

The synthesis and catalytic application of spacer-modified diol-functionalised Merrifield resins

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Abstract—A range of alkyl spacer-tethered 1,2- and 1,3-diols have been prepared from commercially available Merrifield resin (**1**) and (4-chloromethyl)phenylpentyl-polystyrene-co-divinylbenzene (**2**). The utility of these resin-bound diols as supports for the Ti(IV)-catalysed Diels–Alder reaction has been exemplified and it has been demonstrated that the length of the tether has a direct effect upon the catalytic activity.

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Recent years have shown an explosion in the use of polymer-supported reagents and catalysts, largely as a result of their perceived ease of separation and re-use. Whilst many types of solid support have been probed, arguably the most versatile catalyst systems are those based on lightly cross-linked polystyrene resins (e.g., Merrifield resin¹) that combine an ‘innocent’ surface consisting of a largely inert polymeric backbone, with the relative ease with which they may be functionalised.^{2–4}

Despite their prevalence, immobilised reagents often suffer from the near-heterogeneous reaction conditions associated with their use. In many systems polymer-supported catalysts have been found to be less efficient and/or stereoselective than their homogeneous analogues⁵ and in certain cases the ‘non-innocent’ behaviour of the polymeric backbone has been directly implicated.⁶ To overcome these problems, polystyrene resins have been functionalised with polyether units such as poly(ethylene glycol) (PEG) to enhance their compatibility with polar solvents, increase reaction homogeneity, provide bound reagent mobility and to minimise steric and electronic interference from the insoluble polymer

matrix (examples being commercially available ARGO- and TENTA-GELS).

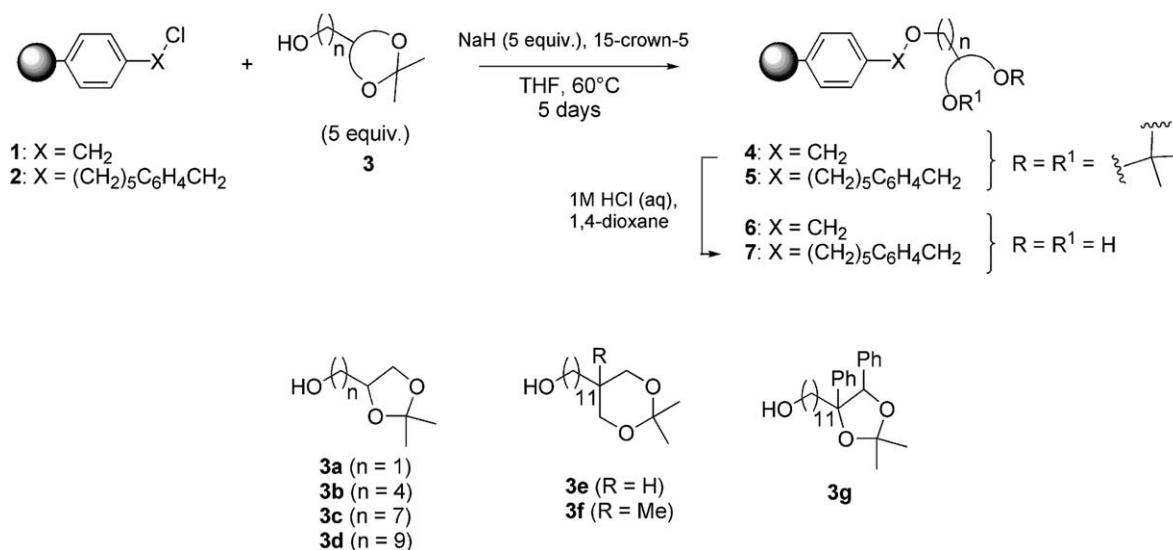
Although highly effective for SPOC (supported-phase organic chemistry), the use of these PEG-modified resins is potentially problematic for the immobilisation of commonly used Lewis acidic catalyst species such as Ti(IV), since the oxygen atoms in the tether may interact detrimentally with the metal centre, thus inhibiting (or slowing) substrate binding. These potential problems can be addressed by employing alternative alkyl tethers, since in the relatively few examples where they have been described the inclusion of such spacers has often been shown to have a beneficial effect on catalyst efficiency or stereoselectivity.⁷ In view of these potential benefits we began a series of investigations into the synthesis and catalytic application of novel alkyl spacer-tethered 1,2- and 1,3-diol-functionalised resins as potentially chelating tethers for Lewis acids. This letter describes our initial results in this area.

We chose to introduce the alkyl tethered diols by etherification of both lightly cross-linked Merrifield resin **1** (Avecia: chloromethylated PS-DVB (2%) beads, 1 mmol g^{−1} Cl) and the related commercially available support **2** (Aldrich: (4-chloromethyl)phenylpentyl PS-DVB (2%) beads, 1 mmol g^{−1} Cl) with an excess (5 equiv) of a ketal-protected triol **3a–g** (Scheme 1).^{8,9} Optimisation studies indicated that the use of sodium hydride and 15-crown-5 in THF were the most efficient reaction conditions giving the highest levels of polymer loading.¹⁰ Using these optimised conditions, a range of ketal-protected triols **3a–g** were grafted onto resins **1**

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Scheme 1.

and **2** to give the corresponding functionalised polymers **4a–g** and **5a,b** (Table 1).¹¹

As may be predicted, there is a clear correlation between the percentage functionalisation of **1** and the length of the alkyl chain with longer spacers giving a lower degree of incorporation of the ketal linker. A similar general trend is also apparent in the reactions of resin **2** (cf. entries 2 and 4 with 9). We believe this variation is a result of mass transport effects, the mobility of the larger substrates being attenuated through the solvent-expanded polymer matrix. In addition, we also observed that for analogous reactions the percentage conversions with resin **1** were greater than those for **2** (cf. entries 1 with 2 and 8 with 9). This is somewhat surprising as it was envisaged that the phenylpentyl linker already present

in **2** would facilitate substrate grafting. However, we observed significant differences in the relative swelling abilities of **1** and **2** (despite both incorporating 2% DVB cross-linker), which is believed to reflect differences in their structure/morphology.¹² Thus, the lower reactivity of **2** over **1** is most likely a consequence of its decreased tendency to swell under the reaction conditions, which renders the tether sites less accessible.

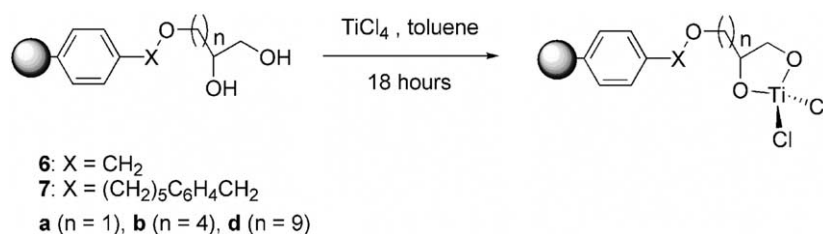
Deprotection of the resin bound ketals **4a–d** and **5a,b** was achieved by reaction with aqueous hydrochloric acid (1 M) in dioxane for 24 h (Scheme 1). Successful cleavage of the protecting group was confirmed by analysis of the product resins **6a–d** and **7a,b** by gel-phase (CDCl₃) CP-MAS ¹³C NMR spectroscopy (disappearance of the ketal carbon resonances was observed) and by IR spectroscopy (the appearance of a strong, broad O–H absorption at ca. 3400 cm^{−1}).¹³

Having successfully prepared a range of spacer-modified diol-functionalised resins we turned our attention to their use as catalyst supports. Reaction of the resins **6a,b,d** and **7a,b** with TiCl₄ (ca. 90 mol% Ti with respect to the diol) in toluene for 18 h was followed by filtration and extensive washing (with dry toluene and dichloromethane) of the resulting polymers. Subsequent ICP-AES analysis of the combined washings for Ti content indicated almost quantitative loading of the added Ti onto the resin (Scheme 2 and Table 2). Non-specific uptake of Ti by the polymer backbone was ruled out in

Table 1. Synthesis of functionalised resins via Scheme 1

Entry	Resin	Tether	Product	Conversion (%) ^a
1	1	3a	4a	>92
2	2	3a	5a	81
3	1	3b	4b	>92
4	2	3b	5b	90
5	1	3c	4c	>92
6	1	3d	4d	89
7	1	3e	4e	41
8	1	3f	4f	35
9	2	3f	5f	<1
10	1	3g	4g	18

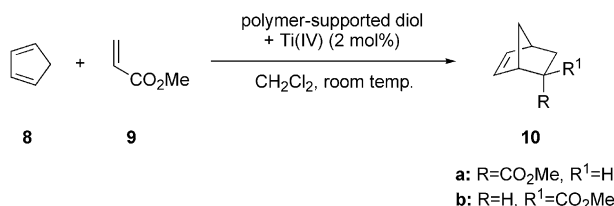
^a Calculated from residual Cl content of the resin.¹⁰



Scheme 2.

Table 2. Indirectly determined Ti loadings for reactions in Scheme 2^a

Entry	Resin	Ti added (μmol)	Ti recovered (μmol) ^b
1	6a	160	<2
2	6b	160	<1
3	6d	160	<2
4	7a	160	<3
5	7b	160	<3
6	1	160	>159

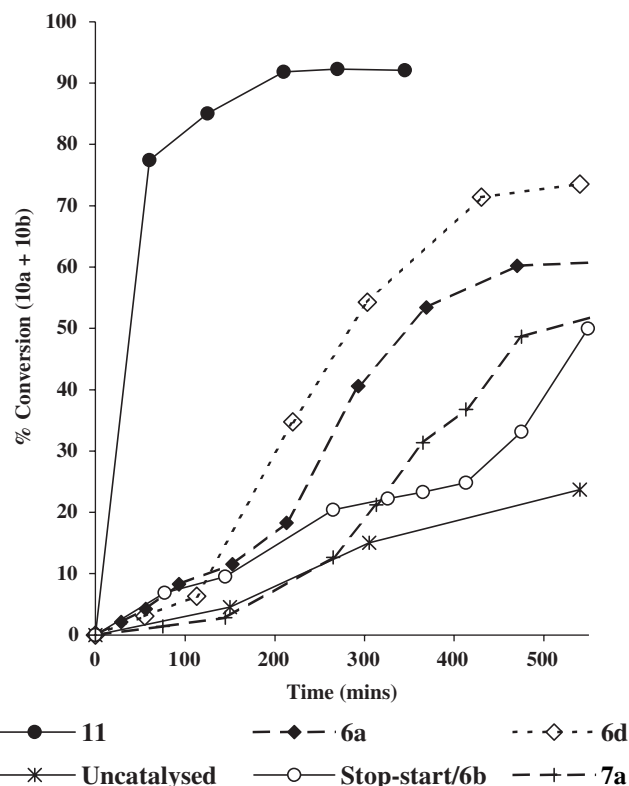
^a 200 mg of functionalised resin was used in each case.^b Total amount of Ti in combined resin washings as determined by ICP-AES analysis—accuracy is $\pm 2\%$.**Scheme 3.**

the control experiment with non-functionalised resin **1** (entry 6), which indicated <1% added Ti remained on the resin after washing.

The polymer-supported Ti(IV) species produced from resins **6a,b,d** and **7a,b** were examined for catalytic activity in the Diels–Alder reaction between cyclopentadiene (**8**) and methyl acrylate (**9**) (Scheme 3).^{14,15} Reactions were carried out in CH_2Cl_2 at room temperature using 2 mol% of polymer-bound Ti(IV) and were followed by GC–MS monitoring for the total yield of *endo+exo* products (**10a+10b**). The results are presented in Table 3 and Figure 1 (only selected plots shown for clarity), with the data revealing a number of findings. Firstly, all the diols **6a,b,d** and **7a,b**, once treated with TiCl_4 , were active catalysts for the Diels–Alder reaction increasing the rate of formation of **10a+10b** over the background non-catalysed transformation (entry 1). Of the Merrifield resin-derived catalysts **6a,b,d** there was no observable difference in the catalytic activities of **6a** and **6b** indicating that the change from a C-1 to C-4 tether did not have any significant effect. However, the C-9 functionalised resin **6d** proved to be the most efficient catalyst, suggesting that this provides the most facile substrate access to the Lewis acidic titanium. In comparison, both of the (4-chloromethyl)phenylpentyl-polystyrene-derived diols **7a,b**, were found to be mark-

Table 3. Percentage conversions of reactions in Scheme 3 after 8 h

Entry	Diol	Yield 10a+10b (%)
1	Non-catalysed	20
2	6a	60
3	6b	61
4	6d	73
5	7a	51
6	7b	53
7	11	92

**Figure 1.** Selected reaction profiles for the catalysed and uncatalysed formation of Diels–Alder products **10a,b**. Stop–start experiment: catalyst removed after 265 min and re-introduced at 413 mins.

edly slower catalysts, presumably as a result of their poor swelling behaviour, something which was also implicated in the low yields observed in their grafting reactions (Scheme 1 and Table 1). However, perhaps not surprisingly, none of the heterogeneous catalysts were as effective as the soluble analogue, diol **11**, which gave greater yields and faster conversions under analogous conditions when combined with TiCl_4 .

In order to show that immobilised Ti species were indeed responsible for catalysis, rather than any residual Lewis acid that had leached from the support during the reaction, a ‘stop–start’ experiment was carried out (Fig. 1). Thus, during a reaction with the catalyst derived from **6b**, the resin was removed by filtration and the reaction rate was observed to decrease to that of the background non-catalysed reaction. Upon subsequent re-addition of the catalyst previously removed by filtration the reaction rate again increased to match that observed before its removal, thus showing that polymer-bound Ti was responsible for catalysis and that the catalyst could also be potentially recycled.

In conclusion we have demonstrated the synthesis of a number of novel alkyl spacer-tethered 1,2- and 1,3-diols from commercially available polystyrene resins **1** and **2**. These diols are efficient bidentate ligands for Ti(IV) with the resulting polymer-supported Lewis acids having been shown to be good catalysts for the Diels–Alder reaction of cyclopentadiene and methyl acrylate.¹⁶ Furthermore, our initial results suggest that the use of alkyl

spacers can have a beneficial effect on the rate of catalysis and that the catalyst systems generated show appreciable activities even at low loadings (e.g., 2 mol%).

Acknowledgements

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- All new compounds gave satisfactory spectroscopic and microanalytical and/or HRMS analysis.
- Full details of the synthetic routes to **3a–g** will be reported in due course.
- Polymer loadings were determined indirectly from microanalysis of the resulting resins **4a–g** and **5a,b** for residual chlorine content.
- Selected spectroscopic data ^{13}C CP-MAS NMR (75.4 MHz, CDCl_3): **4a**: δ = 109.2 (C), 74.6 (CH), 73.3 (CH_2), 70.8 (CH_2), 66.8 (CH_2), 26.7 (CH_3), 25.4 (CH_3); **4b**: δ = 108.6 (C), 76.0 (CH), 72.9 (CH_2), 69.9 (CH_2), 69.5 (CH_2), 33.5 (CH_2), 29.0 (CH_2), 27.0 (CH_3), 25.8 (CH_3), 22.5 (CH_2); **4d**: δ = 108.3 (C), 75.9 (CH), 72.6 (CH_2), 70.0 (CH_2), 69.3 (CH_2), 33.4 ($2 \times \text{CH}_2$), 29.3 ($2 \times \text{CH}_2$), 26.9 ($2 \times \text{CH}_2$), 26.1 (CH_3), 25.8 (CH_3), 25.6 ($2 \times \text{CH}_2$); **5a**: δ = 108.5 (C), 74.7 (CH), 71.0 (CH_2), 66.9 (CH_2), 36.0 ($2 \times \text{CH}_2$), 31.4 ($2 \times \text{CH}_2$), 29.1 (CH_2), 26.8 (CH_3), 25.4 (CH_3); **5b**: δ = 108.5 (C), 75.9 (CH), 72.7 (CH_2), 69.9 (CH_2), 69.4 (CH_2), 35.8 ($2 \times \text{CH}_2$), 33.4 (CH_2), 31.3 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 29.0 (CH_2), 26.9 (CH_3), 25.7 (CH_3), 22.5 (CH_2).
- Resin **1** showed 25% greater swelling than **2** after treatment with THF for 1 h—measured using the procedure reported by: Santini, R.; Griffith, M. C.; Qi, M. *Tetrahedron Lett.* **1998**, *39*, 8951.
- Selected spectroscopic data: **6a**: CP-MAS NMR (75.4 MHz, CDCl_3) δ = 73.6 (CH_2), 72.1 (CH_2 and CH), 67.2 (CH_2); IR (cm^{-1}) ν = 3398; **6b**: CP-MAS NMR (75.4 MHz, CDCl_3) δ = 72.9 (CH_2), 72.1 (CH), 70.0 (CH_2), 66.7 (CH_2), 33.0 (CH_2), 29.7 (CH_2), 22.4 (CH_2); IR (cm^{-1}) ν = 3401; **6d**: CP-MAS NMR (75.4 MHz, CDCl_3) δ = 72.5 (CH_2), 72.2 (CH), 70.3 (CH_2), 66.7 (CH_2), 33.2 ($2 \times \text{CH}_2$), 30.8 (CH_2), 29.7 (CH_2), 26.3 ($2 \times \text{CH}_2$), 25.6 ($2 \times \text{CH}_2$); IR (cm^{-1}) ν = 3400; **7a**: CP-MAS NMR (75.4 MHz, CDCl_3) δ = 73.4 (CH_2), 72.0 (CH_2 and CH), 67.4 (CH_2), 35.7 ($2 \times \text{CH}_2$), 29.5 ($2 \times \text{CH}_2$), 29.1 (CH_2); IR (cm^{-1}) ν = 3408; **7b**: CP-MAS NMR (75.4 MHz, CDCl_3) δ = 73.0 (CH_2), 72.1 (CH), 69.9 (CH_2), 66.8 (CH_2), 35.8 ($2 \times \text{CH}_2$), 33.0 (CH_2), 31.3 (CH_2), 29.7 ($2 \times \text{CH}_2$), 29.0 (CH_2), 22.4 (CH_2); IR (cm^{-1}) ν = 3406.
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- General catalytic procedure: A Schlenk was charged with the polymer-bound diol (200 mg), which was dried in vacuo. After N_2 and toluene (5 mL) were added, the Schlenk was cooled to 0 °C. After 10 min, TiCl_4 (1 M solution in toluene, 0.160 mL, 0.16 mmol, 2 mol%) was added by microsyringe. The mixture was allowed to warm to room temperature then shaken overnight. The solvent was removed in vacuo, and the resulting residue washed with Et_2O (2×10 mL) then dried in vacuo. After backfilling with N_2 , CH_2Cl_2 (5 mL) was added, resulting in a yellow solution to which methyl acrylate (0.72 mL, 8.00 mmol) was added by syringe. After shaking for 30 min, freshly prepared cyclopentadiene (1.5 equiv, 0.88 mL, 12.00 mmol) was added and the mixture shaken at room temperature. At suitable intervals, the reaction solution was analysed for cycloaddition products **10a,b** as follows: an aliquot (25 μL) was removed and transferred to a pipette plugged with cotton wool and a layer of silica (0.5 cm). The aliquot was washed into a vial with ethyl acetate (1.50 mL in two portions) under air. The resulting ethyl acetate solutions were immediately analysed by GC–MS.
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