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General Transition Metal-free Synthesis of NH-Pyrroles from Secondary Alcohols and 2-Aminoalcohols

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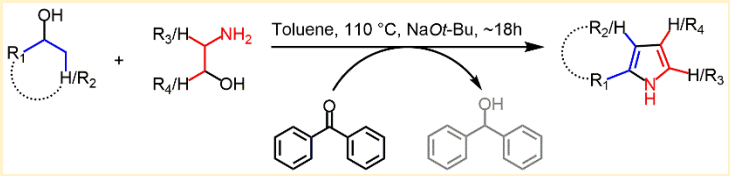
ABSTRACT: A novel, transition-metal free and one pot methodology to synthesize various substituted NH-pyrroles from readily available building blocks such as secondary alcohols and 2-aminoalcohols is described. The process is based on the venerable Oppenauer–Woodward oxidation which uses benzophenone as an inexpensive reagent to achieve oxidation of secondary alcohols under mild condition to ketones, further *in situ* condensation with aminoalcohol and oxidative cyclization to the target pyrrole ring. The reaction occurs under basic conditions, and features a broad substrate scope combined with very good tolerance for sensitive functional-groups. This method can be used to synthesize various substituted pyrroles useful as a starting material for broad applications.

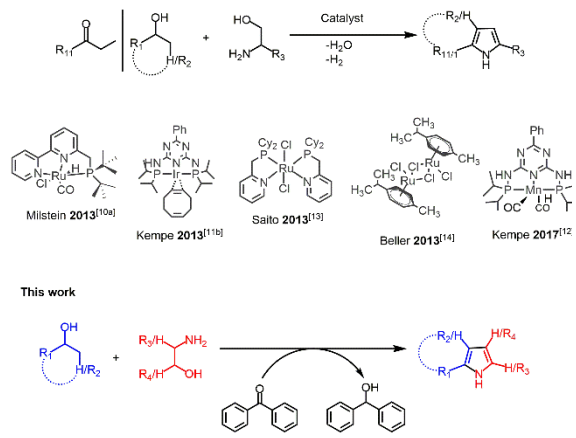


INTRODUCTION

The synthesis of functionalized pyrroles over the past decade has received considerable attention. These heterocycles are crucial starting materials for the synthesis of dyes, porphyrins, and many other functional materials. [1] Pyrroles are important motifs in some modern drugs with antibacterial, [2] antifungal [3] and anti-inflammatory properties. [4] Drugs like Atorvastatin (lipid-lowering agent), Ketorolac (nonsteroidal anti-inflammatory drug) and Sunitinib (anti-cancer) are some medicinally important derivatives of pyrroles. [5] Due to the importance of these pyrrole derivatives, it is necessary to develop sustainable methodologies that preferably are transition metal free, one-pot, and one step. Well known classical methods like the Hantzsch, [6] Knorr, [7] and Paal–Knorr [8] reactions are available for pyrrole synthesis but there are some limitations *e.g.* the Knorr method is limited in scope, usually works only with activated ketones and the yields are low, while other methods have issues with availability of starting materials, regiospecificity, multistep synthetic operation, compatibility etc. Therefore, the direct synthesis of pyrroles using readily available starting materials like alcohols or ketones seems to be the preferred choice. In 1980 Trofimov *et al*. described a simple method to synthesize pyrroles from alkyl or cyclic oximes and acetylene, as well other alkynes as inexpensive starting materials. This method is effective, but it suffers from several drawbacks such as selectivity due to formation of substantial amounts of N-vinyl pyrrole as a side product, [9a] a modern version of Trofimov is also well known. [9b] In recent years' various strategies have been developed, one of them being dehydrogenation of secondary alcohols to ketones *in situ* and then condensation/coupling with β-amino alcohols. In this regard, a very sophisticated and attractive catalytic dehydrogenative method was reported by Milstein (Scheme 1, top). [10a] This method is

called acceptorless dehydrogenation, it uses pincer ruthenium catalysts and potassium tert-butoxide to dehydrogenate the secondary alcohol to a ketone accompanied with hydrogen and water liberation. Then in the presence of β-amino alcohol, condensation occurs into imino-alcohol, and the next step involves subsequent dehydrogenation of alcohol from imino-alcohol to aldehyde or ketone *in situ*, which then leads to the desired pyrrole formation under the basic conditions. Methods using acceptorless dehydrogenation of alcohols as well as borrowing hydrogen methodology [11a] for pyrrole synthesis were reported very recently from Michlik and Kempe. [11b] These methods use iridium complex PN_5P-Ir and Ir@SiCN nanoparticles as a catalyst system to obtain 2,5- and 2,3,5-substituted pyrroles in very high yield. [12] Moreover, in the same line methodology Saito and co-workers [13] and Beller research group [14] were able to synthesize various pyrroles starting from enolizable ketones, diols and primary amines or ammonia. Despite these advances in pyrrole synthesis using very advanced transition metal catalyst systems, the following challenging issues still remain: development of environmentally benign synthetic strategies, access to various substituted pyrroles without using expensive transition metals and ligands which in many cases are not commercially available and need to be synthesized in multi-step procedures. Another important issue is the possible contamination of drug products with heavy metals. Therefore, based on new regulations such as USP <232> and USP <233> [15] such procedures for drug development are not recommended. Herein, we report a new method for pyrrole synthesis based on the venerable Oppenauer–Woodward oxidation. [16] The mechanism proposed by Milstein and others in general can be affected by the Oppenauer oxidation. This method is used very rarely to oxidise secondary alcohols to ketones and even less for the transformation of primary alcohols to aldehydes, because aldol condensation and Tischtschenko reactions cause the formation of undesired side products. The Oppenauer oxidation can be considered the opposite of the

Scheme 1. Synthesis of pyrroles from ketones or secondary alcohols and β-amino alcohols using transition metal catalyst (top), transition metal free pyrrole synthesis using benzophenone as an oxidant (bottom).



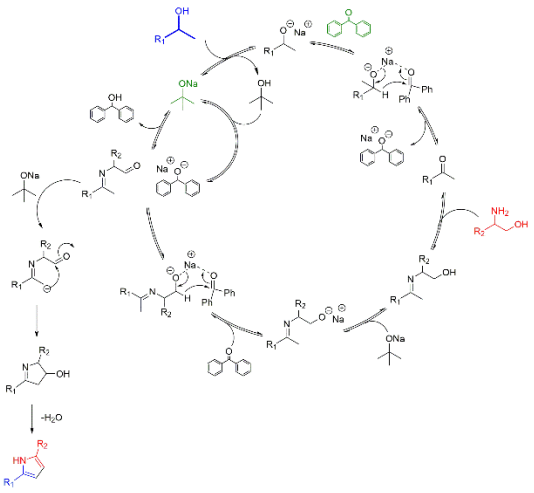
Meerwein–Ponndorf–Verley reaction, [17] depending on the position of the equilibrium, which is controlled by the oxidation potential of the carbonyl compounds involved. Usually, ketones or aldehydes with higher oxidation potential are employed for this purpose. The product can be obtained by removing the reduced alcohol from the solution.

RESULT AND DISCUSION

Based on these facts mentioned above we hypothesized that by using sodium tert-butoxide and benzophenone as a hydride acceptor, it is possible to oxidize secondary alcohols to ketones and then in the presence of amino alcohol condense to an imino-alcohol. The reaction equilibrium in this case can shift to the right, because the ketone is converted to the imine. The oxidation process proceeds in the same way for the alcohol functional group on the iminoalcohol resulting in the formation of a carbonyl compound which under basic conditions can be cyclized to the pyrrole ring (Scheme 2). Thus, we screened the reaction with sodium tert-butoxide as a base which deprotonates and coordinates to

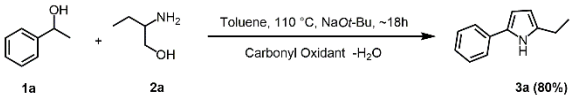
the reacting alcohol enabling hydride transfer to carbonyl compound, we have observed that

Scheme 2. Plausible mechanism of pyrrole synthesis via Oppenauer–Woodward oxidation of alcohols and selective C-C, C-N bond formation.

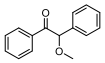
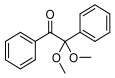
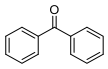
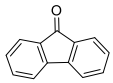


2,5-disubstituted pyrrole forms in fair to good yield (Table 1, top). From the literature we know that the reaction equilibrium is controlled by the oxidation potential of the carbonyl compound, [18] therefore we screened various ketones from higher to lower oxidation potential (Table 1, bottom). To optimize the reaction's conditions, as a model we have chosen 1-phenylethanol **1a**, NaOtBu as a base, 2-amino-1-butanol **2a**, and benzophenone **4e** which was found from preliminary screening to be the best hydride acceptor (Table 1, Entry 5). All carbonyl compounds that we have selected are non enolizable ketones. From screening we found that the oxidation potential of the ketone is very important. If the oxidation potential is too high, like that of benzoin methyl ether **4b**, the performance of the reaction drops drastically. The reason behind this could be that: 1) the oxidant forms a stable imine with β-amino alcohol, because of the presence of a very strong electron donating group at the α carbon in **4b**, 2) the oxidation of alcohol from β-amino alcohol **2a** to aldehyde takes place before the secondary alcohol **1a** gets oxidized and then undergoes self-condensation, 3) the primary alcohol from β-amino alcohol **2a** is over oxidized to carboxylic acid. A similar behavior was observed with 2,2-dimethoxy-2-phenylacetophenone **4d** where to the α carbon are attached two very strong electron donating groups. This affects the reaction and the yield drops by 10%.

Table 1. Screening of carbonyl oxidants of various oxidation potentials. [a]



1a **2a** **3a (80%)**

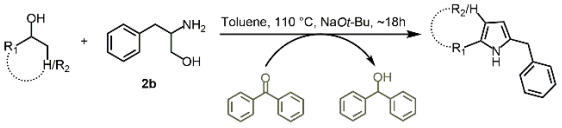
Entry	Oxidant	Oxidation potential [mV] [b]		Yield of **3a** [%] [c]
1		167	**4a**	41
2		199	**4b**	43
3		460	**4c**	trace
4		-	**4d**	33
5		126	**4e**	72
6		117	**4f**	30

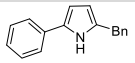
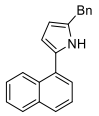
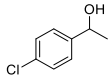
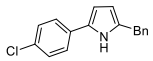
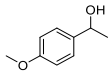
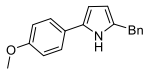
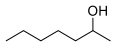
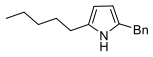
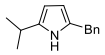
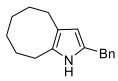
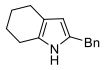
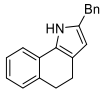
[a] Reaction condition: 1-phenylethanol (1.0 equiv, 2.456 mmol), 2-amino-1-butanol (1.1 equiv, 2.70 mmol), NaOtBu (1.1 equiv, 2.70 mmol), carbonyl oxidant (3.0 equiv), dry toluene 9 ml, 110 °C, ~18 h. [b] Details for oxidation potentials of compounds listed above can be found in Ref.18. [c] Isolated yield after column chromatography.

Moreover, to validate this we have screened a reaction with 9,10-phenanthrenequinone **4c** which has a very high oxidation potential and according to the GC and NMR analysis we found out that pyrrole was formed just in trace amount. The same reaction was repeated with **4c** at various temperatures, starting from 20, then proceeding to 40, 60, and finally 100 °C in order to investigate if the higher oxidation potential can be combined with lower temperature. However, in all cases we have not observed any improvement. From screening experiments, benzophenone **4e** in excess (6.0 equiv) was found to be optimal, NaOtBu was the best base (1.1 equiv) and the optimal temperature was found to be 110 °C. The desired solvents for this reaction are non-polar with a high boiling point except THF which performs as good as non-polar solvents, however

for the direct purification of the crude mixture by column chromatography using non-polar solvents is more convenient.

Table 2. Secondary alcohol scope of the pyrrole synthesis [a].



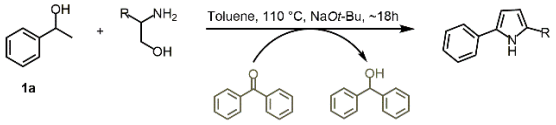
Entry	Secondary alcohol	Product		Isolated Yield [%] [b]
1			**3b**	77
2			**3c**	40
3			**3d**	80
4			**3e**	80
5			**3f**	66
6			**3g**	63
7			**3h**	65
8			**3i**	56
9			**3j**	86

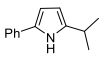
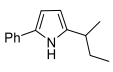
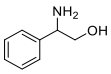
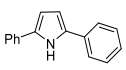
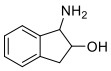
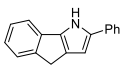
[a] Reaction condition: secondary alcohol (1.0 equiv), phenylalaninol (1.1 equiv), NaOtBu (1.1 equiv), benzophenone (6.0 equiv), dry toluene 9 ml, 110 °C, ~18 h. [b] Isolated yield after column chromatography.

More details regarding the optimization process can be found in the supporting information. It is interesting to note that when we started from acetophenone rather than 1-phenylethanol under otherwise identical conditions, the yields of **3a** were consistently lower (45 compared to 80%).

Next, we have investigated the scope with a wide range of secondary alcohols. For this purpose, we set-up an experiment using secondary alcohol (1.0 equiv) phenylalaninol **2b** (1.1 equiv), NaOtBu (1.1 equiv), benzophenone **4e** (6.0 equiv), and toluene as a solvent under reflux (110 °C) for approximately 18 h. These pyrroles were isolated in yields of up to 80% and under these conditions, various substituted aromatic and aliphatic secondary alcohols are tolerated (Table 2). Substituted phenyl-ethanols **3b**, **3d** and **3e** in most cases convert into 2,5-di-substituted pyrroles in very good yield, 77-80%, however 1-naphthylethanol **3c** gives a moderate yield of 40%. Aliphatic alcohols are tolerated and transformed in their representative pyrroles **3g-i** in good yield (56-63%). According to NMR data of the isolated compound **3f** we have observed the formation of a mixture of two isomers in the case of 2-heptanol (entry 5) which **3f** was the major isomer in a yield of 56% together with a minor product, the 4-methyl-5-butylpyrrole isomer, formed in 10% yield.

Table 3. β-Amino alcohol scope of the pyrrole synthesis [a]

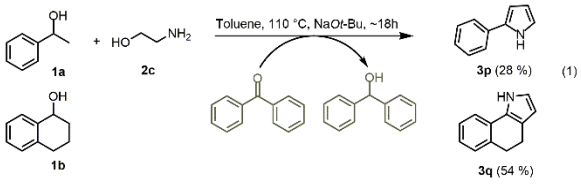


Entry	β-amino alcohol	Product		Isolated yield [%] [b]
1			**3k**	90
2			**3l**	47
3			**3m**	93
4			**3n**	74
5			**3o**	n.r

[a] Reaction condition: 1-phenylethanol (1.0 equiv), β-amino alcohol (1.1 equiv), NaOtBu (1.1 equiv), benzophenone (6.0 equiv), dry toluene 9 ml, 110 °C, ~18 h. [b] Isolated yield after column chromatography.

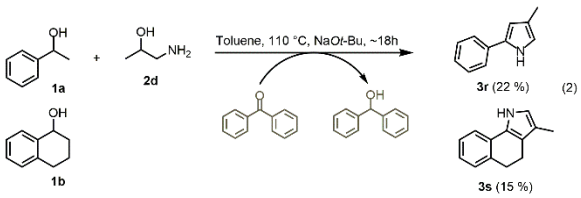
Interestingly, **3j** was isolated in very good yield (86%) compared to other cyclic alcohols. Furthermore, we studied the reactivity of different β-amino alcohols. Aliphatic branched β-amino alcohols (entry 1, and 3, table 3) react better and give very high yields (90% and 93%) of their pyrrole derivatives **3k**, **3m**, compared to non-branched β-amino alcohols, like alaninol (entry 2) and 2-phenylglycinol (entry 4) and their pyrroles (**3l,** 47%) and (**3n**, 74%). However, in the case of 1-amino-2-indanol (entry 5) we have not observed any formation of product **3o**.

In order to extend the scope of our method for pyrrole synthesis we performed a reaction with ethanolamine **2c** to be able to synthetize 2-phenylpyrrole **3p**. Despite the fact that the yield is low, around 28% (considering that they are unstable and get quickly oxidized in the acidic environment), this type of α-unsubstituted pyrroles are very valuable starting materials for the synthesis of BODIPYs, porphyrins, and other functionalized advanced materials [Eq. (1)]. An improvement was observed in the case of 1,2,3,4-tetrahydro-1-naphthol **1b**, for which fused pyrrole **3q** was obtained in an acceptable yield of 54%.



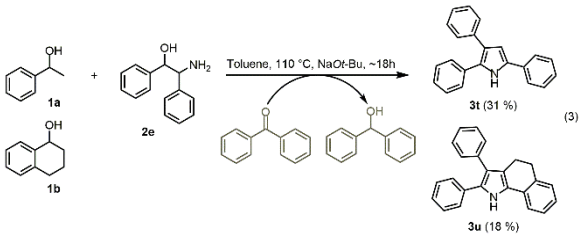
(1)

The same reaction conditions were applied to 1-amino-2-propanol **2d** in order to obtain 2,4-disubstituted pyrroles [Eq. (2)]. As expected for aminoalcohols where the alcohol function group is in secondary position, a competitive reaction takes place, where we have observed a low yield for both pyrroles **3r** (22%) and **3s** (15%).



(2)

Furthermore, we have studied if we can prepare heavily substituted pyrroles using the same conditions and secondary alcohols, therefore we used 2-amino-1,2-diphenylethanol **2e** as a substrate [Eq. (3)]. In case where 2-amino-1,2-diphenylethanol **2e** was used as a substrate and 1-phenylethanol **1a** we have observed a better yield (**3t**, 31%) compared to 1,2,3,4-tetrahydro-1-naphthol **1b** and the corresponding pyrrole **3u** (18%), this perhaps for several reasons:



(3)

1) condensation of 1,2,3,4-tetrahydro-1-naphthol **1b** with 2-amino-1,2-diphenylethanol **2e** is more sterically hindered, 2) because of competitive oxidation, many side reactions take place like self -condensation of 2-amino-1,2-diphenylethanol **2e** which can result in pyrazine formation.

Finally, to check the synthetic utility of the method the reaction was carried out on a 3 gram scale of **1a** and we obtained **3a** without affecting the yield (~79%).

CONCLUSION

In summary, we have developed a novel, transition metal-free, and one pot methodology for synthesizing substituted pyrroles from secondary alcohols and amino alcohols to produce differently substituted pyrroles. The oxidation process occurs selectively for secondary alcohols which under basic conditions and in presence of aminoalcohol leads to pyrrole formation. The reaction operates under mild oxidation conditions and it has a broad scope, working best for 2,5-disubstituted pyrroles. 2-Monosubstituted, 2,4-disubstituted and 2,3,5-trisubstituted pyrroles were also prepared by this method in low to fair yields, that however may still be competitive with the yield offered by other methods like the Trofimov reaction. Sensitive functional groups are tolerated under these reaction circumstances, which makes it very convenient to apply for the synthesis of functionalized pyrroles. The reaction can be easy scaled up to more than 3 grams in the case of **3a** with a ~79% yield.

EXPERIMENTAL SECTION

General Considerations

NMR spectra were recorded on a Bruker 400 Avance (400 MHz) or a Bruker 600 Avance II+ (600 MHz), and chemical shifts (δ) are reported part per million (ppm) referenced to tetramethylsilane (^{1}H). Melting points were determined using a Reichert Thermovar apparatus. For column chromatography 70-230 mesh silica 60 (E. M. Merck) was used as the stationary phase. Chemicals received from commercial sources were used without further purification. Reaction dry solvents were used as received from commercial sources. TLC were carried out on Kieselgel 60 F254 plates (Merck) and stained with iodine or visualized with UV-lamp 254 nm. Exact mass spectra were acquired with a quadrupole orthogonal acceleration time-of-flight mass spectrometer (Synapt G2 HDMS, Waters, Milford, MA). Samples were infused at 3 uL/min and spectra were obtained in positive (or: negative) ionization mode with a resolution of 15000 (FWHM) using leucine enkephalin as lock mass.

General procedure for the preparation of pyrroles

To a screw-capped reaction tube was added secondary alcohol, amino-alcohol, solvent, oxidant and base. The pressure tube was closed with a semi permeable membrane, purged with argon for 10 minutes and heated with stirring for the desired amount of time. The crude reaction mixture was cooled to room temperature and then directly purified by column chromatography (silica gel) using petroleum ether and dichloromethane as an eluent system (*Note: some pyrroles were twice chromatographed. The column was cooled down to prevent from overheating, to increase performance and was protected from the light*).

Large scale synthesis of 2-ethyl-5-phenylpyrrole

To a round bottom flask (250 ml) equipped with a condenser and stirring bar was added 3 g 1-phenylethanol (24.56 mmol), 2.40 g 2-amino-1-butanol (1.1 equiv, 27.0 mmol), 2.6 g NaOtBu (1.1 equiv, 27.0 mmol), 26.8 g benzophenone (6.0 equiv, 147 mmol) and 90 ml dry toluene. The reaction mixture was purged with argon and refluxed (110 °C, oil bath) overnight (~18 h). After the reaction mixture has been cooled to room temperature, it was added directly to a silica column and chromatographed using petroleum ether (PE) 65:35 dichloromethane (DCM) as an eluent. Yield: 3.34 g, 79% as colorless solid (turns pink after contact with air).

*2-Benzyl-5-phenyl-1H-pyrrole (**3b**):* 1-phenylethanol (300 mg, 1.0 equiv, 2.456 mmol), phenylalaninol (241 mg, 1.1 equiv, 2.70 mmol), NaOtBu (260 mg, 1.1 equiv, 2.70 mmol), benzophenone (2.68 g, 6.0 equiv, 14.73 mmol), dry toluene 9 ml, 110 °C, reaction time is overnight (~18 h). The product was purified using column chromatography and as the eluent was used petroleum ether (PE) 65:35 dichloromethane (DCM) affording (**3b**) (439 mg, 77% yield) as slightly pink solid. m.p. 85 °C (m.p. from literature 85.3–89.5 °C). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.00 (s, br, 1H), 7.45 – 7.18 (m, 9H), 7.13 (t, J = 7.3 Hz, 1H), 6.43 (m, 1H), 6.04 (m, 1H), 4.01 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 139.3, 132.8, 132.0, 131.5, 128.8, 128.7, 128.7, 126.5, 125.8, 123.5, 108.6, 106.1, 34.2. HRMS (ESI-quadrupole) m/z: $[M+H]^+$ Calcd for $C_{17}H_{15}N_1H$ 234.1277; found 234.1276. The analytical data for **3b** are consistent with the literature [19.] (m.p, NMR)

CAS Registry Number: 905971-72-4.

*2-Benzyl-5-(naphthalen-1-yl)-1H-pyrrole (**3c**):* 1-(1-Naphthyl)ethanol (300 mg, 1.0 equiv, 1.742 mmol), phenylalaninol (290 mg, 1.1 equiv, 1.916 mmol), NaOtBu (184 mg, 1.1 equiv, 1.916 mmol), benzophenone (1.90 g, 6.0 equiv, 10.45 mmol), dry toluene 9 ml, 110 °C, reaction time is overnight (~18 h). The product was purified using column chromatography and as the eluent was used petroleum ether (PE) 65:35 dichloromethane (DCM) affording (**3c**) (200 mg, 40% yield) as slightly brown oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.39 – 8.22 (m, 1H), 7.99 (s, br, 1H), 7.91 –

7.65 (m, 2H), 7.59 – 7.37 (m, 4H), 7.36 – 7.14 (m, 5H), 6.42 (m, 1H), 6.15 (m, 1H), 4.07 (s, 2H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, δ): 139.3, 134.0, 131.6, 131.2, 129.8, 128.7, 128.7, 128.4, 127.1, 126.5, 126.2, 125.8, 125.8, 125.7, 125.4, 109.7, 107.9, 34.3. HRMS (ESI-quadrupole) m/z: $[M+H]^+$ Calcd for $C_{21}H_{17}N_1H$ 284.1433; found 284.1432. The compound has a CAS number but it is not reported in the literature.

CAS Registry Number: 1858242-20-2

*2-Benzyl-5-(4-chlorophenyl)-1H-pyrrole (**3d**):* 1-(4-Chlorophenyl)ethanol (300 mg, 1.0 equiv, 1.916 mmol), phenylalaninol (319 mg, 1.1 equiv, 2.107 mmol), NaOtBu (203 mg, 1.1 equiv, 2.107 mmol), benzophenone (2.049 g, 6.0 equiv, 11.49 mmol), dry toluene 9 ml, 110 °C, reaction time is overnight (~18 h). The product was purified using column chromatography and as the eluent was used petroleum ether (PE) 65:35 dichloromethane (DCM) affording (**3d**) (439 mg, 80% yield) as slightly light pink solid m.p. 120 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.97 (s, br, 1H), 7.47 – 7.09 (m, 9H), 6.41 (m, 1H), 6.04 (m, 1H), 4.01 (s, 2H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, δ): 139.1, 132.5, 131.3, 131.2, 130.4, 128.9, 128.7, 128.6, 126.6, 124.6, 108.8, 106.6, 34.2. HRMS (ESI-quadrupole) m/z: $[M+H]^+$ Calcd for $C_{17}H_{14}Cl_1N_1H$ 268.0887; found 268.0885. The analytical data for **3d** are consistent with literature. [11b] (NMR)

CAS Registry Number: 1422518-38-4

*2-Benzyl-5-(4-methoxyphenyl)-1H-pyrrole (**3e**):* 1-(4-Methoxyphenyl)ethanol (300 mg, 1.0 equiv, 1.971 mmol), phenylalaninol (328 mg, 1.1 equiv, 2.168 mmol), NaOtBu (208 mg, 1.1 equiv, 2.168 mmol), benzophenone (2.155 g, 6.0 equiv, 11.83 mmol), dry toluene 9 ml, 110 °C, reaction time is overnight (~18 h). The product was purified using column chromatography and as the eluent was used petroleum ether (PE) 95:5 ethyl acetate (EtOAc) affording (**3e**) (439 mg, 80% yield) as off-white solid. m.p. 101 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.91 (s, br, 1H), 7.45 – 7.13 (m, 7H), 6.86 (d, J = 8.7 Hz, 2H), 6.30 (m, 1H), 6.01 (m, 1H), 4.00 (s, 2H), 3.79 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, δ): 158.0, 139.4, 131.5, 131.2, 128.6, 126.5, 126.0, 124.9, 114.2, 108.4, 104.9, 55.3, 34.2. HRMS (ESI-quadrupole) m/z: $[M+H]^+$ Calcd for $C_{18}H_{17}N_1O_1H$ 264.1382; found 264.1378. The analytical data for **3e** are consistent with literature. [11b] (NMR)

CAS Registry Number: 1422518-37-3

*2-Benzyl-5-pentyl-1H-pyrrole (**3f**):* 2-Heptanol (300 mg, 1.0 equiv, 2.58 mmol), phenylalaninol (429 mg, 1.1 equiv, 2.84 mmol), NaOtBu (273 mg, 1.1 equiv, 2.84 mmol), benzophenone (2.82 g, 6.0 equiv, 15.49 mmol), dry toluene 9 ml, 110 °C, reaction time is overnight (~18 h). The product was purified using column chromatography and as the eluent was used petroleum ether (PE) 65:35 dichloromethane (DCM) affording (**3f**) (390 mg, 66% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.47 (s, br, 1H), 7.34 – 7.25 (m, 2H), 7.21 (m, 3H), 5.85 (m, 1H), 5.79 (m, 1H), 3.93 (s, 2H), 2.54 – 2.45 (m, 2H), 1.55 (m, 2H), 1.30 (m, 4H), 0.89 (m, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, δ): 139.8, 132.4, 128.9, 128.7, 128.6, 128.5, 126.3, 106.4, 104.6, 77.2, 77.0, 76.8, 34.2, 31.6, 29.3, 27.7, 25.6, 22.4, 14.0. HRMS (ESI-quadrupole) m/z: $[M+H]^+$ Calcd for $C_{16}H_{21}N_1H$ 228.1746; found 228.1748.

*2-Benzyl-5-isopropyl-1H-pyrrole (**3g**)*: 3-Methyl-2-butanol (300 mg, 1.0 equiv, 3.40 mmol), phenylalaninol (566 mg, 1.1 equiv, 3.74 mmol), NaOtBu (360 mg, 1.1 equiv, 3.74 mmol), benzophenone (3.72 g, 6.0 equiv, 20.42 mmol), dry toluene 9 ml, 110 °C, reaction time is overnight (~18 h). The product was purified using column chromatography and as the eluent was used petroleum ether (PE) 65:35 dichloromethane (DCM) affording (**3g**) (429 mg, 63% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.52 (s, br, 1H), 7.30 (t, 2H), 7.22 (t, 3H), 5.84 (m, 1H), 5.81 (m, 1H), 3.94 (s, 2H), 2.83 (sept, 1H), 1.20 (d, J = 6.9 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, δ): 139.8, 138.4, 128.9, 128.6, 128.5, 126.3, 106.2, 102.7, 34.2, 27.0, 22.6. HRMS (ESI-quadrupole) m/z: $[M+H]^+$ Calcd for $C_{14}H_{17}N_1H$ 200.1433; found 200.1436. The analytical data for **3g** are consistent with literature. [11b] (NMR)

CAS Registry Number: 1422518-36-2

*2-Benzyl-4,5,6,7,8,9-hexahydro-1H-cycloocta[b]pyrrole (**3h**):* cyclooctanol (300 mg, 1.0 equiv, 2.340 mmol), phenylalaninol (389 mg, 1.1 equiv, 2.57 mmol), NaOtBu (247 mg, 1.1 equiv, 2.57 mmol), benzophenone (2.56 g, 6.0 equiv, 14.04 mmol), dry toluene 9 ml, 110 °C, reaction time is overnight (~18 h). The product was purified using column chromatography and as the eluent was used petroleum ether (PE) 65:35 dichloromethane (DCM) affording (**3h**) (367 mg, 65% yield) as slightly brown oil. ^{1}H NMR (600 MHz, $CDCl_3$, δ): 7.31 – 7.24 (m, 3H), 7.21 (d, *J* = 7.8 Hz, 3H), 5.68 (d, *J* = 2.2 Hz, 1H), 3.90 (s, 2H), 2.62 – 2.57 (m, 2H), 2.55 – 2.51 (m, 2H), 1.63 – 1.56 (m, 4H), 1.43 (m, 4H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$, δ): 128.6, 128.5, 127.6, 127.1, 126.2, 119.0, 107.6, 34.2, 30.6, 29.6, 26.0, 25.6, 25.5, 25.0. HRMS (ESI-quadrupole) m/z: $[M+H]^+$ Calcd for $C_{17}H_{21}N_1H$ 240.1746; found 240.1750. The analytical data for **3h** are consistent with literature. [11b] (NMR)

CAS Registry Number: 1422518-52-2

*2-Benzyl-4,5,6,7-tetrahydro-1H-indole (**3i**):* cyclohexanol (300 mg, 1.0 equiv, 3 mmol), phenylalaninol (498 mg, 1.1 equiv, 3.29 mmol), NaOtBu (317 mg, 1.1 equiv, 3.29 mmol), benzophenone (3.27 g, 6.0 equiv, 17.97 mmol), dry toluene 9 ml, 110 °C, reaction time is overnight (~18 h). The product was purified using column chromatography and as the eluent was used petroleum ether (PE) 65:35 dichloromethane (DCM) affording (**3i**) (357 mg, 56% yield) as slightly brown oil. ^{1}H NMR (600 MHz, $CDCl_3$, δ): 7.30 (m, 2H), 7.27 – 7.19 (m, 3H), 5.70 (d, *J* = 2.1 Hz, 1H), 3.91 (s, 2H), 2.47 (m, 4H), 1.77 (m, 2H), 1.72 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$, δ): 139.7, 128.8, 128.5, 126.3, 126.1, 116.8, 105.5, 34.3, 23.8, 23.4, 22.8, 22.7. HRMS (ESI-quadrupole) m/z: $[M+H]^+$ Calcd for $C_{15}H_{17}N_1H$ 212.1433; found 212.1437. The analytical data for **3i** are consistent with literature. [12] (NMR)

CAS Registry Number: 233585-17-6

*2-Benzyl-4,5-dihydro-1H-benzo[g]indole (**3j**):* 1,2,3,4-tetrahydro-1-naphthol (300 mg, 1.0 equiv, 2.024 mmol), phenylalaninol (337 mg, 1.1 equiv, 2.227 mmol), NaOtBu (214 mg, 1.1 equiv, 2.227 mmol), benzophenone (2.21 g, 6.0 equiv, 12.15 mmol), dry toluene 9 ml, 110 °C, reaction time is overnight (~18 h). The product was purified using column chromatography and as the eluent was used petroleum ether (PE) 65:35 dichloromethane (DCM) affording (**3j**) (451 mg, 86% yield) as colorless crystals m.p. 85 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.88 (s, 1H), 7.28 (m, 5H), 7.13 (m, 2H), 6.99 (m, 2H), 5.87 (s, 1H), 4.00 (s, 2H), 2.90 (t, *J* = 7.6 Hz, 2H), 2.69 (t, *J* = 7.6 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 139.3, 134.4, 131.5, 129.3, 128.7, 128.6, 128.2, 127.1, 126.5, 126.3, 124.5, 120.5, 117.7, 106.8, 34.4, 30.0, 21.8. HRMS (ESI-quadrupole) m/z: $[M+H]^+$ Calcd for $C_{19}H_{17}N_1H$ 260.1433; found 260.1418.

*2-Isopropyl-5-phenyl-1H-pyrrole (**3k**):* 1-phenylethanol (300 mg, 1.0 equiv, 2.456 mmol), 2-amino-3-methyl-1-butanol (279 mg, 1.1 equiv, 2.70 mmol), NaOtBu (260 mg, 1.1 equiv, 2.70 mmol), benzophenone (2.68 g, 6.0 equiv, 14.73 mmol), dry toluene 9 ml, 110 °C, reaction time is overnight (~18 h). The product was purified using column chromatography and as the eluent was used petroleum ether (PE) 65:35 dichloromethane (DCM) affording (**3k**) (411 mg, 90% yield) as colorless crystals. m.p. 44 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.11 (s, br, 1H), 7.43 (d, *J* = 7.9 Hz, 2H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.16 (t, *J* = 7.3 Hz, 1H), 6.41 (m, 1H), 5.98 (m, 1H), 2.97 (m, 1H), 1.30 (d, *J* = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 140.3, 133.0, 130.4, 128.8, 125.6, 123.4, 105.8, 104.9, 27.2, 22.6. HRMS (ESI-quadrupole) m/z: $[M+H]^+$ Calcd for $C_{13}H_{15}N_1H$ 186.1277; found 186.1272. The analytical data for **3k** are consistent with literature. [11b] (NMR)

CAS Registry Number: 13713-07-0

*2-Methyl-5-phenyl-1H-pyrrole (**3l**):* 300 mg 1-phenylethanol (1.0 equiv, 2.456 mmol), 203 mg alaninol (1.1 equiv, 2.70 mmol), 260 mg NaOtBu (1.1 equiv, 2.70 mmol), 2.68 g benzophenone (6.0

equiv, 14.73 mmol), dry toluene 9 ml, 110 °C, reaction time is overnight (~18 h). The product was purified using column chromatography and as the eluent was used petroleum ether (PE) 65:35 dichloromethane (DCM) affording (**3l**) (182 mg, 47% yield) as colorless crystals. m.p. 98 °C (m.p. from literature 98-100 °C). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.09 (s, br, 1H), 7.42 (d, *J* = 7.8 Hz, 2H), 7.33 (m, 2H), 7.15 (m, 1H), 6.39 (m, 1H), 5.95 (m, 1H), 2.33 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 132.9, 130.7, 129.0, 128.8, 125.6, 123.3, 107.9, 106.1, 13.1. HRMS (ESI-quadrupole) m/z: $[M+H]^+$ Calcd for $C_{11}H_{11}N_1H$ 158.0964; found 158.0965. The analytical data for **3l** are consistent with literature. [20] (m.p, NMR)

CAS Registry Number: 3042-21-5

*2-(sec-Butyl)-5-phenyl-1H-pyrrole (**3m**)*: 1-phenylethanol (300 mg, 1.0 equiv, 2.456 mmol), L-isoleucinol (317 mg, 1.1 equiv, 2.70 mmol), NaOtBu (260 mg, 1.1 equiv, 2.70 mmol), benzophenone (2.68 g, 6.0 equiv, 14.73 mmol), dry toluene 9 ml, 110 °C, reaction time is overnight (~18 h). The product was purified using column chromatography and as the eluent was used petroleum ether (PE) 65:35 dichloromethane (DCM) affording (**3m**) (457 mg, 93% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.08 (s, br, 1H), 7.43 (d, *J* = 7.9 Hz, 2H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.15 (t, *J* = 7.3 Hz, 1H), 6.42 (m, 1H), 5.97 (m, 1H), 2.71 (m, 1H), 1.78 – 1.47 (m, 2H), 1.28 (d, *J* = 7.0 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 139.1, 133.0, 130.2, 128.7, 125.6, 123.3, 105.8, 105.6, 34.4, 30.2, 20.0, 11.8. HRMS (ESI-quadrupole) m/z: $[M+H]^+$ Calcd for $C_{14}H_{17}N_1H$ 200.1433; found 200.1425. The analytical data for **3h** are consistent with literature. [11b] (NMR)

CAS Registry Number: 1422518-32-8

*2,5-Diphenyl-1H-pyrrole (**3n**):* 1-phenylethanol (300 mg, 1.0 equiv, 2.456 mmol), 2-phenylglycinol (371 mg, 1.1 equiv, 2.70 mmol), NaOtBu (260 mg, 1.1 equiv, 2.70 mmol), benzophenone (2.68 g, 6.0 equiv, 14.73 mmol), dry toluene 9 ml, 110 °C, reaction time is overnight (~18 h). The product was purified using column chromatography and as the eluent was used petroleum ether (PE) 65:35 dichloromethane (DCM) affording (**3n**) (398 mg, 74% yield) as colorless crystals. m.p. 141 °C (m.p. from literature 143 °C). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.57 (s, br, 1H), 7.53 (d, *J* = 7.7 Hz, 4H), 7.39 (m, 4H), 7.23 (m, 2H), 6.58 (d, *J* = 2.6 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 133.1, 132.4, 128.9, 126.3, 123.7, 107.9. HRMS (ESI-quadrupole) m/z: $[M+H]^+$ Calcd for $C_{16}H_{13}N_1H$ 220.1120; found 220.1126. The analytical data for **3n** are consistent with literature. [21] (m.p, NMR)

CAS Registry Number: 838-40-4

*2-Ethyl-5-phenyl-1H-pyrrole (**3a**):* 1-phenylethanol (300 mg, 1.0 equiv, 2.456 mmol), 2-amino-1-butanol (241 mg, 1.1 equiv, 2.70 mmol), NaOtBu (260 mg, 1.1 equiv, 2.70 mmol), benzophenone (2.68 g, 6.0 equiv, 14.73 mmol), dry toluene 9 ml, 110 °C, reaction time is overnight (~18 h). The product was purified using column chromatography and as the eluent was used petroleum ether (PE) 65:35 dichloromethane (DCM) affording (**3a**) (337 mg, 80% yield) as colorless crystals. m.p. 50 °C (m.p. from literature 47.0-48.5 °C). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.09 (s, br, 1H), 7.42 (d, *J* = 7.7 Hz, 2H), 7.32 (m, 2H), 7.15 (m, 1H), 6.41 (m, 1H), 5.98 (m, 1H), 2.67 (m, 2H), 1.28 (t, *J* = 7.6 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 135.6, 132.9, 130.5, 128.8, 125.6, 123.3, 106.2, 105.9, 20.9, 13.5. These analytical data for **3a** are consistent with literature. [22] (m.p, NMR)

CAS Registry Number: 13713-06-9

*2-Phenyl-1H-pyrrole (**3p**):* 1-phenylethanol (300 mg, 1.0 equiv, 2.456 mmol), ethanolamine (165 mg, 1.1 equiv, 2.70 mmol), NaOtBu (260 mg, 1.1 equiv, 2.70 mmol), benzophenone (2.68 g, 6.0 equiv, 14.73 mmol), dry toluene 9 ml, 110 °C, reaction time is overnight (~18 h). The product was purified using column chromatography and as the eluent was used petroleum ether (PE) 65:35 dichloromethane (DCM) affording (**3p**) (98.2 mg, 28% yield) as colorless crystals. m.p. 124 °C (m.p. from literature 126-128 °C). ^{1}H NMR (600

MHz, $CDCl_3$, δ): 8.42 (s, br, 1H), 7.47 (d, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.7 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 6.86 (s, br, 1H), 6.53 (s, br, 1H), 6.30 (s, br, 1H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$, δ): 132.8, 132.1, 128.9, 126.2, 123.8, 118.8, 110.1, 105.9. HRMS (ESI-quadrupole) m/z: $[M+H]^+$ Calcd for $C_{10}H_9N_1H$ 144.0807; found 144.0811. The analytical data for **3p** are consistent with literature. [23] (m.p, NMR)

CAS Registry Number: 3042-22-6

*4,5-Dihydro-1H-benzo[g]indole (**3q**):* 1,2,3,4-Tetrahydro-1-naphthol (300 mg, 1.0 equiv, 2.024 mmol), ethanolamine (136 mg, 1.1 equiv, 2.227 mmol), NaOtBu (214 mg, 1.1 equiv, 2.227 mmol), benzophenone (2.213 g, 6.0 equiv, 12.15 mmol), dry toluene 9 ml, 110 °C, reaction time is overnight (~18 h). The product was purified using column chromatography and as the eluent was used petroleum ether (PE) 65:35 dichloromethane (DCM) affording (**3q**) (187 mg, 54% yield) as slightly green crystals. m.p. 104 °C (m.p. from literature 109-110 °C). ^1H NMR (400 MHz, $CDCl_3$, δ): 8.28 (s, br, 1H), 7.23 – 7.11 (m, 3H), 7.06 (m, 1H), 6.76 (m, 1H), 6.12 (m, 1H), 2.93 (t, *J* = 7.6 Hz, 2H), 2.75 (t, *J* = 7.6 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, δ): 134.8, 129.3, 128.3, 127.7, 126.4, 125.0, 120.1, 118.1, 108.1, 30.0, 21.8. HRMS (ESI-quadrupole) m/z: $[M+H]^+$ Calcd for $C_{12}H_{11}N_1H$ 170.0964; found 170.0961. The analytical data for **3q** are consistent with literature. [23] (m.p, NMR)

CAS Registry Number: 4995-14-6

*4-Methyl-2-phenyl-1H-pyrrole (**3r**):* 1-phenylethanol (300 mg, 1.0 equiv, 2.456 mmol), 203 mg 1-amino-2-propanol (1.1 equiv, 2.70 mmol), NaOtBu (260 mg, 1.1 equiv, 2.70 mmol), benzophenone (2.68 g, 6.0 equiv, 14.73 mmol), dry toluene 9 ml, 110 °C, reaction time is overnight (~18 h). The product was purified using column chromatography and as the eluent was used petroleum ether (PE) 65:35 dichloromethane (DCM) affording (**3r**) (85.3 mg, 22% yield) as colorless crystals. m.p. 150 °C (m.p. from literature 152 °C). ^1H NMR (400 MHz, $CDCl_3$, δ): 8.15 (s, br, 1H), 7.44 (d, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.18 (t, *J* = 7.3 Hz, 1H), 6.62 (s, br, 1H), 6.36 (s, br, 1H), 2.15 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, δ): 132.0, 128.8, 126.0, 123.6, 116.7, 107.4, 11.9. HRMS (ESI-quadrupole) m/z: $[M+H]^+$ Calcd for $C_{11}H_{11}N_1H$ 158.0964; found 158.0959. The analytical data for **3r** are consistent with literature. [24] (m.p, NMR)

CAS Registry Number: 20055-04-3

*3-Methyl-4,5-dihydro-1H-benzo[g]indole (**3s**):* 1,2,3,4-tetrahydro-1-naphthol (300 mg, 1.0 equiv, 2.024 mmol), 1-amino-2-propanol (167 mg, 1.1 equiv, 2.227 mmol), NaOtBu (214 mg, 1.1 equiv, 2.227 mmol), benzophenone (2.213 g, 6.0 equiv, 12.15 mmol), dry toluene 9 ml, 110 °C, reaction time is overnight (~18 h). The product was purified using column chromatography and as the eluent was used petroleum ether (PE) 65:35 dichloromethane (DCM) affording (**3s**) (56.3 mg, 15% yield) as slightly green crystals. m.p. 100 °C. ^1H NMR (400 MHz, $CDCl_3$, δ): 8.06 (s, br, 1H), 7.15 (m, 3H), 7.03 (t, *J* = 7.3 Hz, 1H), 6.55 (s, 1H), 2.93 (t, *J* = 7.6 Hz, 2H), 2.65 (t, *J* = 7.6 Hz, 2H), 2.07 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, δ): 134.7, 128.2, 126.4, 124.8, 118.0, 117.4, 116.1, 29.9, 19.9, 9.8. HRMS (ESI-quadrupole) m/z: $[M+H]^+$ Calcd for $C_{13}H_{13}N_1H$ 184.1120; found 184.1124. The analytical data for **3q** are consistent with literature. [26] (NMR)

CAS Registry Number: 172907-65-2

*2,3,5-Triphenyl-1H-pyrrole (**3t**)*: 1-phenylethanol (300 mg, 1.0 equiv, 2.456 mmol), 2-amino-1,2-diphenylethanol (576 mg, 1.1 equiv, 2.70 mmol), NaOtBu (260 mg, 1.1 equiv, 2.70 mmol), benzophenone (2.68 g, 6.0 equiv, 14.73 mmol), dry toluene 9 ml, 110 °C, reaction time is overnight (~18 h). The product was purified using column chromatography and as the eluent was used petroleum ether (PE) 65:35 dichloromethane (DCM) affording (**3t**) (228.5 mg, 31% yield) as off white crystals. m.p. 127 °C (m.p. from literature 133-135 °C). ^1H NMR (400 MHz, $CDCl_3$, δ): 8.40 (s, br, 1H), 7.54 (d, *J* = 7.7 Hz, 2H), 7.39 (m, 6H), 7.36 – 7.15 (m, 7H), 6.70 (s, br, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, δ):

136.3, 133.0, 132.2, 132.2, 129.3, 128.9, 128.7, 128.4, 128.3, 127.4, 126.9, 126.5, 125.9, 123.8, 123.7, 108.5. HRMS (ESI-quadrupole) m/z: $[M+H]^+$ Calcd for $C_{22}H_{17}N_1H$ 296.1433; found 296.1438. The analytical data for **3t** are consistent with literature. [25] (m.p, NMR)

CAS Registry Number: 3274-61-1

*2,3-Diphenyl-4,5-dihydro-1H-benzo[g]indole (**3u**):* 1,2,3,4-tetrahydro-1-naphthol (300 mg, 1.0 equiv, 2.024 mmol), 2-amino-1,2-diphenylethanol (475 mg, 1.1 equiv, 2.227 mmol), NaOtBu (214 mg, 1.1 equiv, 2.227 mmol), benzophenone (2.213 g, 6.0 equiv, 12.15 mmol), dry toluene 9 ml, 110 °C, reaction time is overnight (~18 h). The product was purified using column chromatography and as the eluent was used petroleum ether (PE) 65:35 dichloromethane (DCM) affording (**3u**) (118.2 mg, 18% yield) as off white crystals. m.p. 156 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, br, 1H), 7.42 – 7.15 (m, 13H), 7.09 (t, *J* = 7.0 Hz, 1H), 2.96 (t, *J* = 7.5 Hz, 2H), 2.76 (t, *J* = 7.5 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 135.5, 133.0, 129.8, 128.6, 128.2, 127.0, 126.5, 126.0, 125.4, 121.2, 121.1, 121.0, 118.3, 29.9, 20.7. HRMS (ESI-quadrupole) m/z: $[M+H]^+$ Calcd for $C_{24}H_{19}N_1H$ 322.1590; found 322.1570.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: xxxx

Screening procedure
Copies of ^{1}H and ^{13}C{1H} NMR spectra

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Notes: The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

B.K. carried out the design, synthesis and data analysis of the experiments, K.G. the synthesis of pyrroles from ketones, W.D. designed the experiments and co-wrote the manuscript.

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