Chromatography-Free Esterification Reactions Using a Bifunctional Polymer

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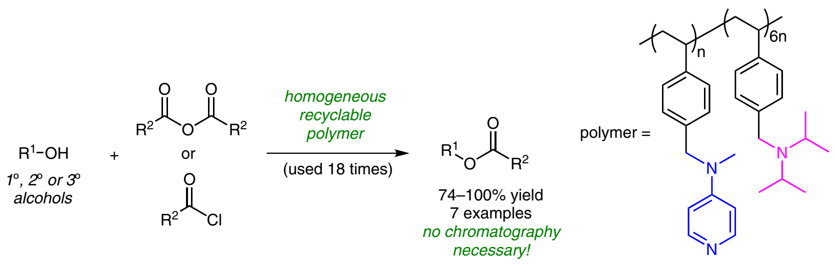

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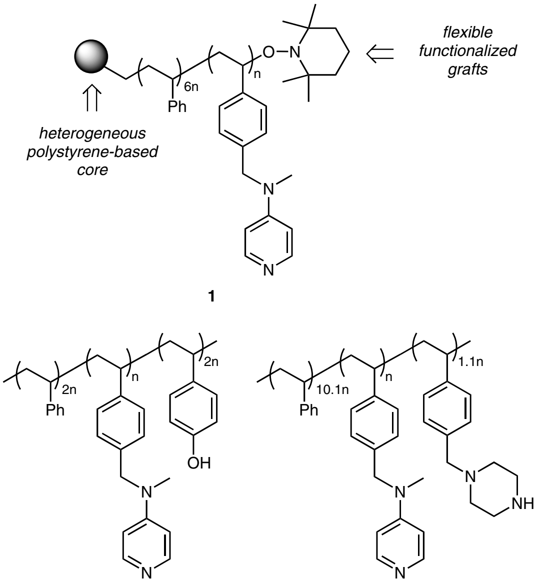
Abstract A linear polystyrene functionalized with both nucleophilic DMAP groups and sterically hindered tertiary amine groups was synthesized and used homogeneously in a range of esterification reactions between alcohols and various carboxylic acid derivatives. The polymer was highly effective in such reactions where the DMAP groups served as catalytic groups. The ester products of these reactions could be isolated in high purity and yield without the need for chromatographic purification, and the polymer could be recovered and reused numerous times with no apparent decrease in utility.

Key words DMAP, esterification reactions, organocatalysis, polymer-supported catalysts, polymer-supported reagents

4-Dimethylaminopyridine (DMAP) is a versatile nucleophilic organocatalyst that is perhaps most commonly used to catalyze ester forming reactions between an alcohol and a carboxylic acid derivative.[1] Due to its versatility, many polymer-supported versions of DMAP have been prepared with the aim of facilitating product isolation and for enabling catalyst recycling.[2,3] Typically, when DMAP is used in an ester forming reaction, including supported versions, an auxiliary sterically hindered tertiary amine base is added to neutralize the acid byproduct that is formed. In this area of research, we have previously reported rasta resin-supported DMAP (**1**, Figure 1) as a catalyst for reactions between epoxides and carbon dioxide to form cyclic carbonates.[4] We have also prepared bifunctional polystyrenes **2**[5] and **3**[6] that were effective catalysts for Morita–Baylis–Hillman and decarboxylative Doebner–Knoevenagel reactions, respectively. Both functional groups of polymers **2** and **3** were found to be required for effective catalysis of the reactions studied, and we wanted to extend our research by developing a polystyrene-supported DMAP catalyst that also possessed auxiliary tertiary amine base reagent groups for use in ester-forming reactions that did not require the need for chromatographic purification of the desired product.[7] Herein we report the realization of this objective through the synthesis and use of a bifunctional polystyrene.



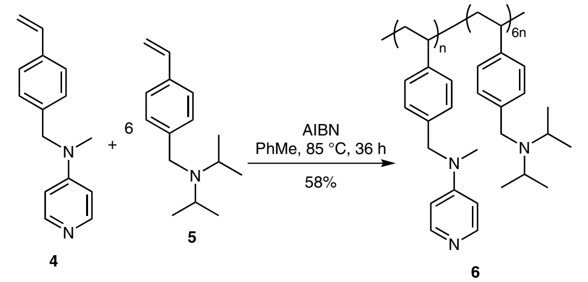
1

2 **3**

Figure 1 Polymer-supported DMAPs

As in all of our prior research regarding multifunctional polymers, we used the notion of simple monomer synthesis in one or two steps from commercially available starting materials as a guiding principle in order to make our polymer as inexpensive and practical as possible.[8] Thus, monomers **4**[4] and **5**[8c] were prepared according to our previously reported procedures from 4-vinyl benzyl chloride and the appropriate amine using substitution reactions. Monomers

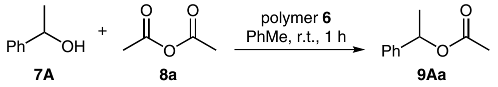
4 and **5** were heated in a 1:6 ratio in toluene at 85 °C for 36 hours to afford polymer **6** in 58% yield as a free-flowing powder after precipitation from MeOH (Scheme 1).[9] This monomer ratio was chosen because we wanted **6** to have at least five tertiary amine groups for each DMAP group since we anticipated using at most 20 mol% of the catalytic groups in the esterification reactions. ^{1}H NMR analysis was used to determine the ratio of monomer incorporation in **6** and indicated that it possessed essentially the same 1:6 ratio of DMAP to tertiary amine groups as the ratio of starting materials used in the polymerization reaction. This ratio corresponds to a DMAP loading level of 0.65 mmol/g.



Scheme 1 Synthesis of bifunctional polystyrene **6**

With bifunctional polymer **6** in hand we examined its utility in the esterification reaction between 1-phenylethanol (**7A**) and excess acetic anhydride (**8a**) to form ester **9Aa**[10] on a 1.5 mmol scale (Table 1). Since we envisioned the need for a slight excess of the basic tertiary amine groups, we used 20 mol% of **6** based on DMAP loading, which corresponded to using 1.2 equivalents of the amine groups (Table 1, entry 1). Gratifyingly, **6** was completely soluble in dry toluene at room temperature, and the reaction was complete after one hour. The expected product **9Aa** could be isolated essentially pure and in quantitative yield after only precipitation of the polymer byproduct using hexane (in which **6** and its protonated form are insoluble), washing of the reaction mixture with aqueous base and brine, and concentration. We next gradually reduced the amount of catalytic DMAP groups used and found that with 5 or 2 mol% DMAP (Table 1, entries 2 and 3), quantitative yield of **9Aa** could still be obtained. Only when 1 mol% of DMAP was used did the reaction not go to completion in one hour (Table 1, entry 4), with only 64% isolated yield obtained after separation of unreacted starting materials. Significantly, when the corresponding homogeneous small molecules DMAP and *i*-Pr$_2$EtN were used instead of polymer **6** (20 and 120 mol%, respectively), **9Aa** was isolated in only 73% yield after one hour (Table 1, entry 5). Thus, it seems that polymer **6** is more efficient in esterification reactions than the combination of DMAP and *i*-Pr$_2$EtN in toluene at room temperature, and the observation that the reactions are efficient even when less than a full equivalent of tertiary amine is used is consistent with similar findings reported by Ishihara and co-workers.[11]

Table 1 Esterification Reactions Using **7A** and **8a**[a]



Entry	Equiv of DMAP (mol%)	Yield (%)[b]
1	20	100
2	5	100
3	2	100
4	1	64
5[c]	20	73

[a] Reaction conditions: alcohol **4A** (1.5 mmol), acid anhydride **5a** (1.8 mmol), polymer **6**, and PhMe (3.0 mL) were stirred at r.t. for 1 h.
[b] Isolated yield.
[c] DMAP (0.3 mmol) and *i*-Pr$_2$EtN (1.8 mmol) were used in place of **6**.

After demonstrating the utility of **6** in an esterification reaction, we next sought to study both the substrate scope and the recyclability of the polymer in order to assess its practicality. Thus, we then conducted a series of larger-scale acylation reactions (15 mmol scale) using hindered

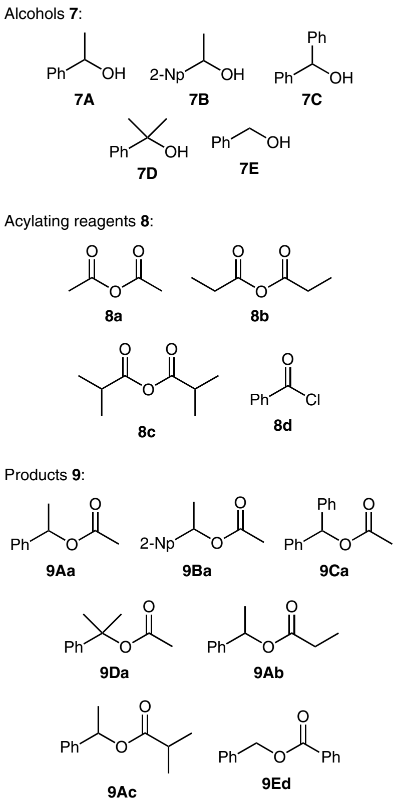
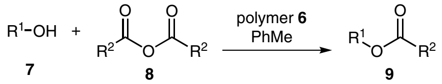


Figure 2 Starting materials and products of esterification reactions

secondary and tertiary alcohols **7A**–**D** and acid anhydrides **8a**–**c** (Figure 2) using the same sample of **6** for each successive reaction (Table 2). It should be noted that we chose to use variously substituted benzylic alcohols simply because we wanted to prepare nonvolatile products that could be easily visualized by TLC analysis, and it is assumed that nonbenzylic alcohols would work equally well as substrates. After each reaction the polymer was precipitated from the reaction mixture, washed with NaOH in MeOH, dried, and weighed prior to use in the next reaction cycle. Initially, **9Aa** was prepared three successive times using 0.467 g of **6** at the outset (0.02 equiv DMAP), with excellent results obtained (Table 2, entries 1–3). Next, **7B** was reacted with **8a** three times to form **9Ba** with excellent results and no evidence of product contamination from the previous reactions (Table 2, entries 4–6). This was followed by reaction of more sterically hindered **7C** with **8a** to form **9Ca** three times in reactions that required three hours for completion, but that still afforded quantitative yield (Table 2, entries 7–9). We then changed the acid anhydride from **8a** to **8b** and **8c**, and reactions of these with **7A** to form **9Ab** and **9Ac**, respectively, were complete in one hour (Table 2, entries 10–15). While high yields were afforded in every cycle, we scaled down the reactions for entries 13 and 14 due to the gradual loss of **6**. Finally, tertiary alcohol **7D** was reacted with **8a** in three reactions that required heating to 100 °C for 48 hours in order to obtain moderate yields of **9Da** (Table 2, entries 16–18).

Table 2 Esterification Reactions Using Various Alcohols **7** and Acid Anhydrides **8** Mediated by **6**[a]

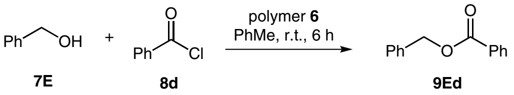


Reaction cycle	7	8	9	Time (h)	Yield (%)[b]	Mass of recovered 6 (mg)
1	**7A**	**8a**	**9Aa**	1	100	461
2	**7A**	**8a**	**9Aa**	1	99	451
3	**7A**	**8a**	**9Aa**	1	98	450
4	**7B**	**8a**	**9Ba**	1	100	448
5	**7B**	**8a**	**9Ba**	1	100	447
6	**7B**	**8a**	**9Ba**	1	100	451
7	**7C**	**8a**	**9Ca**	3	100	452
8	**7C**	**8a**	**9Ca**	3	99	441
9	**7C**	**8a**	**9Ca**	3	100	446
10	**7A**	**8b**	**9Ab**	1	100	441
11	**7A**	**8b**	**9Ab**	1	99	440
12	**7A**	**8b**	**9Ab**	1	99	441
13	**7A**	**8c**	**9Ac**	1	100	342
14	**7A**	**8c**	**9Ac**	1	100	340
15	**7A**	**8c**	**9Ac**	1	100	338
16	**7D**	**8a**	**9Da**	48	82	215[c]
17	**7D**	**8a**	**9Da**	48	74	219[c]
18	**7D**	**8a**	**9Da**	48	75	216[c]

[a] Reaction conditions: for entries 1–13, alcohol **4** (15 mmol), acid anhydride **5** (18 mmol), polymer **6**, and PhMe (30 mL) were stirred at r.t. for the indicated time; for entries 14 and 15, alcohol **4** (10 mmol), acid anhydride **5c** (12 mmol), polymer **6**, and PhMe (20 mL) were stirred at r.t. for 1 h; for entries 16–18, alcohol **4D** (10 mmol), acid anhydride **5a** (12 mmol), polymer **6**, and PhMe (20 mL) were stirred at 100 °C 48 h.
[b] Isolated yield.
[b] Reaction was not complete, and **9Da** was purified by column chromatography.

Next we examined the utility of **6** in esterification reactions using an acid chloride instead of an acid anhydride. Thus, **7E** was reacted with benzoyl chloride (**8d**) using **6** (0.2 equiv DMAP) in dry toluene in a reaction that required six hours to proceed to completion (Table 3, entry 1). As before, the polymer was precipitated at the end of the reaction, treated with NaOH in MeOH, dried, and reused in the next reaction. Gratifyingly we found **6** to be highly recyclable in these reactions as well (Table 3, entries 2–5). In all reactions, quantitative yield of pure **9Ed** was obtained.

Table 3 Esterification Reactions Using **7E** and **8d** Mediated by **6**[a]



Reaction cycle	Yield (%)[b]
1	quant.
2	quant.
3	quant.
4	quant.
5	quant.

[a] Reaction conditions: alcohol **4E** (0.5 mmol), acid chloride **5d** (0.6 mmol), polymer **6** (0.1 mmol DMAP), and PhMe (3.0 mL) were stirred at r.t. for 6 h.
[b] Isolated yield.

In summary, we have developed bifunctional linear polystyrene **6**, bearing both DMAP and tertiary amine groups, which can be used effectively in esterification reactions between an alcohol and an acid anhydride or an acid chloride. The macromolecular nature of **6** allows it to be readily separated from the ester products, and thus chromatographic purification is not necessary. Additionally, **6** is highly recyclable, with no apparent decrease in activity after numerous reaction cycles, and it can be recovered in a highly pure state so that no product contamination is observed when starting materials are changed. Furthermore, it appears that **6** is more efficient in esterification reactions that an equivalent mixture of DMAP and *i*-Pr_2EtN under identical reaction conditions, and this may be due to the polar microenvironment created by the densely functionalized polymer. Studies to determine the generality and origin of this increased efficiency, as well as applying **6** and heterogeneous analogues of it to other reactions, are currently under way, and the results of these efforts will be reported in due course.

Acknowledgement

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560415.

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(9) See Supporting Information for details.

(10) **General Procedure for Esterification Reactions**
Acylating reagent **7** (1.2 equiv) was slowly added dropwise into a stirred solution of alcohol **8** (1.0 equiv) and polymer **6** in dry toluene (30 mL). The reaction mixture was stirred at r.t., and when TLC indicated that **8** had been completely consumed, the reaction mixture was slowly added dropwise into hexane (150 mL). The resulting precipitate was filtered off, and the filtrate was washed with sat. aq Na_2CO_3 (50 mL). The organic layer was washed with brine (50 mL) and dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to afford product ester **9** in an essentially pure state according to ^1H NMR analysis. The collected precipitate was dissolved MeOH (8 mL), and was slowly added dropwise to a vigorously stirred solution of 0.1 N NaOH dissolved in MeOH (100 mL) at 0 °C. The resulting light yellow precipitate was filtered, washed with MeOH (40 mL), and dried under reduced pressure for reuse in the next reaction.
1-Phenylethyl Acetate (9Aa)
^1H NMR (400 MHz, $CDCl_3$): δ = 1.49 (d, 3 H, J = 6.8 Hz), 1.98 (s, 3 H), 5.86 (q, 1 H, J = 6.8 Hz), 7.22–7.33 (m, 5 H). 13C NMR (100 MHz, $CDCl_3$): δ = 21.0. 22.0, 72.0, 125.9 (2 C), 127.6, 128.3 (2 C), 169.8. LRMS: m/z calcd for $C_{10}H_{12}O_2$: 164.1; found: 164.1.

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