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C3-Benzylation of Indole and Synthesis of Bis (indolyl) methanes Catalyzed by Schiff Base Transition Metal Complexes

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Abstract:

Schiff base transition metal complexes $[M(L_2)X_2]$ (C1-C4), $[M(L)(PPh_3)_2X_2]$ (C5-C8) and $[M(L)(Phen)X_2]$ (C9-C12) where M= Co (II), Ni(II), Cu(II) and Zn(II), X= Cl, L= 2-Phenyl 3-benzylamino, 1,2 -dihydroquinazolin-4(3H)-one (PBADQ) were synthesized. All these complexes were characterized by IR, ^{1}H NMR, ^{13}C NMR, TGA, BET, ESR and XRD analysis. These complexes were screened for C3-Benzylation of indole and synthesis of Bis (indolyl) methanes. It is observed that all the complexes worked as the efficient catalysts. Especially mixed ligand transition metal complexes with triphenylphosphine and 1, 10-Phenanthroline ligands show greater activity as compared to other Schiff base complexes.

Keywords: Schiff base, Transition metal complexes, C3-Benzylation of Indole, Bis (indolyl) methanes.

INTRODUCTION

The catalytic alkylation of indoles with alcohols is an environmentally friendly and atom-cost-effective approach to make substituted indoles and indolenine, which have important synthetic applications in dyes, perfumes, medicines, and agricultural compounds [1]. Imines (Schiff bases) are widely used organic compounds that coordinate to metal ions via imine or azomethine nitrogen (C=N) and have a wide range of applications in analytical, biological, medicinal, organic, and inorganic chemistry, as well as as catalysts in a variety of reactions such as polymerization, reduction of thionyl chloride of ketone, oxidation of organic compounds, reduction reaction of ketones, aldol reaction, Henry reaction, and many others. Condensation of an aldehyde or ketone with amine was a common method of making it [2]. The Friedel-Crafts reaction with haloalkanes and related alkyl agents, mediated by Lewis acid, is the most well-known method for alkylation of indoles [3].

Heterocyclic compounds are the fundamental building blocks for developing novel molecular entities for drug development. Among the many bioactive compounds, indole derivatives are found in a considerable number of them [4]. Moreover, substituted indoles have attracted a lot of attention because they've been used in medicines, medications, agrochemicals, and materials research [5]. Most biologically relevant indole alkaloids, such as the natural amino acid tryptophan and the neurotransmitter serotonin, are C-3 substituted [6].

C-3 benzylation of indoles has traditionally been done mostly using Friedel-Crafts reactions or the SN^2 reaction of benzyl halides with indoles [7]. However, the use of a stoichiometric amount of Lewis acids, as well as the formation of unwanted by-products, reduces the efficacy of these techniques [8]. As a result, safe, efficient, and cost-effective techniques for the direct alkylation of indole remnants are a hot topic of research [9]. When compared to the use of comparable halides, esters, carboxylates, or related chemicals for this purpose, benzylic alcohols are gaining popularity as green alkylating agents because the only by-product produced is water, resulting in an environmentally friendly and clean process [10, 11]. In the past few years, many studies have been reported the C-3 benzylation reactions by using expensive transition metal complex based catalytic systems with Fe [12], Ir [13], Au [14] and Pd [15] which are moisture- and air-sensitive and their preparation process needed complex handling and harsh surroundings which limit their practical utility in a large scale.

Bis (bis(indolyl) methanes) (BIMs) and their derivatives are nitrogen-containing compounds that can be found in a wide range of natural and manufactured goods [16]. In addition, BIMs and their relatives exhibit a wide range of biological and pharmacological properties, including antioxidant, anti-inflammatory, antifungal, antibacterial, antibiotic, and analgesic effects [17]. BIMs, when combined, are said to have anticancer properties, limiting the formation of malignant cells in the colon, cervix,

prostate, pancreas, and lungs [18]. The most important metabolite of indole-3-carbinol, dimeric 3,3′ bis(indolyl)methane, is involved in breast cancer prevention [19]. Derivatives of indole-carbazole are known to act as triplet energy materials [20]. Oxidized BIMs [21] and dyes, on the other hand, are utilised as colorimetric sensors [22]. Because of their important biological and pharmacological properties, there is growing interest in a simple method for making BIMs. In general, the electrophilic substitution of indoles with carbonyl compounds is typically mediated by Bronsted or Lewis acids [23], ionic liquids, or heteropolyacids [24].

In the present work we report C3-Benzylation of indole and synthesis of Bis (indolyl) methanes using Schiff base Co(II), Ni(II), Cu(II) and Zn(II) transition metal complexes under mild conditions. It was observed that all the complexes worked as efficient catalysts.

Experimental

Materials and measurements

All of the chemicals for the synthesis of the compounds were commercially obtained and used as purchased. ^{1}H NMR spectra's were recorded on a Bruker, AVANCE II-300 MH_Z using $CDCl_3$ as solvent. ^{13}C NMR spectra of products were recorded on a Bruker, 300 MH_Z using $CDCl_3$ as solvent. The IR spectra were measured on Perkin Elmer, FT-IR/FIR Spectrometer with KBr pellets within the 400–4000 cm−1 region. Thermogravimetric analyses were carried out on instrument: SDT Q600 V20.9 under nitrogen atmosphere.

Synthesis of Schiff base and their transition metal complexes

The Schiff base 2-phenyl, 3-benzylamino, 1, 2-dihydroquinazoli-4(3H)-one (PBADQ) is synthesized by modified reported method [25]. The Schiff base transition metal complexes C-1 to C-12 were synthesized by modified reported method [26-28].

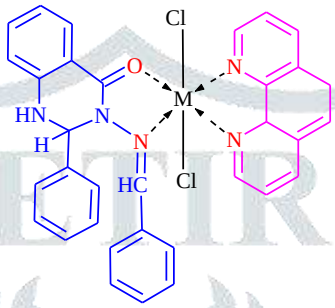


Fig. 1 Mixed ligand complex $[M(L)(Phen)Cl_2]$
Where M= Co(II), Ni(II), Cu(II) and Zn(II)

General Procedure for C3-Benzylation of indole with benzyl alcohol.

A round-bottom flask was charged with indole (1 mmol) and alcohol (1 mmol) in the presence of (0.05 mmol) complex in DMF (5 mL) at 100 °C for 5 h. After completion of reaction (confirmed by TLC), the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to give the desired products [29, 30].

Results and discussion

The catalytic role of Schiff base transition metal complexes and mixed ligand transition metal complexes C-1 to C-12 were studied for C3-Benzylation of indole with benzyl alcoholes. C-1 to C-4, C-5 to C-8, and C-9 to C-12 are three sets of Schiff base transition metal complexes that we have synthesized (Fig. 1). All of the complexes were coloured powders that were stable at room temperature but decomposed at temperatures above 300°C. These moisture-insensitive complexes are insoluble in typical organic solvents such as ethanol, methanol, dichloromethane, and acetonitrile, but extremely soluble in dimethylformamide and dimethylsulphoxide. Under mild circumstances, all of these compounds were evaluated for C3-benzylation of indole with benzyl alcoholes. All of the Schiff base transition metal complexes were shown to be effective catalysts for C3-Benzylation of indole with benzyl alcoholes, with yields ranging from 39 to 87 percent (Table 1). (Scheme 1). From the first series, complex C-1 yielded 55 percent better (Table 1 entry 2), from the second series, complex C-6 yielded 87 percent better (Table 1 entry 7) and from the third series, complex C-11 yielded 76 percent better (Table 1 entry 8). (Table 1 entry 12). DMF was better solvent as compared to other solvents with improved product yields. All of these reactions take place at 100°C for 5 hours. We chose one best performance complex catalyst from each series based on product yield and searched for other catalytic reactions.

We have screened different substituted benzyl alcoholes for C3-benzylation of indole (Table 2) (Scheme 2). Using best performer from each series complexes C-1, C-6 and C-11 gave better yields. Complex C-1 shows 45-51% yield (Table 2 entries 1,4,7,10), complex C-6 shows 71-81% yield (Table 2 entries 2,5,8,11) and complex C-11 shows 47-65% yield (Table 2 entries 3,6,9,12). Especially complex C-6 gave better yield 81% (Table 2 entries 2), less reaction time 5h as compared to other reactions. The complex $[Ni(L)(PPh_3)_2Cl_2]$ is most suitable catalyst for these reactions. It is also screened for C3-benzylation of substituted indole with substituted benzyl alcoholes with electron donating and electron withdrawing group (Table 3) (Scheme 3). 4-methyl indole and 4-methoxy benzyl alcohol gave product yield 65% (Table 3. entry 1). While 4-chloro indole and 4-methyl benzyl alcohol led to the C3-benzylated product with 67% yield (Table 3. entry 2). It was concluded that all the complexes worked as the efficient catalysts for C3-Benzylation reactions and synthesis of bis (indolyl) methanes. The mixed ligand complexes with PPh_3 and Phen ligands show greater activity as compared to other Schiff base transition metal complexes.

3-Benzyl-1H-indole (3a)

The title compound was prepared according to the general procedure using 1H-indole and benzyl alcohol. The product was purified by flash chromatography (cyclohexane/ EtOAc 8:2) to give product as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (br s, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.33−7.29 (m, 4H), 7.24−7.12 (m, 2H), 7.11 (t, J = 7.0 Hz, 1H), 6.94 (s, 1H), 4.16 (s, 2H); HRMS (ESI) m/z calcd for $C_{15}H_{13}N$ (M+) 230.0940; found 230.0946.

3-(4-Methylbenzyl)-1H-indole (3b)

The title compound was prepared according to the general procedure using 1H-indole and p-tolylmethanol. The product was purified by flash chromatography (cyclohexane/EtOAc 9:1) to give product as pinkish solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (br s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.26−7.21 (m, 3H), 7.15−7.12 (m, 3H), 6.93−6.91 (m, 1H), 4.14 (s, 2H), 2.36 (s, 3H); HRMS (ESI) m/z calcd for $C_{16}H_{16}N$ (M + H)+ 222.1277; found 222.1286.

3-(4-Methoxybenzyl)-1H-indole (3c)

The title compound was prepared according to the general procedure using 1H-indole and (4-methoxyphenyl) methanol. The product was purified by flash chromatography (gradient from cyclohexane/EtOAc 95:5 to cyclohexane/ EtOAc 90:10) to give product as brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (br s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.29−7.20 (m, 3H), 7.13 (t, J = 8.0 Hz, 1H), 6.94 (s, 1H), 6.88 (d, J = 8.0 Hz, 2H), 4.11 (s, 2H), 3.84 (s, 3H); HRMS (ESI) m/z calcd for $C_{16}H_{16}NO$ (M + H)+ 238.1226; found 238.1221.

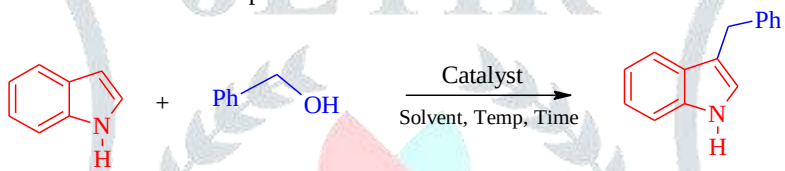
4-((1H-Indol-3-yl) methyl)benzonitrile (3d)

The title compound was prepared according to the general procedure using 1H-indole and 4-(hydroxymethyl) benzonitrile. The product was purified by flash chromatography (from cyclohexane/EtOAc 1:1 to cyclohexane/ EtOAc 1:9) to give product as white solid. ^{1}H NMR (400 MHz, acetone-d6) δ 10.11 (br s, 1H), 7.86 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 7.5 Hz, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.19−7.17 (m,1H), 7.11−7.08 (m,1H), 6.99−6.96 (m,1H), 4.18 (s, 2H); HRMS (ESI) m/z calcd for $C_{16}H_{13}N_2$ (M + H)+ 233.1073; found 233.1068.

3-(4-Methoxybenzyl)-6-methyl-1H-indole (3e)

The title compound was prepared according to the general procedure using 6- methyl-1H-indole and (3-((1H-indol-3-yl)methyl)phenyl)methanol. The product was purified by flash chromatography (cyclohexane/ EtOAc 8:2) to give product as pinkish solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (br s, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.29−7.24 (m, 2H), 7.15 (s, 1H), 6.98 (d, J = 8.0 Hz, 1H), 6.87 (m, 2H), 6.84 (s, 1H), 4.09 (s, 2H), 3.84 (s, 3H), 2.51 (s, 3H); HRMS (ESI) m/z calcd for $C_{17}H_{18}NO$ (M + H)+ 252.1383; found 252.1379.

Table. 1 Optimization of the reaction conditions

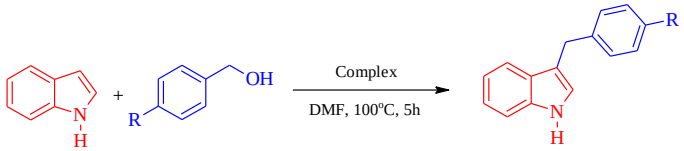


(**Scheme-1**)

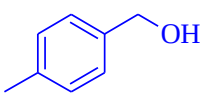
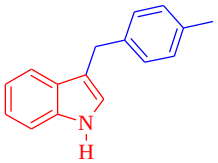
Entry		Complex	Solvent	Temp °C	Time (h)	Yield %
1		-	DMF	100	7	NR
2	C-1	$[Co(L)_2Cl_2]$	DMF	100	5	55
3	C-2	$[Ni(L)_2Cl_2]$	DMSO	90	6	41
4	C-3	$[Cu(L)_2Cl_2]$	DMF	80	7	48
5	C-4	$[Zn(L)_2Cl_2]$	DMSO	100	6	39
6	C-5	$[Co(L)(PPh_3)_2Cl_2]$	DMF	90	7	78
7	C-6	$[Ni(L)(PPh_3)_2Cl_2]$	DMF	100	5	87
8	C-7	$[Cu(L)(PPh_3)_2Cl_2]$	DMF	80	7	61
9	C-8	$[Zn(L)(PPh_3)_2Cl_2]$	DMF	90	6	72
10	C-9	$[Co(L)(Phen)Cl_2]$	DMF	100	5	45
11	C-10	$[Ni(L)(Phen)Cl_2]$	DMF	100	6	43
12	C-11	$[Cu(L)(Phen)Cl_2]$	DMF	100	5	76
13	C-12	$[Zn(L)(Phen)Cl_2]$	DMF	100	6	53

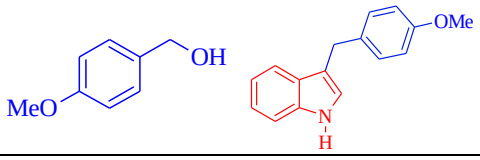
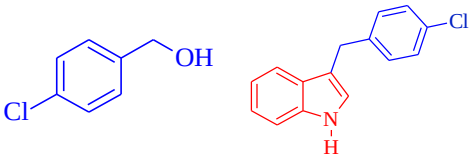
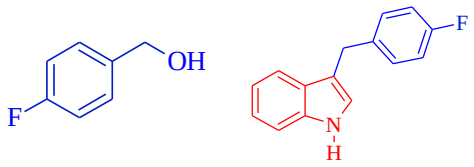
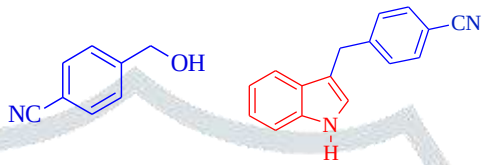
Reaction conditions: Indole (1 mmol), benzyl alcohol (0.5mmol), complex (0.05 mmol), DMF, reflux.

Table. 2 C3-Benzylation of Indole with Substituted Benzyl alcohols



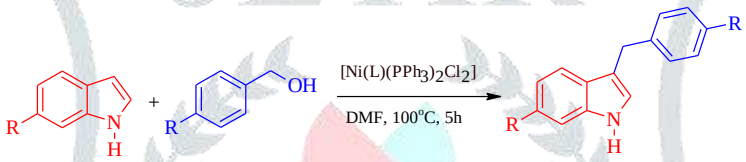
(**Scheme-2**)

Entry	Complex	Sub. alcohols	Product	Yield (%)
1	$[Co(L)_2Cl_2]$			49
2	$[Ni(L)(PPh_3)_2Cl_2]$			81
3	$[Cu(L)(Phen)Cl_2]$			65
4	$[Co(L)_2Cl_2]$			51

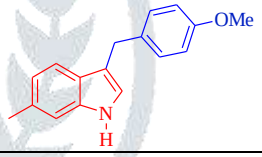
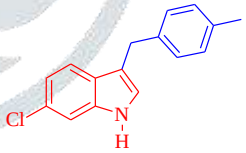
5	$[Ni(L)(PPh_3)_2Cl_2]$		79
6	$[Cu(L)(Phen)Cl_2]$		62
7	$[Co(L)_2Cl_2]$		50
8	$[Ni(L)(PPh_3)_2Cl_2]$		77
9	$[Cu(L)(Phen)Cl_2]$		47
10	$[Co(L)_2Cl_2]$		45
11	$[Ni(L)(PPh_3)_2Cl_2]$		71
12	$[Cu(L)(Phen)Cl_2]$		59
13	$[Co(L)_2Cl_2]$		39
14	$[Ni(L)(PPh_3)_2Cl_2]$		75
15	$[Cu(L)(Phen)Cl_2]$		60

Reaction conditions: Indole (1 mmol), Sub.benzyl alcohol (0.5 mmol), complex (0.05 mmol), DMF, reflux.

Table.3 C3-Benzylation of Substituted indole with Substituted Benzyl alcohol



(**Scheme-3**)

Entry	Complex	Sub. Indole - R	Sub. Benzyl alcohol -R	Product	Yield (%)
1	$[Ni(L)(PPh_3)_2Cl_2]$	$-CH_3$	$-OCH_3$		65
2		-Cl	$-CH_3$		67

Reaction conditions: Sub.indole (1 mmol), Sub.benzyl alcohol (0.5 mmol), complex (0.05 mmol), DMF, reflux.

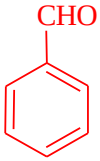
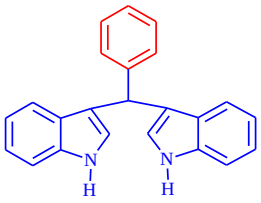
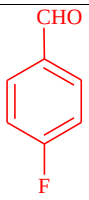
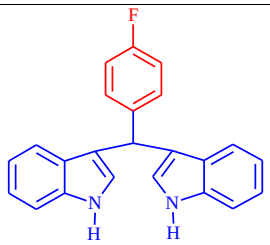
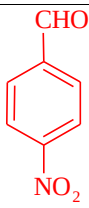
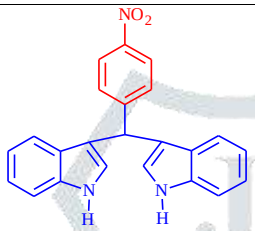
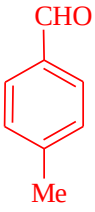
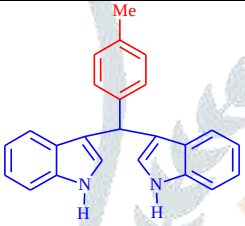
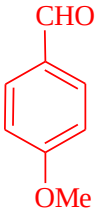
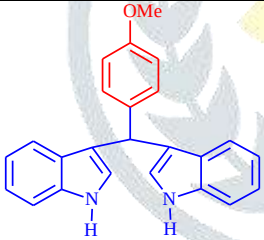
Synthesis of Bis (indolyl) methanes

General procedure for the synthesis of bis (indolyl) methanes

Synthesis of bis (indolyl) methanes reactions were carried out by reported modified procedure [31]. To a mixture of indole (2 mmol, 0.234 g) and benzaldehyde (1 mmol, 0.106 g) in DMF (3 mL), complex (0.04 g) was added. The mixture was allowed to reflux at 100◦C. Upon completion of the reaction monitored by TLC analysis. After the filtration, H_2O (10 mL) was added and the product was extracted into ethyl acetate (3 × 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and then evaporated under vacuum to afford the crude product, which was further purified by thin layer chromatography. We report here complexes C-1, C-2 and C-3 as an efficient catalyst for the synthesis of bis(indolyl)methanes under mild conditions (Scheme 4). Catalyst complex C-2 gave excellent yield as compared to other remaining two complexes C-1 and C-3 (Table 4 entries 1-3). The results clearly indicate the generality and scope of this protocol showing the reaction of aromatic aldehydes with indole which were smoothly converted to the corresponding bis(indolyl)methanes in excellent yield. The reactions aromatic aldehyde derivatives having electron withdrawing groups (Table 4 entries 4-9) were somewhat faster than that of electron donating groups (Table 4 entries 10-15).

Especially catalyst complex C-2 gave excellent product yield as compared to other two Schiff base complexes. It was concluded that all the complexes worked as the efficient catalysts for synthesis of Bis (indolyl) methanes. The mixed ligand complexes with PPh_3 and Phen ligands show greater activity as compared to other Schiff base transition metal complexes.

Table. 4 Synthesis of Bis(indolyl)methanes using complexes C-1, C-2 and C-3 (**Scheme-4**)

Entry	Aldehydes	Product	Complex C-3 Time (h)	Complex C-3 Yield %	Complex C-2 Time (h)	Complex C-2 Yield %	Complex C-1 Time (h)	Complex C-1 Yield %	M.P °C [Ref]
1 2 3			2	66	1	90	3	73	145-146 (148-152) [32]
4 5 6			2	60	1	84	2	69	77-79 (78-80) [33]
7 8 9			2	64	1.5	94	3	70	219-222 (218-221) [33]
10 11 12			2	57	1	89	2	67	96-98 (95-96) [32]
13 14 15			2	52	1.5	80	2	65	187-190 (185-186) [33]

Reaction condition: Indole (2mmol), benzaldehyde sub. (1mmol), Complex (0.05mmol), DMSO (3mL), time 1-3 h, temp 100°C.

3, 3´–Bis (indolyl)–phenylmethane (Table 4 Entry 1)

Yield 90% $C_{23}H_{18}N_2$ IR (KBr) cm^{-1}: 3384, 3080, 3036, 1655, 1620, 1603, 1349, 1335, 1167, 1082, 734, 702; ^1H NMR ($CDCl_3$) ppm: δ 5.8 (s, 1H, CH), 6.2 (s, 2H, >N-CH=), 6.2 (s, 2H, >N-CH=), 6.7 – 7.2, (m, 12H, Ar-H), 7.8, (s, 2H,>N–H). ^{13}C NMR (100MHz, DMSO-d6): δ143.9, 136.5, 128.2, 128.9, 126.5, 125.7, 123.4, 121.8, 119.0, 118.1, 119.0 and 111.3.

3, 3´ – Bis (indolyl)–4– Fluorophenylmethane (Table 4 Entry 2)

Yield 84% $C_{23}H_{17}N_2F$ IR (KBr) cm^{-1}: 3422, 3075, 3023, 2857, 1611, 1487, 1455, 1335, 1166, 1082, 1035, 734; ^1H NMR (400 MHz, DMSO-d6): δ10.88 (s, 1H), 7.47 (d, J=7.2 Hz, 1H), 7.34 (t, J=8 Hz, 3H), 7.3-7.27 (m, 3H), 7.04 (t, J=7.6, 2H), 6.90– 6.86 (m, 4H), 5.89 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d6): δ144.41, 138.52, 129.73, 127.97, 126.96, 125.72, 124.56, 121.62, 120.82, 118.71, 117.91, 110.68. 34.43.

Conclusion

All of the complexes C1 to C12 functioned as efficient catalysts with higher product yields for C3-Benzylation of Substituted Indole with Substituted Benzyl alcohol as well as the synthesis of bis (indolyl) methanes. Especially $[Ni(L)(PPh_3)_2Cl_2]$ complex is more suitable for all these reactions. The mild catalytic reaction conditions, easy synthesis of complexes. The simplicity in experiment and broad substrate scope are the features of this method.

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Supporting Information (SI)

All the experimental details of IR, ^{1}H, ^{13}C NMR, ESR, TGA XRD and BET analysis for this article can be accessed from the publisher's website.

Declarations Competing Interest

The Authors declare that they do not have any conflict of interest.

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Graphical Abstract