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Solid-Supported Tetrahydropyran-Based Hybrid Dipeptide Catalysts for Michael Addition of Aldehydes to Nitrostyrenes

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Abstract: The heterogenization of homogeneous catalysts onto a solid support is a step towards a more sustainable chemistry. The recovery and reuse of catalysts is extremely important from a practical, economic and environmental point of view. In this regards, we report a series of polymer-supported tetrahydropyran-based hybrid dipeptides that serve as active catalysts for the enantioselective Michael addition of aldehydes to β-nitrostyrenes. These supported catalysts have been designed considering the optimal anchor position and orientation between the catalyst and the solid support. Additionally, the influence of the linker length on the catalytic efficiency was studied. The catalysts allowed the transformation of a variety of substrates in 76–98% yield and with 94–97% enantiomeric excess. Detailed deactivation studies have provided important information, which allows to increase the useful life of these immobilized catalysts.

Keywords: asymmetric catalysis; organocatalysis; Michael addition; supported catalysts; peptides

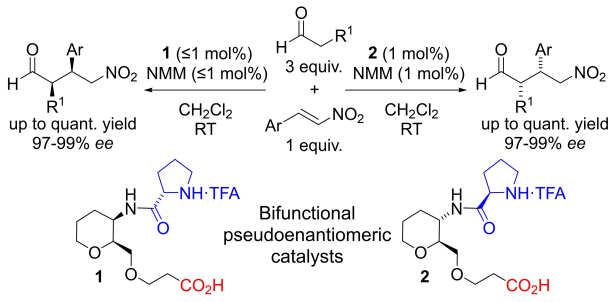
Introduction

The recovery and reuse of a catalyst is a major challenge in the area of catalysis. This can be achieved through immobilization of the catalysts onto a solid support which is insoluble in the reaction medium. In this way, through a simple filtration, the reaction product can be separated and isolated, and the catalyst recovered and reused. This approach can be very useful in saving time and money, and at the same time producing a lower environmental impact. In this sense, numerous approaches have been made to immobilize different types of catalysts.[1] Perhaps the most interesting are those employing organocatalysts, since these lack the problems that arise in the immobilization of organometallic catalysts, such as the leaching of the metal from the immobilized ligand, or instability due to sensitivity to air and humidity. In recent years, numerous immobilized organocatalysts have been prepared on different solid supports.[2] However, some of them show a decrease in their efficiency with respect to the homogeneous phase catalyst, mainly because the solid support can interfere with the catalyst. Therefore, the suitable choice of the linker that binds the catalyst to the solid support, as well as the position through which they are bound are of critical importance. On the other hand, deactivation of the organocatalyst can be a major issue, as it hampers its reuse by limiting the number of catalytic cycles. Deactivation can involve chemical modification[3] or blockage[4] of the catalyst's active site. The latter can be produced by the starting materials, the reaction

products or by products from off-cycle reactions. Furthermore, a large number of organocatalytic systems require the use of additives that act as co-catalysts, such as an acid or a base in substoichiometric amounts. Usually, these co-catalysts are not recovered and additional purification steps are necessary to yield the pure product. For this reason, it seems more convenient to use bifunctional organocatalysts for the immobilization on a solid phase, where one of the functionalities acts as the additive and renders the addition of a co-catalyst unnecessary.

Recently, we presented a series of new bifunctional hybrid dipeptide-like organocatalysts based on ε- or ζ-sugar amino acids (SAAs) and proline that efficiently catalyze the Michael addition of aldehydes to β-nitrostyrenes.[5] These catalysts combine two highly-modular building blocks: amino acids and carbohydrates. Furanoid and pyranoid α-, β-, γ- and δ-sugar amino acids (SAAs) have been described as peptide building blocks and used as conformationally constrained scaffolds. In previous work carried out in our group we have found that the tetrahydropyran units linked through the C2 and C3 positions show inherent conformational preferences in some chiral receptors,[6] and this structural topology was also extended to cyclopeptides, whose conformational preferences can be modulated through the presence or lack of a methoxy group at C4 position of the tetrahydropyran ring.[7] By applying this conformational control to our catalysts we were able to prepare two complementary bifunctional pseudoenantiomeric catalysts **1** and **2** that allow accessing both enantiomers of the synthetically versatile γ-nitroaldehydes, with excelent yields and enantioselectivity between 97% and 99%, using catalytic loads even below 1 mol%. Additionally, these catalysts work in a single solvent system, at room temperature and without the use of additives (Scheme 1).[8]

Considering the high catalytic activity that these hybrid dipeptides have in the homogeneous phase, we decided to explore their performance when immobilized on an inert solid support. Here, we report on the preparation of new immobilized hybrid dipeptide catalysts and study their catalytic activity in the Michael addition of aldehydes to β-nitrostyrenes.[9]



Scheme 1. Michael addition of aldehydes to β-nitrostyrenes in the homogeneous phase using bifunctional pseudoenantiomeric catalysts **1** and **2**. NMM=*N*-methylmorpholine.

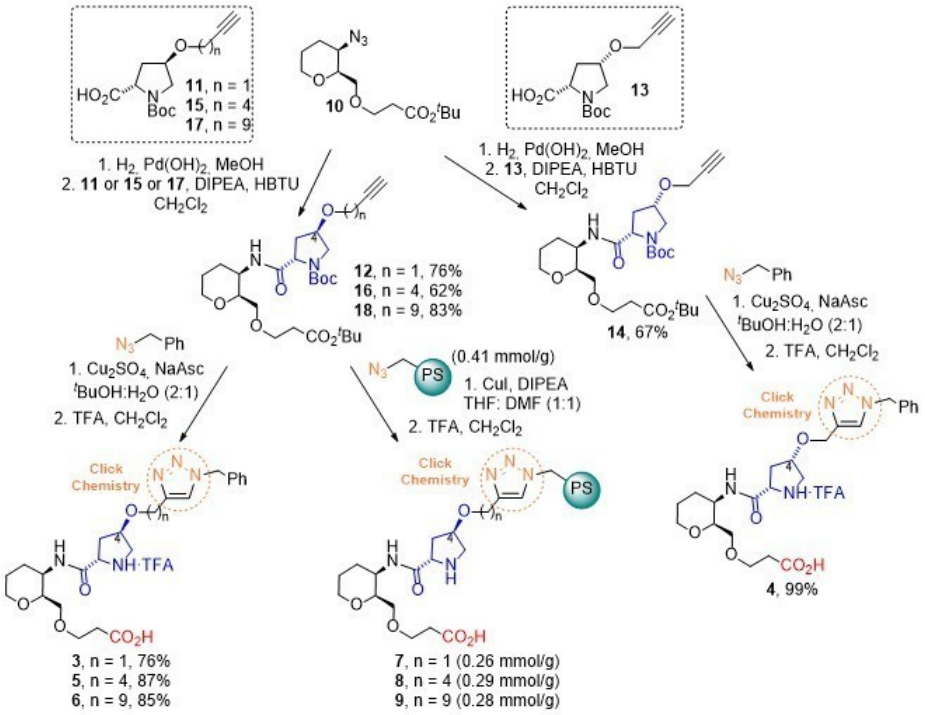
Results and Discussion

To transfer the catalytic activity found in the homogeneous phase to the heterogeneous phase, several issues must be considered: the choice of the appropriate solid support, the type of reaction used for the immobilization, the position and orientation where the catalyst is going to be anchored to the solid support and the length of the linker.

Taking into account the work of Pericàs et al. in the immobilization of *trans*-4-hydroxy-L-proline,[10] we figured that polystyrene (PS) cross-linked with 1% divinylbenzene (DVB) could be a suitable support for our catalysts, and the copper-catalyzed alkyne azide cycloaddition (CuAAC) reaction[11] the appropriate tool for the immobilization.[12] This lead us to the preparation of a derivative of catalyst **1** bearing a terminal alkyne and the use of azidomethyl polystyrene as the solid support.

Regarding the question of which may be the best position and orientation to anchor our catalyst to the solid support, a structural analysis of the enamine formed by the condensation of the aldehyde and the proline unit could provide us with a hint. In a previous work,[5] we carried out a conformational search for these reaction intermediates. Considering these results and how the β-nitrostyrene approaches the enamine, we anticipated that the best option is to use *trans*-4-hydroxy-L-proline as the proline unit, which *N*-Boc derivative is commercially available. This proline unit allows the linker to be far away from the catalytically active amine residue and the stereogenic centers, avoiding perturbation of the enantiodeterminant transition state which could be induced by the linker and the polymeric backbone.[13]

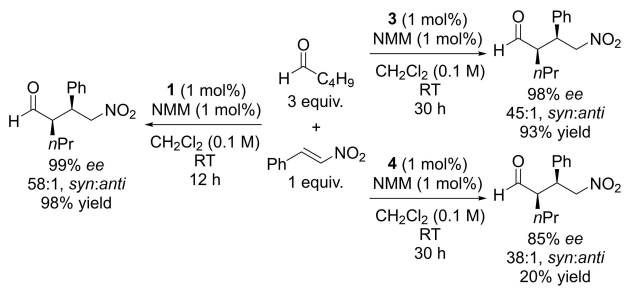
With all these considerations in mind, we designed immobilized catalyst **7** (Scheme 2). However, before carrying out the synthesis of the heterogeneous catalyst we decided to check the influence on the catalytic activity of the appendix incorporated in 4-position of the proline. For this, we prepared catalyst **3**, which is a soluble version of catalyst **7**. Catalyst **3** was prepared by a straightforward route as depicted in Scheme 2. Azide **10**[8] was reduced to amine through catalytic hydrogenation, and subsequently peptide bond formation with the L-proline derivative **11**[14] to give protected dipeptide **12**. The next step was a CuAAC reaction with benzyl azide, which afforded the protected dipeptide. Deprotection of the *N*-Boc group and the *tert*-butyl ester with TFA provided catalyst **3** as the trifluoroacetate salt. In order to study the influence of the stereochemistry at the 4-position of the proline on the catalytic activity, we prepared catalyst **4**, which



Scheme 2. Synthesis of hybrid dipeptide catalysts **3**, **4**, **5** and **6** and immobilized catalysts **7**, **8** and **9**. DIPEA=*N*,*N*-Diisopropylethylamine. HBTU=O-(Benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate. NaAsc = Sodium L-ascorbate.

has the opposite stereochemistry to catalyst **3** at that position. Catalyst **4** was synthetized following the same sequence of reactions described to obtain catalyst **3**, but using L-proline derivative **13**[15] in the formation of the peptide bond (Scheme 2).[16]

Catalysts **3** and **4** were compared with catalyst **1** using the same reaction conditions, with a catalytic load of 1 mol%. Similar diastereo- and enantioselectivity were observed with catalyst **3**, although it required more time to complete the reaction (Scheme 3). Conversely, catalyst **4** displayed worse performance and stereoselectivity. These results clearly indicate that the adequate position and orientation of the appendix



Scheme 3. Study of the influence of the appendage at the 4-position of the proline and its stereochemistry on the catalytic activity.

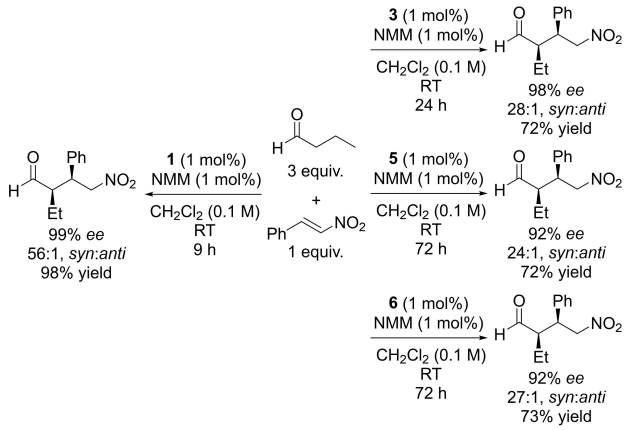
are that of catalyst **3**, since only the stereochemical outcome of the reaction is slightly affected.

Change in the stereochemistry at the 4-position of proline significantly affects the reactivity and enantioselectivity of the process, but not its diastereoselectivity. This is because reactivity and enantioselectivity depend on how the β-nitrostyrene approaches the enamine intermediate. If the attack occurs at the same side as the carboxylic acid, this will activate the electrophilic character of the β-nitrostyrene, making it more reactive. In catalyst **4**, the appendix partially prevents the entry of β-nitrostyrene at the carboxylic acid side, decreasing its catalytic activity and enantioselectivity. However, the diastereoselectivity depends on the enamine conformation. In previous studies, we observed that the enamines mainly adopt a *syn*-conformation.[5] The results of this work (Scheme 3) clearly indicate that the presence of the appendage, regardless of its configuration, does not significantly affect the conformation adopted by the enamine and thus the diastereoselectivity.

Additionally, we checked the influence of the linker length on the catalytic activity in the homogeneous phase. For this, two analogues of the proline derivative **11** were prepared, with different alkyl-chain sizes between the oxygen atom of the ether and the terminal alkyne. Using proline derivatives **15** and **17**, and following the same sequence of the reactions described

above, it was possible to obtain catalysts **5** and **6** (Scheme 2). Unexpectedly, comparison with catalysts **1** and **3** proved that longer appendages in the homogeneous phase decrease the reaction rate, yield and the stereoselectivity of the process (Scheme 4).

Overall, the catalytic activity was affected by the presence of the appendage at the 4-position of proline, which is evidenced by longer reaction times when compared to the catalyst **1**. This may be due to a stereo-electronic effect. On one hand, the oxygen atom at the 4-position of proline exerts an inductive effect by removing electron density from the proline nitrogen, which makes it less reactive for the formation of the enamine intermediate. In addition, the formed enamine is expected to be less nucleophilic and therefore less reactive in the Michael-addition. This effect should be very similar for catalysts **3**, **4**, **5** and **6**. However, if we compare catalysts **3** and **4**, both bear the same appendage but on opposite faces of the pyrrolidine ring, indicating that the difference in reactivity is due to steric effects. In the case of catalysts **5** and **6**, the longer and more flexible appendages can adopt folded conformations that prevent the approximation of the aldehyde to the pyrrolidine or the β-nitrostyrene to the enamine. As a result, they are less reactive in solution than catalyst **3**, bearing a shorter appendage (Scheme 4).[17]

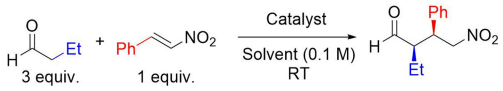


Scheme 4. Effect of longer appendages at 4-position of the proline on the catalytic activity.

To synthesize the immobilized versions, azidomethyl polystyrene was used in the click chemistry reaction to yield the protected dipeptides. Deprotection with TFA and subsequent neutralization provided the immobilized catalysts **7**, **8** and **9** (Scheme 2).[16]

Using the optimal reaction conditions for the homogeneous phase catalysts, we investigated the efficiency of supported catalysts **7**, **8** and **9**. To accomplish this, the Michael addition of *n*-butanal to *trans*-β-nitrostyrene was used. The best results were obtained with catalyst **7**, bearing a shorter chain between the solid support and the catalytic unit. Interestingly, the immobilized catalysts with longer linkers **8** and **9** showed similar performance to catalyst **7** (Table 1, entries 1 to 3). However, their soluble

Table 1. Determination of the influence of linker length and solvent effect on the Michael addition of *n*-butanal to *trans*-β-nitrostyrene using polysterene-supported catalysts.

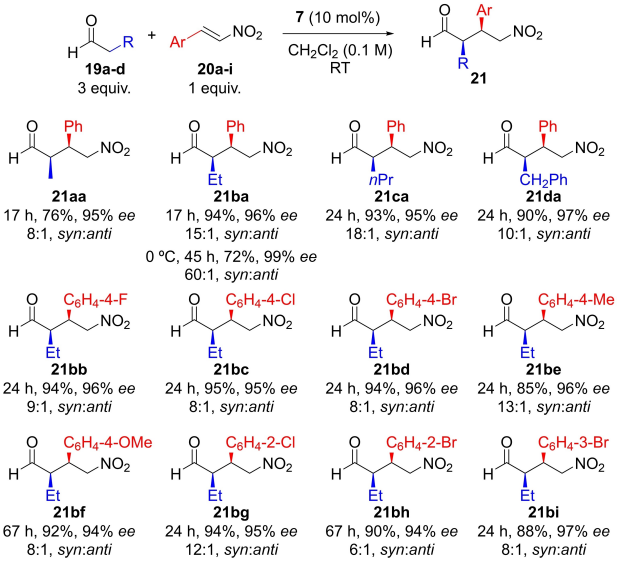


Entry[a]	Catalyst (x mol%)	Solvent	Time (h)	Yield (%)[b]	*syn*:*anti* [c]	*ee* (%)[d]
1	**7** (10)	CH_2Cl_2	17	94	16:1	95.6
2	**8** (10)	CH_2Cl_2	20	99	15:1	91.2
3	**9** (10)	CH_2Cl_2	20	97	10:1	94.1
4	**7** (5)	CH_2Cl_2	41	92	17:1	95.2
5	**7** (5)	THF	41	54	16:1	91.9
6	**7** (5)	MeOH	41	96	4:1	64.7
7	**7** (5)	CH_3CN	41	80	11:1	73.6
8	**7** (5)	Hexane	41	94	5:1	78.7
9	**7** (5)	Toluene	41	90	15:1	87.1
10	**7** (5)	Ether	41	90	6:1	79.9
11	**7** (5)	$CHCl_3$	41	95	16:1	94.8
12	**7** (5)	$CHCl_3$:*i*PrOH (9:1)	41	99	15:1	92.1
13	**7** (5)	CH_2Cl_2:Hexane (4:6)	41	96	10:1	90.0

[a] All reactions were carried out at 0.2 mmol scale in *trans*-β-nitrostyrene, and gentle shaking using a vortex mixer was applied.
[b] Isolated yield.
[c] Determined by ^{1}H NMR spectroscopy of the reaction mixture.
[d] Determined by chiral HPLC, Chiralpak IC-3, *n*-hexane:*i*-PrOH (7:3).

counterparts, catalysts **5** and **6**, were worse than catalyst **3**. This result suggests that the polystyrene backbone plays an important role in the conformational behavior of the longer linkers. On the other hand, using catalyst **7** we checked the influence of the solvent on the reaction outcome (Table 1, entries 4 to 13). We found that the best solvent in terms of enantiomeric excess and *syn*:*anti* ratio was CH_2Cl_2 (Table 1, entry 4).

With the appropriate catalyst in hand, we next explored the scope, using several aldehydes (**19 a**–**d**) and *trans*-β-nitrostyrenes (**20 a**–**i**) in CH_2Cl_2 at room temperature. Forecasting that the catalyst can be easily reused, and in order to make the reaction faster, we increased the catalytic load to 10 mol%. In all cases, the desired γ-nitroaldehyde products (**21**) were obtained with excellent conversions and yields, and enantiomeric excesses between 94 and 97% (Scheme 5). We observed a slight decrease in enantiomeric excesses respect to the previous results obtained in homogeneous phase with catalyst **1**.[8] However these results may be quite useful for synthetic purposes, and even more so if we consider that in many cases a simple filtration and removal of all volatiles under reduced pressure provides the final product in high purity. Furthermore, when the reaction was carried out at 0 °C, compound **21 ba** could be obtained with excellent stereoselectivity (99% *ee* and a *syn*:*anti* ratio of 60:1), although with an increase in reaction time.



Scheme 5. Scope of catalyst **7**. General conditions: *trans*-β-nitrostyrene (0.2 mmol), aldehyde (0.6 mmol), catalyst **7** (10 mol%), in 2 mL of CH_2Cl_2 (0.1 M) at room temperature and gentle shaking using a vortex mixer was applied. Isolated yield (%). The enantiomeric excess (*ee*) was determined by chiral HPLC analysis, using a Chiralpak IC-3 column and mixtures of *n*-hexane:*i*-PrOH. The *syn*:*anti* ratio was determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

As mentioned above, one of the main advantages associated with the use of polymer-supported catalysts is the possibility of recover and reuse. To explore the reusability of polymer-supported catalyst **7**, the reactions were carried out using the optimal conditions of room temperature, CH_2Cl_2 as solvent, with *n*-butanal and *trans*-β-nitrostyrene as reagents, and stirring with a vortex mixer. Mechanical stirring with a magnetic stirring bar was avoided in order to prevent deterioration of the solid support. Immobilized catalyst **7** was reused without any further treatment. The reaction course can be easily followed by the disappearance of the yellow color of the β-nitrostyrene or via TLC. To determine potential loss of the catalytic activity, the reactions were stopped at 24 h, filtered to recover the supported catalyst, which was reused in the following reaction cycle under the same reaction conditions. This process was repeated successively. The result of the recycling tests of supported catalyst **7** can be seen in Table 2. The enantioselectivity of the process remained practically constant throughout the cycles, and the ratio between the *syn* and *anti* isomers increased slightly, however a gradual decrease in yields could be observed starting from the third cycle onwards.

In the homogeneous phase, using catalyst **1**, we observed that most of the *anti* isomer derives from the epimerization of the *syn* isomer. This is due to the reaction of the latter with the catalyst to form an enamine, which is subsequently hydrolyzed in the reaction medium, leading to a mixture of both isomers. Therefore, it can be stated that the *syn*:*anti* ratio is inversely proportional to the catalytic loading and the reaction time. Extrapolating this to the heterogeneous phase, the decrease in yield and the increase in the *syn*:*anti* ratio observed in Table 2 clearly indicated that the amount of catalyst available on the solid support has been decreasing throughout the cycles.

Table 2. Recycling test of the immobilized catalyst **7**.[a]

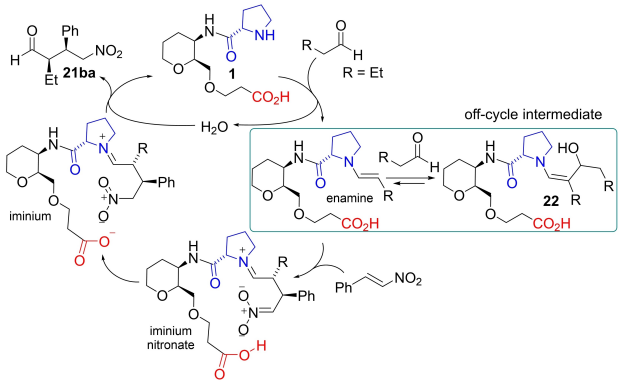
Cycle	Yield (%)[b]	*syn*:*anti*[c]	*ee* (%)[d]
1	98	11:1	95.6
2	97	17:1	94.9
3	90	20:1	94.5
4	89	23:1	95.3

[a] General conditions: *trans*-β-nitrostyrene (**20 a**) (0.2 mmol), *n*-butanal (**19 b**) (0.6 mmol), catalyst **7** (10 mol%), in 2 mL of CH_2Cl_2 (0.1 M) at room temperature, and gentle shaking using a vortex mixer for 24 h was applied.
[b] Isolated yield.
[c] Determined by ^{1}H NMR spectroscopy of the reaction mixture.
[d] Determined by chiral HPLC, Chiralpak IC-3, *n*-hexane:*i*-PrOH (7:3).

The reason for this deactivation could be structural modification or blockage of the active site by starting materials, reaction products or by-products. Determining the cause of catalyst deactivation is not a trivial problem, however, during the course of our research, Schnitzer and Wennemers reported the deactivation of secondary amine catalysts by formation an off-cycle intermediate.[4] They found that the β-hydroxy-aldehydes from the aldol addition block the proline unit, forming an enamine that is stable under the reaction conditions. This deactivation pathway is less pronounced in those catalysts that are more chemoselective, generating mainly the Michael addition products against the undesirable aldol addition products.

In order to check if this could be the reason for deactivation of our catalyst, we carried out a Michael addition reaction between *n*-butanal and *trans*-β-nitrostyrene using catalyst **1** (0.2 M in CH_2Cl_2, 1 mol% of catalyst **1** and 1 mol% of NMM) and monitored the reaction mixture *via* high resolution mass spectrometry.[4] In this way, it was possible to identify catalyst **1** and the different reaction intermediates that are generated throughout the catalytic cycle, such as enamine or immonium formed by **1** with *n*-butanal and with the Michael addition product **21 ba**. Additionally, a small signal was detected at *m/z* 427.2808 ($C_{22}H_{39}N_2O_6$, $[M+H]^+$) corresponding to the mass of the enamine or iminium **22**, formed by the reaction of catalyst **1** with the aldol addition product (Scheme 6). **22** constitutes an off-cycle intermediate and indicates that the same deactivation pathway previously reported by Schnitzer and Wennemers could be occurring with our catalysts.

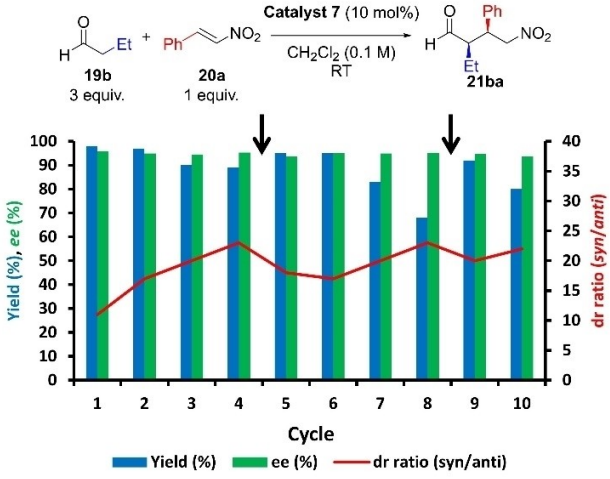
In order to determine if any of the starting materials or the final product cause deactivation, catalyst **7** was pre-treated with *n*-butanal, *trans*-β-nitrostyrene and the reaction product for 24 hours before carrying out the Michael addition. Each of the previously treated supports were used in a reaction of *n*-butanal with *trans*-β-nitrostyrene under optimal conditions and the reactions were stopped at 24 hours. Neither *trans*-β-nitrostyrene nor the reaction product had a significantly negative effect on the catalyst, as full conversion was obtained in those reactions. However, a slight decrease in conversion was observed with the supported catalyst previously treated with *n*-butanal. These results confirm that the deactivation of our immobilized catalyst is due to the aldol addition product. Therefore, we argued that by using the freshly distilled aldehyde and reducing its quantity from 3 to 1.5 equivalents could help to preserve the catalyst activity for a longer time. However, the decrease in aldehyde also produced a decrease in the *syn*/*anti* ratio of the final products. For this reason, we decided to explore the reconditioning of the immobilized catalyst **7**. Thus, after the fourth cycle, we treated the solid support with different solvents, bases and acids, and afterwards its catalytic properties were again evaluated. Fortunately, we found that treatment with a solution of THF:H_2O:TFA (8:1:1) for 24 hours and its subsequent neutralization with a 2% solution of triethylamine in THF regenerates the catalytic activity almost completely while maintaining the stereoselectivity of the process (Scheme 7). This allowed us to maintain the catalytic activity basically unchanged throughout 10 cycles.



Scheme 6. Catalytic cycle and deactivation pathway by aldol addition product.

Conclusion

Using our bifunctional catalysts based on hybrid dipeptide tetrahydropyrans we have developed a series of reusable polymers that possess catalytic activity for the enantioselective Michael addition of aldehydes to



Scheme 7. Reusability of the immobilized catalyst **7**. The black arrows indicate between which cycles the supported catalyst **7** was treated with a mixture of THF:H_2O:TFA (8:1:1) for 24 hours and subsequently neutralized with a 2% solution of triethylamine in THF before use in the next cycle.

β-nitrostyrenes. These organocatalysts were immobilized onto a solid support using the copper-catalyzed alkyne azide cycloaddition (CuAAC) reaction, and the influence of the anchor position, orientation and the length of the linker on the catalytic activity was studied. There are several advantages that are important to highlight: 1) due to the bifunctional character of these catalysts the use of additives is not necessary for the reaction to take place, facilitating the purification process since in many cases a simple filtration and subsequent evaporation of the solvent leads to the final product with a high degree of purity; 2) the catalysts operate at room temperature, which reduces energy consumption, and 3) the optimal conditions takes place in a single aprotic solvent (CH_2Cl_2), which allows combination with other catalytic systems to access greater structural complexity. Additionally, we performed studies on the deactivation of the immobilized catalyst, which allowed us to identify an off-cycle intermediate, the aldol addition product, as the reason for the loss of the catalytic activity. Fortunately, it was possible to restore the catalytic activity of the immobilized catalyst by treating with THF:H_2O:TFA (8:1:1), recovering its efficiency while maintaining the stereoselectivity of the process. The results obtained within this study allowed us to expand the rational design toolbox for organocatalyst immobilization.

Experimental Section

General procedure for the Michael Addition reaction of aldehydes to β-nitrostyrenes in homogeneous phase: The β-nitrostyrenes (0.2 mmol, 1.0 equiv.) and the aldehyde (0.6 mmol, 3.0 equiv.) were added to a solution of the catalyst (0.01 equiv.) and *N*-methylmorpholine (0.01 equiv.) in dry CH_2Cl_2 (2.0 mL, 0.1 M). The reaction mixture was stirred at room temperature until TLC showed the end of the reaction. The organic solvent was removed under vacuum and the crude was purified by column chromatography on silica gel using mixtures of hexanes and ethyl acetate as eluent.

General procedure for the Michael Addition reaction of aldehydes to β-nitrostyrenes in heterogeneous phase: The immobilized catalyst (10 mol% with respect to β-nitrostyrene) was placed in a 4 mL screw cap vial and 2 mL of dry CH_2Cl_2 (0.1 M), β-nitrostyrene (0.2 mmol) and aldehyde (0.6 mmol) were added. The vial was closed and gently shaken using a vortex mixer at room temperature. Upon completion of the reaction, the mixture was filtered and the organic phase was concentrated under vacuum to remove all volatiles, and the crude obtained was purified by column chromatography on silica gel using mixtures of hexanes and ethyl acetate as eluent.

For detailed experimental information and characterization of compounds, see the supporting information.

Acknowledgements

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