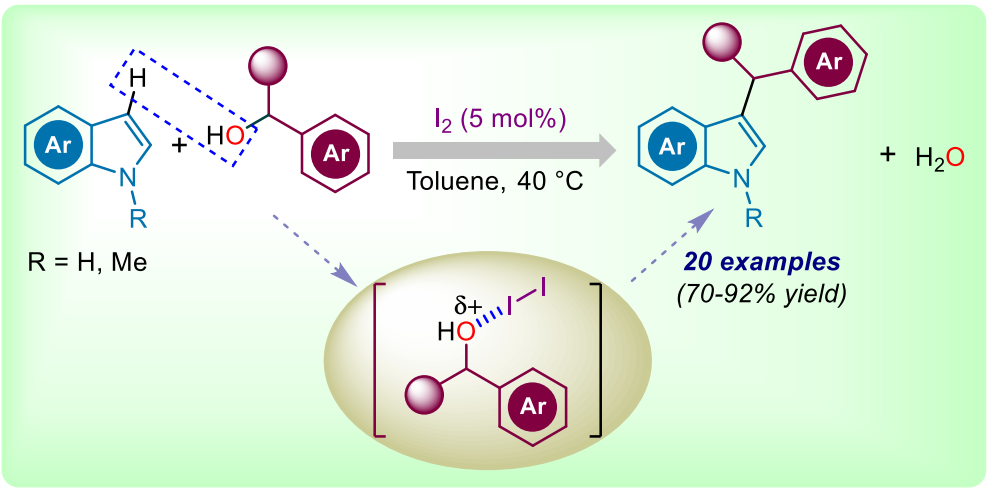
Chapter 2

Molecular Iodine Catalyzed Selective C3-Benzylation of Indoles with Benzyl Alcohol



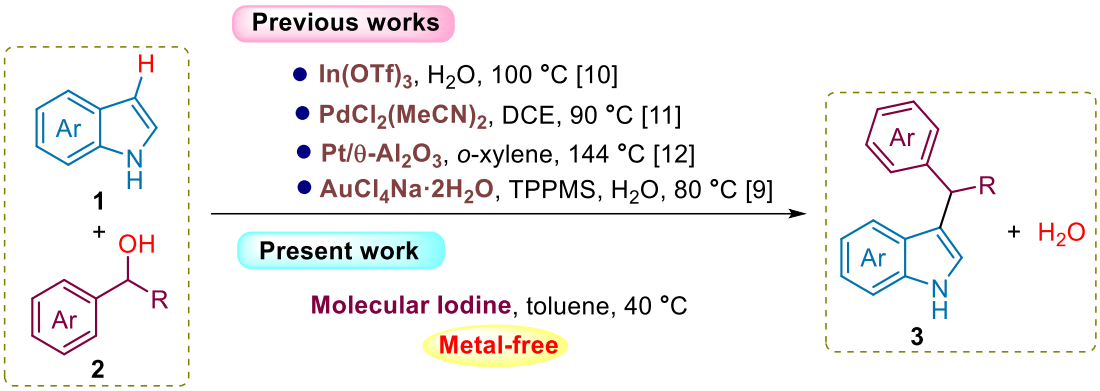
2.1 Introduction

Benzylation at C3 position of indoles was conventionally achieved *via* Friedel-Crafts reaction or S_N2 reaction of benzyl halides with indoles [1,2]. However, the use stoichiometric amount of Lewis acids and formation of unwanted by-products reduce the effectiveness of these methodologies. Therefore, the demand for mild, efficient, and economic methods for the direct alkylation of indoles remain an area of active research. In the present times, benzyl alcohols are gaining interests as green alkylating agents as the only by-product generated is water [3,4] thereby producing an environmentally benign and clean process compared to the use of corresponding halides, esters, or carboxylates for the study [5,6].

In the recent literature, there have been many reported methodologies for the C3-benzylation of indoles by using expensive transition metal complex-based catalytic systems [7], containing Fe [8], Au [9], In [10], Pd [11], Pt [12], Ru [13], Ni [14], Cu [15], which are moisture and air sensitive and their preparation method needs complex handling and harsh reaction conditions, thus limiting their practical utility in large scale. Some methods also require the addition of ligands [9,16], bases [8,16] or other additives to maximize the catalytic activity. Generally, metal-free processes are favorable in pharmaceutical industries due to the additional difficulties associated with the metal impurities [17-19].

Therefore, there is a rising demand for the development of metal-free catalytic system for C3-benzylation, which is less explored till date and will be a beneficial alternative to transition-metal catalysis. Ramón and co-workers have reported non-catalytic C3-alkylation by alcohols through borrowing hydrogen strategy using stoichiometric amount of base [20]. There are reports of C3-benzylation catalyzed by Br_2 [21], *N*-heterocyclic carbene [22], high temperature water [23], and using Lewis [24,25] and Brønsted acids [26,27]. In the recent times, molecular iodine has emerged as a green and environmentally benign reagent and has been successfully employed as a catalyst in different organic transformations forming new C–C, C–N, C–O, C–S bonds in organic compounds [28-30]. It is naturally abundant, inexpensive, non-toxic, environment friendly and active even in very small amounts [31,32]. Inspired by its catalytic activeness and economic viability, this chapter reports a green, efficient, and economical strategy for selective C3-benzylation of indoles

employing molecular iodine as a catalyst under ligand-, metal-, and base-free conditions (Scheme **2.1**).



Scheme 2.1 Previous and present study on C3-benzylation of 1-methylindole

2.2 Results and Discussion

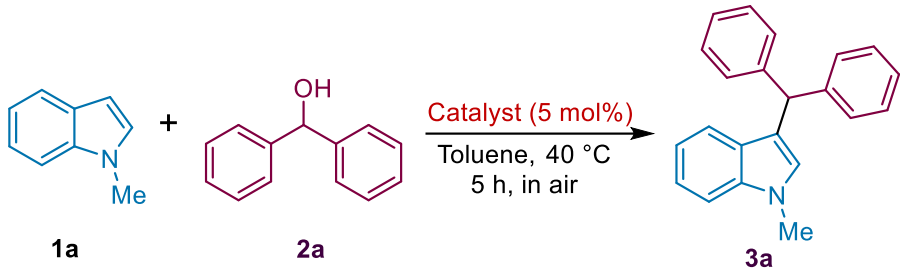
2.2.1 Optimization of Reaction Conditions

The studies were initiated with 1-methylindole and diphenylmethanol as model substrates for the reaction. It was found that 1-methylindole (**1a**) and diphenylmethanol (**2a**) when treated with molecular iodine (5 mol%) in toluene at 40 °C produced the C3-benzylated product (**3a**) in 85% yield in 5 h (Table **2.1**, entry **1**). C3-substituted product formation was confirmed from single crystal X-ray diffraction of **3a**.

No desired product was observed in the absence of I_2 even after 12 h (Table **2.1**, entry **2**). Hence in order to study the activity of I_2 as catalyst, reactions were performed by varying the amount of catalyst. Using 2 mol% of the catalyst showed reduction in the yield to 70% (Table **2.1**, entry **4**), however increasing the amount of catalyst to 10 mol% gave no significant improvement in the yield (Table **2.1**, entry **5**). Hence, the highest activity was observed using 5 mol% of the catalyst (Table **2.1**, entry **1**). In order to study the effect of temperature, reactions were performed at different conditions: rt, 40 °C and 60 °C, and the best result was observed at 40 °C (Table **2.1**, entries **1**, **3**, **6**). When performed under N_2 atmosphere produced similar results indicating no role of oxygen in the reaction (Table **2.1**, entry **7**). The effect of other iodine-containing additives was investigated at 40 °C, however no reaction was observed with 5 mol% KI (Table **2.1**, entry **8**) which proved the effectiveness of I_2 as catalyst for the current protocol. Most of the aprotic solvents such as toluene, DCM,

CH_3CN and 1,4-dioxane resulted in acceptable yields (Table **2.1**, entries **1**, **9-11**) except for DMSO and DMF where no product formation was observed even after extended reaction times (Table **2.1**, entries **12-13**). In contrast, there was no reaction at all in protic solvents such as H_2O, MeOH and EtOH (Table **2.1**, entries **14-16**).

Table 2.1 Screening of the effect of catalysts and solvents[a]



1a 2a 3a

Entry	Catalyst	Solvent	Time (h)	Yield (%)[b] of **3a**
1	I_2	Toluene	5	85
2	-	Toluene	12	nr
3[c]	I_2	Toluene	7	83
4[d]	I_2	Toluene	7	70
5[e]	I_2	Toluene	7	85
6[f]	I_2	Toluene	7	65
7[g]	I_2	Toluene	7	85
8	KI	Toluene	12	nr
9	I_2	DCM	7	67
10	I_2	CH_3CN	7	72
11	I_2	1,4-Dioxane	7	78
12	I_2	DMSO	10	nr
13	I_2	DMF	10	nr
14	I_2	H_2O	7	nr
15	I_2	MeOH	7	nr
16	I_2	EtOH	7	nr

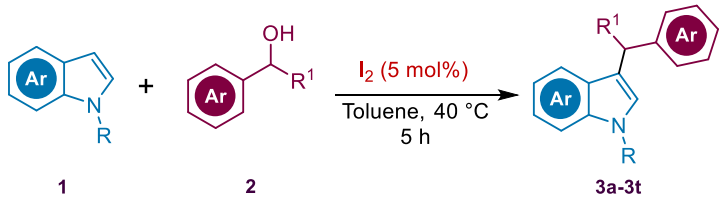
[a]Reaction condition: **1a** (1 mmol), **2a** (1.2 mmol), catalyst (5 mol%), solvent (2 mL), T (40 °C), time (5 h), in air; [b]isolated yield; [c]T (60 °C); [d]catalyst (2 mol%); [e]catalyst (10 mol%); [f]rt; [g]N_2 atmosphere; nr (no reaction).

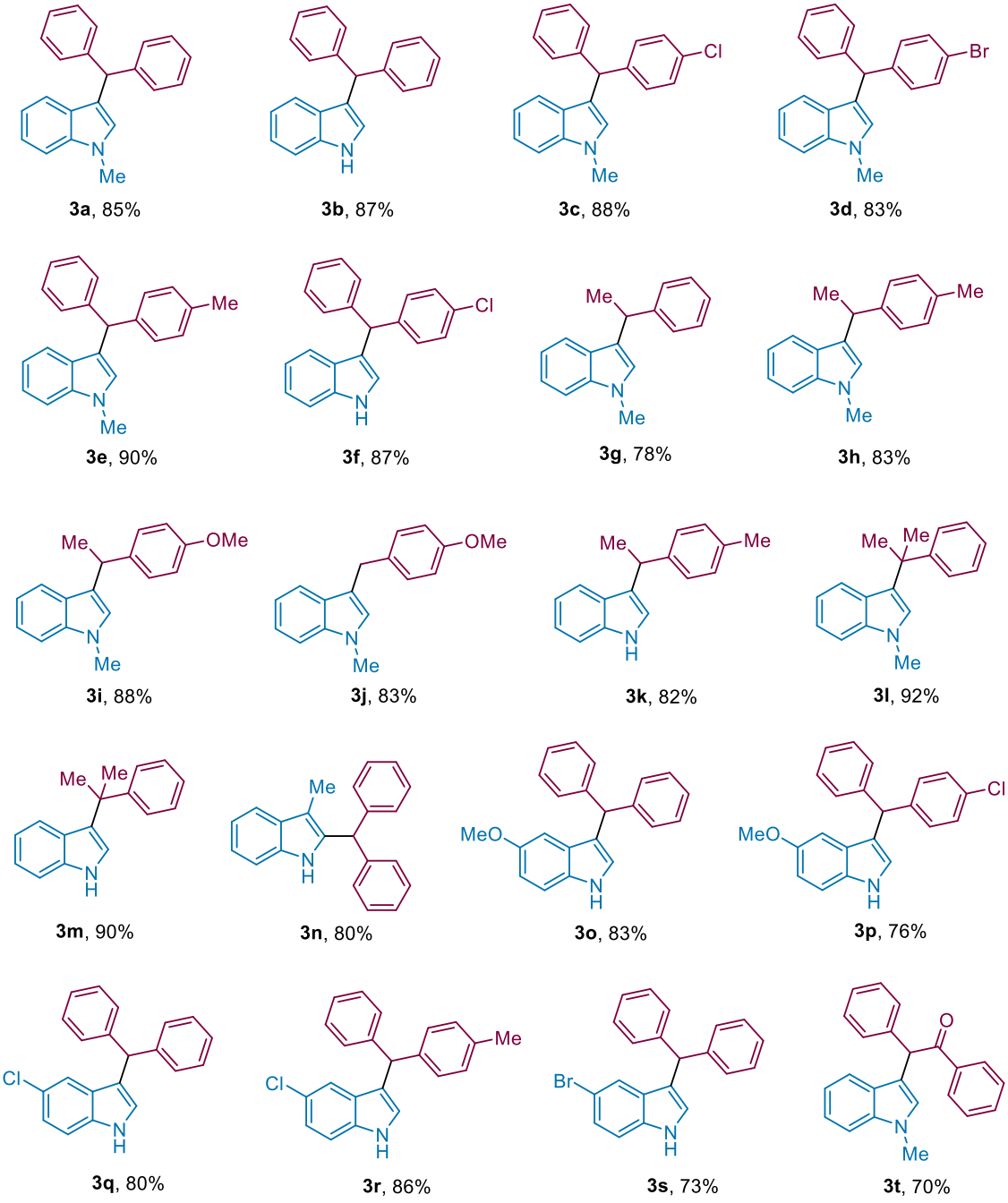
From the study of solvent on the reaction, some important conclusions on the mode of iodine catalysis can be drawn. In the presence of protic solvents, iodine is known to decompose slowly to form Brønsted acid HI which is responsible for further reaction catalysis [33]. But from the observations of Table **2.1**, no reaction proceeds at all in protic solvents such as H_2O, MeOH and EtOH (Table **2.1**, entries **14**-**16**) which clearly rules out the contribution of Brønsted acid mode of catalysis by molecular iodine. On the other hand, iodine in most aprotic solvents give acceptable yields (Table **2.1**, entries **1**, **9**-**11**) which accounts for the halogen-bond activation mechanism of molecular iodine [34]. It also explains why no product formation is observed in DMSO and DMF in spite of being aprotic solvents as they are expected to form strong halogen-bond with molecular iodine resulting in deactivation of the catalyst for further reaction [33]. The reaction did not require any external base or additives.

2.2.2 Substrate Scope Study

The scope and limitations of the C3-benzylation of indoles were investigated based on electronically diverse indole and benzyl alcohol derivatives. The results are summarized in Table **2.2**. Benzyl alcohols with both electron-donating such as Me, OMe (Table **2.2**, **3e**, **3g**-**3m**) and electron-withdrawing substituents such as Cl, Br (Table **2.2**, **3c**, **3d**, **3f**, **3p**) afforded the desired products in 70-92% yield. Primary benzyl alcohols with electron-donating substituents (OMe) formed the desired product in 83% yield (Table **2.2**, **3j**) whereas electron-poor or unsubstituted primary benzyl alcohols resulted in no reaction. This observation can be explained by the increased stability of intermediate species formed during the process in presence of electron-rich benzylic systems. In contrast, secondary benzylic alcohols bearing both electron-donating and electron-withdrawing groups afforded the benzylated products in 80-90% yield. Tertiary benzyl alcohols showed highest reactivity and resulted in the desired products in 90-92% yield (Table **2.2**, **3l**-**3m**) which can be attributed to the carbocation stability. Similarly, indole bearing electron-donating (OMe) substituent (Table **2.2**, **3o-3p**) and electron-poor substituents (Table **2.2**, **3q-3s**) resulted in successful yields of the reaction (73-86%). Interestingly, if 3-position of indole is preoccupied, reaction proceeds at the 2-position (Table **2.2**, **3n**). The protocol was also examined for chain alkyl alcohol but produced no significant result.

Table 2.2 Substrate scope for C3-benzylation of indoles with benzyl alcohols[a]





[a]Reaction condition: **1** (1 mmol), **2** (1.2 mmol), I_2 (5 mol%), toluene (2 mL), T (40 °C), time (5 h), in air; the yields reported are the isolated yields.

2.2.3 Mode of Iodine Catalysis

From Table **2.1**, it was observed that no reaction proceeds in protic solvent due to the decomposition of iodine into HI ruling out the Brønsted acid mode of catalysis.

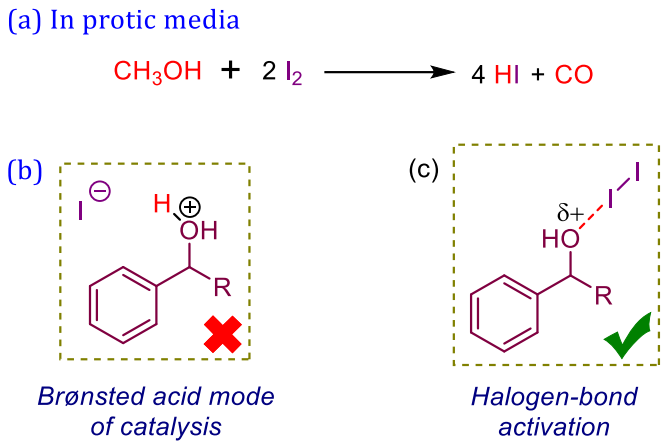


Figure 2.1 Proposed mode of activation for iodine catalysis

To experimentally prove the contribution of halogen-bond activation mechanistic pathway by molecular iodine in the present catalytic pathway, following experiments were performed. 1-methylindole and diphenylmethanol when treated with molecular iodine in toluene at 40 °C produced the C3-benzylated product in 85% yield in 5 h (Table **2.3**, entry **1**). On the other hand, addition of aqueous HI (57 wt%) produced only 26% of the desired product, which supported the earlier observation on solvent studies and excluded the contribution of Brønsted acid mode of catalysis for the reaction pathway (Table **2.3**, entry **5**).

Table 2.3 Comparative study of I_2 and HI mode of catalysis[a]

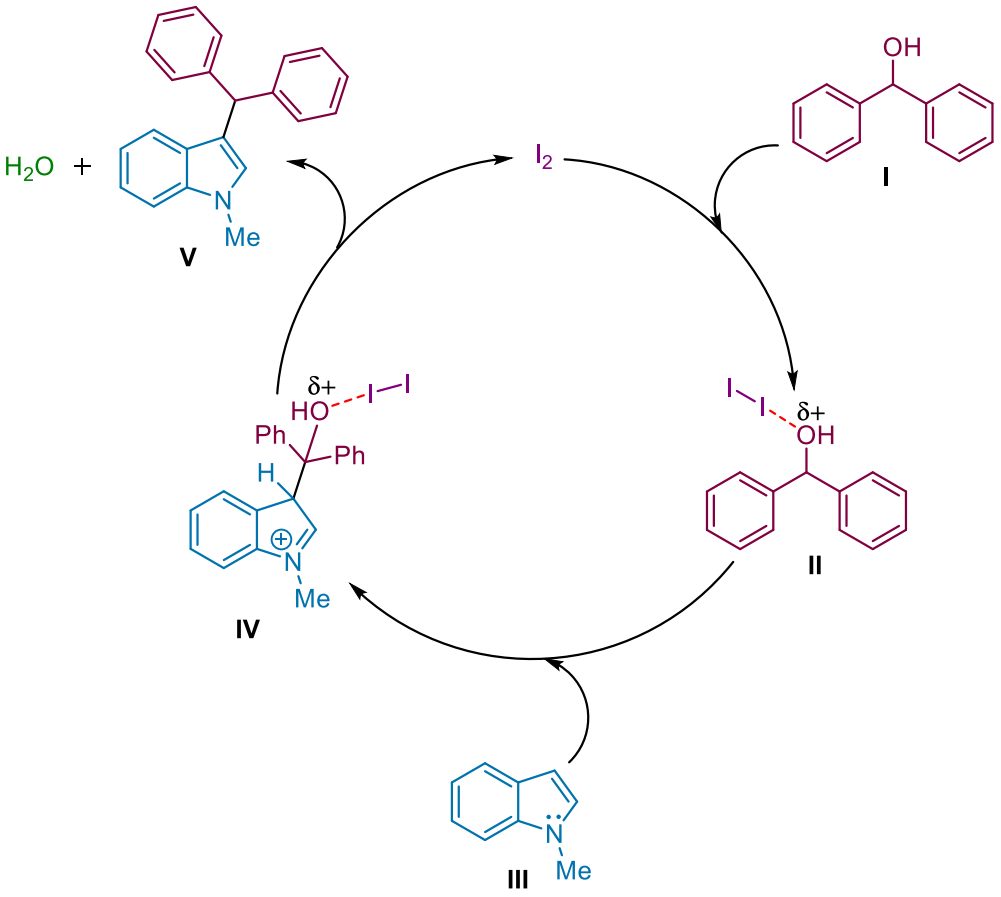
Entry	Catalyst	Yield (%)[b] of **3a**
1	I_2	85
2	I_2 + H_2O[c]	82
3	I_2 + KI	43
4	I_2 + MS[d]	86
5	HI	26
6	HI + KI	26

[a]Reaction condition: **1a** (1 mmol), **2a** (1.2 mmol), catalyst (5 mol%), toluene (2 mL), T (40 °C), time (5 h); [b]isolated yield; [c]28 mol% H_2O; [d]25 mg molecular sieves (MS).

The influence of trace amount of water on the catalytic activity of molecular iodine was analyzed, which showed no comparable change in reactivity (Table **2.3**, entry **2**). The catalytic activity of molecular iodine is suppressed by the addition of KI due to the formation of triiodide ions which is evident from the lowered reaction yield of 43% (Table **2.3**, entry **3**), whereas the activity of HI remains unchanged (Table **2.3**, entry **6**). Addition of 25 mg molecular sieves (MS) resulted in no change in reactivity of molecular iodine (Table **2.3**, entry **4**) indicating no moisture sensitivity in the reaction.

2.2.4 Plausible Mechanism

From the experimental observations and literature findings, a plausible mechanism has been proposed as shown in Scheme **2.2**.



Scheme 2.2 Plausible mechanism for C3-benzylation of indoles

The first step is expected to be the activation of benzyl alcohol by I_2 forming a halogen-bond between the oxygen of benzyl alcohol (**I**) and I_2 [33]. The oxygen atom of the alcohol bears a partial positive charge due to the halogen bonding and forms

an intermediate species (**II**), which is stabilized by the resonance effect (+R effect) of the phenyl rings attached to the nearby secondary carbon center. In the presence of strong π-nucleophile indole (**III**), an electrophilic substitution reaction takes place at the C3 position of the indole ring (the most nucleophilic center on the indole nucleus) to form an intermediate species **IV**, which undergoes rearomatization to form 3-benzylated indole (**V**) with elimination of water and regeneration of molecular iodine to complete the catalytic cycle. No generation of any other side products in the reaction was observed. The stability of the intermediate species **II** can be increased by introducing electron-donating substituents to the phenyl rings or using tertiary benzyl alcohols.

2.3 Summary

This chapter demonstrates a protocol for selective C3-benzylation of indoles with benzyl alcohols employing molecular iodine as a green catalyst. The methodology is simple and environmentally benign and proceeds under ligand-, metal-, and base-free conditions. The mild conditions and wide functional group tolerance makes the protocol suitable for further applications.

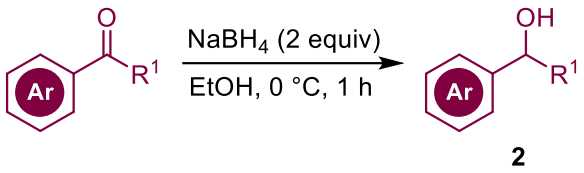
2.4 Experimental Section

2.4.1 General Information

All reactions were carried out in Tarsons spinot digital magnetic stirrers under standard conditions. Analytical thin layer chromatography (TLC) was carried out on Merck silica gel $60F_{254}$ plates using short wave (254 nm) UV light. Column chromatography purifications were performed over silica gel (100-200 mesh) and ethyl acetate/hexane as eluent. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM ECS NMR spectrometer (400 MHz and 100 MHz respectively) using $CDCl_3$ as solvent and TMS as internal standard. The raw data of NMR were processed by MestReNova software. Chemical shifts (δ) are reported in ppm relative to the residual peak of the solvent ($CDCl_3$: ^{1}H NMR, δ = 7.25 ppm and sometimes δ = 1.56 ($CDCl_3$-water); and ^{13}C NMR, δ = 77.0 ppm) and TMS (0 ppm). Multiplicities are indicated as: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet) and br (broad). Coupling constants (*J* values) are given in hertz (Hz). HRMS data were recorded *via* electron spray ionization with a Q-TOF mass analyzer. Single crystal X-

ray diffractions were collected on a Bruker SMART APEX-II CCD diffractometer using Mo Kα (λ = 0.71073 Å) radiation. Melting points were determined with a Buchi-535 apparatus and were not corrected. All chemicals used were purchased commercially and used without further purification until specified. Solvents used for extraction and chromatographic separations were distilled prior to use.

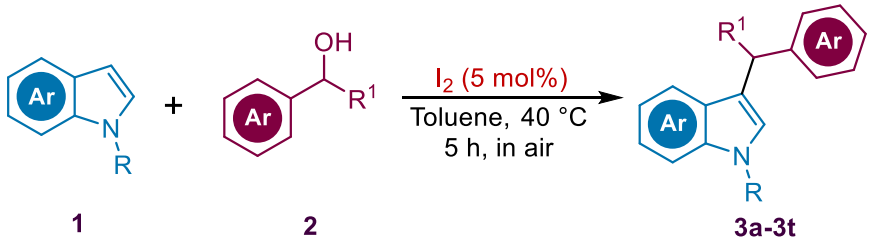
2.4.2 Synthesis of Primary and Secondary Benzyl Alcohols



2

In a round-bottom flask placed in ice-bath, aldehyde/ketone (3 mmol) was dissolved in ethanol (5 mL), to which $NaBH_4$ (6 mmol) was added in portions and stirred for 1 h. After completion of reaction (confirmed by TLC), the reaction mixture was quenched with saturated NH_4Cl solution and extracted with ethyl acetate and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was passed over a short column to give the corresponding primary and secondary benzyl alcohols (**2**) from the reduction of aldehydes and ketones respectively.

2.4.3 General Procedure for C3-Benzylation of Indoles with Benzyl Alcohols

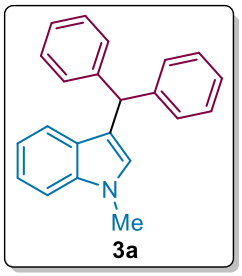


1 **2** **3a-3t**

A round-bottom flask was charged with indole **1** (1 mmol) and benzyl alcohol **2** (1.2 mmol) in presence of 5 mol% (0.05 mmol, 0.0126 g) I_2 in toluene (2 mL) at 40 °C for 5 h. After completion of reaction (confirmed by TLC), the reaction mixture was quenched with saturated solution of sodium thiosulfate ($Na_2S_2O_3 \cdot 5H_2O$) and extracted with ethyl acetate and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography to give the desired products **3a**-**3t**.

2.5 Characterization Data of the Products

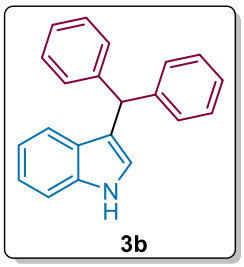
3-Benzhydryl-1-methyl-1H-indole



3a

Obtained as white solid, 252 mg, 85% yield; mp 142-144 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.26–7.18 (m, 13H), 6.97-6.92 (m, 1H), 6.35 (s, 1H), 5.64 (s, 1H), 3.64 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$), δ (ppm): 144.1, 137.4, 129.0, 128.7, 128.2, 127.4, 126.1, 121.6, 120.0, 118.8, 118.3, 109.1, 48.8, 32.6.

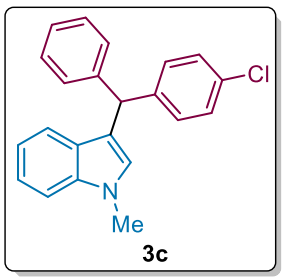
3-Benzhydryl-1H-indole



3b

Obtained as white solid, 246 mg, 87% yield; mp 121-123 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.94 (s, 1H), 7.35 (d, J = 8.2 Hz, 1H), 7.30-7.14 (m, 12H), 6.98 (t, J = 7.3 Hz, 1H), 6.57 (s, 1H), 5.67 (s, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$), δ (ppm): 143.9, 136.7, 135.7, 129.0, 128.3, 127.0, 126.2, 124.0, 122.1, 119.9, 119.4, 111.0, 48.8.

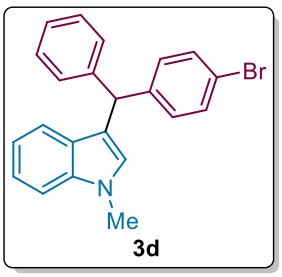
3-[(4-Chlorophenyl)(phenyl)methyl]-1-methyl-1H-indole



3c

Obtained as colorless liquid, 292 mg, 88% yield; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.30-7.14 (m, 12H), 6.98 (t, J = 7.3 Hz, 1H), 6.38 (s, 1H), 5.63 (s, 1H), 3.69 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$), δ (ppm): 143.6, 142.6, 137.4, 131.9, 130.3, 128.9, 128.7, 128.4, 127.1, 126.4, 121.8, 119.8, 118.9, 117.7, 109.2, 48.1, 32.7.

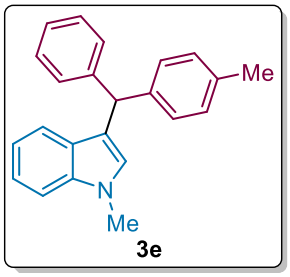
3-[(4-Bromophenyl)(phenyl)methyl]-1-methyl-1H-indole



3d

Obtained as colorless liquid, 312 mg, 83% yield; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.38 (d, J = 8.7 Hz, 2H), 7.27-7.25 (m, 3H), 7.20-7.17 (m, 5H), 7.09 (d, J = 8.2 Hz, 2H), 6.97 (t, J = 8.2 Hz, 1H), 6.38 (s, 1H), 5.60 (s, 1H), 3.67 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$), δ (ppm): 143.5, 143.2, 137.5, 131.3, 130.7, 128.9, 128.7, 128.4, 127.2, 126.4, 121.8, 120.0, 119.8, 118.9, 117.7, 109.2, 48.2, 32.6.

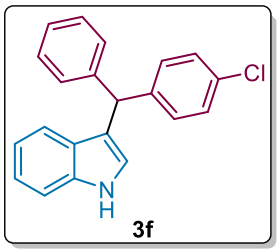
1-Methyl-3-[phenyl(p-tolyl)methyl]-1H-indole



3e

Obtained as colorless liquid, 280 mg, 90% yield; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.27-7.15 (m, 8H), 7.09 (q, J = 8.2 Hz, 4H), 6.96 (t, J = 7.8 Hz, 1H), 6.39 (s, 1H), 5.63 (s, 1H), 3.68 (s, 3H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$), δ (ppm): 144.4, 141.1, 137.5, 135.6, 129.0, 128.9, 128.7, 128.2, 127.4, 126.1, 121.6, 120.0, 118.8, 118.5, 109.1, 48.4, 32.6, 21.0.

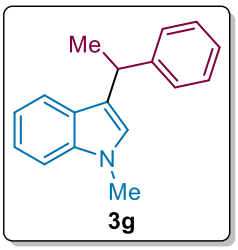
3-[(4-Chlorophenyl)(phenyl)methyl]-1H-indole



3f

Obtained as colorless liquid, 276 mg, 87% yield; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.96 (br s, 1H), 7.34 (d, J = 8.2 Hz, 1H), 7.29-7.13 (m, 11H), 6.98 (t, J = 7.8 Hz, 1H), 6.54 (s, 1H), 5.62 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$), δ (ppm): 143.4, 142.4, 136.7, 132.0, 130.3, 128.9, 128.4, 126.8, 126.4, 124.0, 122.2, 119.8, 119.5, 119.4, 111.1, 48.2.

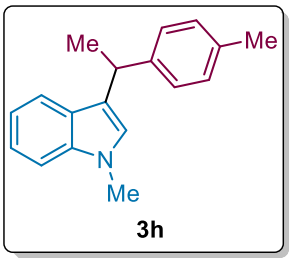
1-Methyl-3-(1-phenylethyl)-1H-indole



3g

Obtained as colorless liquid, 183 mg, 78% yield; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.36 (d, J = 7.8 Hz, 1H), 7.30-7.24 (m, 5H), 7.21-7.14 (m, 2H), 6.99 (t, J = 7.8 Hz, 1H), 6.82 (s, 1H), 4.36 (q, J = 6.9 Hz, 1H), 3.73 (s, 3H), 1.69 (d, J = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$), δ (ppm): 146.9, 137.3, 128.3, 127.4, 127.2, 125.9, 125.8, 121.5, 120.0, 119.7, 118.6, 109.1, 36.9, 32.6, 22.5.

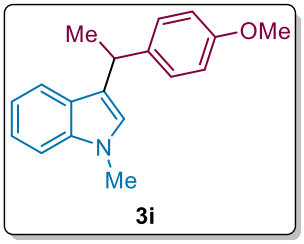
1-Methyl-3-[1-(p-tolyl)ethyl]-1H-indole



3h

Obtained as a colorless liquid, 206 mg, 83% yield; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.38 (d, J = 7.8 Hz, 1H), 7.25 (t, J = 8.2 Hz, 1H), 7.17 (t, J = 7.8 Hz, 3H), 7.07 (d, J = 7.8 Hz, 2H), 6.99 (t, J = 7.3 Hz, 1H), 6.82 (s, 1H), 4.33 (q, J = 6.9 Hz, 1H), 3.73 (s, 3H), 2.30 (s, 3H), 1.67 (d, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$), δ (ppm): 143.9, 137.3, 135.2, 129.0, 127.3, 127.2, 125.8, 121.4, 120.1, 119.7, 118.5, 109.0, 36.4, 32.6, 22.6, 21.0.

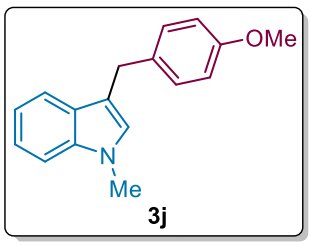
3-[1-(4-Methoxyphenyl)ethyl]-1-methyl-1H-indole



3i

Obtained as colorless liquid, 233 mg, 88% yield; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.36 (d, J = 8.2 Hz, 1H), 7.26-7.14 (m, 4H), 6.99 (t, J = 7.3 Hz, 1H), 6.82-6.79 (m, 3H), 4.32 (q, J = 6.9 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 1.66 (d, J = 7.3 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$), δ (ppm): 157.7, 139.1, 137.3, 128.3, 127.2, 125.8, 121.4, 120.3, 119.8, 118.5, 113.6, 109.0, 55.2, 36.0, 32.6, 22.6.

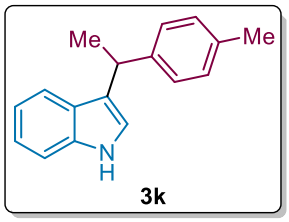
3-(4-Methoxybenzyl)-1-methyl-1H-indole



3j

Obtained as colorless liquid, 208 mg, 83% yield; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.51 (d, J = 7.8 Hz, 1H), 7.27 (d, J = 8.2 Hz, 1H), 7.23-7.18 (m, 3H), 7.06 (t, J = 7.3 Hz, 1H), 6.82 (d, J = 8.2 Hz, 2H), 6.72 (s, 1H), 4.04 (s, 2H), 3.78 (s, 3H), 3.71 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$), δ (ppm): 157.7, 137.1, 133.5, 129.5, 127.8, 127.0, 121.5, 119.2, 118.7, 114.7, 113.7, 109.1, 55.2, 32.5, 30.6.

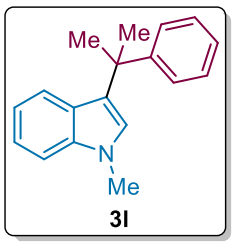
3-[1-(p-Tolyl)ethyl]-1H-indole



3k

Obtained as colorless liquid, 193 mg, 82% yield; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.88 (br s, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 8.2 Hz, 1H), 7.18-7.15 (m, 2H), 7.12 (d, J = 7.3 Hz, 1H), 7.07 (d, J = 7.8 Hz, 2H), 6.99 (t, J = 7.3 Hz, 2H), 4.33 (q, J = 7.3 Hz, 1H), 2.29 (s, 3H), 1.68 (d, J = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$), δ (ppm): 143.8, 136.6, 135.3, 129.0, 127.3, 126.9, 121.9, 121.7, 121.0, 119.7, 119.1, 111.0, 36.5, 22.5, 21.0.

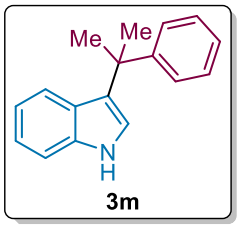
1-Methyl-3-(2-phenylpropan-2-yl)-1H-indole



3l

Obtained as colorless liquid, 229 mg, 92% yield; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.35 (d, J = 7.3 Hz, 2H), 7.25 (q, J = 8.2 Hz, 3H), 7.14 (q, J = 7.3 Hz, 2H), 7.04 (d, J = 8.2 Hz, 1H), 6.94 (s, 1H), 6.86 (t, J = 7.3 Hz, 1H), 3.77 (s, 3H), 1.76 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$), δ (ppm): 150.0, 137.7, 127.9, 126.4, 125.50, 125.46, 124.5, 121.3, 121.1, 118.3, 109.1, 38.9, 32.6, 30.7.

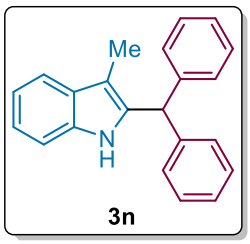
3-(2-Phenylpropan-2-yl)-1H-indole



3m

Obtained as colorless liquid, 211 mg, 90% yield; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.83 (br s, 1H), 7.35-7.29 (m, 3H), 7.25-7.20 (m, 2H), 7.16-7.03 (m, 4H), 6.86 (t, J = 7.8 Hz, 1H), 1.76 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$), δ (ppm): 149.9, 137.1, 128.0, 126.4, 126.1, 126.0, 125.5, 121.6, 121.3, 120.5, 118.8, 111.0, 38.9, 30.6.

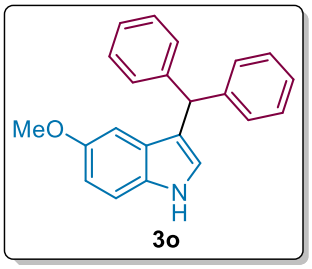
2-Benzhydryl-3-methyl-1H-indole



3n

Obtained as colorless liquid, 237 mg, 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.54 (d, J = 8.7 Hz, 1H), 7.46 (s, 1H), 7.33-7.09 (m, 14H), 5.77 (s, 1H), 2.17 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$), δ (ppm): 142.1, 135.2, 135.1, 129.4, 129.0, 128.7, 126.8, 121.3, 119.2, 118.4, 110.6, 108.2, 48.5, 8.6.

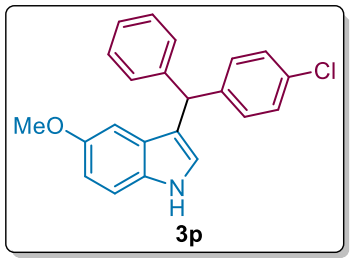
3-Benzhydryl-5-methoxy-1H-indole



3o

Obtained as colorless liquid, 260 mg, 83% yield; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.85 (br s, 1H), 7.30-7.20 (m, 11H), 6.82 (dd, J = 8.7, 2.3 Hz, 1H), 6.62 (d, J = 2.3 Hz, 1H), 6.55 (d, J = 1.4 Hz, 1H), 5.61 (s, 1H), 3.65 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$), δ (ppm): 153.7, 143.8, 131.8, 129.0, 128.3, 127.4, 126.2, 124.8, 119.6, 112.1, 111.7, 101.9, 55.8, 48.8. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{22}H_{20}NO$ is 314.1545; found 314.1538.

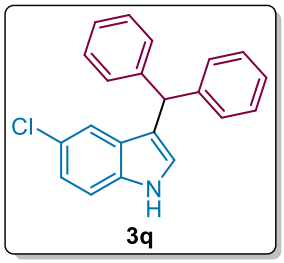
3-[(4-Chlorophenyl)(phenyl)methyl]-5-methoxy-1H-indole



3p

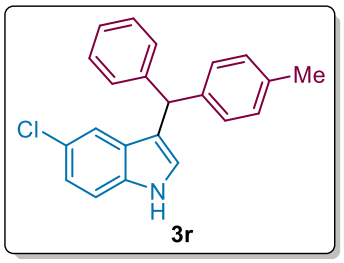
Obtained as colorless liquid, 264 mg, 76% yield; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.07 (br s, 1H), 7.35-7.11 (m, 11H), 6.86 (dd, J = 8.7, 2.3 Hz, 1H), 6.49 (s, 1H), 5.81 (s, 1H), 3.85 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$), δ (ppm): 154.2, 143.4, 142.2, 133.3, 130.9, 130.3, 128.9, 128.63, 128.58, 128.4, 127.9, 126.5, 124.8, 112.3, 111.7, 102.3, 55.8, 48.2. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calculated for $C_{22}H_{19}ClNO$ is 348.1155; found 348.1122.

3-Benzhydryl-5-chloro-1H-indole



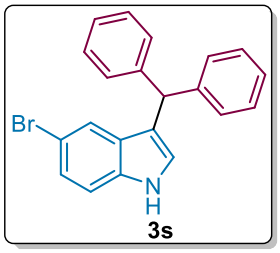
Obtained as colorless liquid, 254 mg, 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.97 (br s, 1H), 7.30-7.19 (m, 12H), 7.11 (dd, J = 8.2, 1.4 Hz, 1H), 6.58 (s, 1H), 5.60 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$), δ (ppm): 143.5, 135.0, 128.9, 128.4, 128.1, 126.4, 125.4, 125.1, 122.5, 119.7, 119.2, 112.0, 48.5. HRMS (ESI/Q-TOF) *m/z*: $[M-H]^+$ calculated for $C_{21}H_{15}ClN$ is 316.0893; found 316.0862.

5-Chloro-3-[phenyl(p-tolyl)methyl]-1H-indole



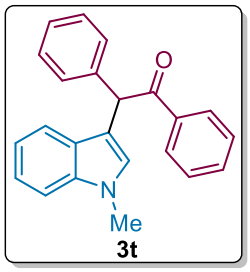
Obtained as colorless liquid, 285 mg, 86% yield; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.96 (br s, 1H), 7.29-7.19 (m, 7H), 7.12 (d, J = 2.3 Hz, 1H), 7.09 (s, 4H), 6.60 (s, 1H), 5.56 (s, 1H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$), δ (ppm): 143.7, 140.5, 135.9, 135.0, 129.1, 128.8, 128.7, 128.3, 128.1, 126.3, 125.3, 125.1, 122.4, 119.9, 119.3, 112.0, 48.1, 21.0.

3-Benzhydryl-5-bromo-1H-indole



Obtained as colorless liquid, 264 mg, 73% yield; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.96 (br s, 1H), 7.35 (s, 1H), 7.30-7.19 (m, 12H), 6.57 (s, 1H), 5.60 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$), δ (ppm): 143.5, 135.3, 128.9, 128.7, 128.4, 126.4, 125.2, 125.0, 122.3, 119.6, 112.7, 112.5, 48.5.

2-(1-Methyl-1H-indol-3-yl)-1,2-diphenylethan-1-one



Obtained as orange liquid, 227 mg, 70% yield; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.05 (d, J = 7.3 Hz, 2H), 7.49 (t, J = 7.3 Hz, 2H), 7.38 (t, J = 8.2 Hz, 4H), 7.29 (t, J = 7.3 Hz, 3H), 7.21 (t, J = 6.4 Hz, 2H), 7.07 (t, J = 7.3 Hz, 1H), 6.88 (s, 1H), 6.27 (s, 1H), 3.68 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$), δ (ppm): 198.4, 139.1, 137.2, 136.9, 132.9, 129.0, 128.8, 128.6, 128.5, 128.4, 127.0, 121.9, 119.3, 118.8, 112.7, 109.4, 50.5, 32.8. HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ calculated for $C_{23}H_{20}NO$ is 326.1545; found 326.1525.

2.6 X-Ray Crystallography Details

Methods to cultivate the crystals of 3a: Solid **3a** (~10 mg) was dissolved in 2 mL acetonitrile-chloroform (1:1) solvent system in a small glass vial. Slow evaporation of this solution at rt produced the fine crystals after two days that were analyzed by X-ray crystallography.

Single crystal X-ray diffraction: Bruker SAINT software has been employed for reducing the data and SADABS for correcting the intensities of absorption. Structure was solved and refined using SHELXL with anisotropic displacement parameters for non-H atoms. C–H atoms were fixed geometrically using the HFIX command in SHELX-TL. No any missed symmetry observed in the final check of CIF file using PLATON. Crystallographic parameters for the structure are furnished in Table **2.4**.

Table 2.4 Crystallographic parameters of structures **3a**

Crystal data	**3a**
Formula unit	$C_{22}H_{19}N$
Formula weight (g mol^{-1})	297.38
Crystal system	orthorhombic
T [K]	296
a [Å]	7.854(4)
b [Å]	22.091(12)
c [Å]	9.597(5)
α [°]	90
β [°]	90
γ [°]	90
Volume [Å^3]	1665.0(15)
Space group	$Pna2_1$
Z	4
D_{cal} [g/cm^3]	1.186
R_1, wR_2	0.0678, 0.1224
Instrument	Bruker CCD Apex II
CCDC Number	1893717

ORTEP diagram for compound 3a: Figure **2.2** shows the Oak Ridge Thermal Ellipsoid Plot (ORTEP) with 50% probability ellipsoid for compound **3a.**

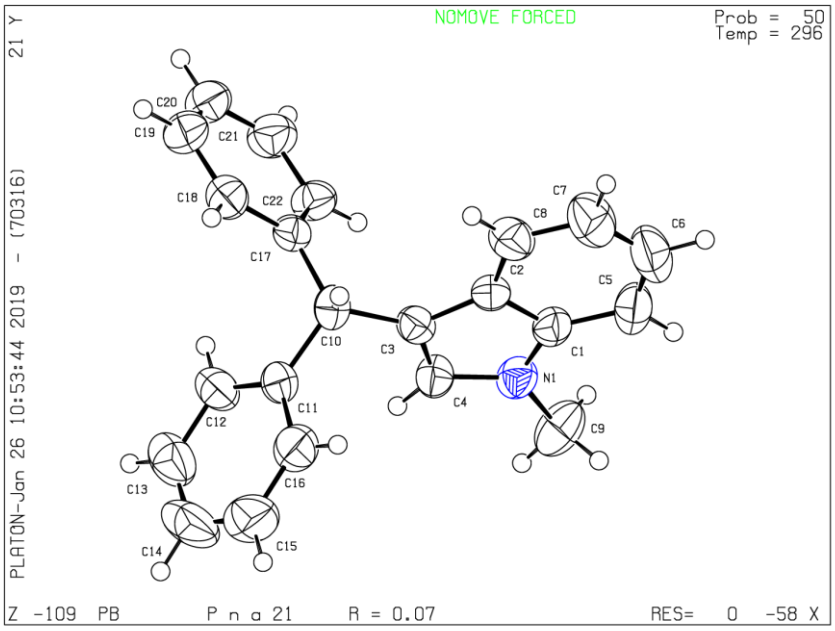


Figure 2.2 ORTEP of **3a** with 50% probability ellipsoids

2.7 Representative HRMS spectra

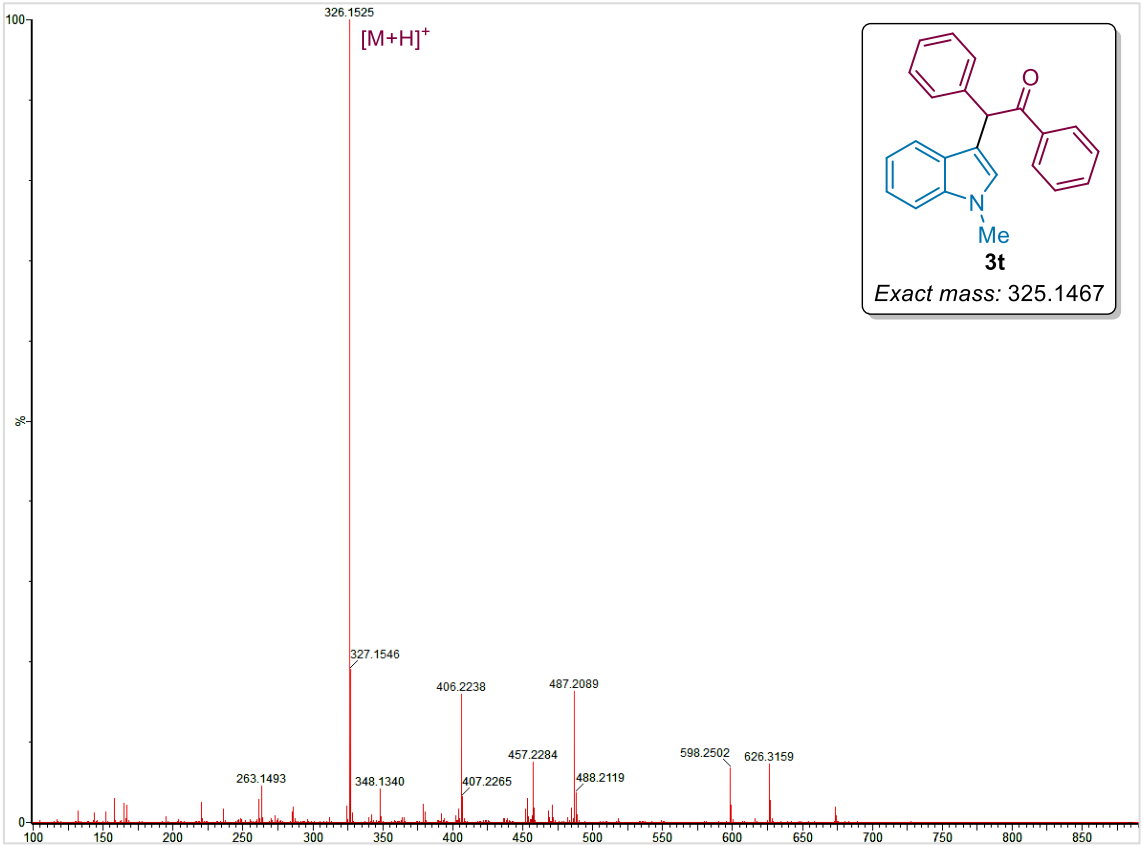


Figure 2.3 HRMS spectrum of **3t**

2.8 Representative ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra

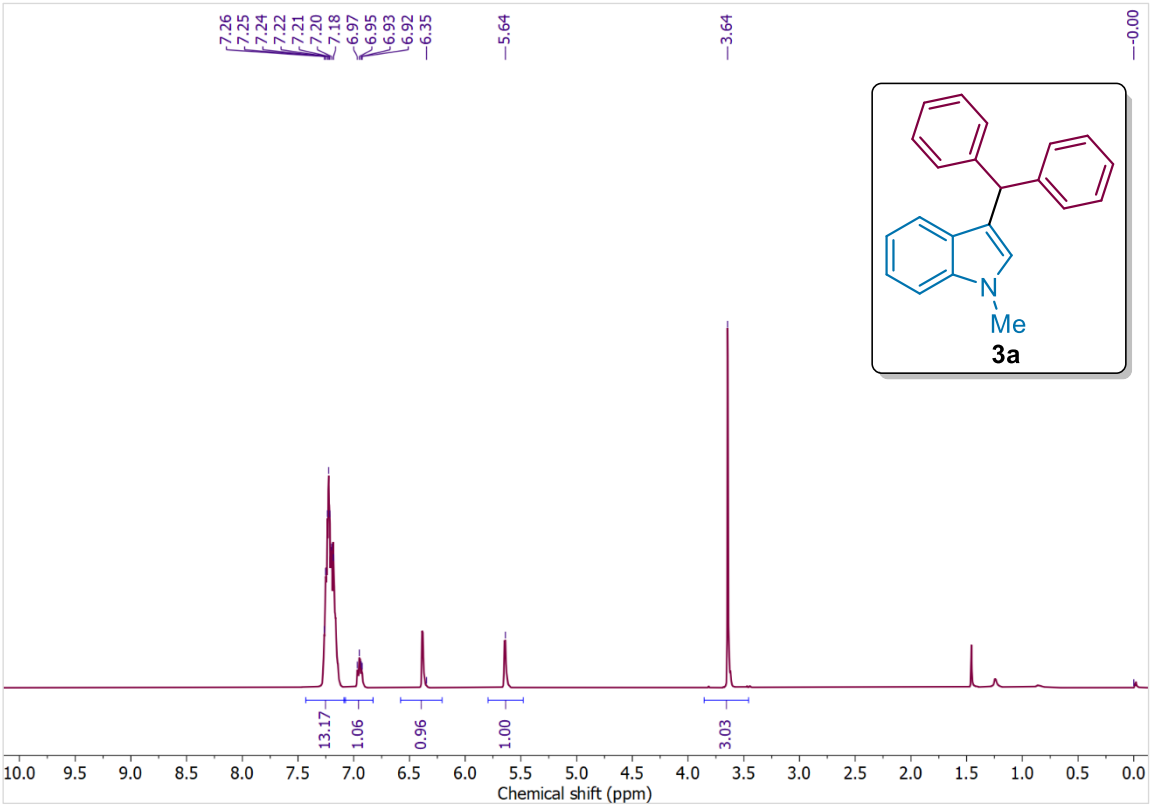


Figure 2.4 ^{1}H NMR (400 MHz) spectrum of **3a** in $CDCl_3$

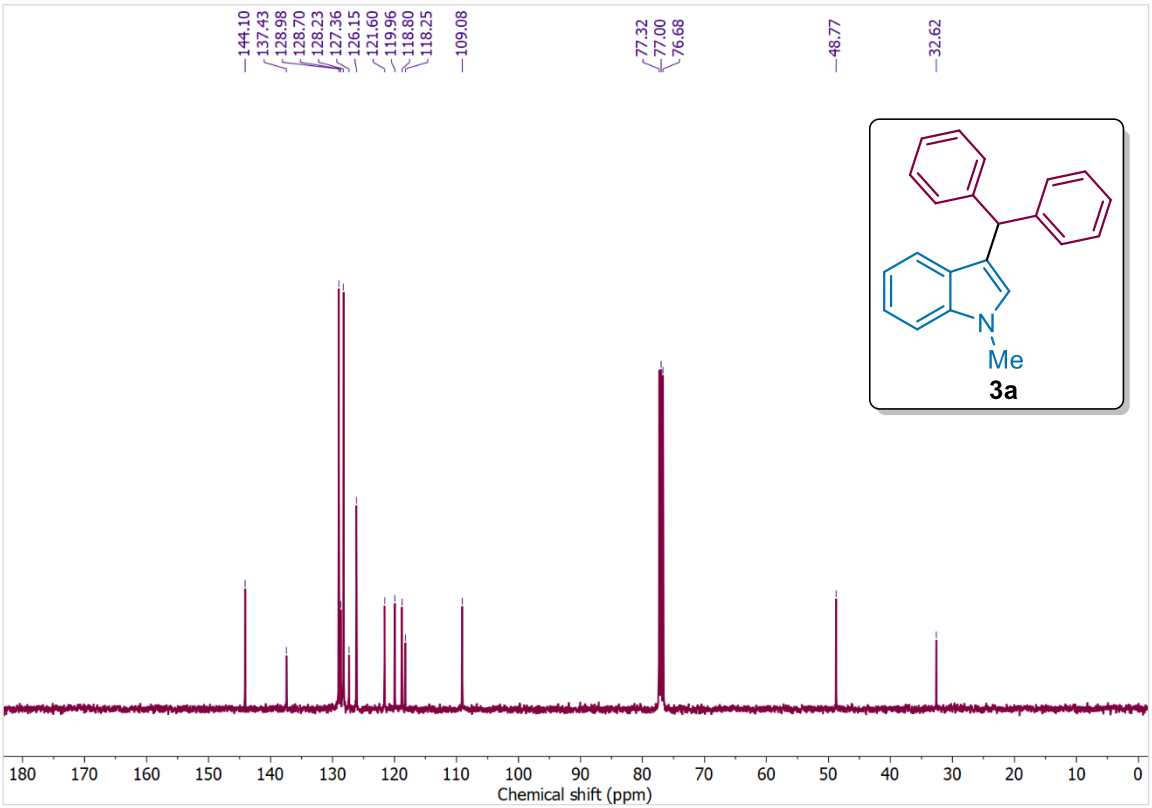


Figure 2.5 $^{13}C\{^{1}H\}$ NMR (100 MHz) spectrum of **3a** in $CDCl_3$

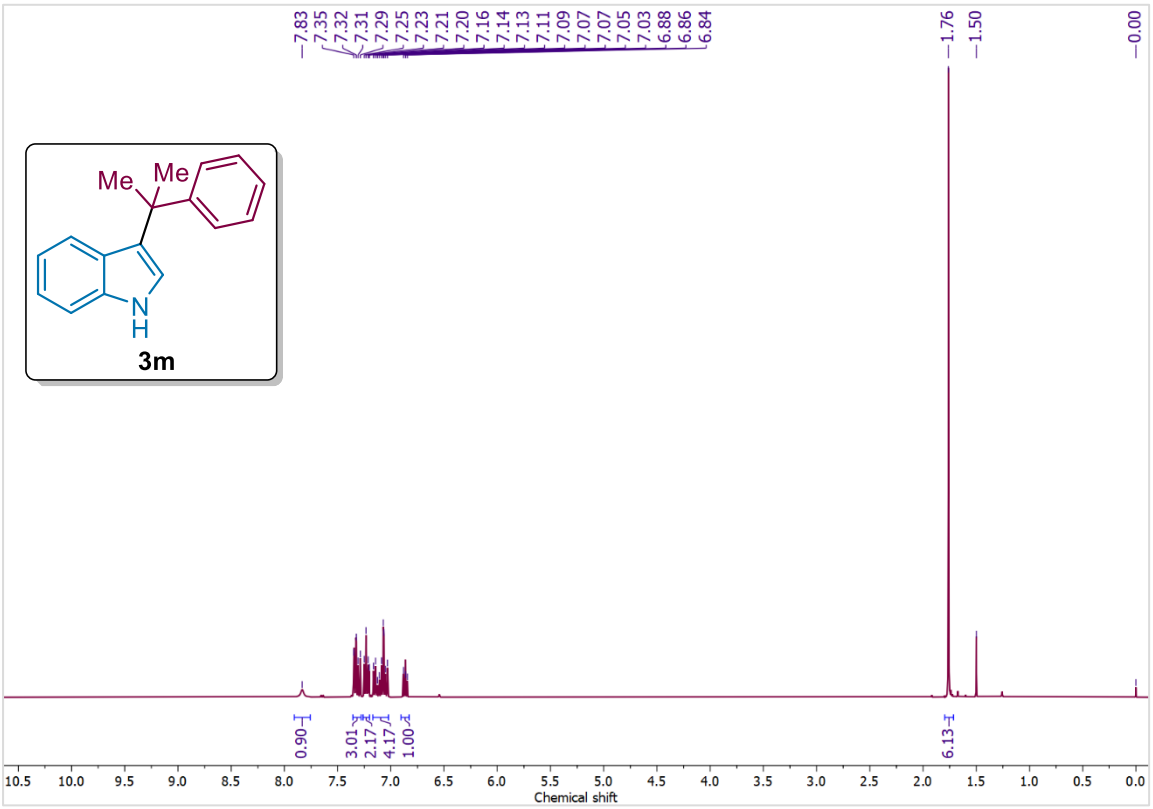


Figure 2.6 ^{1}H NMR (400 MHz) spectrum of **3m** in $CDCl_3$

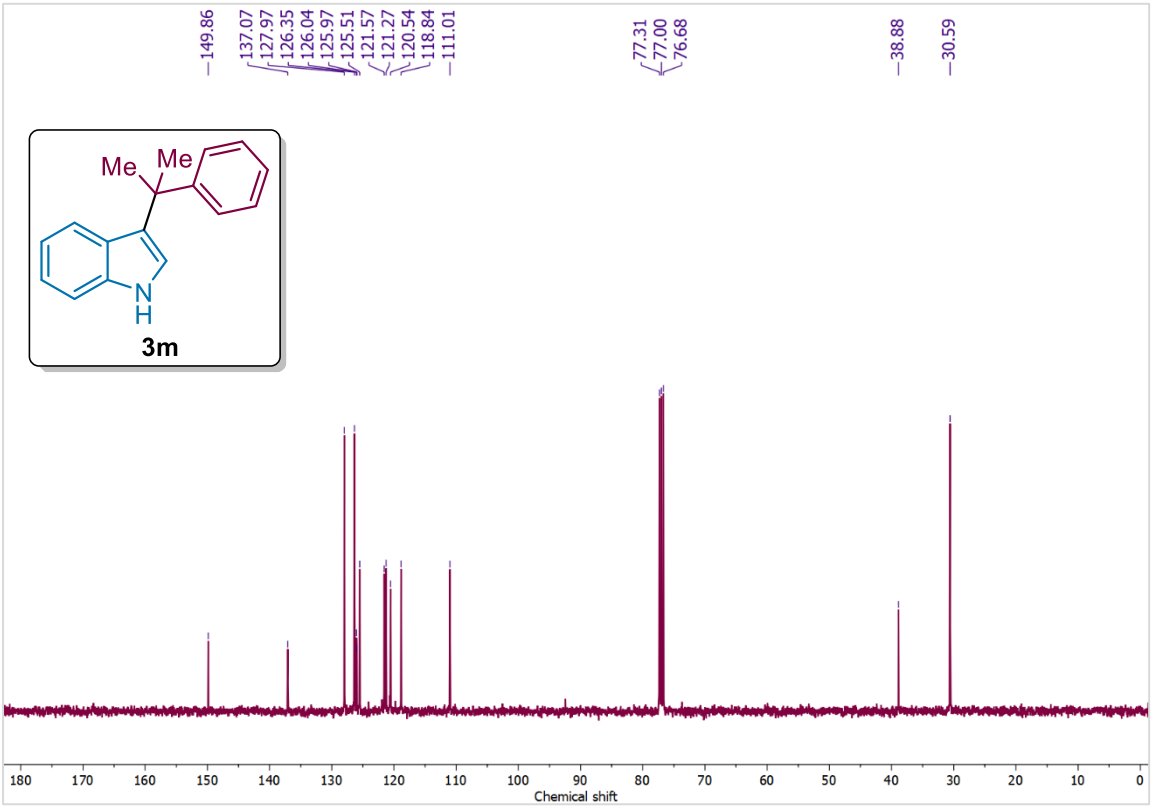


Figure 2.7 $^{13}C\{^{1}H\}$ NMR (100 MHz) spectrum of **3m** in $CDCl_3$

2.9 Bibliography

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and external ligand free conditions. *Advanced Synthesis & Catalysis*, 355(7):1308-1314, 2013.

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