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Asymmetric epoxidation, Michael addition, and triple cascade reaction using polymer-supported prolinol-based auxiliaries

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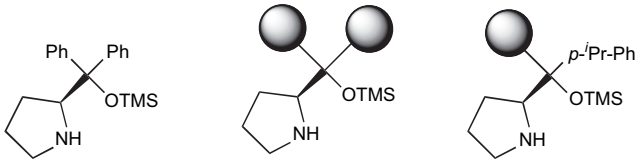
ABSTRACT

The applicability of polymer-supported diphenylprolinol derivatives in directing either asymmetric epoxidation or Michael addition of suitable α,β-unsaturated substrates has been assessed. Epoxidation of cinnamaldehyde in the solid state give poorer yields and stereoselectivities than in the solution-phase systems. In contrast Michael additions of several aldehyde enolates to 2-nitro-1-arylalkenes gave results that approached or surpassed those in solution, and could be extended successfully to a three-component Michael/Michael/aldol cascade process. Comparisons of the results of pendant- versus crosslinked functionalized resins in these applications were revealing of the benefits and limitations of each, as were attempts to reuse the polymer-bound auxiliaries.

1. Introduction

Asymmetric epoxidations and C–C bond forming reactions are cornerstones of modern synthetic methodology. Methods utilizing solution and solid-phase titanium, manganese, and copper complexes have led the way in the synthesis of enantiopure epoxides.[1–4] Asymmetric epoxidations on a wide range of compounds have also been performed using organocatalysts such as TMS-protected diphenylprolinol, **1**.[5,6] Carried out with relative ease and under environmentally friendly conditions, these epoxidations give products in high yields and enantiopurities. Enantioselective Michael additions have similarly been carried out with considerable success using the same proline-based system.[7] In considering solid-state conditions that might permit recycling and reuse of reaction catalysts, we chose to examine these processes using polystyrene-based polymer-supported crosslink- and pendant-bound TMS-protected diarylprolinols **2** and **3**, respectively (the shaded circles represent linkages to a polystyrene backbone).[8,9]

The most significant potential benefits of a solid-phase system are ease of product separation and purification, and ability to reuse the chiral species that facilitate the transformation. In practice, however, many solid-phase systems simply do not perform as well in either yield or selectivity as their solution-phase counterparts. Heterogeneous catalysis depends on the ability of reagents to interact with species in the solid phase, a process that can be diffusionally slow compared with interactions in solution. Thus there is a possibility of interference by unselective side reactions in solution whose rates are too slow to compromise pure solution-phase systems but fast enough to compete against similar processes that involve a solid-state component. Our previous results comparing oxaborolidines related to **1**–**3** ('CBS'-type catalysts) in asymmetric aldehyde reductions[8,9] showed that background reactions do indeed play an important role in processes involving solid-phase catalysts. Our goals in this study, therefore, were to ascertain the advantages and disadvantages of the two polymer systems compared with solution phase in minimizing the effect of deleterious side reactions and optimizing these processes with regard to yield and selectivity.



1 **2** **3**

2. Results and discussion

2.1. Solution-phase asymmetric epoxidation

Prior to working in the solid state, we examined modifications of the reported solution-phase experiments[6] to identify solvent

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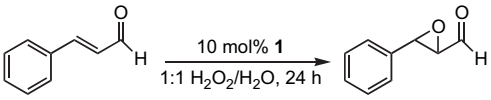
systems that would best suit solid-phase experiments (Eq. 1). A solution of catalyst **1** (0.025 mmol, 10 mol%), derived from the reaction of diphenylprolinol with trimethylsilyl trifluoromethanesulfonate (TMS-OTf), was prepared in 2 mL of a variety of typical Merrifield resin swelling solvents. Once the catalyst was completely dissolved, 0.3 mmol of aqueous H_2O_2 and 0.25 mmol *trans*-cinnamaldehyde were added and the mixtures stirred vigorously for 4 days. No significant product formation was observed using CH_2Cl_2 (DCM), $CHCl_3$, benzene, or toluene. In THF a 64% conversion to the epoxide was observed, and use of a 1:1 ethanol/DCM mixture gave 83% conversion to the epoxide in 24 h, suggesting that inefficient mixing was responsible for the lack of conversion in less polar media. On the basis of these and other results we therefore chose THF and 1:1 EtOH/DCM as solvent systems for initial solid-state experiments.



(1)

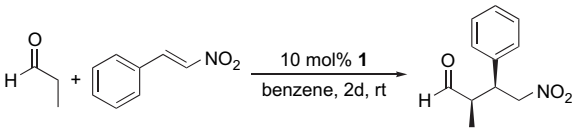
2.2. Solid-phase asymmetric epoxidation

Crosslink-functionalized polymer **2** and pendant-functionalized polymer **3** were prepared by reaction of beads of the polymeric aminoalcohol precursors[8] with TMS-OTf in DCM at 0 °C in the presence of triethylamine (TEA). Polymer **2** was then swollen in a 1:1 DCM/EtOH mixture followed by addition of *trans*-cinnamaldehyde and 50% aqueous H_2O_2. After 7 days of agitation, we found less than 5% conversion to product. Suspecting that the poor yield was a result of inefficient imine formation, we repeated the experiment by adding trimethylorthoformate (TMOF), which is known to promote imine formation on solid phase by removing water and shifting the equilibrium to product.[11] Surprisingly, no improvement in conversion was observed.

Returning to THF as the next-most promising medium for solid-state chemistry, we found that solution-phase reactions using **1** in 1:1 THF/TMOF and TMOF as solvents gave 84% and 99% conversion to the epoxide, respectively. In the solid state, using TMOF as the solvent with crosslink-functionalized polymer **2**, conversion over the course of 72 h improved to 22% but still fell considerably short of solution-phase results. However, 'seeding' the resin with the α,β-unsaturated aldehyde for 24 h prior to addition of the acid showed promise. Using this technique, after 72 h we observed conversions of 54% with **2**. GC analysis of the epoxide showed 85% enantiomeric excess (ee) and 60:40 trans/cis diastereomeric ratio (dr). Pendant-functionalized polymer **3** gave 28% conversion and 84% ee with a 57:43 dr. Taking into account the enantiopurities of the monomers used in the preparation of these resins—90% for **2** and 88% for **3**[9]—the intrinsic ee values produced by these systems are 94% for **2** and 95% for **3**. These results may be compared with the comparable solution phase outcome using *S*-**1** in TMOF: 99% conversion, 99% ee, and an 81:19 dr. It is difficult to draw any mechanistic conclusions from these data, given the fact that the same reaction in solution gives wildly differing yields and stereochemical outcomes with even minor alterations in solvent or catalyst structure.[6]

2.3. Solution-phase asymmetric Michael addition

In contrast to the imine-based mechanism for epoxidation, Michael additions catalyzed by secondary amines proceed via enamine intermediates, whose formation and reactivity might be affected differently in the relatively low-polarity interior of a polystyrene matrix. The reported solution-phase asymmetric Michael additions using **1** were carried out in hexane, a poor swelling solvent for Merrifield type resins.[7] Thus for our preliminary solution-phase studies we added propionaldehyde and *trans*-β-nitrostyrene to a solution of **1** (5 mol%) in 2 mL of benzene, a superior swelling solvent. After agitation at 25 °C for 2 days an 88:12 *syn*/*anti* diastereomer mixture of the γ-nitroaldehyde Michael adduct was obtained in 85% yield and 99% ee, nearly the same results as reported in hexane (Eq. 2).[7]



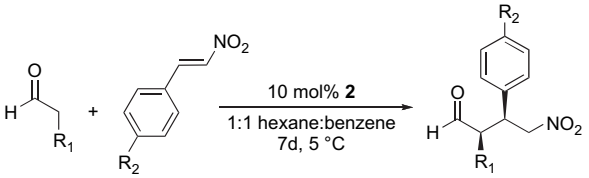
(2)

2.4. Solid-phase asymmetric Michael addition and triple cascade reaction

Based upon these results we proceeded to examine chiral Michael additions in benzene using **2** and **3**.[8,9] At the time we started this work there were reports of asymmetric Michael additions using solid-phase auxiliaries, but these resulted in generally poor to mediocre enantioselectivies.[10]

Beads of resins **2** and **3** were swollen in minimum quantities of benzene followed by addition of the aldehyde and nitrostyrene. The reactions were allowed to proceed for 4 days followed by filtration, acidic workup, and drying. Results are summarized in Table 1 (ee values are corrected for the enantiopurities of the monomeric precursors to **2** and **3**). Both **2** and **3** do well, affording results quite comparable to those obtained in solution with **1**.

Given the slightly superior performance of **2**, we proceeded to examine several combinations of enolates and nitroalkenes using this polymer-supported catalyst. Initial attempts at room temperature with more sterically demanding aldehydes gave lower yields and selectivities. However, reducing the reaction temperature to 5 °C and using a hexane/benzene mixture as solvent gave quite good results. Slightly reduced enantioselectivities were observed in additions of propionaldehyde to *p*-substituted nitrostyrenes, but isolated chemical yields were consistently good and *syn*/*anti* selectivity exceeded that observed in solution in all cases (see Eq. 3 and Table 2).



(3)

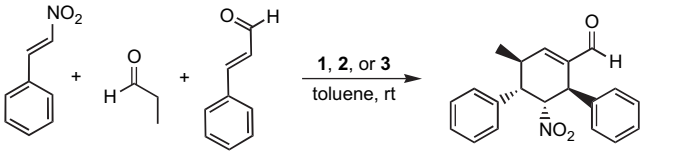
In 2006, Enders and co-workers described a TMS-protected prolinol-catalyzed three-component Michael/Michael/aldol cascade reaction that affords tetrasubstituted cyclohexenecarbaldehydes in modest yield but with excellent stereocontrol.[12] In as much as Enders' reaction conditions closely resembled those of the simpler Michael processes described above, we thought it would be instructive to try to replicate this cascade process in the solid state. The prototype system is shown in Eq. 4. The components are propionaldehyde, *trans*-β-nitrostyrene, and cinnamaldehyde; the catalyst is again a TMS-protected diarylprolinol.

Table 1
Michael additions of propionaldehyde to *trans*-β-nitrostyrene in benzene

Catalyst	ee	*syn*/*anti*	Isolated yield (%)
1	99	88:12	85
2	99	98:2	87
3	99	94:6	83

Table 2
Michael additions using resin **2** at 5 °C

R_1	R_2	ee	*syn/anti*	Isolated yield (%)
Et	H	99	95:5	85
Pr	H	99	≥99:1	80
i-Pr	H	99	≥99:1	83
Me	Br	94	≥99:1	82
Me	OMe	89	≥99:1	85



(4)

In the proposed mechanism,[12] the sequence begins with the same Michael addition of propionaldehyde enamine to nitrostyrene described above (cf. Eq. 2). The γ-nitroaldehyde product then undergoes Michael addition to the iminium derivative of cinnamaldehyde. Intramolecular aldol cyclocondensation of the resulting enamine completes the sequence. For a variety of examples Enders reports isolated yields of 25–58% and virtually total enantioselectivity for the major diastereomer, using 20 mol % of **1** as catalyst. The specific example in Eq. 4 gives 40% yield and ≥99% ee.

In the solid state, this process requires a polymer-supported proline derivative to form an enamine with the saturated aldehyde in the first step and an iminium salt from the unsaturated aldehyde in the second. These requirements would appear to place significant and somewhat differing demands on the characteristics of the reaction environment in solid-state systems. Indeed, replication of the process described in Eq. 4 using crosslink-functionalized polymer **2** gives disappointing results: after 7 days only 15% yield of product is isolated with ee=89%. *In dramatic contrast, however, the pendant-functionalized system **3** catalyzes this process remarkably well, giving 45% yield and 99% ee*. This rather startling result implies that the pendant-proline moieties in **3** are unusually well suited for catalysis via both enamine and iminium pathways. While **2** is still capable of simple enamine-based chemistry, it fares poorly in the multicomponent process. We hypothesize that the more constrained steric environment in **2**, associated with the location of the functionality at a crosslink, is poorly suited to stabilize iminium intermediates and less compatible with construction of the bulky three-component product. For this process to succeed, the initial polymer-bound Michael product must form, detach from the polymer, and then add to the α,β-unsaturated aldiminium salt, which is polymer-bound at, presumably, a different functionalized site. The pendant functionality in **3** is clearly better suited for this sequence of events.

2.5. Attempted polymer recycling and regeneration

Direct reuse of the resin recovered from successful epoxidation of cinnamaldehyde gave only very low (>10%) yields of epoxide, although ee remained at 90%. Assuming that deprotection of the alcohol was responsible for the poor results, we attempted to regenerate the active resin by reprotection; however, the supposedly regenerated resins gave no product. Further attempts to regenerate an active polymer, including full deprotection using tetrabutylammonium fluoride (TBAF) followed by careful reprotection using TMS-OTf were also fruitless. Clearly the epoxidation conditions themselves caused destruction of the polymer-bound auxiliary in a way that could not be reversed.

Before setting out to examine the reuse of polymers **2** and **3** in Michael additions, we investigated the fate of catalyst **1**. ^{1}H NMR analysis showed its decomposition to multiple uncharacterized aromatic products and free methylated silane material, including hexamethyldisiloxane. Similarly, resin-bound moieties **2** and **3** released methylsilanes during use. On this basis, before reuse we treated the resin as though it had undergone partial deprotection. We completed the deprotection by washing with acid and then with base, and then carefully reprotected the alcohol. This procedure afforded resins that catalyzed additional Michael addition of propionaldehyde to β-nitrostyrene with high stereoselectivity but in yields of only 20% for **2** and 17% for **3**. These results and our previous work[9] all point toward the diphenylprolinol system being insufficiently robust for reuse in these sorts of applications. A simple pyrrolidine-based polymer-bound catalyst has recently been successfully reused for asymmetric Michael additions of cyclohexanone to nitroolefins.[14] That system appears to be more robust and gives higher yields but slightly lower stereoselectivities than resin **2**.

3. Conclusions

In accordance with our previous results this study has demonstrated that the crosslinker resin **2** is generally a superior polymer-bound catalyst as compared to its pendant counterpart **3**, at least for simple two-component chemistry. While the two resins give low yields for asymmetric epoxidations, Michael additions proceed quite efficiently. Stereoselectivities for epoxidation are somewhat lower for the polymer-bound catalysts than that found in solution, while in the case of Michael additions the results generally match or exceed those obtained in solution. In addition, three-component tandem Michael/Michael/aldol processes can be adapted to the solid state, giving superior results to solution phase using resin **3**. This difference in efficacy between resins **2** and **3** suggests that the crosslink-functionalized **2**, in which the reactive sites are likely to be in uniformly well-defined environments, is the better choice for good yield and stereoselectivity in cases where the reactions being examined are compatible with its rather non-polar and sterically constrained reactive environment. Where such compatibility is reduced, as in multicomponent chemistry, conventional pendant-functionalized systems such as **3** may emerge as the preferred choice. Despite their capabilities in solution, diphenylprolinol-based systems are not reliably applicable for more than a single use. However, they do afford at least the basic advantages of chemistry carried out on the solid phase in terms of ease of isolation of products of quite high purity after no more than simple filtration, drying, and removal of solvent.

4. Experimental

4.1. General

All reactions were performed in oven-dried glassware under an atmosphere of dry argon unless otherwise stated. An orbital shaker was used for agitation of reactions involving polymer beads. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz in $CDCl_3$. IR spectra of solids were recorded using an FTIR with an ATR attachment. Optical purities of chiral auxiliaries and their precursors were determined using a Waters Alliance LC/MS, a Waters 2695 HPLC, and a Waters PDA 996, equipped with a Chiralcel OD-RH 0.46 cm by 15 cm (I.D. by length) 5.0 μm column employing the following gradient elution: 0–5 min, 100% A; 5–25 min, 0–100% B; 25–30 min, 100–0% B; 30–35 min, 100% A (solvent A: water/0.1% TFA; B: acetonitrile/0.1% TFA); monitored from 200–400 nm with a 0.2 mL/min flow rate. A Waters Micromass ZQ Mass Detector was used for the identification of MS (ESI) for various products, using sample concentrations of ~1 μg/mL. Further chiral analyses were performed on a Waters 2996 Photodiode Array Detector, a Waters 2525 Binary

Gradient Module, and a Waters 2767 Sample Manager equipped with a 4.6×150 mm Waters Xterra® MS C_{18} 5.0 μm column employing: 0–3 min, 100% A; 3–23 min, 0–100% B; 23–27 min, 100–0% B; 27–32 min, 100% A (solvent A: water/0.1% TFA; B: acetonitrile/0.1% TFA); and monitored from 200 to –600 nm with a 1.0 mL/min flow rate. Products were analyzed using a Chromasil CP-Chirasil-Dex CB 25 m GC chiral column.

4.1.1. Solution-phase epoxidation of cinnamaldehyde in TMOF

In a 2-dram vial, 10 mg (0.030 mmol) of **1** was dissolved in 2 mL of trimethylorthoformate. A 50% H_2O_2/H_2O solution (0.020 mL, 0.30 mmol) was added to the solution and stirred vigorously for 10 min. *trans*-Cinnamaldehyde (0.030 mL, 0.24 mmol) was then added via syringe and the solution stirred for 1 day at the end of which a sample was taken for NMR and GC analyses, revealing a 99+% conversion to product, which consisted of (within experimental error) optically pure *trans* and *cis* epoxide in an 81:19 ratio. ^1H and ^{13}C NMR data for the products were identical to the literature values.[13]

4.1.2. Solution-phase Michael addition of propionaldehyde to trans-β-nitrostyrene in benzene

In a 2-dram vial, 20 mg (0.060 mmol) of **1** was dissolved in 2 mL benzene. *trans*-β-Nitrostyrene (0.20 g, 1.3 mmol) and propionaldehyde (0.70 mL, 10 mmol) were added followed by 2 days of stirring. HCl (1 N, 2 mL) was added followed by extraction with 10 mL EtOAc, dried over anhydrous Na_2SO_4, and concentration under reduced pressure. Conversion and stereochemical data for the product mixture are summarized in Table 1. ^1H and ^{13}C NMR data for the products agreed with the literature values.[7]

4.1.3. Crosslink-functionalized beads of polymer-supported catalyst *2*

Into a 100 mL flask, 0.90 g of the aminoalcohol precursor resin (4.2% crosslinked and 0.45 mmol crosslink-functionalized[8,9]) was swollen in 20 mL of dichloromethane (DCM) and cooled to 0 °C. Triethylamine (0.040 mL, 0.26 mmol) and trimethylsilyl trifluoromethanesulfonate (0.050 mL, 0.25 mmol) were added followed by 1 h of agitation. The resin was filtered, and washed with 15 mL of DCM, water, THF, and methanol. Drying under reduced pressure in a 50 °C oil bath yielded 0.80 g (89%) of polymer **2** as off-white beads.

4.1.4. Pendant-functionalized beads of polymer-supported catalyst *3*

Into a 100 mL flask, 1.00 g of the precursor resin (3.7% crosslinked and containing 0.45 mmol pendant-functionalized[8,9]) was swollen in 25 mL of dichloromethane followed by cooling to 0 °C. Triethylamine (0.080 mL, 0.59 mmol) and trimethylsilyl trifluoromethanesulfonate (0.120 mL, 0.59 mmol) were added followed by 1 h of agitation. The resin was then filtered, and washed with 15 mL of DCM, water, THF, and methanol. Drying under reduced pressure in a 50 °C oil bath yielded 0.90 g (90%) of resin **3** as off-white beads.

4.1.5. Polymer-supported asymmetric epoxidation

Into a 2-dram vial, 0.10 g of resin (0.050 mmol **2** or 0.045 mmol **3**) was swollen in 1.5–2 mL of trimethylorthoformate. A 50% H_2O_2/H_2O solution (0.02 mL, 0.30 mmol) was added to the heterogeneous mixture and allowed to stir vigorously for 10 min. *trans*-Cinnamaldehyde (0.045 mL, 0.36 mmol) was added to the mixture via syringe and the solution stirred for 1 day, at the end of which time a sample was removed for NMR and GC analyses.

4.1.6. Representative procedure for polymer-supported Michael addition

Into a 2-dram vial, 0.10 g of resin (0.050 mmol **2** or 0.045 mmol **3**) was swollen in ca. 3 mL benzene followed by the addition of *trans*-β-nitrostyrene (0.20 g, 1.3 mmol) and propionaldehyde (0.70 mL, 10 mmol). The solution was agitated for 4 days at the specified temperature. The resin was filtered away and washed with 15 mL THF followed by 15 mL of methanol. The combined filtrates were washed with 15 mL 1 N HCl and extracted twice with 10 mL EtOAc, and the organic layers combined, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Yield and enantiomeric excess data are summarized in Tables 1 and 2.

4.1.7. Polymer-supported triple cascade reaction

Into a 2-dram vial, 0.10 g of resin (0.050 mmol **2** or 0.045 mmol **3**) was swollen in 2–3 mL of toluene. *trans*-β-Nitrostyrene (0.040 g, 0.26 mmol) was added at 0 °C and allowed to stir for 10 min. Propionaldehyde (0.020 mL, 0.30 mmol) and *trans*-cinnamaldehyde (0.033 mL, 0.26 mmol) were added and the solution was allowed to stir for 1 day during which time the 0 °C bath warmed to room temperature. The reaction mixture was agitated for 7 days further and the product worked up and purified in accordance with the literature.[12] Using resin **3**, the product was obtained as a colorless solid, 0.038 g (45% yield), ee=87% (99%, corrected for the 88% ee of the resin precursor).

Acknowledgements

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