A Platinum Open Access Journal for Organic Chemistry

Paper

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Acid-catalysed N-alkylation of anilines with activated 1-*H*-indanol

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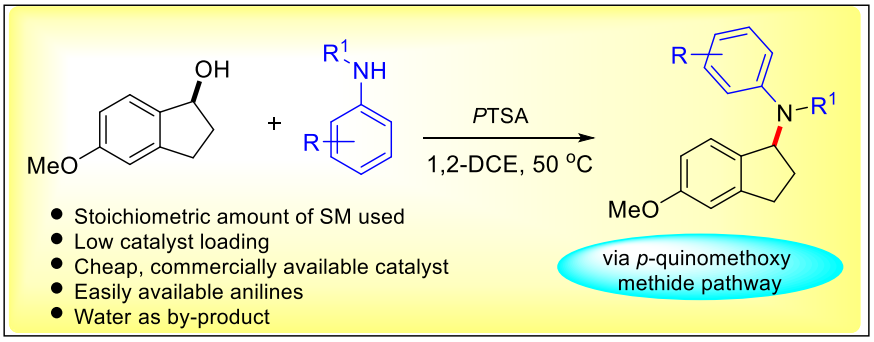
Received 12-10-2023 **Accepted Manuscript** 02-02-2024 **Published on line** 02-07-2024

Abstract

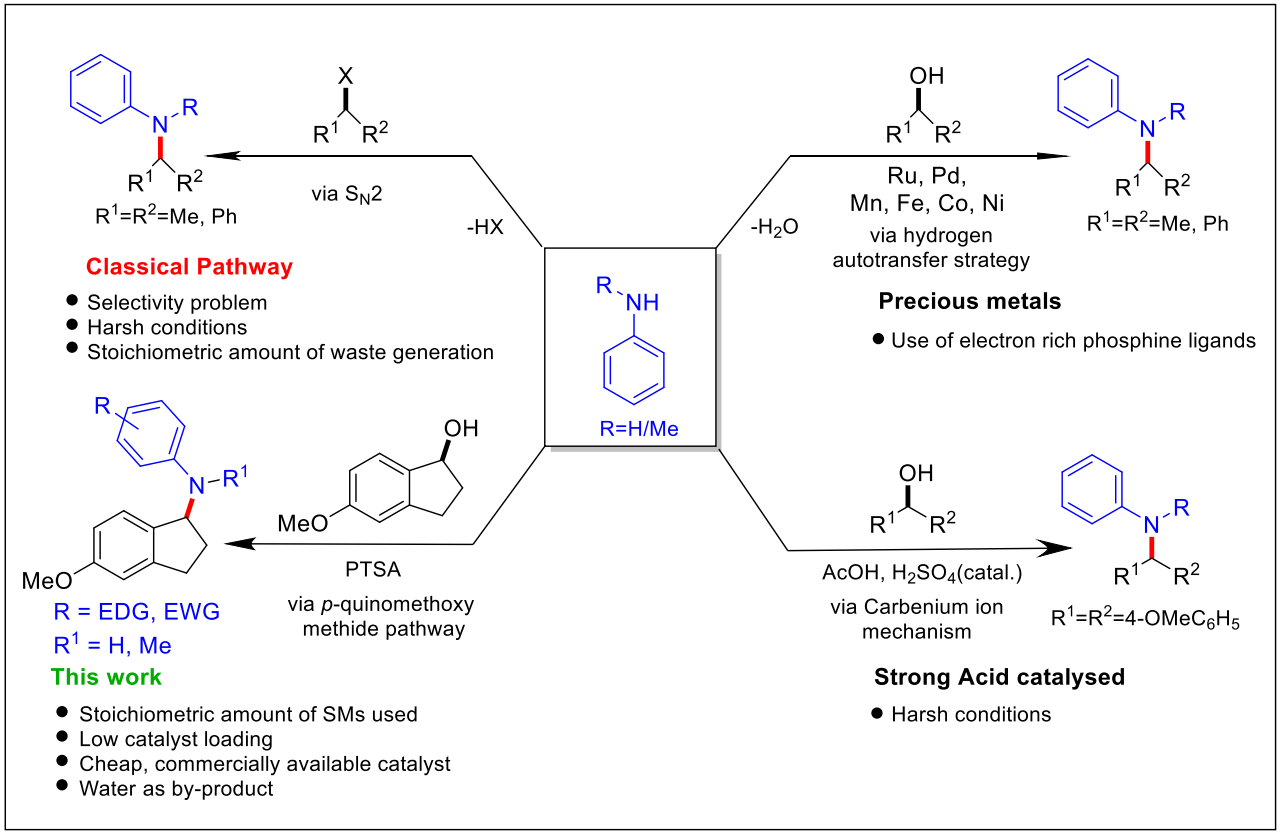
We describe here the acid-catalysed reaction of anilines with activated indanol using the inexpensive catalyst p-toluenesulfonic acid (*p*-TSA). Various electron-donating as well as electron-withdrawing anilines are reacted with activated indanol. The reaction mechanism suggests the *in-situ* formation of a *p*-quinomethoxy methide intermediate, followed by the nucleophilic attack of the substituted or unsubstituted anilines.



Keywords: Acid-catalyzed, indanol, anilines, N-alkylation.

Introduction

It is well known that secondary and tertiary alkylated amines form the basic framework in many organic synthesis reactions which can further be functionalized to form useful agrochemicals, drug molecules, and functional materials.[1] Numerous methods have been developed in this regard, but most important challenge is to reduce the problems of low selectivity and formation of the unwanted products.[2] In pursuit of solving these problems, alcohols have been used for the N-alkylation of amines instead of alkyl halides.[3] This has recently been of considerable interest due to its greener and atom economical approach towards the synthesis of N-alkylated compounds.[4] The first N-alkylation of amines with alcohols was reported in 1981 by Grigg *et.al* using a ruthenium-phosphine complex catalyst, $[RuH(PPh_3)_4]$.[5] Subsequently, a variety of catalysts based on transition metals such as Ru,[6,7] Fe,[8-11] Ni,[12] Ir,[13] Co,[14] Mn,[15] etc. have been developed for this reaction. However, these reactions have many drawbacks such as use of expensive ligands, catalysts that are poorly recyclable, and excess amounts of alcohols to obtain satisfactory yields. In the presence of sub-stoichiometric amounts of base, many complex catalysts such as η^5- $[(IrCl_2Cp^*)_2]$ were used for these N-alkylation reactions.[16-19] A Co/Rh heterobimetallic catalytic system was then developed by Chung *et. al* for the N-alkylation of alcohols without the use of a base or any additive.[20] N-alkylation under harsh conditions such as using strong acids like H_2SO_4 has also been reported.[21] More recently, secondary alcohols have been selectively N-alkylated with amines via hydrogen auto-transfer strategy using Ni(II)-pincer complex as a catalyst.[22] A variety of other transition metal catalysts such as $[Ru_3(CO)_{12}]$, $Pt(cod)Cl_2$, etc. have been reported to catalyse this reaction via the hydrogen auto-transfer strategy.[23] Re_2O_7 mediated reaction has been reported to chemoselectively catalyse C-benzylation of unprotected anilines.[24] Recently, our group also reported the α-benzylation of methyl enol ethers using activated benzyl alcohols as an electrophile source and the reaction has been proposed to proceed via the *in-situ* generation of quinomethoxy methide intermediate.[25] There are a variety of primary and secondary alcohols which have been used as substrates for alkylating amines for a long time. The indane system is an attractive scaffold of two fused rings (one aromatic and the other non-aromatic) forming a rigid system and is commonly found in natural products such as pterosins,[26] indanomycin,[27] and stawamycin.[28] This indane bicyclic core structure is present in many drugs,[29] and have also been used as organic catalysts and ligands.[30,31] Amines, being one of the most vital classes of compounds in chemistry owing to their omnipresence in a wide variety of natural products and other biologically important compounds, the exploration of catalytic methodologies for efficient C-N bond formation is of utmost importance. To the best of our knowledge, apart from these diverse biological and catalytic applications, the amination of activated indanols has not been explored. Herein, we have explored the N-alkylation of anilines with activated indanol using *p*-toluenesulfonic acid as the catalyst. Our approach not only avoids the formation of stoichiometric amounts of by-products but is also environmentally benign since the by-product is water (Scheme 1).

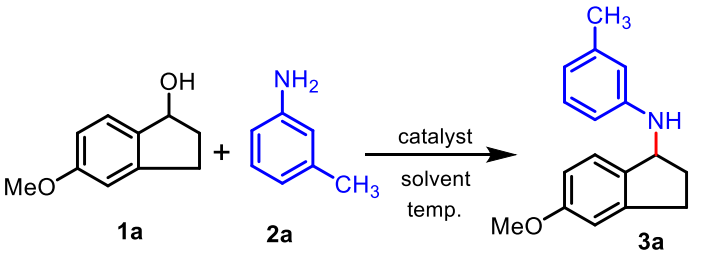


Scheme 1. Strategies for N-alkylation of anilines.

Results and Discussion

In the search of the optimum conditions for this N-alkylation reaction, 5-methoxy-2,3-dihydro-1H-inden-1-ol (**1a**) and m-toluidine (**2a**) were chosen as the benchmark substrates. Initially, the reaction was carried out at 60 ˚C using 20 mol % $ZnBr_2$ as the Lewis acid catalyst in 1,2-dichloromethane and it resulted in the desired product **3a** in 68% yield in 3 hours (entry 1, Table 1). However, when the catalyst was changed to $ZnCl_2$ keeping other parameters same, the yield dropped drastically to 16% (entry 2, Table 1) and in case of ZnI_2, there was no sign of any product formation (by TLC monitoring) (entry 3, Table 1). Under the same reaction conditions, using $FeCl_3$ as the catalyst led to the decomposition of the starting material (entry 4, Table 1), which was also observed in the case of $BF_3.OEt_2$ (entry 5, Table 1). Keeping the other reaction conditions intact and using the Bronsted acid catalyst *p*TSA at room temperature, 20% yield of the desired product **3a** was obtained (entry 6, Table 1). Increasing the temperature to 40 ˚C resulted in the desired product **3a** in 5 hours with 69% yield (entry 7, Table 1). On further increasing the reaction temperature to 50 ˚C, a decrease in reaction time along with an improvement in yield to 78% was observed (entry 8, Table 1). Aiming for further yield improvement, the reaction was also tried using 1,2-DCE under refluxing condition and the desired product **3a** was obtained in 45% yield (entry 9, Table 1). On changing the catalyst from *p*TSA to its pyridinium salt, *p*-PTS under identical reaction conditions, the yield dropped to 13% (entry 10, Table 1). Hence, *p*-TSA in 1,2-DCE was found to be the best optimum reaction condition (78%, entry 8, Table 1).

Table 1. Optimization of reaction conditions[a]

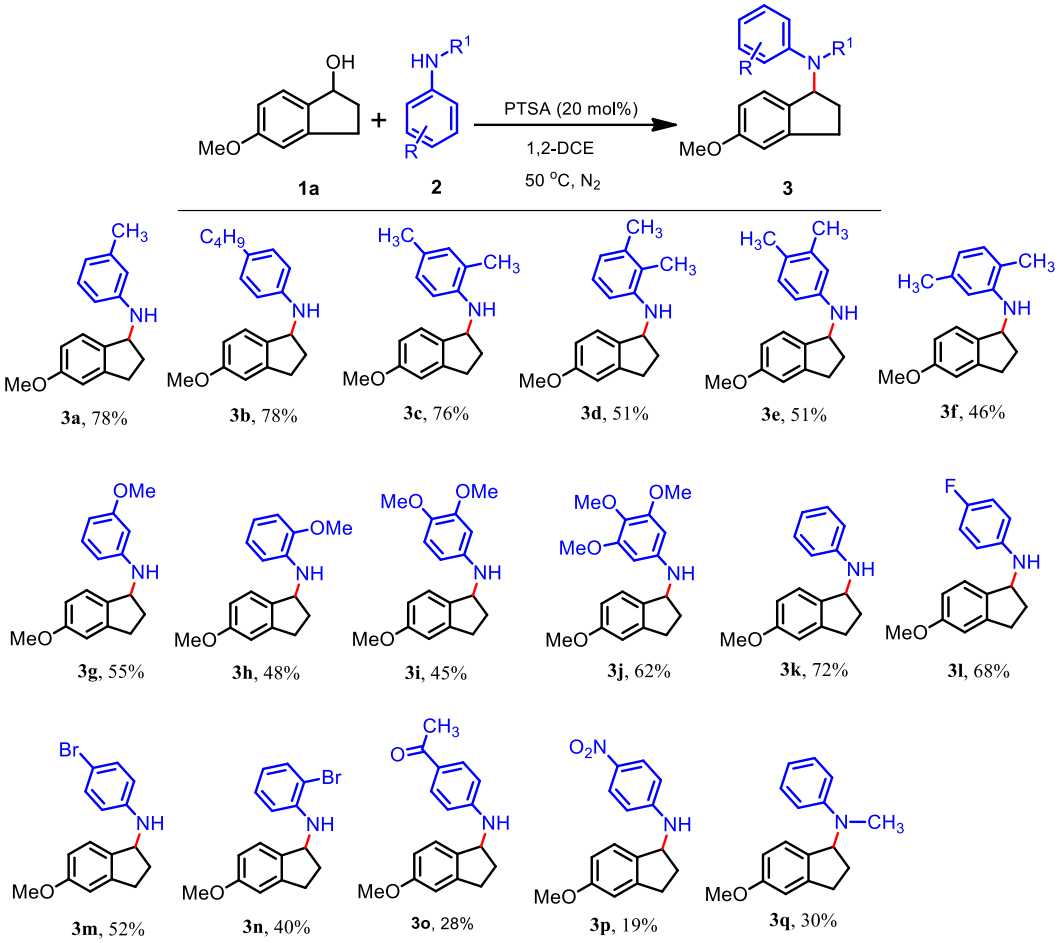


Entry	Solvent	Temperature (°C)	Catalyst (20 mol %)	Time	Yield
1	1,2-DCE	60	$ZnBr_2$	3h	68%
2	1,2-DCE	60	$ZnCl_2$	2h	16%
3	1,2-DCE	60	ZnI_2	2h	--[(a)]
4	1,2-DCE	60	$FeCl_3$	3h	--[(b)]
5	1,2-DCE	60	$BF_3.OEt_2$	3h	--[(b)]
6	1,2-DCE	rt	*p*TSA	3h	20%
7	1,2-DCE	40	*p*TSA	5h	69%
8	1,2-DCE	50	*p*TSA	2.5h	78%
9	1,2-DCE	reflux	*p*TSA	3h	45%
10	1,2-DCE	50	*P*PTS	3h	13%

[a]Reaction conditions: **1a =** 1.0 equiv, **2a** = 1.0 equiv, catalyst = 20 mol %, 1,2-DCE (3 mL) (a) = no product formation, (b) = SM decomposed

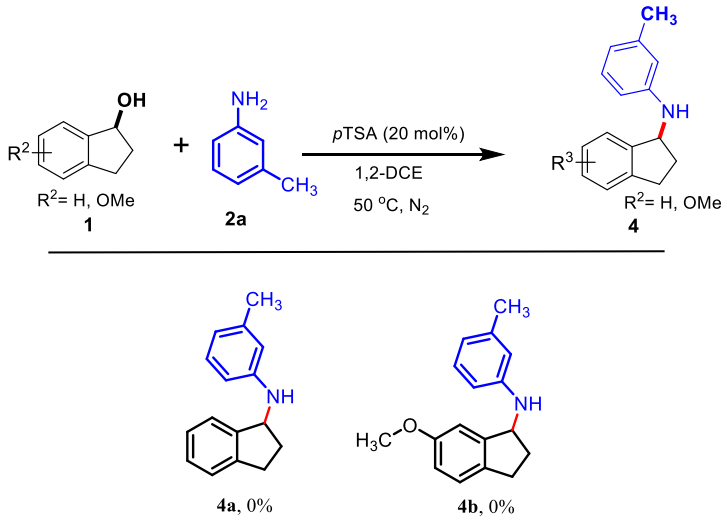
Having optimized reaction conditions, we then began investigating the scope of this reaction (Table 2). Initially, the scope of anilines were explored using 5-methoxy-2,3-dihydro-1H-inden-1-ol (**1a**) as the prime model secondary alcohol. We examined a variety of substituted anilines with electron-donating and electron-withdrawing substituents as well as with protected anilines. First, alkyl substituted anilines such as m-toluidine (Table 2, **2a**) and *p*-butyl aniline (Table 2, **2b**) were N-alkylated with the model indanol under the standard optimized reaction conditions, affording the products **3a** and **3b** in good yield (Table 2). Next, dialkyl substituted anilines were reacted and found to give good to moderate yields of the desired N-alkylated products (Table 2, **3c**-**3f**). Other electron rich anilines having methoxy substituent like *m*-methoxy aniline and *o*-methoxy aniline also afforded the desired N-alkylated product in 55% (Table 2, **3g**) and 48% (Table 2, **3h**) yield respectively. 3,4-dimethoxy aniline and 3,4,5-trimethoxyaniline afforded the desired products in 45% and 62% yield (Table 2, **3i**-**3j**). Aniline itself was successfully N-alkylated to give 72% yield of the desired product (Table 2, **3k**). It was observed that halogen-substituted anilines such as 4-fluoroaniline (**2l**), 4-bromoaniline (**2m**), and 2-bromoaniline (**2n**) also reacted to furnish the desired N-alkylated products in good to moderate yields (Table 2, **3l**-**3n**). Anilines with electron-withdrawing groups were also reacted with our model indanol. For example, *p*-acetyl aniline (**2o**) afforded the N-alkylated product **3o** in 28% yield. A highly electron-deficient *p*-nitro aniline (**2p**) was also N-alkylated forming 19% of the desired product (Table 2, **3p**). The scope of protected aniline such as N-methyl aniline (**2q**) reacted with the model indanol (**1a**) to furnish the desired products in 30% yield (Table 2).

Table 2. Substrate scope of anilines

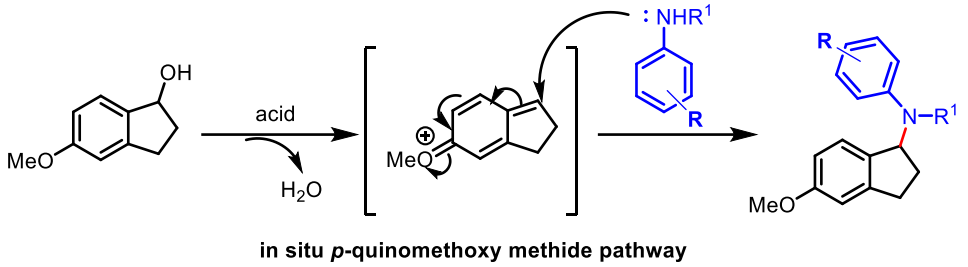


Next, the substrate scope of secondary alcohols were studied with the model amine **2a** (*m*-toluidine) and it was found that the alcohols which did not have a methoxy group at the *para* position (Table 3, **4a**, and **4b**) did not react to furnish the desired product in our developed condition.

Table 3. Substrate scope of alcohols



Thus, we can infer that the presence of the methoxy group at the *para* position is necessary for this reaction to furnish the desired product. This implies that the reaction might proceed via the formation of a *p*-quinomethoxy methide intermediate which is then substituted by the nucleophilic attack of the aniline (Scheme 2).[25]



Scheme 2. Plausible mechanism.

A deuterium exchange experiment was also conducted in an NMR tube, with the N-alkylated product **3k** to substantiate the presence of a free proton attached to the nitrogen atom (see supporting information Fig 1). All the products have been properly characterized using ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), HRMS, and IR spectroscopy. In the synthesized products (**3a**-**3p**), the significant ^{1}H characteristic peak of the N-attached indanol C-H proton appears at ≈ δ 4.9 ppm and the ^{13}C NMR characteristic peak of the N-attached indanol C-H carbon appears at ≈ δ 57-59 ppm.

Conclusions

In summary, a new route for the N-alkylation of amines has been developed using activated indanol in the presence of a readily available Bronsted acid. Various anilines having electron-donating as well as electron-withdrawing groups afforded the desired product in moderate to good yields. Having examined the substrate scope of the alcohols, we also proposed a plausible reaction mechanism, which might proceed via a *p*-quinomethoxy methide pathway. Further, this method can be applicable to study various biological applications.

Experimental Section

General. IR spectra were recorded on FTIR spectrophotometer. ^{1}H NMR spectra were recorded on 400 MHz spectrometer in $CDCl_3$; chemical shifts (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to either internal standard tetramethyl silane (TMS) (δ_H = 0.00 ppm) or $CHCl_3$ (δ_H = 7.25 ppm). ^{13}C NMR spectra were recorded on 100 MHz spectrometer in $CDCl_3$; chemical shifts (δ ppm) are reported relative to $CHCl_3$ [δ_C = 77.00 ppm (central line of triplet)]. In the ^{1}H NMR, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q = quartet, qui =quintet, dd = doublet of doublets, m = multiplet and brs = broad singlet. The assignment of signals was confirmed by ^{1}H, ^{13}C, and DEPT spectra. Melting points were determined on an electrothermal melting point apparatus and are uncorrected. *p*-toluenesulfonic acid was purchased from SRL Pvt. Ltd. and boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) was

purchased from a commercial source and purified immediately before use. 1,2-dichloromethane (1,2-DCE) solvent was dried prior to use by first distilling with P_2O_5 followed by second distillation with calcium hydride under argon. All reactions were performed in an oven-dried apparatus under N_2 atmosphere. Commercial grade solvents were distilled before use. The reactions were monitored by thin-layer chromatography (TLC) on microscopic slides coated with silica gel, and visualization of spots was accomplished by exposure to iodine vapor or by UV radiation. The silica gel (100−200) column chromatography was carried for purification of compounds with various combinations of hexane and EtOAc solvent system as eluent.

General procedure for N-alkylation. To a stirred solution of compounds 5-methoxy-2,3-dihydro-1H-inden-1-ol (**1a)** (20 mg, 0.122 mmol, 1.0 equiv) and m-toluidine (**2a)** (13 mg, 0.122 mmol, 1.0 equiv) in 1,2-DCE (1.5 mL) was added *p*TSA (4.2 mg, 0.024 mmol, 0.2 equiv) at room temperature and the mixture was stirred at 50 ˚C until complete conversion of starting material (monitored by TLC) for 3h. After completion of the reaction, it was diluted with water, and the aqueous layer was extracted with dichloromethane. All organic layers were dried over Na_2SO_4, solvent was evaporated at reduced pressure, and the product was isolated by column chromatography with 2-3% ethyl acetate in petroleum ether as eluent.

5-Methoxy-*N*-(m-tolyl)-2,3-dihydro-1*H*-inden-1-amine (3a). Light yellow liquid (24 mg, 78%), ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34-7.23 (m, 1H), 7.12 (t, *J* 8.1 Hz, 1H), 6.83 (s, 1H), 6.78 (dd, *J* 2.4, 8.3 Hz, 1H), 6.62-6.49 (m, 3H), 4.97 (t, *J* 6.6 Hz, 1H), 3.92-3.75 (m, 4H), 3.00 (dd, *J* 4.9, 8.3 Hz, 1H), 2.94-2.81 (m, 1H), 2.59 (d, *J* 7.3 Hz, 1H), 2.32 (s, 3H), 2.05-1.86 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.9, 147.9, 145.4, 139.1, 136.8, 129.3, 125.0, 118.3, 114.0, 112.8, 110.3, 110.0, 58.0, 55.5, 34.2, 30.5, 21.7. IR ν_{max} (neat): 3393, 2935, 1602, 1491, 1309, 1256, 1172, 1032, 770 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{20}NO$ 254.1539, found 254.1534.

***N*-(4-Butylphenyl)-5-methoxy-2,3-dihydro-1*H*-inden-1-amine (3b).** Compound **3b** was prepared by following general procedure A by treating 5-methoxy-2,3-dihydro-1H-inden-1-ol **1a** (50 mg, 0.305 mmol, 1.0 equiv) and amine **2b** (45 mg, 0.305 mmol, 1.0 equiv) in 1,2-DCE (3 mL). Purification of the crude material by silica gel column chromatography using 5-6% ethyl acetate in petroleum ether as an eluent furnished compound **3b** as a yellow liquid (21 mg, 78%). ^{1}H NMR (400 MHz , $CDCl_3$) δ =7.30 (m, 1H), 7.03 (d, *J* 8.3 Hz, 2H), 6.85-6.75 (m, 2H), 6.65 (d, *J* 8.3 Hz, 2H), 4.94 (t, *J* 6.1 Hz, 1H), 3.86-3.69 (m, 4H), 2.99 (dd, *J* 5.1, 8.6 Hz, 1H), 2.91-2.79 (m, 1H), 2.63-2.48 (m, 3H), 2.02-1.88 (m, 1H), 1.58 (quin, *J* 7.6 Hz, 2H), 1.43-1.31 (m, 2H), 0.94 (t, *J* 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ =159.9, 145.7, 145.4, 136.9, 131.8, 129.2, 125.0, 113.2, 112.7, 110.0, 58.2, 55.5, 34.7, 34.2, 34.1, 30.5, 22.4, 14.0. IR ν_{max} (neat): 3395, 2924, 1607, 1506, 1308, 1252, 1032, 815 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{26}NO$ 296.2009, found 296.2003.

***N*-(2,4-Dimethylphenyl)-5-methoxy-2,3-dihydro-1*H*-inden-1-amine (3c).** Compound **3c** was prepared by following general procedure A by treating 5-methoxy-2,3-dihydro-1H-inden-1-ol **1a** (50 mg, 0.305 mmol, 1.0 equiv) and amine **2c** (37 mg, 0.305 mmol, 1.0 equiv) in 1,2-DCE (3 mL). Purification of the crude material by silica gel column chromatography using 2% ethyl acetate in petroleum ether as an eluent furnished the compound **3c** as a brown solid (62 mg, 76%). Mp = 62 ˚C. ^{1}H NMR (400 MHz ,$CDCl_3$) δ = 7.33 (d, *J* 8.3 Hz, 1H), 7.01 (d, *J* 8.3 Hz, 1H), 6.95 (s, 1H), 6.86 (s, 1H), 6.78 (d, *J* 8.3 Hz, 1H), 6.82 (d, *J* 8.3 Hz, 1H), 5.00 (t, *J* 6.4 Hz, 1H), 3.85 (s, 3H), 3.03 (dd, *J* 5.1, 8.6 Hz, 1H), 2.92 (d, *J* 7.8 Hz, 1H), 2.71-2.59 (m, 1H), 2.29 (s, 3H), 2.12 (s, 3H), 2.03-1.89 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.0, 145.5, 143.5, 137.1, 131.2, 127.4, 126.0, 125.0, 122.2, 112.8, 110.6, 110.0, 58.2, 55.5, 34.5, 30.5, 20.4, 17.7. IR ν_{max} (neat): 3420, 2925, 1608, 1506, 1259, 1302, 808 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{18}H_{21}NONa$ 290.1515, found 290.1528.

***N*-(2,3-Dimethylphenyl)-5-methoxy-2,3-dihydro-1*H*-inden-1-amine (3d).** Compound **3d** was prepared by following general procedure A by treating 5-methoxy-2,3-dihydro-1H-inden-1-ol **1a** (50 mg, 0.305 mmol, 1.0 equiv) and amine **2d** (37 mg, 0.305 mmol, 1.0 equiv) in 1,2-DCE (3 mL). Purification of the crude material by

silica gel column chromatography using 2-3% ethyl acetate in petroleum ether as an eluent furnished the compound **3d** as a red solid (48 mg, 51%). Mp = 67-70 ˚C. ^{1}H NMR (400 MHz ,$CDCl_3$) δ =7.28 (d, *J* 8.3 Hz, 1H), 7.05 (t, *J* 7.8 Hz, 1H), 6.84-6.80 (m, 1H), 6.77 (dd, *J* 2.2, 8.1 Hz, 1H), 6.71 (d, *J* 7.8 Hz, 1H), 6.61 (d, *J* 7.3 Hz, 1H), 4.96 (t, *J* 6.4 Hz, 1H), 3.82-3.76 (m, 3H), 2.98 (dd, *J* 4.9, 8.8 Hz, 1H), 2.92-2.78 (m, 1H), 2.67-2.55 (m, 1H), 2.28 (s, 3H), 2.00 (s, 3H), 1.97-1.87 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ =160.0, 145.7, 145.6, 137.0, 136.8, 126.3, 125.1, 120.3, 119.3, 112.9, 110.0, 108.7, 58.2, 55.5, 34.6, 30.6, 20.8, 12.7. IR ν_{max} (neat): 3531, 2943, 1590, 1480, 1305, 1196, 979, 814 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{22}NO$ 268.1696, found 268.1690.

***N*-(3,4-Dimethylphenyl)-5-methoxy-2,3-dihydro-1*H*-inden-1-amine (3e).** Compound **3e** was prepared by following general procedure A by treating 5-methoxy-2,3-dihydro-1H-inden-1-ol **1a** (50 mg, 0.305 mmol, 1.2 equiv) and amine **2e** (31 mg, 0.254 mmol, 1.0 equiv) in 1,2-DCE (3 mL). Purification of the crude material by silica gel column chromatography using 2-3% ethyl acetate in petroleum ether as an eluent furnished the compound **3e** as a brown solid (41 mg, 51%). Mp = 64-67 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ =7.30 (d, *J* 8.3 Hz, 1H), 7.00 (d, *J* 7.8 Hz, 1H), 6.84 (s, 1H), 6.79 (dd, *J* 2.4, 8.3 Hz, 1H), 6.59-6.55 (m, 1H), 6.52 (dd, *J* 2.4, 8.3 Hz, 1H), 4.96 (t, *J* 6.4 Hz, 1H), 3.87-3.78 (m, 4H), 3.00 (dd, *J* 4.6, 8.6 Hz, 1H), 2.93-2.84 (m, 1H), 2.60 (d, *J* 6.8 Hz, 1H), 2.31-2.15 (m, 6H), 2.00-1.89 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ =159.9, 146.0, 145.4, 137.4, 137.0, 130.4, 125.4, 125.0, 115.1, 112.7, 110.7, 110.0, 58.3, 55.5, 34.3, 30.5, 20.1, 18.7. IR ν_{max} (neat): 3393, 2929, 1610, 1499, 1311, 1253, 1031, 809 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{22}NO$ 268.1696, found 268.1688.

***N*-(2,5-Dimethylphenyl)-5-methoxy-2,3-dihydro-1*H*-inden-1-amine (3f).** Compound **3f** was prepared by following general procedure A by treating 5-methoxy-2,3-dihydro-1H-inden-1-ol **1a** (50 mg, 0.305 mmol, 1.0 equiv) and amine **2f** (37 mg, 0.305 mmol, 1.0 equiv) in 1,2-DCE (3 mL). Purification of the crude material by silica gel column chromatography using 2-3% ethyl acetate in petroleum ether as an eluent furnished the compound **3f** as a reddish-brown liquid (37 mg, 46%). ^{1}H NMR (400MHz , $CDCl_3$) δ = 7.31 (d, *J* 8.3 Hz, 1H), 6.99 (d, *J* 7.3 Hz, 1H), 6.87-6.79 (m, 2H), 6.68 (s, 1H), 6.54 (d, *J* 7.3 Hz, 1H), 5.02 (t, *J* 6.4 Hz, 1H), 3.87-3.81 (m, 3H), 3.70 (br. s., 1H), 3.11-3.00 (m, 1H), 2.97-2.84 (m, 1H), 2.71-2.59 (m, 1H), 2.36 (s, 3H), 2.09 (s, 3H), 2.02-1.91 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ =160.0, 145.7, 145.5, 137.0, 136.8, 130.1, 125.0, 118.9, 117.5, 112.8, 111.2, 110.0, 57.9, 55.5, 34.6, 30.5, 21.7, 17.2. IR ν_{max} (neat): 3531, 3009, 2080, 1594, 1435, 1303, 1032, 801 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{22}NO$ 268.1696, found 268.1686.

5-Methoxy-*N*-(3-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-amine (3g). Compound **3g** was prepared by following general procedure A by treating 5-methoxy-2,3-dihydro-1H-inden-1-ol **1a** (50 mg, 0.305 mmol, 1.0 equiv) and amine **2g** (37.5 mg, 0.305 mmol, 1.0 equiv) in 1,2-DCE (3 mL). Purification of the crude material by silica gel column chromatography using 2-3% ethyl acetate in petroleum ether as an eluent furnished the compound **3g** as a yellowish white liquid (45 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ =7.29 (d, *J* 8.3 Hz, 1H), 7.13 (t, *J* 8.1 Hz, 1H), 6.86-6.75 (m, 2H), 6.37-6.26 (m, 3H), 4.96 (t, *J* 6.4 Hz, 1H), 3.97-3.87 (m, 1H), 3.84-3.80 (m, 6H), 3.08-2.96 (m, 1H), 2.93-2.82 (m, 1H), 2.59 (m, 1H), 2.01-1.91 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ =160.9, 160.0, 149.2, 145.4, 136.6, 130.1, 125.0, 112.8, 110.0, 106.3, 102.4, 99.2, 58.0, 55.5, 55.1, 34.1, 30.5. IR ν_{max} (neat): 3390, 2946, 1603, 1496, 1256, 1208, 1160, 1037, 825 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M-H]^+$ calcd for $C_{17}H_{18}NO_2$ 268.1332, found 268.1327.

5-Methoxy-*N*-(2-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-amine (3h). Compound **3h** was prepared by following general procedure A by treating 5-methoxy-2,3-dihydro-1H-inden-1-ol **1a** (50 mg, 0.305 mmol, 1.0 equiv) and amine **2h** (38 mg, 0.305 mmol, 1.0 equiv) in 1,2-DCE (3 mL). Purification of the crude material by silica gel column chromatography using 3-4% ethyl acetate in petroleum ether as an eluent furnished the compound **3h** as a reddish-brown liquid (39 mg, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37-7.23 (m, 1H), 6.93 (dt, *J* 1.5, 7.6 Hz, 1H), 6.88-6.75 (m, 4H), 6.75-6.67 (m, 1H), 4.98 (t, *J* 6.4 Hz, 1H), 4.48 (br. s., 1H), 3.87-3.76 (m, 6 H), 3.02 (dd, *J* 4.9, 8.8 Hz, 1H), 2.90 (d, *J* 7.8 Hz, 1H), 2.60 (d, *J* 6.8 Hz, 1H), 1.98 (d, *J* 8.8 Hz, 1H). ^{13}C NMR (100

MHz, $CDCl_3$) δ = 159.9, 146.9, 145.5, 137.8, 136.9, 125.1, 121.3, 116.3, 112.7, 110.3, 109.9, 109.6, 57.6, 55.5, 55.4, 34.2, 30.5. IR v_{max} (neat): 3415, 2945, 1601, 1506, 1453, 1303, 1250, 1031, 737 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{20}NO_2$ 270.1489, found 270.1479.

***N*-(3,4-Dimethoxyphenyl)-5-methoxy-2,3-dihydro-1*H*-inden-1-amine (3i).** Compound **3i** was prepared by following general procedure A by treating 5-methoxy-2,3-dihydro-1H-inden-1-ol **1a** (50 mg, 0.305 mmol, 1.2 equiv) and amine **2i** (39 mg, 0.254 mmol, 1.0 equiv) in 1,2-DCE (3 mL). Purification of the crude material by silica gel column chromatography using 10-12% ethyl acetate in petroleum ether as an eluent furnished the compound **3i** as a brown solid (41 mg, 45%). Mp = 80-84 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ =7.25 (d, *J* 8.8 Hz, 1H), 6.82-6.72 (m, 3H), 6.31 (d, *J* 2.4 Hz, 1H), 6.29-6.21 (m, 1H), 4.89 (t, *J* 6.4 Hz, 1H), 3.85-3.77 (m, 9H), 2.96 (dd, *J* 4.9, 8.8 Hz, 1H), 2.86 (d, *J* 8.3 Hz, 1H), 2.55 (d, *J* 6.8 Hz, 1H), 1.92 (d, *J* 8.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.9, 150.1, 145.3, 142.7, 141.6, 136.8, 125.0, 113.4, 112.7, 110.0, 104.2, 99.4, 58.8, 56.8, 55.8, 55.5, 34.1, 30.4. IR v_{max} (neat): 3472, 2947, 1600, 1508, 1302, 1237, 1028, 819 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{18}H_{21}NO_3Na$ 322.1414, found 322.1411.

5-Methoxy-*N*-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1*H*-inden-1-amine (3j). Compound **3j** was prepared by following general procedure A by treating 5-methoxy-2,3-dihydro-1H-inden-1-ol **1a** (30 mg, 0.1829 mmol, 1.0 equiv), *p*-toluene sulfonic acid (*P*TSA) (7 mg, 0.03658 mmol, 0.2 equiv) and amine **2j** (34 mg, 0.1829 mmol, 1.0 equiv) in 1,2-DCE (2 mL). Purification of the crude material by silica gel column chromatography using 24-26% ethyl acetate in petroleum ether as an eluent furnished the compound **3j** as a dark brown liquid (37.4, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ =7.29 (s, 1H), 6.84-6.74 (m, 2 H), 5.95 (s, 2H), 4.92 (t, *J* 6.4 Hz, 1H), 3.86-3.76 (m, 13H), 3.00 (s, 1H), 2.88 (d, *J* 7.8 Hz, 1H), 2.57 (d, *J* 7.3 Hz, 1H), 1.95 (d, *J* 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ =160.0, 154.0, 145.3, 144.6, 136.5, 125.1, 125.0, 113.0, 112.8, 110.0, 109.8, 90.8, 75.9, 61.2, 58.4, 56.0, 55.5, 55.4, 36.3, 34.2, 30.4, 30.0. IR v_{max} (neat): 3379, 2944, 1600, 1494, 1247, 1124, 1025, 810 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{24}NO_4$ 330.1700, found 330.1692.

5-Methoxy-*N*-phenyl-2,3-dihydro-1*H*-inden-1-amine (3k). Compound **3k** was prepared by following general procedure A by treating 5-methoxy-2,3-dihydro-1H-inden-1-ol **1a** (50 mg, 0.305 mmol, 1.0 equiv) and amine **2k** (28 mg, 0.305 mmol, 1.0 equiv) in 1,2-DCE (3 mL). Purification of the crude material by silica gel column chromatography using 2-3% ethyl acetate in petroleum ether as an eluent furnished the compound **3k** as a light-yellow liquid (52.4 mg, 72%). ^{1}H NMR (400 MHz , $CDCl_3$) δ = 7.32 (d, *J* 8.3 Hz, 1H), 7.28-7.22 (m, 2H), 6.86 (s, 1H), 6.83-6.72 (m, 4H), 5.00 (t, *J* 6.4 Hz, 1H), 3.90 (br. s., 1H), 3.85 (s, 3H), 3.03 (dd, *J* 5.1, 8.6 Hz, 1H), 2.96-2.85 (m, 1H), 2.62 (dd, *J* 5.6, 12.5 Hz, 1H), 1.98 (dd, *J* 6.6, 13.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.0, 147.8, 145.4, 136.7, 129.4, 125.0, 117.3, 113.2, 112.8, 110.0, 58.0, 55.5, 34.1, 30.5. IR v_{max} (neat): 3391, 2939, 1602, 1503, 1493, 1304, 1252, 1031, 749, 693 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M]^{2+}$ calcd for $C_{16}H_{17}NO$ 119.5655, found 119.5635.

***N*-(4-Fluorophenyl)-5-methoxy-2,3-dihydro-1*H*-inden-1-amine (3l).** Compound **3l** was prepared by following general procedure A by treating 5-methoxy-2,3-dihydro-1H-inden-1-ol **1a** (50 mg, 0.305 mmol, 1.2 equiv) and amine **2l** (29 mg, 0.254 mmol, 1.0 equiv) in 1,2-DCE (3 mL). Purification of the crude material by silica gel column chromatography using 3-4% ethyl acetate in petroleum ether as an eluent furnished the compound **3l** as a yellow solid (53 mg, 68%). Mp = 84-88 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ =7.31-7.26 (m, 1H), 6.97-6.91 (m, 2H), 6.87-6.77 (m, 2H), 6.69-6.61 (m, 2H), 4.91 (t, *J* 6.4 Hz, 1H), 3.88-3.80 (m, 4H), 3.01 (d, *J* 8.8 Hz, 1H), 2.94-2.84 (m, 1H), 2.64-2.54 (m, 1H), 1.99-1.89 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ =160.0, 157.0, 154.6, 145.4, 144.2, 136.6, 125.0, 115.8 (d, J_{C-F} = 22 Hz), 114.08 (d, J_{C-F} = 7 Hz), 111.4 (d, J_{C-F} = 277 Hz), 58.6, 55.5, 34.0, 30.4. IR v_{max} (neat): 3392, 2948, 1605, 1505, 1256, 1214, 1032, 819 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+NH4(-H_2O)]^+$ calcd for $C_{16}H_{20}FN_2O$ 257.1454, found 257.1437.

***N*-(4-Bromophenyl)-5-methoxy-2,3-dihydro-1*H*-inden-1-amine (3m).** Compound **3m** was prepared by following general procedure A by treating 5-methoxy-2,3-dihydro-1H-inden-1-ol **1a** (50 mg, 0.305 mmol, 1.0 equiv) and amine **2m** (52.4 mg, 0.305 mmol, 1.0 equiv) in 1,2-DCE (3 mL). Purification of the crude material by silica gel column chromatography using 2-3% ethyl acetate in petroleum ether as an eluent furnished the compound **3m** as a light brown solid (50 mg, 52%). Mp = 58-60 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.32 -7.19 (m, 3H), 6.86-6.71 (m, 2H), 6.61-6.53 (m, 2H), 4.89 (t, *J* 6.4 Hz, 1H), 3.89-3.77 (m, 5H), 2.97 (dd, *J* 4.9, 8.3 Hz, 1H), 2.91-2.78 (m, 1H), 2.61-2.47 (m, 1H), 1.97-1.81 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.1, 146.8, 145.4, 136.2, 132.0, 124.9, 114.7, 112.9, 110.0, 108.8, 58.0, 55.5, 33.8, 30.4. IR ν_{max} (neat): 3400, 2941, 1594, 1492, 1306, 1255, 1031, 813 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+K]^+$ calcd for $C_{16}H_{16}BrNOK$ 358.0026, found 358.0028.

N-(2-Bromophenyl)-5-methoxy-2,3-dihydro-1*H*-inden-1-amine (3n). Compound **3n** was prepared by following general procedure A by treating 5-methoxy-2,3-dihydro-1H-inden-1-ol **1a** (100 mg, 0.609 mmol, 1.0 equiv), *p*-Toluenesulfonic acid (21 mg, 0.1218 mmol, 0.2 equiv) and amine **2n** (125.8 mg, 0.609 mmol, 1.0 equiv) in 1,2-DCE (6 mL). Purification of the crude material by silica gel column chromatography using 2% ethyl acetate in petroleum ether as an eluent furnished the compound **3n** as a yellowish white liquid (77 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29-7.21 (m, 1H), 7.09-6.99 (m, 1H), 6.85-6.78 (m, 3H), 6.75 (dd, *J* 2.4, 8.3 Hz, 1H), 6.60-6.54 (m, 1H), 4.89 (s, 1H), 3.83-3.75 (m, 4H), 3.36 (s, 1H), 2.86 (d, *J* 7.8 Hz, 1H), 2.55 (d, *J* 6.8 Hz, 1H), 1.89 (d, *J* 8.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.1, 149.1, 145.4, 136.1, 131.5, 130.6, 125.0, 123.4, 121.1, 120.0, 115.6, 112.9, 112.0, 111.8, 110.3, 110.1, 57.8, 55.5, 39.2, 33.9, 30.5. HRMS (ESI-TOF) *m/z*: $[M]^+$ calcd for $C_{16}H_{16}BrNO$ 317.0415, found 317.0410.

1-(4-((5-Methoxy-2,3-dihydro-1*H*-inden-1-yl)amino)phenyl)ethan-1-one (3o). Compound **3o** was prepared by following general procedure A by treating 5-methoxy-2,3-dihydro-1H-inden-1-ol **1a** (50 mg, 0.305 mmol, 1.0 equiv) and amine **2o** (41 mg, 0.305 mmol, 1.0 equiv) in 1,2-DCE (3 mL). Purification of the crude material by silica gel column chromatography using 2-3% ethyl acetate in petroleum ether as an eluent furnished the compound **3o** as a yellow liquid (10.6 mg, 28%). ^{1}H NMR (400 MHz, $CDCl_3$) δ =7.86-7.80 (m, 2H), 7.26-7.20 (m, 1H), 6.85-6.80 (m, 1H), 6.76 (dd, *J* 2.4, 8.3 Hz, 1H), 6.68-6.61 (m, 2H), 5.02 (t, *J* 6.4 Hz, 1H), 3.84-3.80 (m, 3H), 2.99 (dd, *J* 4.9, 8.8 Hz, 1H), 2.90-2.86 (m, 2H), 2.59 (d, *J* 6.8 Hz, 1H), 2.50 (s, 3 H), 2.01-1.88 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ =196.3, 160.2, 151.7, 145.4, 135.5, 130.9, 126.7, 124.9, 113.0, 111.8, 110.1, 57.5, 55.5, 33.9, 30.5, 26.0. IR ν_{max} (neat): 3344, 2950, 1594, 1274, 1178, 825 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{20}NO_2$ 282.1489, found 282.1480.

5-Methoxy-*N*-(4-nitrophenyl)-2,3-dihydro-1*H*-inden-1-amine (3p). Compound **3p** was prepared by following general procedure A by treating 5-methoxy-2,3-dihydro-1H-inden-1-ol **1a** (50 mg, 0.305 mmol, 1.0 equiv) and amine **2p** (42 mg, 0.305 mmol, 1.0 equiv) in 1,2-DCE (3 mL). Purification of the crude material by silica gel column chromatography using 2-3% ethyl acetate in petroleum ether as an eluent furnished the compound **3p** as a yellow solid (17 mg, 19%). Mp = 122-124 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.10 (d, *J* 9.3 Hz, 2 H), 6.85-6.76 (m, 2H), 6.62 (d, *J* 9.3 Hz, 2H), 5.03 (d, *J* 5.9 Hz, 1H), 4.71 (d, *J* 7.3 Hz, 1H), 3.82-3.76 (m, 4H), 3.09-3.01 (m, 1H), 2.92 (d, *J* 7.3 Hz, 1H), 2.67-2.60 (m, 1H), 2.09-1.93 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.4, 152.7, 145.5, 134.7, 126.5, 124.9, 113.2, 111.4, 110.2, 57.7, 55.5, 33.7, 30.5. IR ν_{max} (neat): 3370, 2942, 2168, 1597, 1307, 1110, 833 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{17}N_2O_3$ 285.1234, found 285.1226.

5-Methoxy-*N*-methyl-*N*-phenyl-2,3-dihydro-1*H*-inden-1-amine (3q). Compound **3q** was prepared by following general procedure A by treating 5-methoxy-2,3-dihydro-1H-inden-1-ol **1a** (50 mg, 0.305 mmol, 1.0 equiv) and amine **2q** (32.6 mg, 0.305 mmol, 1.0 equiv) in 1,2-DCE (3 mL). Purification of the crude material by silica gel column chromatography using 2-3% ethyl acetate in petroleum ether as an eluent furnished the compound **3q** as a yellow liquid (22.7 mg, 30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ =7.30-7.24 (m, 1H), 7.09 (d, *J* 8.3 Hz, 1H), 6.91 (d, *J* 7.8 Hz, 2H), 6.83-6.70 (m, 3H), 5.47 (t, *J* 7.6 Hz, 1H), 3.88-3.76 (m, 4H), 2.94 (d, *J* 3.9 Hz, 1H), 2.96 (d, *J* 3.9 Hz,

1H), 2.90-2.80 (m, 1H), 2.62 (s, 3H), 2.41 (td, *J* 4.0, 8.6 Hz, 1H), 2.06-1.91 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ =159.7, 150.7, 145.1, 134.9, 129.2, 125.4, 116.8, 113.4, 112.8, 109.9, 63.7, 55.4, 32.3, 30.6, 28.7. IR ν_{max} (neat): 3526, 2948, 1595, 1305, 1032, 968 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{20}NO$ 254.1539, found 254.1529

Acknowledgements

We gratefully acknowledge the Science and Engineering Research Board (SERB, CRG/2022/004763), India, for financial support. A. G and T. K. J thanks IIT Hyderabad for providing facilities. S. A. Z. A thanks DST-INSPIRE, India, for the award of PhD fellowship.

Supplementary Material

Copies of ^{1}H and ^{13}C NMR spectra of all newly synthesized compounds and the deuterium experiment are given in the supplementary material file associated with this manuscript.

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