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A Simple Batch Reactor for the Efficient Multiple Use of Polymer-Bound $\alpha,\alpha,\alpha',\alpha'$ -Tetraaryl-1,3-dioxolane-4,5-dimethanol Titanates in the Nucleophilic Addition of Dialkylzinc Reagents to Aldehydes

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Abstract:

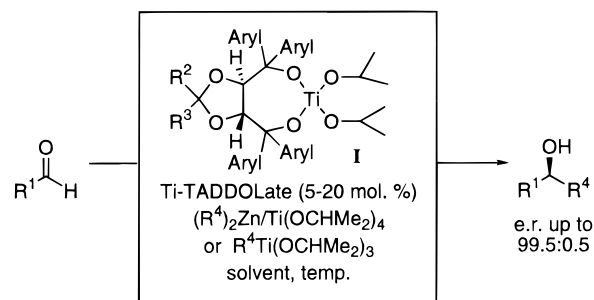
A new apparatus for heterogeneous-catalyst-mediated transformations is described. Results for a variety of enantioselective dialkylzinc additions to aldehydes mediated by polymer-bound $\alpha,\alpha,\alpha',\alpha'$ -tetraaryl-1,3-dioxolane-4,5-dimethanol titanates (pb-Ti-TADDOLs) using this new apparatus are given. In particular the active catalyst, once prepared, can be used many times with minimal loss of activity or enantioselectivity. The relative rate of reaction using the pb-Ti-TADDOLates as compared to a homogeneous Ti-TADDOLate has also been determined.

Introduction

$\alpha,\alpha,\alpha',\alpha'$ -Tetraaryl-1,3-dioxolane-4,5-dimethanols [TADDOLs, e.g., **I** (drawn as the titanate)], prepared from tartrate esters in two steps, are readily accessible chiral diols that can be utilised in many synthetic transformations.¹ For example, TADDOLs have been used as chiral ligands for Lewis acid catalysed additions to aldehydes^{2–5} (for a general example, see Scheme 1), Diels–Alder reactions^{6,7} and “desymmetrisation” of *meso* compounds^{8,9} to name but a few. The versatility of TADDOLs is increased by modification of the diol units into “softer” S-, N-, and P-containing ligands¹⁰ suitable for reactions such as Cu-mediated conjugate additions of alkyl Grignard reagents to enones.¹¹

Sometimes, however, the TADDOL can be difficult to remove from the product. A more convenient method, particularly if a system is to be applied within an industrial process, is to support the catalyst on an insoluble polymer

Scheme 1. General diagram for Ti-TADDOLate mediated addition of dialkylzinc or alkyltitanium reagents to aldehydes

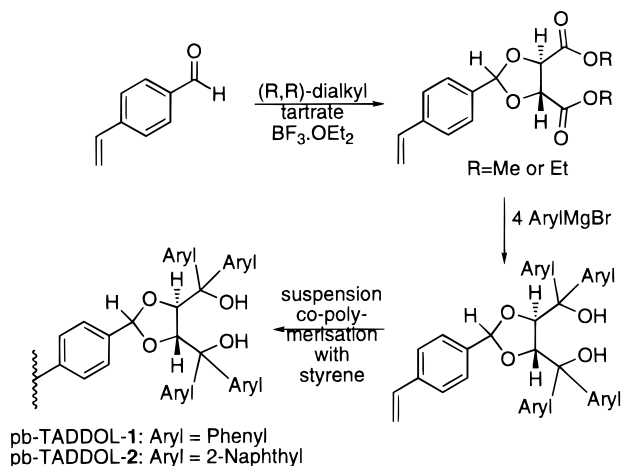


such that it can be more easily recovered after reaction. Indeed, many examples of polymer-supported reagents, catalysts, and reactions have been reported.¹² The advantages of such systems are as follows: (i) the polymers are easily separable from the reactants; (ii) consequently they are efficiently reusable; (iii) potentially toxic or expensive reagents can be made safer or recoverable; and (iv) the polymers are potentially usable within a continuous flow type reactor. Some polymer-bound reagents are even commercially available.¹³ In most instances reactions involving polymer supports have involved forming a new bond directly to the polymer,¹² for example, in the preparation of peptides.¹⁴ There have also been several examples of ligand-mediated reactions in which the chiral ligand was incorporated into a polymeric backbone. Recently, these have included new catalysts for asymmetric dihydroxylation,¹⁵ Diels–Alder

- (1) Dahinden, R.; Beck, A. K.; Seebach, D. In *Encyclopaedia of Reagents for Organic Synthesis*; Paquette, L., Ed.; Wiley & Sons: Chichester, 1995; Vol. 3, p 2167. Seebach, D.; Beck, A. K. *Chimia* **1997**, *51*, 293.
- (2) Seebach, D.; Beck, A. K.; Schmidt, B.; Wang, Y.-M. *Tetrahedron* **1994**, *50*, 4363.
- (3) Ito, Y. N.; Ariza, X.; Beck, A. K.; Bohác, A.; Ganter, C.; Gawley, R. E.; Kühnle, F. N. M.; Tuleja, J.; Wang, Y.-M.; Seebach, D. *Helv. Chim. Acta* **1994**, *77*, 2071.
- (4) Weber, B.; Seebach, D. *Tetrahedron* **1994**, *50*, 7473.
- (5) Weber, B.; Seebach, D. *Tetrahedron* **1994**, *50*, 6117.
- (6) Seebach, D.; Dahinden, R.; Marti, R. E.; Beck, A. K.; Plattner, D. A.; Kühnle, F. N. M. *J. Org. Chem.* **1995**, *60*, 1788.
- (7) Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M. *J. Am. Chem. Soc.* **1989**, *111*, 5340.
- (8) Seebach, D.; Jaeschke, G.; Wang, Y.-M. *Angew. Chem.* **1995**, *107*, 2605; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2395.
- (9) Ramón, D. J.; Guillena, G.; Seebach, D. *Helv. Chim. Acta* **1996**, *79*, 875.
- (10) Seebach, D.; Beck, A. K.; Hayakawa, M.; Jaeschke, G.; Kühnle, F. N. M.; Nägeli, I.; Pinkerton, A. B.; Rheiner, P. B.; Duthaler, R. O.; Rothe, P. M.; Weigand, W.; Wünsch, R.; Dick, S.; Nesper, R.; Wörle, M.; Gramlich, V. *Bull. Soc. Chim. Fr.* **1997**, *134*, 315.
- (11) Seebach, D.; Jaeschke, G.; Pichota, A.; Audergon, L. *Helv. Chim. Acta*, in press.

- (12) For three recent reviews covering the general area of polymer-supported chemistry from 1992 to 1996, see: (a) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1996**, *52*, 4527. (b) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643. (c) Früchtel, J. S.; Jung, G. *Angew. Chem.* **1996**, *108*, 19; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17. For other general references in the area, see: (d) *Syntheses and Separations using Functional Polymers*; Sherrington, D. C., Hodge, P., Eds.; Wiley & Sons: Chichester, 1988. (e) *Polymer Supported Reactions in Organic Synthesis*; Hodge, P., Sherrington, D. C., Eds.; Wiley & Sons: Chichester, 1980. (f) Pittman, C. U. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: Oxford, 1982; Vol. 8; p 553.
- (13) Blaser, H. U. In *Modern Synthetic Methods*; Ernst, B., Leumann, C., Eds.; HVCA/VCH: Basel/Weinheim, 1995; Vol. 7, p 181.
- (14) This procedure was first discovered by Merrifield (Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149) and Letsinger and Kornet (Letsinger, R. L.; Kornet, M. J. *J. Am. Chem. Soc.* **1963**, *85*, 3045).
- (15) (a) Bolm, C.; Gerlach, A. *Angew. Chem.* **1997**, *109*, 773; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 741. (b) Nandan, E.; Sudalai, A.; Ravindranathan, T. *Tetrahedron Lett.* **1997**, *38*, 2577. (c) Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 7632. (d) Salvadori, P.; Pini, D.; Petri, A. *J. Am. Chem. Soc.* **1997**, *119*, 6929.

Scheme 2. Preparation of polymer-bound TADDOL-1 and -2 from tartate esters



reactions,¹⁶ and asymmetric epoxidation.¹⁷ In our own group we have successfully synthesised polymer-bound TADDOLs (referred to hereafter as pb-TADDOLs) as shown in Scheme 2.¹⁸

These pb-TADDOLs are excellent ligands for many of the metal-mediated transformations previously described using homogeneous TADDOLs, with little drop in yield or enantioselectivity. We have also demonstrated efficient reuse of the pb-TADDOL: for example, the same sample of titanated polymer was used 4 times as a catalyst for diethylzinc addition to benzaldehyde and 9 times as a catalyst in the Diels–Alder reaction of 3-crotonyl-1,3-oxazolidin-2-one with cyclopentadiene with no loss of activity from one run to the next. Although this has increased the effectiveness of TADDOL chemistry considerably, the pb-TADDOLs are physically degraded with time.¹⁹ The constant stirring required causes abrasion of the polymer, resulting in a fine powder that can no longer be easily removed from the reaction mixture.

With this problem in mind we turned to the design of a simple apparatus in which polymer motion (and therefore polymer degradation) would be prevented. Our aim was to contain the pb-TADDOL within a polypropylene “tea bag” which would be held between two glass grilles. Although the concept of “tea bag” reactions is not new²⁰ (previous examples have typically utilised the polymer as a means of preparing peptides²¹), the use of “tea bags” containing a polymer as the catalyst for an enantioselective reaction is



Figure 1. Photograph of apparatus setup as it is used (cooling bath removed to show more detail). The reaction mixtures are drawn off into the collecting funnel (left) and drained into a conical flask below.

(if not unprecedented) very uncommon. Such an apparatus would further complement the wide range of synthetic uses of TADDOLs providing a system in which a small amount of catalyst could be reused many times. Demonstration of pb-TADDOL immobilisation would also provide a starting point for applying TADDOL chemistry within a process chemistry environment. This paper describes such an apparatus and the utility of “tea bag” methodology in the pb-TADDOL-mediated dialkylzinc additions to aldehydes.

Results and Discussion

The apparatus is shown in Figures 1 and 2. The pb-TADDOL (prepared as previously described,¹⁸ typically of a particle size range of 0.25–0.40 mm and a loading of 0.63 mmol of TADDOL/g of polymer) was contained within two circles of polypropylene mesh (mesh size 0.10 mm) and sealed using nylon thread forming the “tea bag” (Figure 2, bottom right). As discussed above, the “tea bag” was contained between two glass grilles (Figure 2, bottom left), and these in turn were placed into the apparatus, above a magnetic stirrer flea. The whole system was predried before use and set up as rapidly as possible, with evacuation (0.1 mmHg) and flushing with argon to ensure a dry, inert atmosphere. A funnel, able to collect the reaction solvents and washes, was attached to the side arm of the main reactor vessel. Although this could potentially be kept under an inert atmosphere, for the purposes of the work to follow, this was not necessary.

- (16) (a) Fraile, J. M.; Mayoral, J. A.; Royo, A. J.; Salvador, R. V.; Altava, B.; Luis, S. V.; Burguete, M. I. *Tetrahedron* **1996**, 52, 9853. (b) Kamahori, K.; Ito, K.; Itsuno, S. *J. Org. Chem.* **1996**, 61, 8321. (c) Altava, B.; Burguete, I.; Escuder, B.; Luis, S. V.; Salvador, R. V.; Fraile, J. M.; Mayoral, J. A.; Royo, A. J. *J. Org. Chem.* **1997**, 62, 3126. (d) Iruere, J.; Fernández-Serrat, A.; Rosanas, F. *Chirality* **1997**, 9, 191.
- (17) Canali, L.; Karjalainen, J. K.; Sherrington, D. C.; Hormi, O. *Chem. Commun.* **1997**, 123.
- (18) Seebach, D.; Marti, R. E.; Hintermann, T. *Helv. Chim. Acta* **1996**, 79, 1710.
- (19) This is not an uncommon feature of polystyrene-based polymer supports. For example, see: Blossley, E. C.; Ford, W. T. In *Comprehensive Polymer Science*; Eastmond, G. C., Ledwith, A., Russo, S., Sigwalt, P., Eds.; Pergamon: Oxford, 1989; Vol. 6, p 81.
- (20) The first description of “tea bags” is probably that of Houghten: Houghten, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, 82, 5131.
- (21) This was the primary use of the “tea bags” described by Houghten in ref 20.

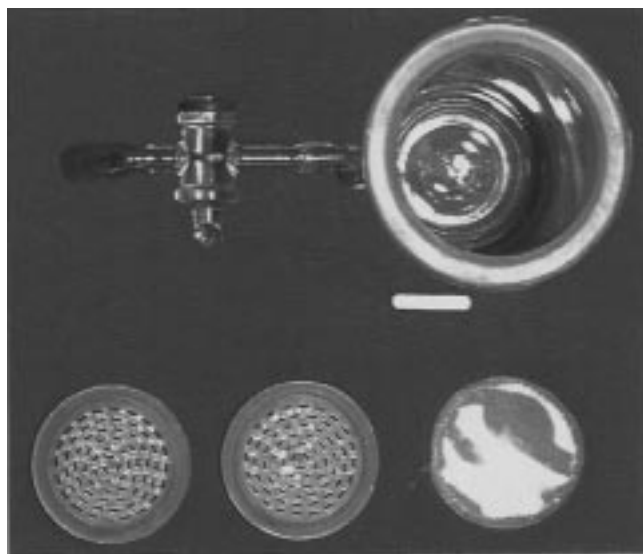
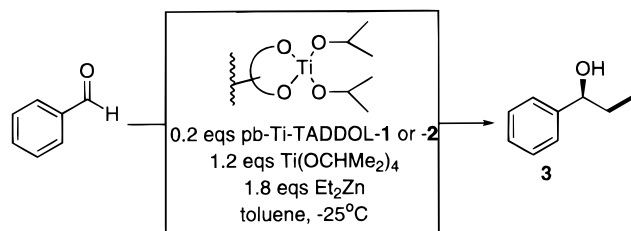


Figure 2. View of some of the apparatus pieces. The “tea bag” (right) is sandwiched between the two glass grilles (left), preventing polymer motion and the resultant degradation.

Scheme 3. Addition of Et_2Zn to PhCHO mediated by “tea bags” containing polymer-bound Ti-TADDOL-1 or -2 (for results, see Figure 3). Each “tea bag” was used 20 times without quenching or recovery of the polymer beads between reactions



Initially we tested the activity of the polymer “tea bags” in the reaction of diethylzinc with benzaldehyde using 20 mol % of the pb-Ti-TADDOL-1 (see Scheme 3). Due to the size of the apparatus and the resulting amount of solvent required to cover the “tea bag” and glass grilles, the reactions were carried out on an 11.1 mmol scale (of PhCHO) with the reaction concentrations being comparable with previously reported results.^{2,18} The active pb-Ti-TADDOLate was prepared, as usual for these systems, by the addition of $\text{Ti}(\text{OCHMe}_2)_4$ (1 equiv with respect to the amount of TADDOL present) in toluene and stirring overnight with subsequent removal of all solvents under high vacuum (0.1 mmHg) (in general the titanated “tea bags” could be kept under argon for several weeks with little loss in activity but were usually used immediately). The addition of toluene, $\text{Ti}(\text{OCHMe}_2)_4$ (1.2 equiv), and then PhCHO (1 equiv) was followed by cooling using a cryostat (internal temperature between -20 and -25°C), and finally by the addition of diethylzinc (2 M in toluene, 1.8 equiv). Upon completion (reactions were typically left to run overnight but generally proceed to completion more rapidly than this) reaction mixtures were drawn off into the collecting funnel and drained onto 1 M HCl to quench. The apparatus was recharged with fresh, dry toluene (again sufficient to cover the top grille) and the reaction mixture stirred for 1 h before

removal of solvent. This washing was carried out three times in all, at which point the “tea bag” was ready for further use. The combined reaction mixture and washings were all extracted and the product alcohols distilled and analysed. This reaction was carried out 20 times using the same “tea bag” of polymer with *no quenching of the pb-Ti-TADDOLate at any point*. An analogous series of reactions were also carried out using a “tea bag” containing the pb-Ti-TADDOL-2 (the tetra-2-naphthyl containing TADDOLs can give improved enantioselectivity compared to the phenyl derivatives).^{1–3,8} Results for both sets of 20 runs are shown in Figure 3. Yields of purified product for all of the reactions were around 90%. The enantiomer ratio of the product alcohol was determined by chiral stationary phase capillary gas chromatography (CGC), and as expected from previous work the product was mainly (*S*)-1-phenyl-1-propanol.^{2,3,18}

The results show that the pb-Ti-TADDOL can be used many times, with consistent yields and little drop in the enantiopurity of the products. The tetraphenyl polymer-bound TADDOL exhibited a more rapid decrease in enantioselectivity with time than the tetranaphthyl polymer. On a simplistic level this may be a function of the polymer pore sizes. Within the tetranaphthyl polymer these should be larger and therefore should not be blocked up so easily (by any titanium oxides formed during use), giving less drop in enantioselectivity with time. It is also of note that, between runs 10 and 11 of the series mediated by pb-Ti-TADDOL-2, the “tea bag” was left standing under argon for approximately 10 days. Even after this time the polymer was still active, giving the highest enantioselectivity in the whole series!

After both of the above sets of 20 reactions, the pb-Ti-TADDOL could be quickly and efficiently recovered from the “tea bags”. Quenching of the pb-Ti-TADDOLs with concentrated HCl followed by washing with water, THF, and diethyl ether gave quantitative isolation of the polymer. Whereas in our previous work the recovered polymers had been ground into a fine powder, the pb-TADDOLs recovered from our “tea bags” showed no apparent degradation or abrasion of the polymer surface. A microscope photograph of the recovered polymers (Figures 4 and 5) demonstrates this very clearly. We have also tested the “reusability” of the recovered pb-TADDOL, with one subsequent reaction giving a 94% yield of (*S*)-1-phenyl-1-propanol with an enantiomer ratio of 88:12.

During the course of this work the rate of reaction of PhCHO with diethylzinc was also studied to establish any differences between using our “tea bag” methodology and the previously established homogeneous TADDOL work. In run 3 of the tetraphenyl pb-Ti-TADDOL mediated reaction sequence, approximately 0.5 mL samples were periodically removed from the apparatus and quenched and separated between HCl solution and diethyl ether. The organic layers were analysed directly by CGC. At the same time a reaction using a typical homogeneous Ti-TADDOL (**I**, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{Ph}$, $\text{aryl} = \text{Ph}$) under identical conditions was carried out and analysed in a similar fashion. Both reactions showed a smooth rate of conversion with respect to time, with the

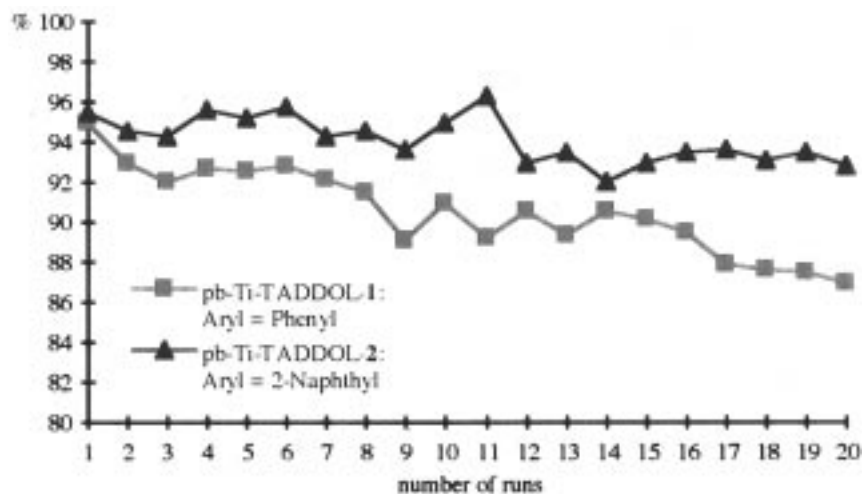


Figure 3. Multiple additions of Et_2Zn to PhCHO mediated by “tea bags” containing pb-Ti-TADDOL-1 or -2. Yields were typically 90%. The enantiopurity is given as % of (*S*)-1-phenyl-1-propanol (3).

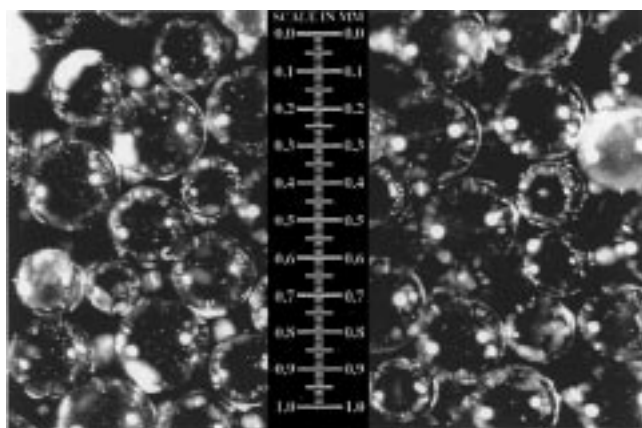


Figure 4. Microscope photograph of beads of pb-TADDOL-1 before (left) and after (right) use in 20 consecutive additions of Et_2Zn to PhCHO (see Figure 3).

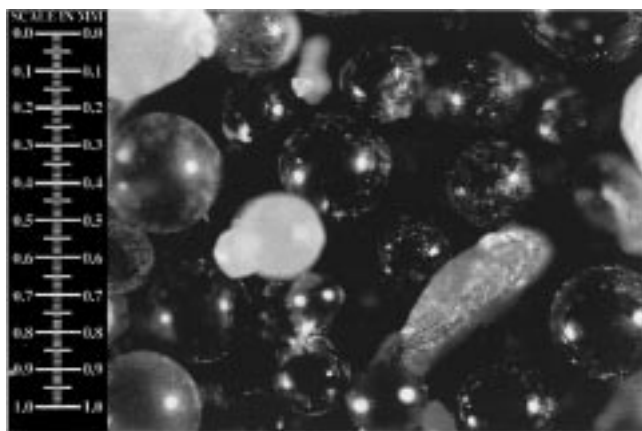


Figure 5. Microscope photograph of beads of pb-TADDOL-2 after use in 20 consecutive additions of Et_2Zn to PhCHO (see Figure 3).

polymer-bound reaction being essentially complete within 5 or 6 h, and the homogeneous reaction within 30 min (Figure 6). Further analysis of these results gave the two first-order (with respect to PhCHO) rate plots shown in Figure 7. A calculation of the rate constants for each reaction shows that the polymer-bound reaction is approximately 20 times slower than the homogeneous reaction.

At this point we were interested in determining how much product was retained on the polymer from one run to the next (or in other words the amount of contamination). Firstly (using a fresh “tea bag” containing the pb-Ti-TADDOL-1) two runs with PhCHO were carried out to establish the reproducibility of our earlier results. Subsequent to this we performed two runs each of five different aldehydes (Scheme 4). Results are shown in Figure 8, runs 1–12. The yields of major product from each reaction were determined from the quantity and CGC purity of the distilled alcohols. The amount of minor product (or contaminant from the previous run) was determined by CGC analysis of the crude reaction mixture. For all products the enantiomer ratio was determined by either CGC or Mosher ester analysis²² (both the *R* and *S* Mosher esters were prepared and compared to ensure that no kinetic resolution was occurring during esterification). Optical rotations were used only to determine the sense of chirality. For those compounds where the absolute configuration was not known in the literature, the product alcohol was assumed to be of *S* configuration by analogy with our previous work.

In all cases a small amount of contamination was observed upon changing from one aldehyde to the next (up to 5%), and one reaction later only 0.5% of the previous product was seen. These results could generally be improved, however, by a slight change in the washing procedure. We assumed that any product not successfully washed out must still be held by the polymer as the alkoxy titanate. With the addition of $\text{Ti}(\text{OCHMe}_2)_4$ (1 mL) to each wash this remaining product could be successfully exchanged and extracted. With three such washes (Figure 9, runs 14–17) a maximum of 1% contamination was observed from one reaction to the next, and with five such washes this value was further decreased to 0.5%.

As a further test of our apparatus we studied the reaction of PhCHO with different dialkylzinc reagents, *all* prepared from the corresponding Grignard reagents.²³ Initially (again

(22) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, 34, 2543.

(23) Bussche-Hünnefeld, J. L. v. d.; Seebach, D. *Tetrahedron* **1992**, 48, 5719.

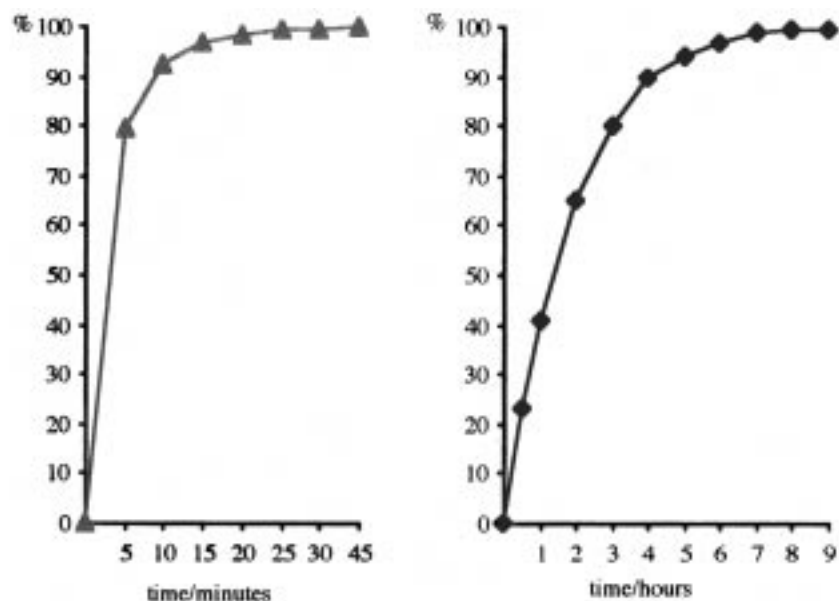


Figure 6. Graphs showing % conversion of PhCHO to 1-phenyl-1-propanol (3) with respect to time for homogeneous (I, $R^2 = H$, $R^3 = Ph$, aryl = Ph, red line) and heterogeneous (pb-Ti-TADDOL-1, blue line) TADDOL mediated reactions.

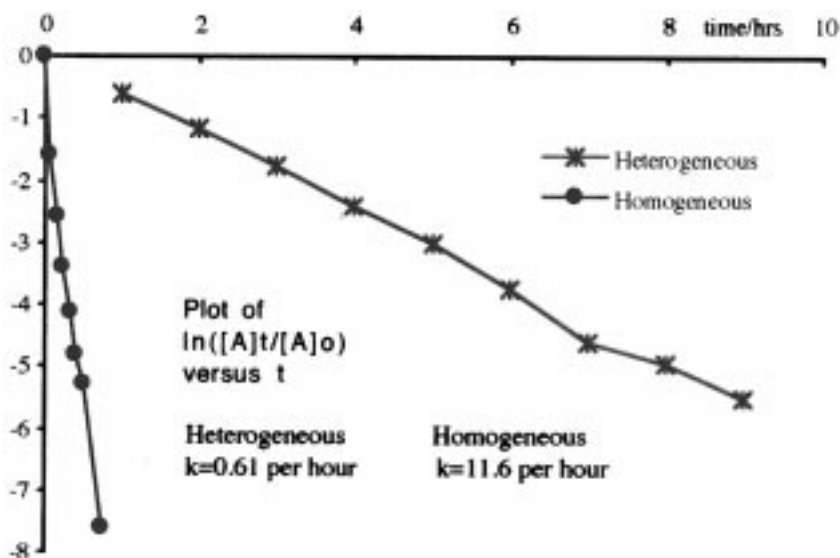


Figure 7. Graph showing first order rate plots (with respect to consumption of PhCHO) for homogeneous and heterogeneous TADDOL mediated addition of Et_2Zn to PhCHO. The pb-Ti-TADDOL-1 (heterogeneous) mediated reaction is approximately 20 times slower than the analogous homogeneous (Ti-TADDOL I, $R^2 = H$, $R^3 = Ph$, aryl = Ph) reaction.

as a check of reproducibility) diethylzinc was prepared (in the reactions above, the diethylzinc solution was prepared by dilution of commercially available, neat diethylzinc with toluene) and allowed to react with PhCHO. Subsequent to the successful isolation of 1-phenyl-1-propanol (3) from this reaction, three other dialkylzinc reagents were prepared and allowed to react with PhCHO (Scheme 5). Results are given in Figure 10. Generally with these reactions a lower yield of product and lower enantioselectivity were observed as compared with our previous results, although the conversion (based upon recovered starting material) was excellent in every case. These results probably reflect the inherent problems that can arise from preparation of the dialkylzinc reagents and the change in solvent from toluene to diethyl ether.²⁴

Conclusions

The above results show that the containment of a polymer-bound catalyst within a polypropylene “tea bag” can successfully be used to prevent decomposition of the polymer. Although the polymer is held within a relatively small area of the apparatus, sufficient solvent circulation through the glass grilles and indeed through the “tea bag” is occurring as evidenced by our results. The contained polymer-bound TADDOLs can be efficiently titanated and the active catalyst generated can be used many times in successive reactions with excellent yields and minimal drop in enantioselectivity

(24) Changes in solvent can often affect the rates of diffusion of solvent and reactants through a particular polymer. The best solvent is usually found by experiment and is typically dependent upon the particular monomer that has been incorporated. This is discussed in a little more detail in refs 12d–f, 13, and 19.

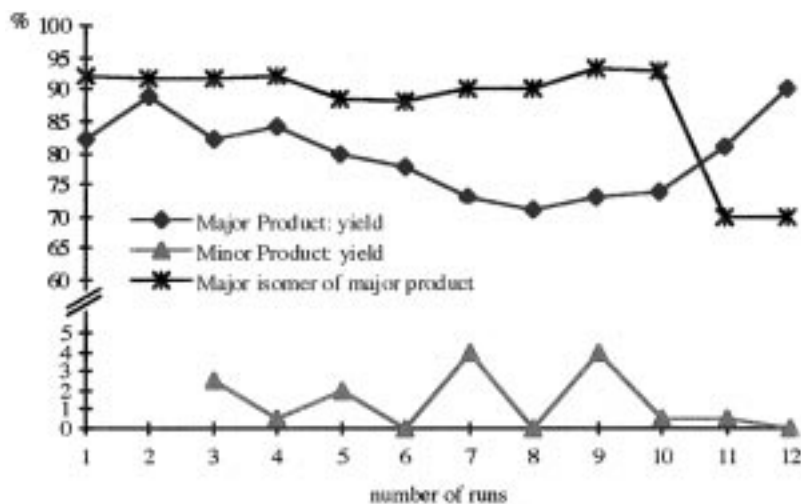
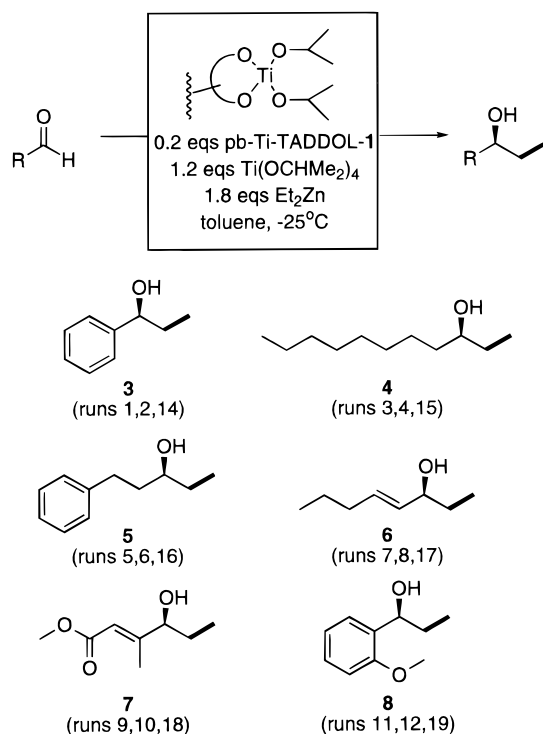


Figure 8. Addition of Et_2Zn to six different aldehydes mediated by pb-Ti-TADDOL-1 (for products see Scheme 4). The enantiopurity of major products is given as % of (*S*)-alcohol. The polymer was washed with toluene (3×50 mL) after each reaction, and then the apparatus was recharged with reactants.

Scheme 4. Addition of Et_2Zn to six different aldehydes mediated by a “tea bag” containing polymer-bound Ti-TADDOL-1. Results are shown in Figures 8 and 9



with time. We have also shown that contamination from one run to the next can be reduced almost completely (down to 0.5%). After a series of reactions the polymer-bound TADDOL can be completely recovered with no polymer degradation, and furthermore the recycled polymer can even be reused with essentially no drop in activity.

Whilst we appreciate that the custom-built nature of the apparatus is not likely to be applicable to process chemistry within an industrial environment (the results described are equivalent to preparing 25 g of product using 1 mol % catalyst: a very small amount by industrial standards!), the principle of supporting the polymer within a polypropylene “tea bag” shows great promise for developing a method in

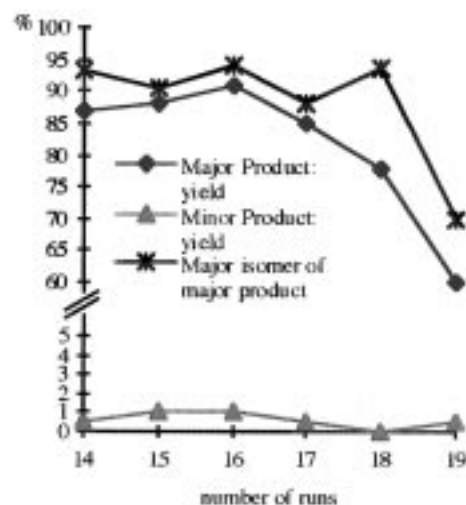


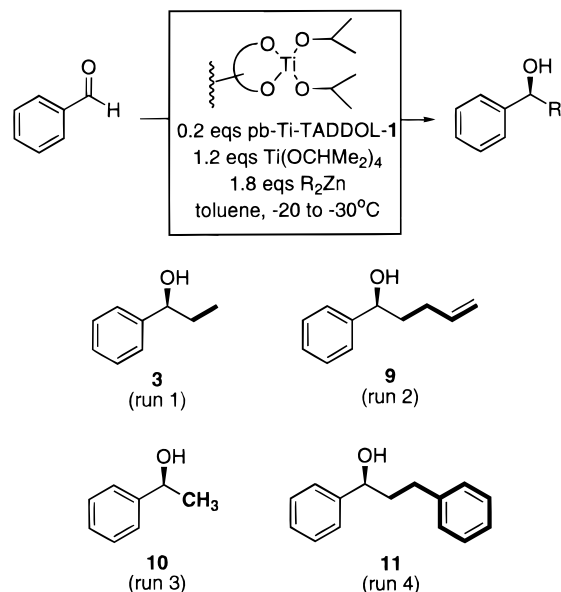
Figure 9. Addition of Et_2Zn to six different aldehydes mediated by pb-Ti-TADDOL-1 with a revised extraction procedure (for products, see Scheme 4). The polymer was washed with (a, runs 14–17) toluene (3×50 mL) with each wash containing $\text{Ti}(\text{CHMe}_2)_4$ (1 mL) or (b, runs 18 and 19) toluene (5×50 mL) with each wash containing $\text{Ti}(\text{CHMe}_2)_4$ (1 mL). The enantiopurity of major products is given as % of (*S*)-alcohol.

which TADDOLs can be successfully utilised in large-scale compound preparation. With an increased number of runs, provided the same minor drop in yield and enantioselectivity already described is continued, then the effective catalyst loading could be further decreased. More efficiently perhaps, the polymer could be utilised within a continuous flow apparatus with the obvious advantages that this provides, and we are currently working to demonstrate this possibility.

Experimental Section

Cooling of the apparatus was achieved using a B. Braun Frigomix S cryostat with a Thermomix UB temperature control unit. NMR experiments were carried out on Varian Gemini 200 or Gemini 300 machines. All ^1H NMR experiments were carried out in CDCl_3 and are referenced to CHCl_3 at 7.26 ppm. Coupling constants are given in Hz. ^{19}F NMR spectroscopy was carried out at 282 MHz in CDCl_3

Scheme 5. Addition of four different dialkylzinc reagents (prepared in situ from the corresponding Grignard reagents) to PhCHO mediated by a “tea bag” containing polymer-bound Ti-TADDOL-1. Results are shown in Figure 10



solutions containing CCl_3F as an internal standard (0.00 ppm). Distillation of products was performed using a Büchi GKR-50 distillation apparatus. All CGC analysis was carried out on a Carlo-Erba Instruments Fractovap 4160 series machine using a DP700 series integrator and a Macherey-Nagel FS-Hydrodex β -PM column [heptakis(2,3,6-tri-*O*-methyl)- β -cyclodextrin, 50 m \times 0.25 mm i.d.]. “Standard conditions” refers to an initial column temperature of 80°C increased at $1^\circ\text{C}/\text{min}$ with a carrier pressure of $1.2\text{ kg}/\text{cm}^2$ of H_2 . Optical rotation measurements were carried out using a Perkin-Elmer 241 polarimeter. Where no temperature is given here (for literature values), a temperature of rt was quoted in the corresponding paper. All organic extracts were routinely dried over MgSO_4 and concentrated using a Büchi rotary evaporator. Flash column chromatography was carried out using Fluka grade Kieselgel-60 SiO_2 (particle size 0.04–0.063 mm).

General Procedure for the pb-Ti-TADDOL Mediated Addition of Diethylzinc to Aldehydes Using the New Apparatus (Figures 3, 8, and 9). The apparatus and polypropylene “tea bag” [mesh size 0.10 mm; containing pb-TADDOL-1 (particle size 0.10–0.25 mm, loading 0.63 mmol/g, 3.50 g, 2.21 mmol) or pb-TADDOL-2 (particle size 0.16–0.40 mm, loading 0.36 mmol/g, 6.20 g, 2.20 mmol)] were predried, the apparatus in an oven at 140°C and the “tea bag” under high vacuum (0.1 mmHg) at 60°C . The apparatus was then rapidly set up (as described in Results and Discussion), evacuated (0.1 mmHg), and flushed with argon three times. Freshly distilled toluene (70 mL) was added followed by $\text{Ti}(\text{OCHMe}_2)_4$ (0.65 mL, 2.21 mmol). After stirring at room temperature overnight, the bulk of the solution was drawn out into the collecting funnel (and quenched and discarded) and the remaining traces of solvent were removed under high vacuum (0.1 mmHg) for 4 h.

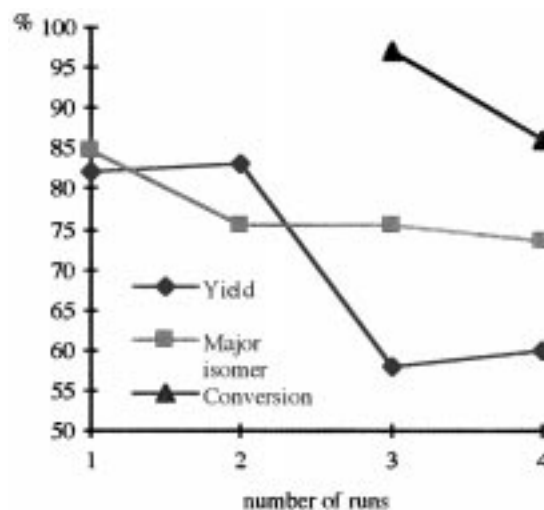


Figure 10. Addition of different dialkylzinc reagents to PhCHO mediated by pb-Ti-TADDOL-1 (for products see Scheme 5). The enantiopurity of the products is given as % of (*S*)-alcohol. (The “tea bag” used in these reactions had been used 4 times previously and stored under Ar for 2 weeks.)

Toluene (70 mL) was added followed by $\text{Ti}(\text{OCHMe}_2)_4$ (3.91 mL, 13.23 mmol) and subsequently RCHO (11.1 mmol). The apparatus was then cooled to the correct internal temperature (typically between -20 and -25°C), at which point diethylzinc (2 M in toluene, 9.92 mL, 19.85 mmol) was added. After completion of the reaction (by TLC analysis) the reaction mixture was drawn into the collecting funnel and drained onto aqueous HCl solution (1 M, 200 mL). The apparatus/“tea bag” was washed with more toluene [3×50 – 60 mL (sufficient to cover the “tea bag”), 1 h of stirring per wash], and the combined reaction mixture and rinses were shaken with the HCl solution. Upon separation the aqueous phase was extracted with diethyl ether (2×100 mL), and the combined organic phases were dried and concentrated under reduced pressure to give (usually) a pale yellow oil, which was purified by distillation (see below). In the meantime the apparatus was recharged (using identical amounts) with toluene, $\text{Ti}(\text{OCHMe}_2)_4$, RCHO, and upon cooling, diethylzinc for subsequent reactions. This procedure was repeated as required.

Multiple addition of diethylzinc to PhCHO (Figure 3) was carried out at approximately -20°C . For the addition of diethylzinc to six different aldehydes (Figures 8 and 9) the reactions were carried out at -25°C . For the latter reactions the polymer “tea bag” was washed as above for runs 1–12, three times with toluene (50 mL) containing $\text{Ti}(\text{OCHMe}_2)_4$ (1 mL) for runs 14–17, and five times with toluene (50 mL) containing $\text{Ti}(\text{OCHMe}_2)_4$ (1 mL) for runs 18 and 19.

General Procedure for the Addition of Different Dialkylzinc Reagents to PhCHO (Figure 10). The apparatus and polypropylene “tea bag” [mesh size 0.10 mm; containing pb-TADDOL-1 (particle size 0.25–0.40 mm, loading 0.63 mmol/g, 3.50 g, 2.21 mmol)] were predried and set up, and the titanate was prepared as described above.

Diethyl ether (40 mL) and subsequently $\text{Ti}(\text{OCHMe}_2)_4$ (4.0 mL, 13.3 mmol) were added to the apparatus followed by cooling (dry ice/acetone) to an internal temperature of

–70 °C. An ethereal solution of dialkylzinc reagent (20 mmol, prepared according to ref 23) was then added slowly to the mixture with the development of a strong yellow colouration. After stirring for approximately 45 min (to allow the mixture to equilibrate to –78 °C), PhCHO (1.12 mL, 11.1 mmol) was added dropwise and the reaction stirred at –78 °C for a further 45–60 min. On being allowed to warm to –30 °C the reaction mixture was stirred for 40–44 h (until completion of the reaction by TLC analysis). The reaction mixture was then drawn off into the collecting funnel, and the “tea bag” was washed with diethyl ether (3 × 60 mL) with each wash containing Ti(OCHMe₂)₄ (1 mL). The combined reaction mixture and washings were quenched onto 1 M HCl, extracted, and purified by flash column chromatography to give the pure alcohols for analysis.

Data for Compounds Prepared via “Tea Bag” Methodology. (*S*)-(-)-1-Phenyl-1-propanol (**3**):²³ purified by distillation at 130 °C, 0.5 mmHg (lit.⁴ 150 °C, 0.3 mmHg), to give a colourless oil, the alcohol **3** (typically 1.36 g, 90%); [α]_D²¹ –24.7 (neat) [lit.²⁵ [α]_D²⁵ –22.2 (neat)]; *R_f* 0.40 (50% diethyl ether in pentane); δ _H (CDCl₃, 200 MHz) 7.39–7.18 (5H, m, Ph), 4.59 (1H, t, *J* 6.6, CHOH), 1.90–1.66 (3H, m, CH₂ + OH) and 0.91 (3H, t, *J* 7.5, CH₃); CGC (standard conditions) *t_R* [(*R*)-alcohol] 45 min, *t_R* [(*S*)-alcohol] 46 min.

(*S*)-(+)-3-Undecanol (**4**):²⁶ purified by distillation at 100–120 °C, 0.2 mmHg (lit.²⁷ 134–137 °C, 37 mmHg), to give a colourless oil, the alcohol **4**; [α]_D²¹ +5.2 (*c* 8.96, EtOH) [lit.²⁸ [α]_D²⁶ +7.79 (*c* 8.63, EtOH)]; *R_f* 0.47 (50% diethyl ether in pentane); δ _H (CDCl₃, 200 MHz) 3.56–3.44 (1H, m, CHOH), 1.61–1.25 (16H, m, 8 × CH₂), 0.92 (3H, t, *J* 7.5, CH₃), and 0.86 (3H, t, *J* 6.6, CH₃); CGC (standard conditions) *t_R* [(*R*)-alcohol] 63 min; ¹⁹F NMR analysis of *R* and *S* Mosher esters, δ _F (CDCl₃, 282 MHz) –71.8 and –71.9 (CF₃).

(*S*)-(+)-1-Phenyl-3-pentanol (**5**):²⁹ purified by distillation at 135 °C, 0.5 mmHg (lit.³⁰ 98–100 °C, 0.03 mmHg), to give a colourless oil, which solidified on standing, the alcohol **5**; [α]_D²¹ +20.3 (*c* 5.07, EtOH) [lit.²⁶ [α]_D²⁷ +26.8 (*c* 5, EtOH)]; *R_f* 0.41 (50% diethyl ether in pentane); δ _H (CDCl₃, 200 MHz) 7.32–7.14 (5H, m, Ph), 3.61–3.46 (1H, m, CHOH), 2.87–2.58 (2H, m, CH₂), 1.89–1.72 (2H, m, CH₂), 1.58–1.38 (3H, m, CH₂ + OH), and 0.94 (3H, t, *J* 7.5, CH₃); CGC (standard conditions) *t_R* [(*R*)-alcohol] 45 min; ¹H NMR analysis of *R* and *S* Mosher esters δ _H (CDCl₃, 300 MHz) 0.94 and 0.84 (CH₃).

(+)-4-Octen-3-ol (**6**):³¹ purified by distillation at 100 °C, 5 mmHg (lit.³² 87 °C, 16 mmHg), to give a colourless oil, the alcohol **6**; [α]_D²¹ +10.2 (*c* 5.15, EtOH); *R_f* 0.42 (50% diethyl ether in pentane); δ _H (CDCl₃, 200 MHz) 5.63 (1H,

dt, *J* 15.4, 6.7, CH₂CH=CH), 5.43 (1H, dd, *J* 15.3, 6.7, CH₂CH=CH), 3.96 (1H, app q, *J* 6.7, CHOH), 2.00 (2H, app q, *J* 7, CH₂CH=CH), 1.64–1.30 (5H, m, 2 × CH₂ + OH), and 0.89 (6H, t, *J* 7, 2 × CH₃); CGC (standard conditions) *t_R* [(*R*)-alcohol] 45 min; ¹⁹F NMR analysis of *R* and *S* Mosher esters, δ _F (CDCl₃, 282 MHz) –72.0 and –72.1 (CF₃).

(-)-Ethyl-3-methyl-4-hydroxy-2-hexenoate (**7**): purified by distillation at 110–130 °C, 0.4 mmHg, to give a colourless oil, the alcohol **7**; [α]_D²¹ –1.0 (*c* 1.57, CHCl₃) [lit.² [α]_D –10.20 (*c* 1.47, CHCl₃)]; *R_f* 0.42 (50% diethyl ether in pentane); δ _H (CDCl₃, 200 MHz) 5.87–5.85 (1H, m, alkene CH), 4.11 (2H, q, *J* 6.7, CH₃CH₂OCO), 3.97 (1H, t, *J* 6.7 CHOH), 2.35 (1H, s, OH), 2.06 (3H, d, *J* 1.7, CH₃), 1.74–1.40 (2H, m, CHOHCH₂CH₃), 1.24 (3H, t, *J* 7.2, CH₃CH₂OCO), and 0.87 (3H, t, *J* 7.2, CHOHCH₂CH₃); CGC (standard conditions) *t_R* [(*R*)-alcohol] 63 min, *t_R* [(*S*)-alcohol] 64 min.

(*S*)-(-)-1-(2'-Methoxyphenyl)-1-propanol (**8**): purified by distillation at 150 °C, 0.2 mmHg (lit.³³ 78–80 °C, 0.1 mmHg), to give a colourless oil, the alcohol **8**; [α]_D²¹ –20.8 (*c* 3.4, toluene) [lit.²⁶ [α]_D²⁷ –50.63 (*c* 3, toluene)]; *R_f* 0.42 (50% diethyl ether in pentane); δ _H (CDCl₃, 200 MHz) 7.34–7.21 (2H, m, 2 × aryl H), 7.01–6.87 (2H, m, 2 × aryl H), 4.81 (1H, t, *J* 6.6, CHOH), 3.85 (3H, s, OCH₃), 1.90–1.75 (2H, app pentet, *J* 7.0, CH₂), and 0.97 (3H, t, *J* 7.5, CH₃); CGC (standard conditions) *t_R* [(*R*)-alcohol] 72 min, *t_R* [(*S*)-alcohol] 68 min.

(-)-1-Phenyl-4-penten-1-ol (**9**): purified by flash column chromatography (25% diethyl ether in pentane) to give a colourless oil, the alcohol **9** (1.49 g, 83%); [α]_D²¹ –18.1 (*c* 3.27, CHCl₃) [lit.²³ [α]_D –31.9 (*c* 3.2, CHCl₃)]; *R_f* 0.60 (50% diethyl ether in pentane); δ _H (CDCl₃, 200 MHz) 7.38–7.27 (5H, m, Ph), 5.96–5.76 (1H, m, alkene CH), 5.10–4.98 (2H, m, 2 × alkene CH), 4.72 (1H, t, *J* 6.5, CHOH), 2.22–2.05 (2H, m, CH₂), and 2.01–1.76 (3H, m, CH₂ + OH); CGC (TFA ester, conditions: 80 °C isotherm, 1.0 kg/cm² of H₂ pressure) *t_R* [(*R*)-alcohol] 125 min, *t_R* [(*S*)-alcohol] 121 min.

(*S*)-(-)-1-Phenyl-1-ethanol (**10**):²³ purified by flash column chromatography (25% diethyl ether in pentane) to give a colourless oil, the alcohol **10** (0.79 g, 58%); [α]_D²¹ –24.3 (*c* 1.9, CHCl₃) [lit.³⁴ [α]_D²⁵ –58 (*c* 1.7, CHCl₃)]; *R_f* 0.41 (50% diethyl ether in pentane); δ _H (CDCl₃, 200 MHz) 7.42–7.25 (5H, m, Ph), 4.89 (1H, q, *J* 6.5, CHOH), 2.44 (1H, s, OH), and 1.50 (3H, d, *J* 6.3, CH₃); CGC (standard conditions) *t_R* [(*R*)-alcohol] 36 min, *t_R* [(*S*)-alcohol] 37 min. Also isolated was PhCHO (0.47 g).

(*S*)-(-)-1,3-Diphenyl-1-propanol (**11**):²³ purified by flash column chromatography (25% diethyl ether in pentane) to give a colourless oil, the alcohol **11** (1.41 g, 60%); [α]_D²¹ –6.16 (*c* 5.7, EtOH) [lit.³⁵ [α]_D –15.6 (*c* 5, EtOH)]; *R_f* 0.56 (50% diethyl ether in pentane); δ _H (CDCl₃, 200 MHz) 7.39–7.16 (10H, m, 2 × Ph), 4.75–4.67 (1H, m, CHOH), 2.86–2.61 (2H, m, CH₂), 2.25–2.02 (2H, m, CH₂), and 1.86 (1H,

(25) Beilsteins Handbuch der Organischen Chemie, 6 EIII, 1793.

(26) Kaufmann, T.; Neiteler, C.; Neiteler, G. *Chem. Ber.* **1994**, 127, 659.

(27) Rickborn, B.; Wood, S. E. *J. Am. Chem. Soc.* **1971**, 93, 3940.

(28) Soai, K.; Yokoyama, S.; Ebihara, K.; Hayasaka, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1690.

(29) Ishizaki, M.; Fujita, K.-I.; Shimamoto, M.; Hoshino, O. *Tetrahedron: Asymmetry* **1994**, 5, 411.

(30) Beilsteins Handbuch der Organischen Chemie, 6 EII, 504; EIII, 1953.

(31) Teo, K.-E.; Barnett, G. H.; Anderson, H. J.; Loader, C. E. *Can. J. Chem.* **1978**, 56, 221.

(32) Schnurpfeil, D. *J. Prakt. Chem.* **1988**, 330, 487.

(33) Bromley, L. A.; Davies, S. G.; Goodfellow, C. L. *Tetrahedron: Asymmetry* **1991**, 2, 139.

(34) Garcia, C.; Collet, A. *Tetrahedron: Asymmetry* **1992**, 3, 361.

(35) Beilsteins Handbuch der Organischen Chemie, 6 EII, 643.

d, J 3, OH); CGC (standard conditions) t_R [($R+S$)-alcohol] 45 min; ^{19}F NMR analysis of R and S Mosher esters, δ_F (CDCl_3 , 282 MHz) -71.7 and -72.1 (CF_3). Also isolated was PhCHO (0.35 g).

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