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The cooperative effect of Lewis pairs in the Friedel–Crafts hydroxyalkylation reaction: a simple and effective route for the synthesis of (±)-carbinoxamine†

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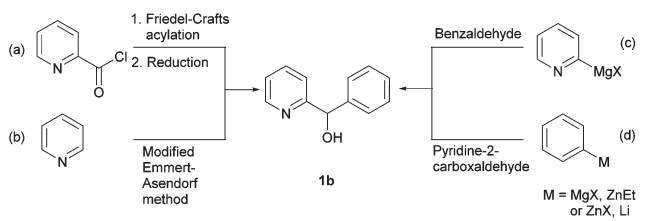
An efficient C–C bond formation strategy between aromatic/heteroaromatic π-nucleophiles and Lewis acid activated aldehydes is described. This aromatic electrophilic substitution reaction of arenes or heteroarenes is facilitated by Lewis acid $AlBr_3$. Aromatic rings with electron donating substituents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

Introduction

Carbinols possessing, in particular, a 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 have also been found to display enormous synthetic utility as intermediates,[2] chiral auxiliaries,[3] organocatalysts[4] and as ligands for transition metal catalyzed organic transformations.[5] Hence, there has been 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] cross coupling reactions[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 groups of acyl pyridine to carbinols exhibited limited success. For example, the lithium aluminium hydride reduction of pyridyl aryl ketone resulted in poor yields of the corresponding carbinols.[9] (b) The most convenient method for the preparation of carbinols, a modified Emmert–Asendorff methodology, involves the condensation of aldehydes/ketones with pyridine in the presence of either aluminium or magnesium, mercuric chloride and iodine *via* pyridyl radical formation.[10] The preparation of these types of carbinols has also been achieved *via* a Grignard reaction between either (c) pyridyl magnesium bromide and aryl aldehydes[11] or (d) aryl magnesium/lithium/zinc reagents and pyridine carboxaldehyde.[12] The former method furnished the carbinols in poor yields.

The synthesis of carbinols using these methodologies involves the generation of reactive nucleophiles such as organo-



Scheme 1 Synthesis of carbinols.

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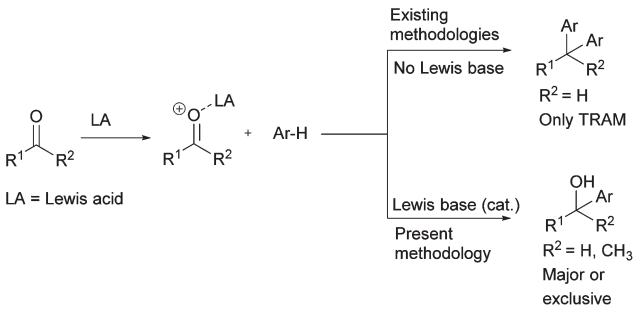
†Electronic supplementary information (ESI) available: Experimental procedures, compound characterization data (^1H and ^{13}C NMR, HRMS) for all compounds. See DOI: 10.1039/c4ob02597k

metallic reagents, followed by reaction with aldehydes or generation of ketones and then reduction of the carbonyl group using rhodium catalysts, and thus, 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 the electrophilic aldehyde group through a 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 was also observed in the case of electron deficient aldehydes with π-nucleophiles.[14] Some aromatic nucleophiles possessing a free phenolic group effectively participated in C–C bond formation reaction in the 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, has been reported.[16] The formation of triarylmethane from pyridine-4-carboxaldehyde and *N*,*N*-dimethylaniline in the presence of a Lewis acid was observed in this report also. The reaction of π-nucleophiles such as arenes or heteroarenes with aldehydes in the presence of a Lewis acid usually furnishes triarylmethanes.[17] Hence, it is evident that there has been less attention paid to develop the C–C bond forming reaction for the preparation of carbinols from aldehydes (aryl/heteroaryl/aliphatic) and aromatic π-nucleophiles through electrophile activation using a 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 a library of carbinols.

Accordingly, we have undertaken a detailed study on the direct hydroxyalkylation of arenes or heteroarenes with aldehydes in the presence of Lewis acid $AlBr_3$. Lewis acid activation has been effectively utilized to establish the C–C bond between a 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 the electrophilic site.[21] For example, Lewis acids are known to polarize the C=O bond of aldehydes *via* interaction with the oxygen lone pair and make it more susceptible to nucleophilic attack (Scheme 2).



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

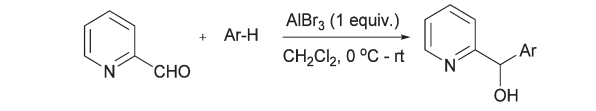
Results and discussion

Based on this fundamental concept, we have disclosed a convenient method for the hydroxyalkylation of aromatic π-nucleophiles using carbonyl compounds such as aldehydes (Scheme 2).[19] The interaction of a Lewis acid with pyridine-2-carboxaldehyde may result in the coordination of either carbonyl oxygen or pyridine nitrogen or both. The coordination of a Lewis acid with only the carbonyl group always leads to triarylmethane formation due to the effective polarization of the carbon oxygen double bond (Fig. 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 the nitrogen atom of the pyridine moiety with a Lewis acid (Lewis pair) may lead to the optimized electrophilicity of the carbonyl group (Fig. 1a).[22] This situation may lead to the mono nucleophile addition across the carbonyl group. To justify this hypothesis we carried out the experiment with π-nucleophile, anthracene and pyridine-2-carboxaldehyde in the presence of various Lewis acids at 0 °C to room temperature. Lewis acids such as $AlBr_3$, $AlCl_3$, $TiCl_4$, $BF_3{\cdot}OEt_2$ 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]

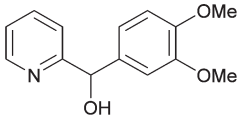
Addition of electron rich aromatic/heteroaromatic nucleophiles

With this optimized reaction condition, to justify the versatility of this methodology and the compatibility of functional groups such as halogens, –NHR and propargyl groups, which are not passive in the presence of organometallic reagents, we carried out a hydroxyalkylation reaction with a variety of electron rich aromatic and heteroaromatic π-nucleophiles in the presence of $AlBr_3$, and the results are summarized in Table 1. An aryl ring bearing an 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 the present reaction conditions 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 a 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 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 the *para* position is blocked in the π-nucleophile, the hydroxyalkyl group becomes introduced at the *ortho* position to the

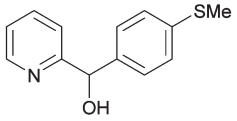
Table 1 Electron rich aromatic/heteroaromatic nucleophiles[a]



(2b-18b)[b]



2b: 81%



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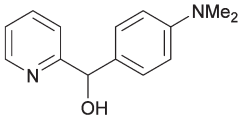

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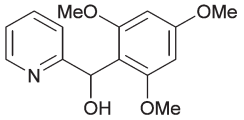
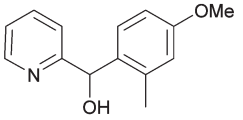
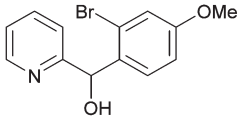


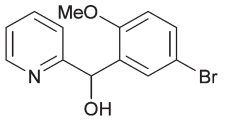
5b: 89%



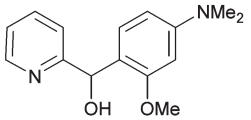
6b: 83%



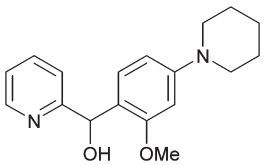
7b: 61%



8b: 67%



9b: 91%



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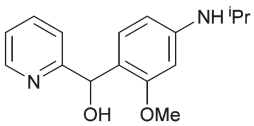
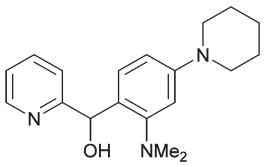
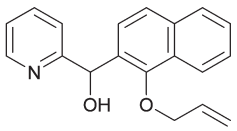


11b: 79%



12b: 94%



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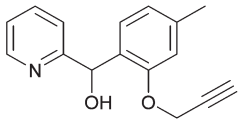
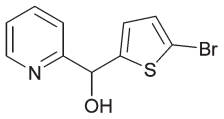
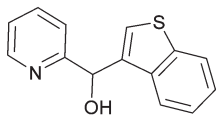


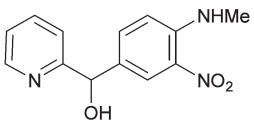
14b: 79%



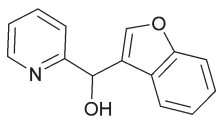
15b: 73%



16b: 74%



17b: 61%



18b: 71%

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

strong electron donating functional group present in the π-nucleophile (Table 1, entry **8b**). The substrates with two electronically complementary functional groups such as strong electron donating and strong electron withdrawing groups present in the aryl ring again furnish 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 yields may be due to the diminished nucleophilicity of the substrate bearing inductively deactivating functional groups such as halogens or nitro groups.

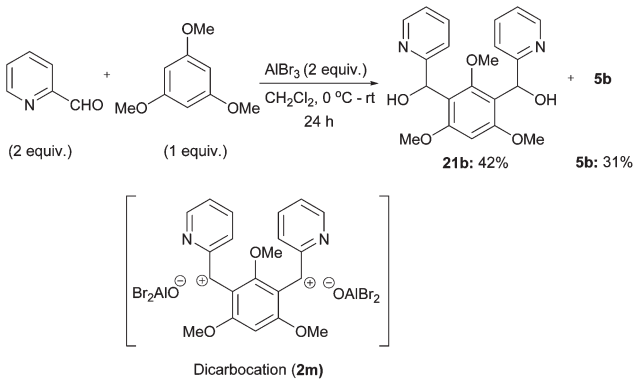
Surprisingly, the alkyl aryl ether remains unaffected by $AlBr_3$, even though the reagent is usually utilized for ether cleavage.[23] We further intend to examine the stability of other sensitive ether groups such as allyl ether and propargyl ether. To our delight these two labile ethers are found to be quite stable in the 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 the 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 a $-NR_2$ group (Table 1, entries **9b–11b**). These results clearly indicate that the electronic properties of substituents on the aromatic ring determine the regioselectivity of the substitution. We investigated the role of steric hindrance in 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 the 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 prefers to establish the C–C bond with the nucleophilic carbon *ortho* to the less sterically hindered electron donating group. The reactivities of electron rich aromatic heterocycles such as bromothiophene, benzothiophene and benzofuran were examined under the present reaction conditions. 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 the present reaction conditions (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), which could be attributed to the higher nucleophilicity of π-nucleophiles due to the presence of strong electron donating groups. The reaction of phenols with terminal dihalides in the 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, possesses two π-nucleophilic components. While performing the reaction with an 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, the reaction of two equivalents of electrophile (pyridine-2-carboxaldehyde) in the 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**).

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

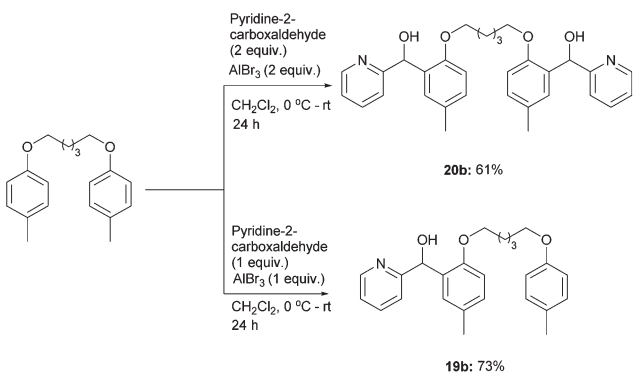


Scheme 4 Two electrophiles on 1,3,5-trimethoxybenzene.

Electron deficient aromatic aldehydes

The reaction of anisole with pyridine-3-carboxyaldehyde and pyridine-4-carboxyaldehyde in the 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 a 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 been generated through the coordination of a Lewis acid with lone pairs of both pyridine nitrogen and aldehyde oxygen (Fig. 1a). Such a type of penta coordination with aluminium is already known in the literature, which causes a sub-coordinate covalent interaction[28] and thus reduces the leaving group ability of the $-OAlBr_2$ group. This speculation prompts us to examine the effect of nitrogen containing ligands, which may stop at the mono nucleophile addition stage through coordination with aluminium in $ROAlBr_2$ (Fig. 1c).

Thus, the experiments were carried out by treating the substrate anisole with benzaldehyde in the presence of a Lewis base, pyridine, as an additive. Under controlled experiment conditions, in the absence of an additive, the electrophiles such as electron deficient aryl aldehydes generate only triarylmethanes. However, the use of a stoichiometric amount of pyridine as additive did not show any effective transformation, including the formation of triarylmethane. The reason for this observation may be the formation of a coordination complex between pyridine nitrogen and $AlBr_3$, completely destroying the carbonyl group activation. Therefore, the reactions were conducted with a sub-stoichiometric quantity of a pyridine base. In the presence of pyridine (0.3 equiv.), carbinol formation was noticed, and the reaction produced the carbinol in 50% yield along with triarylmethane in 23% yield. After a quick survey of the reaction conditions, we found that with the combination of 1 equivalent of $AlBr_3$ and 0.2 equivalent of



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

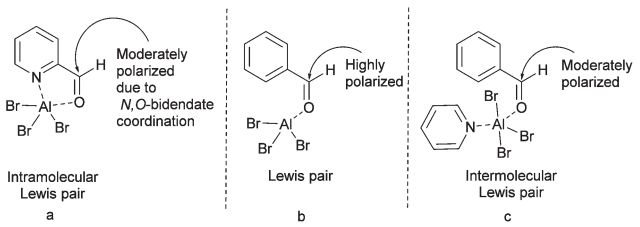
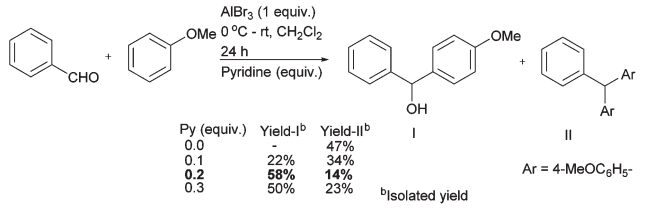


Fig. 1 Possible Lewis pairs.



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.

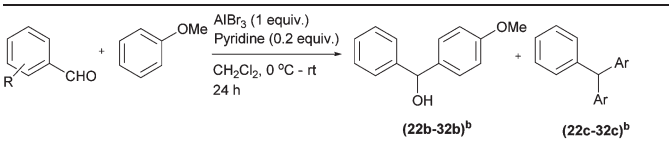
pyridine as additive, the reaction produced the diarylcarbinol in a moderate yield of 58% along with triarylmethane in a minor quantity (14%). However, the yield of the desired product dropped when more than 0.2 equivalent of pyridine was used. Subsequently, to further increase the yield of carbinol, we have examined other Lewis bases such as DABCO, DBU, bipyridine, DIPEA, imidazole, triethylamine, pyrazole, and 8-hydroxy quinoline, as well as 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 additives in this transformation (Scheme 5).

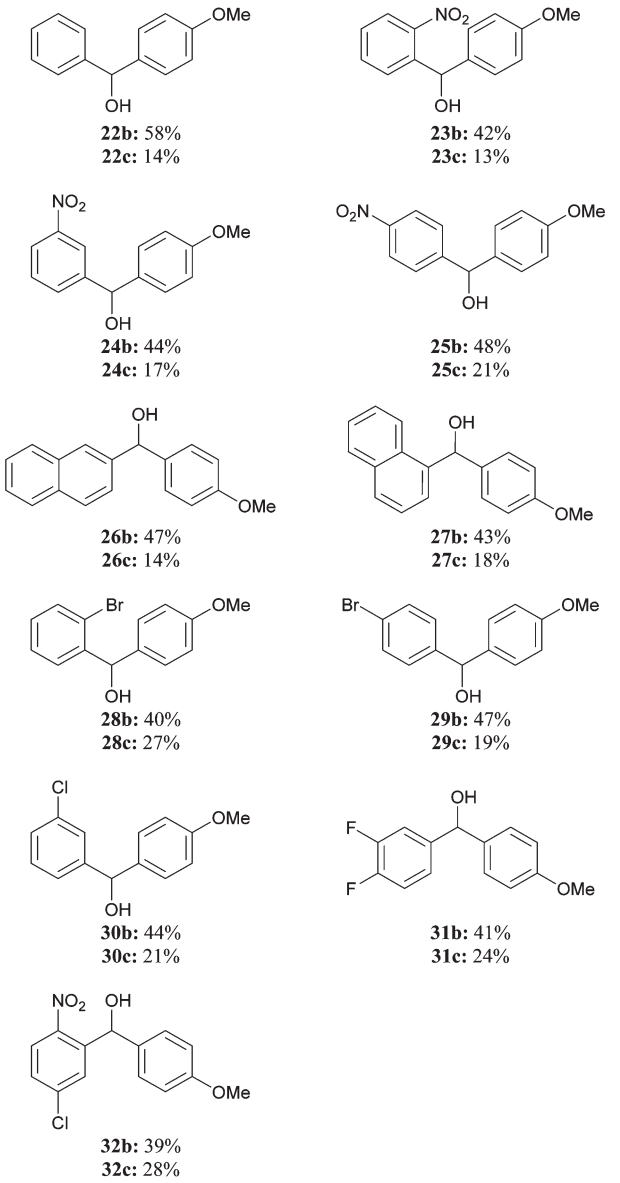
Generalization of this approach was made by studying the reaction of various aromatic aldehydes with anisole, and the results are summarized in Table 2. Aromatic aldehydes with electron withdrawing substituents such as $-NO_2$, weakly activating groups such as halides or the combination of these groups (halides, nitro or dihalides) or without substituents did participate in this reaction, and delivered the corresponding carbinols as major products along with triarylmethane as a minor product. A strong electron withdrawing group (such as $-NO_2$) present in the aromatic aldehydes, irrespective of the position in the aromatic ring (*o*, *p* and *m*) subjected to the present reaction conditions, 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 the present reaction conditions 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 the presence of either $AlBr_3$ or $AlBr_3$ with pyridine (0.2 equiv.) to generate carbinol or triarylmethane. Increasing or decreasing catalyst loading did not provide any fruitful results. These observations indicate that the electronic properties of aldehyde are also crucial for this transformation.

Other pyridine aldehydes with electron rich aromatic nucleophiles

The reaction of pyridine-3-carboxaldehyde/pyridine-4-carboxaldehyde with anisole in the presence of $AlBr_3$ alone generated either the carbinols in poor yield or only triarylmethanes. This may be due to the lack 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 a minor quantity of triarylmethane (**33c**). Increasing of anisole equivalent (1.2 equiv.) in this reaction increased the chemical yield of triarylmethane. Having obtained the opti-

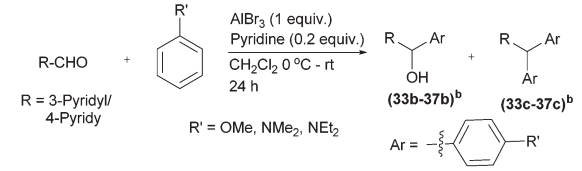
Table 2 Reaction of anisole with benzaldehyde/electron deficient benzaldehydes[a]

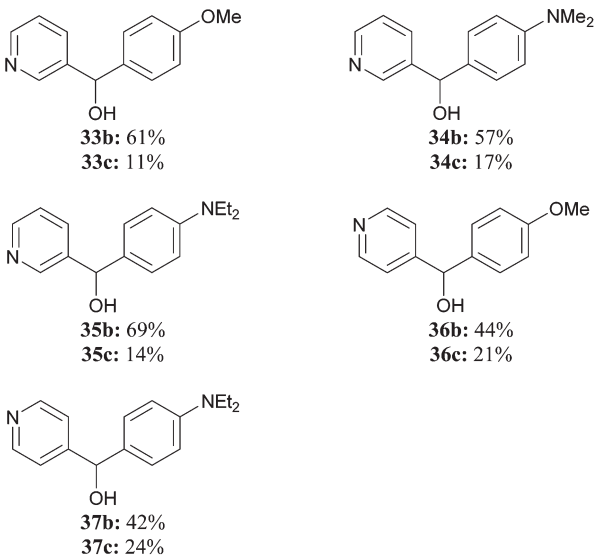




[a] Reaction condition: aromatic aldehydes (1.0 mmol), anisole (1.0 mmol) in dry dichloromethane, pyridine (0.2 mmol), 0 °C–rt. [b] Isolated yield.

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.

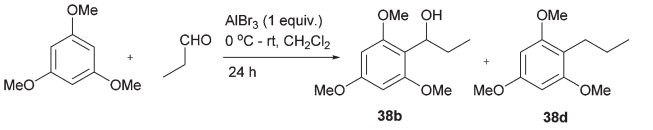
mized reaction conditions, the further scope and generality of this reaction were demonstrated by treating different aromatic π-nucleophiles with pyridine-3-carboxaldehyde as well as pyridine-4-carboxaldehyde.

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

Aliphatic aldehydes with electron rich nucleophiles

To illustrate the efficacy of the Friedel–Crafts hydroxyalkylation in the presence of $AlBr_3$ with an 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 the present reaction conditions (1 equiv. of $AlBr_3$) due to the enolization property of aliphatic aldehydes in the presence of a Lewis acid.[29] In the 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 products. Also, the Lewis acid activation of aliphatic aldehydes was less explored due to the formation of an 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 $AlBr_3$, which 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	—

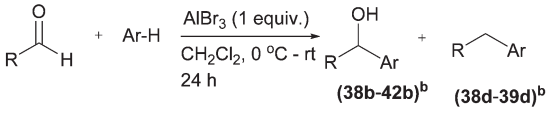
[a] Reaction condition: 1,3,5-trimethoxybenzene (1.0 mmol) and aldehyde in dry dichloromethane, 0 °C–rt. [b] Isolated yield.

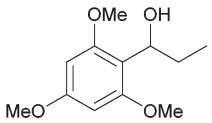
To increase the chemical yield of the expected carbinol, the reactions were performed by increasing the equivalent of propionaldehyde from 1.0 equivalent to 1.2, 1.4, 1.6, 1.8 and 2.0 equivalents. The chemical yield of the carbinol formation increased from 31% to 51% upon the increase of aldehyde equivalent (Table 4, entries **2–6**). To the best of our knowledge examples of such transformations using Lewis acids or involving such hindered substrates with aliphatic aldehyde have not been reported earlier.[31] A better yield of carbinol **38b** was realized when the reaction was performed in the 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, which generated the carbinol **39b** in moderate yield along with alkane **39d** (Table 5).[32] Anisole conveniently reacted with aliphatic aldehydes such as propionaldehyde and 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 the 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 the presence of a mild Lewis acid such as Me_2AlCl, unfortunately, the corresponding carbinol **38b** was isolated in only 7% yield.

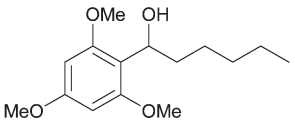
Synthesis of an antihistamine drug

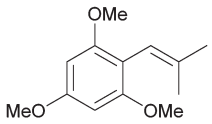
(±)-Carbinoxamine (**43b**), a potent anti-histamine H1 antagonist containing a 4-chlorophenylpyridylcarbinol moiety, was previously synthesized by the reduction of ketone,

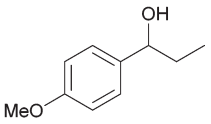
Table 5 Reaction of π-nucleophiles with aliphatic aldehydes[a]

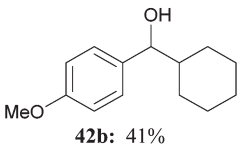






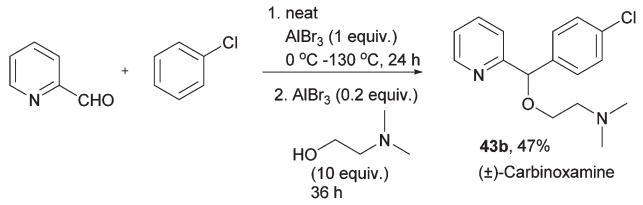






[a] Reaction condition: π-nucleophile (1.0 mmol) and aliphatic aldehyde (1.8 mmol) in dry dichloromethane, 0 °C–rt. [b] Isolated yield.

a rearrangement reaction or by using a Grignard/lithium reagent. Over the years, very few reports have been published for the synthesis of carbinoxamine from the intermediate carbinol. There have been two methods reported so far, for example, the reaction of either haloalkylamines[33] or haloalkylamides[34] (followed by reduction) with carbinols in the 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 the 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 to the devising of an economically viable and simple method of synthesizing the carbinoxamine through Lewis acid assisted ether bond formation. Accordingly, the treatment of pyridine-2-carboxaldehyde with chlorobenzene in the presence of $AlBr_3$ in refluxing dichloromethane afforded the corresponding carbinol in 41% yield after quenching with a saturated sodium bicarbonate solution. The same reaction upon treating with *N*,*N*-dimethyl-2-aminoethanol afforded 23% of carbinoxamine (**43b**) as a 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 the presence of $AlBr_3$ (1 equiv.) furnished the carbinol in 49% yield upon quenching with a saturated sodium bicarbonate solution, whereas the



Scheme 6 Synthesis of (±)-carbinoxamine.

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 the presence of an additional 0.2 equivalent of $AlBr_3$ for 36 h (Scheme 6).

Conclusions

In conclusion, we have developed a simple methodology for the synthesis of a variety of diarylcarbinols from aldehydes and aromatic π-nucleophiles through aldehyde carbonyl group activation using $AlBr_3$. The presence of a Lewis base (pyridine), both intermolecular and intramolecular, cooperatively modulated the reactivity of Lewis acid $AlBr_3$ in a hydroxyalkylation reaction. Under this experimental condition, several functional groups are tolerated, and in particular, halides, allyl and propargyl groups are stable. Depending on the number of equivalents of aldehyde, nucleophiles with two or more reactive sites and $AlBr_3$, one can synthesize biscarbinols or carbinols. Furthermore, *in situ* carbonyl group activation is achieved through chelation control in the case of electron deficient aromatic aldehydes (the cooperative effect of a 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 a 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 a Thermo Nicolet 6700 FT-IR Spectrophotometer and are reported in frequency of absorption (cm^{-1}). Mass spectra were recorded using a micro mass Q-TOF (ESI-HRMS) and an Agilent-6530 B Q-TOF (ESI-HRMS), ^1H and ^{13}C NMR spectra were recorded on a 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 the 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 the corresponding phenols[35] and amines[36] using reported procedures. Solvents used for the reactions were dried following 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 was pre-dried at 120 °C for at least 6 h, assembled while hot and cooled under a 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 a septum in the side arm and fitted with a condenser was cooled to room temperature under a steady stream of nitrogen gas flow. The flask was charged with a stirring bar, $AlBr_3$ (266 mg, 1.0 mmol), in dry dichloromethane (3 mL) and cooled down to 0 °C (using ice). Then pyridine-2-carboxaldehyde (107 mg, 1 mmol) was added. The mixture was stirred for 30 minutes at 0 °C under a nitrogen atmosphere. To this mixture was added a 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, the organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 15 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated on a 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 a septum in the side arm and fitted with a condenser was cooled to room temperature under a steady stream of nitrogen gas flow. The flask was charged with a stirring bar, $AlBr_3$ (266 mg, 1.0 mmol), in dry dichloromethane (3 mL) and cooled down to 0 °C (using ice bath). Then electron deficient aldehydes (1 mmol) in dry dichloromethane (2 mL) at 0 °C was added while being stirred followed by the addition of a dichloromethane solution of pyridine (0.016 mL, 0.2 mmol). Stirring was continued for 30 minutes. To this mixture was added a 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 × 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated on a 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 a septum in the side arm and fitted with a condenser was cooled to room temperature under a steady stream of nitrogen gas flow. The flask was charged with a stirring bar, $AlBr_3$ (266 mg, 1.0 mmol), in dry dichloromethane (3 mL), cooled down to 0 °C (using ice bath) and stirred for 30 minutes. Aliphatic aldehydes (1.8 mmol) and π-nucleophiles (1.0 mmol) in dry dichloromethane (2 mL) were taken in a small round bottom flask and mixed well. This mixture was added to the reaction mixture dropwise 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 × 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated on a 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 an 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; ^1H 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 °C; IR (KBr cm^{-1}): 3197, 3084, 2893, 2804, 1614, 1593, 1526, 1362, 1167, 1051, 806, 775; ^1H 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 °C; 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 °C; 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 °C; 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; ^{1}H 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 °C; IR (KBr cm^{-1}): 3210, 2858, 2743, 1968, 1880, 1857, 1593, 1511, 1155, 1085, 934, 808; ^{1}H 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; ^{1}H 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 °C; IR (KBr cm^{-1}): 3397, 2942, 2839, 1598, 1468, 1436, 1130, 1098, 1037, 754; ^{1}H 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; ^{1}H 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 °C; IR (KBr cm^{-1}): 3384, 3141, 2918, 2852, 1632, 1569, 1523, 1172, 1044, 760; ^{1}H 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; ^{1}H 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; ^{1}H 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; ^{1}H 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 °C; 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 °C; 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 °C; 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. 114 °C; 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 °C; 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 °C; 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 °C; 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 °C; 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 °C 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 °C; 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; ^{1}H 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; ^{1}H 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; ^{1}H 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; ^{1}H 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; ^{1}H 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; ^{1}H 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; ^{1}H 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; ^{1}H 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; ^{1}H 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; ^{1}H 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; ^{1}H 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; ^{1}H 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 °C; 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 °C; 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 °C; 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 °C; 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 °C; 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 °C; 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 °C; 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; ^1H 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 °C; IR (KBr cm^{-1}): 3484, 3003, 2934, 2836, 1600, 1459, 1224, 1201, 1147, 1113, 1054, 813; ^1H 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 a septum in the side arm and fitted with a condenser was cooled to room temperature under a steady stream of nitrogen gas flow. The flask was charged with a 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 a 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). An 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). Refluxing of the reaction mixture was continued for a 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 extracted with ethyl acetate (2 × 25 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated on a rotary evaporator under reduced pressure; the residue was then washed with a 20% ethyl acetate–hexane mixture. The residue was purified through silica gel column chromatography using methanol as an eluent to afford the pure product 2-((4-chlorophenyl)(pyridin-2-yl)methoxy)-*N*,*N*-dimethylethan-1-amine in 138 mg, (47%) of **43b** as a yellow oil. IR (KBr cm^{-1}): 2939, 2867, 2818, 2772, 1589, 1465, 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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