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Synthesis and reactivity profiles of phosphinated poly(alkyl aryl ether) dendrimers

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Abstract—Poly(alkyl aryl ether) dendrimers were utilized to synthesize a series of new triphenylphosphine functionalized dendrimers. Zero, first, second and third generation dendrimers, carrying 3, 6, 12 and 24 triphenylphosphine units, were prepared and characterized. The new triphenylphosphine containing dendrimers were assessed for their reactivity profiles and in this instance, the dendrimers were used as reagents to mediate Mitsunobu etherification reaction between phenol and various primary, secondary and benzylic alcohols. In addition, dendritic poly-phenols were also tested in an *O*-benzylation reaction. A monomeric methoxy group attached triphenylphosphine acted as a control for comparison of reactivity profiles of dendrimers. It was observed that the etherification reaction was mediated efficiently by the dendritic reagent, and in addition, the dendritic phosphine oxide reagents could be recovered quantitatively by precipitation methods. The recovered dendritic phosphine oxides were reduced subsequently to the corresponding phosphines and used as reagents for the Mitsunobu reaction, repetitively.
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1. Introduction

Hyperbranched macromolecules with uniform branches at every branching location are referred generally as dendritic macromolecules. Ever since their prominence in the literature,[1] dendritic macromolecules have been explored in detail as to their synthesis, physical and chemical properties.[2] Uniform branching throughout the structure is one of the unique structural features of dendrimers. This particular structural feature leads to uniform distribution of chain ends within the molecule and it is of immediate interest to find out whether this uniform distribution of chain ends is beneficial for exploring the dendritic architectures further in conjunction with other functional entities of chemical, biological and material relevance. Thus, dendrimers of various constitutions have been functionalized or modified with different types of functional entities.[2] The evolution of the so-called 'dendritic effect' has been observed in few instances, providing credibility to properties arising due to dendritic architecture.[3] Organometallic catalysis is one of the beneficiaries of dendritic structures and many different organometallic complexes have been synthesized and studied extensively.[4] Dendritic catalysts most often react under homogeneous reaction conditions and the reaction kinetics and product selectivities are comparable or better in comparison to the reactions conducted with monomeric catalysts. Phosphination of dendrimers provides an easy access to dendritic organometallic complexes and various phosphinated dendrimers and their metal complexes have thus been prepared and their catalytic properties studied.[5] We were interested in the synthesis and studies of triphenylphosphine containing dendrimers, in view of the manifold reactions known to involve triphenylphosphine as a reagent, apart from its use as a ligand for metal complexations. Here, we describe the synthesis and an assessment of the reactivity profiles of a series of triphenylphosphine containing dendrimers. One of the phenyl groups of triphenylphosphine was involved for covalent attachment at the peripheries of dendrimers and dendrimers carrying 3, 6, 12 and 24 triphenylphosphine units were thus installed at the peripheries of poly(alkyl aryl ether) dendrimers. Following the preparation, these dendrimers were assessed for their reactivity profiles as reagents for Mitsunobu etherification reaction. Details of synthesis and studies are presented herein.

2. Results and discussion

2.1. Synthesis of triphenylphosphine functionalized monomer

The dendrimers of choice for functionalization with

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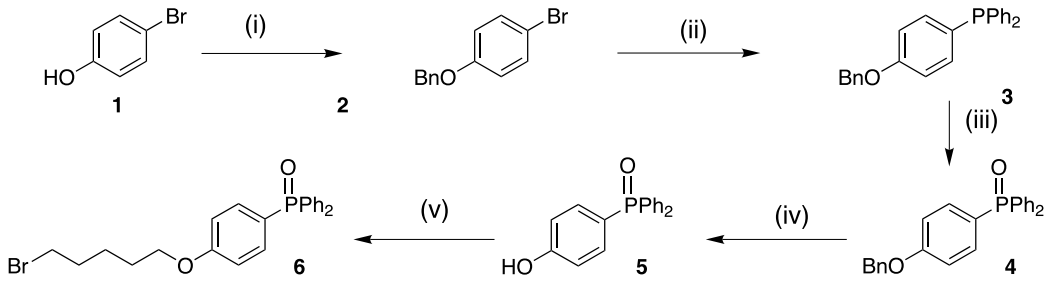
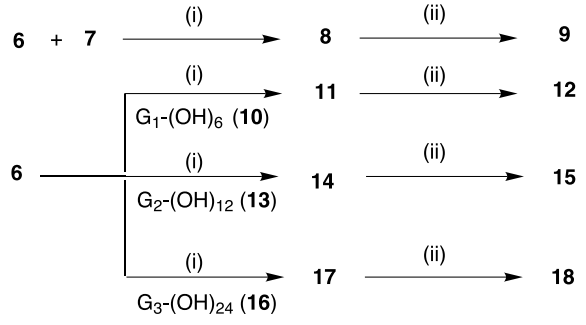


Scheme 1. (i) BnBr, K_2CO_3, 18-Crown-6 (cat.), Me_2CO, reflux, 7 h, 89%; (ii) (a) Mg, I_2 (cat.), THF, reflux, 1 h; (b) $ClPPh_2$, THF, 0 °C to rt, 15 h, 60%; (iii) 30% H_2O_2, Me_2CO, reflux, 1 h, 70%; (iv) Pd–C, EtOH, H_2 (60 bar), 60 °C, 48 h, 72%. (v) 1,5-dibromopentane, K_2CO_3, 18-Crown-6 (cat.), DMF, 70 °C, 7 h, 86%.

triphenylphosphine moiety were the phloroglucinol based poly(alkyl aryl ether) dendrimers, reported recently.[6] Phenolic hydroxyl groups present at the peripheries of these dendrimers were utilized to alkylate a phosphine oxide containing monomer unit (**6**). The monomer **6** was obtained by following a sequence of (i) *O*-benzylation of 4-bromophenol (**1**) to afford **2**; (ii) phosphination with chlorodiphenyl phosphine to **3**; (iii) oxidation of phosphine to phosphine oxide (**4**); (iv) benzyl group deprotection to **5** and (v) alkylation of **5** with dibromopentane to afford **6**, in an overall 23% yield (Scheme 1).

2.2. Synthesis of triphenylphosphine functionalized dendrimer

A three-fold *O*-alkylation of **5** with 1,3,5-tris(5-bromopentyloxy)benzene (**7**)[6] led to the isolation of zero generation triphenylphosphine oxide containing dendrimer (**8**). *O*-Alkylations of first (G_1-$(OH)_6$) (**10**), second (G_2-$(OH)_{12}$) (**13**) and third G_3-$(OH)_{24}$ (**16**) generation dendrimers with the monomer **6**, in the presence of K_2CO_3 and 18-C-6, afforded the corresponding 6 (**11**), 12 (**14**) and 24 (**17**) phosphine oxide containing dendrimers, respectively (Scheme 2). The phosphine oxide containing dendrimers were purified (SiO_2) and were obtained as glassy substances soluble in common organic solvents. Reduction of the phosphine oxide to phopshine was conducted using $CeCl_3$/LAH reagent system[7] in THF (Scheme 2) and the reduction reaction afforded the desired products in nearly quantitative yields. The molecular structures of the phosphinated dendrimers **9**, **12**, **15** and **18** are presented in Figures 1–3. The phosphinated dendrimers were freely soluble in $CHCl_3$, CH_2Cl_2, THF and PhMe. In terms of loading, the triphenylphosphine content was calculated to be 2.58, 2.15, 2.36 and 2.49 mmol/g for the zero (**9**), first (**12**), second (**15**) and third (**18**) generation dendrimers, respectively.



Scheme 2. (i) K_2CO_3, 18-C-6 (cat.), DMF, reflux; (ii) $CeCl_3$, $LiAlH_4$, THF, 60 °C, 5 h.

2.3. Characterization

The purities of new synthesized dendrimers were examined by gel permeation chromatography (GPC) (Phenogel 500 Å, 300×7.80 mm), eluting with THF (flow rate: 1 mL/min., UV–vis detector set at 254 nm). The GPC chromatograms of each phosphine oxide functionalized dendrimers

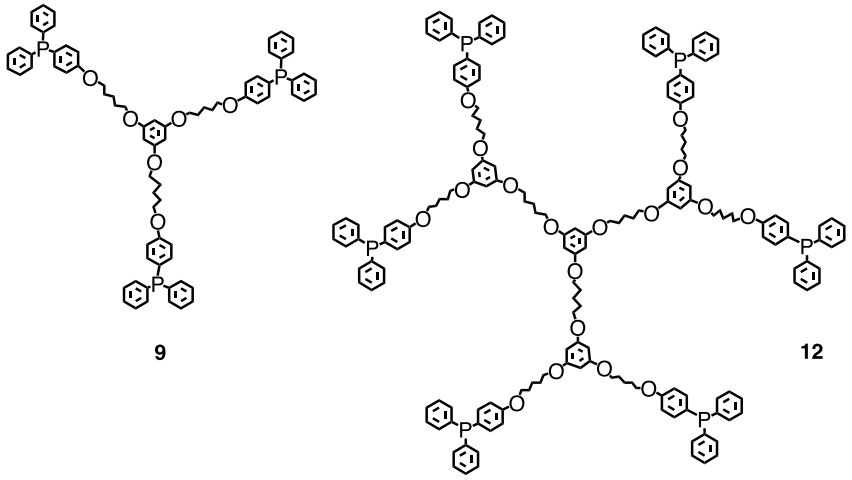


Figure 1. Molecular structures of zero (**9**) and first (**12**) generation phopshinated poly(alkyl aryl ether) dendrimers.

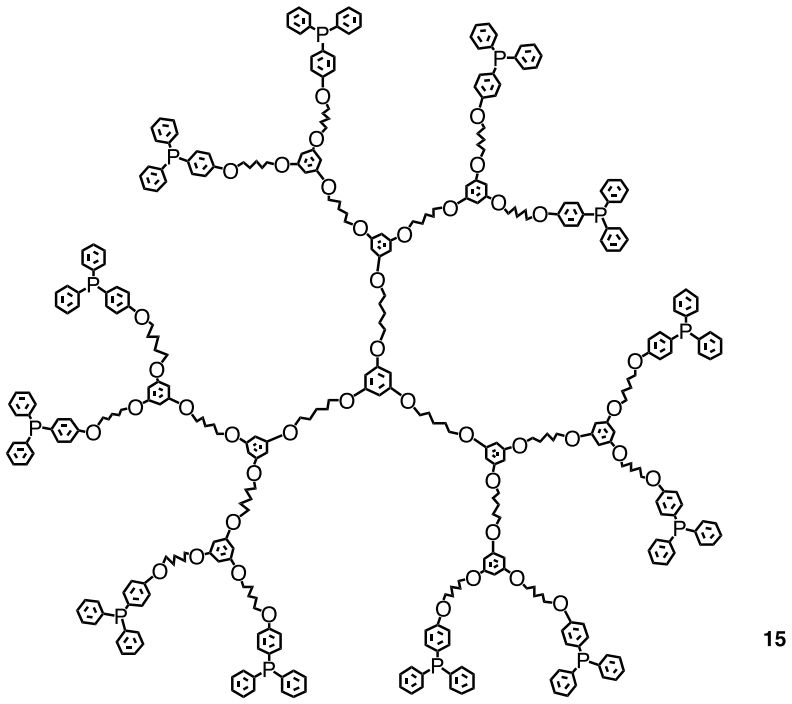


Figure 2. Molecular structure of the second generation phopshinated dendrimer **15**.

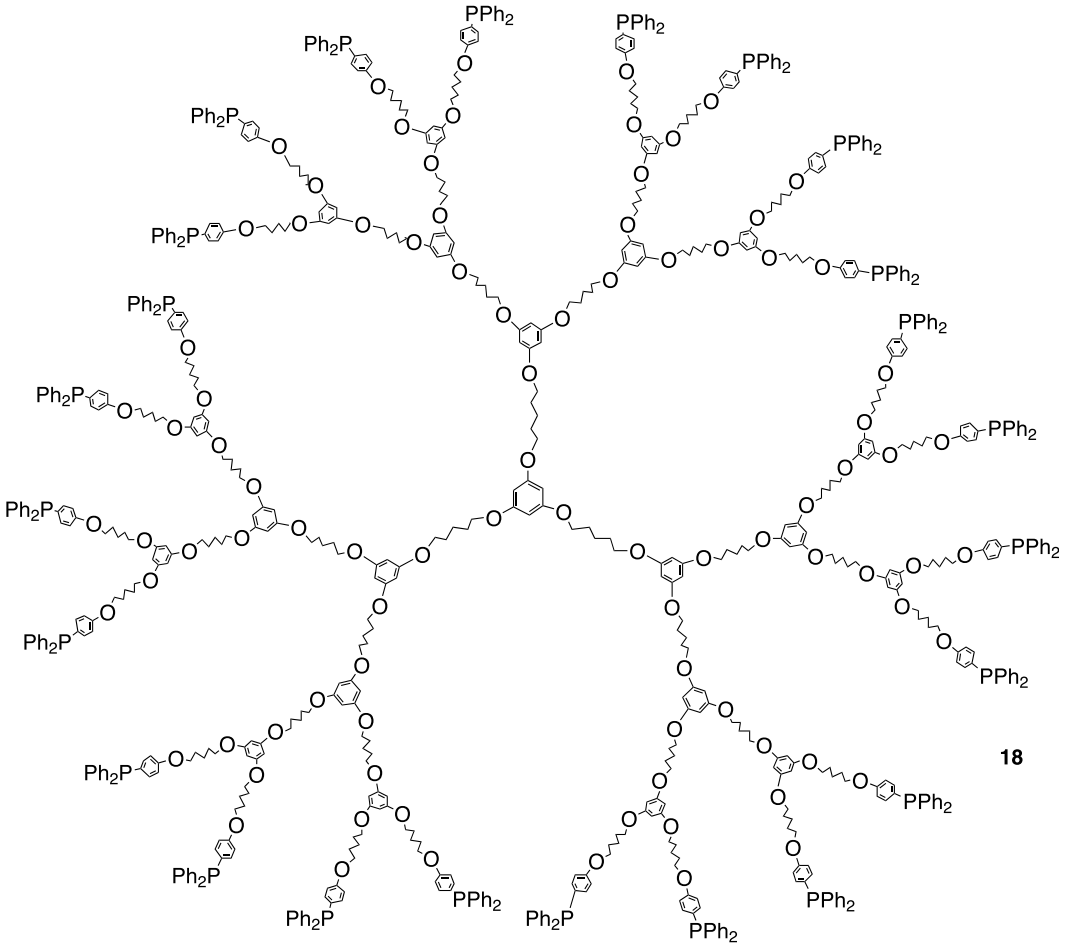


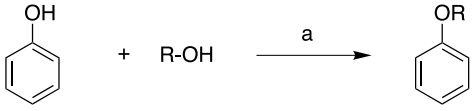
Figure 3. Molecular structure of third generation phosphinated dendrimer **18**.

exhibited decreasing retention times centered at: **8**: 9.31 min, **11**: 8.26 min, **14**: 7.75 min and **17**: 7.58 min.

The phosphine oxide and the phosphinated dendrimers were characterized by ^{1}H, ^{13}C, ^{31}P NMR spectroscopies and elemental composition analysis. Mass spectral characterization was possible for the smaller molecular weight compounds, that of larger molecular weight dendrimers, ionizations by either FAB-MS or MALDI-TOF MS or ES-MS were not successful. In the ^{1}H NMR spectra, the triphenylphosphine oxide unit appeared as multiplets between 7.70 and 7.40 ppm, whereas in the corresponding triphenylphosphine unit in dendrimers, the aromatic rings of the phosphine unit appeared as multiplets between 7.30 and 7.20 ppm. The ^{31}P NMR signals for the phosphine oxide and phosphine moieties in all the compounds were observed at 29.0 and −7.0 ppm, respectively. Elemental composition analyses confirmed further the constitution of each compound.

2.4. Assessment of the reactivity profiles of the phosphinated dendrimers

The reactivities of the phosphinated dendrimers were tested, by involving them as a reagent in an etherification reaction, namely, the Mitsunobu reaction.[8] The reaction of phenol with various alcohols was conducted using diisopropylazidodicaboxylate (DIAD) and dendritic phosphines. The Mitsunobu reaction is prominent in etherification and esterification, in which phosphonium adduct formation between DIAD and phosphine initiates the reaction, leading to an ester or ether depending on the substrate. A systematic mechanistic study has previously been performed[9] on the Mitsunobu reaction, as have reactions involving modified phosphines and azidodicarboxylates.[10] In the etherification reaction performed herein, DIAD and dendritic phosphines (1.1 M equiv, on per phosphine unit basis) were used with respect to phenol and the alcohols (each 1 M equiv) (Scheme 3). Results of the Mitsunobu reaction are presented in Table 1. A good conversion of the alcohols to aryl ethers was observed, for all the dendritic phosphines and the yields were comparable to that of the monomer phosphine reagent, namely, 4-methoxyphenyldiphenyl phosphine **19**.[11]



Scheme 3. Phenol (1.0 M equiv), alcohol (1.0 M equiv), DIAD (1.1 M equiv) and monomeric or dendritic phosphines **9**, **12**, **15** and **18** (1.1 M equiv on a per phosphine unit basis), CH_2Cl_2, room temperature.

Table 1. Mitsunobu etherification of phenol with different alcohols

Alcohol	*n*-Butanol (% Yield)	2-Propanol (% Yield)	Allyl alcohol (% Yield)	Benzyl alcohol (% Yield)
19	84	85	89	90
9	100	77	86	80
12	82	93	73	74
15	92	93	90	78
18	88	87	79	82

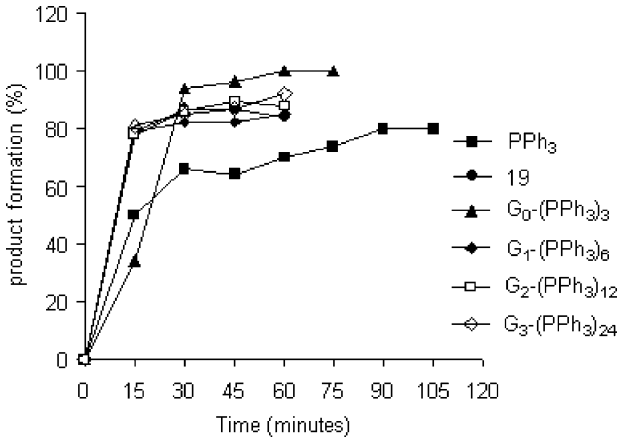
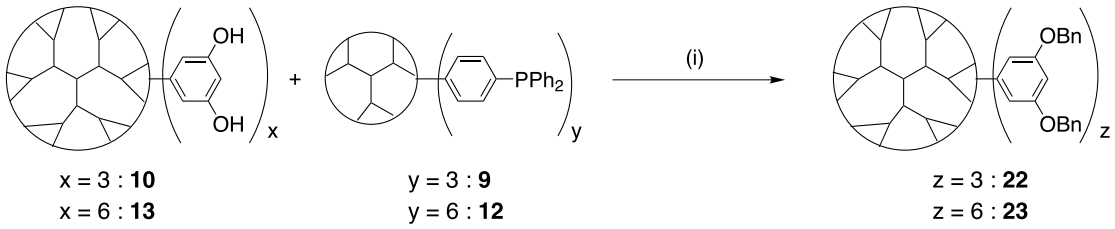


Figure 4. Formation of *n*-butyl phenyl ether with dendritic phosphines.

The time course versus product formation was also monitored by HPLC and the results are presented in Figure 4, for the reaction between phenol and *n*-butanol, mediated by DIAD and dendritic phosphines. The etherification involving these two substrates was facile with the dendritic phosphines, as well as with the monomer **19**. Reaction mediated by PPh_3 was also tested, however, the product formation was sluggish with this reagent. In the case of the dendritic phosphines and the monomer **19**, the reaction was almost complete within the first 15 min and 75–90% of the product formed within this period. In comparison, PPh_3 reaction required 90 min for 75% formation of the product. Very similar reactivity profiles of dendritic phosphines (**9**, **12**, **15** and **18**) and the monomeric phosphine **19** indicate that each phosphine unit on the dendritic scaffold act independently and in an unconnected manner. Upon completion of the reaction, solvents were removed and Et_2O was added to the residue, which solubilized the aryl ether product and the reduced DIAD, leaving the phosphine oxide to be separated from the solution. The Et_2O solution was evaporated and the resulting residue was added to petroleum ether, which solubilized the aryl ether product, leaving the reduced DIAD un-dissolved. In this manner, the aryl ether products were obtained in excellent yields and purities, devoid of reduced DIAD and phosphine oxide reagents. Further purification by column chromatography was required in order to remove un-reacted phenol and the alcohol.

The reactivities of the dendritic phosphines were also tested in the alkylations of different generations of dendritic phenols. Thus poly-benzylation of the phenolic hydroxyl group functionalized poly(alkyl aryl ether) dendrimer was performed in the presence of dendritic phosphines (Scheme 4). 5-Benzyloxy resorcinol (**20**) and **19** were used as monomeric analogs of phenol and phosphine, respectively. Compounds, **10**, **13** and **20** were thus *O*-benzylated, by utilizing **9**, **12** and **19** to afford tri-*O*-benzylated phloroglucinol (**21**), G_1-$(OBn)_6$ (**22**) and G_2-$(OBn)_{12}$ (**23**), respectively (Fig. 5). The time course versus product formation was monitored by HPLC and the results are presented in Table 2, for the reaction between polyphenols and benzyl alcohol, mediated by DIAD and the dendritic/monomeric phosphines. Di-*O*-benzylation of 5-benzyloxy-resorcinol led to the isolation of the



Scheme 4. (i) Dendritic phenol (1 M equiv) (**10** or **13**), triphenylphosphine (1.1 M equiv on per phosphine basis) (**9** or **12**), BnOH (1 M equiv), DIAD (1.1 M equiv), THF, room temperature.

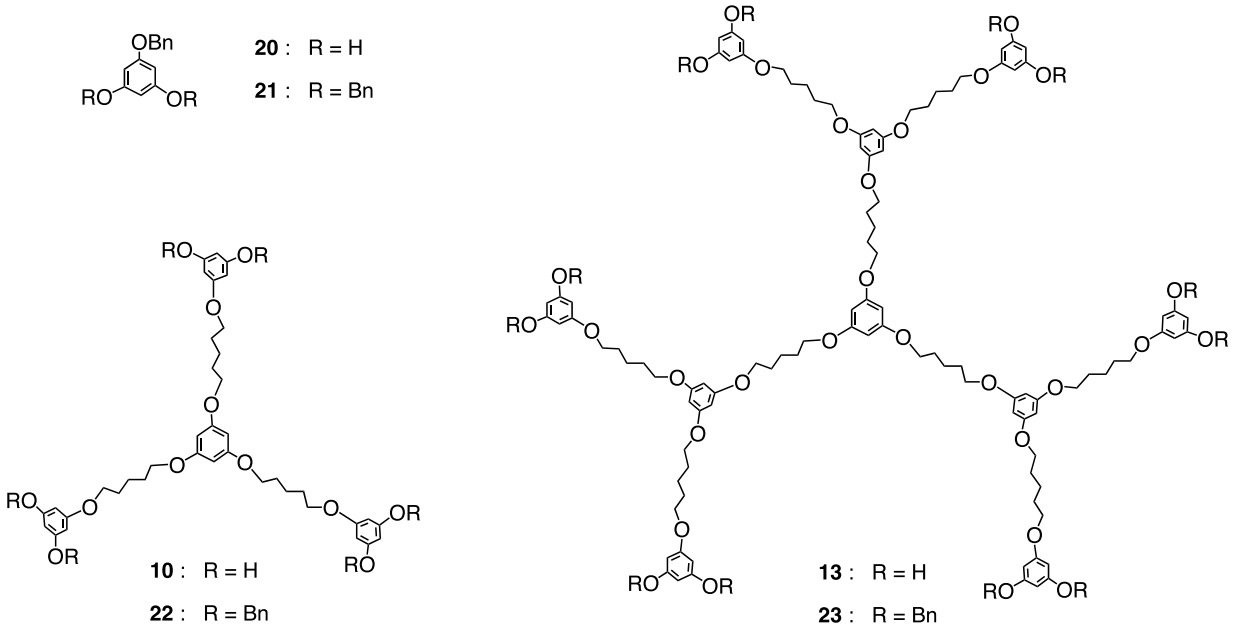


Figure 5. Molecular structures of monomeric (**20**), dendritic phenols (**10** and **13**) and their corresponding benzylated derivatives (**21**, **22** and **23**).

Table 2. Polybenzyl ether formation with dendritic phosphines

Entry	Phenol	Phosphine	Time (h)	Yield (%)
1	**10**	**9**	2.5	77
2	**13**	**9**	3.0	75
3	**20**	**9**	1.0	74
4	**10**	**12**	2.5	75
5	**13**	**12**	3.0	77
6	**20**	**12**	1.0	87
7	**10**	**19**	2.5	82
8	**13**	**19**	3.0	79
9	**20**	**19**	0.75	94

corresponding tri-*O*-benzylated phloroglucinol in good yield within 45 min. Polybenzylation of **10** and **13** afforded moderate yield (70–77%) of product in 3 h and prolonged reaction time did not improve the yield.

After securing the triphenylphosphine oxide by the solvent treatments (vide supra), reduction to the corresponding triphenylphosphines was conducted using $CeCl_3$/LAH, in quantitative yield. The reduced reagents were used again for the Mitsunobu reaction and the reaction could be conducted efficiently as that of first cycle reagents. The oxidation of the dendritic phosphine to mediate the etherification reaction, the reduction of the resulting phosphine oxide to the phosphine and subjecting the phosphine in the etherification reaction could be conducted several times, without any loss in efficiency of the reactions (Table 3).

Table 3. Percentage recovery of the phopshine oxide functionalized dendrimers after each cycle of reduction and reuse of the resulting phosphine in etherification reactions

Dendrimer	Cycle			
	1	2	3	4
8	92	92	93	93
11	>95	>95	>95	95
14	Quant.	Quant.	Quant.	Quant.
17	Quant.	Quant.	Quant.	Quant.

3. Conclusion

The scope and wide application of the Mitsunobu reaction is well documented.[8] The generic trialkyl and triaryl phosphines have led to the development of modified reagents, which assist in simplifying the purification of the reaction mixtures. Several modified phosphines, polymeric phosphines and fluorous phosphines have been developed to make the Mitsunobu reaction a more versatile approach for several etherification, esterification and amidation reactions.[10] The dendritic regents that we have presented

herein are a useful addition as a new types of triarylphosphine reagent.

4. Experimental

4.1. General remarks

4.1.1. Compound 2. To a solution of 4-bromophenol (25.0 g, 144.4 mmol) in Me_2CO (100 mL), BnBr (24.71 g, 144.5 mmol), K_2CO_3 (19.9 g, 144.5 mmol), 18-C-6 (cat.) were added and refluxed for 7 h. The reaction mixture was filtered, solvents removed in vacuo, the resulting residue dissolved in $CHCl_3$ (150 mL), washed with water (2× 150 mL), the organic portion dried (Na_2SO_4) and concentrated to afford **2**, as a white solid (34.0 g, 89%). TLC: R_f 0.65 (Hexane/EtOAc=98:2). Mp: 59–60 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.99 (s, 2H), 6.83 (d, J=6.9 Hz, 2H), 7.34–7.38 (m, 7H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 70.1, 113.1, 116.6, 127.4, 128.1, 128.6, 132.2, 136.5, 157.8. Anal. Calcd for $C_{13}H_{11}BrO$: C, 59.34; H, 4.21; found: C, 59.46; H, 4.35.

4.1.2. Compound 3. To a suspension of Mg (1.01 g, 41.65 mmol) in THF (7 mL) and I_2 (25 mg), **2** (10.0 g, 37.9 mmol) in THF (20 mL) was added dropwise, refluxed for 1 h and cooled to 0 °C. Chlorodiphenyl phosphine (9.61 g, 43.6 mmol) in THF (5 mL) was added over a period of 10 min and stirred for 15 h at room temperature. The reaction mixture was quenched with aq. HCl (5%), washed with $CHCl_3$ (200 mL), followed by H_2O (2×100 mL), dried (Na_2SO_4), concentrated and purified to afford phosphine, **3**, as a colorless solid (8.4 g, 60%). TLC: R_f 0.72 (PhMe). Mp: 48–50 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.99 (s, 2H), 6.93 (d, J=7.5 Hz, 2H), 7.23–7.39 (m, 17H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 69.8, 115.0 (d, J=6.8 Hz), 127.42, 127.9 (d, J=9.8 Hz), 128.4 (d, J=7.6 Hz), 128.5, 129.4, 133.4 (d, J=18.1 Hz), 135.5 (d, J=21.1 Hz), 136.6, 137.8 (d, J=11.3 Hz), 158.7, 159.5; ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ: −7.0; HR-MS *m/z*: calcd for $C_{25}H_{21}OP$ $[M+1]^+$: 369.1408; found: 369.1413 (50%). Anal. Calcd for $C_{25}H_{21}OP$: C, 81.5; H, 5.75; found: C, 81.42; H, 5.96.

4.1.3. Compound 4. Aq. H_2O_2 (30%) (3.33 g, 97.8 mmol) was added cautiously to an ice-cooled solution of **3** (18.0 g, 48.9 mmol) in Me_2CO (75 mL) and refluxed for 1 h. The solvent was removed in vacuo. PhMe (100 mL) and aq. NaOH (10%, 70 mL) were added to the resulting residue and stirred for 1 h at room temperature. The organic layer was separated, washed with brine (2×150 mL), dried (Na_2SO_4), concentrated. Upon addition of Et_2O (70 mL), **4** precipitated, as a white solid (13.2 g, 70%). TLC: R_f 0.5 (EtOAc/PhMe=7:3). Mp: 121–122 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.06 (s, 2H), 7.02 (d, J=6.9 Hz, 2H), 7.26–7.69 (m, 17H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 69.8, 114.7 (d, J=12.9 Hz), 127.2, 127.9, 128.2 (d, J=11.9 Hz), 128.4, 131.6, 131.8 (d, J=9.9 Hz), 133.7 (d, J=11.2 Hz), 135.9, 161.5; ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz,) δ: 27.8; HR-MS *m/z*: calcd for $C_{25}H_{21}O_2P$ $[M+1]^+$: 385.1357; found: 385.1364 (100%). Anal. Calcd for $C_{25}H_{21}O_2P$: C, 78.11; H, 5.51; found: C, 78.02; H, 5.59.

4.1.4. Compound 5. A solution of **4** (20 g, 52.1 mmol) in EtOH (100 mL) was admixed with Pd–C (10%, 2.0 g), stirred under H_2 blanket (60 atm) at 60 °C in an autoclave for 48 h. The reaction mixture was filtered, concentrated and dried in vacuo to afford **5** as a white solid (11.1 g, 72%). TLC: R_f 0.27 (PhMe/EtOAc=7:3). Mp: 240 °C. IR (KBr, cm^{-1}): 3437.5; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.94 (dd, $^3J_{HH}$=8.7 Hz, $^4J_{PH}$=2.1 Hz, 2H), 7.40–7.67 (m, 12H), 10.08 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 115.3 (d, J=13.6 Hz), 127.8 (d, J=12.1 Hz), 131.3 (d, J=10.6 Hz), 131.6, 133.0, 133.3 (d, J=10.6 Hz), 160.7; ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz) δ: 29.8; HR-MS *m/z*: calcd for $C_{18}H_{15}O_2P$ $[M+1]^+$: 295.0888; found: 295.0874 (100%). Anal. Calcd for $C_{18}H_{15}O_2P$: C, 73.46; H, 5.14; found: C, 73.35; H, 5.25.

4.1.5. Compound 6. To a solution of **5** (10.0 g, 34.01 mmol) in DMF (25 mL), 1,5-dibromopentane (23.0 g, 102 mmol), K_2CO_3 (5.64 g, 40 mmol) and 18-crown-6 (cat.) were added and stirred at 70 °C for 7 h. Solvents were removed in vacuo and the resulting crude mixture dissolved in $CHCl_3$ (100 mL), washed with H_2O (2×100 mL), dried (Na_2SO_4), concentrated and purified (SiO_2) to afford **6**, as a brown oil (12.9 g, 86%). TLC: R_f 0.38 (PhMe/EtOAc=1:1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.62 (m, 2H), 1.78 (m, 2H), 1.93 (m, 2H), 3.43 (t, J=6.6 Hz, 2H), 4.00 (t, J=6.0 Hz, 2H), 6.95 (d, $^3J_{HH}$=7.5 Hz, 2H), 7.45–7.69 (m, 12H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 24.7, 28.2, 32.3, 33.5, 67.6, 114.5 (d, J=13.0 Hz), 128.4 (d, J=11.9 Hz), 131.8, 132.0 (d, J=10.0 Hz), 133.4, 133.9 (d, J=11.2 Hz), 162.0; ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz) δ: 28.0; HR-MS *m/z*: calcd for $C_{23}H_{24}BrO_2P$ $[M+Na]^+$: 465.0595; found: 465.0595 $[M+Na]^+$(100%), 467.0618 $[M+Na+2]^+$(98%). Anal. Calcd for $C_{23}H_{24}BrO_2P$: C, 62.31; H, 5.46; found: C, 61.91; H, 5.57.

4.1.6. Compound 8. A mixture of **7**[6] (0.41 g, 0.71 mmol), **5** (0.75 g, 2.55 mmol), K_2CO_3 (0.15 g, 1.1 mmol) and 18-crown-6 (cat.) in DMF (20 mL) was stirred at 70 °C for 12 h. Solvents were then removed in vacuo, the resulting residue dissolved in CH_2Cl_2, washed with water, dried, concentrated and purified (SiO_2, $CHCl_3$/MeOH=95:5) to afford **8**, as colorless oil (0.9 g, 92%). TLC: R_f 0.59 ($CHCl_3$/MeOH=96:4). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.62 (m, 6H), 1.86 (m, 12H), 3.93 (t, J=6.3 Hz, 6H), 4.01 (t, J=6.0 Hz, 6H), 6.07 (s, 3H), 6.95 (dd, $^3J_{HH}$=8.7 Hz, $^4J_{PH}$=1.8 Hz, 6H), 7.42–7.69 (m, 36H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.7, 28.8, 28.9, 67.7, 67.9, 93.8, 114.5 (d, J=12.8 Hz), 128.4 (d, J=11.3 Hz), 131.8, 132.0 (d, J=9.8 Hz), 132.2, 133.6, 133.9 (d, J=11.3 Hz), 160.9, 161.9, 162.0; ^{31}P{^{1}H} NMR ($CDCl_3$, 162.0 MHz) δ: 29.4; MALDI-TOF-MS *m/z*: calcd for $C_{75}H_{75}O_9P_3$: 1213; found: 1213 $[M]^+$(15%), 1235.5 $[M+Na]^+$(100%), 1251.6 $[M+K]^+$(70%). Anal. Calcd for $C_{75}H_{75}O_9P_3$: C, 74.24; H, 6.23; found: C, 73.77; H, 7.1.

4.1.7. Compound 9. To a stirred suspension of $CeCl_3$ (0.29 g, 1.16 mmol) in THF (6 mL), $LiAlH_4$ (0.059 g, 1.55 mmol) and **8** (0.312 g, 0.26 mmol) in THF (3 mL) were added and warmed at 60 °C for 4 h. The reaction mixture was quenched with water, filtered, concentrated and purified by passing through a pad of SiO_2 (2% EtOAc/PhMe) to afford compound **9**, as colorless oil (0.3 g, 98%). TLC R_f 0.65 (PhMe/EtOAc=98:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.63 (m, 6H), 1.83 (m, 12H), 3.95 (m, 12H), 6.06

(s, 3H), 6.87 (d, J=7.8 Hz, 6H), 7.23–7.30 (m, 36H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.7, 28.9, 67.6, 67.7, 93.8, 114.7 (d, J=7.6 Hz), 128.4 (d, J=7.6 Hz), 133.4 (d, J=19.6 Hz), 135.6 (d, J=21.1 Hz), 137.9 (d, J=9.8 Hz) 159.8, 160.8; ^{31}P{^{1}H} NMR ($CDCl_3$, 162.0 MHz) δ: −6.9. Anal. Calcd for $C_{75}H_{75}O_6P_3$: C, 77.3; H, 6.49; found: C, 77.2, H, 6.51.

4.1.8. Compound 11. A mixture of **10**[6] (0.22 g, 0.31 mmol), **6** (1.0 g, 2.25 mmol), K_2CO_3 (0.311 g, 2.25 mmol) and 18-crown-6 (cat.) in DMF (10 mL) was heated at 70 °C for 48 h. Solvents were then removed in vacuo and the resulting residue was dissolved in CH_2Cl_2, washed with water, dried (Na_2SO_4) and concentrated. Excess of **6** was removed by triturating with Et_2O washings and the residue was purified further (SiO_2, $CHCl_3$/MeOH=95:5) to afford **11**, as a brown foamy material (0.69 g, 76%). TLC R_f 0.52 ($CHCl_3$/MeOH=96:4). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.62 (br, 18H), 1.82 (br, 36H), 3.92 (br, 24H), 4.01 (t, J=5.7 Hz, 12H), 6.06 (s, 12H), 6.94 (dd, $^3J_{HH}$=8.4 Hz, $^4J_{PH}$=1.8 Hz, 12H), 7.44–7.67 (m, 72H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.6, 28.7, 28.8, 28.9, 67.6, 67.7, 93.7, 114.4 (d, J=13.1 Hz), 128.3 (d, J=11.8 Hz), 131.7, 131.8, 131.9 (d, J=10.0 Hz), 132.2, 133.5, 133.8 (d, J=11.9 Hz), 160.7, 161.9; ^{31}P{^{1}H} NMR ($CDCl_3$, 162.0 MHz) δ: 28.0; ES-MS m/z: calcd for $C_{177}H_{186}O_{24}P_6$: 2883.2; found: 1442.2 $[M]^{2+}$(93%). Anal. Calcd for $C_{177}H_{186}O_{24}P_6\cdot 3H_2O$: C, 72.32; H, 6.54; found: C, 72.36; H, 7.01.

4.1.9. Compound 12. To a stirred suspension of $CeCl_3$ (0.20 g, 0.82 mmol) in THF (6 mL), $LiAlH_4$ (0.041 g, 1.08 mmol) was added and stirred for 1 h at room temperature. A solution of **11** (0.26 g, 0.09 mmol) in THF (5 mL) was added and refluxed at 60 °C for 5 h. The reaction mixture was quenched with water, filtered and concentrated. The crude reaction mixture was purified by passing through a pad of SiO_2 (2% EtOAc/PhMe) to afford **12**, as a colorless oil (0.24 g, 96%). TLC R_f 0.58 (PhMe/EtOAc=98:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.61 (m, 18H), 1.85 (m, 36H), 3.99 (m, 36H), 6.07 (s, 12H), 6.88 (d, J=6.3 Hz, 12H), 7.25–7.32 (m, 72H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.7, 25.6, 28.9, 67.7, 67.9, 93.8, 114.7 (d, J=7.6 Hz), 128.4 (d, J=7.6 Hz), 133.4 (d, J=19.6 Hz), 135.6 (d, J=21.1 Hz), 137.8, 159.8, 160.9; ^{31}P{^{1}H} NMR ($CDCl_3$, 162.0 MHz) δ: −7.0. Anal. Calcd for $C_{177}H_{186}O_{18}P_6$: C, 76.27; H, 6.73; found: C, 76.02, H, 6.51.

4.1.10. Compound 14. A mixture of **13**[6] (0.2 g, 0.11 mmol), **6** (0.68 g, 1.54 mmol), K_2CO_3 (0.212 g, 1.53 mmol) and 18-C-6 (cat.) in DMF (10 mL) was heated at 70 °C for 72 h. Solvents were then removed in vacuo and the resulting residue was dissolved in CH_2Cl_2, washed with water, dried (Na_2SO_4), concentrated and purified (SiO_2, $CHCl_3$/MeOH=8:2) to afford **14**, as a brown oil (0.45 g, 68%). TLC R_f 0.47 ($CHCl_3$/MeOH=92:8). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.65 (br, 42H), 1.81 (br, 84H), 3.91 (br, 60H), 3.97 (t, J=6.6 Hz, 24H), 6.05 (s, 30H), 6.93 (d, $^3J_{HH}$=8.4 Hz, 24H), 7.43–7.68 (br, 144H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.0, 22.7, 28.8, 29.0, 67.8, 67.9, 68.0, 93.4, 114.6 (d, J=13.6 Hz), 128.5 (d, J=12.1 Hz), 129.3, 131.9, 132.1 (d, J=9.8 Hz), 134.0 (d, J=11.3 Hz), 160.9, 162.1; ^{31}P{^{1}H} NMR ($CDCl_3$, 162.0 MHz) δ: 29.3. Anal. Calcd for $C_{381}H_{408}O_{54}P_{12}$: C, 73.54; H, 6.61; found: C, 73.43; H, 7.12.

4.1.11. Compound 15. To a stirred suspension of $CeCl_3$ (0.086 g, 0.35 mmol) in THF (6 mL), LAH (0.025 g, 0.69 mmol) was added and stirred for 1 h at room temperature. Dendrimer **14** (0.12 g, 0.019 mmol) in THF (5 mL) was added and refluxed at 60 °C for 5 h. The reaction mixture was quenched with water, filtered and concentrated. The crude product was purified by passing through a pad of SiO_2 (5% EtOAc/PhMe) to afford **15**, as a colorless oil. TLC: R_f 0.41 (PhMe/EtOAc=98:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.62 (br, 42H), 1.83 (br, 84H), 3.93 (m, 84H), 6.06 (s, 30H), 6.94 (d, J=8.4 Hz, 24H), 7.23–7.67 (br, 144H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.7, 29.0, 29.7, 67.6, 67.7, 93.8, 114.7 (d, J=7.6 Hz), 128.4 (d, J=7.6 Hz), 133.4 (d, J=15.9 Hz), 133.5, 135.6 (d, J=21.1 Hz), 137.9 (d, J=10.6 Hz), 159.9, 160.9; ^{31}P{^{1}H} NMR ($CDCl_3$, 162.0 MHz) δ: −7.0. Anal. Calcd for $C_{381}H_{408}O_{42}P_{12}$: C, 75.88; H, 6.82; found: C, 75.84; H, 6.54.

4.1.12. Compound 17. A mixture of **16**[6] (0.058 g, 0.014 mmol), **6** (0.183 g, 0.414 mmol), K_2CO_3 (0.046 g, 0.33 mmol) and 18-crown-6 (cat.) in DMF (15 mL) was heated at 70 °C for 6 days. Solvents were removed in vacuo and the resulting residue was dissolved in CH_2Cl_2, washed with water, dried (Na_2SO_4) and concentrated. Excess **6** was removed by triturating with Et_2O and the residue was purified further (SiO_2, EtOAc/MeOH=95/5) to afford **17** as a brown oil (0.098 g, 55%). TLC R_f 0.42 ($CHCl_3$/MeOH=95:5). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.57 (br, 90H), 1.81 (br, 180H), 3.71–4.12 (br, 180H), 6.04 (s, 66H), 6.95 (dd, $^3J_{HH}$=8.4 Hz, $^4J_{PH}$=1.8 Hz, 48H), 7.42–7.69 (br, 288H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.6, 28.7, 29.0, 67.8, 68.0, 93.9, 114.6 (d, J=13.6 Hz), 128.3, 128.4 (d, J=12.1 Hz), 129.1, 131.8, 132.0 (d, J=9.8 Hz), 134.0 (d, J=11.3 Hz), 160.9, 161.8; ^{31}P{^{1}H} NMR ($CDCl_3$, 162.0 MHz) δ: 29.3. Anal. Calcd for $C_{789}H_{852}O_{114}P_{24}$: C, 73.45; H, 6.66; found: 73.23; H, 7.11.

4.1.13. Compound 18. To a stirred solution of **17** (47 mg, 0.006 mmol), $CeCl_3$ (0.033 g, 0.131 mmol) in THF (4 mL)/DMF (0.1 mL), LAH (0.075 g, 1.97 mmol) was added and refluxed for 24 h. The reaction mixture was quenched with water, filtered, concentrated and dried. The crude product was purified by passing through a pad of SiO_2 (10% EtOAc/PhMe) to afford **18**, as a brown oil (0.038 g, 84%). TLC: R_f 0.30 (PhMe/EtOAc=90:10). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.57 (br, 90H), 1.83 (br, 180H), 3.94 (m, 180H), 6.05 (s, 66H), 6.87 (d, J=8.1 Hz, 48H), 7.23–7.30 (br, 288H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.8, 29.0, 29.7, 67.7, 67.8, 93.8, 114.7 (d, J=7.6 Hz), 128.4 (d, J=7.6 Hz), 133.4 (d, J=19.6 Hz), 135.6 (d, J=21.1 Hz), 137.9, 159.9, 160.9; ^{31}P{^{1}H} NMR ($CDCl_3$, 162.0 MHz) δ: −7.0. Anal. Calcd for $C_{789}H_{852}O_{90}P_{24}$: C, 75.7; H, 6.86; found: C, 75.29; H, 6.52.

4.2. General procedure for the alkyl aryl ether formation

To a solution of phenol (1.0 M equiv), alcohol (1.0 M equiv) and phosphine (1.1 M equiv on per phosphine unit basis) in CH_2Cl_2 (1.5 mL), DIAD (1.1 M equiv) was added and the reaction mixture was stirred at room

temperature for 1 h, under N_2 atmosphere. Solvents were removed in vacuo and Et_2O was added to precipitate the phosphine oxide. Et_2O portion was separated, concentrated and the resulting residue was added with petroleum ether. Petroleum ether portion was filtered from un-dissolved reduced DIAD and solvents were removed in vacuo and purified further. For monitoring the reaction, an aliquot of petroleum ether was injected into a normal phase (SiO_2) semi-preparative column, attached to a HPLC. Elution was carried out with EtOAc/pet. ether (3:1), at a rate of 1 mL/min. and monitored at 254 nm. The retention times for the starting materials and products were, benzyl alcohol: 22.5 min; phenol: 17.4 min; phenyl butyl ether: 16.4 min; phenyl isopropyl ether: 16.5 min; phenyl allyl ether: 16.7 min; phenyl benzyl ether: 16.0 min.

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