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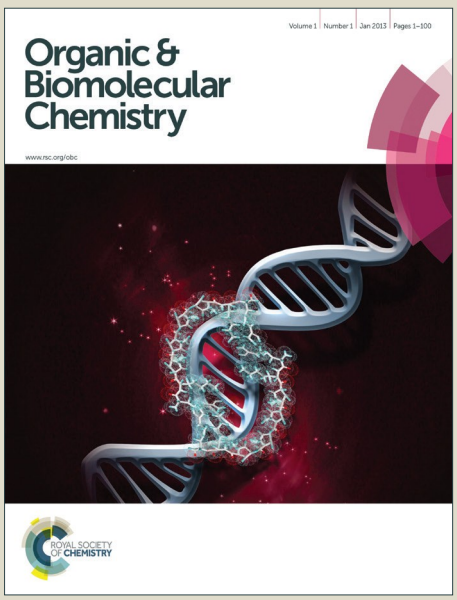

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PAPER

Cooperative effect of Lewis pair in Friedel-Crafts hydroxyalkylation reaction: A simple and effective route for the synthesis of (±)-carbinoxamine

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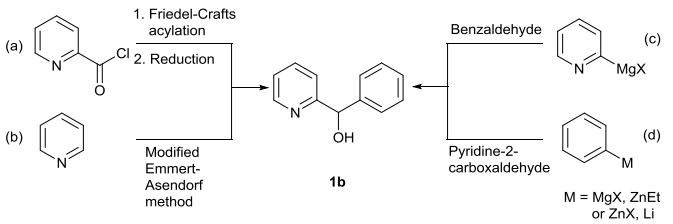
An efficient C-C bond formation strategy between aromatic/heteroaromatic π-nucleophiles and Lewis acid activated aldehydes is described. This aromatic electrophilic substitution reaction of arenes or heteroarenes is facilitated by Lewis acid $AlBr_3$. Aromatic ring with electron donating substituents are excellent nucleophilic counterpart in this reaction generating the carbinols in excellent yields (61-94%). The formation of triarylmethanes also witnessed in the case of certain reactive aldehydes and aromatic π-nucleophiles through reactive carbocation formation. The formation of triarylmethane is reduced to greater extent *via* retardation of second π-nucleophile addition through Lewis base, for example, pyridine, coordination with aluminium alkoxide intermediate. Various aliphatic aldehydes too underwent Friedel-Crafts type hydroxyalkylation and generated the expected carbinols in moderate yields (41-53%) in presence of $AlBr_3$. This protocol has been successfully applied to synthesize the (±)-carbinoxamine, a therapeutically important histamine H_1 antagonist, in a one-pot manner.

Introduction

Carbinols possessing, particularly, the heterocyclic moiety such as pyridine, thiophene, benzothiophene, pyrrole and indole are very important structural motifs present extensively in pharmaceuticals, agrochemicals and biologically relevant molecules.[1] These molecules also found to display enormous synthetic utility as intermediates,[2] chiral auxiliaries,[3] organocatalysts[4] and as a ligand for transition metal catalyzed organic transformations.[5] Hence, there has been a continued effort devoted to develop simple and efficient methods for the synthesis of carbinols. Pyridyl aryl carbinols have been utilized as chiral ligands in enantioselective hydrogenation of unactivated olefins,[6] in cross coupling reaction[7] etc. The preparation of this class of molecules is usually accomplished by five distinct synthetic protocols (Scheme **1**): (a) Friedel-Crafts acylation of arenes with picolyl chloride followed by hydrogenation using appropriate chiral or achiral reducing agents.[8] The reduction of carbonyl group of acyl pyridine to carbinols exhibited limited success. For example, the lithium aluminium hydride reduction of pyridyl aryl ketone resulted in poor yields of corresponding carbinols;[9] (b) The most convenient method for the preparation of carbinols, modified Emmert-Asendorff methodology, involves the condensation of aldehydes/ketones with pyridine in presence of either aluminium or magnesium, mercuric chloride and iodine via pyridyl radical formation.[10] The preparation of these type of carbinols have also been achieved via Grignard reaction between either; (c) pyridyl magnesium bromide and aryl aldehydes[11] or (d) aryl magnesium/lithium/zinc reagents and



Scheme 1. Synthesis of carbinols

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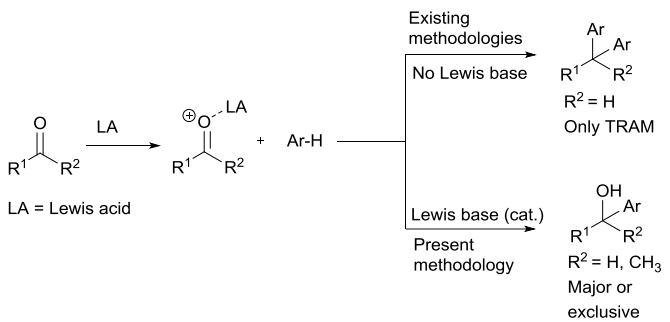
† Electronic Supplementary Information (ESI) available: Experimental procedures, compound characterization data (^{1}H and ^{13}C NMR, HRMS) for all compounds. See DOI: 10.1039/b000000x/

pyridine carboxaldehyde.[12] The former method furnished the carbinols in poor yields.

Synthesis of carbinols using these methodologies involve the generation of reactive nucleophiles such as organometallic reagents followed by reaction with carbonyl aldehydes or generation of ketones followed by reduction of carbonyl group using rhodium catalysts and thus the involvement of multiple steps. In all these reactions, the reactivity of nucleophiles has been exploited over the electrophilic carbonyl groups. The fifth type of protocol involves the activation of electrophilic aldehyde group through Lewis acid to facilitate C-C bond formation. The electrophilic activation of the carbonyl group, either through hydrogen bonding or through other coordination (phenolic), facilitated the carbinol formation.[13] Carbinol formation also observed in the case of electron deficient aldehydes with π-nucleophiles.[14] Some aromatic nucleophiles possessing free phenolic group effectively participated in C-C bond formation reaction in presence of a Lewis acid and generated the carbinols.[15] Following this report, the preparation of (4-(dimethylamino)phenyl)(pyridin-2-yl)methanol along with theoretical studies have been reported.[16] The formation of triarylmethane from pyridine-4-carboxaldehyde and *N*,*N*-dimethylaniline in presence of Lewis acid was observed in this report also. The reaction of π-nucleophiles such as arenes or heteroarenes with aldehydes in presence of Lewis acid usually furnish the triarylmethanes.[17] Hence, it is evident that there has been less attention paid to develop C-C bond forming reaction for the preparation of carbinols from aldehydes (aryl/heteroaryl/aliphatic) and aromatic π-nucleophiles through electrophile activation using Lewis acid. Our interest in the development of Lewis acid/Brønsted acid catalysis chemistry[18,19] led us to explore the possibility of using a simple catalytic system for Friedel-Crafts hydroxyalkylation of aromatic compounds (π-nucleophiles) with aldehydes to generate the library of carbinols.



Scheme 2. Lewis acid-catalyzed C-C bond formation

Accordingly, we have undertaken the detailed study on the direct hydroxyalkylation of arenes or heteroarenes with aldehydes in presence of Lewis acid $AlBr_3$. Lewis acid activation has been effectively utilized to establish the C-C bond between variety of functional groups including carbonyl compounds, imines, epoxides etc. with nucleophiles.[20] The fundamental mechanism by which a Lewis acid promotes the reaction at an organic functional group involves the activation of electrophilic site.[21] For example, Lewis acids, which are known to polarize the C=O bond of aldehydes *via* interaction with the oxygen lone pair and make it more susceptible for nucleophilic attack (Scheme 2).

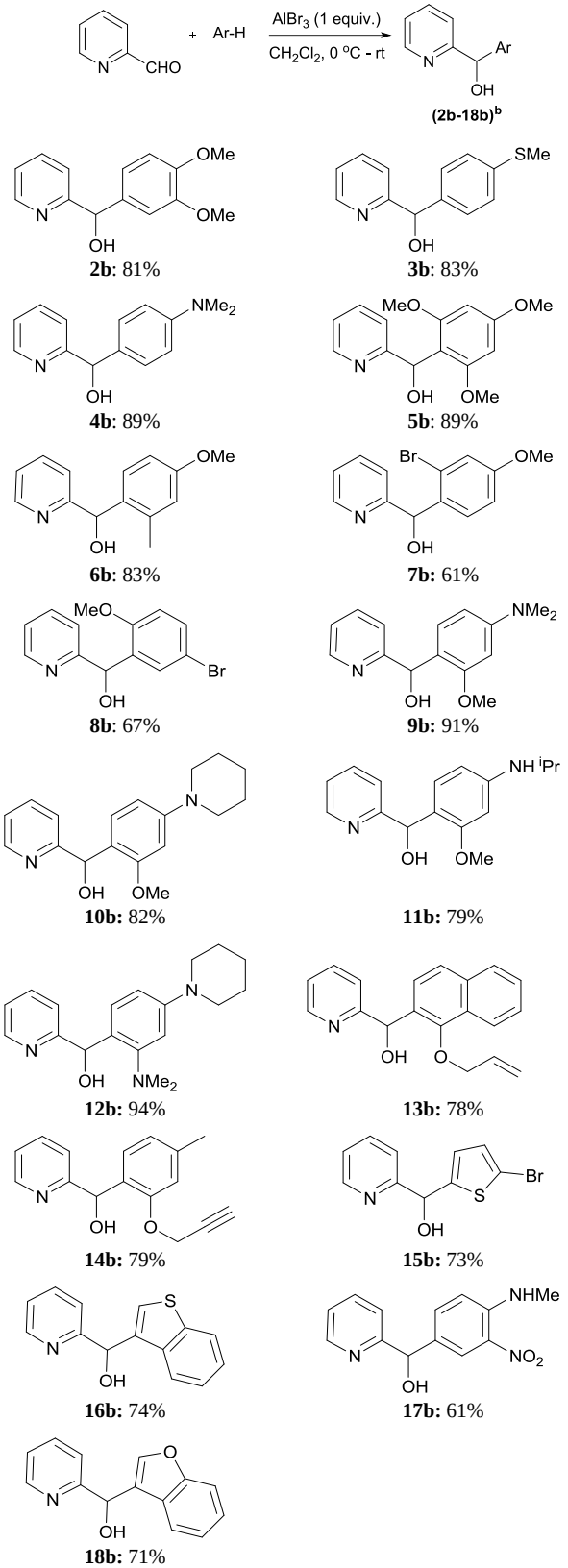
Results and Disscusion

Based on this basic concept, we have disclosed a convenient method for the hydroxyalkylation of aromatic π-nucleophiles using carbonyl compounds such as aldehydes (Scheme 2).[19] Interaction of Lewis acid with pyridine-2-carboxaldehyde may results in the coordination of either carbonyl oxygen or pyridine nitrogen or both. The coordination of Lewis acid with only carbonyl group always leads to triarylmethane formation due to the effective polarization of carbon oxygen double bond (Figure **1b**). This situation facilitated the Friedel-Crafts type hydroxyalkylation of arenes/heteroarenes with aldehydes to generate the carbinoxy Lewis acid intermediate, which in turn underwent Friedel-Crafts alkylation with another molecule of arene/heteroarene to generate finally the triarylmethanes. On the other hand, bidentate coordination of pyridine-2-carboxaldehyde through carbonyl oxygen and nitrogen atom of pyridine moiety with Lewis acid (Lewis pair) may lead to optimized electrophilicity for carbonyl group (Figure **1a**).[22] This situation may lead to the formation of mono nucleophile addition across carbonyl group. To justify this hypothesis we carried out the experiment with π-nucleophile, anthracene and pyridine-2-carboxaldehyde in presence of various Lewis acids at 0 °C to room temperature. Lewis acids such as $AlBr_3$, $AlCl_3$, $TiCl_4$, $BF_3.OEt_2$ and $FeCl_3$ afforded the expected product. However, a clean reaction was observed when the reaction was carried out in the presence of $AlBr_3$ (1 equiv.) to furnish the corresponding carbinol in 49% yield.[19]

Addition of electron rich aromatic/heteroaromatic nucleophiles

With this optimized reaction condition, to justify the versatility of this methodology and compatibility of functional groups such as halogens, –NHR and propargyl groups, which are not passive in presence of organometallic reagents, we carried out hydroxyalkylation reaction with variety of electron rich aromatic and heteroaromatic π-nucleophiles in presence of $AlBr_3$ and the results are summarized in Table 1. Aryl ring bearing electron donating functional group such as $–NR_2$, –OR, or –SR etc facilitated the C-C bond forming reaction to afford the products in good to excellent yields (81-94%). The π-nucleophile, 1,3,5-trimethoxybenzene under present reaction condition generated the carbinol **5b** in 89% yield. These results reveal that the electronic nature of the substituents present in the π-nucleophile (benzene ring) has profound effect on the chemical yield as well as regioselectivity of the product. The aryl ring bearing two electronically different functional groups, for example, the strong electron donating group (such as

Table 1. Electron rich aromatic/heteroaromatic nucleophiles[a]



[a]Reaction conditions: π-Nucleophile (1.2 mmol), pyridine-2-carboxaldehyde (1.0 mmol) in dry dichloromethane, 0 °C – rt. [b]Isolated yield.

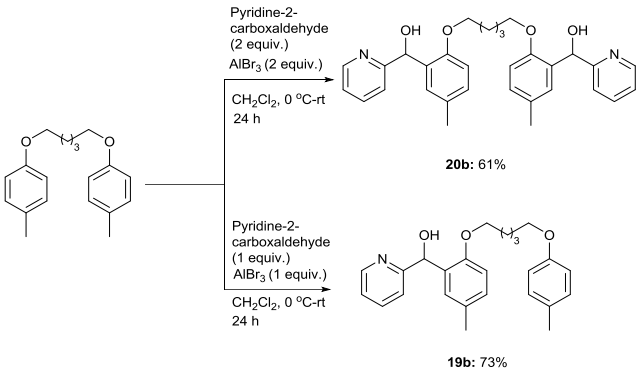
alkoxy) and a weakly activating or weakly deactivating functional group, furnished only one regioisomeric product in which the hydroxyalkyl group attached to the aryl carbon *para* to the strong electron donating alkoxy functional group (Table 1, entries **6b** and **7b**). When *para* position is blocked in π-nucleophile, the hydroxyalkyl group has got introduced at *ortho* to the strong electron donating functional group present in the π-nucleophile (Table 1, entry **8b**). The substrates with two electronically complimentary functional groups such as strong electron donating and strong electron withdrawing groups present in the aryl ring again furnished the single regioisomeric product as dictated by the strong electron donating group in moderate yield (Table 1, entry **17b**). The formation of **7b**, **8b** and **17b** in moderate yield may be due to the diminished nucleophilicity of the substrate bearing inductively deactivating functional groups such as halogens or nitro group.

Surprisingly, the alkyl aryl ether remains unaffected with $AlBr_3$, even though the reagent is usually utilized for ether cleavage.[23] We further intend to examine the stability of other sensitive ether groups such as allyl ether and propargyl ethers. To our delight these two labile ethers are found to be quite stable in presence of $AlBr_3$. For example, the reaction of pyridine-2-carboxaldehyde with 1-(allyloxy)naphthalene and 1-methyl-4-(prop-2-yn-1-yloxy)benzene respectively furnished the corresponding aromatic electrophilic substitution products in presence of $AlBr_3$ (Table 1, entries **13b** and **14b**). The substrates with similar electron donating functional groups such as –OR and $–NR_2$ displayed excellent regioselectivity. For example, the benzene ring possessing –OMe and $–NR_2$ as substituents furnished regioselectively the carbinols as directed by $–NR_2$ group (Table 1, entries **9b**-**11b**). These results clearly indicate that the electronic property of substituents on aromatic ring determines the regioselectivity of the substitution. We investigated the role of steric hindrance on the regioselectivity of the hydroxyalkylation on arene rings. For example, the reaction of *N*,*N*-dimethyl-3-(piperidin-1-yl)aniline with pyridine-2-carboxaldehyde in presence of $AlBr_3$ delivered the carbinol **12b**,[24] in which the hydroxyalkyl group is placed proximal (*ortho*) to the less hindered $–NMe_2$ group and *para* to the bulky piperidine group (Table 1, entry **12b**). This indicates that the incoming electrophilic aldehyde prefer to establish the C-C bond with the nucleophilic carbon *ortho* to the less sterically hindered electron donating group. The reactivity of electron rich aromatic heterocycles such as bromothiophene benzothiophene and benzofuran were examined under present reaction condition. Once again the expected carbinols were generated in good yields (Table 1, entries **15b**, **16b** and **18b**). The arenes with substituents, for example, –Br, –NHMe or proporgyl groups, which are sensitive to the organometallic reagents,[25] are very much compatible with present reaction condition (Table 1, entries **7b**, **8b**, **14b**, **15b** and **17b**).

Ethers with multiple nucleophilic sites

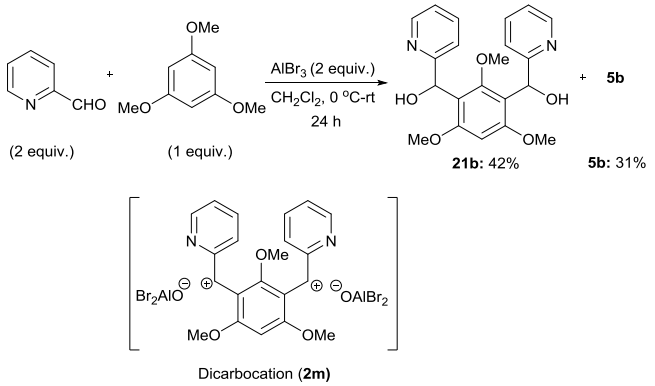
The reaction proceeded smoothly with functionally substituted aromatic π-nucleophiles to afford the corresponding carbinols

in moderate to excellent yields. Among these, the aromatic π-nucleophiles bearing electron donating groups reacted more rapidly than those with electronically poor activating groups (Me, Cl) and that could be attributed to higher



Scheme 3. Reaction of 1,5-bis(*p*-tolyloxy)pentane in presence of $AlBr_3$

nucleophilicity of π-nucleophiles due to the presence of strong electron donating groups. The reaction of phenols with terminal dihalides in presence of a base[26] afforded the aromatic π-nucleophiles with two chemically and electronically equivalent reactive π-nucleophile components separated by an alkyl chain spacer. The symmetrical diether, 1,5-bis(*p*-tolyloxy)pentane, possessess two π-nucleophilic components. While performing the reaction with equimolar mixture (1:1:1) of π-nucleophile, electrophile and $AlBr_3$, only one electrophile is substituted on one of the multiple reactive nucleophilic sites present in 1,5-bis(*p*-tolyloxy)pentane (Scheme 3, **19b**). On the other hand reaction of two equivalents of electrophile (pyridine-2-carboxaldehyde) in presence of two equivalents of $AlBr_3$, the 1,5-bis(*p*-tolyloxy)pentane generated the product with two electrophiles substituted one each on the two aromatic rings (Scheme 3, **20b**).



Scheme 4. Two electrophiles on 1,3,5-trimethoxybenzene

The π-nucleophile, 1,3,5-trimethoxybenzene, possessess three equivalent reactive sites and hence it may be possible to generate tricarbinol, dicarbinol or carbinol depending on the use of number of equivalents of electrophile as well as Lewis acid. Accordingly, the π-nucleophile, 1,3,5-trimethoxybenzene, was treated with pyridine-2-carboxaldehyde (2 equiv.) in presence of $AlBr_3$ (2 equiv.), which generated the dicarbinol (**21b**) in 42% yield along with carbinol in 31% yield. The reaction of 1,3,5-trimethoxybenzene with higher equivalent of pyridine-2-carboxaldehyde (3 equiv.) in presence of $AlBr_3$ (3 equiv.) failed to generate the expected tricarbinol. But the yield of dicarbinol (**21b**) increased to 48% along with mono carbinol in 23% (Scheme 4). The reaction was also performed with dicarbinol (**21b**) as π-nucleophile with pyridine-2-carboxaldehyde (1 equiv.) in presence of $AlBr_3$ (3.4 equiv.) to get the tricarbinol. This condition also failed to generate the tricarbinol as a product. This may be due to the diminished electron density on π-nucleophile, 1,3,5-trimethoxybenzene, after the two electrophile substitution followed by generation of corresponding dicarbocation (**2m**) through expulsion of two $–OAlBr_2$ groups (Scheme 4).

Electron deficient aromatic aldehydes

The reaction of anisole with pyridine-3-carboxyaldehyde and pyridine-4-carboxyaldehyde in presence of $AlBr_3$ (1 equiv.) in dry dichloromethane furnished either carbinol in low yield or exclusively triarylmethane.[19] The formation of triarylmethanes is a common reactivity observed for Lewis acid catalyzed reaction of aryl aldehyde with aromatic π-nucleophiles (Fig. **1b**).[27] But, pyridine-2-carboxaldehyde furnished only carbinols in higher yields. Hence, one can speculate from these observations that, the Lewis pair might have generated through the coordination of Lewis acid with lone pairs of both pyridine nitrogen and aldehyde oxygen (Fig. **1a**). Such type of penta coordination with aluminium is already known in the literature which forms sub coordinate covalent interaction;[28] and thus reduces the leaving group ability of $–OAlBr_2$ group. This speculation opt us to examine the effect of nitrogen containing ligands, which may stop at mono nucleophile addition stage through coordination with aluminium in $ROAlBr_2$ (Fig. **1c**).

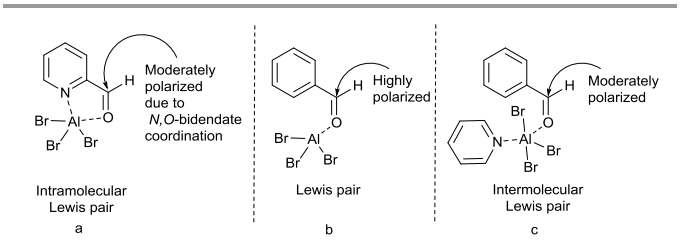
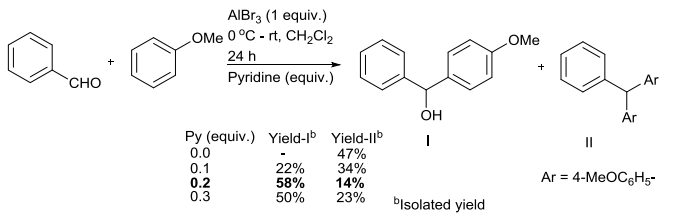


Fig.1 Possible Lewis pairs

Thus, the experiments were carried out by treating the substrate anisole with benzaldehye in presence of Lewis base, pyridine, as an additive. Under controlled experiment, in the absence of additive, the electrophiles, such as electron deficient aryl aldehydes, generated only triarylmethanes. However, the use of stoichiometric amount of pyridine as additive did not show any effective transformation, including the formation of triarylmethane. The reason for this observation may be due to the formation of coordination complex between pyridine

nitrogen with $AlBr_3$, and hence completely destroyed the carbonyl group activation. Therefore, the reactions were conducted with sub stoichiometric quantity of pyridine base. In the presence of pyridine (0.3 equiv.), the carbinol formation was noticed, and the reaction produced the carbinol in 50% yield along with triarylmethane 23%. After a quick survey of reaction condition, we found that the combination of 1 equivalent of $AlBr_3$ and 0.2 equivalent of pyridine as additive, the reaction produced the diarylcarbinol in moderate yield 58% along with triarylmethane in minor quantity (14%). However, the yield of desired product dropped when more than 0.2 equivalent of pyridine was used. Subsequently, to further increase the yield of carbinol, we have examined the other Lewis bases such as DABCO, DBU, bipyridine, DIPEA, imidazole, triethylamine, pyrazole, 8-hydroxy quinoline, as well as the higher equivalents of pyridine in this reaction. Very surprisingly, except pyridine, all other bases failed to effect this transformation. After extensive experimentation, the best condition was found to be 1 equivalent of $AlBr_3$ along with 0.2 equivalent of pyridine as additive in this transformation.

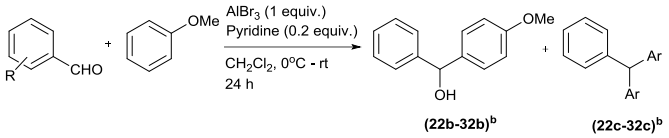


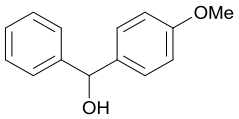
Py (equiv.)	Yield-I[b]	Yield-II[b]
0.0	-	47%
0.1	22%	34%
0.2	**58%**	**14%**
0.3	50%	23%

Scheme 5. Effect of pyridine equivalent on hydroxyalkylation with electron deficient aromatic aldehydes

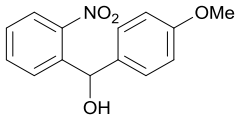
Generalization of this approach was made by studying the reaction of various aromatic aldehydes with anisole and the results are summarized in Table 2. Aromatic aldehydes with electron withdrawing substituents such as $–NO_2$, weakly activating group such as halides or the combination of these groups (halides, nitro or dihalides) or without substituents did participate in this reaction, and delivered the corresponding carbinols as major product along with triarylmethane as minor product. Strong electron withdrawing group (such as $–NO_2$) present in the aromatic aldehydes, irrespective of the position in aromatic ring (*o*, *p* and *m*) subjected to the present reaction condition, furnished the carbinols as well as triarylmethanes (Table 2, entries **23b**-**25b**). Similar results were obtained with other aromatic aldehydes bearing bromo, chloro or fluoro substituents (Table 2, entries **26b**-**32b**). Naphthaldehydes under present reaction condition smoothly delivered the corresponding carbinols in moderate yield (Table 2, entries **25b**-**26b**). The electron rich aryl aldehydes such as anisaldehyde or tolualdehyde failed to react with anisole in presence of either $AlBr_3$ or $AlBr_3$ with pyridine (0.2 equiv.) to generate carbinol or triarylmethane. Increasing or decreasing of catalyst loading did not show any fruitful results. These observations indicate that the electronic property of aldehyde also crucial for this transformation.

Table 2. Reaction of anisole with benzaldehyde/electron deficient benzaldehydes[a]

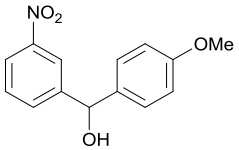




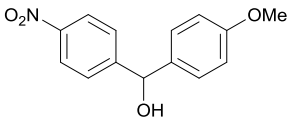
22b: 58%
22c: 14%



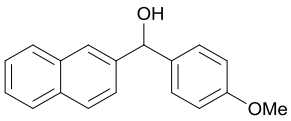
23b: 42%
23c: 13%



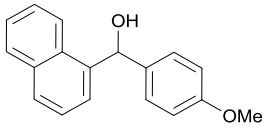
24b: 44%
24c: 17%



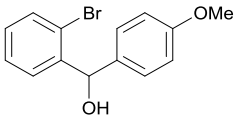
25b: 48%
25c: 21%



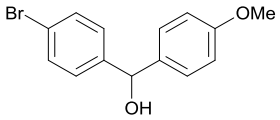
26b: 47%
26c: 14%



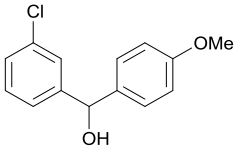
27b: 43%
27c: 18%



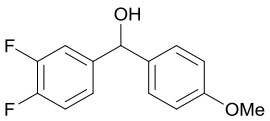
28b: 40%
28c: 27%



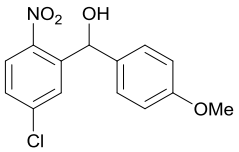
29b: 47%
29c: 19%



30b: 44%
30c: 21%



31b: 41%
31c: 24%



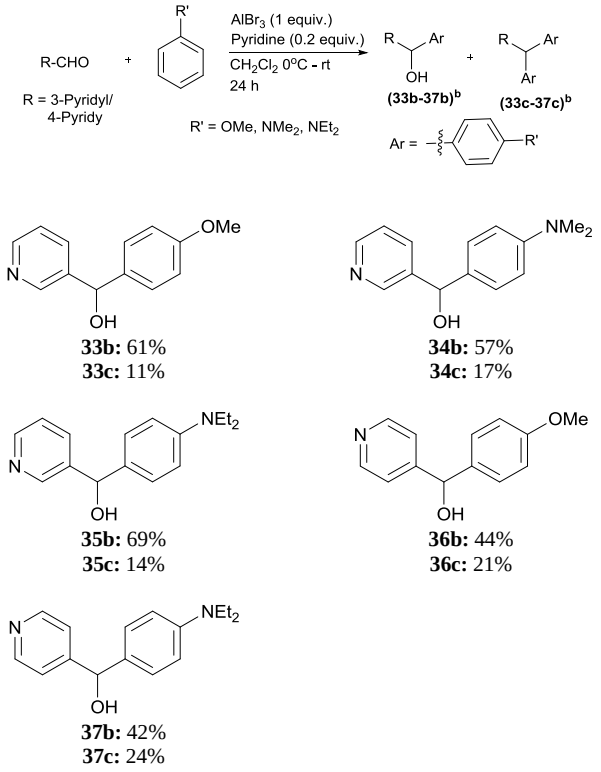
32b: 39%
32c: 28%

[a]Reaction condition: Aromatic aldehydes (1.0 mmol), anisole (1.0 mmol) in dry dichloromethane, pyridine (0.2 mmol), 0 °C-rt. [b]Isolated yield.

Other pyridine aldehydes with electron rich aromatic nucleophiles

The reaction of pyridine-3-carboxaldehyde/pyridine-4-carboxaldehyde with anisole in presence of $AlBr_3$ alone generated either the carbinols in poor yield or only triarylmethanes. This may be due to the lack of existence of bidentate coordination. Whereas, the reaction of pyridine-3-carboxaldehyde with anisole in the presence of $AlBr_3$ (1 equiv.) and pyridine (0.2 equiv.) the desired product, carbinol (**33b**), was produced in moderate yield along with minor quantity of triarylmethane (**33c**). Increasing of anisole equivalent (1.2 equiv.) in this reaction increased the chemical yield of triarylmethane. Having the optimized reaction condition, further scope and generality of this reaction was demonstrated by treating different aromatic π-nucleophiles with pyridine-3-carboxaldehyde as well as pyridine-4-carboxaldehyde.

Table 3. Reaction of anisole with 3 or 4- pyridine carboxaldehydes[a]



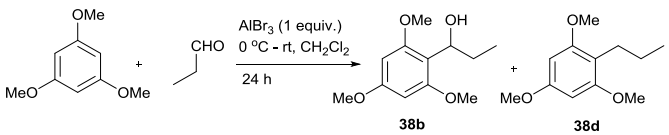
[a]Reaction condition: 3 or 4-Pyridine carboxaldehydes (1.0 mmol), anisole (1.0 mmol) in dry dichloromethane, pyridine (0.2 mmol), 0 °C-rt. [b]Isolated yield.

The reaction delivered the expected carbinols along with triarylmethane derivatives as by products (Table 3, entries **33b-37b** and **33c-37c**). The reaction of aldehyde with electron rich aromatic nucleophiles (1,3,5-trimethoxybenzene, indole) are always susceptible to give two nucleophile added product, the triarylmethanes. This may be due to the facile generation of carbocation and its stability. Based on these studies, we concluded that the complete retardation of triarylmethane formation proved to be difficult though the formation can be reduced to greater extent.

Aliphatic aldehydes with electron rich nucleophiles

To illustrate the efficacy of Friedel-Crafts hydroxyalkylation in presence of $AlBr_3$ with aliphatic aldehyde system, we surveyed the reaction of 1,3,5-trimethoxybenzene with propionaldehyde. Unfortunately, the propionaldehyde did not afford the expected carbinol, instead a complex mixture of unidentified products were witnessed under present reaction condition (1 equiv. of $AlBr_3$) due to the enolization property of aliphatic aldehydes in presence of Lewis acid.[29] In presence of $AlBr_3$ (1 equiv.) and pyridine (0.2 equiv.), the reaction of 1,3,5-trimethoxybenzene with propionaldehyde furnished the carbinol **38b** in 21% yield along with other unidentified product. Also, the Lewis acid activation of aliphatic aldehydes was less explored due to the formation of aldol product or enolization.[30] To avoid the enolization and subsequent aldol reaction, a pre-mixed solution of both propionaldehyde and 1,3,5-trimethoxybenzene in dichloromethane was treated with $AlBr_3$ and that furnished the expected carbinol **38b** in 31% yield along with alkane in 14% yield (Table 4, entry 1).

Table 4. Optimization of reaction condition[a]



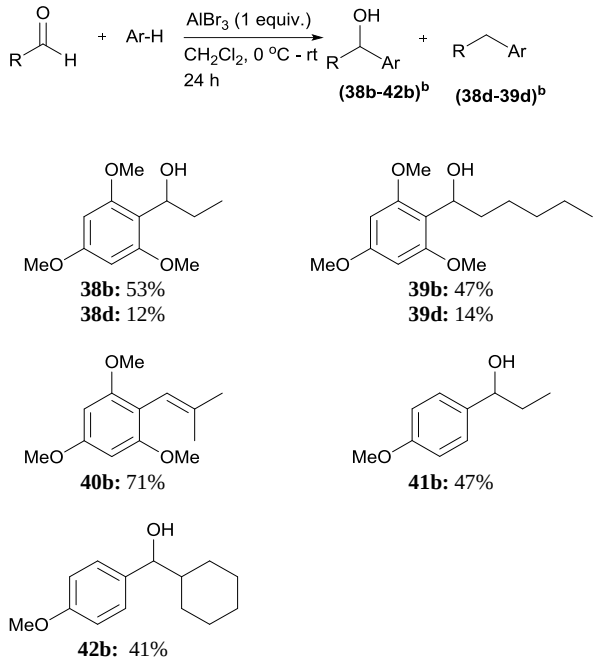
Entry	Aldehyde equiv.	**38b** yield[b]	**38d** yield[b]
1	1.0	31	14
2	1.2	37	21
3	1.4	43	17
4	1.6	48	18
5	**1.8**	**53**	**12**
6	2.0	51	-

[a]Reaction condition: 1,3,5-trimethoxybenzene (1.0 mmol) and aldehyde in dry dichloromethane, 0 °C-rt. [b]Isolated yield.

To increase the chemical yield of expected carbinol, the reactions were performed by increasing the equivalent of aldehydes, from 1.0 equivalent to 1.2, 1.4, 1.6, 1.8 and 2.0 equivalents. The chemical yield of the carbinol formation increased from 31% to 51% upon increase of aldehyde equivalent (Table 4, entries **2-6**). To the best of our knowledge examples of such transformations using Lewis acid or involving such hindered substrates with aliphatic aldehyde have not been reported earlier.[31] Better yield of carbinol **38b** was realized when the reaction was performed in presence of 1.8 equivalent of aliphatic aldehyde (Table 4, entry 5). Encouraged by the success of the carbinol formation, the methodology was extended to hexanal and generated the carbinol **39b** in moderate yield along with alkane **39d**.[32] Anisole conveniently reacted with aliphatic aldehydes such as propionaldehyde, cyclohexane

carboxaldehyde in the presence of 1 equivalent of $AlBr_3$ and delivered the carbinols in moderate yield (Table 5, entries **41b** and **42b**). The reaction of 1,3,5-trimethoxybenzene with isobutyraldehyde in presence of $AlBr_3$ furnished the dehydrated product (**40b**) instead of carbinol. To further increase the chemical yield of carbinol, the reaction of 1,3,5-trimethoxybenzene with propionaldehyde was carried out in presence of mild Lewis acid such as Me_2AlCl, unfortunately, the corresponding carbinol **38b** was isolated only in 7% yield.

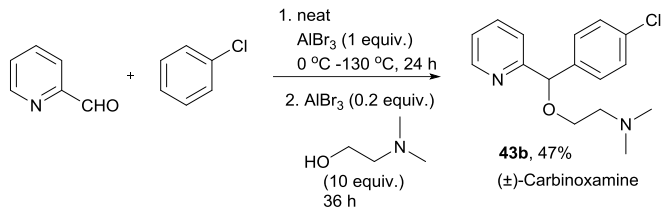
Table 5. Reaction of π-nucleophiles with aliphatic aldehydes[a]



[a]Reaction condition: π-Nucleophile (1.0 mmol) and aliphatic aldehyde (1.8 mmol) in dry dichloromethane, 0 °C-rt. [b]Isolated yield.

Synthesis of antihistamine drug:

(±)-Carbinoxamine (**43b**), potent anti-histamine H1 antagonists, containing 4-chlorophenylpyridylcarbinol moiety, has been synthesized previously by either the reduction of ketones or rearrangement reaction or using Grignard/lithium reagent. Over the years, very few reports have been developed for the synthesis of carbinoxamine from the intermediate carbinol. There are two methods reported so far, for example, the reaction of either haloalkylamines[33] or haloalkylamides[34] (followed by reduction) with carbinols in presence of a base to afford the corresponding aminoalkyl ether in moderate yield. The formation of diarylmethyl carbocation was witnessed during the preparation of carbinols from aldehyde and arene nucleophile in presence of $AlBr_3$. This carbocation was successfully trapped with oxygen nucleophiles such as methanol and allylalcohol to afford the corresponding ether derivatives.[19] This observation led the opportunity to device an economically viable and simple method to synthesize the carbinoxamine through Lewis acid assisted ether bond formation. Accordingly, the treatment of pyridine-2-carboxaldehyde with chlorobenzene in presence of $AlBr_3$ in refluxing dichloromethane afforded the corresponding carbinol in 41% yield after quenching with saturated sodium bicarbonate solution. The same reaction upon treating with *N*,*N*-dimethyl-2-aminoethanol afforded 23% of carbinoxamine (**43b**) as yellow oil in one pot fashion. The use of excess *N*,*N*-dimethyl-2-aminoethanol increased the carbinoxamine (**43b**) formation to 33%. Additional catalyst loading (0.2 equiv.) further enhanced the yield of carbinoxamine (37%) after treating with *N*,*N*-dimethyl-2-aminoethanol. Refluxing of pyridine-2-carboxaldehyde with chlorobenzene under neat condition in presence of $AlBr_3$ (1 equiv.) furnished the carbinol in 49% yield upon quenching with saturated sodium bicarbonate solution. Whereas the carbinoxamine (**43b**) was obtained in 47% yield by refluxing the mixture of pyridine-2-carboxaldehyde, chlorobenzene and $AlBr_3$ (1 equiv.) followed by treating the reaction mixture with excess of *N*,*N*-dimethyl-2-aminoethanol in presence of additional 0.2 equivalent of $AlBr_3$ for 36 h (Scheme 6).



Scheme 6: Synthesis of (±)-carbinoxamine

Conclusions

In conclusion we have developed a simple methodology for the synthesis of variety of diarylcarbinols from aldehydes and aromatic π-nucleophiles through aldehyde carbonyl group activation using $AlBr_3$. The presence of Lewis base (pyridine), both intermolecular and intramolecular, cooperatively modulated the reactivity of Lewis acid $AlBr_3$ in hydroxyalkylation reaction. Under this experimental condition, several functional groups are tolerated, particularly; halides, allyl and propargyl groups are stable. Depending on the number of equivalents of aldehyde, nucleophile with two or more reactive sites and $AlBr_3$, one can synthesize biscarbinols or carbinols. Furthermore, in situ carbonyl activation is achieved through chelation control in the case of electron deficient aromatic aldehydes (cooperative effect of Lewis pair). An efficient procedure has been developed, based on the Lewis acid catalyzed hydroxyalkylation reaction, for the synthesis of (±)-carbinoxamine, a therapeutically important histamine H_1 antagonist, in one pot manner using $AlBr_3$ as a catalyst.

Experimental section

General information

Melting points reported in this paper are uncorrected and were determined using BUCHI M-560, Buchi Labortechnik AG, Switzerland. Infrared spectra were recorded on Thermo Nicolet 6700 FT-IR Spectrophotometer and are reported in frequency of absorption (cm^{-1}). Mass spectra were measured with micro mass Q-TOF (ESI-HRMS) and Agilent-6530 B Q-TOF (ESI-HRMS), ^1H and ^{13}C NMR were recorded on Bruker AVANCE 400 spectrometer. NMR spectra for all the samples were measured in $CDCl_3$ using TMS as an internal standard. The chemical shifts are expressed in δ ppm down field from the signal of internal TMS.

Aluminum bromide and pyridine were purchased from Aldrich and used without further purification. Aldehydes were purchased from Aldrich and purified (liquid sample) by distillation under reduced pressure. Nucleophiles were prepared from corresponding phenols[35] and amines[36] using reported procedure. Solvents used for the reactions were dried using standard procedures.[37] Analytical thin layer chromatographic tests were carried out using pre-coated aluminum TLC plates. The spots were visualized by short exposure to iodine vapour or UV light. Column chromatography was carried out using Merck silica gel (100-200 mesh). All the glassware were pre-dried at 120 ºC for at least 6 h and assembled while hot and cooled under stream of dry nitrogen gas. In all experiments, round bottom flasks of appropriate size were used.

General procedure for the addition of π-nucleophiles to pyridine-2-carboxaldehyde, Condition A: (2b-19b)

An oven dried two neck round bottom flask bearing septum in side arm and fitted with condenser was cooled to room temperature under a steady stream of nitrogen gas flow. The flask was charged with stirring bar, $AlBr_3$ (266 mg, 1.0 mmol), dry dichloromethane (3 mL) and cooled down to 0 ºC (using ice). Then pyridine-2-carboxaldehyde (107 mg, 1 mmol) was added. The mixture was stirred for 30 minutes at 0 ºC under nitrogen atmosphere. To this mixture was added dichloromethane (5 mL) solution of nucleophile (1.2 mmol) in drops. The resulting reaction mixture was stirred at room temperature for 24 h. The reaction mixture was poured into aq. $NaHCO_3$ and stirred for 5 minutes, organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 15 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under reduced pressure. The residue was purified through silica gel column chromatography (silica gel 100-200 mesh), using hexane – EtOAc = 8 : 2 as an eluent to afford the pure products (**2b-19b**). [Note: ($AlBr_3$ (513 mg, 2.0 mmol) and pyridine-2-carboxaldehyde (215 mg, 2 mmol) were used for the synthesis of **20b** and **21b)**, using hexane – EtOAc = 1 : 9 as an eluent to afford the pure products **20b** and **21b**]

General procedure for the addition of π-nucleophiles to electron deficient aldehydes, Condition B: (22b-37b)

An oven dried two neck round bottom flask bearing septum in side arm and fitted with condenser was cooled to room temperature under a steady stream of nitrogen gas flow. The flask was charged with stirring bar, $AlBr_3$ (266 mg, 1.0 mmol), dry dichloromethane (3 mL) and cooled down to 0 ºC (using ice bath). Then electron deficient aldehydes (1 mmol) in dry dichloromethane (2 mL) at 0 ºC with stirring was added followed by the addition of dichloromethane solution of pyridine (0.016 mL, 0.2 mmol). Stirring was continued for 30 minutes. To this mixture was added the dichloromethane (3 mL) solution of anisole (1.0 mmol) in drops. The reaction mixture was stirred at room temperature for 24 h. After cooling to room temperature, the reaction mixture was poured into aq. $NaHCO_3$ and stirred for 5 minutes. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under reduced pressure. The residue was purified through silica gel column chromatography [(silica gel 100-200 mesh), using hexane – EtOAc = 9 : 1 as an eluent to afford the pure products (**22b-32b**) and using hexane – EtOAc = 19 : 1 as an eluent the pure products **22c-32c** were isolated. Hexane – EtOAc in 2 : 1 ratio was used to isolate the products **33b-37b** and hexane – EtOAc in 4 : 1 ratio was used to isolate products **33c-37c**]

General procedure for the addition of π-nucleophiles to aliphatic aldehydes, Condition C: (38b-42b)

An oven dried two neck round bottom flask bearing septum in side arm and fitted with condenser was cooled to room temperature under a steady stream of nitrogen gas flow. The flask was charged with stirring bar, $AlBr_3$ (266 mg, 1.0 mmol), dry dichloromethane (3 mL) and cooled down to 0 ºC (using ice bath) and stirred for 30 minutes. Aliphatic aldehydes (1.8 mmol) and π-nucleophiles (1.0 mmol) in dry dichloromethane (2 mL) was taken in small round bottom flask and mixed well. This mixture was added to the reaction mixture in drops over a period of 30 minutes with stirring. The stirring was continued at room temperature. After 24 h, the reaction mixture was poured into aq. $NaHCO_3$ and stirred for 5 minutes. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under reduced pressure. The residue was purified through silica gel column chromatography (silica gel 100-200 mesh), using hexane – EtOAc = 19 : 1 as eluent to afford the pure products (**38b-42b**) and using hexane as an eluent to afford the pure products (**38d** and **39d**).

3,4-Dimethoxyphenyl)(pyridin-2-yl)methanol[38] (2b)

174 mg (72%) of **2b** as yellow oil; IR (KBr cm^{-1}): 3427, 2932, 2838, 1594, 1513, 1464, 1262, 1142, 1029, 757; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.55 (d, *J* = 4.8 Hz, 1H), 7.63 (td, *J* = 8.0,

2.0 Hz, 1H), 7.20-7.17 (m, 1H) 7.14 (d, *J* = 7.6 Hz, 1H), 6.92-6.90 (m, 2H), 6.82 (d, *J* =8.0 Hz, 1H), 5.69 (s, 1H), 5.26 (br s, 1H), 3.84 (s, 3H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 161.1, 149.2, 148.8, 147.8, 136.9, 135.9, 122.5, 121.3, 119.6, 111.0, 110.0, 74.8, 55.99, 55.92. HRMS-ESI (*m/z*): Calculated for $C_{14}H_{15}NO_3$ (M+H): 246.1130, Found (M+H): 246.1122.

4-(Methylthio)phenyl)(pyridin-2-yl)methanol[38] (3b)

191 mg (83%) of **3b** as pale yellow oil; IR (KBr cm^{-1}): 3414, 3064, 2920, 1652, 1587, 1402, 1091, 749; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.55 (d, *J* = 4.8 Hz, 1H), 7.64 (td, *J* = 7.6, 1.6 Hz, 1H), 7.30-7.27 (m, 2H), 7.22-7.18 (m, 3H), 7.13 (d, *J* = 8.0 Hz, 1H), 5.71 (s, 1H), 5.21 (br s, 1H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 160.8, 147.9, 140.2, 138.1, 137.0, 127.7, 126.8, 122.6, 122.6, 121.4, 74.6, 15.9. HRMS-ESI (*m/z*): Calculated for $C_{13}H_{13}NOS$ (M+H): 232.0790, Found (M+H): 232.0791.

4-(Dimethylamino)phenyl)(pyridin-2-yl)methanol[38] (4b)

203 mg (89%) of **4b** as colorless solid; m.p. 71 ºC; IR (KBr cm^{-1}): 3197, 3084, 2893, 2804, 1614, 1593, 1526, 1362, 1167, 1051, 806, 775; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.55-8.53 (m, 1H), 7.62 (td, *J* = 7.6, 1.6 Hz, 1H), 7.22-7.20 (m, 2H), 7.18-7.15 (m, 2H), 6.71-6.69 (m, 2H), 5.69 (s, 1H), 2.92 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 161.7, 150.3, 147.7, 136.8, 131.3, 128.2, 122.2, 121.4, 112.7, 74.8, 40.7.

Pyridin-2-yl(2,4,6-trimethoxyphenyl)methanol[38] (5b)

246 mg (89%) of **5b** as colorless solid; m.p. 94 ºC; IR (KBr cm^{-1}): 3384, 3004, 2942, 2838, 1593, 1461, 1226, 1118, 1034, 805; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.53-8.52 (m, 1H), 7.58 (td, *J* = 7.6, 2.0 Hz, 1H), 7.22 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.11-7.08 (m, 1H), 6.03 (d, *J* = 7.2 Hz, 1H), 6.12 (s, 2H), 4.75 (d, *J* = 8.0 Hz, 1H), 3.79 (s, 3H), 3.69 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 163.1, 161.1, 159.3, 147.9, 136.1, 121.3, 120.2, 112.4, 91.4, 67.3, 55.9, 55.4. HRMS-ESI (m/z): Calculated for $C_{15}H_{17}NO_4$ (M+H): 298.1055, Found (M+H): 298.1056.

(2-Methoxy-4-methylphenyl)(pyridin-2-yl)methanol (6b)

192 mg (83%) of **6b** as colorless oil; IR (KBr cm^{-1}): 3411, 2999, 2926, 2836, 1607, 1501, 1246, 1043, 756; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.59-8.57 (m, 1H), 7.62 (td, *J* = 7.6, 2.0 Hz, 1H), 7.46 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.21-7.18 (m, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 7.04 (dd, *J* = 8.0, 0.8 Hz, 1H), 6.71-6.84 (m, 2H), 6.15 (br s, 1H), 5.90 (s, 1H), 3.77 (s, 3H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.3, 159.1, 147.8, 138.1, 136.9, 133.2, 129.7, 122.3, 121.3, 116.5, 111.3, 72.6, 55.3, 19.7. HRMS-ESI (m/z): Calculated for $C_{14}H_{15}NO_2$ (M+H):230.1175, Found (M+H): 230.1173.

(2-Bromo-4-methoxyphenyl)(pyridine-2-yl)methanol (7b)

179 mg, (61%) of **7b** as colorless solid; m.p. 121 ºC; IR (KBr cm^{-1}): 3388, 2900, 2831, 1590, 1484, 1438, 1241, 1038, 491; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.57 (d, *J* = 4.8 Hz, 1H), 7.62 (td, *J* = 7.6, 1.6 Hz, 1H), 7.23-7.19 (m, 3H), 7.11 (d, *J* = 2.4 Hz, 1H), 6.82 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.18 (s, 1H), 5.42 (br. s, 1H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.3, 159.6, 147.9, 137.0, 134.6, 129.9, 123.5, 122.7, 121.5, 117.7, 114.4, 72.8, 55.6. HRMS-ESI (m/z): Calculated for $C_{13}H_{13}NO_2Br$ (M+H): 294.0130, Found (M+H): 294.0128.

(5-Bromo-2-methoxyphenyl)(pyridine-2-yl)methanol (8b)

204 mg, (69%) of **8b** as colorless solid; m.p. 127 ºC; IR (KBr cm^{-1}): 3220, 3016, 2957, 2835, 1594, 1482, 1441, 1251, 1035, 798, 600, 536, 438; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.54 (d, *J* = 4.4 Hz, 1H), 7.61 (td, *J* = 7.6, 1.6 Hz, 1H), 7.44 (d, *J* = 2.4 Hz, 1H), 7.32 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.19 (dd, *J* = 6.8, 5.2 Hz, 1H), 6.77 (d, *J* = 8.8 Hz, 1H), 6.15 (d, *J* = 4.4 Hz, 1H), 5.32 (d, *J* = 4.4 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.4, 155.8, 147.9, 136.9, 134.1, 131.4, 130.7, 122.6, 121.3, 113.5, 112.6, 68.4, 55.9. HRMS-ESI (m/z): Calculated for $C_{13}H_{13}BrNO_2$ (M+H); 294.0124 Found: 294.0126.

(4-(Dimethylamino)-2-methoxyphenyl)(pyridin-2-yl)methanol (9b)

236 mg, (91%) of **9b** as brown oil; IR (KBr cm^{-1}): 3389, 2964, 1613, 1586, 1513, 1465, 1210; 1H NMR ($CDCl_3$, 400 MHz): δ 8.53 (d, *J* = 4.8 Hz, 1H), 7.60-7.56 (m, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.15-7.12 (m, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.29-6.25 (m, 2H), 6.08 (s, 1H), 4.94 (br s, 1H) 3.84 (s, 3H), 2.93 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.2, 157.9, 151.6, 147.7, 136.6, 128.8, 122.0, 121.3, 120.0, 105.1, 96.1, 69.5, 55.5, 40.8. HRMS-ESI (m/z): Calculated for $C_{15}H_{18}N_2O_2$ (M+H); 259.1441 Found: 259.1440.

(2-Methoxy-4-(piperidin-1-yl)phenyl)(pyridin-2-yl)methanol (10b)

244 mg, (91%) of **10b** as pale yellow oil; IR (KBr cm^{-1}): 3192, 2934, 2846, 1607, 1511, 1445, 1215, 1118, 1042, 962, 788; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.2 (d, *J* = 4.4 Hz, 1H), 7.60 (td, *J* = 7.6, 1.6 Hz, 1H), 7.26-7.24 (m, 1H), 7.15-7.12 (m, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.47-6.52 (m, 2H), 6.08 (s, 1H), 5.01 (br s, 1H), 3.82 (s, 3H), 3.1-3.11 (m, 4H), 1.71-1.65 (m, 4H), 1.58-1.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.9, 157.6, 153.2, 147.7, 136.6, 128.5, 122.6, 122.0, 121.3, 108.6, 100.1, 69.4, 55.5, 50.8, 25.9, 24.4. HRMS-ESI (m/z): Calculated for $C_{18}H_{22}N_2O_2$ (M+H); 299.1754 Found: 299.1759.

(4-(Isopropylamino)-2-methoxyphenyl)(pyridin-2-yl)methanol (11b)

215 mg, (79%) of **11b** as pale yellow oil; IR (KBr cm^{-1}): 3370, 3236, 2968, 2824, 1591, 1511, 1462, 1206, 1127, 1036, 814, 775, 550; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.52-8.51 (m, 1H), 7.60 (td, *J* = 7.6, 1.2 Hz, 1H), 7.26-7.24 (m, 1H), 7.15-7.12 (m, 1H), 6.96 (dd, *J* = 6.4, 2.4 Hz, 1H), 6.14-6.12 (m, 2H), 6.06 (s, 1H), 3.78 (s, 3H), 3.63-3.56 (m, 1H), 1.18 (d, *J* = 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.1, 158.1, 148.5, 147.6, 136.5, 129.1, 121.9, 121.3, 120.3, 105.3, 96.7, 69.5, 55.4, 44.4, 23.1. HRMS-ESI (m/z): Calculated for $C_{16}H_{20}N_2O_2$ (M+H); 273.1598 Found: 273.1592.

(2-(Dimethylamino)-4-(piperidin-1-yl)phenyl)(pyridin-2-yl)methanol (12b)

292 mg, (94%) of **12b** as yellow oil; IR (KBr cm^{-1}): 3468, 2932, 2852, 2793, 1604, 1507, 1228, 1011; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.54-8.52 (m, 1H), 7.64 (td, *J* = 7.6, 1.6 Hz, 1H), 7.46 (d, *J* = 7.6, 1.6 Hz, 1H), 7.13-7.10 (m, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.55 (d, *J* = 2.8 Hz, 1H), 6.47 (dd, *J* = 7.6, 2.8 Hz, 1H), 6.023 (s, 1H), 2.91 (s, 6H), 2.85-2.83 (m, 4H), 1.73-1.67 (m, 4H), 1.56 (br s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.9, 152.8, 150.7, 148.2, 136.5, 129.9, 126.2, 121.7, 120.8, 109.5, 105.9, 74.7, 54.8, 40.7, 26.7, 24.1. HRMS-ESI (m/z): Calculated for $C_{19}H_{25}N_3O$ (M+H); 312.2076 Found: 312.2066.

(1-(Allyloxy)naphthalen-2-yl)(pyridin-2-yl)methanol (13b)

227 mg, (78%) of **13b** as yellow solid; m.p. 78 ºC; IR (KBr cm^{-1}): 3210, 2858, 2743, 1968, 1880, 1857, 1593, 1511, 1155, 1085, 934, 808; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.54 (d, *J* = 4.8 Hz, 1H), 8.37-8.35 (m, 1H), 8.03-8.01 (m, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.45-7.43 (m, 2H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.21-7.18 (m, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 6.31 (s, 1H), 6.22-6.21 (m, 1H), 5.52 (d, *J* = 17.2 Hz, 1H), 5.34 (d, *J* = 10.4 Hz, 1H), 4.71 (d, *J* = 4.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.4, 154.7, 147.9, 136.9, 133.3, 132.3, 130.4, 126.8, 126.7, 126.5, 125.1, 124.3, 122.8, 122.4, 121.5, 117.5, 104.3, 73.7, 69.0. HRMS-ESI (m/z): Calculated for $C_{19}H_{17}NO_2$ (M+H); 292.1332 Found: 292.1328.

(5-Methyl-2-(prop-2-yn-1-yloxy)phenyl)(pyridin-2-yl)methanol (14b)

201 mg, (79%) of **14b** as yellow oil; IR (KBr cm^{-1}): 3422, 3292, 2922, 2858, 2122, 1594, 1498, 1238, 1034, 673; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.54 (d, *J* = 4.8 Hz, 1H), 7.60 (td, *J* = 8.0, 2.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.18-7.15 (m, 2H), 7.03 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 4.72 (d, *J* = 2.4 Hz, 1H), 2.49 (t, *J* = 2.4 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 161.1, 152.7, 147.7, 136.9, 132.3, 131.5, 129.1, 128.5, 122.3, 121.5, 112.7, 78.8, 75.5, 68.9, 56.6, 20.7. HRMS-ESI (m/z): Calculated for $C_{16}H_{15}NO_2$ (M+H); 254.1176 Found: 254.1176.

(5-Bromothiophen-2-yl)(pyridin-2-yl)methanol (15b)

195 mg, (73%) of **15b** as black solid; m.p. 63 ºC; IR (KBr cm^{-1}): 3397, 2942, 2839, 1598, 1468, 1436, 1130, 1098, 1037, 754; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.57 (d, *J* = 4.8 Hz, 1H), 7.73-7.68 (td, *J* = 8.0, 1.6 Hz, 1H), 7.29-7.25 (m, 2H), 6.90 (d, *J* = 3.6 Hz, 1H), 6.78 (d, *J* = 3.6 Hz, 1H), 5.92 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.3, 149.0, 148.1, 137.4, 129.5, 125.5, 123.2, 121.3, 112.8, 71.1. HRMS-ESI (m/z): Calculated for $C_{10}H_9NOS$ (M+H); 269.9588 Found: 254.269.9588.

Benzo[b]thiophen-3-yl(pyridin-2-yl)methanol[2] (16b)

179 mg, (74%) of **16b** as yellow oil. IR (KBr cm^{-1}): 3139, 2844, 1592, 1430, 1046, 764, 733; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.51 (d, *J* = 4.4 Hz, 1H), 7.48-7.72 (m, 1H), 7.66-7.65 (m, 1H), 7.50 (td, *J* = 7.6, 1.6 Hz, 1H), 7.21-7.17 (m, 2H), 7.12-7.08 (m, 1H), 6.03 (s, 1H) 5.34 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.8, 148.1, 141.2, 137.7, 137.5, 137.1, 125.1, 124.5, 124.2, 123.0, 122.9, 122.8, 121.4, 71.0.

(4-(Methylamino)-2-nitrophenyl)(pyridin-2-yl)methanol (17b)

159 mg, (72%) of **17b** as yellow solid, m.p. 87 ºC; IR (KBr cm^{-1}): 3384, 3141, 2918, 2852, 1632, 1569, 1523, 1172, 1044, 760; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.57 (d, *J* = 4.8 Hz, 1H), 8.20 (d, *J* = 2.0 Hz, 1H), 8.07 (br s, 1H), 7.67 (td, *J* = 8.0, 2.0 Hz, 1H), 7.46 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.24-7.21 (m, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 1H), 5.68 (s, 1H), 5.31 (br s, 1H), 3.01 (d, *J* = 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.3, 148.0, 146.2, 137.2, 135.3, 130.5, 125.4, 122.8, 121.4, 114.2, 73.9, 29.9. HRMS-ESI (m/z): Calculated for $C_{13}H_{13}N_3O_3$ (M+H); 260.1029 Found: 260.1024

Benzofuran-3-yl(pyridin-2-yl)methanol[2] (18b)

163 mg, (72%) of **18b** as yellow oil; IR (KBr cm^{-1}): 3350, 3097, 2978, 1584, 1441, 1148, 1350, 1097, 842; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.61 (d, *J* = 4.8 Hz, 1H), 7.73 (td, *J* = 7.6, 1.6 Hz, 1H), 7.53-7.51 (m, 1H), 7.44-7.38 (m, 2H), 7.29-7.26 (m, 1H), 7.24-7.17 (m, 2H), 6.69 (s, 1H), 6.68 (s, 1H), 5.93 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.9, 157.4, 155.3, 148.2, 137.2, 128.2, 124.3, 123.3, 122.9, 121.6, 121.2, 111.4, 104.2, 69.2. HRMS-ESI (m/z): Calculated for $C_{14}H_{11}NO_2$ (M+H); 226.0859 Found: 226.0858.

(5-Methyl-2-((5-(p-tolyloxy)pentyl)oxy)phenyl)(pyridin-2-yl)methanol (19b)

289 mg, (73%) of **19b** as colorless oil; IR (KBr cm^{-1}):3415, 2922, 1597, 1513, 1242, 816, 509; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.52 (d, *J* = 4.8 Hz, 1H), 7.56 (td, *J* = 7.6, 1.6 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.14-7.12 (m, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 7.02 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.78-6.76 (m, 3H), 6.14 (s, 1H), 5.22 (br s 1H), 4.05-4.01 (m, 1H), 3.96-3.90 (m, 3H), 2.27 (s, 3H), 2.23 (s, 3H), 1.84-1.77 (m, 4H), 1.59-1.58 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.5, 157.0, 154.0, 147.7, 136.7, 131.4, 130.1, 129.9, 129.8, 129.1, 128.6, 122.2, 121.3, 114.4, 111.7, 697, 68.22, 67.8, 29.2, 29.1, 22.9, 20.7, 20.5. HRMS-ESI (m/z): Calculated for $C_{25}H_{29}NO_3$ (M+H); 392.2220 Found: 392.2211.

((Pentane-1,5-diylbis(oxy))bis(5-methyl-2,1-phenylene))bis(pyridin-2-ylmethanol) (20b)

303 mg, (61%) of **20b** as colorless oil; IR (KBr cm^{-1}): 3449, 2996, 2944, 2838, 1606, 1471, 1091, 1031, 917, 816; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.50-8.46 (m, 2H), 7.56 (td, *J* = 7.6, 1.6 Hz, 2H), 7.27-7.14 (m, 2H), 7.14-7.09 (m, 4H), 7.02-6.99 (m, 2H), 6.76 (d, *J* = 8.4 Hz, 1H), 6.14 (s, 1H), 4.03-3.98 (m, 2H), 3.93-3.87 (m, 2H), 2.23 (s, 1H), 1.81-1.73 (m, 3H), 1.59-1.48 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.6, 161.5, 154.0, 147.7, 136.7, 131.3, 130.1, 129.1, 128.6, 128.6, 122.2, 121.2, 11.7, 69.7, 69.7, 68.1, 29.1, 22.9, 20.6. HRMS-ESI (m/z): Calculated for $C_{31}H_{34}N_2O_4$ (M+H); 499.2591 Found: 499.2591.

(2,4,6-Trimethoxy-1,3-phenylene)bis(pyridin-2-ylmethanol) (21b)

163 mg, (42%) of **21b** as colourless solid; m.p. 96 ºC; IR (KBr cm^{-1}): 3008, 2907, 2828, 1610, 1513, 1109, 1020, 836, 820, 800, 785, 757, 736; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.53-8.52 (m, 2H), 7.61-7.56 (m, 2H), 7.23-7.17 (m, 2H), 7.14-7.11 (m, 2H), 6.21 (s, 1H), 6.16 (s, 2H), 3.58-3.57 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.5, 162.4, 159.4, 159.3, 159.2, 147.6, 147.5, 136.36, 136.34, 121.6, 120.3, 120.1, 117.4, 117.3, 93.3, 93.1, 67.7, 64.1, 63.7, 55.7; HRMS-ESI (m/z): Calculated for $C_{21}H_{22}N_2O_5$ (M+H); 383.1601 Found: 383.1601.

(4-Methoxyphenyl)(phenyl)methanol (22b)[39] (Table 2)

125 mg (58%) of **22b** as colorless solid; m.p. 104 ºC; IR (KBr cm^{-1}): 3409, 3006, 2950, 2834, 1610, 1586, 1515, 1255, 1175, 1032, 809, 726; ^{1}H NMR ($CDCl_3$, 400 MHz) : δ 7.35-7.22 (m, 7H), 6.83 (d, *J* = 8.8 Hz, 1H), 5.76 (s, 1H), 3.75 (s, 3H), 2.30 (br, s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.1, 144.1, 136.3, 128.5, 128.0, 127.5, 126.5, 114.0, 75.9, 55.4.

4,4'-(Phenylmethylene)bis(methoxybenzene)[40] (22c)

43 mg (14%) of **22c** as colorless solid; m.p. 79 ºC; IR (KBr cm^{-1}): 3015, 2945, 2835, 1601, 1503, 1446, 1241, 1184, 1025, 816; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30-7.25 (m, 2H), 7.22-7.17 (m, 1H), 7.12-7.09 (m, 2H), 7.03-7.01 (m, 4H), 6.84-6.80 (m, 4H), 5.45 (s, 1H), 3.78 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.9, 144.5, 136.4, 130.2, 129.2, 128.2, 126.1, 113.6, 55.2, 55.1. HRMS-ESI (m/z): Calculated for $C_{21}H_{20}O_2$ (M+K): 343.1100, Found (M+K): 343.1103.

(4-Methoxyphenyl)(2-nitrophenyl)methanol[39] (23b)

110 mg, (42%) of **23b** as yellow oil; IR (KBr cm^{-1}): 3432, 2935, 2837, 1609, 1529, 1349, 1249, 1175, 1029, 733; ^{1}H NMR ($CDCl_3$, 400 MHz) : δ 7.91 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.79 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.64 (td, *J* = 8.0, 1.2 Hz, 1H), 7.46-7.42 (m, 1H), 7.24-7.21 (m, 2H), 6.86-6.84 (m, 2H), 6.40 (s, 1H), 3.78 (s, 3H), 2.69 (br, s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.4, 148.3, 138.8, 133.9, 133.4, 129.1, 128.4, 124.7, 114.0, 71.2, 55.3.

4,4'-((2-Nitrophenyl)methylene)bis(methoxybenzene)[40] (23c)

46 mg, (13%) of **23c** as yellow solid; m.p. 114ºC; IR (KBr cm^{-1}): 3005, 2952, 2837, 1602, 1520, 1462, 1360, 1245, 1032, 751; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.47 (td, *J* = 8.0, 1.2 Hz, 1H), 7.36 (td, *J* = 8.0, 1.2 Hz, 1H), 7.03 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.97-6.95 (m, 4H), 6.83-6.81 (m, 4H), 6.16 (s, 1H), 3.78 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.4, 139.0, 134.5, 132.4, 131.9, 130.4, 127.4, 124.7, 114.0, 55.3, 49.8. HRMS- ESI (*m/z*): Calculated for $C_{21}H_{19}NO_4$ (M+Na): 372.1212, Found (M+Na): 372.1217.

(4-Methoxyphenyl)(3-nitrophenyl)methanol[41] (24b)

115 mg, (42%) of **24b** as yellow solid; m.p. 59 ºC; IR (KBr cm^{-1}): 3344, 3109, 3020, 2965, 2894, 1606, 1513, 1348, 1249, 1175, 1037, 798; ^{1}H NMR ($CDCl_3$, 400 MHz) : δ 8.27 (t, *J* = 2.0 Hz,1H), 8.10 (ddd, *J* = 8.0, 2.0, 0.8 Hz, 1H), 7.71-7.68 (m, 1H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.27-7.25 (m, 2H), 6.90-6.86 (m, 2H), 5.87 (d, *J* = 2.8 Hz, 1H), 3.79 (s, 3H), 2.42 (d, *J* = 3.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.5, 148.3, 146.0, 135.0, 132.3, 129.2, 128.0, 122.2, 121.2, 114.2, 74.9, 55.3.

4,4'-((3-Nitrophenyl)methylene)bis(methoxybenzene)[40] (24c)

60 mg, (17%) of **24c** as yellow solid; m.p. 110 ºC; IR (KBr cm^{-1}): 3002, 2956, 2835, 1609, 1529, 1509, 1461, 1350, 1248, 1178, 1035, 842; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06-8.05 (m, 1H), 7.98-7.97 (m, 1H), 7.46-7.41 (m, 2H), 7.02-6.98 (m, 4H), 6.86-6.83 (m, 4H), 5.54 (s, 1H), 3.79(s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.3, 148.3, 146.9, 135.4, 134.8, 130.1, 129.1, 124.0, 121.4, 114.0, 55.2, 54.8. HRMS-ESI (*m/z*): Calculated for $C_{21}H_{19}NO_4$ (M+Na): 372.1212, Found (M+Na): 372.1219.

(4-Methoxyphenyl)(4-nitrophenyl)methanol[42] (25b)

125 mg, (48%) of **25b** as yellow solid; m.p. 55 ºC; IR (KBr cm^{-1}): 3504, 3093, 2933, 2841, 1609, 1526, 1348, 1237, 1040, 1020, 732; ^{1}H NMR ($CDCl_3$, 400 MHz) : δ 8.16-8.13 (m, 2H), 7.55-7.51 (m, 2H), 7.25-7.20 (m, 2H), 6.87-6.84 (m, 2H), 5.83 (s, 1H), 3.77 (s, 3H), 2.66 (br, s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.6, 151.2, 147.1, 135.1, 128.2, 127.0, 123.6, 114.3, 75.1, 55.4.

4,4'-((4-Nitrophenyl)methylene)bis(methoxybenzene)[40] (25c)

75 mg (21%) of **25c** as yellow solid; m.p. 118 ºC; IR (KBr cm^{-1}): 3001, 2938, 2837, 1603, 1514, 1345, 1298, 1249, 1179, 1030, 816; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14-8.12 (m, 2H), 7.28-7.25 (m, 2H), 7.00-6.97 (m, 4H), 6.86-6.83 (m, 4H), 5.53 (s, 1H), 3.79 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.5, 152.5, 146.5, 134.9, 130.3, 130.2, 123.6, 114.1, 55.4, 55.1. HRMS-ESI (*m/z*): Calculated for $C_{21}H_{19}NO_4$ (M+Na): 372.1212, Found (M+Na): 372.1211.

(4-Methoxyphenyl)(naphthalen-2-yl)methanol[39] (26b)

125 mg, (47%) of **26c** as yellow solid; m.p. 73 ºC IR (KBr cm^{-1}): 3538, 3062, 3003, 2906, 1607, 1509, 1350, 1248, 1179, 1056, 1020, 828,781; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99-7.97 (m, 1H), 7.88 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H) 7.69 (d, *J* = 8.4 Hz, 1H), 7.52-7.50 (m, 1H), 7.48-7.42 (m, 2H), 7.32-7.28 (m, 2H), 6.86-6.83 (m, 2H), 6.48 (s, 1H), 3.77 (s, 3H), 2.42 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.2, 139.0, 135.5, 134.0, 130.7, 128.8, 128.5, 128.4, 126.1, 125.6, 125.4, 124.3, 124.1, 114.0, 73.3, 55.3.

2-(Bis(4-methoxyphenyl)methyl)naphthalene[17] (26c)

51 mg (14%) of **26c** as colorless solid; m.p. 66 ºC; IR (KBr cm^{-1}): 3049, 1687, 1574, 1510, 1299, 1248, 1213, 802, 772; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (d, *J* = 8.0 Hz, 1H), 7.86-7.84 (m, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.45-7.34 (m, 3H), 7.03-7.01 (m, 4H), 6.96 (d, *J* = 7.2 Hz, 1H), 6.17 (s, 1H), 3.78 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.1, 140.7, 136.4, 134.0, 132.0, 130.6, 128.8, 127.5, 127.3, 126.1, 125.5, 125.3, 124.5, 113.9, 55.3, 51.6.

(4-Methoxyphenyl)(naphthalen-1-yl)methanol[39] (27b)

113 mg, (47%) of **27b** as brown solid; m.p. 76 °C IR (KBr cm^{-1}): 3059, 2965, 2833, 1610, 1513, 1019, 820, 757, 582; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.99 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.88 (dd, *J* = 7.2, 2.0 Hz, 1H) 7.69 (d, *J* = 7.2 Hz, 1H), 7.52-7.40 (m, 3H), 7.31-7.28 (m, 2H), 6.85-6.83 (m, 2H), 6.47 (s, 1H), 3.77 (s, 3H), 2.46 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.1, 139.0, 135.5, 133.9, 130.7, 128.8, 128.5, 128.4, 126.1, 125.6, 125.4, 124.2, 124.0, 114.0, 73.2, 55.3.

1-(Bis(4-methoxyphenyl)methyl)naphthalene[44] (27c)

62 mg, (47%) of **27c** as yellow oil; IR (KBr cm^{-1}): 2924, 2853, 1595, 1479, 1238, 749; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.99 (d, *J* = 8.4, Hz, 1H), 7.86-7.83 (m, 1H), 7.73 (d, *J* = 8.0, Hz, 1H), 7.45-7.40 (m, 2H), 7.39-7.33 (m, 1H), 7.02-7.00 (m, 4H), 6.94 (d, *J* = 7.2, Hz, 1H), 6.83-6.80 (m, 4H), 6.17 (s, 1H), 3.78 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.1, 140.7, 136.4, 134.0, 132.0, 130.6, 128.8, 127.5, 127.3, 126.1, 125.5, 125.3, 124.5, 113.8, 55.3, 51.6.

(2-Bromophenyl)(4-methoxyphenyl)methanol[45] (28b)

116 mg, (40%) of **28b** as yellow oil; IR (KBr cm^{-1}):3394, 2952, 2835, 1610, 1510, 1248, 1173, 1032, 750; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.64 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.53 (dd *J* = 8.0, 1.2 Hz, 1H), 7.37 (td, *J* = 7.6, 1.2 Hz, 1H), 7.31-7.28 (m,2H), 7.16 (td, *J* = 7.6, 1.6 Hz, 1H), 6.87-6.84 (m, 2H), 6.11 (s, 1H), 3.78 (s, 3H), 2.46 (br, s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.2, 142.7, 134.5, 132.9, 129.0, 128.5, 128.3, 127.7, 122.7, 113.9, 70.5, 55.3.

1-Bromo-2-((4-methoxyphenyl)(phenyl)methyl)benzene[44] (28c)

105 mg, (27%) of **6k** as yellow oil; IR (KBr cm^{-1}): 2955, 2933, 2835, 1610, 1510, 1248, 1173, 1032, 750; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.57 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.22 (td, *J* = 7.6, 1.2 Hz, 1H), 7.09 (td, *J* = 7.6, 1.6 Hz, 1H), 6.99-6.96 (m, 2H), 6.95 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.84-6.81 (m, 2H), 5.83 (s, 1H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.2, 143.9, 135.2, 133.1, 131.3, 130.6, 128.0, 127.3, 125.6, 113.8, 55.3, 54.5.

(4-Bromophenyl)(4-methoxyphenyl)methanol[45] (29b)

137 mg, (47%) of **29b** as colorless solid; m.p. 79 °C IR (KBr cm^{-1}): 3309, 2959, 2836, 1610, 1513, 1399, 1249, 1172, 1006, 834; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.46-7.43 (m, 2H), 7.26-7.22 (m, 4H), 6.88-6.84 (m, 2H), 575 (s, 1H), 3.79 (s, 3H), 2.19 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.3, 143.0, 135.8, 131.5, 128.2, 128.0, 121.3, 114.1, 75.3, 55.4.

4,4'-((4-Bromophenyl)methylene)bis(methoxybenzene)[44] (29c)

73 mg, (19%) of **29c** as yellow oil; IR (KBr cm^{-1}): 2959, 2906, 1610, 1485, 1258, 1113, 1070, 1006, 857, 555; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40-7.38 (m, 2H), 7.00-6.96 (m, 6H), 6.83-6.81 (m, 4H), 5.40 (s, 1H), 3.79 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.2, 143.8, 135.9, 131.4, 131.1, 130.3, 120.2, 113.9, 55.3, 54.7.

(3-Chlorophenyl)(4-methoxyphenyl)methanol[43] (30b)

110 mg, (47%) of **30b** as pale yellow oil; IR (KBr cm^{-1}): 3426, 2954, 2836, 1611, 1510, 1249, 1174, 1111, 1033, 791; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.39 (m, 1H), 7.27-7.23 (m, 5H), 6.88-6.86 (m, 2H), 5.76 (s, 1H), 3.79 (s, 3H), 2.20 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.4, 146.1, 135.7, 134.5, 129.8, 128.1, 127.6, 126.6, 124.6, 114.2, 75.3, 55.4.

4,4'-((3-Chlorophenyl)methylene)bis(methoxybenzene)[45] (30c)

72 mg, (47%) of **30c** as yellow oil; IR (KBr cm^{-1}): 2934, 2836, 1597, 1510, 1466, 1250, 1173, 1033, 791; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.20-7.18 (m, 2H), 7.08 (t, *J* = 2.0 Hz, 1H), 7.00-6.97 (m, 5H), 6.83-6.81 (m, 4H), 5.41 (s, 1H), 3.78 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 1158.2, 146.9, 135.7, 134.3, 130.3, 129.6, 129.4, 127.6, 126.5, 113.9, 55.3, 55.0.

(3,4-Difluorophenyl)(4-methoxyphenyl)methanol (31b)

103 mg, (41%) of **31b** as yellow oil; IR (KBr cm^{-1}): 2954, 2836, 1609, 1510, 1249, 1178, 1034, 817; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.24-7.21 (m, 2H), 7.20-7.17 (m, 1H), 7.13-7.08 (m, 1H), 7.07 -7.03 (m, 1H), 6.89-6.85 (m, 2H), 5.73 (s, 1H), 3.79 (s, 3H), 2.34 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.4, 151.6 (dd, J_1 = 131 Hz, J_2 = 13 Hz), 149.0 (dd, J_1 = 74 Hz, J_2 = 13 Hz), 141.1 (t, *J* = 4 Hz), 135.6, 128.0, 122.2 (dd, J_1 = 6.4 Hz, J_2 = 3.6 Hz), 117.2 (d, *J* = 17.1 Hz), 115.5 (d, *J* = 17.9 Hz), 114.2, 74.8, 55.3. HRMS-ESI (m/z): Calculated for $C_{14}H_{11}F_2O_2$ (M-H); 249.0727 Found: 249.0723.

4,4'-((3,4-Difluorophenyl)methylene)bis(methoxybenzene)[46] (31c)

81 mg, (24%) of **31c** as yellow oil; IR (KBr cm^{-1}): 3411, 2958, 2838, 1604, 1516, 1343, 1251, 1176, 1030, 832; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.10-7.05 (m, 1H), 7.03-6.99 (m, 4H), 6.93-6.90 (m, 1H), 6.89-6.82 (m, 5H), 5.42 (s,1H), 3.80 (s,1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.3, 151.5 (dd, J_1 = 131 Hz, J_2 = 13 Hz), 149.0 (dd, J_1 = 129 Hz, J_2 = 13 Hz), 149.0 (t, *J* = 4 Hz), 135.6, 130.2, 125.2 (dd, J_1 = 6 Hz, J_2 = 3.4 Hz), 118.3 (d, *J* = 18 Hz), 117.0 (d, *J* = 16.9 Hz), 113.9, 55.3, 54.4.

(5-Chloro-2-nitrophenyl)(4-methoxyphenyl)methanol (32b)

114 mg, (39%) of **32b** as red oil; IR (KBr cm^{-1}): 3409, 3004, 2936, 2840, 1612, 1516, 1247, 1176, 1110, 1032, 822, 761; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.90-7.88 (m, 2H), 7.41 (dd, *J* = 8.8, 2.0 Hz, 1H) 7.22-7.20 (m, 2H), 6.87-6.83 (m, 2H), 6.43 (d, *J* = 2.8 Hz, 1H), 3.78 (s, 3H), 2.64 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.6, 146.2, 141.0, 140.2, 133.3, 129.0, 128.6, 128.5, 126.4, 114.2, 71.0, 55.42. HRMS-ESI (*m/z*): Calculated for $C_{14}H_{12}ClNO_4$ (M+H); 316.0352 Found: 316.0324.

4,4'-((5-Chloro-2-nitrophenyl)methylene)bis(methoxybenzene) (32c)

107 mg, (28%) of **32c** as brown oil; IR (KBr cm^{-1}): 3072, 3001, 2933, 2836, 1605, 1567, 1511, 1345, 1251, 1178, 1033, 827; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.82 (d, *J* = 8.8 Hz, 1H), 7.35 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.06 (d, *J* = 2.4 Hz, 1H), 6.96-6.95 (m,

4H), 6.86-6.83 (m, 4H), 6.19 (s, 1H), 3.79 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.6, 148.0, 141.3, 139.0, 133.6, 131.8, 130.4, 127.6, 126.3, 114.1, 55.3, 49.9.

(4-Methoxyphenyl)(pyridin-3-yl)methanol[38] (33b)

132 mg, (61%) of **33b** pale yellow solid; m.p. 101 ºC; IR (KBr cm^{-1}): 3201, 2994, 2832, 1586, 1511, 1251, 1173, 1029, 808, 715; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.50 (d, *J* = 2.4 Hz, 1H), 8.38 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.70-7.67 (m, 1H), 7.27-7.23 (m, 2H), 7.22-7.20 (m, 1H), 6.87-6.85 (m, 2H), 5.79 (s, 1H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.3, 148.4, 148.1, 139.9, 135.6, 134.3, 128.0, 123.5, 114.1, 73.6, 55.4. HRMS-ESI (*m/z*): Calculated for $C_{13}H_{14}NO_2$ (M+H): 216.1025, Found (M+H): 216.1016.

3-(Bis(4-methoxyphenyl)methyl)pyridine[45] (33c)

34 mg, (11%) of **33c** as brown solid; m.p. 77 ºC; IR (KBr cm^{-1}): 3049, 2980, 1593, 1411, 1242, 1047, 844, 714; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.45 (d, *J* = 4.8 Hz, 1H), 8.41 (d, *J* = 1.2 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.21 (dd, *J* = 7.6, 4.8, Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 4H), 6.83 (d, *J* = 8.4 Hz, 4H), 5.45 (s, 1H), 3.78 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.3, 150.8, 147.6, 140.1, 136.7, 135.3, 130.2, 123.3, 114.0, 55.3, 52.8.

(4-(Dimethylamino)phenyl)(pyridin-3-yl)methanol[16] (34b)

130 mg, (57%) of **34b** pale yellow solid; m.p. 103 ºC; IR (KBr cm^{-1}): 3166, 2855, 1612, 1523, 1347, 1159, 1058, 798; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.85 (d, *J* = 1.6 Hz, 1H), 8.45 (dd, *J* = 4.4, 1.6 Hz, 1H), 7.72 (dt, *J* = 7.6, 3.2, 1.6 Hz, 1H), 7.24-7.23 (m, 1H), 7.21-7.18 (m, 2H), 6.70-6.67 (m, 2H), 5.78 (s, 1H), 2.93 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.5, 148.4, 148.2, 139.8, 134.1, 131.1, 127.9, 123.3, 112.6, 74.0, 40.6.

4,4'-(Pyridin-3-ylmethylene)bis(*N*,*N*-dimethylaniline)[16] (34c)

57 mg, (17%) of **34c** yellow solid; m.p. 106 ºC; IR (KBr cm^{-1}): 2966, 2931, 2869, 1641, 1589, 1546, 1526, 1408, 1272, 1198, 1148; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.45-8.42 (m, 2H), 7.44 (dt *J* = 8.0, 1.6 Hz, 1H), 7.19-7.16 (m,1H), 6.99-6.95 (m, 4H), 6.69-6.65 (m, 4H), 5.38 (s, 1H), 2.92 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.9, 149.2, 147.3, 140.9, 136.7, 131.5, 129.9, 123.1, 112.69, 52.6, 40.7.

(4-(Diethylamino)phenyl)(pyridin-3-yl)methanol (35b)

177 mg, (69%) of **35b** yellow solid; m.p. 63 ºC; IR (KBr cm^{-1}): 3399, 2970, 1612, 1520, 1053, 807, 715; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.52 (s, 1H), 8.36 (dd, *J* = 4.8, 1.2 Hz, 1H), 7.72 (dt, *J* = 8.0, 3.2, 1.6 Hz, 1H), 7.21-7.18 (m, 1H), 7.14-7.12 (m, 2H), 6.62-6.60 (m, 2H), 5.72 (s, 1H), 3.34 (q, *J* = 14.4, 7.2 Hz, 4H), 1.13 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.1, 148.0, 147.6, 140.2, 134.2, 130.1, 128.1, 123.3, 111.7, 73.8, 44.4, 12.6. HRMS-ESI (*m/z*): Calculated for $C_{16}H_{20}N_2O$ (M+H): 257.1648, Found (M+Na): 257.1648.

4,4'-(Pyridin-4-ylmethylene)bis(*N*,*N*-diethylaniline) (35c)

54 mg, (14%) of **35c** brown oil; IR (KBr cm^{-1}): 2969, 1612, 1515, 1265, 1197, 806, 717; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.48 (dd, *J* = 4.8, 1.6 Hz, 2H), 7.10-7.09 (m, 2H), 6.94-6.92 (m, 4H), 6.94-6.92 (m, 4H), 6.62-6.60 (m, 4H), 5.27 (s, 1H), 3.35 (q, *J* = 14, 7.2 Hz, 8H), 1.17 (t, *J* = 7.2 Hz, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.8, 149.6, 146.6, 130.5, 129.1, 124.8, 111.0, 54.9, 44.1, 12.4. HRMS-ESI (*m/z*): Calculated for $C_{26}H_{33}N_3$ (M+H):388.2747, Found (M+Na):388.2742.

(4-Methoxyphenyl)(pyridin-4-yl)methanol[38] (36b)

95 mg, (44%) of **36b** colorless solid; m.p. 107 ºC; IR (KBr cm^{-1}): 3409, 3052, 2922, 2851, 1623, 1587, 1510, 1078, 808, 746; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.38 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.29 (ddd, *J* = 4.8, 1.6, 0.8 Hz, 2H), 7.23-7.21 (m, 2H), 6.85-6.83 (m, 2H), 5.71 (s, 1H), 3.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.5, 153.5, 149.4, 135.3, 128.3, 121.4, 114.2, 74.4, 55.4.

4-(Bis(4-methoxyphenyl)methyl)pyridine (36c)

64 mg, (21%) of **36c** yellow solid; m.p. 117 ºC; IR (KBr cm^{-1}): 3069, 2953, 2834, 1610, 1510, 1412, 1302, 1249, 1181, 1032, 817; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.50-8.48 (m, 2H) 7.03-7.02 (m, 2H), 7.00-6.98 (m, 4H), 6.85-6.82 (m, 4H), 5.39 (s, 1H), 3.78 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.4, 153.7, 149.8, 134.7, 130.3, 124.6, 114.0, 55.4, 54.7. HRMS-ESI (*m/z*): Calculated for $C_{20}H_{20}NO_2$ (M+H): 306.1494, Found (M+H): 306.1483.

(4-(Diethylamino)phenyl)(pyridin-4-yl)methanol (37b)

108 mg, (42%) of **37b** yellow oil; IR (KBr cm^{-1}): 3402, 2966, 2927, 1608, 1589, 1518, 1202, 1150, 1118, 809; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.48-8.47 (m, 2H), 7.33-7.32 (m, 2H), 7.13-7.10 (m, 2H), 6.62-6.60 (m, 2H), 5.68 (s, 1H), 3.35 (q, *J* = 14.4, 7.2 Hz, 4H), 2.44 (br s, 1H) 1.14 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.5, 149.5, 147.9, 129.5, 128.4, 121.4, 111.8, 74.9, 44.5, 12.6. HRMS-ESI (*m/z*): Calculated for $C_{16}H_{20}N_2O$ (M+H): 257.1648, Found (M+Na): 257.1645.

4,4'-(Pyridin-4-ylmethylene)bis(*N*,*N*-diethylaniline) (37c)

93 mg, (24%) of **37c** yellow oil; IR (KBr cm^{-1}): 2969, 1612, 1515, 1265, 1197, 806, 717; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.48 (dd, *J* = 4.8, 1.6 Hz, 2H), 7.10-7.09 (m, 2H), 6.94-6.92 (m, 4H), 6.94-6.92 (m, 4H), 6.62-6.60 (m, 4H), 5.27 (s, 1H), 3.35 (q, *J* = 14, 7.2 Hz, 8H), 1.14 (t, *J* = 7.2 Hz, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.8, 149.6, 146.6, 130.5, 129.1, 124.8, 111.0, 54.9, 44.1, 12.4. HRMS-ESI (*m/z*): Calculated for $C_{26}H_{33}N_3$ (M+H): 388.2747, Found (M+Na): 388.2745.

1-(2,4,6-Trimethoxyphenyl)propan-1-ol (38b)

120 mg, (53%) of **38b** colorless solid; m.p. 129 ºC; IR (KBr cm^{-1}): 3484, 3003, 2934, 2836, 1600, 1459, 1224, 1201, 1147, 1113, 1054, 813; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.12 (s, 2H), 4.98-4.91 (m, 1H), 3.80 (s, 3H), 3.79 (s, 6H), 3.53 (d, *J* = 10.0 Hz, 1H), 1.90-1.83 (m, 1H), 1.76-1.65 (m, 1H), 0.89 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.1, 158.5, 112.7, 91.0, 69.2, 55.7, 55.3, 30.6, 10.7. HRMS-ESI (*m/z*): Calculated for $C_{15}H_{24}O_4$ (M+Na): 249.1102 Found: 249.1100.

1,3,5-Trimethoxy-2-propylbenzene[46] (38d)

25 mg, (12%) of **38d** colorless oil; IR (KBr cm^{-1}): 2934, 2838, 1604, 1460, 1201, 1152, 1123, 1042, 811; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.13 (s, 2H), 3.80 (s, 3H), 3.78 (s, 6H), 2.54-2.50 (m, 2H), 1.50-1.41 (m, 2H), 0.92 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.1, 158.9, 112.0, 90.71, 55.8, 55.4, 24.7, 22.8, 14.3.

1-(2,4,6-Trimethoxyphenyl)hexan-1-ol (39b)

127 mg, (53%) of **39b** yellow oil; IR (KBr cm^{-1}): 3425, 2931, 2852, 1602, 1459, 1200, 1143, 811; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.13 (s, 2H), 5.04-5.00 (m, 1H), 3.80 (s, 3H), 3.79 (s, 6H), 3.50 (d, *J* = 11.2 Hz, 1H), 1.88-1.81 (m, 1H), 1.71-1.63 (m, 2H), 1.47-1.41 (m, 1H), 1.39-1.25 (m, 5H), 0.86 (t, *J* = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.2, 158.5, 113.1, 91.1, 67.8, 55.7, 55.4, 37.8, 31.9, 26.0, 22.82, 14.2. HRMS-ESI (m/z): Calculated for $C_{15}H_{24}O_4$ (M+H); 291.1562 Found: 291.1562.

2-Hexyl-1,3,5-trimethoxybenzene[46] (39d)

36 mg, (14%) of **39d** yellow oil; IR (KBr cm^{-1}): 2931, 2857, 1605, 1461, 1417, 1205, 1150, 813; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.13 (s, 2H), 3.80 (s, 3H), 3.79 (s, 6H), 2.56-2.52 (m, 2H), 1.44-1.41 (m, 2H), 1.32-1.29 (m, 6H), 0.93-0.89 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.0, 158.9, 112.3, 90.7, 55.8, 55.4, 31.9, 29.7, 29.5, 22.8, 22.6, 14.3.

1,3,5-Trimethoxy-2-(2-methylprop-1-en-1-yl)benzene (40b)

158 mg, (71%) of **40b** as colorless oil; IR (KBr cm^{-1}): 1649, 1509, 1404, 1336, 1244, 815, 686; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.14 (s, 2H), 5.91 (s, 1H), 3.82 (s, 3H), 3.79 (s, 6H), 1.93 (s, 3H), 1.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.1, 158.5, 137.3, 115.5, 109.0, 90.6, 55.8, 55.4, 26.0, 20.5. HRMS-ESI (*m/z*): Calculated for $C_{13}H_{18}O_3$ (M+H): 245.1154 Found: 245.0802.

1-(4-Methoxyphenyl)propan-1-ol[47] (41b)

81 mg, (48%) of **41b** as yellow oil; IR (KBr cm^{-1}): 3419, 2963, 2932, 2875, 1611, 1512, 1461, 1246, 1176, 1036, 832; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.27-7.25 (m, 2H), 6.89-6.86 (m, 2H), 4.53 (t, *J* = 6.8 Hz, 1H), 3.80 (s, 1H), 1.87 (br, s, 1H), 1.86-1.68 (m, 2H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.1, 136.88, 127.3, 113.8, 75.7, 55.4, 31.8, 10.3.

Cyclohexyl(4-methoxyphenyl)methanol[47] (42b)

90 mg, (48%) of **42b** as colorless solid; m.p. 85 °C IR (KBr cm^{-1}): 3457, 2941, 2915, 2853, 1612, 1515, 1446, 1251, 1033, 1001, 824; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.22-7.20 (m, 2H), 6.88-6.85 (m, 2H), 4.29 (d *J* = 7.2 Hz, 1H), 3.80 (s, 3H), 2.02-1.98 (m, 2H), 1.82 (br, s, 1H), 1.79-1.73 (m, 1H), 1.64-1.57 (m, 2H), 1.39-1.32 (m, 1H), 1.27-0.97 (m, 4H), 0.93-0.82 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.0, 135.9, 127.8, 113.6, 79.1, 55.3, 45.0, 29.3, 29.2, 26.5, 26.2, 26.1.

Synthesis of (±)-carbinoxamine

An oven dried two neck round bottom flask bearing septum in side arm and fitted with condenser was cooled to room temperature under a steady stream of nitrogen gas flow. The flask was charged with stirring bar, $AlBr_3$ (266 mg, 1.0 mmol) and cooled down to 0 °C (using ice bath). Then pyridine-2-carboxaldehyde (107 mg, 1 mmol) was added. The mixture was stirred for 30 minutes at 0 °C under nitrogen atmosphere and dry chlorobenzene (226 mg, 2 mmol) was added in drops. The resulting mixture was stirred at 130 °C for 24 h (monitor by TLC). Additional (0.2 mmol) $AlBr_3$ was added to this reaction mixture and stirred for 15 minutes, followed by addition of 2-(dimethylamino)ethan-1-ol (10 mmol). The refluxing the reaction mixture was continued for further 36 h (monitor by TLC). After cooling to room temperature, the reaction mixture was poured into aq. $NaHCO_3$ and stirred for 5 minutes. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 25 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under reduced pressure and then the residue was washed with 20% ethyl acetate/hexane mixture. The residue was purified through silica gel column chromatography using methanol as an eluent to afford the pure product of 2-((4-chlorophenyl)(pyridin-2-yl)methoxy)-*N*,*N*-dimethylethan-1-amine in 138 mg, (47%) of **43b** as yellow oil. IR (KBr cm^{-1}): 2939, 2867, 2818, 2772, 15891465, 1091, 809, 771; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.52 (ddd, *J* = 4.8, 0.8, 0.8 Hz, 1H), 7.69 (td, *J* = 7.6, 1.6, Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.39-7.36 (m, 2H), 7.29-7.27 (m, 2H), 7.17-7.13 (m, 1H), 3.64-3.55 (m, 2H), 2.62 (t, *J* = 6.0 Hz, 2H), 2.26 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.4, 149.1, 139.7, 137.0, 133.5, 128.7, 128.4, 122.6, 120.7, 84.5, 67.7, 59.0, 46.0.

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