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Synthesis of dendritic self-immolative molecules triggered by reactive electrophilic alkylating agents: Assessment for colorimetric disclosure of such agents

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ABSTRACT

The development of efficient chemoselective self-immolative molecules for use as sensors necessitates optimization of the degradation characteristics of the self-immolative unit to permit effective signal generation (e.g. colour changes) in relation to the triggering event. One approach is to utilise degradable dendritic structures to allow multiple copies of signalling molecules to be released in return for a single triggering event. To this end, degradable isomeric dendrons featuring aniline-core units for the detection of reactive electrophilic species have been prepared and their reactions studied. A route employing protected phosphorous-borane adducts was key to their synthesis. Following deprotection of these adducts, to activate the self-immolative dendron, alkylation by an electrophilic species and subsequent elimination events, under basic conditions as employed for related molecules incapable of generating an amplified response, were investigated. These studies revealed, in contrast to the findings with other structurally-related self-immolative dendritic molecules, that the degradation profiles of these dendrons do not afford amplified responses in relation to the number of triggering events. In the light of the expenditure of resources required to generate well-defined dendritic materials, this study provides a cautionary perspective against the assumption that such branched molecules will always afford an amplified signal.

1. Introduction

Effective disclosure of the presence of toxic electrophilic compounds [1–3] in the environment could present advantages in the mitigation of their deleterious health effects. Identification and validation of areas of contamination would allow for effective decontamination by a dedicated response team or contribute to a post-decontamination assurance process. The ability to generate a chemoselective visual disclosure event via production of a colorimetric or fluorimetric signal upon contact with the contaminant material represents an extremely attractive solution to this problem. It may be possible that such methods could be employed with minimal training for the end users and without the need for dedicated instrumentation. Focusing on the toxic electrophile sulfur mustard (HD), for example, chromo-fluorogenic disclosure molecules have been reported for this Chemical Warfare Agent (CWA) but require complex multicomponent reactive formulations that include a signalling element [4–6]. In 2014, Goud et al. reported [7] a fluorescent chemidosimeter for the presence of sulfur mustard that was based upon a rhodamine dye derivative. Both chromogenic and fluorogenic responses to sulfur mustard were also described by Knighton et al. [8a] and Kumar et al. [8b].

The present report concerns self-immolative molecules (SIMs); these are based upon a bond between trigger and reporter groups whose stability is sensitive to specific chemical or biological targets. Several chemically specific triggers have been developed for applications spanning drug delivery [5–7], biological and chemical sensors [8–10], diagnostics [11] and degradable polymers [12–18]. Many of these self-immolative molecules operate by activation of the trigger group by nucleophiles (such as fluoride or thiols) or enzymatic action to render the degradable unit labile with concomitant generation of an electron

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rich, nucleophilic centre that then causes a cascade of electrons within the molecule resulting in release of the reporter group(s) [13–15]. Recently, we have reported a SIM for the visual disclosure of reactive electrophilic alkylating agents (Scheme 1) [16,17]. Molecule **1** was based upon a nucleophilic phosphorus centre, the alkylation of which acidified protons on adjacent carbon centres, facilitating base mediated β-elimination of a single reporter group. Further optimization of **1** led to compound **2** with an enhanced stability profile [17]. An alternative SIM for disclosure of electrophilic alkylating agents, based on fragmentation-induced FRET, has been developed by Taran and Le Gall. In this case, N-alkylation to form an ammonium ion leaving group preceded fragmentation by 1,6-elimination to form a *para*-quinone [18].

When generating a colorimetric or fluorometric disclosure response to the presence of a specific chemically reactive entity a key requirement is that the visual change must be clear in order to avoid any ambiguity in the eyes of the end user. To this end, amplification of the visual disclosure response is an attractive proposition. Several approaches to signal amplification from self-immolative molecules have been reported to date. The use of dendritic self-immolative architectures was reported independently in 2003 by de Groot et al. [19], Amir et al. [20] and Szalai et al. [21] who developed molecules whereby electronic relays operate throughout their branched structures to yield the release of multiple reporter groups. Comb-polymer structures have also been effective in amplifying a signal response – a trigger event at one end of the polymer results in an electronic relay that breaks down the polymer backbone and in doing so releases multiple copies of the coloured or fluorescent reporter unit. An alternative approach to the dendritic and comb-polymer structures makes use of a dendritic chain reaction or auto inductive signal amplification whereby each cycle of reaction creates an increasing amount of the signal molecule or ion. Frequently, a multi-component reactive cycle is required, and readouts occur via a variety of means, e.g. colorimetric or physical changes (such as gelation) [22,23]. Examples have been demonstrated for a variety of analytes, such as palladium (0) and H_2O_2, but particular success has been reported for the detection of fluoride anions and their use as chain carriers. For example, amplifiers for the detection of fluoride anions have been demonstrated by Shabat, Huang, Akkaya, Phillips and Anslyn [22,24-26, 27d]. These reports describe methods that either directly detect low levels of fluoride or include a preliminary reaction of an analyte with a molecule that releases fluoride. The fluoride present or generated initiates a reaction, by silyl ether deprotection, to release further fluoride anions. The amplified fluoride 'signal' is formed either concomitantly with a reporter moiety or after further reaction with a reporter-bearing low generation dendron.

In this study, the synthesis and reactivity profiles of two dendritic self-immolative disclosure molecules **3** and **4**, designed for the amplified visual disclosure of a non-acidic electrophilic species, is described. Both molecules afforded the desired visual colorimetric response to exposure with benzyl bromide, following treatment with mild base, but exhibited very different degradation rates.

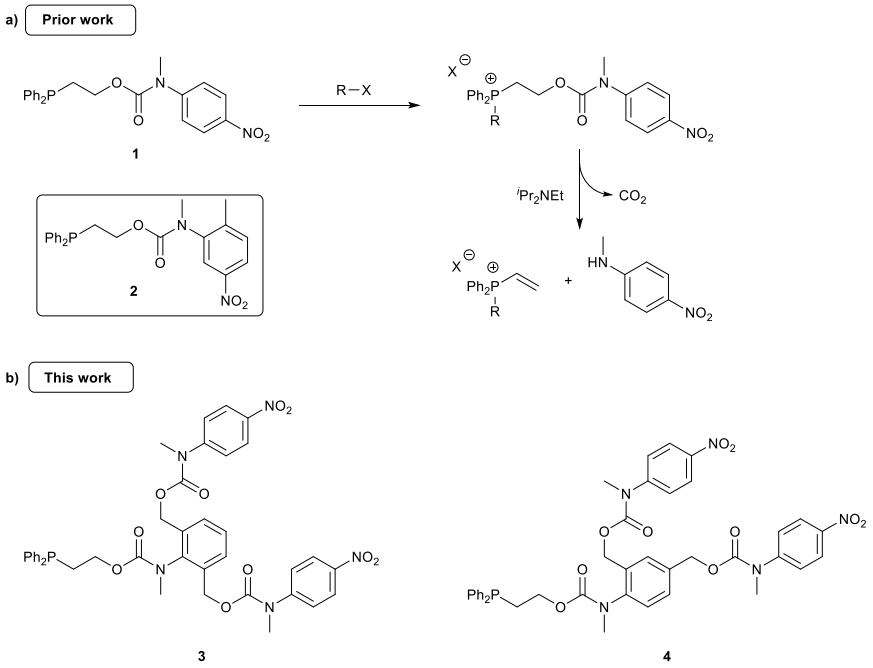
2. Results and discussion

It is important that visual disclosure occurs at an optimum rate as well as the molecules exhibiting suitable shelf-life (*ca.* years) plus robust resistance toward fluctuations in ambient conditions (such as moisture and/or temperature) in the absence of any alkylating agents (to avoid 'false positives'). In principle, an AB_2-type dendritic version of the prototype SIM reported by our group [16,17] could satisfy these requirements and afford amplification, with two reporter groups being released for each alkylation event. Two such branched molecules (Scheme 1; **3** and **4**) have thus been designed and synthesized, and their ability to efficiently disclose reactive alkylating agents has been assessed. Both compounds are based around aniline core units; such units, featuring substituents at the 2,4- and 2,4,6-positions, have been deployed by a number of groups and shown to fragment in a facile manner, via both 1,4- and 1,6-elimination pathways [27,28].

2.1. Synthesis of amplified self-immolative molecules *3* and *4*

Dendritic SIMs **3** and **4** (Scheme 1) were synthesized employing a comparable overall strategy, subject to a number of minor modifications between the pathways used to afford **4** when compared to **3**. The Supplementary Information (SI) file contains characterisation data for the compounds reported in this manuscript.

The dendritic core unit **5**, used as a precursor for **3** (with the reporter



Scheme 1. (a) Structure of previously reported disclosure molecules for reactive alkylating agents [16,17]; (b) Structures of the AB_2 dendrons synthesized and studied in the present work.

units situated 2,6- in relation to the aniline nitrogen) was synthesized from readily available 1,3-dimethyl-2-nitrobenzene **6** as the starting material (Scheme 2). Intermediate **7** was first synthesized in three steps from **6**, according to the procedure reported by Meiries et al. [29] Selective *N*-monomethylation of **7** was then carried out in the presence of methyl trifluoromethanesulfonate as the methylating agent in hexafluoro-2-propanol as described by Legros and co-workers [30], affording the desired *N*-methyl aniline **8**. The dendritic core **5** was then obtained by the reduction of the methyl esters to the corresponding benzylic alcohols using lithium aluminium hydride ($LiAlH_4$) as a reducing agent, followed by subsequent protection of the alcohol groups in the presence of *tert*-butyldimethylchlorosilane (TBSCl) (see Fig. S1−S6 in the SI for analytical data for **5, 7,** and **8**).

The application of the same synthetic strategy to afford the dendritic core unit **9** (see Scheme 3), used as a precursor for **4** (with the reporter units situated 2,4- to the aniline nitrogen), proved not to be so straightforward. Following oxidation of the methyl groups and reduction of the nitro moiety of **10** to give **11** and subsequent N-methylation to afford **12** (see Fig. S7−S11 in the SI for analytical data for **11** and **12**), over-reduction of the *para*-methyl ester group of **12**, by $LiAlH_4$, disappointingly led to the *para*-tolyl derivative **13** (see Scheme 3). Although the reductive deoxygenation of benzylic ethers with $LiAlH_4$ is known [31], the particular selectivity with which this deoxygenation occurs probably reflects participation of the nitrogen lone pair of the aniline in breaking the C–O bond. As such, careful control of the reductive reaction conditions was essential.

Such conjugation of the lone pair of the aniline nitrogen would require it to be aligned with the π-system of the benzene ring with concomitant adoption of a conformation that places the *N*-methyl group in the plane of the ring. To further investigate this point, a crystalline derivative (**14**) of compound **13** was prepared and studied by X-ray diffraction analysis (see the SI file, Figs. S12–S14 plus Tables S1–2). The solid-state structure of **14** (derived from single crystal X-ray diffraction data) is shown in Fig. 1 but with the phenyl groups on the silicon centre removed for clarity. As is evident from Fig. 1, in the solid state, the *N*-methyl group lies approximately in the plane of the aniline ring thus permitting the orbital overlap outlined above.

Such a conformation is very unlikely to occur in the di-alkoxide corresponding to **5** because of the two *ortho*-alkoxymethyl groups and hence the good yield obtained for reduction of **8** to give the desired diol precursor of **5** (92 %). This observation proved prescient with respect to fragmentation of the dendrons **3** and **4** (*vide infra*).

Whilst examining an alternative approach to **9** that allowed its synthesis in only three steps from 4-bromoisophthalic acid **15**, an unexpected improvement in the reduction was observed when the dicarboxylic acid **16** was reduced (see Scheme 4). First, substitution of the bromide by methylamine was carried out in the presence of copper, as a catalyst, to yield the N-methylaniline **16** in 76 % yield [32]. The required reduction of the carboxylic acids to give diol **17** proceeded in 58 % yield under similar conditions to those applied to the reduction of **12**. The reason for this is not clear, but some change in the exact nature of the reducing agent would be expected, given the different by-products from the reduction of a carboxylic acid as compared to those from an ester (hydroxy *versus* methoxy). Subsequent protection of the alcohol groups in presence of *tert*-butyldimethylchlorosilane (TBSCl) afforded **9** in 85 % yield (see Fig. S15−S21 in the SI for analytical data for **9, 16**, and **17**).

For the phosphorus-based trigger element, intermediate **18** was synthesized in two steps from the borane-diphenyl phosphine complex **19**, which was first converted into the borane-complexed phosphine alcohol **20** using *n*-butyllithium and bromoethanol (Scheme 5, see Fig. S22−S24 in the SI for analytical data for **20**). The desired chloroformate **18** was then obtained upon addition of phosgene to **20** and was used without further purification in the next synthetic step. It should be noted that protection of the lone pair of electrons on the phosphine by borane both prevented detrimental oxidation of the phosphine trigger from P(III) to P(V) and removed the nucleophilicity of the phosphorus, which was not only essential to the stability of chloroformate **18**, but also facilitated access to similarly electrophilic chloroformates formed in subsequent synthetic steps, *vide infra*.

Dendritic molecules **3** and **4** were synthesized according to the general route displayed in Scheme 6. The protected phosphorus-based trigger motif **18** was conjugated to the dendritic cores units **5** or **9**, leading to the carbamate derivatives **21** or **22**. Selective deprotection of the silyl ether groups, whilst maintaining the borane-phosphorus complex, was then achieved using the acidic resin Amberlyst® 15 in methanol to afford **23** or **24**. Conversion of the benzylic alcohol groups to chloroformates was performed in presence of phosgene, yielding the crude products **25** or **26** that were directly reacted with the reporter moiety, *N*-methyl-4-nitroaniline, to obtain protected **27** or **28**. Cleavage of the borane-phosphine complex was carried out using 1,4-diazabicyclo [2.2.2]octane solution (DABCO® 33-LV) [33], thus affording the desired SIMs **3** or **4** (see Fig. S25−S48 in the SI for the analytical data for **3**, **4** and **21**–**28**).

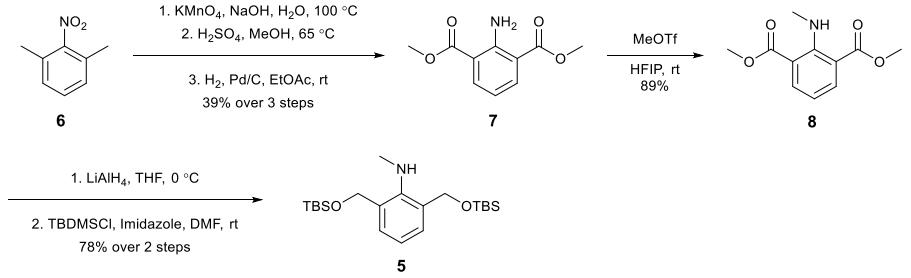
2.2. Characterisation of amplified self-immolative molecules *3* and *4*

NMR spectroscopic analysis of **3** and **4** revealed the presence of two rotamers at room temperature as a result of the restricted rotation about their carbamate C–N bonds to the dendrimeric core (see Scheme 7). Rotamers were not observed for the *para*-nitroaniline units at room temperature. SIMs **3** and **4** exhibited similar rotamer ratios of 61/39 and 62/38, respectively, under these conditions. Those results are in good agreement with Smith et al. [34] as well as our previous study featuring non-dendritic SIMs [17], with the rotameric ratio depending on the number of electron-donating groups present on the aromatic ring.

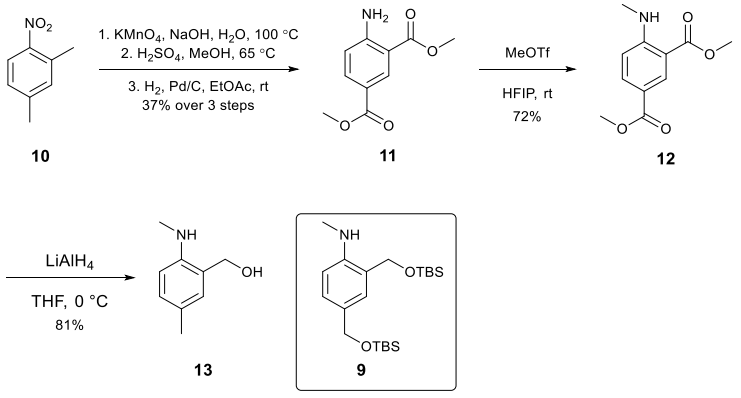
[†]The different features observed in both ^1H and $^{31}P\{^1H\}$ NMR for the amplified SIMs **3** and **4**, at room temperature, were consistent with their non-dendritic counterparts, for which a comparative study was reported [17]. Since the energy barrier to free rotation of the C–N bonds of the carbamate group can be overcome at elevated temperatures, we selected **4** for variable-temperature (VT) ^1H and $^{31}P\{^1H\}$ NMR spectroscopic studies. Fig. 2 shows the ^1H NMR spectra obtained for the **4** at four selected temperatures. The resonances at 4.06−4.25 ppm (CH_2CH_2–O), 5.12–5.26 ppm ($ArCH_2$−O) began to broaden as the temperature was increased and eventually coalesced by ca. 50 °C into two single broad resonances. Meanwhile, the resonances corresponding to the aromatic protons of the nitroaniline moiety at 7.58–7.66 ppm sharpened from a broad signal to two overlapping doublets. Upon further heating to 70 °C, the resonances corresponding to the protons CH_3–N and CH_2CH_2–O changed to a sharp singlet and a relatively broad resonance, respectively.

The stabilities of **3** and **4** were investigated over an extended period of time at room temperature, both were monitored in the solution state ($C = 0.1$ mol L^{-1} in CD_3CN, that was used as a solvent for the subsequent alkylation-elimination steps) as well as in their neat state. Degradation was not observed for **3** and **4** in solution over a period of 72 h at 22 °C. However, unsurprisingly under the experimental conditions, a small amount of oxidation to the corresponding phosphine oxide was observed. Similarly, degradation was not observed for either **3** or **4** in their neat state [17]. In direct comparison to our earlier work; SIM **1** was stable in solution but underwent 33 % degradation as a neat liquid after 24 h; whereas, SIM **2** was found to be stable both in neat form and in solution [17].

[†] With respect to the syn/anti conformation of the carbamate unit, in agreement with Smith et al. [34], we observe in solution that the methylene protons in the α-position to the carbamate group of the major rotamer are always at higher field.



Scheme 2. Synthesis of the dendritic core unit **5**.



Scheme 3. Initial synthetic pathway toward the dendritic core unit **9**.

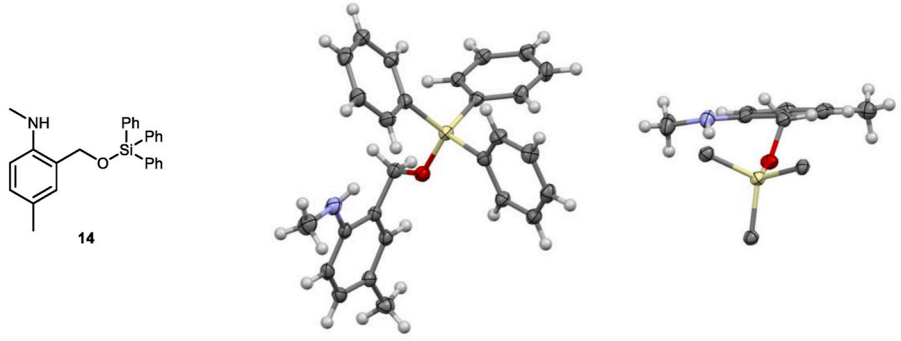
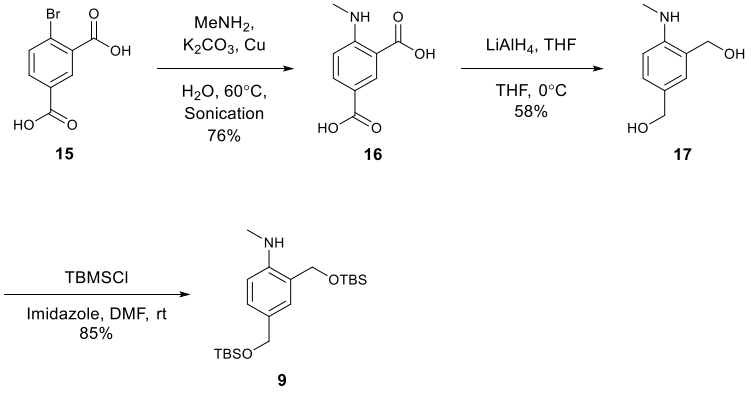
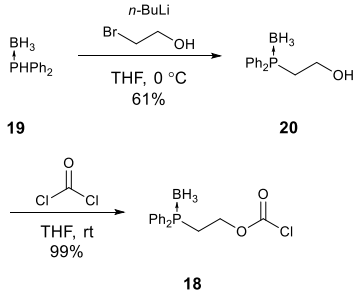


Fig. 1. The partial solid-state molecular structure of compound **14** (phenyl groups omitted for clarity in the right-hand image).



Scheme 4. Alternative synthetic pathway of the dendritic core unit **9**.



Scheme 5. Synthetic route for the phosphorus-based trigger motif **18**.

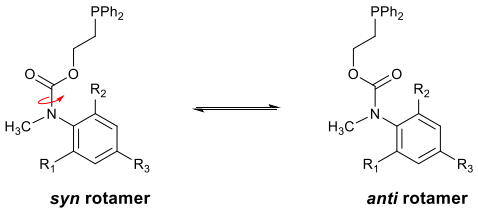
2.3. Assessment of self-immolative molecules 3 and 4 to disclose electrophilic alkylating agents

To assess the ability of **3** and **4** to disclose the presence of reactive electrophilic alkylating agents via a two-step process, described previously [16,17], that involved alkylation followed by elimination/decarboxylation (see Scheme 8), the reactivity of each toward alkylation was first investigated, using benzyl bromide as the alkylating agent. Solvent effects were to be expected, e.g. the alkylation was a Type II S_N2 reaction [35,36], and we had previously reported on the use of a selection of solvents and found acetonitrile to be the most suitable [17]. Thus, alkylation of **3** and **4** were each conducted by dissolution in dipolar aprotic solvent CD_3CN, followed by the addition of 1–10 molar equivalents of the electrophilic species and recording the ^1H NMR spectra at regular time intervals at 20 °C.

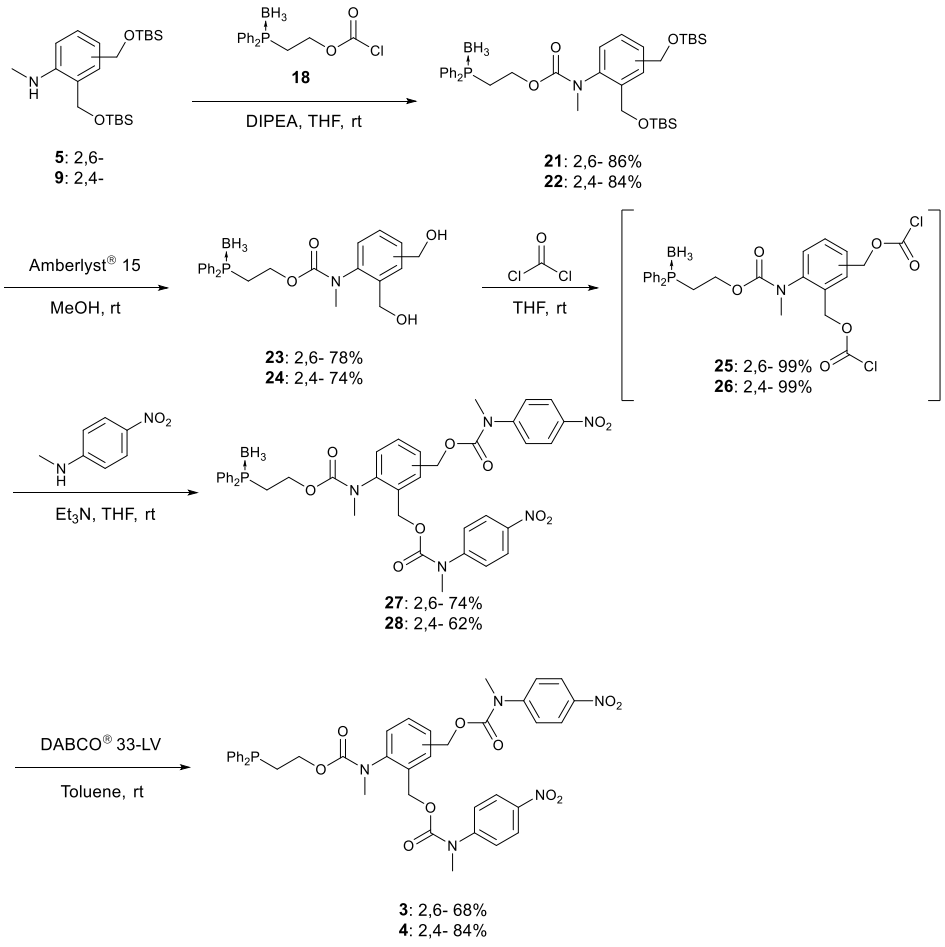
In agreement with our previous study, involving the equivalent non-amplified molecules, that showed only a modest effect of the reporter group on the rate of alkylation [17], treatment of **3** or **4** (with sterically different dendritic cores) with benzyl bromide proceeded at a similar rate to give the corresponding alkylated species **3a** and **4a**, respectively. Complete alkylation of both **3** and **4** was obtained within 24 h in the presence of 1 molar equivalent of benzyl bromide (see Figs. S49 and S50).

Alkylation performed in the presence of 10 molar equivalents of benzyl bromide (*pseudo*-first order conditions) in CD_3CN led to faster alkylation rates, with half-lives of 15.4 and 13.9 min calculated for **3a** and **4a**, respectively (see Fig. S51).

The *β*-elimination of the alkylated SIMs **3a** and **4a** was then performed using 2 molar equivalents of *N,N*-diisopropylethylamine (DIPEA). The elimination profile of **3a** in CD_3CN was monitored over an extended period of time (four days) using both ^1H and $^{31}P\{^1H\}$ NMR spectroscopy.



Scheme 7. Syn−anti rotamer equilibrium caused by the restricted rotation of the dendrimeric core carbamate C–N bond.



Scheme 6. General synthetic pathway for the synthesis of the dendritic SIMs **3** and **4**.

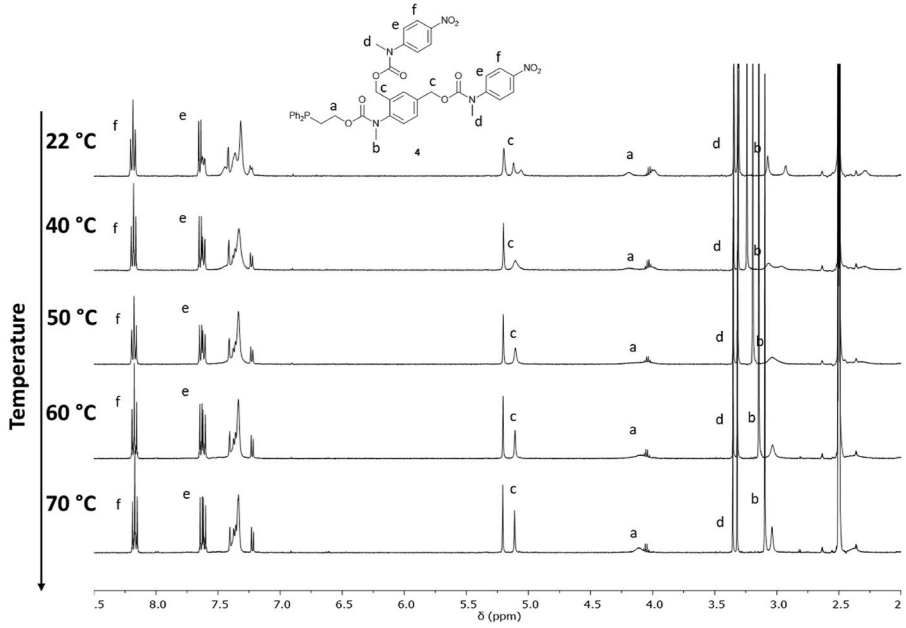
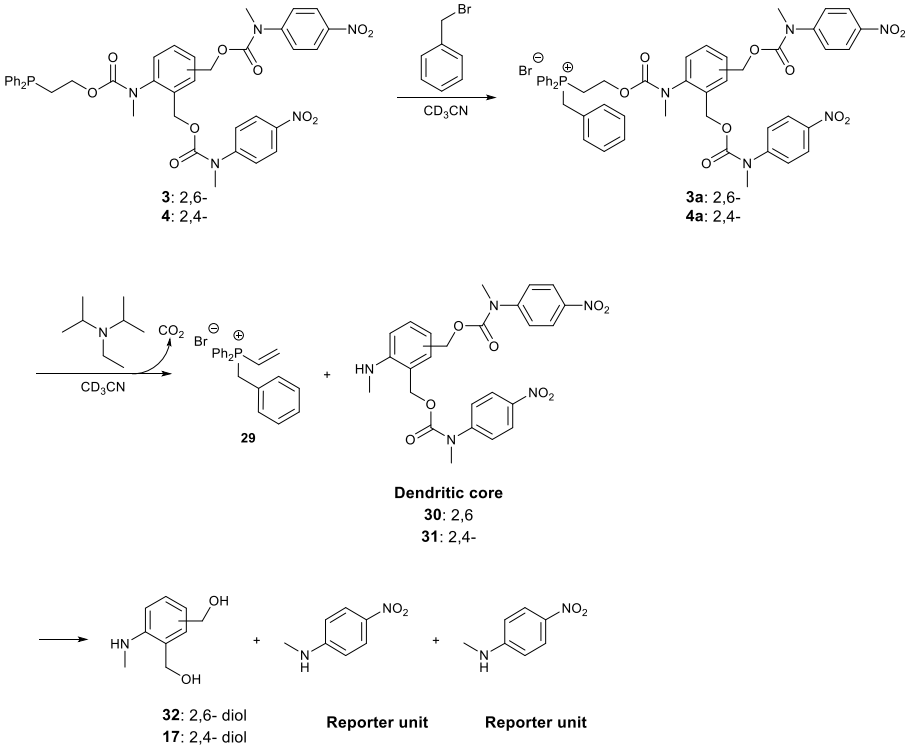


Fig. 2. VT ^{1}H NMR spectroscopic analysis of **4** DMSO-d_6 (500 MHz).



Scheme 8. Proposed self-immolative degradation pathway of **3** and **4**.

Elimination of alkylated **3a** with and without an excess of benzyl bromide was investigated. Cleavage of the phosphorous trigger group was faster in the absence of excess benzyl bromide; presumably, when present, it reacts slowly with DIPEA thus decreasing both the concentration of DIPEA and rates of elimination (see SI, Figs. S52 and S53). Indeed, 50 % of the trigger group was cleaved after 2 h without excess benzyl bromide compared to 16 h with an excess. This result is consistent with that previously observed for the non-amplified self-immolative molecules [17].

Following loss of CO_2 the 2,6-dendritic core **30** was released, but showed remarkable stability with almost no further degradation to release the reporter group, even after an extended period of 32 h (see Fig. S53).

Previous reports in the literature concerning the degradation of various aniline-type self-immolative spacers noted fast rates when water was present in the reaction mixture [27,28]. Additionally, Phillips reported detailed observations on rate enhancement of the release of phenol reporter groups in mixed aqueous acetonitrile solutions, during their work on fragmentation from aniline spacers: the highest rates attending the highest percentage of water in the mixture [37]. Thus, the

influence of the presence of water on the elimination rate was also studied by addition of 10 % D_2O in CD_3CN. Under these conditions, complete cleavage of the phosphorous trigger group was observed within 6 min after addition of DIPEA, releasing the 2,6-dendritic core **30**. The presence of the yellow-coloured reporter group, *para*-nitro-N-methylaniline, was evidenced by ^{1}H NMR spectroscopy after 22 h, although in a very small amount (see Fig. S54). Moreover, only 12 % release of the *para*-nitro-N-methylaniline reporter group was observed after 46 h, emphasising the stability of **30** under reaction conditions. Interestingly, the expected compound **32** resulting from the 2,6-dendritic core degradation was not present in solution, with no evident resonance signals observed in the range 4.0–4.8 ppm in the ^{1}H NMR spectrum, corresponding to the methylene protons of the proposed benzylic alcohol. The same observation can be made for the presence of methylene protons of compounds of the general type ArCH_2-N(CH_3)-Ar', this excluded coupling reactions involving either the *para*-nitro-N-methylaniline moiety or the 2,6-dendritic core **30** with the intermediate aza-quinone species. Such recombination of coupling fragments has been reported previously; for example, Phillips noted that released 4-aminobenzaldehyde underwent re-addition to *para*-quinonemethide, whilst studying a hydrogen peroxide triggered SIM [38]. Instead, a complex pattern is observed at 4.9–5.2 ppm, which could arise owing to the presence of intermediates featuring carbamate functional groups. Furthermore, integration of the signals at 4.8–5.3 ppm, calculated using CD_3CN as an internal standard, remains constant over time. These observations indicate that the release of the reporter group does not affect the molar amount of carbamate groups present in solution and thus suggests that the degradation pathway is probably not self-immolative in character and involves the reaction (possibly intramolecular cyclisation) of the amine groups of the 2,6-cores generated with the carbamate groups present, leading to release of the *para*-nitro-N-methylaniline reporter group.

The resistance of the dendritic core of **30** to undergo self-immolative elimination stands in marked contrast to earlier aniline-based dendritic cores; the critical difference being that these molecules were not *N*-methylated [27,28]. The presence of substituents on the aniline, in both the 2- and 6-positions, appears to preclude the *N*-methyl group achieving planarity with the benzene ring and thus prevent the lone pair on the nitrogen from participating in fragmentation of the dendritic core. Considering the crystal structure in Fig. 1, where a benzene ring is 2,4-disubstituted, the *N*-methyl group lies in the plane of the ring. Based on this observation, **4a** would be expected to exhibit enhanced fragmentation.

Elimination of alkylated SIM **4a** was then investigated. To gain a greater understanding of the elimination profile, **4a** was subjected to two equivalents of DIPEA without the presence of excess benzyl bromide (Fig. 3). Similarly to **3a**, 50 % of the phosphonium triggering group was cleaved from **4a** to afford **29** and core **31** after 2 h with complete cleavage observed after 16 h. Unlike **3a**, the 2,4-dendritic core slowly released the *para*-nitro-N-methylaniline moiety resulting in a yellow solution over time, consistent with our previous reports [16,17]. However, surprisingly, after 16 h only 16 % of the total 2 equivalents that could be released was evident despite only 38 % of the 2,4-dendritic core unit **31** remaining (see Fig. S55) and after 4.8 days 38 % of the reporter motif was observed. Upon analysis of the aromatic region ranging from 6.5 ppm to 8.4 ppm the resonances at 6.65 ppm and 8.06 ppm are attributed to the *para*-nitro-N-methylaniline reporter group.

Similarly for the elimination of **3a**, in the case of **4a** integration of the signals at 7.95–8.23 ppm, calculated using CD_3CN as an internal standard, remains constant over time. These observations indicate that the remaining reporting motif is not absent due to precipitation from the reaction medium but through a decomposition profile which does not result in the release of *para*-nitro-N-methylaniline; from the ^{1}H NMR spectrum of the elimination we see no evidence of a cyclisation of the aniline amine onto the carbamate in the 2-position of the dendritic core nor do we observe the formation of discrete low molecular weight species. Aqueous acetonitrile was also trialled as solvent to enhance the elimination rate; however, a control experiment in the aqueous medium revealed **4** to be unstable and therefore this medium is not suitable as a solvent (see Fig. S56).

The kinetics shown in Fig. 3 were markedly superior to those of **3a**, supporting the significance of the plane of the nitrogen functional group achieving co-planarity with the benzene ring. However, the rate and extent of release of the reporter unit was problematical as the rate of reporting is key in its proposed application, both **3** and **4** were deemed less desirable for the application of disclosing electrophilic species than the previously reported non-amplifying molecules, $t_{1/2}$ for the elimination of benzylated **1** in the presence of excess benzyl bromide was found to be 40 min [17]. The manifest advantages of molecules offering amplification are well-described in the literature *i.e.* delivery of multiple payloads, both numerically and, for example, release of two different reporter groups. However, these must be balanced with disadvantages such as complexity in synthesis and potentially significantly different rates for triggering and self-immolation. In the present case, the sluggish kinetics in comparison to the simpler, non-amplified self-immolative molecules under comparable reaction conditions are significant with **2** being superior to both **3** and **4**. In the application of visual disclosure, using twice the concentration of **2** rather than **3** and **4** to achieve the desired colorimetric response would appear the better option, providing that no other issues, e.g. solubility prevent this.

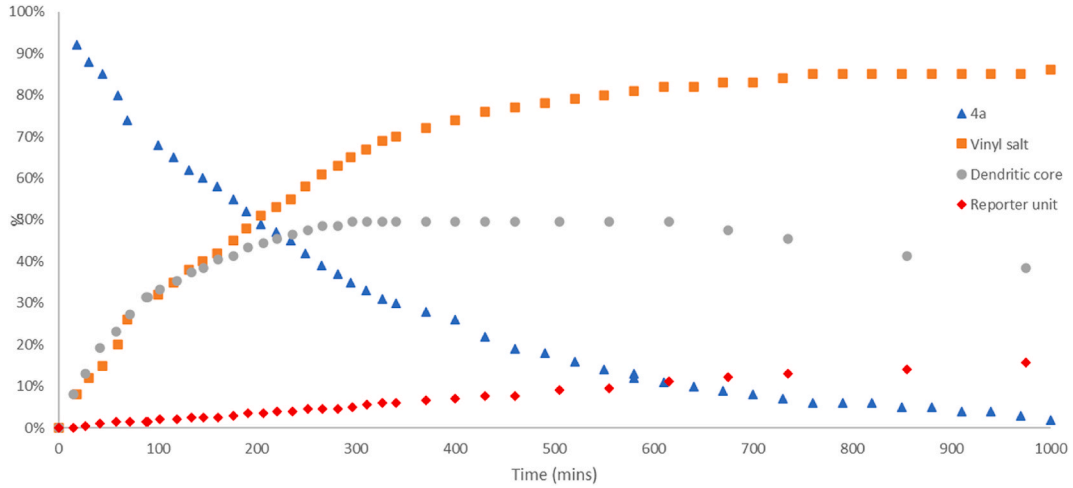


Fig. 3. Reaction kinetics calculated from the ^{1}H NMR spectra (20 °C) obtained following the addition of 2 M equiv. *N*,*N*-diisopropylethylamine (DIPEA) to **4a**.

3. Experimental

3.1. General information

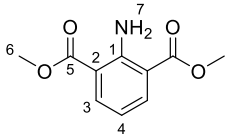
All chemical reagents were purchased from Sigma-Aldrich and were used as received, without purification. Solvents were purchased from Fisher Scientific except for ethyl acetate and hexane which were purchased from Sigma Aldrich. All solvents were used as supplied with the exception of THF that was distilled under argon from sodium and benzophenone prior to use. Fisher Scientific Silica 60A (particle size 35–70 μm) was used to perform column chromatography. Thin-layer chromatography (TLC) was performed on aluminium sheets coated with Merck 5735 Kieselgel 60 F_{254}. Developed plates were air-dried and stained using a potassium permanganate solution. ^{1}H (400 MHz), ^{31}P (162 MHz) and ^{13}C (100 MHz) NMR spectra were recorded at 20 °C on a Bruker Nanobay 400 MHz (9.39 T) or Bruker DPX 400 (9.39 T) instrument. ^{1}H (500 MHz), ^{31}P (203 MHz) and ^{13}C (125 MHz) variable temperature NMR (VT-NMR) were recorded on a Bruker Avance III 500 MHz instrument. This instrument was calibrated at installation with ethylene glycol with an associated error of ±0.1 °C. ^{1}H NMR spectra recorded in $CDCl_3$ were referenced to tetramethylsilane (TMS) as the internal standard; whereas, those recorded in CD_3CN and DMSO-d_6 Chemical shifts (δ) are reported in parts per million (ppm) from high to low. Coupling constants (J) are reported in Hertz (Hz). Standard abbreviations indicating multiplicity are used as follows: br. = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app. = apparent. Fourier transform infrared (FTIR) spectra were recorded on a PerkinElmer Spectrum FT-IR directly using a diamond ATR sampling accessory. Mass spectrometry was conducted using ThermoFisher Scientific Orbitrap XL LCMS. The sample was introduced by liquid chromatography and sample ionisation was achieved by electrospray ionisation (ESI). Melting points were recorded using a Stuart MP10 melting point apparatus and are uncorrected.

A crystal of **14** was mounted under Paratone-N oil and flash cooled to 100 K under nitrogen in an Oxford Cryosystems Cryostream. Single-crystal X-ray intensity data were collected using a Rigaku XtaLAB Synergy diffractometer (Cu Kα radiation (λ = 1.54184 Å)). The data were reduced within the CrysAlisPro software [39]. The structures were solved using the program Superflip [40] and all non-hydrogen atoms located. Least-squares refinements against F was carried out using the *CRYSTALS* suite of programs [41]. All the hydrogen atoms were located in difference Fourier maps. The position and U_{iso} of the hydrogen atom attached to the nitrogen atom were freely refined. The hydrogen atoms attached to carbon were placed geometrically with a C–H distance of 0.95 Å and a U_{iso} of ~1.2–1.5 times the value of U_{eq} of the parent C atom, and the positions refined with riding constraints.

3.2. Synthesis of dendritic self-immolative molecules

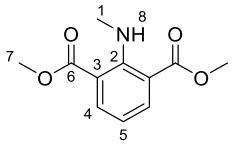
For the characterisation data of the dendritic self-immolative molecules **3** and **4** and their precursors, please refer to the Supplementary File.

3.2.1. Synthesis of dimethyl 2-aminoisophthalate (7)



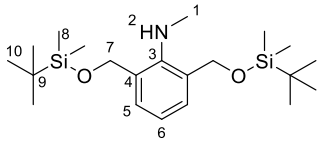
To a suspension of nitroarene **6** (4.00 g, 16.73 mmol, 1.0 equiv) and Pd/C (10 %, dry, 0.25 g, 0.19 mmol, 1.2 mol%) in ethyl acetate (45 mL) was placed under vacuum then purged with nitrogen and finally placed under positive pressure of hydrogen at room temperature overnight. The mixture was filtered through a sintered funnel and the volatiles were removed under vacuum to afford the desired aniline as white powder (3.47 g, 99 %). Mp 142–144 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) 3.87(6H, s, H-6), 6.55 (1H, t, ^{3}J = 7.8 Hz, H-4), 8.08 (2H, d, ^{3}J = 7.8 Hz, H-3), 8.14 (2H, br.s, H-7) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) 51.9 (C-6), 111.8 (C-2), 113.7 (C-4), 137.5 (C-3), 153.3 (C-1), 168.3 (C-5) ppm. FTIR (ATR/ν_{max}) 3365, 2959, 2200, 1713, 1329, 1143 cm^{-1}. ESI-MS m/z calculated for $[C_{10}H_{12}NO_4]^+$; 210.0761, found m/z 210.0760.

3.2.2. Synthesis of dimethyl 2-(methylamino)isophthalate (8)



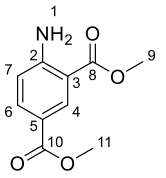
To a solution of aniline **7** (2.00 g, 9.56 mmol) in hexafluoro-2-propanol (10.0 mL, 100.00 mmol) MeOTf (1.6 mL, 14.36 mmol) was added. The mixture was stirred for 1 h at room temperature and then quenched by a solution of HCl (2 N, 10.0 mL). The volatile components were evaporated under reduced pressure, and the resulting mixture was neutralised with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and solvent was removed under reduced pressure. The crude product was purified by silica-gel column chromatography (EtOAc:Hex 30:70) to give the desired compound to give the desired product (1.90 g, 89 %). Mp 127–129 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) 2.83 (3H, s, H-1), 3.88 (6H, s, H-7), 6.62 (1H, t, ^{3}J = 7.7 Hz, H-5), 7.87 (2H, d, ^{3}J = 7.7 Hz, H-4) 8.29 (1H, br.s, H-8) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) 34.1 (C-1), 52.2 (C-7), 114.5 (C-5), 115.5 (C-3), 136.1 (C-4), 152.5 (C-2), 168.9 (C-6) ppm. FTIR (ATR/ν_{max}) 3368, 2961, 2411, 1709, 1588, 1334, 1152 cm^{-1}. ESI-MS m/z calculated for $[C_{11}H_{14}NO_4]^+$; 224.0917, found 224.0914.

3.2.3. Synthesis of 2,6-bis(((tert-butyldimethylsilyl)oxy)methyl)-N-methylaniline (5)



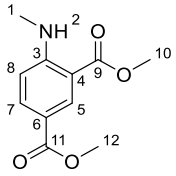
N-Methyl aniline diol (0.50 g, 3.0 mmol) was dissolved in DMF (5 mL) and cooled to 0 °C. Imidazole (0.49 g, 7.2 mmol) and TBDMSCl (1.09 g, 7.2 mmol) were added. The reaction was stirred at room temperature overnight. The reaction was then diluted with ether and was washed with a saturated solution of NH_4Cl. The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by silica-gel column chromatography (EtOAc:Hex 5:95) to give the desired compound **5** as a colourless oil (1.01 g, 85 %). ^{1}H NMR ($CDCl_3$, 400 MHz) 0.07 (12H, s, H-8), 0.92 (18H, s, H-10), 2.78 (3H, s, H-1), 4.25 (1H, br.s, H-2), 4.74 (4H, s, H-7), 6.93 (1H, t, ^{3}J = 7.5 Hz, H-6), 7.24 (2H, d, ^{3}J = 7.5 Hz, H-5) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) −5.1 (C-8), 18.5 (C-9), 26.1 (C-10), 36.4 (C-1), 63.3 (C-7), 121.3 (C-6), 127.9 (C-5), 132.5 (C-4), 147.7 (C-3) ppm. FTIR (ATR/ν_{max}) 3383, 2952, 2927, 2855, 1598, 1471, 1252, 1057 cm^{-1}. ESI-MS m/z calculated for $[C_{21}H_{42}O_2NSi_2]^+$ 396.2749, found 396.2747.

3.2.4. Synthesis of dimethyl 4-aminoisophthalate (11)



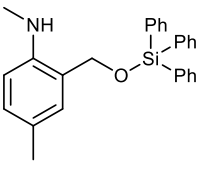
A suspension of nitroarene dimethyl ester (6.00 g, 25.10 mmol, 1.0 equiv) and Pd/C (10 %, dry, 0.368 g, 0.29 mmol, 1.2 mol%) in ethyl acetate (70 mL) was placed under vacuum then purged with nitrogen and finally placed under positive pressure of hydrogen at room temperature overnight. The mixture was filtered through a sintered funnel and the volatiles were removed under vacuum to give the desired aniline **11** (5.21 g, 99 %) as off-white powder. Mp 119–121 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) 3.87 (3H, s, H-11), 3.90 (3H, s, H-9), 6.21 (2H, br.s, H-1), 6.65 (1H, d, $^{3}J = 8.5$ Hz, H-7), 7.91 (1H, dd, $^{3}J = 8.5$ Hz, $^{4}J = 2.0$ Hz, H-6), 8.59 (1H, d, $^{4}J = 2.0$ Hz, H-4) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) 51.90 (C-11), 51.92 (C-9), 109.9 (C-3), 116.3 (C-7), 118.0 (C-5), 134.4 (C-4), 135.1 (C-6), 158.8 (C-2), 166.7 (C-10), 168.2 (C-8) ppm. FTIR (ATR/ν_{max}) 3362, 2959, 2200, 1714, 1708, 1332, 1146 cm^{-1}. ESI-MS *m/z* calculated for $[C_{10}H_{12}NO_4]^+$; 210.0761, found *m/z* 210.0769.

3.2.5. Synthesis of dimethyl 4-(methylamino)isophthalate (12)



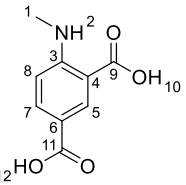
To a solution of aniline **11** (2.50 g, 11.95 mmol) in hexafluoro-2-propanol (12.50 mL), MeOTf (1.98 mL, 17.95 mmol) was added. The mixture was stirred for 1 h at room temperature and then quenched by a solution of HCl (2 M, 15 mL). The solvent and volatile components were evaporated under reduced pressure, and the resulting mixture was neutralised with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 80 mL). The combined organic phases were dried over $MgSO_4$, filtered and solvent was removed under reduced pressure. The crude product was purified by silica-gel column chromatography (EtOAc:Hex 30:70) to give the desired compound to give the desired product (1.93 g, 72 %). Mp 94–96 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) 2.97 (3H, d, $^{3}J = 5.0$ Hz, H-1), 3.87 (3H, s, H-10 or H-12), 3.88 (3H, s, H-10 or H-12), 6.66 (1H, d, $^{3}J = 9.0$ Hz, H-8), 8.02 (1H, dd, $^{3}J = 9.0$ Hz, $^{4}J = 2.0$ Hz, H-7), 8.17 (1H, br.s, H-2), 8.61 (1H, d, $^{4}J = 2.0$ Hz, H-5) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) 29.7 (C-1), 51.8 (C-10 and C-12), 109.4 (C-4), 110.4 (C-8), 116.0 (C-6), 134.5 (C-5), 135.7 (C-7), 154.8 (C-3), 166.9 (C-9 or C-11), 168.8 (C-9 or C-11) ppm. FTIR (ATR/ν_{max}) 3361, 2955, 2401, 1708, 1706, 1596, 1324, 1150, 1105 cm^{-1}. ESI-MS *m/z* calculated for $[C_{11}H_{14}NO_4]^+$; 224.0917, found 224.0921.

3.2.6. Synthesis of N,4-dimethyl-2-(((triphenylsilyl)oxy)methyl)aniline (14)



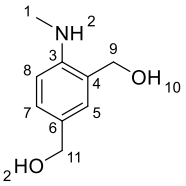
Para-tolyl derivative **13** (0.5 g, 3.31 mmol) was dissolved in DMF (5 mL) and cooled to 0 °C. Imidazole (0.27 g, 3.97 mmol) and triphenylchlorosilane (1.17 g, 3.97 mmol) were added. The reaction was stirred at room temperature overnight. The reaction was then diluted with ether (20 mL) and was washed with a saturated solution of NH_4Cl (20 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by silica-gel column chromatography (EtOAc:Hex 5:95), followed by a recrystallization from MeOH, to obtain a white crystalline solid (0.83 g, 61 %). ^{1}H NMR ($CDCl_3$, 400 MHz) 2.17 (3H, s, C*H*$_3$-Ar), 2.81 (3H, s, C*H*$_3$–N), 4.55 (1H, s, N*H*), 4.79 (2H, s, C*H*$_2$–O), 6.56 (1H, d, $^{3}J = 8.0$ Hz, Ar*H*), 6.62 (1H, s, Ar*H*), 7.02 (1H, d, $^{3}J = 8.0$ Hz, Ar*H*), 7.39 (6H, m, Ar*H*), 7.46 (3H, m, Ar*H*), 7.62 (6H, m, Ar*H*) ppm.

3.2.7. Synthesis of 4-(methylamino)isophthalic acid (16)



To a solution of 4-bromoisophthalic acid **15** (5.00 g, 20.4 mmol), K_2CO_3 (8.46 g, 61.22 mmol) and copper powder (0.064 g, 1.02 mmol) in water (50 mL), methylamine 40 % wt. (9.04 mL, 102.3 mmol) was added. The vessel was placed in sonicating bath at 60 °C for 3 h. The mixture was then filtered through a Celite pad and acidified to pH 1 with HCl, with the precipitate filtered through a sintered funnel. The pH of the aqueous solution was then adjusted to pH 4, the mixture was then filtered through a sintered funnel to isolate the precipitate. The precipitate was taken into ethyl acetate (50 mL), dried over $MgSO_4$, filtered, and volatiles removed *in vacuo* to afford the desired material **16** as a white solid (3.01 g, 76 %). Mp 301–303 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) 2.90 (3H, s, H-1), 6.75 (1H, d, $^{3}J_{HH} = 9.0$ Hz, H-8), 7.90 (1H, dd, $^{3}J_{HH} = 9.0$ Hz, $^{4}J_{HH} = 2.0$ Hz, H-7), 8.41 (1H, d, $^{2}J_{HH} = 2.0$ Hz, H-5) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz) 29.7 (C-1), 109.7 (C-4), 111.1 (C-8), 116.2 (C-6), 134.5 (C-5), 135.6 (C-7), 154.7 (C-3), 167.4 (C-11), 167.9 (C-9) ppm. FTIR (ATR/ν_{max}) 3374, 2870, 2575, 1646, 1605, 1409 cm^{-1}. ESI-MS *m/z* calculated for $[C_9H_{10}O_4N]^+$ 196.0604, found 196.0604.

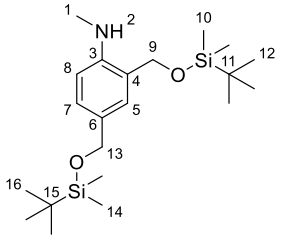
3.2.8. Synthesis of (4-(methylamino)-1,3-phenylene)dimethanol (17)



Into a 100 mL flask was added lithium aluminium hydride (1.22 g, 32.08 mmol) followed by diethyl ether (25 mL) and the mixture was cooled down to 0 °C. The *N*-methyl aniline diacid **16** (1.35 g, 8.05 mmol) in THF (10 mL) was added dropwise. After the mixture had been stirred at room temperature overnight, the reaction was quenched by the dropwise addition of cold water and 50 mL of diethyl ether was added. The salts formed were filtrated and washed with diethyl ether (4 × 100 mL). The solvents were removed under reduced pressure and the residue obtained was diluted in dichloromethane, dried over Mg_2SO_4, filtered and the solvent was removed *in vacuo*. The crude product was purified by silica-gel column chromatography (EtOAc:Hex 40:60) to give the desired product as an off white solid (0.87 g, 58 %). Mp 90–92 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) 1.77 (2H, br.s, H-10 and H-12), 2.87 (3H, s, H-1), 4.54 (2H, s, H-11), 4.63 (2H, s, H-9), 4.75 (1H, br.s, H-2), 6.64 (1H, d, $^{3}J = 8.0$ Hz, H-8), 7.07 (1H, d, $^{4}J = 2.0$ Hz, H-5), 7.23 (1H, dd, $^{3}J = 8.0$ Hz, $^{4}J = 2.0$ Hz, H-7) ppm.^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) 30.5 (C-1),

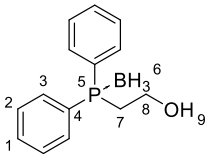
64.8 (C-9), 65.5 (C-11), 110.1 (C-8), 124.5 (C-4), 128.7 (C-6), 128.8 (C-5), 129.3 (C-7), 148.5 (C-3) ppm. FTIR (ATR/ν_{max}) 3403, 3258, 2879, 2811, 1617, 1517, 1447 cm^{-1}. ESI-MS *m/z* calculated for $[C_9H_{14}O_2N]^+$ 168.1019, found 168.1018.

3.2.9. Synthesis of 2,4-bis(((tert-butyldimethylsilyl)oxy)methyl)-N-methylaniline (9)



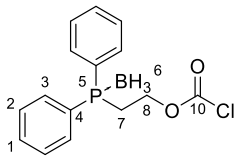
The *N*-methyl aniline diol **17** (0.50 g, 3.0 mmol) was dissolved in DMF (5 mL) and cooled to 0 °C. Imidazole (0.49 g, 7.2 mmol) and TBDMSCl (1.09 g, 7.2 mmol) were added. The reaction was stirred at room temperature overnight. The reaction was then diluted with ether (15 mL) and was washed with a saturated solution of NH_4Cl (15 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by silica-gel column chromatography (EtOAc:Hex 5:95) to give the desired compound **9** as a colourless oil (1.01 g, 85 %). ^1H NMR ($CDCl_3$, 400 MHz) 0.05 (6H, s, H-10 or H-14), 0.07 (6H, s, H-10 or H-14), 0.88 (9H, s, H-12 or H-16), 0.92 (9H, s, H-12 or H-16), 2.85 (3H, s, H-1), 4.62 (2H, s, H-9 or H-13), 4.66 (2H, s, H-9 or H-13), 4.85 (1H, br.s, H-2), 6.59 (1H, d, $^3J = 8.0$ Hz, H-8), 6.98 (1H, d, $^4J = 2.0$ Hz, H-5), 7.15 (1H, dd, $^3J = 8.0$ Hz, $^4J = 2.0$ Hz, H-7) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) −5.1 (C-10 or C-14), −4.9 (C-10 or C-14), 18.3 (C-11 or C-15), 18.6 (C-11 or C-15), 26.0 (C-12 or C-16), 26.2 (C-12 or C-16), 30.6 (C-1), 65.3 (C-9 or C-13), 65.5 (C-9 or C-13), 109.7 (C-8), 124.8 (C-4), 127.0 (C-5), 127.5 (C-7), 129.1 (C-6), 148.1 (C-3) ppm. FTIR (ATR/ν_{max}) 3410, 2953, 2928, 2883, 2855, 1051, 831, 773 cm^{-1}. ESI-MS *m/z* calculated for $[C_{21}H_{42}O_2NSi_2]^+$ 396.2749, found 396.2742.

3.2.10. Synthesis of borane-2-(diphenylphosphaneyl)ethan-1-ol (20)



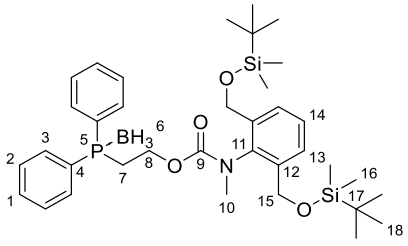
To a solution of borane-diphenylphosphine **19** (1.00 g, 5.00 mmol) and 2-bromoethanol (0.39 mL,5.50 mmol) in THF (20 mL) was added *n*-butyl lithium (7.1 mL, 1.6 M in hexanes). The mixture was stirred for 6 h at 0 °C. The THF was removed under reduced pressure and the residue extracted using CH_2Cl_2 (2 × 20 mL). The resulting solution was treated with an excess of solid NH_4Cl in CH_2Cl_2 and the suspension was filtered, and the solution concentrated under reduced pressure. The remaining residue was extracted with EtOAc (2 × 15 mL), and the volatiles were removed. The crude residue was further purified via silica-gel column chromatography (hexane/CH_2Cl_2 1/1→CH_2Cl_2/EtOAc 7/3) to yield the product (0.750g, 61 %) as a colourless oil which solidified upon standing. Mp 69–71 °C. ^1H NMR ($CDCl_3$, 400 MHz) 0.55–1.51 (3H, m, H-6), 2.17 (1H, br.s, H-9), 2.56 (2H, dt, $^2J_{HP} = 11.0$ Hz, $^3J = 6.5$ Hz, H-7), 3.91 (2H, dt, $^3J_{HP} = 15.0$ Hz, $^3J = 6.5$ Hz, H-8), 7.42–7.53 (6H, m, H-1 and H-2), 7.65–7.73 (4H, m, H-3) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) 29.4 (d, $^1J_{CP} = 36.5$ Hz, C-7), 57.6 (d, $^2J_{CP} = 3.0$ Hz, C-8), 129.0 (d, $^3J_{CP} = 11.0$ Hz, C-2), 129.0 (d, $^1J_{CP} = 56.5$ Hz, C-4), 131.4 (d, $^4J_{CP} = 2.0$ Hz, C-1), 132.07 (d, $^2J_{CP} = 10.0$ Hz, C-3) ppm. $^{31}P\{^1H\}$ NMR 11.58 (P-5) ppm. FTIR (ATR/ν_{max}) 3293, 3060-2952, 1484, 1435 cm^{-1}. ESI-MS *m/z* calculated for $[C_{14}H_{19}BOP]^+$; 245.1204, found *m/z* 245.1206.

3.2.11. Synthesis of borane-2-(diphenylphosphaneyl)ethyl carbonochloridate (18)



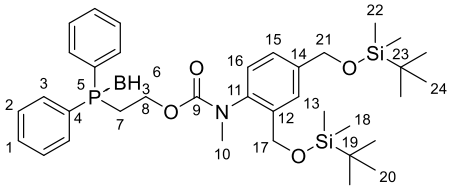
To a solution of phosgene (28.0 mL, 36.87 mmol, 15 wt % in toluene) at 0 °C, a solution of the borane complexed phosphine alcohol **20** (3.0 g, 12.3 mmol) in THF (10 mL) was added dropwise and left to stir at room temperature overnight. The volatiles were removed *in vacuo* and the remaining residue was used without further purification.

3.2.12. Synthesis of borane-2-(diphenylphosphaneyl) ethyl(2,6-bis(((tert-butyldimethylsilyl)oxy)methyl)phenyl)(methyl)carbamate (21)



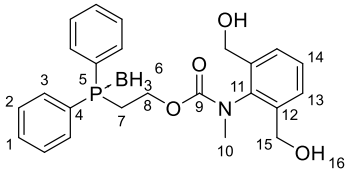
The *N*-methyl aniline derivative **5** (0.775 g, 2.53 mmol) was dissolved in THF (5 mL) and cooled to 0 °C. DIPEA (0.48 mL, 2.78 mmol) and chloroformate derivative **18** (0.780 g, 2.53 mmol) were added. The reaction was stirred at room temperature overnight. The precipitate was filtered off and volatile components removed from the filtrate. The crude product was purified by silica-gel column chromatography (EtOAc:Hex 25:85) to give the desired compound (1.45 g, 86 %) as a colourless oil in a rotameric ratio of 62:38. ^1H NMR ($CDCl_3$, 400 MHz) 0.06 (6H, s, rotamer B, H-16), 0.08 (6H, s, rotamer A, H-16), 0.37–1.38 (21H, m, rotamer A and rotamer B, H-6 and H-18), 2.44–2.56 (2H, m, rotamer A, H-7), 2.72 (2H, dt, rotamer B, $^3J_{HP} = 11.2$ Hz, $^3J_{HH} = 7.5$ Hz, rotamer B, H-7), 2.93 (3H, s, rotamer B, H-10), 3.14 (3H, s, rotamer A, H-10), 4.16–4.24 (2H, m, rotamer A, H-8), 4.42 (2H, app. q, rotamer B, H-8), 4.58 (4H, AB, rotamer A and rotamer B, H-15), 7.30–7.40 (1H, m, rotamer A and rotamer B, H-14), 7.40–7.54 (8H, m, rotamer A and rotamer B, H-1 + H-2 + H-13), 7.66 (4H, app. t, rotamer A, H-3), 7.74 (4H, app. t, rotamer B, H-3) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) −5.19 (rotamer A, C-16), −5.16 (rotamer B, C-16), 18.5 (rotamer A and rotamer B, C-17), 26.00 (d, $^1J_{CP} = 34.8$ Hz, rotamer A and rotamer B, C-7), 26.07 (rotamer A, C-18), 26.09 (rotamer B, C-18), 36.8 (rotamer A, C-10), 37.0 (rotamer B, C-10), 60.08 (d, rotamer B, $^2J_{CP} = 5.4$ Hz, C-8), 61.05 (d, rotamer A, $^2J_{CP} = 9.0$ Hz, C-8), 61.13 (rotamer A, C-15), 61.4 (rotamer B, C-15), 126.6 (rotamer A, C-13), 127.0 (rotamer B, C-13), 128.2 (rotamer B, C-14), 128.3 (rotamer A, C-14), 128.6 (d, $^1J_{CP} = 55.6$ Hz, rotamer A, C-8), 129.10 (d, $^1J_{CP} = 55.4$ Hz, rotamer B, C-8), 129.12 (d, $^3J_{CP} = 10.1$ Hz, rotamer A and rotamer B, C-2), 131.55 (d, $^4J_{CP} = 2.3$ Hz, rotamer B, C-1), 131.60 (d, $^4J_{CP} = 2.2$ Hz, rotamer A, C-1), 132.1 (d, $^2J_{CP} = 9.5$ Hz, rotamer A, C-3), 132.2 (d, $^2J_{CP} = 9.0$ Hz, rotamer A, C-3), 136.0 (rotamer A, C-11), 137.1 (rotamer B, C-11), 138.4 (rotamer A, C-12), 138.6 (rotamer B, C-12), 154.7 (rotamer B, C-9), 155.3 (rotamer A, C-9) ppm. $^{31}P\{^1H\}$ NMR ($CDCl_3$, 162 MHz) 10.53–13.21 (m, rotamer A and rotamer B, P-5) ppm. FTIR (ATR/ν_{max}) 2924, 2848, 2377, 1700, 1594, 1496, 1336, 1152, 1105, 1063 cm^{-1}. ESI-MS *m/z* calculated for $[C_{36}H_{58}O_4NBPSi_2]^+$ 666.3730, found 666.3731.

3.2.13. Synthesis of borane-2-(diphenylphosphaneyl)ethyl (2,4-bis(((tert-butyldimethylsilyl)oxy) methyl)phenyl)(methyl)carbamate (22)



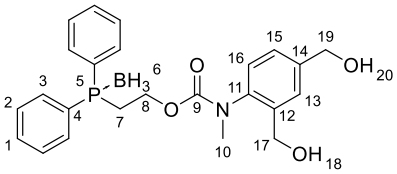
N-Methyl aniline derivative **9** (0.50 g, 1.62 mmol) was dissolved in THF (5 mL) and cooled to 0 °C. DIPEA (0.31 mL, 1.78 mmol) and chloroformate derivative **18** (0.50 g, 1.62 mmol) were then added. The reaction was stirred at room temperature overnight under an inert atmosphere. The precipitate was removed by filtration and the mixture concentrated *in vacuo*. The crude product was purified by silica-gel column chromatography (EtOAc:Hex 25:85) to give the desired compound (0.93 g, 86 %) as a colourless oil in a rotameric ratio of 72:28. ^{1}H NMR ($CDCl_3$, 400 MHz) 0.04–0.09 (6H, m, rotamer A and rotamer B, H-18), 0.09–0.13 (6H, m, rotamer A and rotamer B, H-22), 0.91 (9H, s, rotamer A and rotamer B, H-20), 0.93–0.96 (9H, m, rotamer A and rotamer B, H-24), 1.02 (3H, br.s, H-6), 2.52 (2H, AA'BB', rotamer A, H-7), 2.71 (2H, AA'BB', rotamer B, H-7), 2.93 (3H, s, rotamer B, H-10), 3.16 (3H, s, rotamer A, H-10), 4.19 (2H, AA'BB', rotamer A, H-8), 4.43 (2H, AA'BB', rotamer B, H-8), 4.51–4.64 (2H, m, rotamer A and rotamer B, H-17), 4.70–4.78 (2H, m, rotamer A and rotamer B, H-21), 6.94 (1H, d, ^{3}J = 8.0 Hz, rotamer A, H-15), 7.02 (1H, d, ^{3}J = 8.0 Hz, rotamer B, H-15), 7.16–7.24 (1H, m, rotamer A and rotamer B, H-16), 7.39–7.54 (7H, m, rotamer A and rotamer B, H-1, H-2 and H-13), 7.60–7.79 (4H, m, rotamer A and rotamer B, H-3). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) −5.22 to −5.12 (m, rotamer A and rotamer B, C-20 + C-24), 18.5–18.6 (m, rotamer A and rotamer B, C-18 + C-22), 26.1 (rotamer A and rotamer B, C-7), 37.7 (rotamer B, C-10), 38.0 (rotamer A, C-10), 60.7–61.5 (m, rotamer A and rotamer B, C-8 + C-17), 64.7 (rotamer A and rotamer B, C-21), 125.3 (rotamer A, C-16), 125.5 (rotamer B, C-16), 125.6 (rotamer B, C-15), 126.7 (rotamer A, C-15), 128.3 (d, $^{1}J_{CP}$ = 10.5 Hz, rotamer A and rotamer B, C-4), 129.0 (rotamer A and rotamer B, C-13), 129.2–129.4 (m, rotamer A and rotamer B, C-2), 131.5 (d, $^{4}J_{CP}$ = 2.5 Hz, rotamer A and rotamer B, C-1), 132.0–132.3 (m, rotamer A and rotamer B, C-3), 138.0 (rotamer A and rotamer B, C-14), 138.2 (rotamer A and rotamer B, C-12), 141.0 (rotamer B, C-11), 141.2 (rotamer A, C-11), 155.1 (rotamer B, C-9), 155.5 (rotamer A, C-9) ppm. ^{31}P{^{1}H} NMR 10.82–13.14 (m, P-5) ppm. FTIR (ATR/ν_{max}) 2927, 2854, 2378, 1702, 1103, 850, 834 cm^{-1}. ESI-MS *m/z* calculated for $[C_{36}H_{58}O_4NBPSi_2]^+$ 666.3730, found 666.3716.

3.2.14. Synthesis of borane-2-(diphenylphosphaneyl)ethyl (2,6-bis (hydroxymethyl)phenyl)(methyl) carbamate (23)



The silyl ether **21** (1.20 g, 1.8 mmol) and Amberlyst 15 (0.30 g) were dissolved in MeOH (5 mL) and left to stir at room temperature overnight. The resin was filtered off and the volatiles removed. The crude product was purified by silica-gel column chromatography (EtOAc:Hex 25:85) to give the desired compound (0.58 g, 74 %) as white solid in a rotameric ratio of 59:41. Mp 56–58 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) 0.89 (3H, br. s, rotamer A and rotamer B, H-6), 2.59 (3H, s, rotamer A, H-10), 2.61 (2H, m, rotamer A, H-7), 2.91 (2H, dt, $^{2}J_{HP}$ = 11.6 Hz, $^{3}J_{HH}$ = 6.6 Hz, rotamer B, H-7), 3.02 (3H, s, rotamer B, H-10), 3.99 (2H, app. q, rotamer A, H-8), 4.27 (H, app. q, rotamer B, H-8), 4.28–4.43 (4H, m, rotamer A and rotamer B, H-15), 5.14 (2H, br.s, rotamer A and rotamer B, H-16), 7.27–7.35 (1H, rotamer A and rotamer B, H-14), 7.35–7.42 (2H, m, rotamer A and rotamer B, H-13), 7.44–7.62 (6H, m, rotamer A and rotamer B, H-9 + H-10), 7.68 (4H, app. t, rotamer A, H-1), 7.80 (4H, app. t, rotamer B, H-1) ppm. ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz) 24.1 (d, $^{1}J_{CP}$ = 35.9 Hz, rotamer A, C-7), 24.2 (d, $^{1}J_{CP}$ = 37.6 Hz, rotamer B, C-7), 35.89 (rotamer B, C-10), 36.7 (rotamer A, C-10), 58.8 (rotamer B, C-15), 59.0 (rotamer A, C-15), 60.1 (d, $^{2}J_{CP}$ = 9.4 Hz, rotamer A, C-8), 60.4 (br. s, rotamer B, C-8), 125.8 (rotamer B, C-13), 126.5 (rotamer A, C-13), 127.4 (rotamer B, C-14), 127.5 (rotamer A, C-14), 128.4 (d, $^{1}J_{CP}$ = 55.6 Hz, rotamer A, C-4), 129.06 (d, $^{3}J_{CP}$ = 9.8 Hz, rotamer B, C-2), 129.11 (d, $^{3}J_{CP}$ = 9.9 Hz, rotamer A, C-2) 129.4 (d, $^{1}J_{CP}$ = 55.6 Hz, rotamer B, C-4), 131.5 (d, $^{4}J_{CP}$ = 1.8 Hz, rotamer B, C-1), 131.9 (d, $^{4}J_{CP}$ = 1.7 Hz, rotamer B, C-1), 131.8 (d, $^{2}J_{CP}$ = 10.0 Hz, rotamer A, C-3), 131.9 (d, $^{2}J_{CP}$ = 10.1 Hz, rotamer B, C-3), 136.6 (rotamer A, C-11), 136.8 (rotamer B, C-11), 139.3 (rotamer A, C-12), 139.6 (rotamer B, C-12), 153.8 (rotamer A, C-9), 154.8 (rotamer B, C-9) ppm. ^{31}P{^{1}H} NMR (DMSO-d_6, 162 MHz) 10.76 (rotamer A, P-5), 12.46 (rotamer B, P-5) ppm. FTIR (ATR/ν_{max}) 3382, 3046, 2929, 2368, 1681, 1354, 1166, 1069, 999 cm^{-1}. ESI-MS *m/z* calculated for $[C_{24}H_{28}O_4NBP]^-$ 436.1844, found 436.1844.

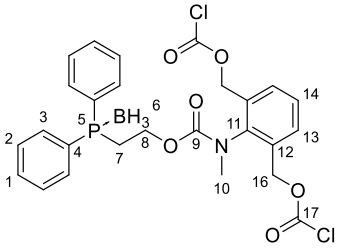
3.2.15. Synthesis of borane-2-(diphenylphosphaneyl)ethyl (2,4-bis (hydroxymethyl)phenyl)(methyl) carbamate (24)



Silyl ether **22** (0.80 g, 1.20 mmol) and Amberlyst 15 (0.20 g) were dissolved in MeOH (5 mL) and left to stir at room temperature overnight. The resin was removed by filtration and the volatile components removed under reduced pressure. The crude product was purified by silica-gel column chromatography (EtOAc:Hex 25:75) to give the desired compound **24** (0.38 g, 74 %) in a rotameric ratio of 60:40. Mp 47–50 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) 0.49–1.49 (3H, br.s, H-6), 2.41–2.60 (2H, m, rotamer B, H-7), 2.63–2.78 (2H, m, rotamer A, rotamer A, H-7), 2.87 (3H, s, rotamer A, H-10), 3.11 (3H, s, rotamer B, H-10), 3.36 (2H, br.s, rotamer A and rotamer B, H-18 and H-20), 4.10–4.25 (2H, m, rotamer A, H-8), 4.27–4.39 (2H, m, rotamer B, H-8), 4.40–4.49 (2H, m, rotamer A and rotamer B, H-17), 4.51 (2H, s, rotamer A, H-19), 4.53 (2H, s, rotamer B, H-19), 6.94 (1H, d, ^{3}J = 8.0 Hz, rotamer B, H-16), 7.01 (1H, d, ^{3}J = 8.0 Hz, rotamer A, H-16), 7.14–7.24 (1H, m, rotamer A and rotamer B, H-15), 7.35–7.52 (7H, m, rotamer A and rotamer B, H-1, H-2 and H-13), 7.62 (4H, t, $^{3}J_{HP}$ = 8.5 Hz, rotamer B, H-3), 7.72 (4H, t, $^{3}J_{HP}$ = 8.5 Hz, rotamer A, H-3) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) 25.6 (1C, d, $^{1}J_{CP}$ = 18.5 Hz, rotamer B, C-7), 26.0 (1C, d, $^{1}J_{CP}$ = 18.5 Hz, rotamer A, C-7), 37.8 (rotamer A, C-10), 38.1 (rotamer B, C-10), 60.4–61.3 (2C, m, rotamer A and rotamer B, C-8 and C-17), 64.2 (rotamer A, C-19), 64.3 (rotamer B, C-19), 126.8 (rotamer A, C-16), 126.9 (rotamer A, C-15) 127.3 (rotamer B, C-15 and C-16), 128.3 (rotamer A and rotamer B, C-13), 128.95 (2C, d, $^{1}J_{CP}$ = 28.0 Hz, rotamer A rotamer B, C-4), 129.05 (4C, d, $^{3}J_{CP}$ = 10.5 Hz, rotamer A and rotamer B, C-2), 131.5 (2C, d, $^{4}J_{CP}$ = 2.5 Hz, rotamer A and rotamer B, C-1), 132.1 (4C, d, $^{2}J_{CP}$ = 10.5 Hz, rotamer A and rotamer B, C-3), 137.9 (rotamer A, C-14), 138.2 (rotamer B, C-14), 139.1 (rotamer B, C-11), 139.9 (rotamer A, C-11), 141.0 (rotamer B, C-12), 141.3 (rotamer A, C-12), 155.5 (rotamer B, C-9), 156.4 (rotamer A, C-9) ppm. ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz) 10.97–13.24 (m, P-5) ppm. FTIR (ATR/ν_{max}) 3369, 3056, 2923, 2379, 1679, 1435, 1353, 1160, 1058, 999 cm^{-1}. ESI-MS *m/*

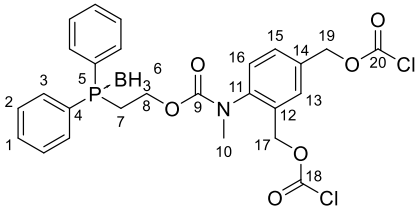
z calculated for $[C_{24}H_{28}O_4NBP]^-$ 436.1844, found 436.1833.

3.2.16. Synthesis of Borane-(2-(((2-(diphenylphosphaneyl)ethoxy) carbonyl)(methyl)amino)-1,3-phenylene)bis(methylene) bis (carbonochloridate) (25)



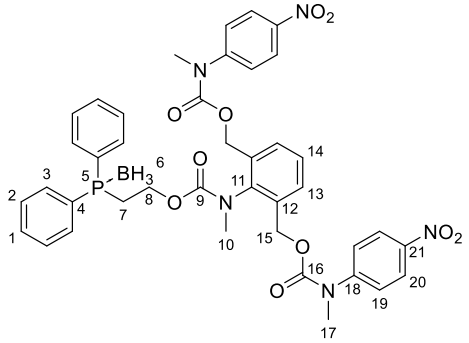
Diol **23** (0.5 g, 1.14 mmol) was dissolved in dry THF and cooled to 0 °C. A 15 % weight solution of phosgene in toluene (2.18 mL, 2.86 mmol) was added dropwise. The solution was left to stir at room temperature overnight. The volatiles were removed *in vacuo* to afford the dichloroformate **25** as a colourless oil and used immediately without further purification.

Synthesis of Borane-(4-(((2-(diphenylphosphaneyl)ethoxy)carbonyl) (methyl)amino)-1,3-phenylene)bis(methylene) bis(carbonochloridate) (26).



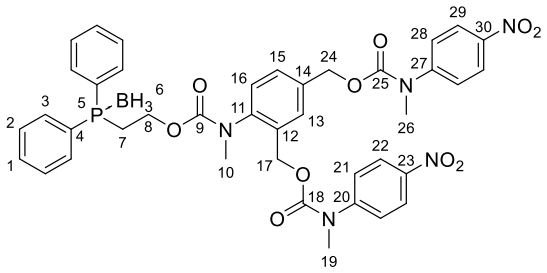
The diol **24** (0.5 g, 1.14 mmol) was dissolved in dry THF and cooled to 0 °C. A 15 % weight solution of phosgene in toluene (2.18 mL, 2.86 mmol) was added dropwise. The solution was left to stir at room temperature overnight under an inert atmosphere. The volatiles were removed *in vacuo* to afford the dichloroformate **26** as a colourless oil which was used without further purification.

3.2.17. Synthesis of borane-2-(diphenylphosphaneyl)ethyl (2,6-bis (((methyl(4-nitrophenyl) carbamoyl)oxy)methyl)phenyl)(methyl) carbamate (27)



Chloroformate **25** (0.50 g, 0.09 mmol) was dissolved in dry THF (10 mL). *N*-Methyl-4-nitroaniline (0.27 g, 1.78 mmol) and triethylamine (0.26 mL, 1.87 mmol) were added and left to stir overnight under an inert atmosphere. The precipitate was filtered off and volatile components removed from the filtrate *in vacuo*. The crude product was purified by silica-gel column chromatography (EtOAc:Hex 20:80) to give the desired compound (0.44 g, 62 %) in a rotameric ratio of 60:40. Mp 38–40 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) 0.98 (3H, br.s, rotamer A and rotamer B, H-6), 2.48–2.57 (2H, m, rotamer A, H-7), 2.70 (2H, dt, $^2J_{HP}$ = 11.3 Hz, $^3J_{HH}$ = 7.4 Hz, rotamer B, H-7), 2.89 (3H, s, rotamer B, H-10), 3.12 (3H, s, rotamer A, H-10), 3.37 (6H, s, rotamer A and rotamer B, H-17), 4.10–4.19 (2H, m, rotamer A, H-8), 4.39 (2H, dt, $^3J_{HP}$ = 10.0 Hz, $^3J_{HH}$ = 7.4 Hz, rotamer A, H-8), 5.02–5.20 (4H, m, rotamer A and rotamer B, H-15), 7.31–7.52 (13H, m, rotamer A and rotamer B, H-1 + H-2 + H-13 + H-14 + H-19), 7.59–7.67 (4H, m, rotamer A, H-3), 7.67–7.74 (4H, m, rotamer B, H-3), 8.18 (4H, AA'XX', rotamer A and rotamer B, H-20) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) 25.6 (d, $^1J_{CP}$ = 35.2 Hz, rotamer A, C-7), 26.0 (d, $^1J_{CP}$ = 35.8 Hz, rotamer B, C-7), 37.2 (rotamer B, C-17), 37.25 (rotamer A, C-17), 37.33 (rotamer B, C-10), 37.4 (rotamer A, C-10), 61.1 (d, $^2J_{CP}$ = 5.0 Hz, rotamer B, C-8), 61.4 (d, $^2J_{CP}$ = 8.6 Hz, rotamer A, C-8), 63.9 (rotamer A, C-15), 64.1 (rotamer B, C-15), 124.4 (rotamer B, C-20), 124.5 (rotamer A, C-20), 124.8 (rotamer A and rotamer B, C-19), 128.40 (d, $^1J_{CP}$ = 49.7 Hz, rotamer A, C-4), 128.43 (d, $^1J_{CP}$ = 55.7 Hz, rotamer B, C-4), 128.76 (rotamer B, C-14), 128.79 (rotamer A, C-14), 129.12 (d, $^3J_{CP}$ = 10.2 Hz rotamer A, C-2), 129.13 (d, $^3J_{CP}$ = 10.2 Hz rotamer B, C-2), 129.7 (rotamer A, C-13), 130.3 (rotamer B, C-13), 131.59 (d, $^4J_{CP}$ = 2.2 Hz rotamer B, C-1), 131.65 (d, $^4J_{CP}$ = 2.2 Hz rotamer A, C-1), 134.3 (rotamer A, C-12), 134.5 (rotamer B, C-12), 139.0 (rotamer A, C-11), 140.1 (rotamer B, C-11), 144.65 (rotamer B, C-21), 144.74 (rotamer A, C-21), 148.7 (rotamer A, C-18), 148.8 (rotamer B, C-18), 154.4 (rotamer A, C-16), 154.6 (rotamer B, C-16), 155.0 (rotamer B, C-9), 155.1 (rotamer A, C-9) ppm. ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz) 11.12 (rotamer A, P-5), 12.34 (rotamer B, P-5) ppm. FTIR (ATR/ν_{max}) 3077, 2949, 1701, 1593, 1512, 1323, 1147, 1103 cm-1 $[C_{40}H_{40}O_{10}N_5B]^-$ 792.2600, found 792.2599.

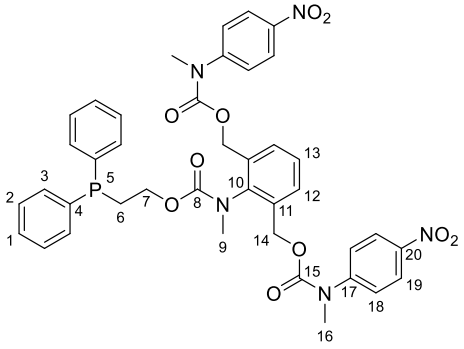
3.2.18. Synthesis of borane-2-(diphenylphosphaneyl)ethyl (2,4-bis (((methyl(4-nitrophenyl) carbamoyl)oxy)methyl)phenyl)(methyl) carbamate (28)



Chloroformate **26** (0.30 g, 0.05 mmol) was dissolved in dry THF (5.00 mL). *N*-Methyl-4-nitroaniline (0.16 g, 1.07 mmol) and triethylamine (0.16 mL, 1.12 mmol) were added and left to stir overnight under an inert atmosphere. The precipitate was filtered off and the volatiles were removed *in vacuo* to afford the crude material. The crude product was purified by silica-gel column chromatography (EtOAc:Hex 20:80) to give the desired compound **28** (0.26 g, 62 %) in a rotameric ratio of 62:48. Mp 32–35 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) 2.45–2.79 (2H, m, H-7), 2.93 (3H, s, rotamer B, H-10), 3.16 (3H, s, rotamer A, H-10), 3.34–3.43 (6H, m, rotamer A and rotamer B, H-19 and H-26), 4.10–4.28 (2H, m, rotamer A, H-8), 4.37–4.48 (2H, m, rotamer B, H-8), 5.07–5.15 (2H, m, rotamer A and rotamer B, H-17), 5.16–5.23 (2H, m, rotamer A and rotamer B, H-24), 7.04 (1H, d, ^3J = 8.0 Hz, rotamer A, H-13) 7.14 (1H, d, ^3J = 8.0 Hz, rotamer B, H-13), 7.28–7.52 (12H, m, rotamer A and rotamer B, H-1 + H-2 + H-15 + H-16 + H-21 + H-28), 7.59–7.76 (4H, m, rotamer A and rotamer B, H-3), 8.19 (4H, t, $^3J_{HP}$ = 8.5 Hz, H-3) ppm. ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz) 25.6–26.0 (rotamer A and rotamer B, C-7), 37.2–37.4 (rotamer A and rotamer B, C-19 + C-26), 37.7 (rotamer B, C-10), 38.2 (rotamer A, C-10), 60.9–61.2 (rotamer A and rotamer B, C-8), 64.0 (rotamer A, C-17), 64.2 (rotamer B, C-17), 67.4 (rotamer A, C-24), 67.5 (rotamer B, C-24), 124.5 (rotamer A and rotamer B, C-22 + C-29),

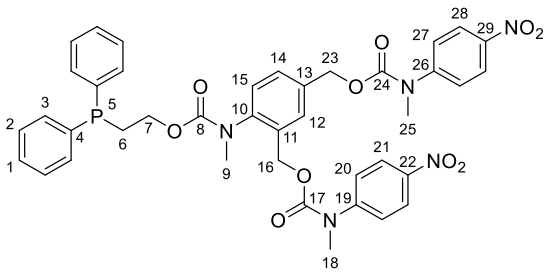
124.8 (rotamer A and rotamer B, C-21 + C-28), 127.8 (rotamer B, C-13), 128.1 (rotamer A, C-13), 128.8–129.8 (rotamer A and rotamer B, C-2 + C-4 + C-15 + C-16), 131.4 (rotamer A and rotamer B, C-1), 131.9–132.1 (rotamer A and rotamer B, C-3), 133.8–134.1 (rotamer A and rotamer B, C-14), 135.6–136.0 (rotamer A and rotamer B, C-11), 144.7 (rotamer A and rotamer B, C-23 + C-30), 148.9 (rotamer A and rotamer B, C-20 + C-27), 154.5 (rotamer A and rotamer B, C-18), 154.8 (rotamer A and rotamer B, C-25), 155.2 (rotamer A and rotamer B, C-9) ppm. FTIR (ATR/ν_{max}) 3051, 2959, 2381, 1703, 1700, 1593, 1511, 1325, 1149 cm^{-1}. ESI-MS *m/z* calculated for $[C_{40}H_{40}O_{10}N_5B]^-$ 792.2600, found 792.2600.

3.2.19. Synthesis of 2-(diphenylphosphaneyl)ethyl (2,6-bis(((methyl(4-nitrophenyl) carbamoyl)oxy)methyl)phenyl)(methyl)carbamate 3



Boron protected dendron **27** (0.197 g, 0.252 mmol) and DABCO®-33LV (0.128 g, 0.378 mmol) were dissolved in toluene (5 mL). The reaction was left to stir overnight. The volatile components were removed *in vacuo*. The crude product was purified by silica-gel column chromatography (EtOAc:Hex 25:75) to give the desired compound (0.134 g, 68 %) in a rotameric ratio of 60:40. Mp 41–43 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) 2.25 (2H, app. t, rotamer A, H-6), 2.49 (2H, app. t, rotamer B, H-6), 3.02 (3H, s, rotamer B, H-9), 3.13 (3H, s, rotamer A, H-9), 3.36 (6H, s, rotamer A and rotamer B, H-16), 4.07 (2H, app. q, rotamer A, H-7), 4.27 (2H, app. q, rotamer B, H-7), 5.09–5.24 (4H, m, rotamer A and rotamer B, H-14), 7.23–7.49 (17H, m, rotamer A and rotamer B, H-1 + H-2 + H-3 + H-12 + H-13 + H-18), 8.18 (4H, app. d, rotamer A and rotamer B, H-19) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) 28.3 (d, $^1J_{CP}$ = 14.9 Hz, rotamer A, C-6), 28.4 (d, $^1J_{CP}$ = 13.9 Hz, rotamer B, C-6), 37.19 (rotamer B, C-16), 37.23 (rotamer A, C-16), 37.35 (rotamer A, C-9), 37.42 (rotamer B, C-9), 63.7 (d, $^2J_{CP}$ = 25.5 Hz, rotamer A, C-7), 63.8 (d, $^2J_{CP}$ = 24.5 Hz, rotamer B, C-7) 64.16 (rotamer A, C-15), 64.21 (rotamer B, C-15), 124.41 (rotamer B, C-19), 124.45 (rotamer A, C-19), 124.7 (rotamer A and rotamer B, C-18), 128.5–128.8 (5C, m, rotamer A and rotamer B, C-2 + C-13), 128.9 (rotamer A, C-1), 129.0 (rotamer B, C-1), 129.7 (rotamer A, C-12), 130.3 (rotamer B, C-12), 132.7 (d, $^2J_{CP}$ = 19.0 Hz, rotamer A, C-3), 132.8 (d, $^2J_{CP}$ = 19.0 Hz, rotamer B, C-3), 134.4 (rotamer A, C-11), 134.6 (rotamer B, C-11), 137.5 (d, $^1J_{CP}$ = 12.3 Hz, rotamer A, C-4), 137.7 (d, $^1J_{CP}$ = 11.9 Hz, rotamer B, C-4), 139.3 (rotamer A, C-10), 140.2 (rotamer B, C-10), 144.6 (rotamer B, C-20), 144.7 (rotamer A, C-20), 148.8 (rotamer A, C-17), 148.9 (rotamer B, C-17), 154.5 (rotamer A, C-15), 154.6 (rotamer B, C-15), 155.3 (rotamer A and rotamer B, C-8) ppm. ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz) −23.61 (rotamer A, P-5), −22.73 (rotamer B, P-5) ppm. FTIR (ATR/ν_{max}) 2923, 1702, 1513, 1324, 1146, 1102 cm^{-1}. ESI-MS *m/z* calculated for $[C_{40}H_{39}O_{10}N_5P]^+$ 780.2429, found 780.2431.

3.2.20. Synthesis of 2-(diphenylphosphaneyl)ethyl (2,4-bis(((methyl(4-nitrophenyl) carbamoyl)oxy) methyl)phenyl)(methyl)carbamate **4**



Boron protected dendron **28** (0.150 g, 0.189 mmol) and DABCO®-33LV (0.100 g, 0.284 mmol) were dissolved in toluene (2.00 mL). The reaction was left to stir overnight. The volatiles were removed *in vacuo*. The crude product was purified by silica-gel column chromatography (EtOAc:Hex 25:75) to give the desired compound (0.098 g, 68 %) in a rotameric ratio of 62:48. Mp 34–36 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) 2.21–2.38 (2H, m, rotamer A, H-6), 2.44–2.56 (2H, m, rotamer B, H-6), 3.05 (3H, s, rotamer B, H-9), 3.18 (3H, s, rotamer A, H-9), 3.37 (6H, s, rotamer A, H-18 + H-25), 3.40 (6H, s, rotamer B, H-18 + H-25), 4.07–4.19 (2H, m, rotamer A, H-7), 4.25–4.38 (2H, m, rotamer B, H-7), 5.14–5.23 (4H, m, rotamer A + rotamer B, H-16 + H-23), 7.12 (1H, d, ^3J = 8.0 Hz, rotamer A, H-15), 7.17 (1H, d, ^3J = 8.0 Hz, rotamer B, H-15), 7.28–7.50 (16H, m, rotamer A + rotamer B, H-1 + H-2 + H-3 + H-12 + H-14 + H-27), 8.18 (4H, AA'XX', rotamer A, H-28), 8.19 (4H, AA'XX', rotamer B, H-28) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) 28.1–28.5 (m, rotamer A and rotamer B, C-6), 37.0–37.2 (m, rotamer A and rotamer B, C-18), 37.8 (rotamer B, C-9), 38.1 (rotamer A, C-9), 63.4–67.0 (m, rotamer A and rotamer B, C-7), 64.2 (rotamer A and rotamer B, C-23), 67.3 (rotamer A and rotamer B, C-16), 124.3 (rotamer A and rotamer B, C-21 + C-28), 124.7 (rotamer A and rotamer B, C-20 + C-27), 127.7–129.7 (m, rotamer A and rotamer B, C-1 + C-2 + C-4 + C-12 + C-14 + C-15), 132.5–132.9 (m, rotamer A and rotamer B, C-3), 133.9 (rotamer A, C-13), 134.0 (rotamer B, C-13), 134.5 (rotamer B, C-11), 135.7 (rotamer A, C-11), 137.4–137.8 (rotamer A and rotamer B, C-10), 144.6 (rotamer A and rotamer B, C-22 + C-29), 148.8 (rotamer A and rotamer B, C-19 + C-26), 154.4 (rotamer A and rotamer B, C-17), 154.6 (rotamer A and rotamer B, C-24), 155.4 (rotamer A and rotamer B, C-8) ppm. ^{31}P{^{1}H} NMR -23.17 (rotamer A, P-5), −22.23 (rotamer B, P-5) ppm. FTIR (ATR/ν_{max}) 2930, 1705, 1701, 1593, 1516, 1328, 1150, 1099 cm^{-1}. ESI-MS *m/z* calculated for $[C_{40}H_{39}O_{10}N_5P]^+$ 780.2429, found 780.2422.

4. Conclusions

In summary, the synthesis and characterisation of two positionally isomeric aniline-core dendrons **3** and **4** has been described. The use of borane-phosphorous adducts to facilitate the synthesis, by masking the trigger group, has been set out. The alkylation and fragmentation of **3** and **4**, under basic conditions, has been described and compared to the corresponding non-amplified molecules. The importance of detailed consideration of the favoured conformation of such compounds and its influence on their subsequent fragmentation is highlighted. Specifically, the 2,6-disubstituted geometry of the dendritic core of **3** led, after cleavage of the trigger group, to a particularly stable intermediate **30**. Unlike previously reported aniline-based dendrons [27,28], N-methylation of the aniline nitrogen precludes the amino group achieving planarity with the benzene ring, preventing its lone pair from participating in fragmentation of the dendritic core. By contrast, the 2,4-disubstituted geometry of **4** leads to intermediate **32** wherein the *N*-methyl group can lie in the plane of the ring, facilitating self-immolation. In earlier work on aniline-based self-immolative molecules, careful consideration of reactive conformation led Phillips to the development of a molecule that fragmented with release of phenols under neutral conditions [37]. The comparative complexity of synthesis and ease of

fragmentation between amplified and non-amplified molecules under the same conditions was addressed with the finding, in these cases, that the former are not always the better option.

CRediT authorship contribution statement

Alexander G. Gavriel: Writing – original draft, Investigation, Formal analysis. **Flavien Leroux:** Writing – original draft, Investigation, Formal analysis. **Ann M. Chippindale:** Formal analysis. **Mark R. Sambrook:** Writing – review & editing, Resources, Project administration. **Wayne Hayes:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization. **Andrew T. Russell:** Writing – review & editing, Supervision, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2024.134377.

Data availability

Data will be made available on request.

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