermolecular *anti*-Markovnikov addition of indoles has been by Wang *et al.*[18] who have demonstrated a rhenium

catalyzed synthetic protocol in toluene as the solvent (Scheme 1B). Interestingly, they have reported that under neat conditions, the regioselectivity of the reaction is reoriented towards Markovnikov addition with phenylacetylenes as substrates. Further, the scope of the reaction is restricted to *N*-alkyl or *N*-benzyl indoles, and does not support free N-H indoles. Challenged by the scarcity of effective *anti*-Markovnikov hydroindolation methods for terminal aryl alkynes, coupled with our ongoing interest in developing operationally simple metal mediated reactions,[19] we investigated a copper catalyzed route to achieve the same. Herein, we demonstrate a valuable and economical approach to C3-hydroindolation of unactivated terminal aryl alkynes using copper salt as catalyst.

RESULTS AND DISCUSSION

We initiated our studies with the reaction of indole (**1a)** and phenylacetylene (**2a)** as model substrates using CuBr as catalyst in toluene as the solvent. Pleasantly as desired, the *anti*-Markovnikov product 3,3'-(2-phenylethane-1,1-diyl)bis(1H-indole) (**3a)** was isolated in 42% yield (Table 1, entry 1). It is important to point out that no copper catalyst has previously been reported for such transformation. Taking this forward, we optimized the reaction with respect to catalyst, solvent, oxidant, time and temperature (Table 1). Different copper salts were screened (Table 1, entries 1-5); and $CuBr_2$ was found to be the most effective giving **3a** in 71% yield (Table 1, entry 2) along with unreacted **1a**. Other copper salts such as $Cu(OAc)_2$, CuI, and $Cu(OTf)_2$ failed to promote the reaction (Table 1, entries 3-5). Notably, **3a** was formed as a single product when $CuBr_2$ was used as catalyst, though the yield reduced to 62% on decreasing $CuBr_2$ to 15 mol% (Table 1, entry 2). Effect of solvents on the reaction was investigated next. It was found that replacing toluene with 1,4-dioxane or 1,2-dichloroethane (DCE) decreased the yield, while DMF inhibited the reaction completely (Table 1, entries 6-8).

Table 1. Optimization table for reaction of **1a** and **2a**.[a]



1a **2a** **3a**

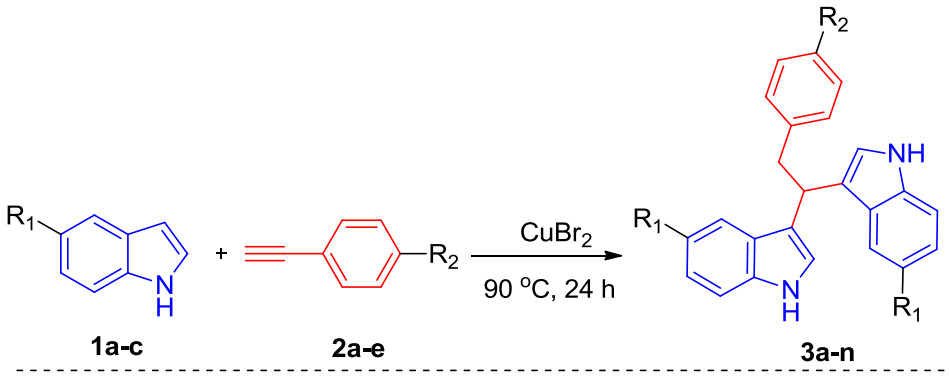
entry	catalyst	additive	solvent	yield%
1.	CuBr	-	toluene	42
2.	$CuBr_2$	-	toluene	71, 0[b], 62[c]
3.	$Cu(OAc)_2$	-	toluene	Traces
4.	CuI	-	toluene	Traces
5.	$Cu(OTf)_2$	-	toluene	-[d]
6.	$CuBr_2$	-	dioxane	22
7.	$CuBr_2$	-	DMF	-[d]
8.	$CuBr_2$	-	DCE	28
9.	**$CuBr_2$**	**-**	**neat**	**72, 57[e]**
10.	$CuBr_2$	DIB	toluene	35
11.	$CuBr_2$	BQ	toluene	64
12.	$CuBr_2$	Oxone	toluene	traces
13.	$CuBr_2$	$K_2S_2O_8$	toluene	traces
14.	$CuBr_2$	TBHP	toluene	-[d]
15.	$CuBr_2$	1,10-Phenanthroline	toluene	-[d]
16.	$CuBr_2$	K_2CO_3	toluene	-[d]
17.	$CuBr_2$	AcOH	toluene	40
18.	$CuBr_2$	-	neat	52[f], 30[g]

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), catalyst (20 mol%), additive (0.5 mmol) in solvent (2 mL) for 24 h at 90 °C, [b]reaction in absence of catalyst, [c]15 mol% $CuBr_2$, [d]no conversion was detected, [e]1.0 mmol of **2a**, [f]reaction time was 18 h, [g]reaction was run at 120 °C.

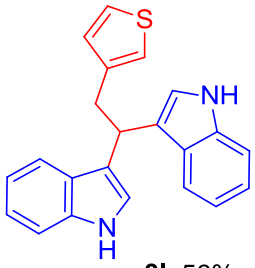
Notably, the reaction was equally facile under neat conditions (Table 1, entry 9). It is noteworthy to mention that in this case, the regioselectivity was preserved in sharp contrast to the previous report with Re wherein regiodivergence was observed in toluene and neat conditions. Further, decreasing the amount of alkyne to 1 equiv. reduced the yield to 57% (Table 1, entry 9) suggesting that the reaction performs best with an excess of alkyne. Addition of oxidants such as benzoquinone (BQ), diacetoxyiodobenzene (DIB), oxone, $K_2S_2O_8$ and *t*-butylhydroperoxide (TBHP) proved detrimental to the reaction, and reduced the yield drastically (Table 1, entries 10-14). Addition of ligand, base, or acid did not help the reaction either, and diminished conversions were seen (Table 1, entries 15-17). Increasing the reaction time from 24 h to 36 h did not bring about higher conversions, whereas reducing it to 18 h decreased the yield to 52% (Table 1, entry18). Further, elevating the reaction temperature to 120 ^oC worsened the yield presumably due to the decomposition of **3a** (Table 1, entry 18). Hence, the best optimized conditions for the reaction were found to be with 1.5 equiv. of **2a**, 20 mol% $CuBr_2$ at 90 ^oC for 24 h (Table 1, entry 9). To the best of our knowledge, this protocol is the first successful demonstration of copper catalyzed intermolecular *anti*-Markovnikov addition of indoles to unactivated terminal alkynes without any directing group.

The scope of this reaction with respect to indoles and alkynes was tested, and the results are summarized in Table 2. When the substituent in the 5-position on the indole was electron donating, it had little effect on the reaction, and gave the corresponding bisindolylalkane derivatives in moderate to good yields (**3a-3k**). In contrast, electron withdrawing nitro or ester groups at 5-position of indole rendered it unreactive, and the reaction did not occur under these conditions. It is noteworthy to mention that the bromo group on indole remained intact after the reaction, thus providing an easy handle for further synthetic elaborations (**3c**). 2-methyl indole was found to be

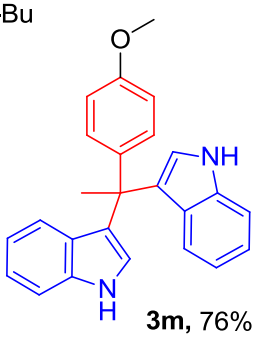
Table 2. *Anti*-Markovnikov addition of indoles to phenylacetylenes.[a]



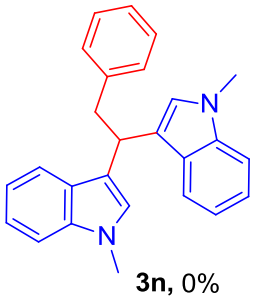
3a (72%), R_1 = H, R_2 = H
3b (76%), R_1 = OMe, R_2 = H
3c (67%), R_1 = Br, R_2 = H
3d (71%), R_1 = H, R_2 = Me
3e (74%), R_1 = OMe, R_2 = Me
3f (78%), R_1 = H, R_2 = *t*-Bu
3g (79%), R_1 = OMe, R_2 = *t*-Bu
3h (77%), R_1 = H, R_2 = $(CH_2)_4CH_3$
3i (78%), R_1 = OMe, R_2 = $(CH_2)_4CH_3$
3j (72%), R_1 = H, R_2 = F
3k (75%), R_1 = OMe, R_2 = F



3l, 56%



3m, 76%



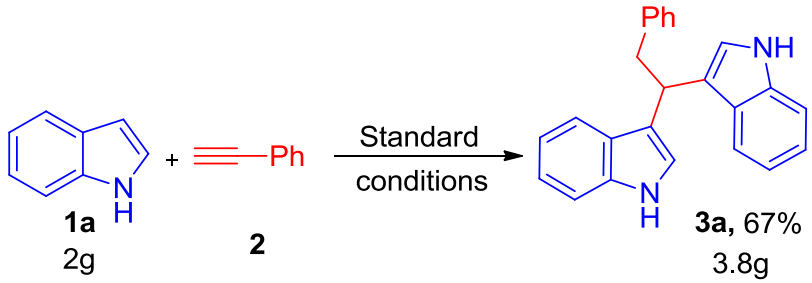
3n, 0%

[a]Reaction conditions: **1** (0.5 mmol), **2** (0.75 mmol), $CuBr_2$ (20 mol%) for 24 h at 90 °C.

inert under the optimized conditions probably due to steric effects. The diversity in phenyl acetylene derivatives was also explored. Reaction with phenyl acetylene bearing substitutents such as methyl, *tert*-butyl, n-pentyl, and fluoro on the phenyl ring was carried out, and the corresponding products were obtained in good yields (**3d**-**3k**). The reaction was tolerated by the heterocyclic alkyne, 3-thienylacetylene, and the desired product **3l** was isolated in 56% yield. Interestingly, Markovnikov's product (**3m**) was formed when indole was reacted with 4-methoxy phenylacetylene derivative due to a strong +R effect. Furthermore, when the properties on the

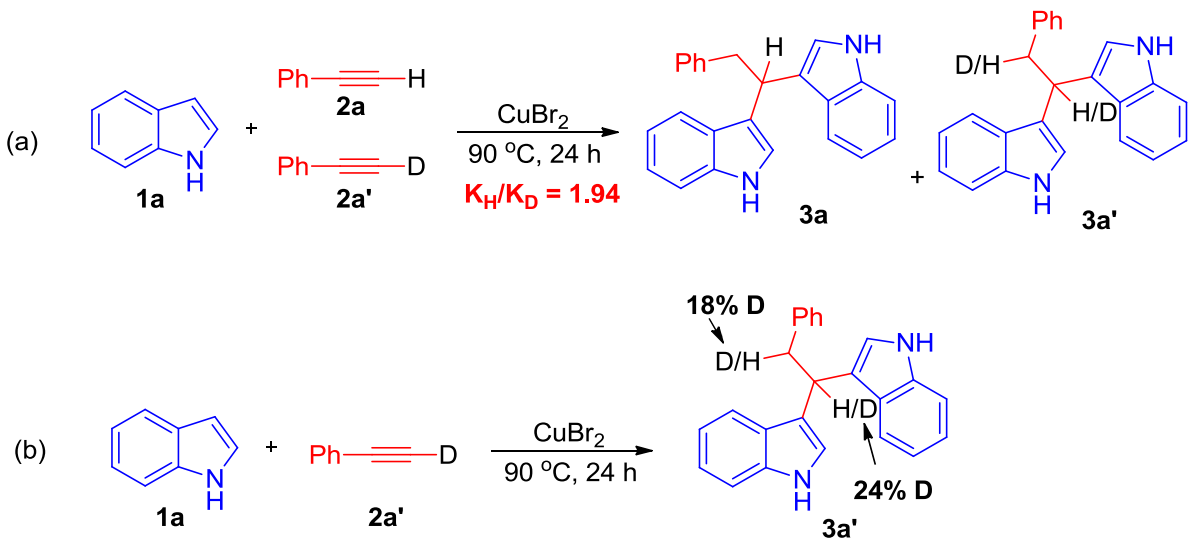
nitrogen were altered, as in 1-methyl indole; the reaction did not occur at all, suggesting that free N-H proton was a requisite for the reaction. Further, with alkyl substituted acetylene such as n-hexyne, a mixture of two unidentified products was isolated, though the desired product was not obtained.

Further, the synthetic utility of the developed protocol was established by carrying out a gram scale reaction. Starting from 2g of **1a**, **3a** was isolated in 67% yield (Scheme 2) demonstrating the practical potential of this method for rapid and efficient construction of bis(indolyl)alkanes.



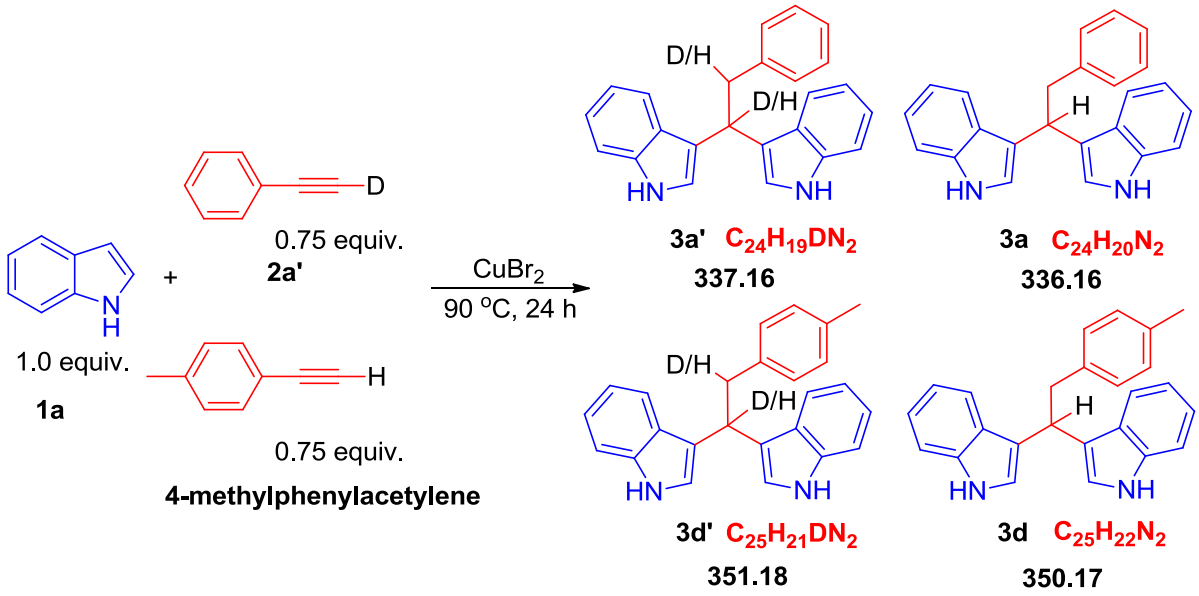
Scheme 2. Practical synthesis of **3a** on gram scale.

Next, to study the kinetics of the reaction, a cross-over reaction was performed by mixing **1a**, **2a** and its deuterated analog **2a'**(Scheme 3a). The LC-MS spectrum (see supporting information) of the reaction mixture revealed a K_H/K_D ratio of 1.94 indicating that secondary isotope effects prevail, and that the formation of copper acetylide (**I**) is not the rate-determining step. Further, to identify the position of D-incorporation in **3a'**, a reaction of **1a** and **2a'** was placed (Scheme 3b). ^{1}H NMR analysis of **3a'** showed that 24% of D-atom resided at the original terminal carbon of alkyne **2a'**, while 18% of D-atom was installed at the benzylic carbon in **3a'**. The deuterium scrambling in the product revealed the reaction to follow a non-concerted pathway.



Scheme 3. Kinetic hydrogen isotope effect.

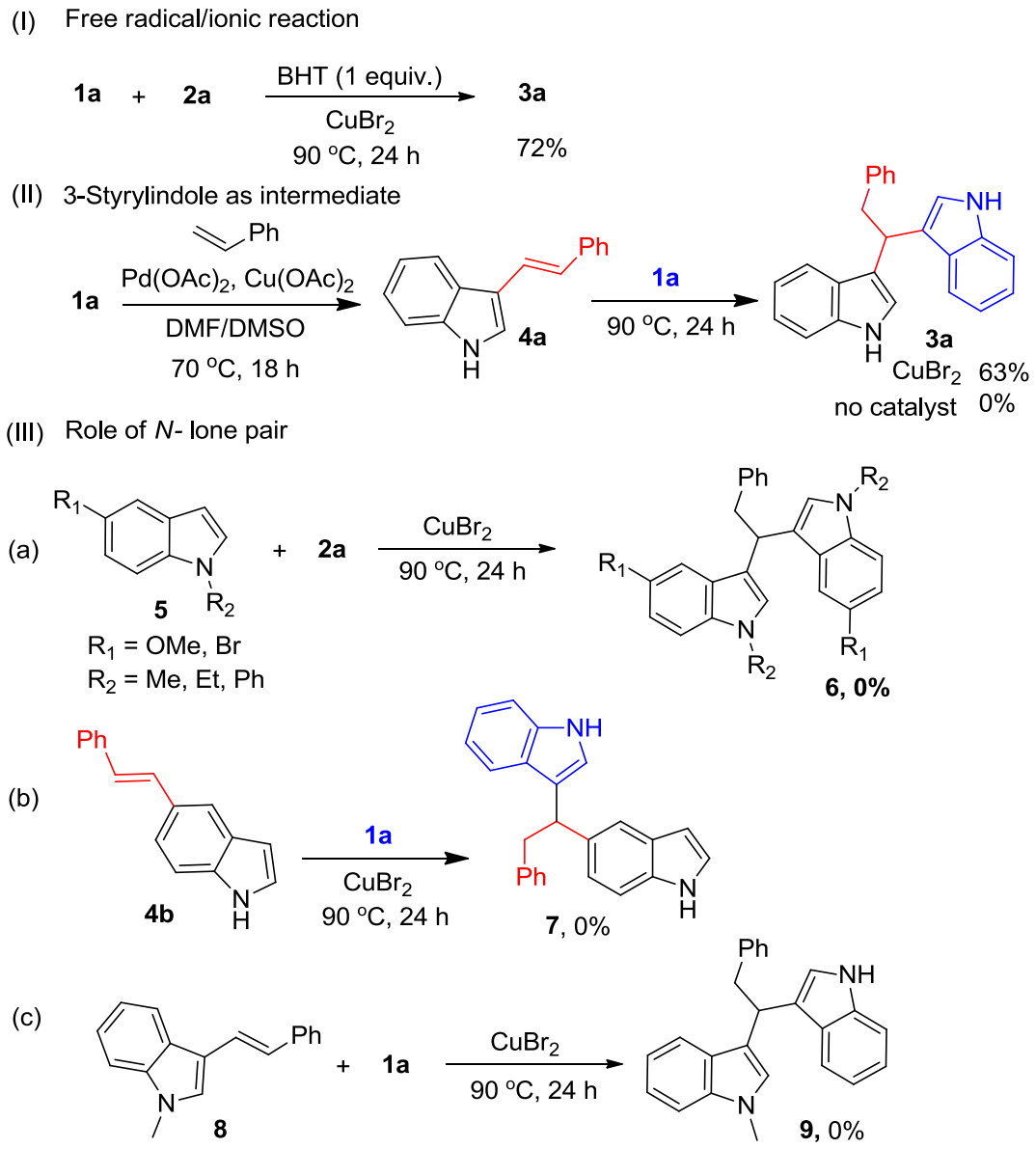
Furthermore, the reaction of indole was carried out using a mixture of two different alkynes, deuterated phenyl acetylene (**2a'**) and 4-methyl phenyl acetylene under optimized conditions (Scheme 4). The LC-MS spectrum (see supporting information) of the reaction mixture revealed formation of four different products with and without deuterium incorporation in varied ratios. The results were in accordance with the K.H.I.E studies reinforcing the observation that Cu-vinylidene formation is reversible, and provides a source of H^+ by H/D scrambling.



Scheme 4. Cross-over experiments demonstrating H/D scrambling

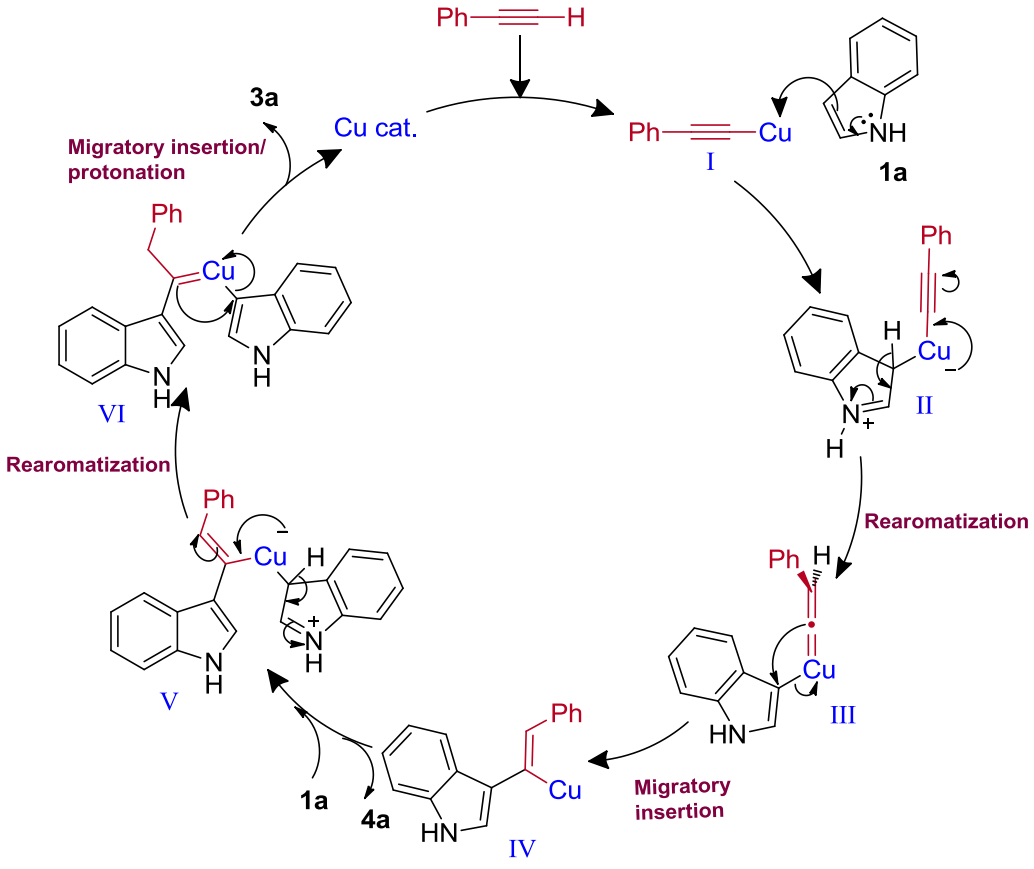
To understand the reaction mechanism, several control experiments were carried out (Scheme 5). First, we performed a reaction of **1a** and **2a** in the presence of 20 mol% $CuBr_2$ and 1 equiv. of butylated hydroxytoluene (BHT) at 90 °C for 24 h. **3a** was isolated in 72% yield, suggesting that the reaction did not follow a free-radical pathway (Scheme 5(I)). Next, to identify the reaction intermediate, (E)-3-styryl-1H-indole (**4a**) was synthesized from **1a** using a reported procedure, and subsequently treated with another molecule of **1a** under aforementioned conditions (Scheme 5(II)). With $CuBr_2$ as the catalyst, **3a** was obtained in 63% yield, suggesting **4a** to be the most probable intermediate formed during the reaction. However, no conversions were seen in the absence of $CuBr_2$, confirming its necessity in the second hydroindolation step. Involvement of the N-lone pair in the mechanism was probed by invoking the C−H activation onto substituted *N*-methyl/ethyl/phenylindole (**5**), wherein the reaction failed to yield the desired product **6** in all cases (Scheme 5(IIIa)). This control reaction confirmed that free NH of indole was crucial for the indolation reaction.[20] Next, the reaction of **1a** with **4b** (5-styryl-1H-indole) was carried out under

the optimized conditions. While **4a** reacted with **1a** to yield the expected product **3a** with excellent regioselectivity, no traces of the desired product 5-(1-(1H-indol-3-yl)-2-phenylethyl)-1H-indole (**7**) were seen (Scheme 5(IIIb)). Furthermore, when (E)-1-methyl-3-styryl-1H-indole (**8**) was treated with **1a**, the corresponding product 3-(1-(1H-indol-3-yl)-2-phenylethyl)-1-methyl-1H-indole (**9**) was not formed, reinforcing yet again the role of N-lone pair in the second indolation step (Scheme 5(IIIc)).



Scheme 5. Preliminary mechanistic studies.

On the basis of above experimental results, a plausible mechanism is proposed (Scheme 6). We hypothesize that in the first step, coordination of copper with alkyne affords the Cu-acetylide intermediate **I**. This is followed by a nucleophilic attack of **1a** at the Cu terminal of **I** to yield an intermediate **II** which transforms to Cu-vinylidene[21] intermediate **III**. Subsequently, the vinyl group of **III** undergoes a migratory insertion into the indole carbon to form intermediate **IV**.[22] The evidence in favour of formation of **III** and **IV** comes from the GC−MS analysis of the reaction mixture taken after 1 h of reaction time, which shows the molecular ion peak at 281.1 corresponding to the mass of Cu olefin complexes (see the Supporting Information). Protonolysis of **IV** can yield the intermediate product **4a**. Eventually, the second hydroindolation of **IV** followed by protonolysis leads to the formation of the *anti*-Markovnikov product **3a**.



Scheme 6. Proposed mechanism.

Conclusions

In summary, we have developed efficient and economical catalytic conditions for a regioselective *anti*-Markovnikov C3-hydroindolation of terminal aryl alkynes to access bis(indolyl)alkanes. The protocol tolerates a variety of indoles and alkynes, which have not been easily accessible through existing synthetic methods. Another noteworthy feature is that the methodology works for the more challenging free N-H indoles. The demonstrable applicability of this direct hydroindolation to the rapid synthesis of pharmaceutical agents from easily available substrates is a practical merit. The involvement of Cu-vinylidene complex, and 3-styryl-1H-indole as key reaction intermediates is proposed through preliminary mechanistic studies.

EXPERIMENTAL SECTION:

***Reagent information*:**

All reactions were carried out under an air atmosphere pressure in oven-dried round bottom flasks. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on a 0.25 mm silica gel plates (60F–254) and visualized under UV illumination at 254 nm. Further visualization was achieved by iodine vapour adsorbed on silica gel depending on the product type. Organic extracts were dried over anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Column chromatography was performed on silica gel 100–200 mesh using a mixture of hexane and ethyl acetate as eluent.

***Analytical information*:**

All isolated compounds were characterized by ^{1}H NMR, $^{13}C\{^{1}H\}$ NMR, and HRMS. NMR spectra for all the samples were measured in deuterochloroform ($CDCl_3$) and dimethylsufoxide-*d6* (DMSO-*d6*). ^{1}H and $^{13}C\{^{1}H\}$NMR spectra were recorded at ambient temperature on 300 MHZ and 75 MHz spectrometer using tetramethylsilane (TMS) as internal reference. The chemical shifts are quoted in δ units, parts per million (ppm) up field from the signal of internal TMS. ^{1}H NMR data is represented as follows: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration and coupling constant(s) *J* in Hertz (Hz). High resolution mass spectra (HRMS) were recorded on a Mass spectrometer using electrospray ionization-time of flight (ESI-TOF) reflectron experiments.

General procedure for synthesis of compounds (3a-n):

$CuBr_2$ (22.3 mg, 0.1 mmol, 20 mol %), indole **1a** (58.5 mg, 0.5 mmol, 1.0 equiv.) and phenylacetylene **2a** (76.5 mg, 0.75 mmol, 1.5 equiv.) were added to an oven-dried reaction vessel. The reaction mixture was stirred in an oil bath at 90 °C for 24 h. After completion of the reaction (as indicated by TLC), the reaction mixture was cooled to room temperature, diluted with ethylacetate (5 mL), and water was added. This mixture was extracted with ethylacetate and the combined organic layers were put together and dried upon Na_2SO_4. Solvents were removed under reduced pressure, and the crude was purified by column chromatography on silica gel to afford **3a** in 72% yield.

Reaction mechanism investigation:

(i) Free Radical/Ionic Mechanism:

$CuBr_2$ (22.3 mg, 0.1 mmol, 20 mol %), **1a** (58.5 mg, 0.5 mmol, 1.0 equiv.), butylated hydroxytoluene (BHT) (110.0 mg, 0.5 mmol, 1.0 equiv.) and **2a** (76.5 mg, 0.75 mmol, 1.5 equiv.) were added to an oven-dried reaction vessel. The reaction mixture was stirred in an oil bath at 90

°C for 24 h. After completion of the reaction (as indicated by TLC), the reaction mixture was cooled down to room temperature, diluted with ethylacetate (5 mL), and water was added. This mixture was extracted with ethylacetate and the combined organic layers were put together and dried upon Na_2SO_4. Solvents were removed under reduced pressure, and the crude was purified by column chromatography on silica gel to afford **3a** in 70% yield.

(ii) Synthesis of proposed intermediate 3-Styryl-1 H-indole (4a):[23]

4a was prepared according to the reported procedure.[23] Palladium acetate (0.1 equiv.) was added to a mixture of styrene (1.0 equiv.), copper (II) acetate (1.8 equiv.), and indole (2.0 equiv.) in DMF: DMSO (9:1, 0.4M), and the contents were stirred at 70 ˚C. After stirring at 70 ˚C for 18 h, the reaction mixture was cooled to room temperature, partitioned between water and ethyl acetate, and then filtered through a plug of celite. The layers were separated; the organic layer was washed with aqueous saturated brine solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography afforded **4a**.

Procedure for hydroindolation of 4a:

$CuBr_2$ (22.3 mg, 0.1 mmol, 20 mol %), **1a** (58.5 mg, 0.5 mmol, 1.0 equiv.), and **4a** (109.5 mg, 0.5 mmol, 1.0 equiv.) were added to an oven-dried reaction vessel. The contents were stirred in preheated oil bath at 90 °C for 24 h. After completion of the reaction (as indicated by TLC), the reaction mixture was cooled down to room temperature, diluted with ethylacetate (5 mL), and water was added. This mixture was extracted with ethylacetate and the combined organic layers were put together and dried upon Na_2SO_4. Solvents were removed under reduced pressure, and the crude was purified by column chromatography on silica gel to afford **3a** in 63% yield. It was found that no reaction occurred in the absence of $CuBr_2$.

(iii) Role of N-lone pair:

Procedure for preparation of *N*-alkylindoles 5 and 8:[24]

N-alkylindoles were prepared from the corresponding commercially available *N*-H indoles according to the known procedure.[24] To a solution of indole (10 mmol) in 15 mL DMF, NaH (60%, 11 mmol) was added in portions at 0 ℃. The resulting solution was stirred for 30 min., and then MeI (12 mmol) was added dropwise. The contents were stirred for 10 min, quenched with saturated NH_4Cl, and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with H_2O (5 × 10 mL) and brine, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel to afford *N*-alkyl indole.

Procedure for synthesis of compound 6:

$CuBr_2$ (20 mol %), **5** (0.5 mmol, 1.0 equiv.) and **2a** (0.75 mmol, 1.5 equiv.) were added to an oven-dried reaction vessel. The contents were stirred in an oil bath at 90 °C for 24 h. After 24 h, no distinguish peak for compound **6** was observed by GC and starting materials were recovered by column chromatography.

Procedure for synthesis of 5-Styryl-1H-indole (4b):[25]

4b was synthesized according to a reported procedure.[25] To an oven dried Schlenk tube charged with a magnetic stir bar, $Pd(OAc)_2$ (22.5 mg, 0.10 mmol, 0.05 equiv.), tri(o-tolyl)phosphine (60.9 mg, 0.20 mmol, 0.10 equiv.), 5-bromo-1H-indole (393 mg, 2.0 mmol, 1.0 equiv.), styrene (287 µL, 2.5 mmol, 1.25 equiv.), and triethylamine (NEt_3, 2.0 mL) were added. The mixture was degassed using three vacuum/N_2 back-fill cycles, and heated at 100 °C for 24 h. Upon cooling to room temperature, the mixture was filtered through a plug of silica/sand/celite using acetone as the eluent. The acetone was concentrated in vacuo, and purification by flash chromatography with a mixture of EtOAc:hexanes afforded **4b**.

Procedure for hydroindolation of 4b:

$CuBr_2$ (22.3 mg, 0.1 mmol, 20 mol %), **1a** (58.5 mg, 0.5 mmol, 1.0 equiv.), and **4b** (109.5 mg, 0.5 mmol, 1.0 equiv.) were added to an oven-dried reaction vessel. The reaction mixture was stirred in preheated oil bath at 90 °C for 24 h. After 24 h, no distinguish peak for compound **7** was observed by GC and starting materials were recovered by column chromatography.

(iv) Procedure for deuterio-1-phenyl acetylene (2a'):[26]

An oven dried 10mL round bottomed flask was charged with phenyl acetylene (1 equiv.) and potassium carbonate (1.5 equiv.) in MeCN (2 mL). This was allowed to stir under an atmosphere of N_2 for 30 minutes. To this D_2O (500 μL, ~50 equiv.) was added and left to stir for 1 h. The resulting crude reaction mixture was diluted with DCM (5 mL) and transferred to a separating funnel. The organic layer was separated and dried with Na_2SO_4, filtered and solvent removed under reduced pressure.

^{1}H NMR of 2a' (300 MHz, $CDCl_3$): δ 7.49 (m, 2H), 7.33 (m, 3H), 3.05 (s, 0.09 H).

3,3'-(deuterio-2-phenylethane-1,1-diyl)bis(1H-indole) (**3a'**):

White viscous liquid, Hexane/EtOAc = 17/3, 0.5 mmol scale, yield 118 mg, 70%; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.78 (s, 2H), 7.56 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 7.17 (m, 7H), 7.00 (t, J = 8.1 Hz, 2H), 6.89 (s, 2H), 4.78 (t, J = 7.2 Hz, 0.76H), 3.53 (d, J = 7.2 Hz, 1.63H); **^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$):** δ 141.3, 136.6, 129.0, 127.9, 127.0, 125.7, 121.9, 121.7, 119.7, 119.5, 119.1, 111.1, 41.7, 36.3.

Characterization data:

3,3'-(2-phenylethane-1,1-diyl)bis(1H-indole) (**3a**):[27]

White viscous liquid, Hexane/EtOAc = 17/3, 0.5 mmol scale, yield 120 mg, 72%; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.81 (s, 2H), 7.58 (d, J = 10.8 Hz, 2H), 7.31 (d, J = 10.8 Hz, 2H), 7.19-7.09 (m, 7H), 7.06-7.0 (m, 2H), 6.92 (d, J = 2.8 Hz, 2H), 4.81 (t, J = 9.6 Hz, 1H), 3.54 (d, J

= 9.6 Hz, 2H); **$^{13}C\{^{1}H\}$NMR (75 MHz, $CDCl_3$):** δ 141.3, 136.6, 129.0, 127.9, 127.0, 125.7, 121.9, 121.7, 119.7, 119.5, 119.1, 111.1, 41.8, 36.3; **HRMS** (ESI/TOF-Q) m/z: $[M+Na]^+$ Calcd for $C_{24}H_{20}N_2Na$ 359.1518; Found 359.1524.

3,3'-(2-phenylethane-1,1-diyl)bis(5-methoxy-1H-indole) (3b):

Brown viscous liquid, Hexane/EtOAc = 4/1, yield 150 mg, 76%; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.78 (s, 2H), 7.21 (d, J = 7.2 Hz, 2H), 7.17-7.08 (m, 5H), 6.94 (dd, J_1 = 2.4 Hz, J_2 = 13.4 Hz, 4H), 6.79 (dd, J_1 = 0.4 Hz, J_2 = 10 Hz , 2H), 4.67 (t, J = 7.2 Hz, 1H), 3.73 (s, 6H), 3.50 (d, J = 7.2 Hz, 2H); **$^{13}C\{^{1}H\}$NMR (75 MHz, $CDCl_3$):** δ 153.6, 141.3, 131.8, 129.1, 128.2, 127.9, 127.5, 125.8, 122.8, 119.2, 111.7, 101.9, 55.9, 41.7, 36.3; **HRMS** (ESI/TOF-Q) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{24}N_2O_2Na$ 419.1729; Found 419.1717.

3,3'-(2-phenylethane-1,1-diyl)bis(5-bromo-1H-indole) (3c):

Dark brown viscous liquid, Hexane/EtOAc = 17/3, yield 164 mg, 67%; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.97 (s, 2H), 7.56 (s, 2H), 7.24-7.29 (m, 4H), 7.15 (d, J = 6.0 Hz, 3H), 7.03 (d, J = 6.6 Hz, 2H), 6.96 (s, 2H), 4.64 (t, J = 7.8 Hz, 1H), 3.40 (d, J = 7.5 Hz, 2H); **$^{13}C\{^{1}H\}$NMR (75 MHz, $CDCl_3$):** δ 140.6, 135.2, 128.9, 128.6, 128.4, 128.1 126.0, 124.8, 123.1, 122.1, 118.7, 112.6, 112.5, 41.5, 36.2; **LRMS** (ESI/TOF-Q) m/z: $[M-Br+Na]^+$ Calcd for $C_{24}H_{19}BrN_2Na$ 437.06; Found 437.19.

3,3'-(2-(p-tolyl)ethane-1,1-diyl)bis(1H-indole) (3d):

White viscous liquid, Hexane/EtOAc = 17/3, yield 124 mg, 71%; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.87 (s, 2H), 7.58 (d, J = 8 Hz, 2H), 7.32 (d, J = 8 Hz, 2H), 7.16-7.12 (m, 3H), 7.04-7.02 (m, 5H), 7.01-6.94 (m, 2H), 4.78 (t, J = 8.1 Hz, 1H), 3.51 (d, J = 7.2 Hz, 2H), 2.26 (s, 2H); **$^{13}C\{^{1}H\}$NMR (75 MHz, $CDCl_3$):** δ 138.2, 136.6, 135.1, 128.8, 128.6, 127.0, 121.9, 121.7, 119.7, 119.5, 119.0, 111.1, 41.2, 36.3, 21.0; **HRMS** (ESI/TOF-Q) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{22}N_2Na$ 373.1675; Found 373.1671.

3,3'-(2-(p-tolyl)ethane-1,1-diyl)bis(5-methoxy-1H-indole) (3e):

Pale yellow viscous liquid, Hexane/EtOAc = 4/1, yield 151 mg, 74%; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.79 (s, 2H), 7.20 (d, J = 11.6 Hz, 2H), 7.01-6.93 (m, 7H), 6.81 (dd, J_1 = 11.6 Hz, J_2 = 2.8 Hz, 2H), 4.66 (t, J = 10.0 Hz, 1H), 3.75 (s, 6H), 3.46 (d, J = 10 Hz, 2H), 2.25 (s, 3H); **^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$):** δ 153.6, 138.2, 135.1, 131.8, 128.9, 128.6, 127.5, 122.7, 119.3, 111.6, 101.9, 55.9, 41.2, 36.3, 20.9; **HRMS** (ESI/TOF-Q) m/z: $[M + K]^+$ Calcd for $C_{27}H_{26}N_2O_2K$ 449.1625; Found 449.1615.

3,3'-(2-(4-(tert-butyl)phenyl)ethane-1,1-diyl)bis(1H-indole) (3f):

Light brown viscous liquid, Hexane/EtOAc = 17/3, yield 152 mg, 78%; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.83 (s, 2H), 7.52 (d, J = 8 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 7.18-7.11 (m, 4H), 7.05 (d, J = 8 Hz, 2H), 7.00 (t, J = 7.6 Hz, 2H), 6.93 (s, 2H), 4.80 (t, J = 7.2 Hz, 1H), 3.50 (d, J = 7.2 Hz, 2H), 1.25 (s, 9H); **^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$):** δ 148.5, 138.2, 136.6, 128.6, 127.1, 124.9, 121.9, 121.7, 119.8, 119.7, 119.0, 111.0, 41.3, 35.9, 34.3, 31.4; **HRMS** (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{28}H_{29}N_2$ 393.2325; Found 393.2318.

3,3'-(2-(4-(tert-butyl)phenyl)ethane-1,1-diyl)bis(5-methoxy-1H-indole) (3g):

Brown viscous liquid Hexane/EtOAc = 4/1, yield 178 mg, 79%; **^{1}H NMR (300 MHz, DMSO-*d6*):** δ 10.53 (s, 2H), 7.16-7.19 (m, 8H), 7.00 (d, J = 2.1, 2H), 6.66 (dd, J_1 = 8.7 Hz, J_2 = 2.1 Hz 2H), 4.67 (t, J = 7.5 Hz, 1H), 3.68 (s, 6H), 3.44 (d, J = 7.5 Hz, 2H), 1.22 (s, 9H); **^{13}C{^{1}H}NMR (75 MHz, DMSO-d_6):** δ 153.0, 148.0, 138.8, 132.1, 128.9, 127.4, 125.0, 123.5, 118.5, 112.2, 110.8, 101.8, 55.8, 35.6, 34.4, 31.6; **HRMS** (ESI/TOF-Q) m/z: $[M+K]^+$ Calcd for $C_{30}H_{32}N_2O_2K$ 491.2087; Found 491.2095.

3,3'-(2-(4-pentylphenyl)ethane-1,1-diyl)bis(1H-indole) (3h):

White viscous liquid, Hexane/EtOAc = 17/3, yield 156 mg,77%; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.80 (s, 2H), 7.54 (d, J = 7.8 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.12 (t, J = 7.2 Hz, 2H), 6.99 (t, J = 8.1 Hz, 6H), 6.91 (s, 2H), 4.77 (t, J = 7.2 Hz, 1H), 3.49 (d, J = 7.5 Hz, 2H), 2.49 (t, J = 7.8 Hz, 2H), 1.54 (quint, J = 7.8 Hz, 2H), 1.29 (m, 4H), 0.872 (t, J = 6.6 Hz, 3H); **^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$):** δ 140.2, 138.4, 136.6, 128.8, 128.0, 127.1, 121.9, 121.7,

119.7, 119.7, 119.0, 111.0, 41.4, 36.2, 35.5, 31.5, 31.2, 22.5, 14.0; **HRMS** (ESI/TOF-Q) m/z: $[M + Na]^+$ Calcd for $C_{29}H_{30}N_2Na$ 429.2301; Found 429.2299.

3,3'-(2-(4-pentylphenyl)ethane-1,1-diyl)bis(5-methoxy-1H-indole) (3i):

Light brown viscous liquid, Hexane/EtOAc = 4/1, yield 181 mg, 78%; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.73 (s, 2H), 7.19 (d, J = 8.7 Hz, 2H), 7.03-7.17 (m, 6H), 6.90 (s, 2H), 6.79 (d, J = 10.8 Hz, 2H), 4.66 (t, J = 7.5 Hz, 1H), 3.73 (s, 6H), 3.46 (d, J = 7.2 Hz, 2H), 2.50 (t, J = 7.5 Hz, 2H), 1.54 (quint, J = 7.8 Hz, 2H), 1.29 (m, 4H), 0.87 (t, J = 6.3 Hz, 3H); **^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$):** δ 153.6, 140.3, 138.4, 131.8, 128.9, 128.0, 127.5, 122.8, 119.4, 111.6, 101.9, 55.9, 41.3, 36.1, 35.5, 31.6, 31.2, 22.5, 14.0; **HRMS** (ESI/TOF-Q) m/z: $[M + K]^+$ Calcd for $C_{31}H_{34}N_2O_2K$ 505.2251; Found 505.2235.

3,3'-(2-(4-fluorophenyl)ethane-1,1-diyl)bis(1H-indole) (3j):

Dark brown viscous liquid, Hexane/EtOAc = 17/3, yield 127 mg, 72%; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.80 (s, 2H), 7.53 (d, J = 7.8 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.13 (t, J = 6.9 Hz, 2H), 6.95-7.03 (m, 4H), 6.87 (s, 2H), 6.79 (t, J = 8.7 Hz, 2H), 4.70 (t, J = 7.5 Hz, 1H), 3.48 (d, J = 8.7 Hz, 2H); **^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$):** δ 161.2 (d, $^1J_{CF}$ = 241.8 Hz), 136.9, 136.6, 130.3 (d, $^3J_{CF}$ = 7.6 Hz), 126.9, 121.9, 121.8, 119.6, 119.2, 119.2, 114.6 (d, $^2J_{CF}$ = 20.8 Hz), 111.1, 40.9, 36.6; **HRMS** (ESI/TOF-Q) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{19}FN_2Na$ 377.1424; Found 377.1412.

3,3'-(2-(4-fluorophenyl)ethane-1,1-diyl)bis(5-methoxy-1H-indole) (3k):

Light brown viscous liquid, Hexane/EtOAc = 4/1, yield 155 mg, 75%; **^{1}H NMR (300 MHz, DMSO-*d6*):** δ 10.56 (s, 2H), 7.22 (m, 6H), 6.99-6.93 (m, 4H), 6.68 (d, J = 8.7 Hz, 2H), 4.64 (t, J = 7.5 Hz, 1H), 3.72 (s, 6H), 3.48 (d, J = 7.5 Hz, 2H); **^{13}C{^{1}H}NMR (75 MHz, DMSO-*d6*):** δ 160.9 (d, $^1J_{CF}$ = 239.1 Hz), 153.1, 138.0, 137.9, 132.1, 131.0 (d, $^3J_{CF}$ = 7.7 Hz), 127.4, 123.5, 118.2, 114.8 (d, $^2J_{CF}$ = 20.7 Hz), 112.3, 110.9, 101.8, 55.8, 36.0; **HRMS** (ESI/TOF-Q) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{23}FN_2O_2Na$ 437.1635; Found 437.1655.

3,3'-(2-(thiophen-2-yl)ethane-1,1-diyl)bis(1H-indole) (3l):

Light brown viscous liquid, Hexane/EtOAc = 4/1, Yield 95 mg, 56%; **^{1}H NMR (300 MHz, DMSO-*d6*):** δ 10.70 (s, 2H), 7.53 (d, *J* = 7.8 Hz, 2H), 7.31 (m, 1H),7.26 (m, 2H), 7.21 (s, 2H), 7.08 (s, 1H), 6.98 (t, *J* = 8.1 Hz, 2H), 6.91 (d, *J* = 4.8 Hz, 1H), 6.86 (t, *J* = 7.8 Hz, 2H), 4.74 (t, *J* = 7.8 Hz, 1H), 3.50 (d, *J* = 7.5 Hz, 2H); **^{13}C{^{1}H}NMR (75 MHz, DMSO-*d6*):** δ 150.8, 137.4, 129.1, 126.4, 125.2, 123.2, 123.1, 121.2, 120.9, 120.8, 118.3, 111.9, 41.2; **HRMS** (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{22}H_{19}N_2S$ 343.1263 ; Found 343.1264.

3,3'-(1-(4-methoxyphenyl)ethane-1,1-diyl)bis(1H-indole) (3m):

Brown solid, Hexane/EtOAc = 4/1, yield 139 mg, 76%; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.85 (s, 2H), 7.35 (m, 6H), 7.14 (t, *J* = 7.2 Hz, 2H), 6.94 (t, *J* = 7.8 Hz, 2H), 6.79 (d, *J* = 9.0 Hz, 2H), 6.61 (s, 2H), 3.79 (s, 3H), 2.34 (s, 3H); **^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$):** δ 157.5, 140.3, 137.1, 129.1, 126.4, 125.0, 123.3, 122.1, 121.5, 118.9, 113.0, 111.1, 55.2, 43.1, 28.8; **HRMS** (ESI/TOF-Q) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{22}N_2ONa$ 389.1624; Found 389.1622. **HRMS** (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for $C_{25}H_{23}N_2O^+$ 367.1805; Found 367.1807.

3-styryl-1H-indole (4a):

Light brown viscous liquid, Hexane/EtOAc = 19/1, 2 mmol scale, yield 262 mg, 60%; **^{1}H NMR (300 MHz, DMSO-*d6*):** δ 11.37 (s, 1H), 8.04 (d, *J* = 7.2 Hz, 1H), 7.67 (s, 1H), 7.58 (d, *J* = 7.2 Hz, 2H), 7.47 (d, *J* = 4.8 Hz, 1H), 7.43 (s, 1H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.21-7.09 (m, 4H); **^{13}C{^{1}H}NMR (75 MHz, DMSO-*d6*):** δ 139.0, 137.5, 129.1, 126.7, 126.5, 125.9, 125.6, 123.7, 123.0, 122.2, 120.3, 120.1, 114.1, 112.4.

(E)-5-styryl-1H-indole (4b):

Yellow viscous liquid, Hexane/EtOAc = 19/1, 2 mmol scale, yield 315 mg, 72%; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.06 (s, 1H), 7.75 (s, 1H), 7.52 (d, *J* = 7.5 Hz, 2H), 7.43 (d, *J* = 8.7 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 3H), 7.24 (m, 2H), 7.15 (m, 1H), 7.07 (d, *J* = 16.2 Hz, 1H), 6.54 (s, 1H); **^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$):** δ 138.1, 135.6, 130.1, 129.6, 128.6, 128.3, 127.0, 126.3, 126.1, 124.8, 120.7, 119.5, 111.3, 103.0.

ASSOCIATED CONTENT

AUTHOR INFORMATION

Corresponding Author

*Department of Chemistry, Indian Institute of Technology Delhi, Hauz Khas, New Delhi, Delhi-110016; E-mail: njain@chemistry.iitd.ac.in

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

The authors thank Council of Scientific and Industrial Research (CSIR), India 02(0180)/14/EMR-II for financially supporting this work, and providing the fellowship to NC. We acknowledge DST-FIST for funding the ESI-HRMS facility at IIT Delhi. AS and SSP thank CSIR for their graduate fellowships.

Supporting Information

Copies of ^{1}H NMR, ^{13}C{^{1}H}NMR and HR-MS for all the synthesized compounds, GC-MS spectrum of **III**/**IV** and LC-MS spectra for determination of K_H/K_D and cross-over experiment for determination of scrambling of H/D has been included. This material is available free of charge *via* the internet at http://pubs.acs.org.

REFERENCES

1. Shiri, M.; Zolfigol, M. A.; Kruger, H. G.; Tanbakouchian, Z. *Chem. Rev.* **2010**, *110*, 2250-2293.

2. a) Ji, S. -J.; Zhou, M. -F.; Gu, D. -G.; Jiang, Z. -Q.; Loh, T. -P. *Eur. J. Org. Chem.* **2004**, 1584-1587. b) Nagarajan, R.; Perumal, P. T. *Tetrahedron* **2002**, *58*, 1229-1232. c) Mahadevan, A.; Sard, H.; Gonzaleza, M.; McKew, J. C. *Tet. Lett.* **2003**, *44*, 4589-4591.
3. Chakrabarty, M.; Ghosh, N.; Basaka, R.; Harigaya, Y. *Tet. Lett.* **2002**, *43*, 4075-4078.
4. Xiang, J.; Wang, J.; Wang, M.; Meng, X.; Wu, A. *Org. Biomol. Chem.* **2015**, *13*, 4240-4247.
5. Xu, H.-Y.; Zi, Y.; Xu, X.-P.; Wang, S.-Y.; Ji, S.-J. *Tetrahedron* **2013**, *69*, 1600-1605.
6. Yang, Q.; Wang, L.; Guo, T.; Yu, Z. *J. Org. Chem.* **2012**, *77*, 8355-8361.
7. Bhuvaneswari, S.; Jeganmohan, M.; Cheng, C. -H. *Chem. Eur. J.* **2007**, *13*, 8285-8293.
8. Wang, M.-Z.; Zhou, C.-Y.; Che, C.-M. *Chem. Commun.* **2011**, *47*, 1312-1314.
9. Barluenga, J.; Fernandez, A.; Rodriguez, F.; Fananas, F. J. *Chem. Eur. J.* **2009**, *15*, 8121.
10. Yadav, J. S.; Reddy, B. V. S.; Padmavani, B.; Gupta, M. K. *Tet. Lett.* **2004**, *45*, 7577.
11. a) Tsuchimoto, T.; Nagase, Y.; Miyamura, T.; Matsubayashi, H.; Kaneko, M.; Shirakawa, E. *J. Am. Chem. Soc.* **2008**, *130*, 15823. b) Bhaskar, G.; Saikumar, C.; Perumal, P. T. *Tet. Lett.* **2010**, *51*, 3141.
12. a) Gao, R.; Yi, C. S. *J. Org. Chem.* **2010**, *75*, 3144. b) Cadierno, V.; Francos, J.; Gimeno, J. *Chem. Commun.* **2010**, *46*, 4175.
13. Lu, W.; Jia, C.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **2000**, *2*, 2927.
14. Donets, P. A.; Hecke, K. V.; Meervelt, L. V.; Van Der Eycken, E. V.; *Org. Lett.* **2009**, *11*, 3618.
15. Xie, M.-H.; Xie, F.-D.; Lin, G.-F.; Zhang, J.-H. *Tet. Lett.* **2010**, *51*, 1213.

16. a) Ferrer, C.; Escribano-Cuesta, A.; Echavarren, A. M. *Tetrahedron* **2009**, *65*, 9015. b) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem. Eur. J.* **2007**, *13*, 1358. c) Ferrer, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 1105.

17. Barluenga, J.; Fernandez, A.; Rodriguez, F.; Fananas, F. J. *J. Organomet. Chem.* **2009**, *694*, 546.

18. Xia, D.; Wang, Y.; Du, Z.; Zheng, Qi-Yu; Wang, C. *Org. Lett.* **2012**, *14*, 588.

19. a) Jha, A. K.; Jain, N. *Chem. Commun.* **2016**, *52*, 1831-1834. b) Sharma, P.; Rohilla, S.; Jain, N. *J. Org. Chem.* **2015**, *80*, 4116-4122. c) Premi, C.; Dixit, A.; Jain, N. *Org. Lett.* **2015**, *17*, 2598-2601.

20. Verma, A.K., Danodia, A.K., Saunthwal, R.K., Patel, M., Choudhary, D. *Org. Lett.* **2015**, *17*, 3658-3661.

21. Beckhaus, R.; Oster, J.; Wang, R. *Organometallics* **1998**, *17*, 2215-2221.

22. a) Hein, J. E.; Fokin, V. V. *Chem. Soc. Rev.* **2010**, *39*, 1302-1315. b) Xiao, Q.; Xia, Y.; Li, H.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 1114 -1117. c) Xiao, T.; Donga, X.; Zhou, L. *Org. Biomol. Chem.* **2013**, *11*, 1490-1497.

23. Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 3125-3129.

24. Peng, J.-B.; Qi, Y.; Ma, A.-J.; Tu, Y.-Q.; Zhang, F.-M.; Wang, S.-H.; Zhang, S.-Y. *Chem. Asian J.* **2013**, *8*, 883-887.

25. Frei, R.; Breitbach, A. S.; Blackwel, H. E. *Angew. Chem. Int. Ed.* **2012**, *51*, 5226-5229.

26. Bew, S. P.; Hiatt-Gipson, G. D.; Lovell, J. A.; Poullain, C. *Org. Lett.* **2012**, *14*, 456-459.

27. Noguchi-Yachide, T.; Tetsuhashi, M.; Aoyama, H.; Hashimoto, Y. *Chem. Pharm. Bull.* **2009**, *57*, 536-540.