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Efficient Recovery and Reuse of an Immobilized Peptidic Organocatalyst

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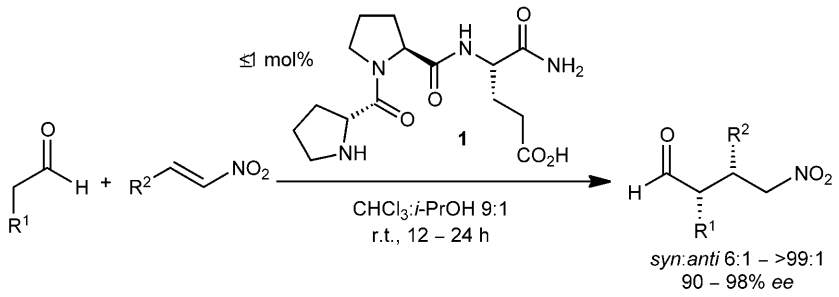
Abstract: Readily reusable immobilized organocatalysts are important from a practical, economic, and environmental viewpoint. However, their successful development has proven challenging and only limited reaction and recovery cycles have been achieved. We report an extraordinarily robust resin-bound tripeptidic organocatalyst that can be readily reused for at least 30 reaction and recovery cycles without loss in catalytic activity or stereoselectivity. The immobilized catalyst can be directly reused for conjugate addition reactions between aldehydes and nitroolefins after a simple filtration from the reaction products. The catalytic efficiency and chemoselectivity of the immobilized peptidic catalysts is so high that a broad range of γ-nitroaldehydes were isolated easily after filtration and removal of all volatiles in quantitative yields, excellent diastereoselectivities and enantioselectivities and, most remarkably, perfect analytical purities. The ease of handling allows for a facile scale-up of reactions catalyzed by the immobilized peptidic catalyst. In addition, the results provide a guide for the further development of immobilized organocatalysts.

Keywords: asymmetric catalysis; catalyst reuse; conjugate addition reactions; immobilization; peptides

The concept of immobilizing asymmetric catalysts on an insoluble support is highly attractive since it allows in principle for easy recovery and reusability of the catalyst as well as facile product isolation.[1] Readily reusable heterogeneous catalysts have therefore advantages over soluble catalysts both from an environmental and economic viewpoint. As a result, a lot of research has been devoted to the development of immobilized organometallic catalysts and organocatalysts.[2,3] Organocatalysts are arguably even more attractive than metal-based catalysts for immobilization since they are typically air- and moisture-stable and issues such as leaching of the active metal center from the immobilized ligand are no concern.[3] Several recent examples demonstrate the potential of immobilized organocatalysts.[4] However, often catalyst deactivation has hampered efficient catalyst reuse and only allowed for a limited number of reaction and recovery cycles. This has in particular been a concern for the development of immobilized chiral amine-based organocatalysts that are highly valuable for iminium and enamine catalysis.[5–7] Catalyst deactivation can be caused by an intrinsic chemical instability of the catalyst itself or by reaction of the immobilized catalyst with the starting materials or products to form stable, undesired adducts. For example, desilylation or product inhibition of immobilized diphenylprolinol silyl ether derivatives has hindered their efficient recycling and even reactivation protocols did not allow for restoring the efficiency over more than ≤ 6 cycles.[6a,e,m,7] Likewise, also the catalytic performance of immobilized proline and imidazolidinone derivatives was found to be reduced significantly after a few reaction and recycling cycles.[3] As a result, a readily reusable chiral amine-based organocatalyst has so far not been developed.

Recently, we introduced the peptide H-D-Pro-Pro-Glu-NH_2 (**1**) as an efficient catalyst for asymmetric conjugate addition reactions of aldehydes to nitroolefins.[8,9] In the presence of peptide **1** aldehydes and nitroolefins react readily with each other to provide synthetically versatile γ-nitroaldehydes in excellent yields and stereoselectivities (Scheme 1). In contrast to many other chiral amine-based organocatalysts,[5] the peptidic catalyst is highly active, therefore allowing for catalyst loadings of as little as ≤ 1 mol%.[8,9] This high effectiveness of H-D-Pro-Pro-Glu-NH_2 (**1**) led us to explore whether the versatility of the pepti-



Scheme 1. Conjugate addition reactions catalyzed by peptide **1**.

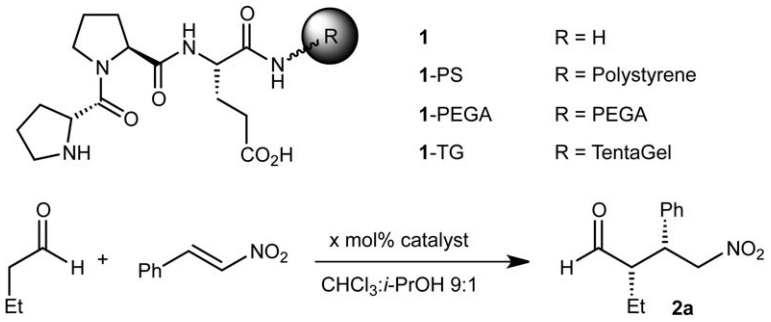
dic catalyst can be further improved by immobilization on a solid support.

Within this manuscript we show that the immobilized peptide H-D-Pro-Pro-Glu-TentaGel is an efficient catalyst for conjugate addition reactions of aldehydes to nitroolefins.[7] We demonstrate that H-D-Pro-Pro-Glu-TentaGel can be easily recovered and reused for at least 30 times with the same high catalytic performance. In addition, we show that analytically clean products are isolated after a simple filtration followed by removal of all volatiles.

We started our investigations by exploring the effect of a solid support on the catalytic performance of peptide **1** and an analysis as to which resin would be best suited. Cross-linked hydrophobic polystyrene (PS) resin as well as hydrophilic TentaGel (polyethylene glycol-PS) and PEGA (polyethylene glycol-polyacrylamide) resins were used to immobilize peptide **1** (Table 1). The immobilization of peptide **1** onto the different amino-functionalized solid supports was easily accomplished by standard solid-phase peptide synthesis following the Fmoc/*t*-Bu protocol (for details see Supporting Information).[10,11]

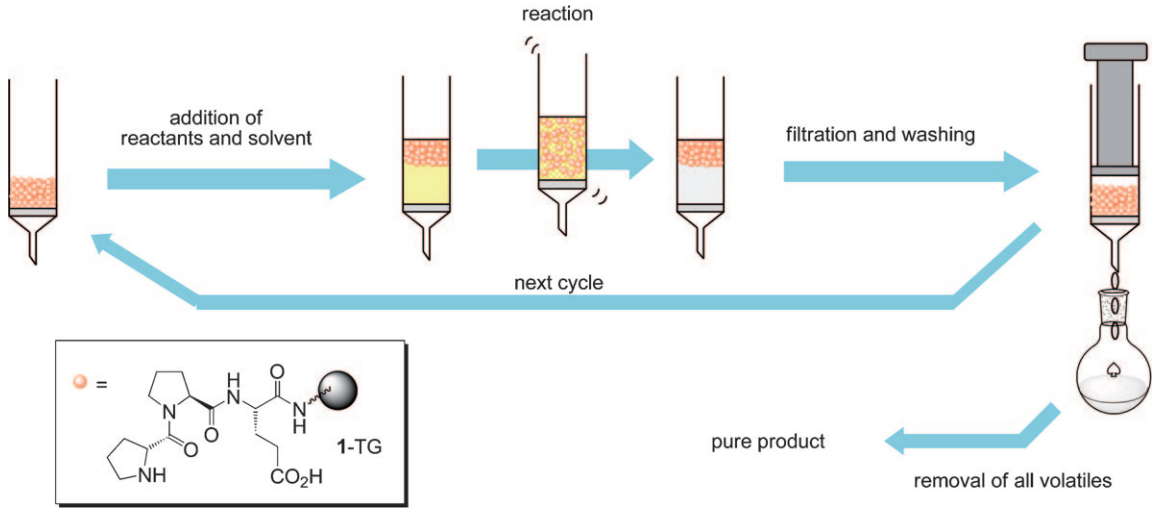
The reaction between *n*-butanal and β-nitrostyrene was used as a test reaction to evaluate the catalytic properties of the solid-supported peptidic catalysts. Conditions were used that had previously been developed for reactions with peptide **1** in homogeneous phase.[8] Satisfyingly, the reactions proceeded as cleanly in the presence of all three immobilized catalysts to

Table 1. Conjugate addition reactions between *n*-butanal and β-nitrostyrene catalyzed by the immobilized peptidic catalysts.[a]



Entry	Cat.	mol%	Temperature [°C]	Time [h]	Conversion [%][b]	*syn*:*anti*[b]	*ee* [%][c]
1[d]	**1**	1	r.t.	12	quant.	50:1	97
2	**1**-PS	3	r.t.	4	quant.	25:1	91
3	**1**-PEGA	3	r.t.	24	quant.	28:1	89
4	**1**-TG	3	r.t.	4	quant.	28:1	91
5	**1**-TG	3	0	20	quant.	>99:1	95
6	**1**-TG	3	−15	20	78	>99:1	96
7	**1**-TG	10	−15	20	quant.	>99:1	96
8	**1**-TG	10	−40	70	56	>99:1	97
9	**1**-TG	20	−70	96	0	–	–

[a] Reactions were performed using 1.32 mmol of butanal, 0.44 mmol of nitrostyrene in the presence of the catalyst.
[b] Determined by ^{1}H NMR spectroscopy of the reaction mixture.
[c] Determined by chiral-phase HPLC analysis.
[d] Data taken from ref.[8c]



Scheme 2. Reaction, recycling and work-up protocol.

the desired conjugate addition product as those catalyzed by the soluble analogue **1** (Table 1, entries 1–4). Side products were not observed.

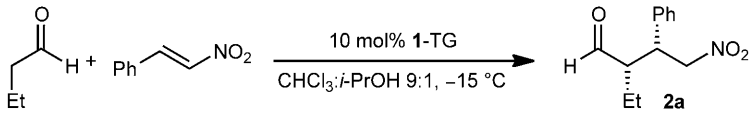
The diastereoselectivities and enantioselectivities of the γ-nitroaldehyde were lower compared to those observed with peptide **1** in solution phase but still in a range of *syn*:*anti* ratios of ~25:1 and enantioselectivities of 89–91% *ee* (Table 1, entries 2–4).[12] Comparatively small differences were observed between the three solid-supported catalysts, demonstrating that the type of resin has only a minor effect on the properties of the peptidic catalyst (Table 1, entries 2–4). The best results were observed with the peptide immobilized on TentaGel resin. Using 3 mol% of the immobilized peptide, the γ-nitroaldehyde was obtained within 4 h in quantitative yield, a diastereoselectivity of 28:1 (*syn*:*anti*) and an enantioselectivity of 91% *ee* (Table 1, entry 4). Thus, for all further studies the peptide immobilized on TentaGel resin (**1**-TG) was used.

With the appropriate resin in hand we next sought to further improve the enantioselectivity of the solid-supported peptidic catalyst **1**-TG. Whereas variations in the solvent did not result in further improvements (see Supporting Information), reducing the temperature led to a significant increase both in the diastereoselectivity and the enantioselectivity. Already at 0 °C the product was isolated in perfect diastereoselectivity (>99:1) and an enantioselectivity of 95% *ee* (Table 1, entry 5). A further reduction of the temperature to −15 °C required 10 mol% of the immobilized catalyst to achieve complete conversion to the product within 20 h but allowed for a further increase in the enantioselectivity to 96% *ee* (Table 1, entries 6 and 7). At lower temperature the catalytic activity was too low to be practical (Table 1, entries 8 and 9). Provided that the catalyst can be readily reused, a higher catalyst loading does not restrict its usefulness. Thus, we next evaluated the reusability of the solid-supported catalyst **1**-TG and performed these reactions at −15 °C using 10 mol% of the solid-supported catalyst.

To explore the reusability of the immobilized peptide **1**-TG, reactions were carried out under the optimized conditions described above. The reaction mixtures were not mechanically stirred but agitated by gentle shaking to allow for efficient mixing of the reaction components but prevent destruction of the resin. The immobilized catalyst was used without any further treatment with additives. The reaction course was easily monitored not only by TLC analysis but also the disappearance of the yellow color of the nitroolefin. After complete consumption of the nitroolefin, the catalyst was recovered by a simple filtration and then reused directly for the second reaction cycle under the same reaction conditions (Scheme 2). This reaction and recycling protocol was repeated 30 times. After each cycle, the conjugate addition product was isolated from the filtrate simply by evaporating the solvent and the excess of the aldehyde (Scheme 2).

This facile work-up procedure provided the γ-nitroaldehyde **2a** in each of the reaction cycles in perfect *syn*-diastereoselectivity, an enantiomeric excess of 96% *ee*, yields of ≥96% and, most remarkably, perfect purity (Table 2). The excellent purity of the γ-nitroaldehyde obtained after this simple protocol involving reaction, filtration, and evaporation of all volatiles was confirmed by NMR spectroscopic analysis and elemental analysis. Only in cycles 27–30 was the activity of the catalyst slightly reduced requiring reaction times of ≥24 h to obtain the γ-nitroaldehyde **2a** in the same perfect yields and high stereoselectivities (Table 2).

Table 2. Reusability of the solid-supported catalyst **1**-TG.



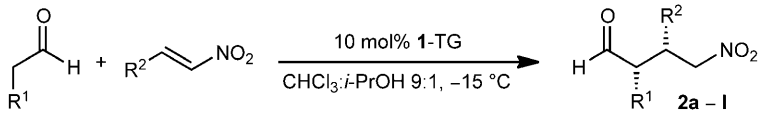
Cycle	Time [h]	Conversion [%][a]	Yield [%][b]	*syn*:*anti*[c]	*ee* [%][d]
1	20	quant.	quant.	>99:1	96
2–10	20–24	quant.	96–quant.	>99:1	96
11–13	20–24	quant.	nd[e]	nd[e]	nd[e]
14	23	quant.	quant.	>99:1	96
15–25	20–24	quant.	97–quant.	>99:1	96
26	24	99	nd[e]	>99:1	96
27–30	24 (48)[f]	≥95 (quant.)	quant.	>99:1	96

[a] Determined by ^{1}H NMR spectroscopy of the reaction mixture.
[b] Isolated yields.
[c] Determined by ^{1}H NMR spectroscopy of the isolated product.
[d] Determined by chiral-phase HPLC analysis.
[e] not determined.
[f] After 24 h a trace of the nitrostyrene (≤5%) was left as judged by TLC analysis which was consumed after 48 h.

These results demonstrate that the solid-supported peptide **1**-TG is an extraordinarily robust, chemoselective, and efficient catalyst. It does not suffer from irreversible deactivation reactions and does not require any kind of reactivation to maintain its excellent catalytic performance.

Also the substrate scope of the immobilized catalyst **1**-TG proved to be broad. A wide range of different aldehydes and nitroolefins react readily with each other in the presence of **1**-TG to provide γ-nitroaldehydes in excellent yields and stereoselectivities (Table 3). Most remarkably, all products were obtained in perfect purities as judged by NMR spectroscopy and elemental analysis and did not require any further purification after their simple isolation by filtration and evaporation of the solvent and excess of the aldehydes. This facile purification protocol also prevents possible epimerisation at the α-carbon of the γ-nitroaldehyde which can occur during a column chromatographic work-up. Only in the case of non-

Table 3. Conjugate addition reactions between aldehydes and nitroolefins catalyzed by immobilized peptide **1**-TG.[a]



Entry	R^1	R^2	Time [h]	Yield [%][b]	*syn*:*anti*[c]	*ee* [%][d]
1	Et	Ph	20	quant.	>99:1	96
2	Me	Ph	17	quant.	40:1	96
3	*n*-Bu	Ph	19	quant.	84:1	95
4	*i*-Pr	Ph	72	quant.	>99:1	95
5[e]	Bn	Ph	24	92	37:1	97
6	Et	C_6H_4-4-Cl	22	quant.	83:1	95
7	Et	C_6H_4-4-Br	22	quant.	>99:1	95
8	Et	C_6H_4-4-OMe	24	quant.	72:1	95
9	Et	C_6H_4-2-CF_3	24	quant.	>99:1	97
10	Et	C_6H_3-2,4-Cl_2	22	quant.	74:1	95
11	Et	2-thienyl	16	quant.	85:1	93
12	Et	$(CH_2)_5CH_3$	24	quant.	>99:1	92

[a] Reactions were performed using 1.32 mmol of aldehyde, 0.44 mmol of nitroolefin. Products were isolated after filtration of the catalyst and removal of all volatiles under reduced pressure unless otherwise noted.
[b] Isolated yields.
[c] Determined by ^{1}H NMR spectroscopy of the isolated product.
[d] Determined by chiral-phase HPLC analysis.
[e] The product was purified by flash column chromatography on silica gel.

volatile aldehydes (e.g., 3-phenylpropionaldehyde, Table 3, entry 5) was a column chromatographic purification necessary to isolate the pure γ-nitroaldehyde.

To evaluate the versatility of the immobilized peptidic catalyst further, we performed the reaction on a larger scale. 7.5 g (50.4 mmol) of nitrostyrene were reacted with 10.9 g (151.2 mmol) of butanal in the presence of 10 mol% of **1**-TG. The conjugate addition product **2a** formed also on this scale readily and was isolated in quantitative yield (11.2 g), perfect purity and *syn*-diastereoselectivity and an enantioselectivity of 96% *ee*.

Finally, we explored whether the reaction time can be readily reduced by using higher amounts of the immobilized catalyst **1**-TG. Reassuringly, the use of 30 mol% instead of 10 mol% of the catalyst under the same conditions allowed for a three-fold reduction of the reaction time (6 h instead of 20 h) and provided the product in the same high purity, yield and stereoselectivities. These results suggest that the immobilized peptidic catalyst is amenable for the development of a continuous flow system.

In conclusion, we have developed a highly efficient and reusable immobilized peptidic catalyst for asymmetric conjugate addition reactions of aldehydes to β-substituted nitroolefins. This is the first example of an immobilized chiral amine-based organocatalyst that can be reused after a simple filtration for at least 30 times without a loss in activity and stereoselectivity and without requiring reactivation. Reactions catalyzed by **1**-TG are so clean and high-yielding that simple removal of all volatiles under reduced pressure suffices to provide the desired products in excellent yields, purities and stereoselectivities. Thus, the immobilized peptidic catalyst is highly cost effective both with respect to its own reuse and the product isolation process. The reasons for this extraordinary performance of the solid-supported peptidic catalyst are manifold: (i) the catalyst is highly chemoselective for conjugate addition reactions – side reactions such as homo-aldol reactions that are common for other amine-based organocatalysts do not occur; (ii) additives are not required for the high catalytic efficiency – as a result, product purification is simple and no reactivation of the catalyst is necessary; (iii) the catalyst is chemically stable and is not deactivated over the reaction course by irreversible formation of undesired stable adducts. Thus, aside from the practical advances, the research also provides a guide for the development of other efficient immobilized organocatalysts. Furthermore, the results highlight the versatility of peptidic catalysts[13] in general. Since peptidic catalysts are routinely prepared by solid-phase peptide synthesis on a solid support and are generally chemically robust, they are arguably among the most attractive catalysts for immobilization.

Experimental Section

General Procedure for Conjugate Addition Reactions of Aldehydes to Nitroolefins Catalyzed by 1-TG

A glass reactor with Teflon filter (MultiSynTech, V050TF118) equipped with a Luer stopper (MultiSynTech, V000 LS100) was charged with **1**-TG (44 μmol, 10 mol%) and cooled to −15 °C. A solution of the aldehyde (1.32 mmol) and the nitroolefin (0.44 mmol) in a mixture of $CHCl_3$ and *i*-PrOH (9:1, 1 mL) was added and the reaction mixture was agitated using a shaker (IKA VIBRAX VXR basic) at ~600 rpm at −15 °C for 16–72 h. After complete consumption of the nitroolefin, the reaction mixture was directly filtered from the glass reactor and the remaining immobilized catalyst was washed with a mixture of $CHCl_3$ and *i*-PrOH (9:1) ~5 times. All volatiles (solvent and excess reagents) of the combined filtrate and washings were removed under reduced pressure to isolate the product. The immobilized catalyst **1**-TG was reused for the next reaction without any further treatment.

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