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A study of the reactivity of cyclic aminomethylammonium mannich salts

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ABSTRACT

A novel method for the preparation of aminoalkylaminomethyl products was developed utilising novel Mannich-type salts featuring a $R_2NCH_2NR_3^+$ moiety. This methodology showed good nucleophile scope and was successfully employed in reactions under basic, acidic, and neutral conditions. A wide range of diamine products was successfully synthesised, including a neuropeptide Y antagonist.

1. Introduction

α-Functionalisation of tertiary amines **1** is an important area of research due to its potential use in synthetic and medicinal chemistry [1,2]. Recently, a number of oxidative photochemical methods, employing visible light photocatalysis, have been reported [3–20]. Non-photochemical oxidative methods have also been reported, most of which involve the formation of an iminium intermediate **2** that is trapped with a nucleophile to form product **3** (Scheme 1, A) [21–31].

An alternative approach was disclosed recently where hydrogen atom transfer (HAT) rather than oxidation was used to functionalise methyldialkylamines R_2NCH_3 **7**, by DABCO radical cation **5** giving radical **8**; coupling of this radical with a radical cation **5** afforded electrophilic intermediate **9** [32]. In situ reaction with a defined range of organometallic nucleophiles led to products **10** (Scheme 1, B). Overall, this resulted in a highly regioselective functionalisation of the N–Me groups of complex and medicinally relevant trialkylamines, such as the opioid dextromethorphan **11** (Scheme 1, C). The key intermediate **9** was challenging to characterise and could not be isolated. To understand the reactivity of such α-aminoammonium Mannich salts, we proposed to prepare and study the reactivity of this family with a range of nucleophiles.

Compounds such as **13** in Scheme 2, containing the $R_2NCH_2NR_3^+$ moiety, have been sporadically mentioned in the literature, mainly in the context of by-product formation, or as intermediates in reaction mechanisms [33–40]. To the best of our knowledge, the reactivity of $R_2NCH_2NR_3^+$-containing compounds has not been systematically studied apart from one report by Hoge et al. that mentions that the *in situ* formed compound **16** in Scheme 2 undergoes a nucleophilic displacement resulting in loss of a trimethylamine moiety in the presence of phosphorus nucleophiles, resulting in the formation of salt **17** [41]. Hoge et al. highlighted the challenging nature of handling acyclic $R_2NCH_2NR_3^+$ compounds **13**, due to their tendency to decompose, supporting our observations with **9**. This moved us to consider cyclic versions of such salts **14** and **15**, where any unimolecular ring-opening could more easily be reversed; this should lead to molecules of enhanced stability. Indeed, the synthesis of cyclic compounds of the type **14** proved far less challenging and we now report our findings. Earlier reactions of **9** with nucleophiles had been confined to Grignard reagents and organoindium compounds [32]; our wish was to explore reactions of **14** with a wider range of nucleophiles.

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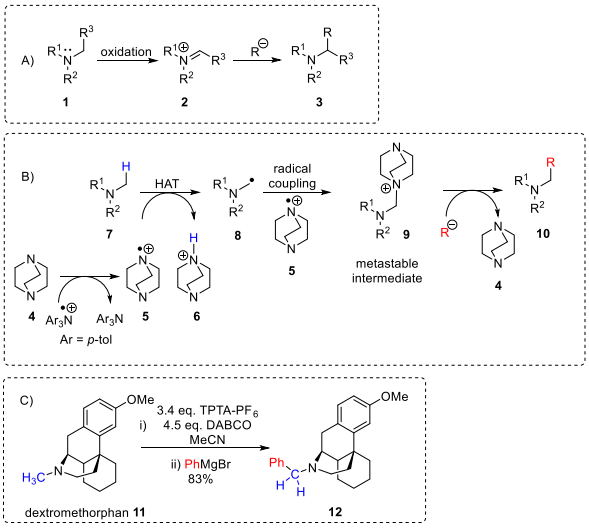
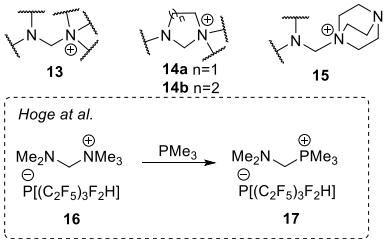


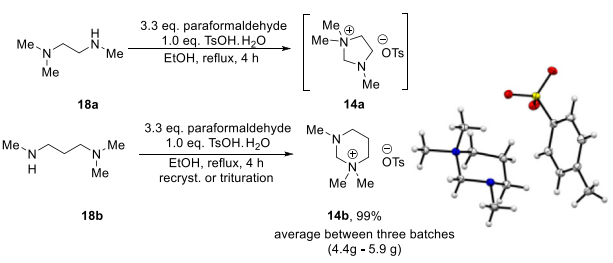
Scheme 1. α-Functionalisation of amines Scheme 3.



Scheme 2. Aminomethylammonium salts and the transformation with phosphines by Hoge et al.

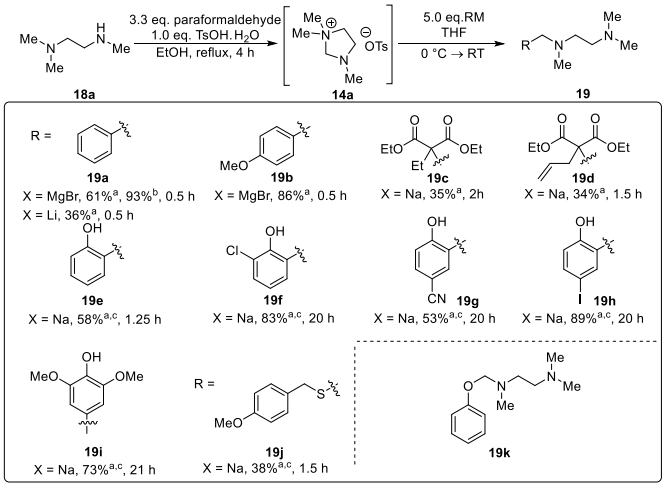
2. Results and discussion

Our studies began with the synthesis of **14a** and **14b** in Scheme 3 from the corresponding trimethyldiamine starting materials, **18a** and **18b**. Other acids such as glacial AcOH and conc. HCl did not facilitate the formation of **14a**. However, the addition of pre-activated 3 Å molecular sieves to the reaction, where conc. HCl was used, resulted in the formation of the chloride salt of **14a**. The use of molecular sieves did require a further step of purification (*i.e.* filtration of the residual insoluble solid matter resulting from erosion of the sieves on stirring) and the resulting chloride salt appeared less soluble in organic solvents such as $CDCl_3$. Therefore, for operational ease and for solubility considerations, $TsOH.H_2O$ was deemed a superior acid for this reaction. Product **14a** was obtained as a dark yellow oil by means of evaporation of the solvent and any volatile by-products after reaction completion. Attempts to recrystallise crude product **14a** from a range of solvents proved unfeasible but the compound was successfully telescoped as the crude product to the next reaction without a significant impact on the product yields. In contrast, salt **14b** was isolated as a white solid after evaporation of the volatile components. The minor impurities in both crude **14a** and **14b** appeared by ^{1}H NMR to be oligomers of formaldehyde. Later in our work, it was demonstrated that heating a sample of **14a** results in complete by-products decomposition to volatile formaldehyde and this method was used to purify **14a** when required. Crude **14b** was easily purified by trituration with hexane or was recrystallised from $CHCl_3$/THF for analysis by X-ray crystallography (Scheme 3). The scalability and robustness of these reactions was also demonstrated by the preparation of three large scale batches of **14b** (ranging from 4.4 to 5.9 g), each affording product **14b** in a quantitative yield. Salt **14b** is air- and bench-stable on storage for months and is not decomposed on heating in D_2O by ^{1}H NMR.



Scheme 3. Synthesis of salts **14a** and **14b**, together with X-ray crystal structure of **14b**.

The reactivity of intermediates **14** with a range of nucleophiles was then investigated (Scheme 4). For each reaction, a fresh batch of crude intermediate **14a** was synthesised on 1 mmol scale prior to treatment with a nucleophile and the product yields are based on the trimethylethylenediamine **18a** used for the synthesis of **14a**. Excess nucleophile was used to achieve full conversions of salt **14a**. Purification of the desired products was, in most cases, easily achieved. However, separation of salt **14a** from diamine products **19** was challenging. A wide range of nucleophiles afforded moderate-to-excellent yields of products following purification by column chromatography as shown in Scheme 4. Carbon-centred nucleophiles such as Grignard and organolithium reagents were competent nucleophiles (**19a** and **19b**) as were deprotonated tertiary alkyl malonates (**19c** and **19d**). The more reactive organolithium reagent afforded a more complex crude reaction mixture, hence, a decreased yield of **19a** was obtained when PhLi was used compared to PhMgBr. O-Centred and S-centred nucleophiles were also successful. O-Centred nucleophiles such as phenol exhibited *ortho*-selectivity by reacting through the *ortho*-carbon and reacted with **14a** through S_EAr mechanism (**19e**–**19h**). When the *ortho* positions on phenols were unavailable, *para*-selectivity was observed (**19i**). Other non-conjugated alcohols such as benzyl alcohol were found to be unsuccessful in this reaction and only the tosylate salt of trimethylpropylenediamine **18a** was detected in the crude reaction mixture post work-up with all **14a** having been consumed. This



Scheme 4. Salt **14a** - Nucleophile scope under basic conditions-listing of products. [a]Isolated yield [b]NMR yield determined by the addition of 1,3,5-trimethoxybenzene as an internal standard [c]derived from the corresponding sodium phenolate or thiophenolate as appropriate.

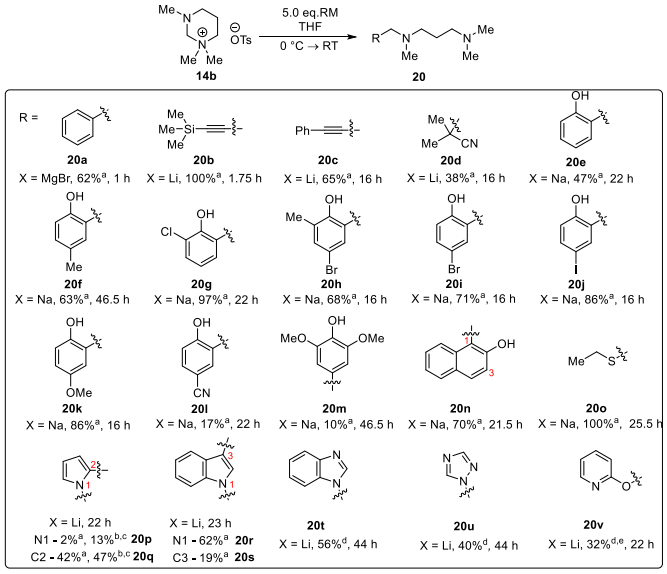
indicates that if a reaction takes place between **14a** and benzyl alcohol, the resulting hemiaminal is unstable to aqueous work-up and cannot be isolated. The analogous hemithioaminals were more stable and compound **19j** was isolated after purification by column chromatography. Substituted phenols were used to study the functional group tolerance of this reaction – both electron-donating (OMe, **19i**) and electron-withdrawing groups (halogens and CN, **19f**-**19h**) were tolerated. The nucleophile scope was similar to that reported by Chen for the nucleophilic displacement of trimethylamine groups in benzyltrimethylammonium salt substrates [42]. When phenolates were used as nucleophiles by Chen, O-functionalisation was observed as opposed to the *ortho*-C-functionalisation reported for compounds **19e**-**19h**. This can be rationalised by the fact that the products formed in Chen's reactions are stable ether compounds. A nucleophilic attack of the phenolate oxygen onto salt **14a** produces a less stable hemiaminal intermediate **19k**, which is activated for either an intramolecular or an intermolecular nucleophilic attack to afford the experimentally observed *ortho*-functionalised product **19**.

The reactivity of salt **14b** towards analogous and an expanded range of nucleophiles, to the ones shown in Scheme 4, was also investigated. Salt **14b** was reactive towards organomagnesium (**20a**) and organolithium reagents, including lithium acetylides (**20b** and **20c**). Deprotonated nitriles (**20d**) and phenol were also successful nucleophiles (**20e**-**20n**). Product yields obtained when **14b** was reacted with phenolates were comparable to those obtained for salt **14a**, except for products **20l** and **20m**, which were obtained in significantly decreased yields. 2-Naphtholate presented the expected regioselectivity in forming (**20n**). Next, deprotonated heterocycles such as pyrroles, indoles, benzimidazoles, triazoles and pyridines, relevant to medicinal chemistry, were tested as nucleophiles. Our work demonstrated that the reactions between deprotonated heterocycles and **14b** do take place but the stability of the resulting products on silica gel varies significantly. For example, deprotonated pyrrole affords products **20p** and **20q** in 60% combined yield with C2-substituted product **20q** being the major product. Purification by column chromatography afforded **20p** in 2% yield and **20q** in 42% yield, along with 16% mixture of **20p**:**20q** = 2.1:1. For indole, a different selectivity was observed, where the N-substituted product **20r** was the major product isolated in 62% yield along with C3-substituted product **20s** isolated in 19% yield after purification by column chromatography. Introduction of more nitrogen atoms to the nucleophile heterocyclic core resulted in more basic diamine products, that were unstable on silica gel (eluent: MeOH). Therefore, it was not practical for products **20t**, **20u** and **20v** to be purified by column chromatography on silica gel and their yields were determined by the addition of an internal standard to the crude reaction mixture (see SI). Nevertheless, aminals **20t** and **20u** as well as hemiaminal **20v** can be prepared *in situ*.

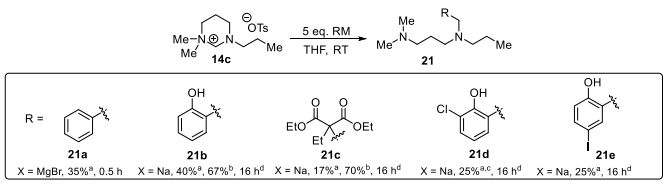
Analogous salt **14c** was synthesised next, where one of the methyl groups of **14b** was exchanged for the more sterically hindered *n*-propyl group (see Scheme 6). Electrophile **14c** reacted with the same main classes of nucleophiles as **14a** and **14b**. However, the respective diamine products were isolated in decreased yields. This can be rationalised by the increased steric bulk exerted by the *n*-propyl substituent near the electrophilic carbon centre, which can impede attack by the nucleophile.

The reactions discussed so far were carried out under strictly basic conditions *i.e.* all nucleophiles were either intrinsically basic e.g. Grignard reagents, or had been irreversibly deprotonated with a base (NaH or *n*BuLi) and were reacted with the appropriate electrophile **14**. Our study went on to explore the reactivity of salts **14** under neutral and acidic conditions.

Interception of intermediates **14a** and **14b** *in situ* by an enol was



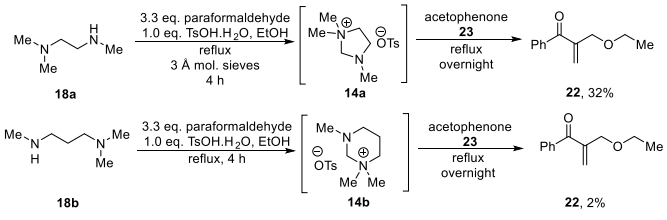
Scheme 5. Salt **14b** - Nucleophile scope under basic conditions [a]Isolated yield [b]NMR yield [c]16% yield of mixture of **20p:20q** = 2.1:1 was also isolated [d]NMR yield determined by the addition of 1,3,5-trimethoxybenzene as an internal standard due to instability of products on silica gel [e]9% yield of remaining **14b**.



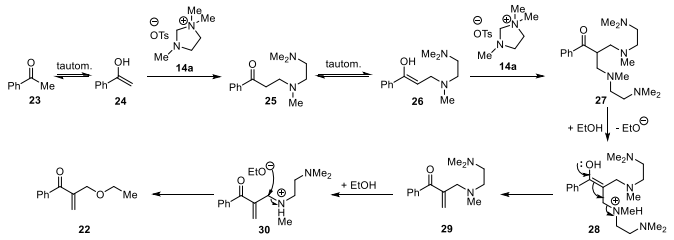
Scheme 6. Salt **14c** - Nucleophile scope under basic conditions. [a]Isolated yield [b]Yield determined by the addition of 1,3,5-trimethoxybenzene as an internal srtandard [c]<4% of para-isomer was also detected [d]arising from the sodium phenolate as nucleophile.

attempted by adding acetophenone **23** to the crude reaction mixture in EtOH (Scheme 7). This resulted, in both cases, in the formation of the unexpected product **22**. In the case of **14a**, product **22** was isolated in 32% yield. Compound **22** is interesting because it appears that two of its carbons (the terminal alkenyl and the β-carbon with respect to the carbonyl) are derived from **14a** or **14b** while the ethoxy functional group is derived from the solvent, indicating that **14** can act as a methylene transfer agent (more examples will be discussed later in this report).

Our proposal for the mechanism is shown in Scheme 8. Here, acetophenone **23** tautomerises to enol **24**, which intercepts salt **14a** or **14b** (only **14a** is shown). The resulting ketone **25** tautomerises again to enol **26**, which reacts with another equivalent of the electrophilic salt **14a** or **14b**, affording intermediate **27**. Ketone **27** undergoes another tautomerisation to **28**, followed by proton-mediated elimination of trimethylethylenediamine, producing



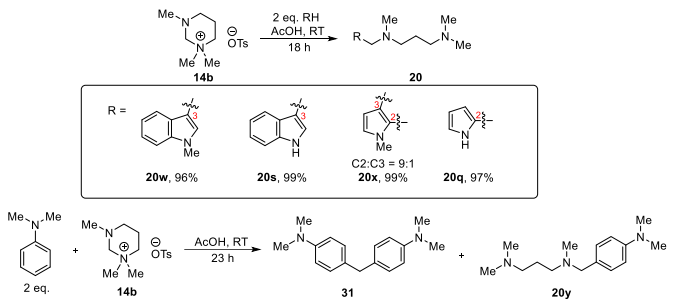
Scheme 7. Synthesis of α-functionalised product **22**.



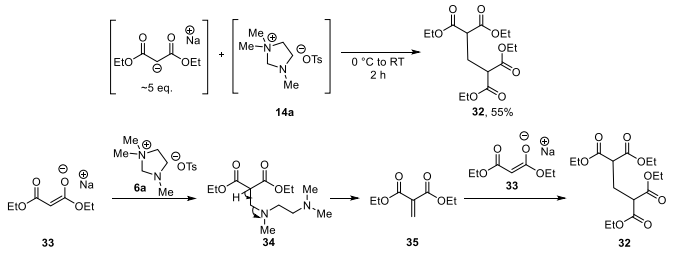
Scheme 8. Proposed mechanism for the formation of α-functionalised product **22**.

α,β-unsaturated carbonyl **29**. Intermediate **29** is proposed to undergo nucleophilic displacement of trimethylethylenediamine by the solvent, either by S_N2 or by S_N2', yielding the observed product **22**.

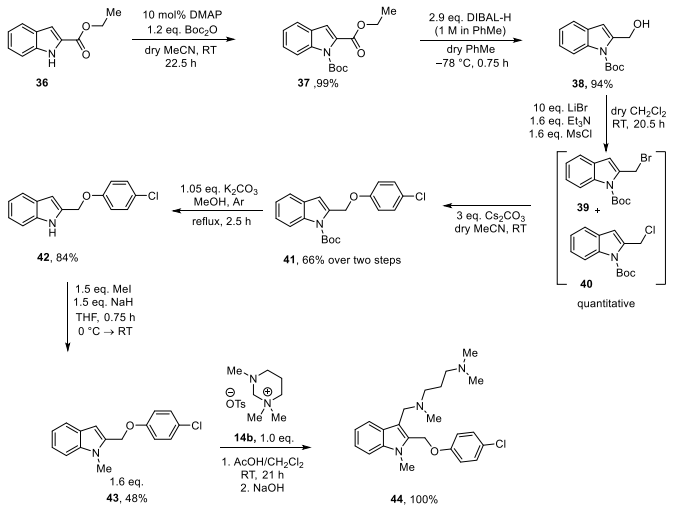
Next, salts **14** were studied under acidic conditions. AcOH was chosen as solvent – salts **14a** and **14b** as well as all neutral nucleophiles studied here readily dissolve in AcOH. The operational simplicity of the reactions under acidic conditions is notable. They only required stirring three reagents (nucleophile, electrophile, and solvent) in an appropriate container under air. Nitrogen-based nucleophiles such as NH- and NMe-pyrroles and indoles were successful in affording the expected products in near quantitative yields. NH-indole and NH-pyrrole were functionalised selectively at C3 and C2 positions respectively, which is in contrast to results from the analogous reactions carried out under basic conditions, where mixtures of N- and C-functionalised products were obtained (Scheme 5). Diamines **20w** and **20x** (Scheme 9), which cannot be synthesised under basic conditions, showed that N-substituted pyrroles and indoles are also competent nucleophiles. This demonstrated that nucleophiles, that cannot be formally deprotonated, can also engage in reaction with **14** under acidic conditions. However, other oxygen and sulfur-based nucleophiles such as phenol, anisole, benzofuran and benzothiophene failed to afford any diamine products when reacted with **14b** and only starting materials were detected in these reactions by ^{1}H NMR. Despite the fact that the reaction between **14b** and dimethylaniline did produce some of the expected triamine product **20y**, the major product from this reaction was the methylene bridged dimer of dimethylaniline **31**, which was isolated in 78% yield by recrystallisation of the crude mixture. Compound **20y** was clearly detected in the mother liquor of the recrystallisation by ^{1}H NMR. The reaction with dimethylaniline exhibits *para*-selectivity, possibly due to the steric influence of the two methyl groups, which hinder the two *ortho*-positions. The formation of product **31** shows that triamine **20y** is unstable enough to react with another equivalent of the nucleophile. This is also in line with our previous observation that attempts to purify compounds such **20y** by column chromatography on silica gel (eluent: MeOH) resulted in complete decomposition. The formation of dimer **31** provided a further example, where salt **14b** acted as a methylene unit donor.



Scheme 9. Salt **14b** - Nucleophile scope under acidic conditions.



Scheme 10. Synthesis of methylene-bridged dimer **32.**



Scheme 11. Synthetic route to indolyl neuropeptide Y receptor antagonist **44**.

Another example of a methylene-bridged dimeric product **32** obtained from the reaction between **14a** and deprotonated diethyl malonate under basic conditions is shown in Scheme 10. Our proposed mechanism involves the formation of intermediate **34**, that undergoes elimination to the Michael acceptor **35**. The α,β-unsaturated diester **35** is activated for a nucleophilic attack by another equivalent of deprotonated diethyl malonate **33**, affording the methylene-bridged dimeric product **32**.

The principal use of salts like **14**, is their ability to aminoalkylaminomethylate nucleophiles; diamine functional groups are building blocks of a significant number of biologically active compounds [43]. Therefore, to demonstrate the synthetic utility of our method for installing diamine moieties, the indolyl neuropeptide Y receptor antagonist **44** and its precursor **43** were targeted, the synthesis of which had previously been reported in a patent by Eli Lilly (Scheme 11) [44]. The route involved Boc-protection of the commercially available ester **36** to compound **37**, followed by reduction of **37** to alcohol **38**, which was converted to a mixture of bromide **39** and chloride **40**. The mixture of the two halo products was then treated with 4-chlorophenol as nucleophile affording indole **41**. Indole **41** was deprotected and methylated to produce precursor **43**. In our hands, the diamine moiety was installed in a single step under acidic conditions [44] as opposed to the multiple steps reported in the patent and the target molecule **44** was produced in quantitative yield.

3. Conclusion

In summary, a novel method for the preparation of aminoalkylaminomethyl products was developed utilising new Mannich-type salts featuring a $R_2NCH_2NR_3^+$ moiety. This methodology

showed good nucleophile scope and was successfully employed in reactions under basic, acidic, and neutral conditions. A wide range of diamine products was successfully synthesised, including neuropeptide Y antagonist **44**.

4. Experimental section

4.1. General experimental methods

All solvents and reagents were used as received without any further purification. Anhydrous hexane and THF and toluene were obtained from Pure-Solv 400 solvent purification system (by Innovative Technology Inc., USA). Anhydrous MeCN was purchased from Sigma-Aldrich. EtOH was dried over 3 Å pre-activated molecular sieves. Molecular sieves were activated by three heating cycles (5 min) in a microwave oven, followed by evacuation. Powder-form NaH was obtained by washing a mixture of 60% NaH dispersed in mineral oil three times with anhydrous hexane under argon, followed by drying of the powder under high vacuum. IR spectra were recorded on Shimadzu 1 IRAffinity-1 instrument. NMR data were recorded on Bruker instruments operating at 400 MHz or 500 MHz for ^{1}H and 101 or 126 MHz for ^{13}C NMR experiments. All chemical shifts are recorded in parts per million (ppm) and coupling constants are measured in Hertz (Hz). Peak multiplicity is abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), sxt (sextet), m (multiple) and br s (broad singlet). All spectra were referenced with respect to $CHCl_3$ peak at 7.26 ppm for ^{1}H and with respect to $CDCl_3$ peak at 77.16 ppm for ^{13}C. High resolution mass spectrometry analysis was carried out at the University of Strathclyde and the University of Glasgow. LC-MS data were recorded on Agilent Technologies 1200 series instrument utilising APCI coupled with ESI with UV detection at 254 nm. All sampled were prepared in MeOH or MeCN. GC-MS data were recorded on Thermo Finnigan Polaris Q, mass range 50−650 Da. The column temperature was 320 °C, and the carrier gas was helium with a flow rate of 1 mL/min. The adsorbent was Crossbond® (0.25 μm) with column dimensions of 30 m × 0.25 mm. Results are reported as *m/z*. All samples were prepared in $CHCl_3$ and electron ionisation (EI) was used as the ionisation method. Direct injection MS data was recorded utilising ESI as an ionisation method. All samples were prepared in MeOH or MeCN.

4.2. General procedure A for formation of 14a, 14b in situ

A mixture containing paraformaldehyde (3.3 eq., 3.3 mmol, 99.10 mg), N^1,N^1,N^2-trimethylethane-1,2-diamine **18a** (1.0 eq., 1 mmol, 130 μL) or N^1,N^1,N^3- trimethylpropane-1,3-diamine **18b** (1.0 eq., 1 mmol, 146.5 μL), TsOH.H_2O (1.0 eq., 1 mmol, 190.22 mg) and dry EtOH (5 mL) was stirred and refluxed for 4 h under argon. The reaction mixture was cooled to room temperature before it was concentrated and dried under high vacuum for ~9 h.

4.3. General procedure B for reactions of nucleophiles with 14c

Previously synthesised 1,1-dimethyl-3-propylhexahydropyrimidin-1-ium tosylate **14c** (1.0 eq. 1.0 mmol, 329 mg) was added to a dry round bottom flask under argon. NaH (5.0 eq., 5 mmol) was added to a separate dry flask under argon followed by anhydrous THF (10 mL). Nucleophile (5.0 eq., 5 mmol) was added dropwise to the THF slurry and allowed to stir at room temperature for 30 min or until effervescence had stopped. The resultant slurry or solution was then added to the flask containing 1,1-dimethyl-3-propylhexahydropyrimidin-1-ium tosylate **14c** (1.0 eq., 1.0 mmol, 329 mg) and the reaction was allowed to stir at room temperature for 16 h. The reaction was quenched with water (5 mL) and the reaction mixture was extracted with EtOAc (5 × 30 mL). The combined organics were dried over Na_2SO_4 and then concentrated under vacuum. The product was isolated *via* flash silica chromatography.

4.4. General procedure C for reactions of nucleophiles with 14b

A solution of 1,1,3-trimethylhexahydropyrimidin-1-ium 4-methyl benzenesulfonate **14b** and an appropriate nucleophile (2 eq, 0.2, 0.3 or 1 mmol) in AcOH (0.3 or 1.5 or mL) was stirred at RT overnight. The reaction mixture was concentrated. The resulting residue was redissolved in water (10 mL), basified with solid NaOH until pH~9 and extracted with CH_2Cl_2 (5 × 20 mL). Combined organic phases were dried over $MgSO_4$, filtered and concentrated.

4.4.1. Preparation of 1,1,3-trimethylimidazolidin-1-ium chloride

A mixture containing pre-activated molecular sieves, paraformaldehyde (3.3 eq., 3.3 mmol, 99.10 mg), N^1,N^1,N^2-trimethylethane-1,2-diamine **18a** (1.0 eq., 1 mmol, 130 μL), HCl (240 μL) as a 37% solution in water and dry EtOH (5 mL) was refluxed under argon for 4 h. A sample of the reaction mixture was concentrated, re-dissolved in $CDCl_3$, filtered and analysed by NMR, IR and MS. All evidence suggests that 1,1,3-trimethylimidazolidin-1-ium chloride product was present in the crude reaction mixture: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.25 (br s, 2H, NCH_2N), 3.91 (br s, 2H, $Me_2NCH_2CH_2$), 3.56 (br s, 6H, 2 x Me), 3.13 (br s, 2H, MeNCH_2CH_2), 2.48 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 85.8, 65.0, 53.7, 52.0, 38.1. ATR-IR ν_{max} (neat)/cm^{-1} 3372, 3017, 2957, 2928, 2855, 2785, 1655, 1468, 1254, 1156, 1069, 1042, 961, 874, 644. *m/z* (ESI(+)): 115.0 $(M_{cat})^+$. HRMS (ESI) calcd. for $C_6H_{15}N_2^+$ [M(cation)$^+$]: 115.1230, found 115.1230.

4.4.2. Preparation of 1,1,3-trimethylimidazolidin-1-ium 4-methylbenzenesulfonate (**14a**)

A mixture containing pre-activated molecular sieves (optional), paraformaldehyde (3.3 eq., 3.3 mmol, 99.10 mg), N^1,N^1,N^2-trimethylethane-1,2-diamine **18a** (1.0 eq., 1 mmol, 130 μL), TsOH.H_2O (1.0 eq., 1 mmol, 190.22 mg) and dry EtOH (5 mL) was refluxed for 4 h under argon. Reaction mixture was concentrated and analysed by NMR, IR and MS. All evidence suggests that 1,1,3-trimethylimidazolidin-1-ium 4-methylbenzenesulfonate product **14a** was present in the crude reaction mixture. The crude material was most routinely used for subsequent experiments without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.1 Hz, 2H, 2 x ArH), 7.15 (d, J = 8.1 Hz, 2H, 2 x ArH), 4.08 (s, 2H, NCH_2N), 3.80 (t, J = 7.3 Hz, 2H, $Me_2NCH_2CH_2$), 3.44 (s, 6H, 2 x Me), 3.04 (t, J = 7.3 Hz, 2H, MeNCH_2CH_2), 2.41 (s, 3H, Me), 2.34 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.2, 139.9, 129.0, 125.9, 85.6, 64.8, 53.2, 51.9, 37.9, 21.0. ATR-IR ν_{max} (neat)/cm^{-1} 3422, 3034, 2953, 2922, 2862, 2791, 1655, 1468, 1179, 1121, 1034, 1011, 961, 816, 681, 602. *m/z* (ESI(+)): 115.1 $(M_{cat})^+$, *m/z* (ESI(−)): 171.1 (M_{anion})-. HRMS (ESI) calcd. for $C_6H_{15}N_2^+$ [M(cation)$^+$]: 115.1230, found 115.1228. HRMS (ESI) calcd. for $C_7H_7O_3S^-$ [M(anion)$^-$]: 171.0121, found 171.0120. Attempts to recrystallise the title compound were unsuccessful. It was found that heating a sample of the titled compound significantly decomposes the minor paraformaldehyde-derived impurities.

4.4.3. Preparation of 1,1,3-trimethylhexahydropyrimidin-1-ium 4-methylbenzenesulfonate (**14b**)

A mixture containing paraformaldehyde (3.3 eq., 66 mmol, 1.982 g), N^1,N^1,N^3- trimethylpropane-1,3-diamine **18b** (1.0 eq., 20 mmol, 2.93 mL), TsOH.H_2O (1.0 eq., 20 mmol, 3.804 g) and EtOH (100 mL) was refluxed for 4 h under argon. The reaction mixture was concentrated and triturated with hexane (2x) affording 1,1,3-

trimethylhexahydropyrimidin-1-ium 4-methylbenzenesulfonate **14b** as a white solid (5.903 g, 98%). Alternatively, the reaction mixture was triturated with hexane and recrystallised from THF/$CHCl_3$. (Mp = 100–103 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.1 Hz, 2H, 2 x ArH), 7.14 (d, J = 7.9 Hz, 2H, 2 x ArH), 3.91 (br s, 2H, NCH_2N), 3.50 (br s, 2H, Me_2NCH_2), 3.32 (br s, 6H, 2 x Me), 2.58 (br s, 2H, $MeNCH_2$), 2.32 (2 x s, 6H, 2 x Me), 1.88 (br s, 2H, $CH_2CH_2CH_2$). ^{13}C NMR (101 MHz, $CDCl_3$, 323 K) δ 144.5, 139.3, 128.8, 126.1, 82.1, 61.1, 51.4, 49.8, 42.1, 21.3, 20.8.^{13}C NMR (101 MHz, $CDCl_3$, 233 K) δ 142.9, 139.7, 128.9, 125.6, 81.3, 60.4, 52.2, 51.2, 46.2, 42.0, 21.5, 20.4. ATR-IR ν_{max} (neat)/cm^{-1} 3456, 3026, 2949, 2864, 2793, 1647, 1487, 1470, 1450, 1396, 1287, 1188, 1121, 1094, 1057, 1034, 1011, 970, 934, 893, 818, 681, 617. *m/z* (ESI(+)): 129.1 $(M_{cat})^+$, *m/z* (ESI(−)): 171.1 (M_{anion})-. HRMS (ESI) calcd. for $C_7H_{17}N_2^+$ [M(cation)$^+$]: 129.1386, found 129.1386. HRMS (ESI) calcd. for $C_7H_7O_3S^-$ [M(anion)$^-$]: 171.0121, found 171.0117.

4.4.4. Preparation of N^1,N^1-dimethyl-N^3-propylpropane-1,3-diamine

To a pressure tube containing 3-(dimethylamino)propyl chloride hydrochloride (25.94 mmol 4.10 g) under an argon atmosphere, propylamine (72.98 mmol, 6 mL, 4.31 g) was added in accordance with a literature procedure [45]. The vessel was sealed and allowed to stir at 100 °C for 24 h. The reaction mixture was then allowed to cool and then NaOH [aq (25% w/w)] (62.5 mmol, 10 mL) was added. The upper layer of the resultant biphasic mixture was separated, and the aqueous layer was extracted with Et_2O (5 × 30 mL). The combined organics were dried over Na_2SO_4 and the solvent and residual propylamine were removed under vacuum to afford N^1,N^1-dimethyl-N^3-propylpropane-1,3-diamine as a slightly yellow liquid (2.47 g, 17.16 mmol, 67%) which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62 (t, J = 7.2 Hz, 2H), 2.55 (t, J = 7.2 Hz, 2H), 2.29 (t, J = 7.2 Hz, 2H), 2.19 (s, 6H), 1.64 (qu, J = 7.2 Hz, 2H), 1.50 (sextet, J = 7.4 Hz, 2H), 0.89 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 58.2, 52.1, 48.6, 45.7, 28.2, 23.3, 11.9. HRMS (ESI) calcd. for $C_9H_{23}N_2^+$ [(M + H)$^+$]: 145.1699, found 145.1693.

4.4.5. Preparation of 1,1-dimethyl-3-propylhexahydro pyrimidin-1-ium 4-methylbenzenesulfonate (**14c**)

TsOH.H_2O (190.2 mg, 1.00 mmol) and paraformaldehyde (3.33 eq., 3.33 mmol, 99.9 mg) were added to a 50 mL round bottom flask fitted with a condenser and the atmosphere was replaced with argon. Previously prepared N^1,N^1-dimethyl-N^3-propylpropane-1,3-diamine (190 μL, approx. 1 mmol) was added followed by 5 mL anhydrous EtOH. The reaction mixture was allowed to stir at reflux for 4 h and then the ethanol was removed under vacuum. Anhydrous THF (2 mL) was then added to the off-white solid and brought to reflux, which afforded complete dissolution. Precipitation of a white solid was observed when the reaction mixture was cooled below 40 °C (with stirring) and so the reaction mixture was allowed to stir at room temperature for 16 h. The precipitated white solid was 1,1-dimethyl-3-propylhexahydropyrimidin-1-ium 4-methylbenzenesulfonate **14c** (129 mg, 0.39 mmol, 39%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.1 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H), 3.93 (s, 2H), 3.49–3.42 (m, 2H), 3.21 (s, 6H), 2.62–2.56 (m, 2H), 2.41–2.35 (m, 2H), 2.29 (s, 3H), 1.84–1.74 (m, 2H), 1.37 (sextet, J = 7.3 Hz, 2H), 0.79 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.5, 139.2, 128.7, 126.0, 81.5, 61.5, 56.1, 49.3, 48.7, 21.2, 20.7, 20.1, 11.4. ATR-IR ν_{max} (neat)/cm^{-1} 3021, 2957, 2922, 2870, 1579, 1489, 1467, 1454, 1375, 1356, 1341, 1317, 1285, 1269, 1215, 1192, 1171, 1119, 1101, 1032, 1009, 970, 928, 893, 854, 818, 791, 714, 700, 679, 638, 619. Mp = 103–106 °C. HRMS (ESI) calcd. for $C_9H_{21}N_2^+$ [M(cation)$^+$]: 157.1699, found 157.1693.

4.4.6. Preparation of 2-(ethoxymethyl)-1-phenylprop-2-en-1-one (**22**)

4.4.6.1. Two procedures were employed

(Procedure 1) A mixture containing pre-activated molecular sieves, paraformaldehyde (3.3 eq., 3.3 mmol, 99.10 mg), N^1,N^1,N^2-trimethylethane-1,2-diamine **18a** (1.0 eq., 1 mmol, 130 μL), TsOH.H_2O (1.0 eq., 1 mmol, 190.22 mg) and dry EtOH (5 mL) was refluxed for 4 h under argon. The reaction was then cooled to room temperature and acetophenone (1.0 eq., 1 mmol, 116.65 μL) was added. The reaction mixture was refluxed for 16.5 h before it was cooled to room temperature and concentrated. The reaction residue was diluted with water (20 mL) and EtOAc (40 mL). The organic phase was separated, and the aqueous phase was further washed with EtOAc (2 × 40 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (CH_2Cl_2) afforded 2-(ethoxymethyl)-1-phenylprop-2-en-1-one **22** (60 mg, 32%) as a mobile yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90–7.65 (m, 2H, 2 x ArH), 7.52 (t, J = 7.4 Hz, 1H, ArH), 7.42 (t, J = 7.4 Hz, 2 x ArH), 6.14 (d, J = 1.0 Hz, 1H, C=CH_2), 5.77 (d, J = 1.0 Hz, 1H, C=CH_2), 4.34 (s, 1H, CCH_2O), 3.59 (q, J = 7.0 Hz, 2H, OCH_2CH$_3$), 1.23 (t, J = 7.0 Hz, 3H, OCH$_2$$CH_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.9, 144.9, 137.6, 132.4, 129.5, 128.3, 126.3, 69.3, 66.5, 15.2. ATR-IR ν_{max} (neat)/cm^{-1} 3082 3061, 2974, 2928, 2864, 1651, 1630, 1597, 1578, 1485, 1447, 1395, 1378, 1358, 1317, 1267, 1240, 1198, 1188, 1173, 1159, 1113, 1076, 1013, 1001, 978, 949, 935, 887, 851, 814, 752, 733, 694, 667, 635. *m/z* (EI): 189.1 [(M − H)$^+$, 61], 161.1 (31), 145.1 (14), 131.1 (10), 115.1 (11), 105.1 (100), 91.0 (7), 77.0 (80), 63.0 (2), 51.0 (23). HRMS (ESI) calcd. for $C_{12}H_{14}O_2^+$ [(M + Na)$^+$]: 213.0886, found 213.0885.

(Procedure 2) A mixture containing paraformaldehyde (3.3 eq., 3.3 mmol, 99.10 mg), N^1,N^1,N^3- trimethylpropane-1,3-diamine **14b** (1.0 eq., 1 mmol, 146.5 μL), TsOH.H_2O (1.0 eq., 1 mmol, 190.22 mg) and dry EtOH (5 mL) was refluxed for 4 h under argon. Acetophenone **23** (1.0 eq., 1 mmol, 116.65 μL) was added. The reaction mixture was refluxed overnight before it was cooled to room temperature and concentrated. The reaction residue was diluted with water (10 mL) and extracted with EtOAc (4 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (CH_2Cl_2) afforded 2-(ethoxy methyl)-1-phenylprop-2-en-1-one **22** (3 mg, 2%) as a yellow oil. Spectroscopic data agreed with the data outlined above.

4.4.7. Preparation of N^1-benzyl-N^1,N^2,N^2-trimethylethane-1,2-diamine (**19a**)

4.4.7.1. Two procedures were employed

(Procedure 1) A mixture containing $MgSO_4$ (1.0 eq., 1 mmol, 120.37 mg), paraformaldehyde (3.3 eq., 3.3 mmol, 99.10 mg), N^1,N^1,N^2-trimethyl ethane-1,2-diamine **18a** (1.0 eq., 1 mmol, 130 μL), TsOH.H_2O (1.0 eq., 1 mmol, 190.22 mg) and dry EtOH (5 mL) was stirred

and refluxed for 4 h under argon. The reaction mixture was cooled to room temperature before it was filtered through a phase separator, concentrated, and dried under high vacuum overnight. The reaction residue was cooled to 0 °C, PhMgBr (5.0 eq., 5 mmol, 5 mL) as a 1 M solution in THF was added dropwise under argon and the reaction was stirred at room temperature for 30 min before it was quenched with water (1 mL) at 0 °C. The reaction mixture was further diluted with water (40 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (hexane → EtOAc → MeOH) afforded N^1-benzyl-N^1,N^2,N^2-trimethylethane-1,2-diamine **19a** (117 mg, 61%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.13 (m, 5H, 5 x ArH), 3.52 (s, 2H, Ph*CH*$_2$N), 2.58–2.41 (m, 4H, 2 x N*CH*$_2$CH$_2$N), 2.24–2.23 (2 x s, 9H, 3 x Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.0, 129.3, 128.3, 127.1, 63.1, 57.5, 55.3, 45.9, 42.7. ATR-IR ν_{max} (neat)/cm^{-1} 3084, 3061, 3026, 2968, 2941, 2855, 2812, 2764, 1495, 1452, 1364, 1314, 1281, 1263, 1184, 1155, 1123, 1098, 1074, 1024, 974, 934, 908, 880, 841, 826, 783, 735, 696, 671, 638, 611. *m/z* (ESI): 193.1 ([M+H]$^+$). HRMS (ESI) calcd. for $C_{12}H_{21}N_2^+$ [(M + H)$^+$]: 193.1699, found 193.1701.

(Procedure 2) Prepared according to **General Procedure A** for the first step, using paraformaldehyde (3.3 eq., 3.3 mmol, 99.10 mg), N^1,N^1,N^2-trimethyl ethane-1,2-diamine **18a** (1.0 eq., 1 mmol, 130 μL), TsOH.H_2O (1.0 eq., 1 mmol, 190.22 mg) and dry EtOH (5 mL). The reaction residue was redissolved in dry THF (5 mL) and cooled to 0 °C. PhLi (5.0 eq., 5 mmol, 3.2 mL) as a 1.56 M solution in dibutyl ether was added dropwise under argon and the reaction was stirred at room temperature for 30 min before it was quenched with water (15 mL) at 0 °C. The reaction mixture was further diluted with water (5 mL) and extracted with EtOAc (4 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (hexane → EtOAc → MeOH) afforded N^1-benzyl-N^1,N^2,N^2-trimethylethane-1,2-diamine **19a** (70 mg, 36%) as a yellow oil. Spectroscopic data agreed with the data outlined above.

4.4.8. Preparation of N^1-(4-methoxybenzyl)-N^1,N^2,N^2-trimethylethane-1,2-diamine (**19b**)

Prepared according to General Procedure A for the first step, using paraformaldehyde (3.3 eq., 3.3 mmol, 99.10 mg), N^1,N^1,N^2-trimethylethane-1,2-diamine **18a** (1.0 eq., 1 mmol, 130 μL), TsOH.H_2O (1.0 eq., 1 mmol, 190.22 mg) and dry EtOH (5 mL). The reaction residue was cooled to 0 °C, 4-MeOC_6H_4MgBr (5.0 eq., 5 mmol, 10 mL) as a 0.5 M solution in THF was added dropwise under argon and the reaction was stirred at room temperature for 30 min before it was quenched with water (5 mL) at 0 °C. The reaction mixture was further diluted with water (35 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (EtOAc → 50% EtOAc/50% MeOH) afforded N^1-(4-methoxybenzyl)-N^1,N^2,N^2-trimethylethane-1,2-diamine **19b** (192 mg, 86%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.6 Hz, 2H, 2 x ArH), 6.84 (d, *J* = 8.6 Hz, 2H, 2 x ArH), 3.79 (s, 3H, OCH_3), 3.45 (s, 2H, Ar*CH*$_2$N), 2.56–2.36 (m, 4H, 2 x N*CH*$_2$CH$_2$), 2.21 (s, 9H, 3 x Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 131.0, 130.4, 113.7, 62.4, 57.5, 55.4, 55.1, 45.9, 42.5. ATR-IR ν_{max} (neat)/cm^{-1} 2938, 2832, 2768, 1611, 1584, 1572, 1510, 1457, 1443, 1364, 1300, 1240, 1180, 1134, 1103, 1049, 1028, 1015, 924, 841, 814, 760, 706, 694, 650, 637, 619. *m/z* (ESI): 223.1, ([M+H]$^+$). HRMS (ESI) calcd. for $C_{13}H_{23}N_2O^+$ [(M + H)$^+$]: 223.1805, found 223.1806.

4.4.9. Preparation of tetraethyl propane-1,1,3,3-tetra carboxylate (**32**)

Prepared according to General Procedure A for the first step using paraformaldehyde (3.3 eq., 3.3 mmol, 99.10 mg), N^1,N^1,N^2-trimethyl ethane-1,2-diamine **18a** (1.0 eq., 1 mmol, 130 μL), TsOH.H_2O (1.0 eq., 1 mmol, 190.22 mg) and dry EtOH (5 mL). Diethyl malonate (5.0 eq., 5 mmol, 759.1 μL) was added to a slurry of NaH (5.5 eq., 5.5 mmol, 132 mg) in dry THF (5 mL) dropwise at 0 °C under argon and the reaction was stirred at RT for 2 h, resulting in a pale-yellow solution of **33**. The reaction residue containing **14a** was redissolved in dry THF (5 mL) under argon and it was added to the reaction mixture containing **33** dropwise at 0 °C under argon. The reaction mixture was stirred at room temperature for 2 h before it was quenched with water (5 mL) at 0 °C. The reaction mixture was further diluted with water (35 mL) and extracted with EtOAc (3 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (hexane → 20% EtOAc/80% hexane) afforded tetraethyl propane-1,1,3,3-tetracarboxylate **32** (182 mg, 55%) as a pale-yellow mobile oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23–4.17 (m, 8H, 4 x *CH*$_2$CH$_3$), 3.46 (t, *J* = 7.6 Hz, 2H, 2 x CH), 2.46 (t, *J* = 7.6 Hz, 2H, C*CH*$_2$C), 1.26 (t, *J* = 7.1 Hz, 12H, 4 x CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 61.8, 49.6, 27.5, 14.2. ATR-IR ν_{max} (neat)/cm^{-1} 2982, 2940, 2909, 1728, 1466, 1445, 1391, 1369, 1344, 1298, 1269, 1227, 1196, 1148, 1096, 1074, 1032, 1020, 947, 916, 854, 789, 692. *m/z* (EI): 332.0 (M$^+$, 1), 287.1 (23), 258.1 (9), 241.1 (30), 213.1 (7), 186.1 (11), 173.1 (100), 160.1 (20), 140.0 (11), 127.1 (56), 112.1 (10), 99.0 (20), 86.0 (11), 73.1 (8), 55.1 (23). (HRMS?)

4.4.10. Preparation of 2-(((2-(dimethylamino)ethyl) (methyl) amino)methyl)-2-ethyl malonate (**19c**)

Prepared according to General Procedure A for the first step using paraformaldehyde (3.3 eq., 3.3 mmol, 99.10 mg), N^1,N^1,N^2-trimethyl ethane-1,2-diamine **18a** (1.0 eq., 1 mmol, 130 μL), TsOH.H_2O (1.0 eq., 1 mmol, 190.22 mg) and dry EtOH (5 mL). Diethyl ethylmalonate (5.0 eq., 5 mmol, 937 μL) was added to a slurry of NaH (5.0 eq., 5.0 mmol, 120 mg) in dry THF (5 mL) dropwise at 0 °C under argon and the reaction was stirred at RT for 2 h, resulting in a pale-yellow solution. The reaction residue containing **14a** was redissolved in dry THF (5 mL) under argon and it was added to the reaction mixture containing the deprotonated diethyl ethylmalonate dropwise at 0 °C under argon. The reaction mixture was stirred at room temperature for 2 h before it was quenched with water (5 mL) at 0 °C. The reaction mixture was further diluted with water (35 mL) and extracted with EtOAc (3 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (20% EtOAc/80% hexane → 50% MeOH/50% EtOAc) afforded diethyl 2-(((2-(dimethyl amino) ethyl)(methyl)amino)methyl)-2-ethyl malonate **19c** (107 mg, 35%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31–4.08 (m, 4H, 2 x *CH*$_2$CH$_3$), 2.99 (s, 2H, CCH$_2$N), 2.63–2.52 (m, 2H, N*CH*$_2$CH$_2$N), 2.49–2.36 (m, 2H, NCH$_2$*CH*$_2$N), 2.26 (s, 6H, 2 x NCH_3), 2.23 (s, 3H, NCH_3), 2.04 (q, *J* = 7.5 Hz, 2H, *CH*$_2$CH$_3$), 1.24 (t, *J* = 7.1 Hz, 6H, 2 x CH$_2$*CH*$_3$), 0.83 (t, *J* = 7.5 Hz, 3H, CH$_2$*CH*$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 61.1, 59.5, 59.4, 57.4, 57.1, 45.6, 44.1, 24.6, 14.2, 8.8. ATR-IR ν_{max} (neat)/cm^{-1} 2974, 2940, 2880, 2857, 2816, 2768, 1728, 1603, 1460, 1449, 1387, 1368, 1296, 1244, 1233, 1215, 1184, 1134, 1113,

1094, 1030, 860, 814, 783, 745, 694, 604. HRMS (ESI) calcd. for $C_{15}H_{31}N_2O_4^+$ [(M + H)$^+$]: 303.2278, found 303.2276.

4.4.12. Preparation of 2-((2(dimethylamino)ethyl) (methyl)amino) methyl)phenol (**19e**)

Prepared according to General Procedure A for the first step using paraformaldehyde (3.3 eq., 3.3 mmol, 99.10 mg), N^1,N^1,N^2-trimethyl ethane-1,2-diamine **18a** (1.0 eq., 1 mmol, 130 μL), TsOH.H_2O (1.0 eq., 1 mmol, 190.22 mg) and dry EtOH (5 mL). Phenol (5.0 eq., 5 mmol, 439 μL) was added to a slurry of NaH (5.0 eq., 5.0 mmol, 120 mg) in dry THF (5 mL) dropwise at 0 °C under argon and the reaction was stirred at RT, resulting in a yellow solution. Reaction mixture containing **14a** was dissolved in dry THF (5 mL). The reaction mixture containing the phenolate nucleophile was added to the reaction mixture containing **14a** dropwise at 0 °C under argon. The reaction mixture was stirred at room temperature for 1.25 h before it was quenched with water (5 mL) at 0 °C. The reaction mixture was further diluted with water (35 mL) and extracted with EtOAc (4 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (hexane → EtOAc → MeOH) afforded 2-(((2-(dimethylamino)ethyl)(methyl)amino)methyl)phenol **19e** (121 mg, 58%) as a straw-coloured oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (td, J = 7.9, 1.7 Hz, 1H, ArH), 7.01–6.93 (m, 1H, ArH), 6.83 (dd, J = 8.1, 1.0 Hz, 1H, ArH), 6.76 (td, J = 7.4, 1.2 Hz, 1H, ArH), 3.62 (s, 2H, $ArCH_2N$), 2.63–2.57 (m, 2H, NCH_2CH_2N), 2.55–2.48 (m, 2H, NCH_2CH_2N), 2.27 (s, 3H, Me), 2.26 (s, 6H, 2 x Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.9, 129.1, 128.9, 122.8, 118.9, 116.5, 59.8, 56.7, 54.4, 45.4, 42.2. ATR-IR ν_{max} (neat)/cm^{-1} 3044, 2972, 2943, 2857, 2816, 2772, 1612, 1584, 1485, 1456, 1364, 1256, 1236, 1125, 1026, 922, 812, 752, 721. *m/z* (ESI): 209.1 ([M+H]$^+$). HRMS (ESI) calcd. for $C_{12}H_{21}N_2O^+$ [(M + H)$^+$]: 209.1648, found 209.1648.

4.4.11. Preparation of diethyl 2-allyl-2-(((2-(dimethylamino) ethyl)(methyl)amino)methyl)malonate (**19d**)

Prepared according to General Procedure A for the first step using paraformaldehyde (3.3 eq., 3.3 mmol, 99.10 mg), N^1,N^1,N^2-trimethyl ethane-1,2-diamine **18a** (1.0 eq., 1 mmol, 130 μL), TsOH.H_2O (1.0 eq., 1 mmol, 190.22 mg) and dry EtOH (5 mL). Diethyl 2-allylmalonate (5.0 eq., 5 mmol, 986 μL) was added to a slurry of NaH (5.0 eq., 5.0 mmol, 120 mg) in dry THF (5 mL) dropwise at 0 °C under argon and the reaction was stirred at RT for 1 h, resulting in a pale yellow solution. The reaction residue containing **14a** was redissolved in dry THF (49 mL) under argon. 1 mL of the solution containing the deprotonated diethyl 2-allylmalonate (~1.0 eq., ~1 mmol) was added dropwise to the imidazolidinium salt solution **14a** in dry THF dropwise at RT under argon. The reaction mixture was stirred at room temperature for 1.5 h before it was quenched with water (5 mL) at 0 °C and concentrated. The residue was dissolved in water (10 mL) and extracted with CH_2Cl_2 (4 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (hexane → 15% MeOH/85% EtOAc) afforded diethyl 2-allyl-2-(((2-(dimethylamino)ethyl)(methyl)amino)methyl) malonate **19d** (107 mg, 34%) as a yellow mobile oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (ddt, J = 17.4, 10.1, 7.3 Hz, 1H, alkene CH), 5.15–4.99 (m, 2H, alkene CH_2), 4.24–4.07 (m, 4H, 2 x OCH_2), 2.97 (s, 2H, CCH_2N), 2.75 (d, J = 7.3 Hz, 2H, $CHCH_2C$), 2.56–2.53 (m, 2H, NCH_2CH_2N), 2.40–2.36 (m, 2H, NCH_2CH_2N), 2.23 (2 x s, 9H, 3 x NMe), 1.22 (t, J = 7.1 Hz, 6H, 2 x CH_2CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 133.2, 118.9, 61.2, 60.0, 58.9, 57.5, 57.3, 45.7, 43.9, 36.1, 14.2. ATR-IR ν_{max} (neat)/cm^{-1} 2976, 2940, 2857, 2816, 2768, 1728, 1670, 1641, 1464, 1368, 271, 1202, 1184, 1121, 1096, 1032, 1011, 918, 858, 818, 781, 758, 681, 654, 604. *m/z* (ESI) 315.2 ([M+H]$^+$). HRMS (ESI) calcd. for $C_{16}H_{31}N_2O_4^+$ [(M + H)$^+$]: 315.2278, found 315.2279.

4.4.13. Preparation of 2-chloro-6-(((2-(dimethylamino) ethyl)(methyl)amino)methyl)phenol (**19f**)

Prepared according to General Procedure A for the first step using paraformaldehyde (3.3 eq., 3.3 mmol, 99.10 mg), N^1,N^1,N^2-trimethylethane-1,2-diamine 18a (1.0 eq., 1 mmol, 130 μL), TsOH.H_2O (1.0 eq., 1 mmol, 190.22 mg) and dry EtOH (5 mL). 2-Chlorophenol (5.0 eq., 5 mmol, 518 μL) was added to a slurry of NaH (5.0 eq., 5.0 mmol, 120 mg) in dry THF (5 mL) dropwise at 0 °C under argon and the reaction was stirred at RT, resulting in a clear yellow solution. Reaction mixture containing **14a** was dissolved in dry THF (5 mL). The reaction mixture containing the chlorophenolate was added to the reaction mixture containing **14a** dropwise at 0 °C under argon. An extra portion of dry THF (5 mL) was used as a wash to transfer the residual 2-chlorophenolate solution. The reaction mixture was stirred at room temperature for 20 h before it was quenched with water (5 mL) at 0 °C. The reaction mixture was further diluted with water (5 mL) and extracted with EtOAc (4 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (hexane → EtOAc → MeOH) afforded 2-chloro-6-(((2-(dimethylamino)ethyl)(methyl)amino)methyl)phenol **19f** (201 mg, 83%) as a light brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.49 (br s, 1H, OH), 7.22 (dd, J = 8.0, 1.6 Hz, 1H, ArH), 6.90–6.82 (m, 1H, ArH), 6.74–6.61 (t, J = 7.8 Hz, 1H, ArH), 3.62 (s, 2H, $ArCH_2N$), 2.66–2.58 (m, 2H, NCH_2CH_2N), 2.58–2.50 (m, 2H, NCH_2CH_2N), 2.28 (s, 6H, 2 x Me), 2.26 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.9, 129.3, 127.4, 124.0, 121.1, 119.1, 59.6, 56.5, 54.1, 45.3, 42.0. ATR-IR ν_{max} (neat)/cm^{-1} 2945, 2916, 2818, 2789, 2770, 2714, 1676, 1603, 1570, 1456, 1364, 1302, 1261, 1229, 1159, 1136, 1072, 1026, 928, 826, 814 764, 731, 694, 656, 606. *m/z* (ESI): 243.1 ([M+H]$^+$). HRMS (ESI) calcd. for $C_{12}H_{20}N_2OCl^+$ [(M + H)$^+$]: 243.1259, found 243.1259.

4.4.14. Preparation of 3-(((2-(dimethylamino)ethyl) (methyl) amino)methyl)-4-hydroxybenzonitrile (**19g**)

Prepared according to General Procedure A for the first step using paraformaldehyde (3.3 eq., 3.3 mmol, 99.10 mg), N^1,N^1,N^2-trimethyl ethane-1,2-diamine 18a (1.0 eq., 1 mmol, 130 μL), TsOH.H_2O (1.0 eq., 1 mmol, 190.22 mg) and dry EtOH (5 mL). 4-Cyanophenol (5.0 eq., 5 mmol, 595.95 mg) was added to a slurry of NaH (5.0 eq., 5.0 mmol, 120 mg) in dry THF (5 mL) portion wise at 0 °C under argon and the reaction was stirred at RT, resulting in a fine white slurry. The reaction mixture containing **14a** was dissolved in dry THF (5 mL). The reaction mixture containing the phenolate nucleophile was added to the reaction mixture containing **14a** dropwise at 0 °C under argon. An extra portion of dry THF (5 mL) was used as a wash to transfer the residual 2-cyanophenolate solution. The reaction mixture was stirred at room temperature for 20 h before it was quenched with water (5 mL) at 0 °C. The reaction mixture was further diluted with water (5 mL) and extracted with EtOAc (4 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (hexane → EtOAc → MeOH) afforded 3-(((2-(dimethylamino)ethyl)(methyl)amino) methyl)-4-hydroxybenzonitrile **19g** (123 mg, 53%) as a white solid (Mp = 59–61 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.86 (br s, 1H, OH), 7.43 (dd, J = 8.4, 1.2 Hz, 1H, ArH), 7.27 (s, 1H, ArH), 6.82 (d, J = 8.4 Hz, 1H, ArH), 3.51 (s, 2H, $ArCH_2N$), 2.62–2.58 (m, 2H, NCH_2CH_2N), 2.55–2.52 (m, 2H, NCH_2CH_2N), 2.27 (s, 6H, 2 x Me), 2.22 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6, 133.5, 133.4, 124.5, 119.9, 117.8, 101.2, 57.3, 55.9, 53.5, 44.9, 42.3. ATR-IR ν_{max} (neat)/cm^{-1} 2965, 2951, 2882, 2839, 2820, 2808, 2787, 2766, 2214, 1605, 1560, 1458, 1437, 1368, 1306, 1298, 1273, 1198, 1167, 1126, 1109, 1072, 1053, 1040, 1024, 930, 907, 827, 808, 777, 750, 733, 714, 669, 650, 602. *m/z* (ESI): 234.1 ([M+H]$^+$), 232.2 ([M − H]$^-$). HRMS (ESI) calcd. for $C_{13}H_{20}N_3O^+$ [(M + H)$^+$]: 234.1601, found 234.1600.

*4.4.15. Preparation of 2-(((2-(dimethylamino)ethyl) (methyl) amino)methyl)-4-iodophenol (**19h**)*

Prepared according to General Procedure A for the first step using paraformaldehyde (3.3 eq., 3.3 mmol, 99.10 mg), N^1,N^1,N^2-trimethyl ethane-1,2-diamine **18a** (1.0 eq., 1 mmol, 130 μL), TsOH.H_2O (1.0 eq., 1 mmol, 190.22 mg) and dry EtOH (5 mL). 2-Iodophenol (5.0 eq., 5 mmol, 1.100 g) was added to a slurry of NaH (5.0 eq., 5.0 mmol, 120 mg) in dry THF (5 mL) portion wise at 0 °C under argon and the reaction was stirred at RT, resulting in a pale pink solution. The reaction mixture from containing **14a** was dissolved in dry THF (5 mL). The reaction mixture containing the phenolate nucleophile was added to the reaction mixture containing 14a dropwise at 0 °C under argon. An extra portion of dry THF (5 mL) was used as a wash to transfer the residual 2-iodophenolate solution. The reaction mixture was stirred at room temperature for 20 h before it was quenched with water (5 mL) at 0 °C. The reaction mixture was further diluted with water (5 mL) and extracted with EtOAc (4 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (hexane → EtOAc → MeOH) afforded 2-(((2-(dimethylamino)ethyl)(methyl)amino)methyl)-4-iodophenol **19h** (297 mg, 89%) as a brown solid (Mp = 48–52 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (br s, 1H, OH), 7.40 (dd, J = 8.5, 2.0 Hz, 1H, ArH), 7.26 (d, J = 2.9 Hz, 1H, ArH), 6.60 (d, J = 8.5 Hz, 1H, ArH), 3.51 (s, 2H, $ArCH_2N$), 2.64–2.56 (m, 2H, NCH_2CH_2N), 2.56–2.48 (m, 2H, NCH_2CH_2N), 2.27 (s, 6H, 2 x Me), 2.24 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.9, 137.5, 125.7, 119.0, 80.1, 58.5, 56.3, 53.9, 45.1, 42.2 (one signal missing due to overlap). ATR-IR ν_{max} (neat)/cm^{-1} 3044, 2976, 2943, 2820, 2803, 2779, 2762, 2633, 2544, 1560, 1477, 1452, 1364, 1337, 1300, 1277, 1231, 1217, 1186, 1157, 1126, 1070, 1047, 1038, 1026, 1013, 995, 978, 943, 926, 887, 870, 824, 810, 777, 727, 692, 656, 633, 610. *m/z* (ESI): 335.1 ($[M+H]^+$), 333.0 ($[M-H]^-$). HRMS (ESI) calcd. for $C_{12}H_{20}IN_2O^+$ $[(M+H)^+]$: 335.0615, found 335.0614.

*4.4.16. Preparation of 4-(((2-(dimethylamino)ethyl) (methyl) amino)methyl)-2,6-dimethoxyphenol (**19i**)*

Prepared according to General Procedure A for the first step using paraformaldehyde (3.3 eq., 3.3 mmol, 99.10 mg), N^1,N^1,N^2-trimethyl ethane-1,2-diamine **18a** (1.0 eq., 1 mmol, 130 μL), TsOH.H_2O (1.0 eq., 1 mmol, 190.22 mg) and dry EtOH (5 mL). 2,6-Dimethoxyphenol (5.0 eq., 5 mmol, 770.8 mg) was added to a slurry of NaH (5.0 eq., 5.0 mmol, 120 mg) in dry THF (10 mL) portion wise at 0 °C under argon and the reaction was stirred at RT, resulting in a white slurry. Reaction mixture containing 14a was dissolved in dry THF (5 mL). The reaction mixture containing the phenolate nucleophile was added to the reaction mixture containing **14a** dropwise at 0 °C under argon. An extra portion of dry THF (5 mL) was used as a wash to transfer the residual 2,6-dimethoxyphenolate solution. The reaction mixture was stirred at room temperature for 20 h before it was quenched with water (5 mL) at 0 °C. The reaction mixture was further diluted with water (5 mL) and extracted with EtOAc (5 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (hexane → EtOAc → MeOH) afforded 4-(((2-(dimethyl amino)ethyl) (methyl)amino) methyl) −2,6-dimethoxyphenol **19i** (195 mg, 73%) as a brown solid [Mp = 108–110 °C (decomp.)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (s, 2H, 2 x ArH), 3.82 (s, 6H, 2 x OMe), 3.40 (s, 2H, $ArCH_2N$), 2.54–2.33 (m, 4H, NCH_2CH_2N, NCH_2CH_2N), 2.23 (s, 3H, Me), 2.18 (s, 6H, 2 x Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.2, 133.9, 130.0, 105.7, 63.5, 57.4, 56.3, 54.8, 45.9, 42.8. ATR-IR ν_{max} (neat)/cm^{-1} 2994, 2945, 2818, 2779, 2722, 2633, 1603, 1591, 1516, 1454, 1425, 1366, 1339, 1296, 1261, 1244, 1217, 1184, 1155, 1115, 1043, 1013, 986, 968, 845, 829, 797, 737, 696, 648. *m/z* (ESI): 269.1 ($[M+H]^+$), 267.1 ($[M-H]^-$). HRMS (ESI) calcd. for $C_{14}H_{25}N_2O_3^+$ $[(M+H)^+]$: 269.1860, found 269.1857.

*4.4.17. Preparation of N^1-(((4-methoxybenzyl)thio) methyl)-N^1,N^2,N^2-trimethylethane-1,2-diamine (**19j**)*

Prepared according to General Procedure A for the first step using paraformaldehyde (3.3 eq., 3.3 mmol, 99.10 mg), N^1,N^1,N^2-trimethylethane-1,2-diamine **18a** (1.0 eq., 1 mmol, 130 μL), TsOH.H_2O (1.0 eq., 1 mmol, 190.22 mg) and dry EtOH (5 mL). (4-Methoxyphenyl) methanethiol (5.0 eq., 5 mmol, 696.6 μL) was added to a slurry of NaH (5.0 eq., 5.0 mmol, 120 mg) in dry THF (10 mL) dropwise at −5 °C under argon and the reaction was stirred at RT for 30 min, resulting in a white slurry. The reaction residue containing **14a** was redissolved in dry THF (15 mL) under argon and it was added to the reaction mixture containing the thiolate nucleophile dropwise at 0 °C under argon. The reaction mixture was stirred at room temperature for 1.5 h before it was quenched with water (5 mL) at 0 °C and concentrated under reduced pressure. The reaction mixture was redissolved in water (35 mL) and extracted with EtOAc (3 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (hexane → EtOAc → MeOH) afforded N^1-(((4-methoxy benzyl)thio) methyl)-N^1,N^2,N^2-trimethylethane-1,2-diamine **19j** (102 mg, 38%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 8.6 Hz, 2H, 2 x ArH), 6.83 (d, J = 8.6 Hz, 2H, 2 x ArH), 3.98 (s, 2H, SCH_2Ar), 3.78 (s, 3H, OMe), 3.73 (s, 2H, NCH_2S), 2.56 (t, J = 6.7 Hz, 2H, NCH_2CH_2N), 2.38–2.27 (m, 5H, NCH_2CH_2N and Me), 2.21 (s, 6H, 2 x Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7, 131.1, 130.1, 114.0, 62.4, 57.3, 55.4, 52.7, 45.8, 41.0, 36.6. ATR-IR ν_{max} (neat)/cm^{-1} 2938, 2855, 2832, 2816, 2766, 1674, 1609, 1584, 1510, 1462, 1441, 1300, 1248, 1173, 1105, 1034, 934, 829, 743, 640. *m/z* (EI): 267.1 [$(M-H)^+$, 1], 154.1 (10), 135.1 (3), 121.1 (100), 109.1 (3), 91.0 (11), 78.0 (25), 65.0 (6), 58.0 (16), 51.0 (13).

*4.4.18. Preparation of N^1-benzyl-N^1,N^3,N^3-trimethyl propane-1,3-diamine (**20a**)*

Prepared according to General Procedure A for the first step, using paraformaldehyde (3.3 eq., 3.3 mmol, 99.10 mg), N^1,N^1,N^3-trimethyl propane-1,3-diamine **14b** (1.0 eq., 1 mmol, 146.5 μL), TsOH.H_2O (1.0 eq., 1 mmol, 190.22 mg) and dry EtOH (5 mL). The reaction residue was cooled to 0 °C, PhMgBr (5.0 eq., 5 mmol, 5 mL) as a 1 M solution in THF was added dropwise under argon and the reaction was stirred at room temperature for 1 h before it was quenched with water (5 mL) at 0 °C. The reaction mixture was further diluted with water (5 mL) and extracted with EtOAc (2 × 50 mL) and CH_2Cl_2 (2 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (hexane → EtOAc → MeOH) afforded N^1-benzyl-N^1,N^3,N^3-trimethylpropane-1,2-diamine **20a** (128 mg, 62%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.25 (m, 4H, 4 x ArH), 7.25–7.18 (m, 1H, ArH), 3.46 (s, 2H, $PhCH_2N$), 2.42–2.34 (m, 2H, $NCH_2CH_2CH_2N$), 2.30–2.24 (m, 2H, $NCH_2CH_2CH_2N$), 2.19 (s, 6H, 2 x Me), 2.17 (s, 3H, Me), 1.71–1.63 (m, 2H, $NCH_2CH_2CH_2N$). ^{13}C NMR (101 MHz, $CDCl_3$) 139.2, 129.0, 128.2, 126.9, 62.4, 57.9, 55.7, 45.6, 42.2, 25.8. ATR-IR ν_{max} (neat)/cm^{-1} 3061, 3026, 2968, 2941, 2855, 2812, 2779, 2760, 1584, 1495, 1452, 1364, 1314, 1254, 1213, 1179, 1161, 1123, 1098, 1042, 1026, 964, 908, 833, 733, 696, 669, 650, 619. *m/z* (ESI): 207.1 ($[M+H]^+$). HRMS (ESI) calcd. for $C_{13}H_{23}N_2^+$ $[(M+H)^+]$: 207.1856, found 207.1850.

*4.4.19. Preparation of N^1,N^1,N^3-trimethyl-N^3-(3-(trimethylsilyl) prop-2-yn-1-yl)propane-1,3-diamine (**20b**)*

*n*BuLi (1.6 M solution in hexanes, 5.0 eq., 5.0 mmol, 3.125 mL) was added dropwise to a solution of ethynyltrimethylsilane (5.1 eq., 5.1 mmol, 707 μL) in dry THF (5 mL) at −78 °C under argon and the

reaction was stirred at −78 °C for ~ 1 h, resulting in a yellow solution. This yellow solution was added to a slurry of ground 1,1,3-trimethylhexahydropyrimidin-1-ium 4-methylbenzenesulfonate **14b** (1.0 eq., 1.0 mmol, 300.42 mg) in dry THF (5 mL) at −78 °C under argon. An extra portion of dry THF (10 mL) was used as a wash to facilitate the transfer of most of the residual lithium trimethylsilylacetylide solution. The mixture was warmed to RT and was stirred for 1.75 h, resulting in a pale brown solution. The reaction mixture was quenched with water (10 mL) and the organic phase was separated. The aqueous phase was further washed with EtOAc (4 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated to afford N^1,N^1,N^3-trimethyl-N^3-(3-(trimethyl silyl)prop-2-yn-1-yl)propane-1,3-diamine **20b** (226 mg, 100%) as a brown oil in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.31 (s, 2H, CH_2), 2.45−2.40 (m, 2H, N*C*$H_2$$CH_2$$CH_2$N), 2.36−2.25 (m, 5H, Me + NCH_2CH_2*C*H_2N), 2.23 (s, 6H, 2 x Me), 1.70−1.56 (m, 2H, NCH_2*C*$H_2$$CH_2$N), 0.15 (s, 9H, 3 x Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 101.1, 90.0, 58.0, 54.0, 46.8, 45.6, 42.0, 25.9, 0.2. ATR-IR ν_{max} (neat)/cm^{-1} 2953, 2901, 2857, 2814, 2779, 2764, 2162, 1595, 1576, 1458, 1420, 1381, 1319, 1248, 1215, 1182, 1125, 1042, 1036, 1013, 978, 839, 816, 758, 683, 652, 617. *m/z* (ESI): 227.2 ([M+H]$^+$). HRMS (ESI) calcd. for $C_{12}H_{27}N_2Si^+$ [(M + H)$^+$]: 227.1938, found 227.1940.

4.4.20. Preparation of N^1,N^1,N^3-trimethyl-N^3-(3-phenyl prop-2-yn-1-yl)propane-1,3-diamine (**20c**)

Ethynylbenzene (5.6 eq., 5.46 mmol, 0.6 mL) in anhydrous THF (5 mL) was deprotonated by the addition of *n*BuLi (1.6 M in hexane, 3 eq., 5.12 mmol, 3.2 mL) to the solution of nucleophile in THF at −78 °C. The nucleophile solution was allowed to stir at room temperature for 30 min or until effervescence had stopped and the resultant solution was added to a dry flask containing 1,1,3-trimethylhexahydro pyrimidin-1-ium tosylate **14b** (1.0 eq., 0.97 mmol, 292 mg) under argon. The volume was made up to 10 mL with anhydrous THF and allowed to stir for 16 h at room temperature. The reaction was quenched with H_2O (5 mL) and extracted with 5 × 30 mL EtOAc. The combined organics were dried over Na_2SO_4 and then concentrated under vacuum. The product N^1,N^1,N^3-trimethyl-N^3-(3-phenylprop-2-yn-1-yl)propane-1,3-diamine **20c** was isolated as a yellow oil (143 mg, 0.63 mmol, 65%) *via* flash silica chromatography using an elution gradient of 0−100% MeOH in acetone. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.35 (m, 2H), 7.21−7.19 (m, 3H), 3.47 (s, 2H), 2.46−2.42 (m, 2H), 2.30 (s, 3H), 2.26−2.22 (m, 2H), 2.15 (s, 6H), 1.64−1.57 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.6, 128.1, 127.8, 123.2, 85.2, 84.4, 57.7, 54.0, 46.4, 45.4, 41.9, 25.8. ATR-IR ν_{max} (neat)/cm^{-1} 2970, 2940, 2891, 2857, 2812, 2762, 1597, 1489, 1458, 1441, 1418, 1375, 1360, 146, 1321, 1250, 1209, 1155, 1121, 1098, 1069, 1032, 1009, 968, 945, 871, 835, 818, 754, 731, 690.

4.4.21. Preparation N^1,N^1,N^3-trimethyl-N^3-(3-phenylprop-2-yn-1-yl)propane-1,3-diamine (**20d**)

Lithium diisopropylamide was prepared by treating diisopropylamine (5.6 eq., 5.34 mmol, 0.7 mL) in anhydrous THF (5 mL) with *n*BuLi (1.6 M in hexanes, 5.2 eq., 4.96 mmol, 3.1 mL) in hexane at −78 °C. The solution was allowed to stir at room temperature for 1 h and then added to isobutyronitrile (5.3 eq., 5.01 mmol, 0.45 mL) and allowed to stir for 30 min. The resultant solution was added to a dry flask containing 1,1,3-trimethylhexahydro pyrimidin-1-ium tosylate **14b** (1.0 eq., 0.95 mmol, 285 mg) under argon. The volume was made up to 10 mL with anhydrous THF and allowed to stir for 16 h at room temperature. The reaction was quenched with H_2O (5 mL) and extracted with 5 × 30 mL EtOAc. The combined organics were dried over Na_2SO_4 and then concentrated under vacuum. The N^1,N^1,N^3-trimethyl-N^3-(3-phenylprop-2-yn-1-yl)propane-1,3-diamine product **20d** was isolated as a yellow oil (67 mg, 0.36 mmol, 38%) *via* flash silica chromatography using an elution gradient of 0−100% MeOH in acetone. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49−2.46 (m, 2H), 2.39 (s, 2H), 2.34 (s, 3H), 2.27−2.24 (m, 2H), 2.17 (s, 6H), 1.62−1.54 (m, 2H), 1.26 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 125.5, 66.8, 57.8, 57.5, 45.5, 44.1, 33.8, 25.9, 24.9. ATR-IR ν_{max} (neat)/cm^{-1} 2972, 2943, 2857, 2812, 2764, 2232, 1458, 1387, 1364, 1317, 1254, 1211, 1206, 1154, 1117, 1098, 1042, 1011, 966, 868, 851, 827, 754, 700. HRMS (ESI) calcd. for $C_{11}H_{24}N_3^+$ [(M + H)$^+$]: 198.1965, found 198.1955.

4.4.22. Preparation of 2-(((3-(dimethylamino)propyl) (methyl) amino)methyl)phenol (**20e**)

Phenol (5.0 eq., 5 mmol, 470.55 mg) was added to a slurry of NaH (5.0 eq., 5.0 mmol, 120 mg) in dry THF (10 mL) portion wise at 0 °C under argon and the reaction was stirred at RT for ~ 0.5 h, resulting in a yellow solution. The sodium phenolate solution was added to a slurry of ground 1,1,3-trimethylhexahydropyrimidin-1-ium 4-methylbenzenesulfonate **14b** (1.0 eq., 1.0 mmol, 300.42 mg) in dry THF (5 mL) at 0 °C under argon. An extra portion of dry THF (10 mL) was used as a wash to facilitate the transfer of most of the residual sodium phenolate solution. Reaction was stirred at RT for 21.5 h, resulting in a white slurry that was quenched with water (10 mL) and extracted with EtOAc (4 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (hexane → EtOAc → MeOH) afforded 2-(((3-(dimethylamino) propyl)(methyl)amino)methyl)phenol **20e** (104 mg, 47%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (td, J = 8.0, 1.7 Hz, 1H, ArH), 6.99−6.92 (m, 1H, ArH), 6.81 (dd, J = 8.1, 1.0 Hz, 1H, ArH), 6.76 (td, J = 7.4, 1.1 Hz, 1H, ArH), 3.69 (s, 2H, $ArCH_2N$), 2.64−2.47 (m, 2H, N*C*$H_2$$CH_2$$CH_2$N), 2.36−2.25 (m, 5H, Me + NCH_2CH_2*C*H_2N), 2.21 (s, 6H, 2 x Me), 1.80−1.65 (m, 2H, NCH_2*C*$H_2$$CH_2$N). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 128.8, 128.5, 122.1, 119.1, 116.2, 61.7, 57.5, 55.3, 45.6, 41.3, 25.3. ATR-IR ν_{max} (neat)/cm^{-1} 3053, 2945, 2857, 2814, 2783, 1612, 1589, 1476, 1458, 1422, 1400, 1389, 1256, 1234, 1211, 1182, 1099, 1036, 1015, 964, 930, 868, 845, 816, 750, 719, 692, 625. *m/z* (ESI): 223.1 ([M+H]$^+$). HRMS (ESI) calcd. for $C_{13}H_{23}N_2O^+$ [(M + H)$^+$]: 223.1805, found 223.1807.

4.4.23. Preparation of 2-(((3-(dimethylamino)propyl) (methyl) amino)methyl)-4-methylphenol (**20f**)

p-Cresol (5.0 eq., 5 mmol, 541.7 mg) was added to a slurry of NaH (5.0 eq., 5.0 mmol, 120 mg) in dry THF (5 mL) portionwise at 0 °C under argon and the reaction was stirred at RT for ~ 0.5 h, resulting in a clear yellow solution. The sodium 4-methylphenolate solution was added to a slurry of ground 1,1,3-trimethylhexahydropyrimidin-1-ium 4-methylbenzene sulfonate **14b** (1.0 eq., 1.0 mmol, 300.42 mg) in dry THF (5 mL) at 0 °C under argon. An extra portion of dry THF (15 mL) was used as a wash to facilitate the transfer of most of the residual sodium 4-methylphenolate solution. Reaction was stirred at RT for 46 h, resulting in a white slurry on pale orange liquors that was quenched with water (10 mL) and extracted with EtOAc (4 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (hexane → EtOAc → MeOH) afforded 2-(((3-(dimethylamino) propyl) (methyl)amino)methyl)-4-methylphenol **20f** as a mixture with a trace amount of the isomeric 3-(((3-(dimethylamino)propyl)(methyl) amino)methyl)-4-methylphenol (148 mg, 63% combined yield of both isomers) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (dd, J = 8.1, 1.7 Hz, 1H, ArH), 6.76 (d, J = 1.2 Hz, 1H, ArH), 6.71 (d, J = 8.1 Hz, 1H, ArH), 3.64 (s, 2H, $ArCH_2N$), 2.57−2.44 (m, 2H, N*C*$H_2$$CH_2$$CH_2$N), 2.33−2.25 (m, 5H, Me + NCH_2CH_2*C*H_2N), 2.23 (s, 3H, ArMe), 2.21 (s, 6H, 2 x Me), 1.80−1.60 (m, 2H, NCH_2*C*$H_2$$CH_2$N). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7, 129.2, 129.1,

128.1, 121.8, 115.9, 61.7, 57.6, 55.4, 45.6, 41.3, 25.4, 20.6. ATR-IR ν_{max} (neat)/cm^{-1} 2943, 2918, 2857, 2814, 2781, 2764, 2633, 1616, 1599, 1570, 1497, 1449, 1391, 1356, 1312, 1256, 1234, 1182, 1134, 1119, 1049, 1043, 1015, 997, 970, 924, 880, 814, 770, 754, 741, 694, 650, 619, 611. *m/z* (ESI): 237.2 ([M+H]$^+$). HRMS (ESI) calcd. for $C_{14}H_{25}N_2O^+$ [(M + H)$^+$]: 237.1961, found 237.1959.

4.4.24. Preparation of 2-chloro-6-(((3-(dimethylamino) propyl)(methyl)amino)methyl)phenol (**20g**)

2-Chlorophenol (5.0 eq., 5 mmol, 518 μL) was added to a slurry of NaH (5.0 eq., 5.0 mmol, 120 mg) in dry THF (5 mL) dropwise at 0 °C under argon and the reaction was stirred at RT for ~ 1 h, resulting in a clear yellow solution. The sodium 2-chlorophenolate solution was added to a slurry of ground 1,1,3-trimethylhexahydropyrimidin-1-ium 4-methylbenzene sulfonate **14b** (1.0 eq., 1.0 mmol, 300.42 mg) in dry THF (5 mL) at 0 °C under argon. An extra portion of dry THF (15 mL) was used as a wash to facilitate the transfer of most of the residual sodium 2-chlorophenolate solution. Reaction was stirred at RT for 21 h, resulting in slurry that was quenched with water (10 mL) and extracted with EtOAc (4 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (hexane → EtOAc → MeOH) afforded 2-chloro-6-(((3-(dimethylamino)propyl)(methyl) amino)methyl) phenol **20g** (248 mg, 97%) as a pale brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.54 (br s, 1H, OH), 7.20 (d, *J* = 8.0 Hz, 1H, ArH), 6.82 (d, *J* = 7.4 Hz, 1H, ArH), 6.66 (t, *J* = 7.7 Hz, 1H, ArH), 3.68 (s, 2H, $ArCH_2N$), 2.58−2.46 (m, 2H, $NCH_2CH_2CH_2N$), 2.31−2.22 (m, 5H, Me + $NCH_2CH_2CH_2N$), 2.18 (s, 6H, 2 x Me), 1.78−1.65 (m, 2H, $NCH_2CH_2CH_2N$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.0, 129.0, 126.7, 123.1, 120.7, 119.2, 61.3, 57.3, 55.2, 45.5, 41.1, 25.1. ATR-IR ν_{max} (neat)/cm^{-1} 3063, 2945, 2857, 2814, 2783, 2764, 2722, 1603, 1580, 1456, 1422, 1400, 1296, 1263, 1254, 1229, 1204, 1169, 1136, 1098, 1072, 1042, 1015, 964, 893, 826, 766, 731, 694, 654, 627, 613, 602. *m/z* (ESI): 257.1 ([M+H]$^+$), 255.1 ([M − H]$^-$). HRMS (ESI) calcd. for $C_{13}H_{22}N_2OCl^+$ [(M + H)$^+$]: 257.1415, found 257.1415.

4.4.25. Preparation of 4-bromo-2-(((3-(dimethylamino) propyl)(methyl)amino)methyl)-6-methylphenol (**20h**)

4-Bromo-2-methylphenol (5.0 eq., 5.19 mmol, 971 mg) in anhydrous THF (5 mL) was deprotonated by addition to NaH (5.0 eq., 5.0 mmol, 120 mg) in anhydrous THF (5 mL). The nucleophile solution was allowed to stir at room temperature for 30 min or until effervescence had stopped and the resultant solution was added to a dry flask containing 1,1,3-trimethylhexahydropyrimidin-1-ium tosylate **14b** (1.0 eq., 1.03 mmol, 310 mg) under argon. The volume was made up to 10 mL with anhydrous THF and allowed to stir for 16 h at room temperature. The reaction was quenched with H_2O (5 mL) and extracted with 5 × 30 mL EtOAc. The combined organics were dried over Na_2SO_4 and then concentrated under vacuum. The 4-bromo-2-(((3-(dimethylamino)propyl)(methyl)amino) methyl)-6-methylphenol product **20h** was purified using an elution gradient of 0−100% MeOH in acetone as a brown oil (222 mg, 0.70 mmol, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, *J* = 2.0 Hz, 1H), 6.86 (d, *J* = 2.4 Hz, 1H), 3.56 (s, 2H), 2.47−2.43 (m, 2H), 2.24−2.20 (m, 5H), 2.15 (s, 6H), 2.13 (s, 3H), 1.66 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3, 132.1, 128.4, 127.1, 123.0, 110.0, 60.9, 57.2, 55.0, 45.4, 41.1, 25.1, 15.5. ATR-IR ν_{max} (neat)/cm^{-1} 3007, 2982, 2955, 2920, 2889, 2849, 2818, 2797, 1466, 1425.1395, 1379, 1360, 1285, 1254, 1229, 1171, 1132, 1036, 1024, 1015, 970, 924, 908, 864, 841, 723. HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{14}H_{24}N_2O^{79}Br^+$ 315.1067; found 315.1066.

4.4.26. Preparation of 4-bromo-2-(((3-(dimethylamino) propyl)(methyl)amino)methyl)phenol (**20i**)

4-Bromophenol (5.2 eq., 5.15 mmol 891 mg) in anhydrous THF (5 mL) was deprotonated by addition to NaH (5.0 eq., 4.92 mmol, 118 mg) in anhydrous THF (5 mL). The nucleophile solution was allowed to stir at room temperature for 30 min or until effervescence had stopped and the resultant solution was added to a dry flask containing 1,1,3-trimethylhexahydropyrimidin-1-ium tosylate **14b** (1.0 eq., 0.99 mmol, 296 mg) under argon. The volume was made up to 10 mL with anhydrous THF and allowed to stir for 16 h at room temperature. The reaction was quenched with H_2O (5 mL) and extracted with 5 × 30 mL EtOAc. The combined organics were dried over Na_2SO_4 and then concentrated under vacuum. The 4-bromo-2-(((3-(dimethylamino)propyl)(methyl)amino) methyl) phenol product **20i** was isolated as a yellow oil (212 mg, 0.70 mmol, 71%) *via* flash silica chromatography using an elution gradient of 0−100% MeOH in acetone. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.07 (d, *J* = 2.4 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 3.65 (s, 2H), 2.54−2.50 (m, 2H), 2.30−2.26 (m, 5H), 2.21 (s, 6H), 1.75−1.68 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4, 131.5, 131.1, 124.1, 118.0, 110.7, 61.2, 57.4, 55.3, 45.6, 41.3, 25.3. ATR-IR ν_{max} (neat)/cm^{-1} 2947, 2884, 2857, 2814, 2783, 2764, 1605, 1580, 1476, 1460, 1414, 1387, 1352, 1263, 1254, 1211, 1179, 1163, 1113, 1096, 1072, 1034, 1009, 968, 885, 874, 856, 814, 766, 716, 681, 652, 625. HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{13}H_{22}N_2O^{79}Br^+$ 300.0900; found 300.0910.

4.4.27. Preparation of 2-(((3-(dimethylamino)propyl) (methyl) amino)methyl)-4-iodophenol (**20j**)

4-Iodophenol (5.4 eq., 5.32 mmol, 1.17 g) in anhydrous THF (5 mL) was deprotonated by addition to NaH (4.8 eq., 4.79 mmol 115 mg) in anhydrous THF (5 mL). The nucleophile solution was allowed to stir at room temperature for 30 min or until effervescence had stopped and the resultant solution was added to a dry flask containing 1,1,3-trimethylhexahydropyrimidin-1-ium tosylate **14b** (1.0 eq., 0.99 mmol, 298 mg) under argon. The volume was made up to 10 mL with anhydrous THF and allowed to stir for 16 h at room temperature. The reaction was quenched with H_2O (5 mL) and extracted with 5 × 30 mL EtOAc. The combined organics were dried over Na_2SO_4 and then concentrated under vacuum. The 2-(((3-(dimethylamino) propyl)(methyl)amino)methyl)-4-iodophenol product **20j** was purified by column chromatography using an elution gradient of 0−100% MeOH in acetone as a brown oil (299 mg, 0.85 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.25 (d, *J* = 2.4 Hz, 1H), 6.59 (d, *J* = 8.4 Hz, 1H), 3.63 (s, 2H), 2.53−2.49 (m, 2H) 2.32−2.28 (m, 2H), 2.28 (s, 3H), 2.23 (s, 6H), 1.76−1.68 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.5, 136.9, 136.3, 124.1, 118.0, 79.7, 60.3, 56.8, 54.6, 44.9, 40.7, 24.5. HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{13}H_{22}IN_2O^+$ 349.0771; found 349.0774. ATR-IR ν_{neat} (neat)/cm^{-1} 2951, 2814, 2785, 2770, 1574, 1474, 1412, 1387, 1263, 1169, 1117, 1065, 1032, 1009, 962, 883, 874, 814, 681, 611.

4.4.28. Preparation of 2-(((3-(dimethylamino)propyl) (methyl) amino)methyl)-4-methoxyphenol (**20k**)

4-Methoxyphenol (5.1 eq., 5.40 mmol, 670 mg) in anhydrous THF (5 mL) was deprotonated by addition to NaH (5.0 eq., 5.0 mmol, 120 mg) in anhydrous THF (5 mL). The nucleophile solution was allowed to stir at room temperature for 30 min or until effervescence had stopped and the resultant solution was added to a dry flask containing 1,1,3-trimethylhexahydropyrimidin-1-ium tosylate **14b** (1.0 eq., 1.06 mmol, 319 mg) under argon. The volume was made up to 10 mL with anhydrous THF and allowed to stir for 16 h at room temperature. The reaction was quenched with H_2O (5 mL) and extracted with 5 × 30 mL EtOAc. The combined organics were dried over Na_2SO_4 and then concentrated under vacuum. The 2-

(((3-(dimethylamino)propyl) (methyl)amino)methyl)-4-methoxyphenol product **20k** was purified by column chromatography using an elution gradient of 0–100% MeOH in acetone as a brown oil (140 mg, 0.55 mmol, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74–6.73 (m, 2H), 6.54 (dd, J = 2.4, 0.4 Hz, 1H) 3.74 (s, 3H), 3.65 (s, 2H), 2.54–2.50 (m, 2H), 2.35–2.32 (m, 2H), 2.28 (s, 3H), 2.25 (s, 6H), 1.79–1.71 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.6, 151.9, 122.8, 116.5, 114.5, 113.6, 61.8, 57.5, 55.9, 55.3, 45.5, 41.4, 25.2. ATR-IR ν_{max} (neat)/cm^{-1} 2943, 2907, 2899, 2855, 2814, 2783, 2764, 1492, 1460, 1418, 1389, 1356, 1306, 1250, 1213, 1182, 1148, 1132, 1120, 1098, 1078, 1040, 974, 930, 866, 812, 771, 742. . HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{14}H_{25}N_2O_2^+$ 253.1911; found 253.1911.

4.4.29. Preparation of 3-(((3-(dimethylamino)propyl) (methyl) amino)methyl)-4-hydroxybenzonitrile (**20l**)

4-Cyanophenol (5.0 eq., 5 mmol, 596 mg) was added to a slurry of NaH (5.0 eq., 5.0 mmol, 120 mg) in dry THF (5 mL) portion wise at 0 °C under argon and the reaction was stirred at RT for ~ 1 h, resulting in a fine white slurry. The sodium 4-cyanophenolate slurry was added to a slurry of ground 1,1,3-trimethylhexahydropyrimidin-1-ium 4-methylbenzene sulfonate **14b** (1.0 eq., 1.0 mmol, 300.42 mg) in dry THF (5 mL) at 0 °C under argon. An extra portion of dry THF (15 mL) was used as a wash to facilitate the transfer of most of the residual sodium 4-cyanophenolate solution. Reaction was stirred at RT for 21 h, resulting in slurry that was quenched with water (10 mL) and extracted with EtOAc (4 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (hexane → EtOAc → MeOH) afforded 3-(((3-(dimethylamino)propyl)(methyl)amino)methyl)-4-hydroxybenzonitrile **20l** (41 mg, 17%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (br s, 1H, OH), 7.44 (d, J = 8.4 Hz, 1H, ArH), 7.24 (s, 1H, ArH), 6.82 (d, J = 8.5 Hz, 1H, ArH), 3.71 (s, 2H, $ArCH_2N$), 2.55–2.52 (m, 2H, $NCH_2CH_2CH_2N$), 2.33–2.23 (m, 5H, Me + $NCH_2CH_2CH_2N$), 2.19 (s, 6H, 2 x Me), 1.80–1.63 (m, 2H, $NCH_2CH_2CH_2N$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 133.4, 132.5, 122.8, 119.7, 117.2, 101.9, 60.8, 57.2, 55.1, 45.5, 41.2, 25.0. ATR-IR ν_{max} (neat)/cm^{-1} 2945, 2857, 2816, 2783, 2766, 2727, 2220, 1597, 1495, 1458, 1418, 1283, 1283, 1165, 1115, 1040, 974, 964, 897, 826, 768, 739, 708, 658, 615. *m/z* (ESI): 248.2 ([M+H]$^+$), 246.2 ([M − H]$^-$). HRMS (ESI) calcd. for $C_{14}H_{22}N_3O^+$ [(M + H)$^+$]: 248.1757, found 248.1756.

4.4.30. Preparation of 4-(((3-(dimethylamino)propyl) (methyl) amino)methyl)-2,6-dimethoxyphenol (**20m**)

2,6-Dimethooxyphenol (5.0 eq., 5 mmol, 770.8 mg) was added to a slurry of NaH (5.0 eq., 5.0 mmol, 120 mg) in dry THF (5 mL) portionwise at 0 °C under argon and the reaction was stirred at RT for ~ 0.5 h, resulting in a white slurry on dark liquors. The sodium 2,6-dimethoxyphenolate slurry was added to a slurry of ground 1,1,3-trimethylhexahydropyrimidin-1-ium 4-methylbenzenesulfonate **14b** (1.0 eq., 1.0 mmol, 300.42 mg) in dry THF (5 mL) at 0 °C under argon. An extra portion of dry THF (15 mL) was used as a wash to facilitate the transfer of most of the residual sodium 2,6-dimethoxyphenolate slurry. Reaction was stirred at RT for 46 h, resulting in a white slurry on dark green liquors that was quenched with water (10 mL) and extracted with EtOAc (4 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (hexane → EtOAc → MeOH) afforded 4-(((3-(dimethylamino)propyl)(methyl) amino)methyl)-2,6-dimethoxyphenol **20m** (28 mg, 10%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (s, 2H, 2 x ArH), 3.85 (s, 6H, 2 x OMe), 3.38 (s, 2H, $ArCH_2N$), 2.42–2.31 (m, 2H, $NCH_2CH_2CH_2N$), 2.33–2.24 (m, 2H, $NCH_2CH_2CH_2N$), 2.21 (s, 6H, 2 x Me), 2.19 (s, 3H, Me), 1.73–1.62 (m, 2H, $NCH_2CH_2CH_2N$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.0, 133.7, 130.5, 105.6, 62.9, 58.1 56.4, 55.5, 45.7, 42.5, 25.8. ATR-IR ν_{max} (neat)/cm^{-1} 2938, 2857, 2833, 2816, 2776, 1668, 1595, 1512, 1499, 1456, 1423, 1360, 1325, 1211, 1115, 1040, 988, 968, 914, 818, 806, 748, 735, 689, 642, 635, 615. *m/z* (ESI): 283.1 ([M+H]$^+$), 281.1 ([M − H]$^-$). HRMS (ESI) calcd. for $C_{15}H_{27}N_2O_3^+$ [(M + H)$^+$]: 283.2016, found 283.2015.

4.4.31. Preparation of 1-(((3-(dimethylamino)propyl) (methyl) amino)methyl)naphthalen-2-ol (**20n**)

2-Naphthol (2.0 eq., 2 mmol, 288.34 mg) was added to a slurry of NaH (2.0 eq., 2.0 mmol, 48 mg) in dry THF (10 mL) portion wise at 0 °C under argon and the reaction was stirred at RT for ~ 0.5 h, resulting in a black solution. The sodium 2-naphtholate solution was added to a slurry of ground 1,1,3-trimethylhexahydropyrimidin-1-ium 4-methylbenzene sulfonate **14b** (1.0 eq., 1.0 mmol, 300.42 mg) in dry THF (5 mL) at 0 °C under argon. An extra portion of dry THF (10 mL) was used as a wash to facilitate the transfer of most of the residual sodium 2-naphtholate solution. Reaction was stirred at RT for 21 h, resulting in a white slurry on dark liquors that was quenched with water (10 mL) and extracted with EtOAc (4 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (hexane → EtOAc → MeOH) afforded 1-(((3-(dimethylamino)propyl)(methyl) amino)methyl)naphthalen-2-ol **20n** (189 mg, 70%) as a dark red/brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.71 (s, 1H, OH), 7.80 (d, J = 8.5 Hz, 1H, ArH), 7.75 (d, J = 8.0 Hz, 1H, ArH), 7.68 (d, J = 8.8 Hz, 1H, ArH), 7.43 (td, J = 8.4, 1.3 Hz, 1H, ArH), 7.33–7.24 (m, 1H, ArH), 7.10 (d, J = 8.8 Hz, 1H, ArH), 4.14 (s, 2H, $ArCH_2N$), 2.69–2.57 (m, 2H, $NCH_2CH_2CH_2N$), 2.40–2.30 (m, 5H, Me + $NCH_2CH_2CH_2N$), 2.24 (s, 6H, 2 x Me), 1.88–1.74 (m, 2H, $NCH_2CH_2CH_2N$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.8, 132.7, 129.2, 129.0, 128.5, 126.4, 122.4, 121.0, 119.3, 111.5, 57.3, 56.6, 55.4, 45.4, 41.6, 25.2. ATR-IR ν_{max} (neat)/cm^{-1} 3061, 2941, 2855, 2814, 2764, 1622, 1597, 1585, 1520, 1464, 1420, 1410, 1368, 1331, 1267, 1236, 1211, 1180, 1165, 1134, 1098, 1063, 1042, 1013, 989, 964, 916, 856, 812, 745, 710, 692, 683, 665, 635, 615. *m/z* (ESI): 273.1 ([M+H]$^+$), 271.1 ([M − H]$^-$).

4.4.32. Preparation of N^1-((ethylthio)methyl)-N^1,N^3,N^3-trimethylpropane-1,3-diamine (**20o**)

Ethanethiol (5.0 eq., 5 mmol, 370 μL) was added to a slurry of NaH (5.0 eq., 5.0 mmol, 120 mg) in dry THF (5 mL) dropwise at 0 °C under argon and the reaction was stirred at RT for ~ 1 h, resulting in a white slurry. The sodium thiolate slurry was added to a slurry of ground 1,1,3-trimethylhexahydropyrimidin-1-ium 4-methylbenzenesulfonate **14b** (1.0 eq., 1.0 mmol, 300.42 mg) in dry THF (5 mL) at 0 °C under argon. An extra portion of dry THF (10 mL) was used as a wash to facilitate the transfer of most of the residual sodium thiolate slurry. The resulting white slurry was stirred at RT for 24.5 h. The reaction mixture was quenched with water (10 mL) and the organic phase was separated. The aqueous phase was further washed with EtOAc (4 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated to afford N^1-((ethylthio)methyl)-N^1,N^3,N^3-trimethylpropane−1,3-diamine **20o** (191 mg, 100%) as a yellow oil in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.03 (s, 2H, $EtSCH_2N$), 2.60 (q, J = 7.4 Hz, 2H, CH_3CH_2S), 2.54–2.43 (m, 2H, $NCH_2CH_2CH_2N$), 2.32 (s, 3H, Me), 2.30–2.23 (m, 2H, $NCH_2CH_2CH_2N$), 2.22 (s, 6H, 2 x Me), 1.67–1.56 (m, 2H, $NCH_2CH_2CH_2N$), 1.26 (t, J = 7.4 Hz, 3H, CH_3CH_2S). ^{13}C NMR (101 MHz, $CDCl_3$) δ 62.7, 57.9, 52.9, 45.7, 40.9, 27.5, 26.0, 15.7. ATR-IR ν_{max} (neat)/cm^{-1} 3478, 2940, 2928, 2855, 2812, 2783, 2762, 1572, 1456, 1449, 1375, 1308, 1194, 1123, 1096, 1036, 1013, 970, 935, 893, 814, 754, 640, 619, 606. *m/z* (ESI): 213.1 ([M+Na]$^+$).

*4.4.33. Preparation of N^1-((1H-pyrrol-1-yl)methyl)-N^1,N^3,N^3-trimethylpropane-1,3-diamine and N^1-((1H-pyrrol-2-yl)methyl)-N^1,N^3,N^3-trimethylpropane-1,3-diamine (**20p** and **20q**)*

*n*BuLi (1.6 M solution in hexanes, 5.0 eq., 5.0 mmol, 3.125 mL) was added dropwise to a solution of 1*H*-pyrrole (5.1 eq., 5.1 mmol, 354 μL) in dry THF (10 mL) at −78 °C under argon and the reaction was stirred at −78 °C for ~ 1 h, resulting in a white slurry. This white slurry was added to a slurry of ground 1,1,3-trimethylhexahydropyrimidin-1-ium 4-methyl benzenesulfonate **14b** (1.0 eq., 1.0 mmol, 300.42 mg) in dry THF (5 mL) at −78 °C under argon. An extra portion of dry THF (10 mL) was used as a wash to facilitate the transfer of most of the residual lithium pyrrolidide slurry. The mixture was warmed to RT and was stirred for 5 h, resulting in a brown solution. The reaction mixture was quenched with water (10 mL) and the organic phase was separated. The aqueous phase was further washed with EtOAc (4 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (hexane → EtOAc → MeOH) afforded pure N^1-((1*H*-pyrrol-1-yl) methyl)-N^1,N^3,N^3-trimethylpropane-1,3-diamine **20p** (3 mg, 2%) and pure N^1-((1*H*-pyrrol-2-yl)methyl)-N^1,N^3,N^3-trimethylpropane-1,3-diamine **20q** (82 mg, 42%) as brown oils as well as a mixture of both compounds (32 mg, 2.1:1 mol ratio by ^{1}H NMR, N^1-((1*H*-pyrrol-1-yl) methyl)-N^1,N^3,N^3-trimethylpropane-1,3-diamine **20p** − 22 mg, 13%; N^1-((1*H*-pyrrol-2-yl)methyl)-N^1,N^3,N^3-trimethylpropane-1,3-diamine **20q** − 10 mg, 5%)

N^1-((1*H*-pyrrol-1-yl)methyl)-N^1,N^3,N^3-trimethylpropane-1,3-diamine **20p** (3 mg, 2%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (t, J = 2.1 Hz, 2H, 2 x ArH), 6.15 (t, J = 2.1 Hz, 2H, 2 x ArH), 4.64 (s, 2H, NCH_2N), 2.47−2.43 (m, 2H, $NCH_2CH_2CH_2N$), 2.40−2.33 (m, 2H, $NCH_2CH_2CH_2N$), 2.27−2.28 (2 x s, 9H, 3 x Me), 1.72−1.64 (m, 2H, $NCH_2CH_2CH_2N$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 121.6, 108.1, 70.6, 57.6, 52.1, 45.4, 39.8, 25.5. ATR-IR ν_{max} (neat)/cm^{-1} 3096, 2938, 2855, 2814, 2770, 1582, 1491, 1450, 1375, 1246, 1219, 1182, 1123, 1082, 1069, 1057, 1034, 1011, 966, 818, 725, 683, 635, 610. *m/z* (ESI): 196.1 ($[M+H]^+$). HRMS (ESI) calcd. for $C_{11}H_{22}N_3^+$ $[(M + H)^+]$: 196.1808, found 196.1809.

N^1-((1*H*-pyrrol-2-yl)methyl)-N^1,N^3,N^3-trimethylpropane-1,3-diamine **20q** (82 mg, 42%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H, NH), 6.71 (td, J = 2.6, 1.6 Hz, 1H, ArH), 6.12 (dd, J = 5.8, 2.7 Hz, 1H, ArH), 6.00−5.96 (m, 1H, ArH), 3.54 (s, 2H, $ArCH_2N$), 2.42−2.38 (m, 2H, $NCH_2CH_2CH_2N$), 2.30−2.34 (m, 2H, $NCH_2CH_2CH_2N$), 2.22−2.24 (2 x s, 9H, 3 x Me), 1.70−1.63 (m, 2H, $NCH_2CH_2CH_2N$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 129.3, 117.3, 107.7, 106.8, 57.5, 55.0, 54.8, 45.4, 42.2, 25.1. ATR-IR ν_{max} (neat)/cm^{-1} 3379, 3188, 3098, 2943, 2857, 2814, 2778, 1458, 1375, 1356, 1306, 1250, 1209, 1179, 1165, 1119, 1098, 1080, 1061, 1024, 1003, 968, 883, 862, 826, 793, 752, 710, 662, 610. *m/z* (ESI): 196.1 ($[M+H]^+$). HRMS (ESI) calcd. for $C_{11}H_{22}N_3^+$ $[(M + H)^+]$: 196.1808, found 196.1806.

*4.4.34. Preparation of N^1-((1H-indol-1-yl)methyl)-N^1,N^3,N^3-trimethylpropane-1,3-diamine and N^1-((1H-indol-3-yl)methyl)-N^1,N^3,N^3-trimethylpropane-1,3-diamine (**20r** and **20s**)*

*n*BuLi (5.0 eq., 5.0 mmol, 3.125 mL) as a 1.6 M solution in hexanes was added dropwise to a solution of 1*H*-indole (5.1 eq., 5.1 mmol, 597 mg) in dry THF (10 mL) at −78 °C under argon and the reaction was stirred at −78 °C for ~ 1 h, resulting in a white slurry. This white slurry was added to a slurry of ground 1,1,3-trimethylhexahydropyrimidin-1-ium 4-methyl benzenesulfonate **14b** (1.0 eq., 1.0 mmol, 300.42 mg) in dry THF (5 mL) at −78 °C under argon. An extra portion of dry THF (10 mL) was used as a wash to facilitate the transfer of most of the residual lithium indol-1-ide slurry. The mixture was warmed to RT and was stirred for 23 h, resulting in a red solution. The reaction mixture was quenched with water (10 mL) and the organic phase was separated. The aqueous phase was further washed with EtOAc (4 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (hexane → EtOAc → MeOH) afforded N^1-((1*H*-indol-1-yl) methyl)-N^1,N^3,N^3-trimethylpropane-1,3-diamine 20r (153 mg, 62%) as a brown oil and N^1-((1*H*-indol-3-yl)methyl)-N^1,N^3,N^3-trimethyl propane-1,3-diamine 20s (47 mg, 19%) as a yellow oil.

N^1-((1*H*-indol-1-yl)methyl)-N^1,N^3,N^3-trimethylpropane-1,3-diamine **20r** (153 mg, 62%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66−7.58 (m, 1H, ArH), 7.46 (dd, J = 8.3, 0.8 Hz, 1H, ArH), 7.20 (ddd, J = 8.3, 7.1, 1.2 Hz, 1H, ArH), 7.15 (d, J = 3.2 Hz, 1H, ArH), 7.10 (ddd, J = 8.0, 7.1, 1.0 Hz, 1H, ArH), 6.50 (dd, J = 3.2, 0.8 Hz, 1H, ArH), 4.82 (s, 2H, NCH_2N), 2.60−2.44 (m, 2H, $NCH_2CH_2CH_2N$), 2.34−2.25 (m, 5H, Me + $NCH_2CH_2CH_2N$), 2.22 (s, 6H, 2 x Me), 1.68 (dt, J = 16.4, 7.3 Hz, 2H, $NCH_2CH_2CH_2N$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.9, 128.7, 128.5, 121.6, 120.8, 119.6, 110.1, 101.5, 67.9, 57.6, 52.6, 45.5, 39.8, 25.7. ATR-IR ν_{max} (neat)/cm^{-1} 3051, 2940, 2855, 2812, 2764, 1611, 1512, 1458, 1425, 1396, 1381, 1356, 1310, 1287, 1263, 1254, 1233, 1200, 1155, 1121, 1096, 1038, 1011, 964, 924, 881, 837, 822, 762, 737, 681, 662, 621. *m/z* (ESI): 246.1 ($[M+H]^+$). HRMS (ESI) calcd. for $C_{15}H_{24}N_3^+$ $[(M + H)^+]$: 246.1965, found 246.1965.

N^1-((1*H*-indol-3-yl)methyl)-N^1,N^3,N^3-trimethylpropane-1,3-diamine **20s** (47 mg, 19%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H, NH), 7.72 (d, J = 7.9 Hz, 1H, ArH), 7.35 (d, J = 8.1 Hz, 1H, ArH), 7.22−7.16 (m, 1H, ArH), 7.14−7.07 (m, 2H, 2 x ArH), 3.70 (s, 2H, NCH_2N), 2.50−2.42 (m, 2H, $NCH_2CH_2CH_2N$), 2.34−2.30 (m, 2H, $NCH_2CH_2CH_2N$), 2.24 (s, 3H, Me), 2.22 (s, 6H, 2 x Me), 1.78−1.70 (m, 2H, $NCH_2CH_2CH_2N$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.4, 128.1, 123.6, 122.1, 119.7, 119.6, 113.6, 111.1, 58.2, 55.7, 53.0, 45.7, 42.4, 26.0. ATR-IR ν_{max} (neat)/cm^{-1} 3412, 3140, 3100, 3057, 2940, 2859, 2812, 2778, 1618, 1551, 1454, 1420, 1369, 1352, 1339, 1306, 1236, 1207, 1179, 1109, 1096, 1070, 1061, 1038, 1022, 1009, 964, 926, 907, 810, 773, 737, 625, 611. *m/z* (ESI): 246.1 ($[M+H]^+$). HRMS (ESI) calcd. for $C_{15}H_{24}N_3^+$ $[(M + H)^+]$: 246.1965, found 246.1964.

*4.4.35. Preparation of N^1-benzyl-N^3,N^3-dimethyl-N^1-propyl propane-1,3-diamine (**21a**)*

$TsOH.H_2O$ (1.0 eq., 1.00 mmol, 189.6 mg) and paraformaldehyde (3.33 eq., 3.33 mmol, 99.9 mg) were added to a 50 mL round bottom flask fitted with a condenser and the atmosphere was replaced with argon. Previously prepared N^1,N^1-dimethyl-N^3-propylpropane-1,3-diamine (190 μL, approx. 1 mmol) was added followed by 5 mL anhydrous EtOH. The reaction mixture was allowed to stir at reflux for 4 h and then the EtOH was removed under vacuum. The solid resin was then placed under high vacuum for 7 h in order to ensure removal of residual water and ethanol from the crude mixture. 1 M PhMgBr in THF (5.0 eq., 5 mmol, 5 mL) was added, followed by anhydrous THF such that the total solvent volume was 10 mL. The reaction mixture was allowed to stir for 0.5−2 h and then quenched with H_2O (40 mL). The reaction mixture was then extracted with EtOAc (5 × 30 mL). The combined organics were dried over Na_2SO_4 and concentrated under vacuum. The product N^1-benzyl-N^3,N^3-dimethyl-N^1-propylpropane-1,3-diamine **21a** ((81.8 mg, 0.35 mmol, 35%) was isolated as a brown oil *via* flash silica chromatography (elution gradient 0−100% MeOH in EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.27 (m, 4H, 4 x ArH), 7.24−7.20 (m, 1H, ArH), 3.55 (s, 2H, $ArCH_2N$), 2.45−2.42 (m, 2H, NCH_2), 2.39−2.36 (m, 2H, NCH_2), 2.27−2.23 (m, 2H, NCH_2), 2.20 (s, 6H, 2 x Me), 1.67−1.60 (m, 2H, CH_2), 1.52−1.43 (m, 2H, CH_2), 0.86 (t, J = 7.4 Hz, 3H, CH_2CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.7, 128.3, 127.6, 126.1, 58.2, 57.5, 55.4, 51.4, 45.0, 24.9, 19.7, 11.4. ATR-IR ν_{max} (neat)/cm^{-1} 2938, 2899, 2870, 2857, 2810, 2785, 2762, 2729, 1493, 1452, 1365, 1339, 1313, 1300, 1261, 1198, 1163, 1153, 1125, 1072, 1063, 1042, 1028, 964, 907, 866. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{15}H_{27}N_2^+$ 235.2169; found 235.2167.

*4.4.36. Preparation of 2-(((3-(dimethylamino)propyl) (propyl) amino)methyl)phenol (**21b**)*

NaH (1.0 eq., 0.99 mmol, 23.8 mg) was added to a dry round bottom flask under a nitrogen atmosphere. To a separate flask, PhOH (1.18 eq., 1.18 mmol, 111 mg) was added followed by 5 mL anhydrous tetrahydrofuran. Once the PhOH had fully dissolved, the solution was added dropwise to the NaH and allowed to stir at room temperature until evolution of H_2 was no longer observed and the resultant solution was added dropwise to a flask containing 1,1-dimethyl-3-propylhexahydropyrimidinium tosylate **14c** (1.0 eq., 1.00 mmol, 329 mg). The reaction was allowed to stir at room temperature for 16 h after which the reaction mixture had turned from a pinkish slurry to an off-white slurry. The crude product was purified *via* flash silica chromatography, elution gradient 0–100% MeOH in EtOAc. Pure fractions were combined, and solvent was removed under vacuum to afford 2-(((3-(dimethylamino)propyl)(-propyl)amino) methyl)phenol (99 mg, 40%) **21b** as a slightly brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (td, J = 8.0, 0.8 Hz, 1H, ArH), 6.94 (dd, J = 7.2, 1.2 Hz, 1H, ArH) 6.79 (dd, J = 8.0 Hz, 0.8 Hz, 1H, ArH) 6.75 (td, J = 7.2 Hz, 1.2 Hz, 1H, ArH), 3.74 (s, 2H, $ArCH_2N$), 2.59–2.53 (m, 2H, NCH_2), 2.52–2.58 (m, 2H, NCH_2), 2.31–2.27 (m, 2H, NCH_2), 2.20 (s, 6H, 2 x Me), 1.75–1.78 (m, 2H, CH_2), 1.61–1.52 (m, 2H, CH_2), 0.88 (t, J = 7.4 Hz, 3H, CH_2CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 128.6, 128.5, 122.3, 119.0, 116.1, 58.3, 57.5, 55.6, 51.6, 45.4, 23.9, 19.6, 11.9. ATR-IR ν_{max} (neat)/cm^{-1} 2957, 2936, 2872, 2857, 2814, 2783, 2764, 2723, 1612, 1589, 1475, 1458, 1406, 1375, 1342, 1304, 1256, 1184, 1151, 1121, 1098, 1080, 1061, 1036, 1022, 964, 930, 910, 866. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{15}H_{27}N_2O^+$ 251.2118; found 251.2116.

*4.4.37. Preparation of 2-(((3-(dimethylamino)propyl) (propyl) amino)methyl)-2-ethylmalonate (**21c**)*

1,1-Dimethyl-3-propylhexahydropyrimidinium tosylate 14c (1.0 eq., 0.96 mmol 315 mg) was added to a dry round bottom flask followed by anhydrous THF (2 mL) under argon. NaH (5.2 eq., 5 mmol 120 mg) was then added to a dry round bottom flask followed by anhydrous THF (3 mL) under argon. Diethyl ethylmalonate (5.5 eq., 5.31 mmol 1.0 mL) was added dropwise to the NaH slurry and allowed to stir at room temperature for 30 min. The resultant solution was added to the flask containing 1,1-dimethyl-3-propylhexahydropyrimidinium tosylate **14c** and allowed to stir at room temperature for 16 h. The reaction mixture was then concentrated under vacuum. The expected diethyl 2-(((3-(dimethylamino)propyl)(propyl)amino)methyl)-2-ethylmalonate **21c** (55 mg, 0.16 mmol, 17%) was isolated *via* flash silica chromatography (elution gradient 0–100% MeOH in acetone). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20–4.06 (m, 4H, 2 x OCH_2), 3.00 (s, 2H, $NCH_2CEt(CO_2Et)_2$), 2.46–2.38 (m, 2H, NCH_2), 2.37–2.31 (m, 2H, NCH_2), 2.17 (s, 6H, 2 x Me), 2.20–2.14 (m, 2H, NCH_2), 2.01 (q, J = 7.5 Hz, 2H, CH_2), 1.58–1.48 (m, 2H, CH_2), 1.42–1.31 (m, 2H, CH_2), 1.21 (t, J = 7.1 Hz, 6H, 2 x CH_2CH_3), 0.79 (m, 6H, 2 x CH_2CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.65, 60.9, 59.5, 57.9, 56.6, 56.3, 52.8, 45.6, 24.9, 24.4, 19.5, 14.2, 11.8, 8.8. ATR-IR ν_{max} (neat)/cm^{-1} 3399, 3375, 3356, 2965, 2936, 2905, 2874, 1722, 1630, 1464, 1449, 1420, 1387, 1366, 1341, 1300, 1236, 1209, 1179, 1159, 1111, 1096, 1074, 1030, 989, 924, 893, 860. HRMS (ESI) m/z. $[M+H]^+$ calcd for $C_{18}H_{37}N_2O_4$ 345.2748; found 345.2738.

*4.4.38. Preparation of 2-chloro-6-(((3-(dimethylamino) propyl)(propyl)amino)methyl)phenol (**21d**)*

Prepared according to General Procedure B using 1,1-dimethyl-3-propylhexahydropyrimidin-1-ium tosylate **14c** (1.0 eq., 0.97 mmol, 318 mg), NaH (5.2 eq.,5.04 mmol, 121 mg) and 2-chlorophenol (5.2 eq., 5.09 mmol, 0.52 mL). The 2-chloro-6-(((3-(dimethylamino)propyl)(propyl) amino)methyl)phenol product **21d** was isolated as a colourless oil (73 mg, 0.26 mmol, 25%) *via* flash silica chromatography with an elution gradient of 0–100% MeOH in acetone. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, J = 8.0, 1.5 Hz, 1H, ArH), 6.86–6.79 (m, 1H, ArH), 6.67 (d, J = 8.0 Hz, 1H, ArH), 3.75 (s, 2H, $ArCH_2N$), 2.60–2.43 (m, 4H, 2 x NCH_2), 2.23 (t, J = 7.1 Hz, 2H, NCH_2), 2.17 (s, 6H, 2 x Me), 1.75–1.63 (m, 2H, CH_2), 1.63–1.48 (m, 2H, CH_2), 0.88 (t, J = 7.4 Hz, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.2, 129.0, 126.7, 123.5, 120.8, 119.2, 58.1, 57.4, 55.5, 51.5, 45.5, 24.4, 19.5, 11.8. ATR-IR ν_{max} (neat)/cm^{-1} 2959, 2938, 2872, 2859, 2814, 2764, 2729, 2683, 1603, 1582, 1456, 1409, 1372, 1292, 1265, 1252, 1223, 1194, 1169, 1136, 1123, 1096, 1072, 1042, 1024, 964, 907, 893. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{15}H_{26}N_2O^{35}Cl$ 285.1728; found 285.1727.

*4.4.39. Preparation of 2-(((3-(dimethylamino)propyl) (propyl) amino)methyl)-4-iodophenol (**21e**)*

Prepared according to General Procedure B using 1,1-dimethyl-3-propylhexahydropyrimidin-1-ium tosylate **14c** (1.0 eq., 1.03 mmol, 339 mg), NaH (4.8 eq.,4.96 mmol, 119 mg) and 4-iodophenol (4.8 eq., 4.90 mmol, 1.08 g). The 2-(((3-(dimethylamino)propyl)(propyl)amino) methyl)-4-iodophenol product **21e** was isolated as a brown oil (243 mg, 0.65 mmol, 63%) *via* flash silica chromatography using an elution gradient of 0–100% MeOH in acetone. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, J = 8.4 Hz, 2.0 Hz, 1H, ArH) 7.23 (d, J = 2.4 Hz, 1H, ArH), 6.57 (d, J = 8.4 Hz, 1H, ArH), 3.69 (s, 2H, $ArCH_2N$), 2.56–2.52 (m, 2H, NCH_2), 2.48–2.44 (m, 2H, NCH_2), 2.24 (t, J = 6.8 Hz, 2H, NCH_2), 2.19 (s, 6H, 2 x Me), 1.72–1.65 (m, 2H, CH_2), 1.59–1.49 (m, 2H, CH_2), 0.88 (t, J = 7.6 Hz, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0, 137.1, 136.7, 124.8, 118.4, 80.2, 57.4, 57.3, 55.3, 51.3, 45.3, 24.3, 19.3, 11.7. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{15}H_{26}IN_2O^+$ 377.1084; found 377.1082. ATR-IR ν_{max} (neat)/cm^{-1} 2987, 2959, 2938, 2897, 2872, 2859, 2814, 2783, 2764, 1599, 1576, 1474, 1458, 1387, 1356, 1263, 1177, 1094, 1080, 1065, 1040, 964, 833, 814, 766.746.

*4.4.40. Preparation of N^1,N^1,N^3-trimethyl-N^3-((1-methyl-1H-indol-3-yl)methyl)propane-1,3-diamine (**20w**)*

N^1,N^1,N^3-trimethyl-N^3-((1-methyl-1*H*-indol-3-yl)methyl)propane-1,3-diamine **20w** was prepared according to General Procedure C on 0.1 mmol scale from 1,1,3-trimethylhexahydropyrimidin-1-ium 4-methyl benzenesulfonate **14b** (1 eq., 0.1 mmol, 30 mg), 1-methyl-1*H*-indole (2 eq., 0.2 mmol, 25 μL) and AcOH (0.3 mL). The crude mixture was purified by column chromatography (hexane → EtOAc → 2% Et_3N/98% MeOH). N^1,N^1,N^3-trimethyl-N^3-((1-methyl-1*H*-indol-3-yl)methyl)propane-1,3-diamine **20w** (25 mg, 96%) was isolated as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 7.9 Hz, 1H, ArH), 7.31 (d, J = 8.2 Hz, 1H, ArH), 7.29–7.25 (m, 1H, ArH), 7.18–7.14 (m, 1H, ArH), 7.03 (s, 1H, ArH), 3.80 (s, 3H, NMe), 3.74 (s, 2H, NCH_2N), 2.56–2.47 (m, 2H, $NCH_2CH_2CH_2N$), 2.41–2.33 (m, 2H, $NCH_2CH_2CH_2N$), 2.28 (2 x s, 9H, 3 x Me), 1.86–1.73 (m, 2H, $NCH_2CH_2CH_2N$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.1, 128.6, 128.4, 121.6, 119.7, 119.0, 111.8, 109.2, 58.1, 55.6, 52.8, 45.6, 42.3, 32.8, 25.9. ATR-IR ν_{max} (neat)/cm^{-1} 3049, 2940, 2882, 2857, 2812, 2760, 1663, 1614, 1558, 1545, 1458, 1423, 1373, 1325, 1261, 1246, 1198, 1157, 1126, 1098, 1063, 1040, 1011, 966, 924, 831, 808, 785, 737, 689, 640, 611, 604. m/z (ESI + APCI): 260.2 ($[M+H]^+$). HRMS (ESI) calcd. for $C_{16}H_{26}N_3^+$ $[(M+H)^+]$: 260.2121, found 260.2122.

*4.4.41. Preparation of N^1-((1H-indol-3-yl)methyl)-N^1,N^3,N^3-trimethylpropane-1,3-diamine (**20s**)*

N^1-((1*H*-indol-3-yl)methyl)-N^1,N^3,N^3-trimethylpropane-1,3-diamine 20s was prepared according to General Procedure C on 0.5 mmol scale from 1,1,3-trimethylhexahydropyrimidin-1-ium 4-methylbenzenesulfonate **14b** (1 eq., 0.5 mmol, 150.2 mg), 1*H*-indole (2 eq., 1.0 mmol, 117.2 mg) and AcOH (1.5 mL). The crude mixture was purified by column chromatography (hexane → EtOAc

→ 3% Et_3N/97% MeOH). N^1-((1*H*-indol-3-yl)methyl)-N^1,N^3,N^3-trimethylpropane-1,3-diamine **20s** (122 mg, 99%) was isolated as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H, NH), 7.72 (d, J = 7.9 Hz, 1H, ArH), 7.35 (d, J = 8.0 Hz, 1H, ArH), 7.21–7.16 (m, 1H, ArH), 7.15–7.06 (m, 2H, 2 x ArH), 3.71 (s, 2H, NCH_2N), 2.50–2.41 (m, 2H, $NCH_2CH_2CH_2N$), 2.35–2.28 (m, 2H, $NCH_2CH_2CH_2N$), 2.25 (s, 3H, Me), 2.23 (s, 6H, 2 x Me), 1.78–1.70 (m, 2H, $NCH_2CH_2CH_2N$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.4, 128.1, 123.7, 122.0, 119.6, 119.5, 113.4, 111.1, 58.1, 55.6, 52.9, 45.6, 42.4, 25.9. ATR-IR ν_{max} (neat)/cm^{-1} 3406, 3167, 3148, 3102, 3055, 3013, 2940, 2859, 2783, 1653, 1616, 1541, 1535, 1456, 1352, 1341, 1304, 1271, 1238, 1206, 1196, 1152, 1107, 1099, 1070, 1061, 1040, 1009, 966, 930, 878, 822, 775, 741, 660, 625, 611. *m/z* (ESI + APCI): 246.2 ([M+H]$^+$). HRMS (ESI) calcd. for $C_{15}H_{24}N_3^+$ [(M + H)$^+$]: 246.1965, found 246.1964.

4.4.42. Preparation of N^1,N^1,N^3-trimethyl-N^3-((1-methyl-1*H*-pyrrol-2-yl)methyl)propane-1,3-diamine (**20x**)

N^1,N^1,N^3-trimethyl-N^3-((1-methyl-1*H*-pyrrol-2-yl)methyl)propane-1,3-diamine **20x** was prepared according to General Procedure C on 0.5 mmol scale from 1,1,3-trimethylhexahydropyrimidin-1-ium 4-methyl benzenesulfonate **14b** (1 eq., 0.5 mmol, 150.2 mg), 1-methyl-1*H*-pyrrole (2 eq., 1.0 mmol, 89 μL) and AcOH (1.5 mL). Concentration of the crude mixture afforded N^1,N^1,N^3-trimethyl-N^3-((1-methyl-1*H*-pyrrol-2-yl)methyl) propane-1,3-diamine **20x** and N^1,N^1,N^3-trimethyl-N^3-((1-methyl-1*H*-pyrrol-3-yl)methyl)propane-1,3-diamine as a ~9:1 mixture (104 mg, 99%) as a brown oil (NMR data for the major isomer reported). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59–6.56 (m, 1H, ArH), 6.03–6.01 (m, 1H, ArH), 5.97 (dd, J = 3.4, 1.8 Hz, 1H, ArH), 3.63 (s, 3H, NMe), 3.39 (s, 2H, NCH_2N), 2.40–2.33 (m, 2H, $NCH_2CH_2CH_2N$), 2.30–2.24 (m, 2H, $NCH_2CH_2CH_2N$), 2.21 (s, 6H, 2 x Me), 2.13 (s, 3H, Me), 1.61–1.68 (m, 2H, $NCH_2CH_2CH_2N$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 130.0, 122.5, 109.4, 106.3, 58.1, 55.6, 54.3, 45.7, 41.9, 33.9, 25.8. ATR-IR ν_{max} (neat)/cm^{-1} 2941, 2835, 2810, 2783, 2762, 1605, 1541, 1497, 1458, 1412, 1375, 1360, 1346, 1300, 1267, 1250, 1207, 1184, 1163, 1121, 1086, 1034, 1011, 961, 889, 851, 827, 783, 748, 704, 685, 611. *m/z* (ESI + APCI): 210.2 ([M+H]$^+$). HRMS (ESI) calcd. for $C_{12}H_{24}N_3^+$ [(M + H)$^+$]: 210.1965, found 210.1967.

4.4.43. Preparation of N^1-((1H-pyrrol-2-yl)methyl)-N^1,N^3,N^3-trimethylpropane-1,3-diamine (**20q**)

N^1-((1*H*-pyrrol-2-yl)methyl)-N^1,N^3,N^3-trimethylpropane-1,3-diamine **20q** was prepared according to General Procedure C on 0.5 mmol scale from 1,1,3-trimethylhexahydropyrimidin-1-ium 4-methylbenzenesulfonate **14b** (1 eq., 0.5 mmol, 150.2 mg), 1*H*-pyrrole (2 eq., 1.0 mmol, 72 μL) and AcOH (1.5 mL). Concentration of the crude mixture afforded N^1-((1*H*-pyrrol-2-yl)methyl)-N^1,N^3,N^3-trimethylpropane-1,3-diamine **20q** (95 mg, 97%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (s, 1H, NH), 6.73 (br s, 1H, ArH), 6.12 (d, J = 2.5 Hz, 1H, ArH), 5.99 (br s, 1H, ArH), 3.57 (s, 2H, $ArCH_2N$), 2.44 (t, J = 7.1 Hz, 2H, $NCH_2CH_2CH_2N$), 2.34 (t, J = 7.0 Hz, 2H, $NCH_2CH_2CH_2N$), 2.25 (s, 9H, 3 x Me), 1.77–1.62 (m, 2H, $NCH_2CH_2CH_2N$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 128.9, 117.5, 107.9, 106.9, 57.4, 54.8, 54.6, 45.4, 42.2, 24.9. ATR-IR ν_{max} (neat)/cm^{-1} 3368, 3098, 2945, 2857, 2814, 2781, 1570, 1458, 1375, 1360, 1306, 1250, 1209, 1177, 1165, 1119, 1096, 1061, 1026, 1011, 968, 883, 797, 714, 681, 650, 610. *m/z* (ESI + APCI): 196.2 ([M+H]$^+$). HRMS (ESI) calcd. for $C_{11}H_{22}N_3^+$ [(M + H)$^+$]: 196.1808, found 196.1806.

4.4.44. Preparation of 4,4′-methylenebis(N,N-dimethyl aniline) (**31**)

4,4′-methylenebis(*N*,*N*-dimethylaniline) **31** was prepared according to General Procedure C on 0.5 mmol scale from 1,1,3-trimethylhexahydro pyrimidin-1-ium 4-methylbenzenesulfonate **14b** (1 eq., 0.5 mmol, 150.2 mg), *N*,*N*-dimethylaniline (2 eq., 1.0 mmol, 127 μL) and AcOH (1.5 mL). Crude mixture was recrystallised from EtOAc/hexane affording a crop of 4,4′-methylenebis(*N*,*N*-dimethylaniline) 31 (82 mg) as a white-off solid. The mother liquor was concentrated and was recrystallised from hexane and a second crop of 4,4′-methylenebis(*N*,*N*-dimethylaniline) 31 (18 mg) was isolated as an off-white solid. The first and second crop of 4,4′-methylenebis(*N*,*N*-dimethylaniline) **31** (100 mg, 78%) were combined (Mp = 66–68 °C, lit. 66–68 °C)[2].^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, J = 8.6 Hz, 4H, 4 x ArH), 6.69 (d, J = 8.7 Hz, 4H, 4 x ArH), 3.81 (s, 2H, CH_2), 2.90 (s, 12H, 4 x Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.2, 130.5, 129.6, 113.2, 41.1, 40.0. ATR-IR ν_{max} (neat)/cm^{-1} 3073, 3005, 2887, 2805, 1612, 1560, 1518, 1479, 1443, 1341, 1310, 1275, 1229, 1188, 1165, 1121, 1070, 1007, 941, 899, 829, 793, 739, 714, 702, 687, 669, 637, 615. *m/z* (EI): 254.3 (M$^+$, 100), 237.2 (25), 223.2 (4), 210.2 (52), 194.2 (8), 165.2 (20), 152.1 (5), 134.2 (48), 126.2 (18), 118.2 (47), 104.1 (8), 91.2 (16), 77.1 (10), 65.2 (5). 51.1 (4). The data for this compound are consistent with those previously reported in the literature [46]. N^1-(4-(dimethylamino) benzyl)-N^1,N^3,N^3-trimethylpropane-1,3-diamine (**20y**) was the major consituent of the mother liquor.

4.4.45. Preparation of 1-(tert-butyl) 2-ethyl 1H-indole-1,2-dicarboxylate (**37**)

1-(*tert*-Butyl) 2-ethyl 1*H*-indole-1,2-dicarboxylate **37** was prepared according to a modified literature procedure [47,48]. A solution of Boc_2O (1.2 eq., 33.0 mmol, 7.202 g) in dry MeCN (20 mL) was added to a solution of ethyl 1*H*-indole-2-carboxylate (1.0 eq., 27.7 mml, 5.241 g) and DMAP (0.1 eq., 2.8 mmol, 338 mg) in dry MeCN (65 mL) under argon. The resulting dark yellow solution was stirred at RT 22.5 h before N^1,N^1-dimethylethane-1,2-diamine (0.2 eq., 5.0 mmol, 546 μL) was added to quench unreacted Boc_2O. The reaction mixture was stirred at RT for 2 h before it was concentrated, redissolved in CH_2Cl_2 (100 mL) and extracted with 1 M HCl (150 mL) and water (75 mL). The combined aqueous layers were extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and filtered. Concentration of the filtered organic phases afforded 1-(*tert*-butyl) 2-ethyl 1*H*-indole-1,2-dicarboxylate **37** (7.920 g, 99%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (dd, J = 8.4, 0.8 Hz, 1H, ArH), 7.65–7.55 (m, 1H, ArH), 7.41–7.39 (m, 1H, ArH), 7.26 (td, J = 7.5, 1.0 Hz, 1H, ArH), 7.10 (d, J = 0.7 Hz, 1H, ArH), 4.38 (q, J = 7.1 Hz, 2H, CH_2), 1.63 (s, 9H, ^{t}Bu), 1.40 (t, J = 7.1 Hz, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1, 149.4, 138.0, 131.0, 127.7, 126.9, 123.4, 122.3, 115.0, 114.9, 84.7, 61.5, 28.0, 14.4. ATR-IR ν_{max} (neat)/cm^{-1} 3067, 2980, 2934, 2905, 1726, 1609, 1584, 1541, 1476, 1447, 1393, 1369, 1321, 1273, 1260, 1227, 1196, 1152, 1134, 1115, 1096, 1070, 1015, 941, 849, 833, 810, 745, 665, 610. *m/z* (ESI): 312.3 ([M+Na]$^+$). The data for this compound are consistent with those previously reported in the literature [47–49].

4.4.46. Preparation of tert-butyl 2-(hydroxymethyl)-1H-indole-1-carboxylate (**38**)

tert-Butyl 2-(hydroxymethyl)-1*H*-indole-1-carboxylate **38** was prepared according to a modified literature procedure [47,48]. DIBAL-H (2.9 eq., 78.0 mmol, 78 mL), as a 1 M solution in toluene, was added dropwise to a solution of 1-(*tert*-butyl) 2-ethyl 1*H*-indole-1,2-dicarboxylate 37 (1.0 eq., 26.9 mmol, 7.787 g) in dry toluene (56 mL) under argon at −78 °C over 45 min. Reaction mixture was stirred for 45 min at −78 °C before it was quenched with MeOH (11 mL) and water (10 mL), added dropwise at −78 °C. Reaction mixture was then warmed to RT, resulting in a white precipitate that was filtered. The filter cake was washed with copious amounts of CH_2Cl_2. The filtrate was extracted with water (100 mL) and the water layer was extracted with CH_2Cl_2 (3 × 50 mL). Combined organic phases were dried over $MgSO_4$, filtered, and concentrated affording *tert*-butyl 2-(hydroxymethyl)-1*H*-indole-1-carboxylate **38** (6.227 g, 94%) as a yellow oil. ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.99 (dd, J = 8.3, 0.8 Hz, 1H, ArH), 7.57–7.48 (m, 1H, ArH), 7.33–7.27 (m, 1H, ArH), 7.25–7.19 (m, 1H, ArH), 6.58 (d, J = 0.5 Hz, 1H, ArH), 4.81 (d, J = 7.3 Hz, 2H, CH_2), 3.72 (t, J = 7.5 Hz, 1H, OH), 1.73 (s, 9H, ^{t}Bu). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.5, 140.4, 136.4, 129.1, 124.6, 123.2, 121.0, 115.8, 109.8, 85.2, 59.1, 28.4. ATR-IR ν_{max} (neat)/cm^{-1} 3428, 3051, 3003, 2980, 2924, 2870, 1726, 1667, 1607, 1593, 1580, 1568, 1526, 1474, 1452, 1443, 1410, 1360, 1325, 1306, 1252, 1217, 1159, 1119, 1088, 1053, 1020, 962, 947, 853, 833, 824, 768, 743, 710, 656, 637, 619. *m/z* (ESI + APCI): 247.1 ([M+H]$^+$). The data for this compound are consistent with those previously reported in the literature [47–49].

*4.4.47. Preparation of a mixture of tert-butyl 2-(bromo methyl)-1H-indole-1-carboxylate and tert-butyl 2-(chloro methyl)-1H-indole-1-carboxylate (**39** and **40**)*

A mixture of *tert*-butyl 2-(chloromethyl)-1*H*-indole-1-carboxylate **40** and *tert*-butyl 2-(bromomethyl)-1*H*-indole-1-carboxylate **39** was prepared according to a modified literature procedure [47,48]. Et_3N (1.6 eq., 39.4 mmol, 5.486 mL) and MsCl (1.6 eq., 39.4 mmol, 3.046 mL) were added to a mixture containing LiBr (10 eq., 246 mmol, 21.365 g) and *tert*-butyl 2-(hydroxymethyl)-1*H*-indole-1-carboxylate **38** (1.0 eq., 24.6 mmol, 6.094 g) in dry CH_2Cl_2 (320 mL) under argon at RT. The resulting yellow slurry was stirred at RT for 20.5 h before it was diluted with 2:1 water/sat. $NaHCO_3$ (100/50 mL). The aqueous layer was separated and was further washed with CH_2Cl_2 (100 mL + 2 × 50 mL). Combined organic phases were dried over $MgSO_4$, filtered, and concentrated. ^{1}H NMR quantitative conversion. The mixture taken through the next step of the synthesis without any further purification.

*4.4.48. Preparation of tert-butyl 2-((4-chlorophenoxy) methyl)-1H-indole-1-carboxylate (**41**)*

tert-Butyl 2-((4-chlorophenoxy)methyl)-1*H*-indole-1-carboxylate **41** was prepared according to a modified literature procedure [48]. A slurry consisting of the *tert*-butyl 2-(chloromethyl)-1*H*-indole-1-carboxylate **40** and *tert*-butyl 2-(bromomethyl)-1*H*-indole-1-carboxylate mixture **39** (1.0 eq., 24.6 mmol), Cs_2CO_3 (3.0 eq., 73.8 mmol, 24.05 g) and 4-chlorophenol (1.1 eq., 27.1 mmol, 3.479 g) in dry MeCN (368 mL) was stirred at RT under argon for 47 h. Reaction mixture was concentrated, diluted with water (150 mL) and extracted with CH_2Cl_2 (3 × 100 mL + 25 mL). Combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (hexane → 2% EtOAc/98% hexane) afforded a yellow solid, that was further triturated with hexane. *tert*-Butyl 2-((4-chlorophenoxy)methyl)-1*H*-indole-1-carboxylate **41** (5.827 g, 66%) was isolated as a pale yellow solid (Mp = 109–111 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, J = 8.3, 0.7 Hz, 1H, ArH), 7.51 (d, J = 7.2 Hz, 1H, ArH), 7.33–7.19 (m, 4H, 4 x ArH), 6.96–6.89 (m, 2H, 2 x ArH), 6.70 (d, J = 0.8 Hz, 1H, ArH), 5.38 (d, J = 1.1 Hz, 2H, CH_2), 1.66 (s, 9H, ^{t}Bu). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3, 150.4, 136.9, 136.0, 129.6, 129.1, 126.1, 124.5, 123.1, 120.8, 116.2, 115.7, 109.2, 84.6, 65.7, 28.3. ATR-IR ν_{max} (neat)/cm^{-1} 3123, 3053, 3005, 2978, 2913, 2866, 1722, 1597, 1582, 1574, 1491, 1476, 1452, 1427, 1412, 1402, 1393, 1368, 1358, 1329, 1308, 1285, 1246, 1219, 1161, 1152, 1119, 1103, 1088, 1038, 1007, 966, 953, 930, 854, 820, 797, 764, 748, 714, 696, 665, 633, 606. *m/z* (ESI): 380.4 ([M+Na]$^+$). HRMS (ESI) calcd. for $C_{20}H_{20}ClNO_3Na^+$ [(M + Na)$^+$]: 380.1024, found 380.1023; calcd. for $C_{40}H_{40}Cl_2N_2O_6Na^+$ [(2 M + Na)$^+$]: 737.2156, found 737.2159.

*4.4.49. Preparation of 2-((4-chlorophenoxy)methyl)-1H-indole (**42**)*

2-((4-Chlorophenoxy)methyl)-1*H*-indole **42** was prepared according to a modified literature procedure [50]. A slurry containing *tert*-butyl 2-((4-chlorophenoxy)methyl)-1*H*-indole-1-carboxylate **41** (1.0 eq., 15.6 mmol, 5.577 g) and K_2CO_3 (1.05 eq., 16.4 mmol, 2.262g) in MeOH (312 mL) was refluxed under argon for 3.5 h before it was cooled to RT and concentrated. Reaction mixture was diluted with water (70 mL) and was extracted with EtOAc (2 × 100 mL + 2 × 50 mL). Combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Crude mixture was recrystallised from EtOAc/hexane, affording a crop of the titled product. The mother liquor was concentrated and was recrystallised from EtOAc/hexane, affording a second crop of the titled compound. 2-((4-Chlorophenoxy)methyl)-1*H*-indole **42** (3.378 g, 84%) was isolated, after combining both crops, as a white solid (Mp = 108–110 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (br s, 1H, NH), 7.60 (dd, J = 7.8, 0.8 Hz, 1H), 7.37 (dd, J = 8.1, 0.9 Hz, 1H), 7.29–7.23 (m, 2H, 2 x ArH), 7.22–7.18 (m, 1H, ArH), 7.14–7.10 (m, 1H, ArH), 6.99–6.90 (m, 2H, 2 x ArH), 6.54 (dd, J = 2.0, 0.8 Hz, 1H, ArH), 5.20 (s, 2H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0, 136.6, 133.4, 129.6, 128.1, 126.5, 122.7, 120.9, 120.3, 116.3, 111.1, 102.3, 64.3. ATR-IR ν_{max} (neat)/cm^{-1} 3420, 3092, 3075, 3057, 2972, 2945 2916, 2857, 1595, 1580, 1489, 1454, 1416, 1406, 1377, 1339, 1300, 1283, 1231, 1173, 1155, 1140, 1119, 1107, 1105, 1096, 1003, 995, 982, 959, 935, 883, 858, 835, 814, 795, 770, 752, 731, 702, 689, 656, 637, 625, 610. *m/z* (EI): 257.1 (M$^+$, 45), 220.2 (8), 204.2 (5), 191.2 (10), 165.2 (7), 130.2 (34), 117.2 (100), 102.2 (8), 89.2 (12), 77.2 (11), 63.1 (14), 51.1 (10). HRMS (ESI) calcd. for $C_{15}H_{13}ClNO^+$ [(M + H)$^+$]: 258.0680, found 258.0684.

*4.4.50. Preparation of 2-((4-chlorophenoxy)methyl)-1-methyl-1H-indole (**43**)*

2-((4-Chlorophenoxy)methyl)-1-methyl-1*H*-indole **43** was prepared according to a modified literature procedure [51,52]. A solution of 2-((4-chlorophenoxy)methyl)-1*H*-indole 42 (1.0 eq., 1.0 mmol, 257.7 mg) in dry THF (6 mL) was added to a slurry of NaH (36 mg) in dry THF (1 mL) under argon at 0 °C. Reaction mixture was warmed to RT and was stirred at RT for 15 min before it was cooled to 0 °C and MeI (1.5 eq., 1.5 mmol, 93.4 μL) was added. The resulting brown mixture was stirred at RT for 30 min before it was cooled to 0 °C and sat. NH_4Cl (10 mL) was added. Reaction mixture was extracted with Et_2O (3 × 20 mL). Combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (hexane → 15% CH_2Cl_2/85% hexane) afforded 2-((4-chlorophenoxy)methyl)-1-methyl-1*H*-indole **43** (130 mg, 48%) as a white solid (Mp = 161–163 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.57 (m, 1H, ArH), 7.34 (dd, J = 8.3, 0.8 Hz, 1H, ArH), 7.29–7.21 (m, 3H, 3 x ArH), 7.09–7.13 (m, 1H, ArH), 6.98–6.92 (m, 2H, 2 x ArH), 6.59 (s, 1H, ArH), 5.17 (s, 2H, CH_2), 3.80 (s, 3H, NMe). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0, 138.4, 134.1, 129.6, 127.2, 126.4, 122.5, 121.1, 119.9, 116.4, 109.4, 103.6, 63.1, 30.2. ATR-IR ν_{max} (neat)/cm^{-1} 3102, 3076, 3057, 3028, 2928, 2864, 1593, 1582, 1553, 1518, 1487, 1468, 1435, 1427, 1400, 1381, 1360, 1339, 1315, 1298, 1281, 1231, 1171, 1146, 1115, 1094, 1053, 999, 972, 937, 912, 864, 820, 793, 752, 725, 696, 681, 667, 650, 633, 623. *m/z* (EI): 271.1 (M$^+$, 47), 234.2 (4), 191.2 (5), 144.2 (36), 131.2 (100), 115.2 (10), 102.2 (7), 89.2 (10), 77.2 (14), 63.1 (12), 51.1 (8). HRMS (ESI) calcd. for $C_{16}H_{15}ClNO^+$ [(M + H)$^+$]: 272.0837, found 272.0840.

*4.4.51. Preparation of N^1-((2-((4-chlorophenoxy)methyl)-1-methyl-1H-indol-3-yl)methyl)-N^1,N^3,N^3-trimethyl propane-1,3-diamine (**44**)*

N^1-((2-((4-chlorophenoxy)methyl)-1-methyl-1*H*-indol-3-yl) methyl)-N^1,N^3,N^3-trimethylpropane-1,3-diamine **44** was prepared according to General Procedure C on 0.3 mmol scale from 1,1,3-trimethylhexahydropyrimidin-1-ium 4-methylbenzenesulfonate **14b** (1 eq., 0.3 mmol, 90.1 mg), 2-((4-chlorophenoxy)methyl)-1-methyl-1*H*-indole **43** (1.6 eq., 0.48 mmol, 129 mg), AcOH (3 mL) and CH_2Cl_2 (5 mL). Purification by column chromatography (hexane → EtOAc → 1% Et_3N in MeOH) afforded N^1-((2-((4-chlorophenoxy)methyl)-1-methyl-1*H*-indol-3-yl)methyl)-N^1,N^3,N^3-trimethylpropane-1,3-

diamine **44** (120 mg, 100%) as a beige solid (Mp = 92–95 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.9 Hz, 1H, ArH), 7.35–7.32 (m, 1H, ArH), 7.29–7.25 (m, 3H, 3 x ArH), 7.14 (t, J = 7.4 Hz, 1H, ArH), 7.06–6.94 (m, 2H, 2 x ArH), 5.27 (s, 2H, OCH_2), 3.79 (s, 3H, Me), 3.72 (s, 2H, NCH_2Ar), 2.46 (t, J = 7.2 Hz, 2H, $NCH_2CH_2CH_2N$), 2.39–2.27 (m, 2H, $NCH_2CH_2CH_2N$), 2.22 (s, 6H, 2 x Me), 2.19 (s, 3H, Me), 1.88–1.66 (m, 2H, $NCH_2CH_2CH_2N$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2, 137.4, 132.1, 129.5, 127.8, 126.3, 122.5, 119.9, 119.5, 116.4, 112.5, 109.2, 60.6, 58.0, 55.9, 52.2, 45.5, 42.1, 30.1, 25.9. ATR-IR ν_{max} (neat)/cm^{-1} 3098, 3049, 2949, 2932, 2862, 2843, 2822, 2808, 2779, 2760, 2722, 1593, 1580, 1487, 1470, 1450, 1404, 1377, 1362, 1346, 1337, 1283, 1261, 1231, 1215, 1194, 1169, 1153, 1126, 1105, 1092, 1070, 1061, 1034, 997, 957, 926, 891, 876, 856, 833, 814, 804, 791, 764, 746, 737, 714, 685, 665, 648, 613. *m/z* (ESI + APCI): 400.2 ($[M+H]^+$). HRMS (ESI) calcd. for $C_{23}H_{31}ClN_3O^+$ $[(M + H)^+]$: 400.2150, found 400.2138.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Daniela Dimitrova, Connor McMahon reports financial support was provided by GlaxoSmithKline Plc. Daniela Dimitrova, Connor McMahon reports financial support was provided by Engineering and Physical Sciences Research Council.

Data availability

Data will be made available on request.

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