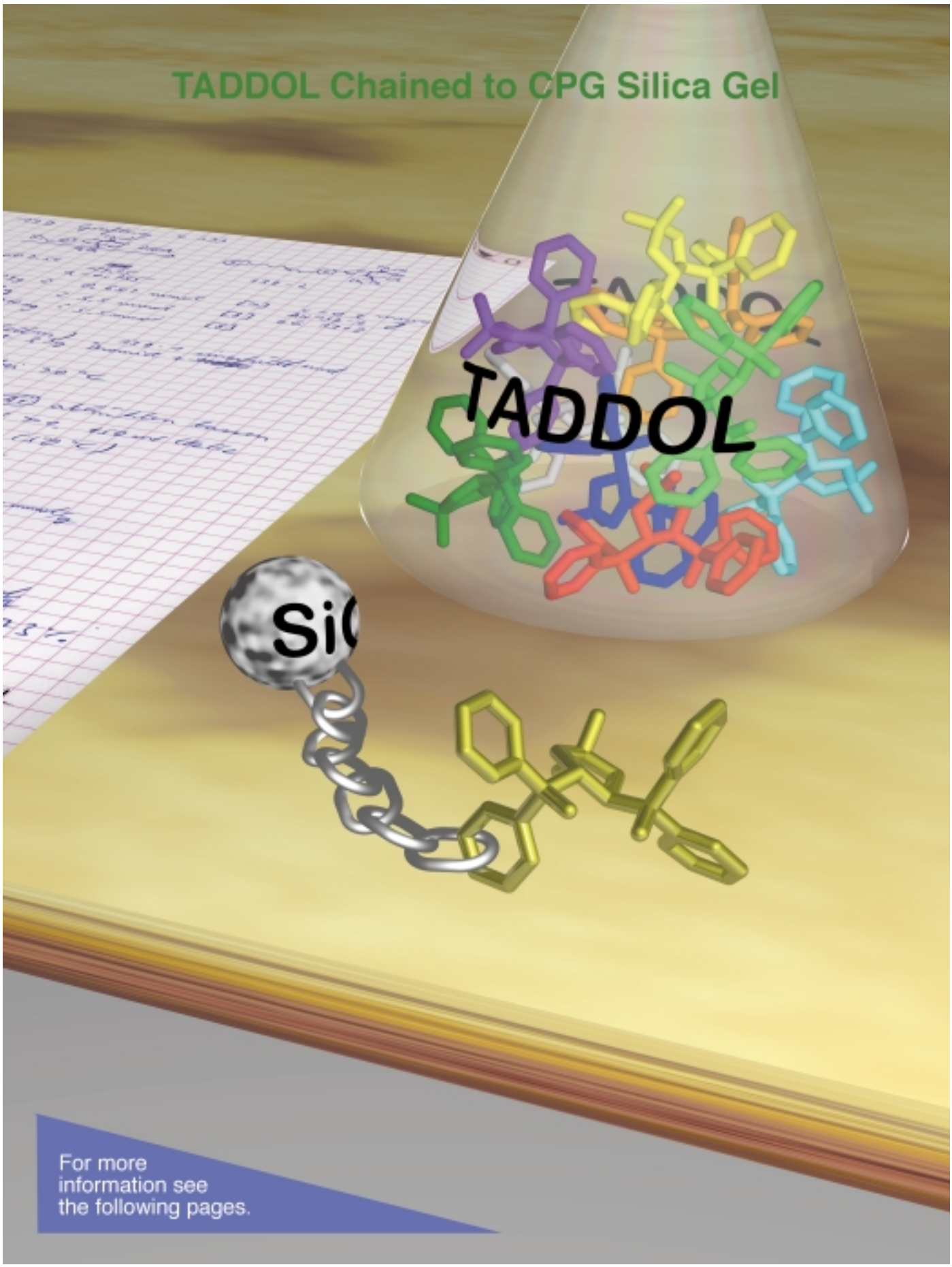

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Preparation and Characterization of TADDOLs Immobilized on Hydrophobic Controlled-Pore-Glass Silica Gel and Their Use in Enantioselective Heterogeneous Catalysis**

Alexander Heckel and Dieter Seebach*[a]

Abstract: Highly porous silica gel (controlled-pore glass, CPG, ca. 300 $m^2 g^{-1}$) with covalently attached TADDOLs (loading 0.3 – 0.4 $mmol g^{-1}$) and Me_3Si-hydrophobized surface has been prepared: First, mercaptopropyl groups were attached to the silica gel by treatment with (mercaptopropyl)trimethoxysilane; then the SH groups were tritylprotected, and the remaining accessible SiOH groups hydrophobized by silylation (heating with Me_3Si-imidazole); after deprotection, the SH groups were used as nucleophiles for benzylation with TADDOLs carrying a 4-bromomethyl-phenyl group in the 2-position of their dioxolane rings; alternatively, the SH groups have been benzylated with the 4-bromomethyl-benzaldehyde acetal of diethyltartrate, and the diarylmethanol moieties of the TADDOLs created on the solid support by addition of excess phenyl, or 1- or 2-naphthyl magnesium bromide. Each step of the immobilizing procedure was carefully monitored and analyzed (Ellman's test, methyl-red test), and resulting materials characterized by electron microscopy, DRIFT spectroscopy (IR), ^{13}C- and ^{29}Si NMR solid-state NMR spectroscopy, and elemental analysis. The immobilized TADDOLs were titanated to give $(iPrO)_2Ti$-, Cl_2Ti-, or $(TosO)_2Ti$-TADDOLates which were used for catalyzing the additions of Et_2Zn or Bu_2Zn to PhCHO and of diphenyl nitrone to 3-crotonoyl-oxazolidinone. The following findings are remarkable: i) The enantioselectivities and conversions of the reactions mediated by the CPG-immobilized Ti-TADDOLates match those observed under standard homogeneous conditions. ii) If and when the rates and/or the enantioselectivities of reactions have dropped after several applications of the same catalyst batch, washing with aqueous HCl/acetone and reloading with titanate leads to full restoration of its performance. iii) There is no detectable loss of the hydrophobizing Me_3Si groups after nine acidic washes! iv) There is a seasoning of the catalyst material in the Cl_2Ti-TADDOLate-mediated [3+2] cycloaddition of diphenylnitrone: Initially it is necessary to use 0.5 equivalents of the immobilized catalyst to match the performance of the homogeneous catalyst; after three runs the reaction rate, enantio- and diastereoselectivity have dropped considerably; acidic washing after each subsequent run completely restores the performance; after a total of seven runs the amount of catalyst can be reduced to 0.4, 0.3, 0.2, and 0.1 equivalents in the following runs, with identical good results!

Keywords: CPG · heterogeneous catalysis · stereoselective catalysis · supported catalysts · TADDOL

Introduction

Since its introduction in 1983[1] the TADDOL (*α*,*α*,*α*′,*α*′-*t*etra*a*ryl-2,2-*d*imethyl-1,3-*d*ioxolan-4,5-dimethan*ol*) has developed into a true chiral auxiliary system with broad applicability—a fact that has recently been accounted for in a comprehensive review article.[2] In 1996 our group was the first one to report on the successful immobilization of TADDOL.[3] We used styryl-substituted derivatives for the immobilization by suspension copolymerization with styrene and divinylbenzene. Already in this investigation it was shown that the derived titanate catalysts could be reused, which should be—apart from the convenient separability from the reaction mixture—one of the key features of heterogeneous catalysts of this type. We then studied the reusability and especially the large-scale application in more detail.[4] In the meantime other groups had started to work in this field, too. In fact, the very first publication comes from Mayoral and Luis who tried to immobilize TADDOL in an acetalization reaction of a tartaric acid ester using a Merrifield-type polymer bearing aldehyde groups,[5] but they failed to build up the TADDOL structure in the successive Grignard-addition step. Later, Irurre et al. succeeded with exactly this

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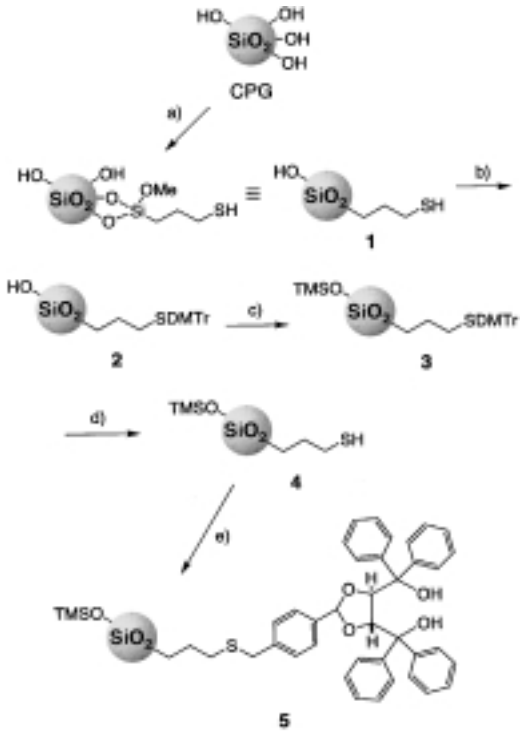
strategy[6] and they went on evaluating different linkers for the immobilization.[7] Apart from the work already mentioned, the groups of Mayoral and Luis have immobilized a tartaric acid amide through an ether linkage to one of the hydroxyl groups and—after saponification to the ester—added a solution of PhMgBr. The resulting structure resembles an immobilized TADDOL but does not have the dioxolane ring—an important element of order in the TADDOL structure. Thus, it is not too surprising that no enantioselectivity could be achieved in the test reaction.[8] So these authors went on to immobilize phenol-substituted TADDOLs by grafting onto Merrifield resin.[8] The derived heterogeneous titanates showed good performance in a Diels–Alder test reaction. In a more recent investigation the same groups prepared monolithic polymers by bulk polymerization, which can be used in a continuous-flow reactor.[9] Our group has also further elaborated the immobilization strategies, and we found that surrounding TADDOLs with dendritic branches and using these dendrimers as the only cross-linkers in a suspension-copolymerization afforded beads with superior performance.[10] In all of the studies mentioned so far a polystyrene backbone has been used. Apart from that the only other support for TADDOL found in the literature are polyethylene fibers that were activated by irradiation and reacted with styryl-substituted TADDOLs, which were thus immobilized.[11]

Some time ago we have started to extend the variety of available supports to silica gel (CPG, controlled-pore glass).[12] In our studies with dendritic cross-linkers[10c] we had found that the catalytic performance can be correlated with the swelling ability of the polymer. CPG is a rigid support that offers an openly accessible pore structure in all possible solvents and in a wide temperature and pressure range. Here, we would like to give a full account of our work in this field.

Results and Discussion

Preparation of TADDOLs immobilized on hydrophobic silica gel: The first problem to face was the intrinsic reactivity of silica gel: The pK_a of the silanol (Si-OH) groups is relatively low (7.1[13]) and this is incompatible with many of the reactions for which TADDOLs are used. Also, the surface of normal silica gel is very hydrophilic. Water can be adsorbed through hydrogen bonds[14] and liberated easily, and two adjacent silanol groups can form a Si-O-Si bridge expelling a molecule of water. Thus, if one tries, for example, to add Et_2Zn to PhCHO, using *soluble* $(i\mathrm{PrO})_2$Ti-TADDOLate as a catalyst, which usually proceeds to completion within 60 minutes with 98% *es*,[15] in the presence of silica gel no conversion is detected after 17 hours. This demonstrates the necessity to "protect" the Si-OH groups, which can be done in various ways: Apart from a possible fluorination[16] or perfluoroalkylation[17] of the surface that could have been considered, we have tested various procedures to trimethylsilylate[18] or methylate[19] silica gel, and we obtained, indeed, better conversions in the above-mentioned test reaction. Not until we chose trimethylsilylimidazole (TMSIm) as silylating agent[20] did we obtain results with *soluble* TADDOLates in the presence of such hydrophobized silica gel, which were similar to those observed in the absence of silica gel.

Of the two procedures of immobilizing ligands on silica gel—grafting and incorporating by the sol-gel process—we chose to study the former one first. Thus, we selected CPG as support and began with the introduction of a mercaptopropyl linker (→ **1**, Scheme 1). A general problem with solid-phase synthesis is monitoring the reaction, since, of course, the



Scheme 1. Preparation of the immobilized TADDOL **5** starting from commercially available CPG. a) $(MeO)_3Si(CH_2)_3SH$, imidazole, DMF, 100 °C, 20 h; b) DMTrCl, Et_3N, 4 h, r.t.; c) TMSIm, neat, 60 °C, 1 h; d) 1% TFA in CH_2Cl_2, Et_3SiH; e) benzyl bromide derivative of TADDOL, $EtNiPr_2$, toluene, 70 °C, 12 h.

routine tools (TLC, solution NMR, etc.) cannot be applied. However, as in this case the solid material is the final product, purification after the reaction sequence is not possible. This means that every single step had to be optimized, and therefore analytical tools to monitor every reaction were required. The degree of loading of mercaptopropyl silica had been determined by Ford et al.[21] (cf. Figure 1a) who used Ellman's test[22] which had originally been designed for the determination of the amount of SH groups in proteins.[23] As can be seen from Table 1 a typical loading of 0.46 mmol g^{-1} could be obtained, when (mercaptopropyl)trimethoxysilane in DMF was used, together with imidazole.[24, 25] In the next step, the mercapto groups were protected by reaction with DMTrCl (→ **2**); no SH groups could be detected after this step (Table 1). The choice of this particular protecting group allows for an easy determination of the DMTr content (cf. Figure 1b) with a test that is used in oligonucleotide solid-phase synthesis.[26] Indeed, the amount of detectable DMTr groups was in the same order as the amount of SH groups had

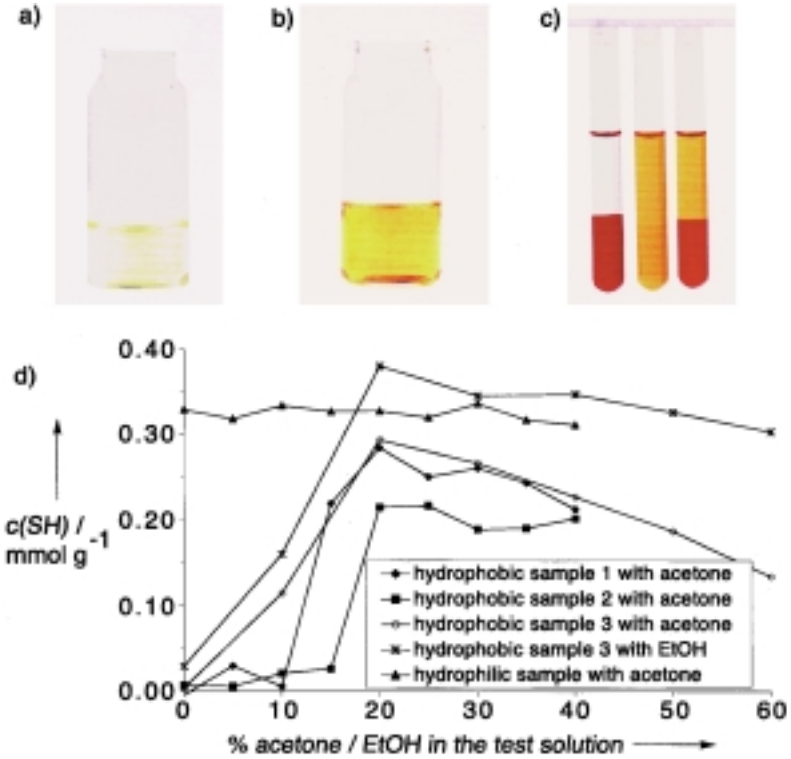


Figure 1. Analytical tools for monitoring the reaction sequence shown in Scheme 1. a) Determination of the mercapto group concentration with Ellman's SH test. b) Determination of the DMTr group concentration by addition of acid to a sample. c) Methyl-red test for the semiquantitative determination of the degree of hydrophobization of silica gel (for more details see text). d) Correlation between the detectable amount of SH groups in hydrophilic (silica gel **1**) and hydrophobic (silica gel **4**) samples of mercaptopropyl silica gel and the addition of acetone or ethanol to the test solution (Ellman's test).

Table 1. Analysis of the modified silica gels **1**–**5** (using CPG with 200 Å pore diameter). The loading with TADDOL (determined by the reduction of the amount of SH groups when going from silica gel **4** to silica gel **5**) was 0.44 mmol g^{-1}.

Material	SH Test mmol g^{-1}	DMTr Test mmol g^{-1}	Methyl red test
CPG	–	–	dark red
1	0.46	–	dark red
2	0.01	0.46	dark red
3	–	–	no color change
4	0.46	0.02	light red
5	0.02	–	light red

been before. In the next step the silica gel was made hydrophobic by heating with neat TMSIm (→ **3**).[20] The amount of Si-OH groups in a silica gel sample can be determined by treatment with BuLi and measurement of the amount of butane evolved;[27] in addition, the amount of adsorbed water has to be determined in a Karl-Fischer titration.[28] A much simpler, but only semiquantitative alternative is mentioned in the literature:[13, 27a, 29] When normal silica gel is added to a solution of methyl red in benzene—depending on the concentration and the amount of silica gel—all methyl red is adsorbed on its surface; the supernatant solution turns colorless and the silica gel dark red (cf. Figure 1c, left test tube); when the same amount of silica gel, which had been made hydrophobic by Me_3SiCl/base, is added, it still turns red, but less dye is adsorbed and the solution remains orange (Figure 1c, test tube on the right-hand side). Finally, when a silica-gel sample is added, which had been treated with TMSIm, no color change was observed (Figure 1c, test tube in the middle). This test proved that TMSIm gave the best hydrophobization, which is in accord with previously published observations.[20, 30] The next step in the sequence was the deprotection of the mercapto groups (→ **4**), which could be achieved with TFA solution (and Et_3SiH as scavenger). It was crucial to know how much of the SH groups were restored in that procedure because this measurement and the corresponding test after attachment of TADDOL (→ **5**) would result in a value for the final loading of the silica gel with TADDOL. Ellman's test had to be modified since the original procedure uses an aqueous test medium, which does not wet hydrophobic silica gel. Various amounts of acetone and ethanol were added to the test solution to allow for penetration of the pores.[31] As can be seen in Figure 1d, the value determined for the loading with SH groups was unaffected by addition of acetone when we analyzed a (*hydrophilic*) sample of silica gel **1**. When using the original procedure (without acetone or ethanol) no mercapto groups could be detected in three different samples of the (*hydrophobic*) silica gel **4**. With addition of acetone or, preferably, ethanol the SH groups "became detectable"; the values reach a maximum with 20% additive.[32] In most cases we used ethanol as an additive to the test solution. In the final step of the sequence the TADDOL ligand was introduced in a nucleophilic substitution reaction, and the loading with TADDOL was determined by the reduction of detectable mercapto groups. Typically, loadings of 0.3–0.4 mmol TADDOL g^{-1} were obtained.

We then wanted to study the influence of the pore size of the support on the loading and later, also on the catalytic activity. Unless stated otherwise, throughout these investigations CPG with a pore size of 200 Å has been used. As can be seen in Table 2, the loadings obtained with a 500 Å or 1000 Å material were much lower. The loading obtained with the latter material was so low that we have actually never tested it for a reaction. For an explanation one has to consider the different specific surface areas of the three supports which were 280–355, 70–90 and 30–55 $m^2 g^{-1}$ for the 200, 500, and 1000 Å material, respectively. Rough calculations show that the loadings obtained in all three cases are close to the maximum possible ones.[33]

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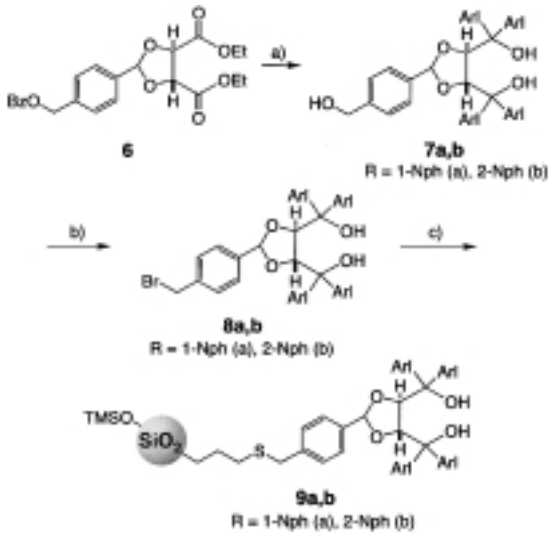
Table 2. Influence of the pore diameter of the support on the loading.

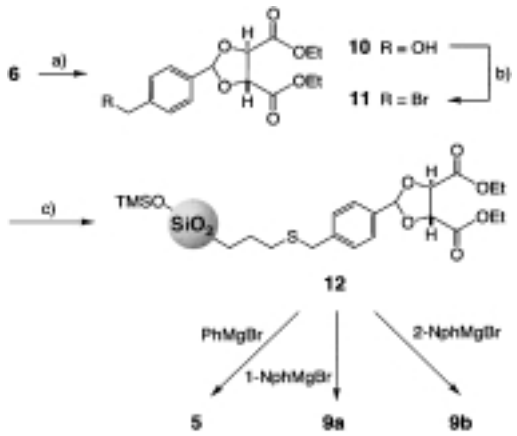
Pore diameter silica gel	500 Å SH test mmol g^{-}	500 Å DMTr test mmol g^{-1}	500 Å methyl red test	1000 Å SH test mmol g^{-1}	1000 Å DMTr test mmol g^{-1}	1000 Å methyl red test
1	0.15	–	dark red	0.08	–	dark red
2	0.00	0.17	dark red	0.00	0.11	dark red
3	–	–	no color change	–	–	no color change
4	0.15	0.00	light red	0.09	0.00	light red
5	0.00	–	light red	0.02	–	light red

We also wanted to immobilize different TADDOLs. With the substitution of the acetal center of the dioxolane ring being determined by the linker chosen, the aryl groups could still be varied. From a statistical survey[34] we knew that, apart from phenyl groups, 1- and 2-naphthyl substituents were the ones used most frequently. Thus, starting from the known[3] compound **6** (Scheme 2) we prepared the TADDOLs **7a**, **b** and **8a**, **b** in analogy to the phenyl derivatives. These compounds turned out to be difficult to purify. Finally, they, too, were grafted on hydrophobic mercaptopropyl silica gel **4** (→ **9a**, **b**).



Scheme 2. Preparation of the heterogeneous TADDOLs **9a** and **9b** bearing 1-naphthyl- and 2-naphthyl-groups by the grafting method. a) 1- or 2-NphMgBr, THF, reflux; b) CBr_4, PPh_3, THF, r.t.; c) silica gel **4**, EtNiPr$_2$, toluene, 70 °C, 24 h.

Another procedure of producing various immobilized TADDOLs with different aryl groups is outlined in Scheme 3: Again starting from the known compound **6** we isolated compound **10** after a titanate-catalyzed transesterification. Under Appel conditions this compound was converted to the corresponding bromide **11**, which was grafted on silica gel **4** to give the immobilized tartaric ester **12**. By adding solutions of different aryl Grignard reagents to this material it was possible to build up the TADDOL structure on the solid support! This route has several advantages: First of all it avoids the laborious purification of the compounds **7a**, **b** and **8a**, **b** and it can also serve as a kind of combinatorial precursor for TADDOLs on silica gel with different aryl groups. However, it remained to be proven (see below) that



Scheme 3. Alternative route leading to heterogeneous TADDOLs **5**, **9a** and **9b** by Grignard addition to the immobilized tartate ester **12**, which serves as a combinatorial precursor of TADDOLs with different aryl groups. This method avoids the laborious purification of the compounds **7a**, **b** and **8a**, **b**. a) $Ti(OEt)_4$, EtOH, reflux, 5 h; b) CBr_4, PPh_3, THF, r. t.; c) silica gel **4**, EtNiPr$_2$, toluene, 70 °C, 12 h.

the heterogeneous TADDOLs **5** and **9a**, **b** prepared by this route show the same catalytic performance as those prepared in the previously shown manner (Schemes 1 and 2).

We have also tried to immobilize TADDOLs on silica gel bearing chlorobenzyl groups, trying to avoid the protection and deprotection steps necessary as outlined in Scheme 1. After modification of CPG with (chlorobenzylmethyl)trimethoxysilane and direct hydrophobization with TMSIm, the TADDOL was to be introduced, again in a nucleophilic substitution reaction. For this purpose the phenyl analogue of TADDOL **7** or its mercapto derivative were envisaged to be used, but we found that most of the benzyl chloride linker had been destroyed during the hydrophobization step. Using TMSCl and Hünig's base or di-*tert*-butylpyridine instead did not solve this problem and afforded only less hydrophobic material. Thus, this strategy was abandoned.

Characterization of the heterogeneous TADDOLs: Since the routine tools of characterization—as mentioned before—cannot be applied to ligands immobilized on silica gel, other techniques had to be used. To demonstrate the preservation of the porous structure of the materials we have taken electron-microscope pictures (Figure 2a).

Another analysis is IR spectroscopy; because we could not observe suitable IR spectra with our silica gels in KBr pellets, we used the DRIFT (diffuse reflection infrared fourier transform) technique (Figure 2b). After modifying CPG with mercaptopropyl groups, the signals of the stretching vibration

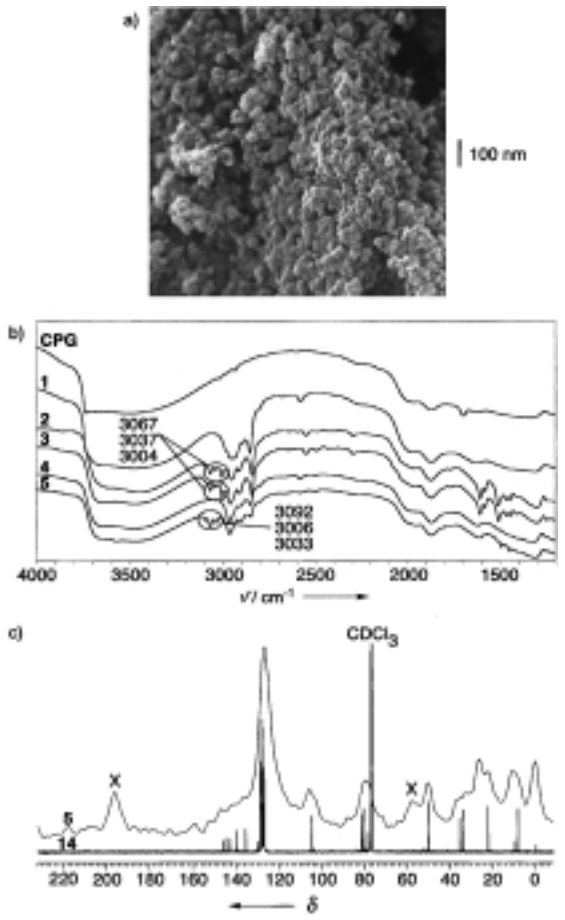
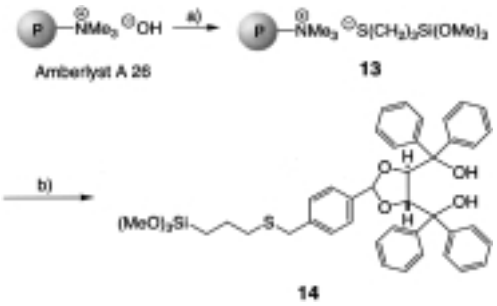


Figure 2. Characterization of some of the modified silica gels prepared: a) Scanning electron-microscopy image of the immobilized TADDOL **5**. The picture shows a square region of 1075 nm length. b) DRIFT (diffuse reflection infrared fourier transform) spectra (in "transmission") of CPG and the silica gels **1**–**5**. The figures show the exact wavenumbers of the peaks. c) Superposition of a ^{13}C NMR solid-phase spectrum of silica gel **5** (upper curve, 100 MHz, 7 kHz rotational frequency of the sample) and a ^{13}C solution-phase NMR spectrum of compound **14** (lower curve, in $CDCl_3$, 100 MHz). The peaks labeled with "X" are rotational side bands of the phenyl signals (shifted in a spectrum taken with different rotational frequency).

of the aliphatic CH bonds could be seen. The aromatic CH bonds of silica gel **2** are observed at the same wavenumbers as the ones of DMTrCl in CCl_4 (3065, 3037, 3002 cm^{-1}), and they disappear after deprotection. Finally, after grafting the TADDOL, its characteristic aromatic CH-stretching signals were detected at the expected wavenumbers (3089, 3061, 3028 cm^{-1}, reference spectrum taken in CCl_4). The broad band between 3000 and 3700 cm^{-1} is usually explained as the signals of the OH-stretching vibrations of the silanol groups on the surface of silica gel.[14, 35] This appears to be in contradiction to our claim of a thorough hydrophobization but again we have to stress that we have never determined the numerical degree of hydrophobization but found (see below) the "capping" procedure using TMSIm to be satisfactory for the use in reactions involving organozinc reagents.

Solid-phase NMR is another powerful tool for the characterization of modified silica gels since the backbone—in contrast to organic polymers—does not contain any carbon atoms. In Figure 2c the solid-phase ^{13}C NMR spectrum of the immobilized TADDOL **5** is depicted (upper curve). For correlation purposes and to study ways of introducing trimethoxysilyl groups ("silyl anchors") for sol–gel experiments we wanted to prepare compound **14** (Scheme 4). Some strategies for the introduction of these "silyl anchors" can be found in the literature but only few have a broader



Scheme 4. Preparation of compound **14**, a TADDOL with "silyl anchor", using the solid-phase reagent **13**. a) $(MeO)_3Si(CH_2)_3SH$, MeOH; b) benzyl bromide derivative of TADDOL, MeOH, 17 h, r.t.

potential.[36, 37] The problem is the isolation and purification since, for example, column chromatography is usually accompanied with major loss of material. This problem can be circumvented elegantly by using supported reagents: In a slight modification of a procedure for the synthesis of unsymmetrical sulphides[38] we treated a basic ion-exchange resin with an excess of (mercaptopropyl)trimethoxysilane and obtained reagent **13**, after thorough washing of the solid phase. Using an excess of this reagent, compound **14** could be obtained under very mild conditions, and in fact the spectrum on the bottom of Figure 2c is taken from the crude material! The bromide liberated and the excess mercaptan could be removed by filtration. Comparing the spectra of compound **14** and silica gel **5**, most of the peaks in the solid-phase spectrum have a corresponding signal in the liquid-phase spectrum of the reference compound, except for the rotational side bands (labelled "X") which come from the solid-phase technique. Also, in the solid-phase spectrum, the peak of the TMS groups can be seen at about $\delta = 0$.

Finally, elemental analysis might be expected to give interesting information, too. For simple silica gel derivatives this is true, but since the TMS groups, the linker, and the TADDOL all contribute to the carbon content, this is no option. However, we determined the sulphur content in some batches and found values around 0.5 mmol g^{-1}. In thermogravimetric experiments we found silica gel **5** to be stable up to at least 200 °C (less than 0.3 % weight loss).

Enantioselective nucleophilic additions to aldehydes catalyzed by CPG-immobilized Ti-TADDOLates: The first reaction we studied was the addition of Et_2Zn to PhCHO. Therefore, we prepared the heterogeneous Ti-TADDOLate **15a** (Scheme 5). The results have already been published elsewhere.[12] We have found that in ten successive runs the enantioselectivity of the reaction had somewhat decreased but the catalytic activity of the heterogeneous catalyst could be fully restored by washing with HCl/H_2O/acetone and

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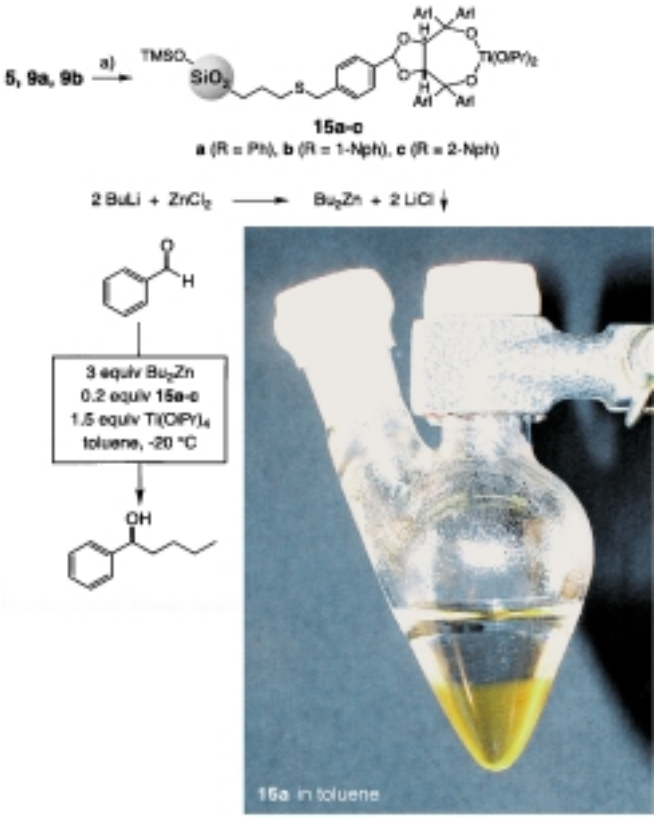

Scheme 5. Preparation of the immobilized Ti-TADDOLates **15a–c** and their use in the addition of Bu_2Zn to PhCHO. The picture shows a reaction flask with silica gel **15a** in Et_2O. The usually colorless silica gel **5** turns yellow upon titanation. For conversions and enantioselectivities obtained with the different catalysts, see Figure 4. a) $Ti(OiPr)_4$, toluene, azeotropic removal of the *i*PrOH formed.

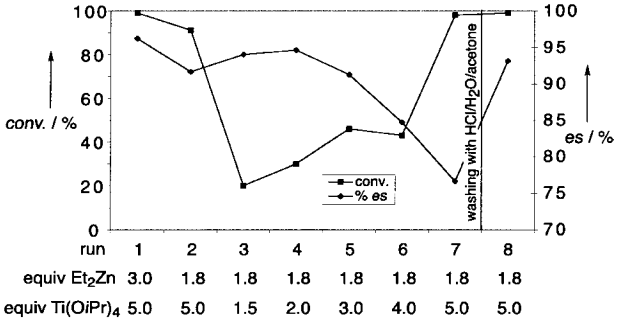

Figure 3. Results of the addition of Et_2Zn to PhCHO in the presence of a hydrophilic analogue of silica gel **5** (made by grafting of a suitable benzyl bromide-substituted TADDOL on silica gel **1**). The curve showing the conversion belongs to the left *y* axis and the curve showing the enantioselectivity belongs to the right *y* axis with a different scale!

reloading with titanate. This washing procedure could be repeated several times, which shows that the decrease in selectivity is not due to catalyst leaching or decomposition but rather to accumulation of by-products (most probably hydrolysis products).

As previously mentioned, with *hydrophilic* silica gel present, there is no addition of Et_2Zn to PhCHO. However, knowing that this addition reaction is catalyzed much less efficiently by achiral $Ti(OiPr)_4$ than by the chiral Ti-TADDOLates,[2] we wanted to see if, by the addition of a large excess of $Ti(OiPr)_4$, this reaction becomes possible with TADDOLs on normal, *hydrophilic* CPG, thus avoiding the hydrophobization procedure altogether. Indeed, with both a large excess of Et_2Zn and $Ti(OiPr)_4$, almost complete conversion and an acceptable enantioselectivity was achieved (Figure 3, mind the different scales for the conversion and enantioselectivity!). Using less Et_2Zn in the second run was possible, without much loss in enantioselectivity. In runs three to seven we tried to find out what the optimum amount of $Ti(OiPr)_4$ was: The enantioselectivity dropped sharply. Washing with HCl/H_2O/acetone could almost restore the degree of enantioselectivity to the value of the first run, but it is clear that—unless one decides to regenerate the catalyst after every run—using TADDOLs on *hydrophobic* silica gel gives better results in multiple use.

Our incentive to choose the addition reaction of Et_2Zn to PhCHO as first test reaction was that it is an easily performable test reaction that should help us to optimize the procedure of preparing heterogeneous TADDOLs on silica gel and we had demonstrated previously that, at least with soluble Ti-TADDOLates, many Zn organyls other than Et_2Zn can be added to carbonyl groups stereoselectively.[2, 39] For the investigations with CPG-immobilized TADDOL, the Zn-organyls were prepared in situ by transmetallation from Grignard reagents or Li-organyls. To show that the addition of Zn reagents, prepared in this way, is also possible with Ti-TADDOLates supported on silica gel, we chose the addition of Bu_2Zn to PhCHO as next test reaction. The choice of BuLi as Li-organyl is explained by our wish to use standardized starting material during the tests. The transmetallation was carried out by addition of $ZnCl_2$ and the LiCl formed was removed with a syringe filter. Apart from the heterogeneous Ti-TADDOLate **15a**, the corresponding 1-naphthyl and 2-naphthyl derivatives **15b** and **15c** were also tested. Additionally, for reasons of comparison, each of the heterogeneous TADDOLs was prepared, both by grafting of preformed TADDOLs (Schemes 1 and 2) and by Grignard addition to the supported tartrate ester (Scheme 3). In Figure 4 the results are outlined. In the first two runs with catalyst **15a**, prepared by grafting (Figure 4, upper diagram, left-hand side), only two equivalents of Bu_2Zn were used (following the literature procedure for soluble Ti-TADDOLates[39]), which resulted in a low conversion. In all other runs, also with the other catalysts, three equivalents of Bu_2Zn were used. This might be a tribute one has to pay due to the smaller scale of the reaction compared with the one of the previous investigations.[39, 40] Once this problem was solved, the results concerning conversion and enantioselectivity were satisfactory for catalyst **15a**, which turned out to be reusable (for a comment on the third and fifth run with **15a**, prepared by the Grignard route, see below). With the soluble "progenitor" TADDOL (with phenyl groups and a dimethyl-substituted acetal center) 82% yield and 99% *es* can be obtained in this reaction.[39] Catalyst **15b**, prepared by grafting, showed a surprising behaviour: In the first run the enantioselectivity was very poor. After HCl/H_2O/acetone washing the enantioselectivity was better in the second run and rose even more in

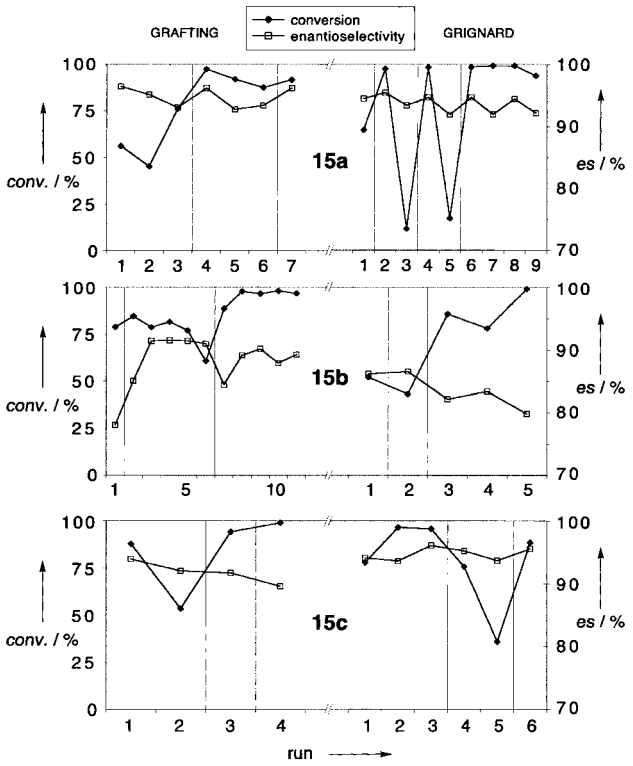

Figure 4. Results of the addition of in situ prepared Bu_2Zu to PhCHO (cf. Scheme 5) with the heterogeneous Ti-TADDOLates **15a** (top), **15b** (center) and **15c** (bottom). On the left side of each diagram are the results obtained with the respective catalysts that have been prepared as outlined in Schemes 1 and 2. The right side shows the results with the catalyst obtained by the alternative route presented in Scheme 3. Mind the different scales for the conversion (left *y* axes) and the enantioselectivity (right *x* axes)! Each vertical line between two runs stands for a hydrolysis procedure with HCl/H_2O/acetone with successive reloading by titanate.

the third run. In the sixth run the conversion was lower than usual. This problem could be solved by another hydrolysis, but in the seventh run the enantioselectivity was lower than usual. Finally, both conversion and enantioselectivity were good in the last four runs without the need for another treatment with HCl/H_2O/acetone. As under homogeneous conditions with the Et_2Zn addition, the 1-naphthyl derivative performed less well in this reaction than the phenyl-substituted analogue.[41, 42] The material **15c** carrying 2-naphthyl groups, prepared either way, gave rise to satisfactory catalytic performance with a drop in conversion for each catalyst. Regenerating the titanate after hydrolysis did solve the problem in both cases. In summary, it is safe to say that the route one chooses for the preparation of the titanates **15a–c** seems to have little influence on their performance in this reaction.

The respective third and fifth run with catalyst **15a** prepared by the Grignard route are particularly interesting. In run three the syringe filter broke and LiCl entered the reaction suspension. This led to almost complete loss of conversion. Instead of restarting the whole series, we decided to apply the HCl/H_2O/acetone hydrolysis procedure with successive reloading with titanate. As can be seen, the catalytic activity could be completely restored, even though by normal washing with reaction solvent the salts could never have been removed. Similarly, in the fifth run, the seal of the reaction flask had loosened, resulting, again, in complete hydrolysis, but our catalyst regeneration procedure worked once more. This demonstrates the power of this procedure even after an event that could be considered as the worst case in organometallic reactions.

The TMS groups introduced for hydrophobization might have been expected to be labile towards acid, similar to the acid lability of TMS-protecting groups of hydroxy substituents. However, in the present application they appeared to be extremely stable. This could be confirmed by comparing ^{13}C and ^{29}Si solid-phase NMR spectra of the heterogeneous TADDOL **5** after nine HCl/H_2O/acetone hydrolyses with those of unused material (Figure 5). Acid hydrolyses have been used before in investigations on immobilized titanates, sometimes successfully,[3, 4, 44] sometimes not.[6]

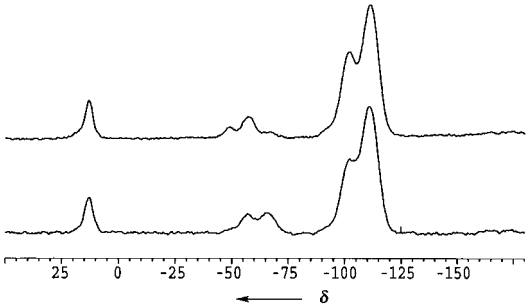

Figure 5. ^{29}Si Solid-phase NMR spectrum (79.5 MHz) of silica gel **5** before (top) and after (bottom) nine hydrolyses with HCl/H_2O/acetone and successive reloading with titanate. The peak at $\delta \approx 15$ arises from the Si atoms of the TMS groups making the silica gel hydrophobic. It is still there after nine hydrolyses, which demonstrates the stability of the TMS groups towards acid. The peaks between $\delta = -50$ and -75 are the signals of the Si atoms to which the mercaptopropyl linker is attached. The change of their shape is probably due to the hydrolysis and condensation of the remaining[43] methoxy group which is indicated in the more detailed formula representation of silica gel **1** in Scheme 1. Finally, the peaks between $\delta = -80$ and -120 are those of the Si atoms of the silica gel backbone.[43]

Stereoselective 1,3-dipolar cycloadditions with CPG-immobilized Ti-TADDOLates: Apart from nucleophilic additions to carbonyl groups, cycloadditions are the type of reaction for which Ti-TADDOLates are mostly used.[2] Some time ago Jørgensen et al. have reported on the successful catalysis of 1,3-dipolar cycloadditions[45] with Ti-TADDOLates.[46] Not only could the configuration of the major enantiomer be controlled by using (*R*,*R*) or (*S*,*S*)-TADDOL but also, by going from a Cl_2Ti-TADDOLate to a $(TosO)_2$Ti-TADDOLate. In analogy, we prepared the heterogeneous Cl_2Ti-TADDOLate **16** and $(TosO)_2$Ti-TADDOLate **17** (Scheme 6).[47]

However, whereas Jørgensen's results in the addition of crotonoyloxazolidinone (**18**) to diphenylnitrone (**19**) could be reproduced with soluble Ti-TADDOLates, the result with catalyst **16** was very poor (40% conversion, 83% *ds*, 64% *es*).[48] We tried different conditions and found that the reaction worked well with 0.5 equivalents of the catalyst (first run in Figure 6). After washing with reaction solvent, the conversion in the second run was lower and even lower in the third run. We then hydrolyzed and reloaded the catalyst with

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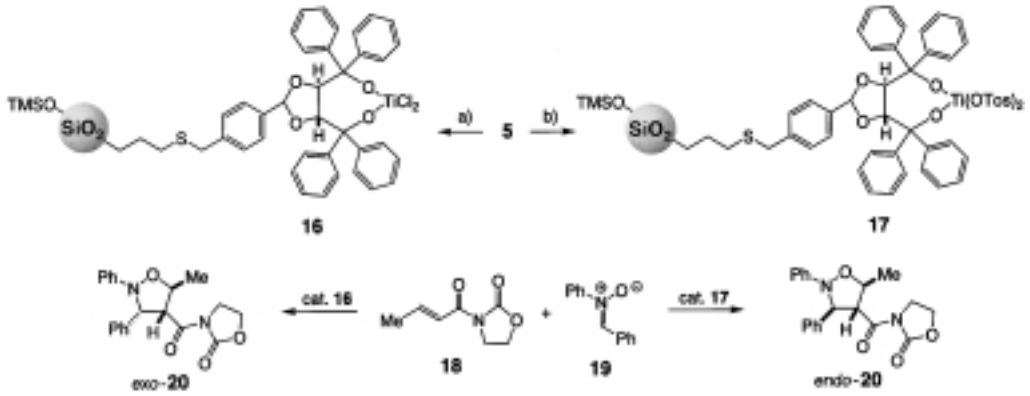

Scheme 6. Preparation of the heterogeneous Ti-TADDOLates **16** and **17** and their use in the 1,3-dipolar cycloaddition of crotonoyloxazolidinone **18** to diphenyl nitrone **19** to give either ***exo*-20** (using the titanate **16**) or ***endo*-20** (using the titanate **17**).[47] For the results concerning conversion and stereoselectivities, see Figures 6 and 7, respectively. a) $TiCl_2(OiPr)_2$, toluene, azeotropic removal of the *i*PrOH formed; b) $Ti(OTos)_2(OiPr)_2$, toluene, azeotropic removal of the *i*PrOH formed.

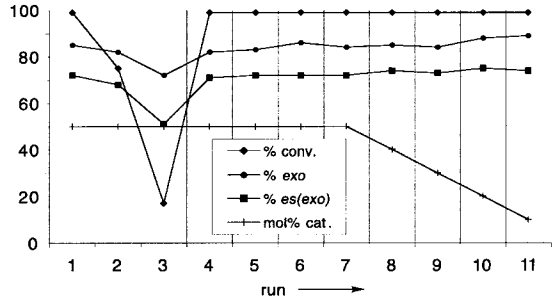

Figure 6. 1,3-Dipolar cycloaddition of nitrone **19** to the crotonoyl double bond of compound **18** (Scheme 6) using variable amounts of the heterogeneous Cl_2Ti-TADDOLate **16**. A vertical bar between two runs stands for a HCl/H_2O/acetone hydrolysis step with subsequent reloading by titanate between these corresponding two runs.

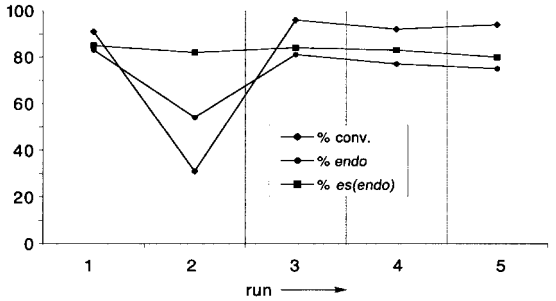

Figure 7. 1,3-Dipolar cycloaddition (**18**+**19**) (Scheme 6) mediated by the heterogeneous $(Tos)_2$Ti-TADDOLate **17**. A vertical bar between two runs indicates a HCl/H_2O/acetone washing step, with subsequent reloading with titanate between these two runs.

titanate and it again performed well and gave rise to very stable values for conversion and stereoselectivity. In the eighth run we wanted to check whether 0.4 equivalents of catalyst **16** might be sufficient. This turned out to be the case. In the following runs we lowered the catalyst concentration each time, until, finally, we found that in the eleventh run 0.1 equivalents could be used with equal success. This is most surprising, because the unused catalyst had given poor results under these conditions. Again, we have no explanation, due to the difficult analytical access of the system, but we have observed a similar behaviour with TADDOLs as dendritic crosslinkers in polymers.[10c] The heterogeneous $(TosO)_2$Ti-TADDOLate **17** also performed well in this reaction (Figure 7) and the results concerning conversion and stereoselectivity were similar to those obtained with the soluble analogues.[49] Here, too, the catalyst had to be hydrolyzed and reloaded with titanate after every run. Thus, the power of the protocol for the catalyst recycling has once more been demonstrated.

Conclusion

We have presented two possible routes to TADDOLs, immobilized on hydrophilic silica gel (CPG) and the derived titanates perform well in two standard Ti-TADDOLate-mediated reactions. Reuse of the catalyst is possible and we were able to find a cleansing protocol that could reliably restore the catalyst's performance after accumulation of by-products, or after "accidents". The CPG-immobilized catalysts described here and in a previous paper[50] have great potential for multiple applications and are in many ways superior to polymer-bound or polymer-incorporated analogues. Multiple applications for the type of reactions requiring Lewis acid catalysis is an essential feature, because such reactions notoriously require rather high catalyst-to-substrate ratios, and cannot be compared with transition metal catalyzed transformations, such as hydrogenations, isomerizations, polymerizations, in which record substrate-to-catalyst ratios of 10^6 or more can be realized, and are actually necessary to achieve (catalysts can normally not be separated or recovered from a polymer, they are often inherent constituents of the resulting material!).

Experimental Section

General: For more detailed descriptions of some of the procedures see A. Heckel, Dissertation No. 14310, ETH Zürich, **2001**.

Starting materials and reagents: The phenyl analogue of compounds **8**,[3] used for the preparation of silica gel **5** and of compound **14**, the compounds **6**,[3] **18**,[51] and **19**[52] and TMSIm[53] were prepared according to literature procedures. The solution of Et_2Zn in toluene was also prepared following a reported procedure.[54] CPG was donated by the Grace Company and had

the following specifications: a) "Type 332", batch nr. SP 2-8319.01, pore diameter 200 Å, spec. surface 280–355 $m^2 g^{-1}$, pore volume 1.55 $mL g^{-1}$, particle size 35–70 μm; b) batch nr. SP 18-9042, pore diameter 500 Å, spec. surface 70–90 $m^2 g^{-1}$, pore volume 1.10 $mL g^{-1}$, particle size 35–70 μm; c) batch nr. SP 2-8696.01, pore size 1000 Å, spec. surface 30–55 $m^2 g^{-1}$, pore volume 1.05 $mL g^{-1}$, particle size 35–70 μm. All other reagents and solvents used were purchased at the usual suppliers.

Techniques: For the filtration of the CPG sinter filters of pore size 2 (=P100, 40–100 μm) were used. Whenever vacuum was applied to a flask containing CPG, a sinter filter, preferably of large diameter, was fitted between the vessel and the pump. Silica gel suspensions must not be stirred with a magnetic stirring bar because this causes abrasion. Thus, the reaction flasks containing the suspensions were either shaken (with a regular shaker) or rotated by a motor (for example in a Büchi Kugelrohr oven). Washing of silica gel under argon can for example be done by adding the washing solvent with a syringe, waiting until the silica gel has completely sedimentated (1–2 min) and withdrawing the supernatant liquid with a syringe. If done carefully, this leads to little loss of material.

Equipment: Thin-layer chromatography (TLC): precoated glass plates, silica gel 60 F_{254}, 20 × 20 cm, Merck; visualization by UV (254 nm) or by staining with phosphomolybdic acid solution (phosphomolybdic acid (25 g), $CeSO_4 \cdot H_2O$ (10 g), conc. H_2SO_4 (60 mL), H_2O (940 mL)). Flash chromatography (FC): silica gel 60 (Fluka), 230–400 mesh ASTM), 0.2 bar N_2 pressure. M.p.: open glass capillaries, Büchi 510, uncorrected. $[\alpha]_D^{20}$: at 20 °C, Perkin–Elmer polarimeter 241, cell length: 1 dm, *c* in g per 100 mL. Gas chromatography (GC): Carlo Erba GC 8000 top; column: Supelco *α*-DEX or *β*-DEX (30 m, 0.25 mm), injector temperature: 200 °C, detector temperature: 225 °C (FID), carrier gas: H_2. High pressure liquid chromatography (HPLC): Waters 515 HPLC pump, Waters 484 tunable absorbance detector, Waters automated gradient controller, column: Daicel Chiracel OD, UV detection at 254 nm. Nuclear magnetic resonance (NMR): liquid-phase spectra: Bruker AMX-II-500, AMX-400, Varian Mercury-300, Gemini-300; solid-phase spectra: Bruker AMX 400, Avance 400, rotor: 4 mm or 7 mm; δ in ppm. Infrared spectroscopy (IR): Perkin–Elmer 1600 FT-IR, values in cm^{-1}, s = strong, m = medium, w = weak. Diffuse reflection infrared fourier transform spectroscopy (DRIFT): Perkin–Elmer 2000 FT-IR, argon stream, 50 °C, background KBr. Mass spectroscopy (MS): VG ZAB2-SEQ (FAB), Finnigan MAT TSQ 7000 (ESI), Bruker Reflex spectrometer with N_2 laser (337 nm), positive ion mode (MALDI), Ion Spec Ultima 4.7 FT ion cyclotron resonance mass spectrometer (HR-MALDI), MALDI matrices: 2,5-dihydroxybenzoic acid (DHB), 2-(4-hydroxyphenylazo)benzoic acid (HABA); fragment ions in *m*/*z* with relative intensities (%) (for peaks >10%, except for molecular ion peak) in parenthesis. Elemental analyses were performed by the Microanalytical Laboratory of the Laboratory for Organic Chemistry (ETH Zürich), except for the silica gel analyses (Analytische Laboratorien, Prof. Dr. H. Malissa und G. Reuter GmbH, Industriepark Kaiserau, Haus Heidbruch, 51789 Lindlar, Germany). Syringe filters: Infochroma AG, 25 mm Titan HPLC filter, PTFE, pore size 0.45 μm (identical to prod. nr. 44525-NP, SRi Company).

Determination of the SH content of a (hydrophobic) silica gel. General procedure I (GP I): In a modification of Ellman's procedure[22] the following solutions were needed: phosphate buffer (0.04 M, pH 8), "Komplexon III" solution (dihydrate of the disodium salt of EDTA, 0.2 M in buffer), 5,5′-dithio-bis-(2-nitrobenzoic acid) (DTNB) solution (50 mg in 50 mL buffer). These solutions can be stored in the refrigerator. For the determination a sample of the silica gel (1–4 mg) was suspended in buffer (8.6 mL) and EDTA solution (1 mL) was added. For hydrophobic silica gel samples EtOH (2–3 mL) or acetone (2–3 mL) were added. After addition of DTNB solution (0.4 mL) the reaction flask was closed and shaken for 4 h at r.t. Then the silica gel was allowed to sedimentate (5 min) and the absorbance of the supernatant solution was determined at 412 nm. (ε = 13597 $L mol^{-1} cm^{-1}$ for aqueous solutions or in case of addition of acetone; ε = 12915 $L mol^{-1} cm^{-1}$ in case of addition of EtOH; *N*-acetyl cysteine as reference substance).

Determination of the DMTr content of a silica gel. General procedure II (GP II): According to a procedure described in the literature[26] a sample of the silica gel (1–4 mg) was suspended in a mixture (25 mL) of $HClO_4$ and EtOH (3:2). The closed reaction flask was shaken for 30 min at r.t. Then the silica gel was allowed to sedimentate (5 min) and the absorbance of the supernatant solution was determined at 495 nm (ε = 71.7 $L mol^{-1} cm^{-1}$[26]).

Silica gel 1: The CPG to be functionalized (50 g) was first suspended in H_2O (210 mL) and HCl (conc., 40 mL) was added. The suspension was then heated to 90 °C for 5 h. Then the silica gel was filtered off, washed thoroughly with H_2O (5 L) and acetone (1 L) and dried in vacuo at 50 °C. Then, following a literature procedure,[24] part of the silica gel (10 g) was suspended under argon in DMF (50 mL) and imidazole (0.73 g, 10 mmol) and 3-(mercaptopropyl)trimethoxysilane (1 mL, 5.4 mmol) were added. The suspension was heated at 100 °C for 20 h. Then the silica gel was filtered off, washed with acetone (500 mL), toluene (100 mL), CH_2Cl_2 (100 mL) and dried in vacuo (1 h at 50 °C and 2 h at 150 °C). Thus, silica gel **1** was isolated as colorless powder (10.43 g, c(SH) = 0.46 $mmol g^{-1}$ (GP I)).

Silica gel 2: Silica gel **1** (10.2 g, 4.7 mmol, c(SH) = 0.46 $mmol g^{-1}$) was suspended under argon in toluene (75 mL). Then Et_3N (3.3 mL, 23.5 mmol, 5 equiv) and DMTrCl (6.4 g, 18.6 mmol, 4 equiv) were added and the reaction flask was rotated for 4 h at r.t. Then the silica gel was filtered off, washed with acetone, toluene, CH_2Cl_2 (100 mL each), MeOH (50 mL) and again CH_2Cl_2 (100 mL) and dried in vacuo at 50 °C. Thus, silica gel **2** was isolated as yellowish powder (12 g, c(SH) = 0.01 $mmol g^{-1}$ (GP I), c(DMTr) = 0.46 $mmol g^{-1}$ (GP II)).

Silica gel 3: Following a literature procedure,[20] prior to the reaction silica gel **2** (11.24 g, loading 0.46 mmol) was heated at 90 °C in vacuo for 1 h (without sinter filter between flask and vacuum pump). Then the flask was flushed with argon, TMSIm[53] (60 mL) was added and the resulting suspension was rotated at 60 °C for 1 h and at r.t. for another 3 h. After washing with toluene (100 mL), CH_2Cl_2 (100 mL), MeOH (50 mL) and CH_2Cl_2 (100 mL) and drying in vacuo at 60 °C, silica gel **3** was isolated as colorless powder (11.4 g).

Silica gel 4: Silica gel **3** (11.4 g, loading 0.46 $mmol g^{-1}$) was treated alternatingly with 1% TFA in CH_2Cl_2, MeOH and CH_2Cl_2 in portions until 1 L of the TFA solution, 500 mL MeOH and 1 L of CH_2Cl_2 were consumed. Then the silica gel was again suspended in 1% TFA solution in CH_2Cl_2 (50 mL) and Et_3SiH was added in portions with a delay of 30 min until the suspension became light red (for example after 9 mL of Et_3SiH). Then the silica gel was washed with CH_2Cl_2, MeOH and again CH_2Cl_2 (100 mL each), and dried in vacuo at 50 °C. Thus, silica gel **4** was isolated as colorless powder (10.6 g, c(SH) = 0.46 $mmol g^{-1}$ (GP I, 3 mL EtOH), c(DMTr) = 0.02 $mmol g^{-1}$ (GP II)). Sometimes this procedure had to be repeated to obtain a better deprotection.

Grafting of TADDOLs on silica gel 4. General procedure III (GP III): Detailed example for the preparation of silica gel **5**: Silica gel **4** (9.9 g, 3.1 mmol SH, 1 equiv, c(SH) = 0.31 $mmol g^{-1}$) was suspended under argon in toluene (30 mL). Then (4*R*,5*R*)-2-[4-(bromomethyl)phenyl]-*α*,*α*′,*α*′,*α*′-tetraphenyl-1,3-dioxolane-4,5-dimethanol[3] (15 g, 24.8 mmol, 8 equiv) and DIEA (4.2 mL, 24.8 mL, 8 equiv) were added and the suspension was heated for 12 h at 70 °C. After washing with toluene, acetone and CH_2Cl_2 (100 mL each), silica gel **5** was isolated as colorless powder (11.1 g, c(SH) = 0.02 $mmol g^{-1}$ (GP I, 2 mL acetone), calculated loading with TADDOL: 0.29 $mmol g^{-1}$). From the filtrate, unreacted TADDOL could be recovered and purified by FC (300 g silica gel, hexane/acetone 3:2) (13.1 g, 21.5 mmol).

Grignard addition to the immobilized tartrate ester 12. General procedure IV (GP IV): Detailed example for the preparation of silica gel **5**: Silica gel **12** (800 mg, 0.274 mmol, 1 equiv, loading 0.34 $mmol g^{-1}$) was suspended in toluene (4 mL) and dried again in vacuo to azeotropically remove H_2O. Then the silica gel was suspended in THF (5 mL) and an aliquot of a freshly prepared solution of PhMgBr in THF (1.5 mL, 2.2 mmol, 8 equiv) was added through a syringe filter. The mixture was heated for 2 h at 50 °C. Then the silica gel was filtered off, washed with THF, acetone, acetone/H_2O 1:1, acetone, hexane and CH_2Cl_2 (100 mL each) and dried in vacuo. Thus, silica gel **5** was isolated as colorless powder (863 mg).

Compound 7a: From Mg (3.69 g, 152 mmol, 8 equiv) and 1-naphthylbromide (31.47 g, 152 mmol, 8 equiv) a solution of 1-NphMgBr in THF (250 mL) was prepared in the usual way. Within 75 min a solution of compound **6**[3] (8.12 g, 19 mmol, 1 equiv) in THF (120 mL) was added and the resulting mixture was heated under reflux for 4 h. After cooling to r.t. the mixture was carefully hydrolyzed with an aqueous NH_4Cl solution and extracted three times with Et_2O. The combined organic phases were dried with $MgSO_4$ and the solvent was evaporated. The residue was triturated over night with pentane (100 mL). After filtration a yellow powder was

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obtained which was further purified by FC (1 kg silica gel, $CH_2Cl_2 \rightarrow CH_2Cl_2$+1.5% acetone), affording compound **7a** as colorless foam (9.8 g, 13.2 mmol, 69%). M.p. 217 °C; R_f (hexane/acetone 3:2) = 0.34; $[\alpha]_D^{20} = +75.6$ ($c = 1$ in $CHCl_3$); ^{1}H NMR (500 MHz, [D$_6$]DMSO, 160 °C, TMS): $\delta = 4.36$ (s), 4.85 (br s), 5.88 (s), 5.95 (d), 6.20 (br s), 6.51 (s), 6.78–8.23 (m) (all signals very broad); ^{13}C NMR (125 MHz, [D$_6$]DMSO, 160 °C): $\delta =$ 62.10, 80.05, 81.14, 81.77, 103.46, 123.22, 12.37, 123.66, 123.71, 123.86, 123.90, 124.28, 125.02, 125.30, 125.55, 125.70, 126.02, 126.18, 126.77, 126.89, 127.29, 127.43, 127.54, 127.67, 127.76, 128.01, 130.58, 130.72, 131.37, 131.58, 133.62, 133.68, 133.74, 133.78, 134.11, 139.08, 139.34, 140.78, 140.99, 142.62; IR ($CHCl_3$): $\tilde{\nu} = 3569$ (m), 3385 (w), 3046 (m), 2995 (m), 2933 (w), 2882 (w), 1949 (w), 1841 (w), 1815 (w), 1621 (w), 1595 (m), 1503 (m), 1431 (w), 1390 (m), 1349 (m), 1297 (m), 1113 (m), 1082 (s), 1051 (m), 1010 (s), 959 (m), 892 (m), 862 (w); MS (HR-MALDI, DHB): *m*/*z*: 784.2496 (3), 783.2474 (6), 770.2853 (4), 769.2827 (17), 768.2801 (58), 767.2767 (100) $[M+Na]^+$ (calcd for: 767.2768), 410.0283 (26), 393.0239 (11), 392.0174 (32), 374.0068 (19), 361.9728 (42), 333.0201 (18), 318.1030 (13), 273.0407 (53), 267.1181 (30), 255.7798 (10); elemental analysis calcd (%) for $C_{52}H_{40}O_5$ (744.89): C 83.82, H 5.41; found: C 83.30, H 6.11.

Compound 7b: From Mg (9.9 g, 408 mmol, 7 equiv) and 2-naphthylbromide (84.5 g, 408 mmol, 7 equiv) a solution of 2-NphMgBr in THF (380 mL) was prepared in the usual way. Within 30 min a solution of compound **6**[3] (25 g, 58.3 mmol, 1 equiv) in THF (100 mL) was added and the resulting mixture was heated for 4 h under reflux. After cooling to r.t. the mixture was carefully hydrolyzed with an aqueous NH_4Cl solution and extracted three times with Et_2O. The combined organic phases were extracted with brine, dried with $MgSO_4$ and the solvent was evaporated. The crude product was purified by FC (1 kg silica gel, hexane/acetone 2:1 and then 350 g silica gel, CH_2Cl_2), thus affording compound **7b** as colorless foam (27.9 g, 39.8 mmol, 68%). M.p. 184–185 °C; R_f (hexane/acetone 2:1) = 0.21; $[\alpha]_D^{20} = +176.7$ ($c = 0.73$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.59$ (t, ^3J(H,H) = 6.0 Hz, 1H; CH_2OH), 2.87 (s, 1H; OH), 3.44 (s, 1H; OH), 4.57 (d, ^3J(H,H) = 5.7 Hz, 2H; CH_2OH), 5.59 (d, ^3J(H,H) = 4.3 Hz, 1H; OC*H*CHO), 5.76 (d, ^3J(H,H) = 4.3 Hz, 1H; OCHC*H*O), 5.9 (s, 1H; OCH(Arl)O), 6.78–8.29 (m, 28H; arom. H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 64.93$, 79.27, 80.27, 81.36, 81.59, 105.54, 124.54, 124.77, 124.89, 125.06, 125.94, 125.98, 126.05, 126.19, 126.28, 126.37, 126.46, 126.55, 126.73, 126.89, 127.33, 127.35, 127.45, 127.52, 127.66, 127.80, 127.90, 128.33, 128.36, 128.49, 128.57, 132.18, 132.31, 132.50, 132.58, 132.72, 132.76, 132.89, 136.93, 140.51, 141.29, 141.67, 141.99, 142.06; IR ($CHCl_3$): $\tilde{\nu} = 3570$ (m), 3374 (m), 3059 (m), 3008 (m), 2930 (w), 2882 (w), 1954 (w), 1920 (w), 1836 (w), 1800 (w), 1631 (w), 1600 (m), 1506 (m), 1433 (m), 1360 (m), 1301 (m), 1272 (m), 1156 (m), 1122 (s), 1092 (s), 1018 (s), 901 (m), 859 (m); MS (HR-MALDI, DHB): *m*/*z* (%): 769.2848 (19), 768.2803 (55), 767.2767 (100) $[M+Na]^+$ (calcd for: 767.2768), 335.1039 (18), 273.0390 (25), 267.1164 (26); elemental analysis calcd (%) for $C_{52}H_{40}O_5$ (744.89): C 83.85, H 5.41; found: C 83.80, H 5.52.

Compound 8a: Compound **7a** (5.0 g, 6.7 mmol, 1 equiv) was dissolved under argon in THF (20 mL). Then CBr_4 (2.78 g, 8.38 mmol, 1.25 equiv) and PPh_3 (2.20 g, 8.38 mmol, 1.25 equiv) were added and the reaction mixture was stirred at r.t. After 4 h more CBr_4 (1.32 g, 4.02 mmol, 0.6 equiv) and PPh_3 (1.06 g, 4.02 mmol, 0.6 equiv) were added. When no starting material could be detected any more by TLC, the solvent was evaporated and the crude product was purified by FC (500 g silica gel, CH_2Cl_2/acetone 3:1). Thus, compound **8a** could be isolated as colorless powder (4.18 g, 5.2 mmol, 77%), which was stored under exclusion of light and in a refrigerator. M.p. 201 °C (decomp); R_f (hexane/acetone 3:2) = 0.49; $[\alpha]_D^{20} = +85.5$ ($c = 1$ in $CHCl_3$); due to line broadening (steric hindrance), even at 160 °C no appropriate NMR spectra could be obtained; IR ($CHCl_3$): $\tilde{\nu} = 3575$ (s), 3383 (m), 3051 (s), 3008 (s), 2959 (m), 1949 (w), 1841 (w), 1810 (w), 1723 (w), 1599 (m), 1509 (s), 1435 (s), 1395 (s), 1349 (m), 1299 (m), 1161 (m), 1085 (s), 1020 (s), 964 (m), 896 (m), 862 (w); MS (ESI, neg. mode): *m*/*z* (%): 810.4 (4), 809.4 (16), 808.4 (50), 807.4 (100), 806.4 (50), 805.4 (85) $[M-H]^-$ (calcd for: 805.2); elemental analysis calcd (%) for $C_{52}H_{39}O_4Br$: C 77.32, H 4.87; found: C 77.42, H 4.99.

Compound 8b: Compound **7b** (5.0 g, 6.7 mmol, 1 equiv) was dissolved under argon in THF (20 mL). Then CBr_4 (2.78 g, 8.38 mmol, 1.25 equiv) and PPh_3 (2.20 g, 8.38 mmol, 1.25 equiv) were added and the reaction mixture was stirred for 4 h at r.t. Then more CBr_4 (1.32 g, 4.02 mmol, 0.6 equiv) and PPh_3 (1.06 g, 4.02 mmol, 0.6 equiv) were added. When no starting material could be detected any more by TLC, the solvent was evaporated and the crude product was purified by FC (500 g silica gel, CH_2Cl_2/acetone 3:1). Thus, compound **8b** could be isolated as colorless powder (4.18 g, 5.2 mmol, 77%), which was stored under exclusion of light and in a refrigerator. M.p. 174–176 °C (decomp); R_f (hexane/acetone 3:1) = 0.28; $[\alpha]_D^{20} = +154.3$ ($c = 1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 2.77$ (s, 1H; OH), 3.35 (s, 1H; OH), 4.40 (s, 2H; CH_2Br), 5.58 (d, ^3J(H,H) = 4.3 Hz, 1H; OC*H*CHO), 5.76 (d, ^3J(H,H) = 4.3 Hz, 1H; OCHC*H*O), 5.87 (s, 1H; OCH(Arl)O), 6.80–8.28 (m, 28H; arom. H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 32.87$, 79.27, 80.24, 81.39, 81.61, 105.30, 124.56, 124.78, 124.89, 125.05, 125.98, 126.00, 126.08, 126.23, 126.30, 126.41, 126.54, 126.98, 127.34, 127.37, 127.46, 127.48, 127.54, 127.70, 127.83, 127.95, 128.34, 128.38, 128.51, 128.58, 129.09, 132.20, 132.34, 132.52, 132.59, 132.72, 132.75, 132.76, 132.90, 137.67, 138.82, 140.52, 141.19, 141.68, 141.92; IR ($CHCl_3$): $\tilde{\nu} = 3570$ (m), 3378 (m), 3059 (s), 3008 (s), 2961 (w), 1921 (w), 1805 (w), 1631 (w), 1600 (s), 1506 (s), 1434 (m), 1359 (s), 1298 (m), 1272 (m), 1156 (m), 1123 (s), 1020 (s), 950 (m), 901(m), 859 (m); MS (FAB): *m*/*z* (%): 807.09 (5) $[M]^+$, 791.09 (13), 789.07 (12), 591.11 (13), 478.98 (17), 476.98 (17), 391.17 (13), 325.02 (10), 309.02 (19), 308.03 (31), 307.00 (29), 297.03 (12), 296.03 (18), 295.02 (34), 289.01 (12), 284.03 (28), 283.03 (83), 279.04 (21), 268.05 (29), 267.04 (100), 265.04 (15), 252.04 (10); elemental analysis calcd (%) for $C_{52}H_{39}BrO_4$ (807.78): C 77.32, H 4.87; found 77.29, H 5.04.

Silica gel 9a

"*Grafting route*": According to GP III, using silica gel **4** (6.02 g, 2.05 mmol, 1 equiv, c(SH) = 0.34 mmol g^{-1} (GP I, 2 mL EtOH)), compound **8a** (9.73 g, 12.05 mmol, 6 equiv) and EtN*i*Pr$_2$ (2.06 mL, 12.05 mmol, 6 equiv), silica gel **9a** was obtained as ochre powder (6.62 g, c(SH) = 0.09 mmol g^{-1} (GP I, 2 mL EtOH), calculated loading with TADDOL: 0.25 mmol g^{-1}).

"*Grignard route*": According to GP IV, using silica gel **12** (800 mg, 0.274 mmol, 1 equiv, loading: 0.34 mmol g^{-1}) and an aliquot of a freshly prepared solution of 1-NphMgBr in THF (2.5 mL, 2.2 mmol, 8 equiv) and heating for 24 h at 50 °C, silica gel **9a** was isolated as colorless powder (879 mg).

Silica gel 9b

"*Grafting route*": According to GP III, using silica gel **4** (4.46 g, 1.3 mmol, 1 equiv, c(SH) = 0.29 mmol g^{-1} (GP I, 3 mL acetone)), compound **8b** (8.38 g, 10.4 mmol, 8 equiv) and EtN*i*Pr$_2$ (1.78 mL, 10.4 mmol, 8 equiv), silica gel **9b** was obtained as ochre powder (4.95 g, c(SH) = 0.0 mmol g^{-1} (GP I, 3 mL acetone), calculated loading with TADDOL: 0.29 mmol g^{-1}).

"*Grignard route*": According to GP IV, using silica gel **12** (800 mg, 0.274 mmol, 1 equiv, loading 0.34 mmol g^{-1}) and an aliquot of a freshly prepared solution of 2-NphMgBr in THF (2.5 mL, 2.2 mmol, 8 equiv) and heating for 28 h at 50 °C, silica gel **9b** was isolated as colorless powder (874 mg).

Compound 10: Following a general literature procedure[55] compound **6**[3] (1 g, 2.33 mmol, 1 equiv) was dissolved under argon in EtOH (20 mL) and $Ti(OEt)_4$ (318 μL, 1.52 mmol, 0.65 equiv) was added. After heating the mixture under reflux for 5 h, dilute aqueous HCl (0.5 M, 20 mL) and Et_2O were added, the phases were separated and the aqueous phase was extracted two more times with Et_2O. The combined organic phases were extracted with an aqueous $NaHCO_3$ solution and dried with $MgSO_4$. After evaporation of the solvent the crude product was purified by FC (100 g silica gel, hexane/acetone 2:1). Thus, compound **10** was isolated as colorless oil (0.575 g, 1.77 mmol, 76%). R_f (hexane/acetone 3:2) = 0.4; $[\alpha]_D^{20} = -22.1$ ($c = 1$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, $CHCl_3$): $\delta = 1.31$ (t, ^3J(H,H) = 7.2 Hz, 3H; CH_3), 1.35 (t, ^3J(H,H) = 7.2 Hz, 3H; CH_3), 1.74 (br s, 1H; OH), 4.28 (q, ^3J(H,H) = 7.27 Hz, 2H; CH_2CH_3), 4.32 (q, ^3J(H,H) = 7.2 Hz, 2H; CH_2CH_3), 4.71 (s, 2H; CH_2OH), 4.82 (d, ^3J(H,H) = 4.0 Hz, 1H; OC*H*CHO), 4.93 (d, ^3J(H,H) = 4.2 Hz, 1H; OCHC*H*O), 6.15 (s, 1H; OCH(Arl)O), 7.38 (d, ^3J(H,H) = 8.4 Hz, 2H; arom. H), 7.57 (d, ^3J(H,H) = 8.1 Hz, 2H; arom. H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, $CDCl_3$): $\delta = 13.95$, 14.01, 62.02, 64.95, 77.34, 77.62, 106.56, 126.87, 127.56, 135.00, 142.87, 169.22, 169.82; IR ($CHCl_3$): $\tilde{\nu} = 3607$ (m), 3434 (w), 2985 (m), 1449 (s), 1442 (m), 1374 (m), 1103 (s), 1024 (s); MS (FAB): *m*/*z* (%): 327.08 (4), 326.09 (20), 325.11 (100) $[M+H]^+$, 324.06 (12), 323.09 (40), 307.08 (13), 251.07 (31); elemental analysis calcd (%) for $C_{16}H_{20}O_7$ (324.33): C 59.25, H 6.22; found: C 59.22, H 6.02.

Compound 11: Compound **10** (521 mg, 1.61 mmol, 1 equiv) was diluted under argon with THF (2 mL). After cooling the solution with an ice bath, CBr_4 (666 mg, 2.01 mmol, 1.25 equiv) and PPh_3 (527 mg, 2.01 mmol,

1.25 equiv) were slowly added. After stirring for 45 min at r.t. the solvent was evaporated and the crude product was purified by FC (50 g silica gel, hexane/acetone 4:1). Thus, compound **11** was isolated as colorless oil (669 mg, 1.73 mmol, quant). R_f (hexane/acetone 3:2) = 0.46; $[\alpha]_D^{20} = -8.2$ ($c = 1$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.30$ (t, ^3J(H,H) = 7.2 Hz, 3H; CH_3), 1.35 (t, ^3J(H,H) = 7.2 Hz, 3H; CH_3), 4.27 (q, ^3J(H,H) = 7.2 Hz, 2H; CH_2CH_3), 4.32 (q, ^3J(H,H) = 7.2 Hz, 2H; CH_2CH_3), 4.49 (s, 2H; CH_2Br), 4.82 (d, ^3J(H,H) = 4.1 Hz, 1H; OC*H*CHO), 4.93 (d, ^3J(H,H) = 4.1 Hz, 1H; OCHC*H*O), 6.16 (s, 1H; OCH(Arl)O), 7.41 (m, 2H; arom. H), 7.56 (m, 2H; arom. H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, $CDCl_3$): $\delta = 14.03$, 14.11, 32.80, 62.04, 77.30, 77.59, 106.14, 127.61, 129.02, 135.76, 139.42, 168.94, 169.49; IR ($CHCl_3$): $\tilde{\nu} = 2984$ (m), 2907 (m), 1749 (s), 1467 (m), 1436 (m), 1374 (m), 1109 (s), 1024 (s), 962 (m); MS (FAB): *m*/*z* (%): 392.07 (2), 391.07 (8), 389.88 (14), 388.90 (72), 387.88 (23), 386.89 (100), 385.86 (9), 384.87 (33), 314.84 (29), 312.84 (28), 307.97 (19), 306.97 (26), 305.95 (14), 217.02 (18), 198.93 (13); elemental analysis calcd (%) for $C_{16}H_{19}BrO_6$ (387.23): C 49.63, H 4.95; found: C 49.74, H 5.10.

Silica gel 12: According to GP III, using silica gel **4** (4.2 g, 1.6 mmol, 1 equiv, c(SH) = 0.37 mmol g^{-1} (GP I, 2 mL EtOH)), compound **11** (4.0 g, 10.3 mmol, 6.4 equiv) and EtN*i*Pr$_2$ (2.2 mL, 12.5 mmol, 8 equiv), silica gel **12** was obtained as ochre powder (c(SH) = 0.15 mmol g^{-1} (GP I, 2 mL EtOH). To increase the loading the procedure was repeated, this time with DMF as solvent, affording silica gel **12** as ochre powder (4.4 g, c(SH) = 0.03 mmol g^{-1} (GP I, 2 mL EtOH), calculated loading with tartaric acid ester: 0.34 mmol g^{-1}).

Solid-phase reagent 13: Following a literature procedure[38] Amberlyst A 26 (OH^- form, 3.75 g, 16.46 mmol NMe^+, 1 equiv) was washed with MeOH (during the whole procedure the beads should never run dry). Then (3-mercaptopropyl)trimethoxysilane (3 mL, 16.46 mmol, 1 equiv) was added to the MeOH suspension and this mixture was allowed to stand for 5 min at r.t. Then the beads were washed with MeOH and the loading procedure was repeated two more times. After thorough washing the beads were immediately used for the synthesis.

Compound 14: Following a literature procedure,[38] (4*R*,5*R*)-2-[4-(bromomethyl)phenyl]-$\alpha,\alpha,\alpha',\alpha'$-tetraphenyl-1,3-dioxolane-4,5-dimethanol[3] (1 g, 1.65 mmol, 1 equiv) was dissolved under argon in MeOH (30 mL), a suspension of the solid-phase reagent **13** (16.46 mmol, 10 equiv) was added and the resulting mixture was shaken at r.t. for 17 h. Then the beads were filtered off and thoroughly washed with MeOH. The filtrate contained only few impurities (no starting material or free thiol could be detected) and was used without further purification. In another batch, for the characterization, the solvent was evaporated, affording compound **14** as colorless foam (813 mg, 1.12 mmol, 68 %). $[\alpha]_D^{20} = +34.8$ ° ($c = 1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 0.66-0.77$ (m, 2H; $SiCH_2$), 1.51–1.69 (m, 2H; $SiCH_2CH_2$), 2.34–2.45 (m, 2H; $SiCH_2CH_2CH_2$), 3.45–3.70 (m, 11H, Si(OCH_3)$_3$, SCH_2Arl), 5.12 (d, ^3J(H,H) = 5.2 Hz, 1H; OC*H*CHO), 5.13 (s, 1H; OCH(Arl)O), 5.30 (d, ^3J(H,H) = 5.0 Hz, 1H; OCHC*H*O), 7.10–7.57 (m, 24H; arom. H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 8.54$, 22.49, 34.27, 35.75, 50.52, 78.42, 78.51, 80.74, 81.51, 104.76, 126.89, 126.98, 127.06, 127.12, 127.21, 127.28, 127.39, 127.51, 127.66, 127.73, 127.89, 127.93, 127.99, 128.01, 128.08, 128.17, 128.24, 128.32, 128.55, 128.59, 128.71, 130.01, 135.61, 139.97, 140.01, 142.97, 144.21, 144.32, 146.13; MS (FAB): *m*/*z* (%): 1398.07 (3) $[2M - Et_2O]^+$, 722.23 (4) $[M]^+$, 721.24 (7), 602.32 (5), 601.31 (14), 600.30 (35), 587.30 (28), 586.31 (70), 551.14 (16), 527.23 (11), 526.22 (23), 391.17 (12), 373.17 (11), 329.11 (12), 297.15 (20), 285.11 (10), 284.10 (12), 283.10 (52), 269.15 (16), 209.15(11), 207.14 (13), 197.16 (40), 196.15 (19), 195.15 (45), 183.15 (47), 179.16(36), 178.14 (19), 168.15 (24), 167.15 (100), 165.12 (17), 121.00 (20), 120.01 (15), 119.00 (14), 104.93 (56); MS (MALDI, HABA): *m*/*z* (%): 2102.2 (<1) $[3M - 2Et_2O + Na]^+$, 1422.7 (2) $[2M - Et_2O + Na]^+$, 744.9 (8) $[M + Na]^+$, 585.5 (100) $[HSCH_2Arl + Na]^+$.

Silica gels 15a–c: Detailed example for the preparation of silica gel **15a**: Silica gel **5** (627 mg, 0.2 mmol, 1 equiv, loading 0.32 mmol g^{-1}) was suspended in toluene (5 mL) and the solvent was evaporated under vacuum to azeotropically remove H_2O. After flushing with argon, toluene (10 mL) was added again, followed by Ti(O*i*Pr)$_4$ (60 μL, 0.2 mmol, 1 equiv). After shaking for 10 h at r.t. the silica gel was again dried in vacuo, affording a slightly yellowish powder which was immediately used for catalysis.

Addition of Et_2Zn to PhCHO with immobilized Ti-TADDOLates: Freshly prepared silica gel **15** (0.2 mmol, 0.2 equiv, loading 0.32 mmol g^{-1}) was suspended under argon in toluene (10 mL) and Ti(O*i*Pr)$_4$ (443 μL, 1.5 mmol, 1.5 equiv) and PhCHO (102 μL, 1 mmol, 1 equiv) were added. After cooling the reaction mixture to −20 °C a solution of Et_2Zn (0.9 mL, 1.8 mmol, 1.8 equiv, 2 M in toluene) was added and the suspension was further shaken at −20 °C. To monitor the reaction a sample of the liquid phase (ca. 50 μL) was carefully withdrawn with a syringe and Et_2O (0.5 mL), H_2O (0.5 mL) and dilute HCl (1 M, three drops) were added. After shaking, the organic layer was analyzed with GC (β-DEX, 1.3 bar, 110 °C, 1.5 °C min^{-1}, t_R (PhCHO) = 2.9 min, t_R ((*R*)-1-phenyl-1-propanol) = 10.1 min, t_R ((*S*)-1-phenyl-1-propanol) = 10.4 min). After 1 h the silica gel was allowed to sedimentate. Then the supernatant solution was carefully withdrawn with a syringe. After washing of the silica gel (see "Techniques") an aqueous solution of NH_4Cl was added to the combined organic phases and the mixture was filtrated through Celite. The phases of the filtrate were separated and the aqueous phase was extracted once more with Et_2O. The combined organic layers were then extracted with brine, dried with $MgSO_4$ and the solvent was evaporated, thus affording (*S*)-1-phenyl-1-propanol as colorless oil (121 mg, 0.89 mmol, 89 %). The spectroscopic data were in accord with the ones found in the literature.[42] For the next run with the catalyst, the solvent level was adjusted to the one of the previous run and the starting materials were added again. Alternatively, the catalyst was hydrolyzed (GP V) and reloaded with titanate for the next run. Thus, after 10 runs and one hydrolysis 600 mg (96 %) and after 20 runs and two hydrolyses 582 mg (93 %) of silica gel **5** were recovered.

Hydrolysis of the immobilized Ti-TADDOLates 15a–c, 16, and 17. General procedure V (GP V): On a sinter filter the used catalysts **15a–c**, **16** or **17** were washed with a mixture of aqueous HCl (1 M, 100 mL) and acetone (100 mL), then with acetone (200 mL) and finally with CH_2Cl_2 (in portions of 50 mL each). After drying in vacuo at 50 °C colorless powders were obtained, which could be reloaded with titanate (see preparation of **15a–c**, **16** and **17**).

Addition of in situ-generated Bu_2Zn to PhCHO with the immobilized Ti-TADDOLates 15a–c: A solution of $ZnCl_2$ (1 M in Et_2O, 3 mL, 3 mmol, 3 equiv) was diluted under argon with toluene (2 mL) and slowly BuLi (1.6 M in hexane, 3.75 mL, 6 mmol, 6 equiv) was added. The resulting mixture was stirred for 1 h at r.t. Then freshly prepared silica gel **15** (0.2 mmol, 0.2 equiv, loading 0.3 mmol g^{-1}) was suspended in Et_2O (3 mL) and Ti(O*i*Pr)$_4$ (443 μL, 1.5 mmol, 1.5 equiv) and PhCHO (102 μL, 1 mmol, 1 equiv) were added. After cooling the reaction mixture to −20 °C the Bu_2Zn solution was added through a syringe filter and the suspension was further shaken at −20 °C. To monitor the reaction, a sample of the liquid phase (ca. 20 μL) was carefully withdrawn with a syringe. Et_2O (0.5 mL) and dilute HCl (1 M, 0.5 mL) were added, the mixture was shaken and then the organic phase was directly analyzed with GC (α-DEX, 1.0 bar, 105 °C, t_R (PhCHO) = 3.8 min, t_R ((*S*)-1-phenyl-1-pentanol) = 39.9 min, t_R ((*R*)-1-phenyl-1-pentanol) = 41.7 min). After 12 h the silica gel was allowed to sedimentate and then the yellow supernatant was carefully withdrawn with a syringe. After washing of the silica gel (see "Techniques") the solvent level was adjusted to the one of the previous run and the starting materials were added once more. Alternatively the catalyst was hydrolyzed (GP V), reloaded with titanate and use for the next run. Thus, after six runs and two hydrolyses silica gel **5** (623 mg, 93 %) was reisolated.

Silica gel 16: A stock solution (0.1 M) of $TiCl_2$(O*i*Pr)$_2$ was prepared by diluting Ti(O*i*Pr)$_4$ (1.48 mL, 5 mmol) with toluene (100 mL) and adding $TiCl_4$ (0.55 mL, 0.5 mmol). After stirring for 5 min, this solution was stored in the refrigerator. Then silica gel **5** (862 mg, 0.275 mmol, 0.55 equiv, loading: 0.32 mmol g^{-1}) was suspended in toluene (5 mL) and dried in vacuo to azeotropically remove water. After flushing with argon toluene (6 mL) was added again and part of the $TiCl_2$(O*i*Pr)$_2$ solution (2.5 mL, 0.25 mmol, 0.5 equiv) was added. The suspension was shaken at r.t. over night and then dried in vacuo.

Silica gel 17: AgOTos (210 mg, 0.75 mmol) was added to a $TiCl_2$(O*i*Pr)$_2$ solution (see above) (2.5 mL, 0.25 mmol) and the reaction mixture was stirred at r.t. over night under exclusion of light. Then silica gel **5** (862 mg, 0.275 mmol, loading: 0.32 mmol g^{-1}) was suspended in toluene (5 mL) and dried in vacuo to azeotropically remove water. After flushing with argon, toluene (3 mL) was added again and the $Ti(OTos)_2$(O*i*Pr)$_2$ solution was added through a syringe filter. The silica gel became slightly red. The suspension was shaken at r.t. for 7 h and dried in vacuo.

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1,3-Dipolar cycloaddition of compounds 18 and 19 with silica gel 16 to give the compound *exo*-20: Inspired by a literature procedure,[46a] freshly prepared silica gel **16** (0.275 mmol, 0.55 equiv, loading: 0.32 mmol g^{-1}) was suspended in toluene (3 mL). Then compound **18** (78 mg, 0.5 mmol, 1 equiv) and compound **19** (119 mg, 0.6 mmol, 1.2 equiv) were added, dissolved in toluene (4 mL). The mixture was shaken at r.t. for 2 d. After sedimentation of the silica gel, the supernatant was carefully withdrawn with a syringe and the silica gel was washed three times with toluene (see "Techniques"; the silica gel remained dark). The organic phases were combined and the solvent was evaporated. From the crude product (171 mg) conversion and diastereoselectivity were determined by ^{1}H NMR spectroscopy. Then the crude product was purified by FC (20 g silica gel, pentane/Et_2O 1:1). The diastereomers could be separated and the enantiopurity of ***exo*-20** was determined by ^{1}H NMR spectroscopy using $Eu(hfc)_3$ as chiral shift reagent. The spectroscopic data of the isomers isolated were in accord with the ones found in the literature.[46] For the next run the catalyst was hydrolyzed (GP V). After 11 runs and nine hydrolyses silica gel **5** (769 mg, 89%) was be reisolated.

1,3-Dipolar cycloaddition of compounds **18** and **19** with silica gel **17** to give the compound ***endo*-20**: Inspired by a literature procedure,[46b] freshly prepared silica gel **17** (0.275 mmol, 0.55 equiv, loading: 0.32 mmol g^{-1}) was suspended in toluene (4 mL) and the suspension was cooled to 0 °C. Then an ice cold solution of compound **18** (78 mg, 0.5 mmol, 1 equiv) and compound **19** (119 mg, 0.6 mmol, 1.2 equiv) in toluene (3 mL) was added. After the addition, the cooling bath was removed and the mixture was shaken at r.t. for 2 d. Then the silica gel was allowed to sedimentate and the supernatant was carefully withdrawn with a syringe. The silica gel was washed three more times with toluene (see "Techniques"; the silica gel remained dark). Then the organic phases were combined and the solvent was evaporated. From the crude product (175 mg) conversion and diastereoselectivity were determined by ^{1}H NMR spectroscopy. Then the diastereomers were separated by FC (20 g silica gel, pentane/Et_2O 1:1), affording ***endo*-20** (80 mg, 0.23 mmol, 45%) and ***exo*-20** (27 mg, 0.077 mmol, 15%) as colorless foams. The enantiopurity of ***endo*-20** was then determined by HPLC (Daicel Chiracel OD, hexane/*i*PrOH 9:1, 1 mL min^{-1}, t_R (***ent-endo*-20**) = 53 min, t_R (***endo*-20**) = 63 min). The spectroscopic data were in accord with the ones found in the literature.[46]

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[49] With the "progenitor" TADDOL Jørgensen obtained 99 % conversion, > 95 % *ds* and 97 % *es* in this reaction.[46b] However, our results should rather be compared with the ones obtained using a TADDOL made from acetophenone (86 % conv., 85 % *ds*, 93 % *es*).[46b]
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