ENVIRONMENTALLY BENIGN CATALYSIS: ASYMMETRIC MICHAEL-ADDITIONS USING HOMOGENEOUS AND HETEROGENIZED CHIRAL 1,2-DIAMINE DERIVATIVES

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Abstract

We have studied the asymmetric Michael-addition of aldehydes to maleimides using optically pure 1,2-diamine catalysts. Investigations on the effect of the structure of the catalyst, maleimide and aldehyde led to valuable conclusions as concern the steric and electronic requirements for obtaining high activities and stereoselectivities in these asymmetric reactions. Based on these observations a plausible reaction intermediate for explaining the stereoselective addition of the nucleophile to the activated olefin is suggested. Furthermore, the results were used for selecting the chiral catalyst and the appropriate linker for the preparation of heterogenized chiral materials. The activities and enantioselectivities obtained using the catalysts immobilized on a proper support approached those obtained with their soluble counterparts and kept their stereoselectivities upon reuse.

Introduction

Asymmetric Michael-additions are among the most often-used stereospecific reactions for coupling organic molecules, widely applied for preparing optically pure fine chemicals. Succinimide derivatives may be obtained by the enantioselective addition of nucleophiles, such as aldehydes, to maleimides.[1] These reactions are catalyzed efficiently by chiral diamines and derivatives thereof, among which cyclohexane-1,2-diamines, 1,2-diphenylethylene diamines, their sulfonamides and thiocarbamides are privileged chiral catalysts.[2-4] However, a systematic comparison of their performances in the enantioselective addition of aldehydes to maleimides is still missing. A detailed study is of paramount importance for selecting the proper catalyst structure and the linker for the immobilization of these organocatalysts in order to obtain heterogeneous, recyclable chiral catalysts. The heterogeneous catalysts obtained by immobilization of the diamines could be applied in environmentally friendly, sustainable processes as convenient alternatives of their soluble counterparts for the preparation of optically pure succinimides.

Our aim during this work was to study the effect of the chiral 1,2-diamine derivatives' structure on the results obtained in the asymmetric addition of various aldehydes to maleimides, in order to find an efficient, easily accessible catalyst for these reactions. Based on the results of this study we planned to attempt the immobilization of the selected chiral 1,2-diamine catalyst using an appropriate linker over several inorganic and organic supports. Our goal was to develop a highly efficient, reusable heterogeneous chiral catalyst for the asymmetric Michael-addition of aldehydes to maleimides.

Experimental

The chiral 1,2-diamine derivatives, functionalized inorganic oxides or organic polymers used as supports, maleimide derivatives and aldehydes were obtained from commercial sources and were used as received. Asymmetric Michael-additions were carried out in closed glass reactors heated in oil bath if necessary. In reactions catalyzed by solid materials, the mixtures were stirred magnetically or mixed using shakers. In a typical run the chiral catalyst was dissolved in the proper solvent amount followed by addition of the maleimide derivative and the aldehyde. The solution or the suspension (in case of the solid chiral catalysts) was stirred at the given temperature for the desired time. Following the reactions the soluble catalysts were extracted with saturated NH_4Cl aqueous solution and the organic products were analysed. After the heterogeneously catalyzed reactions the catalyst was separated by decantation before the aqueous washing of the products. These materials were reused in several successive runs. Products resulted in the Michael-additions were analysed by GC-MSD and GC-FID using chiral capillary column. Larger scale experiments were also carried out, the resulted products were purified by column chromatography for determination of the yields. The pure compounds were characterized by ^{1}H- and ^{13}C-NMR spectroscopy.

Results and discussion

The addition of isobutanal to N-phenylmaleimide was selected as test reaction for investigating the effect of the chiral 1,2-diamine structure. Selected results are presented in Figure 1. Cyclohexane-1,2-diamine derivatives gave the Michael adducts in few hours, however, provided lower enantioselectivities (not shown in figure) as compared with the 1,2-diphenylethylene diamine derivatives, the latter however needed longer reaction times, up to 24 hours, for complete conversion of the maleimide. An acidic group, such as the sulfonamide group, needed to obtain high ee, however, the methanesulfonamide was equally efficient as the toluenesulfonyl derivative. Using the opposite (*R*,*R*) enantiomer of the catalysts resulted in identical conversion and ee values except the *R*-succinimide derivative was obtained in excess. Similar tendencies were observed using N-ethyl, N-*terc*-butyl and unsubstituted maleimides or propanal and cyclohexanecarbaldehyde nucleophiles. Reactions carried out at 1 mmol scale gave the optically pure isolated adducts in good yields. Based on the steric and electronic effect of the substituents we suggested a plausible reaction intermediate and a mechanism able to rationalize the obtained enantioselectivities.

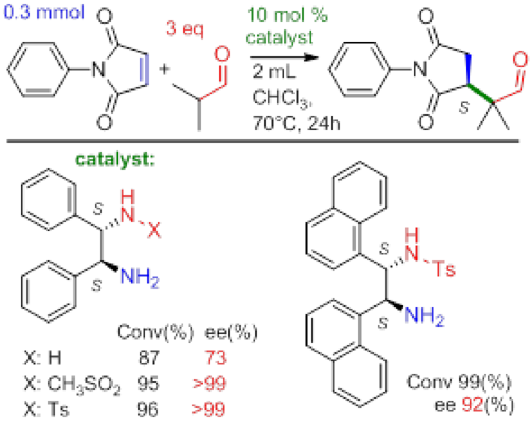

Figure 1. Results of the test Michael-addition using 1,2-diamine catalyst (Ts: p-toluenesulfonyl).

Accordingly, we immobilized optically pure 1,2-diphenylethylene diamine using linkers having acidic, H-bond donor character, such as sulfonamide, thiocarbamide or squaramide groups over silica or polystyrene resin supports. Selected catalysts and results obtained in the addition of isobutanal to N-phenylmaleimide using these materials are summarized in Figure 2.

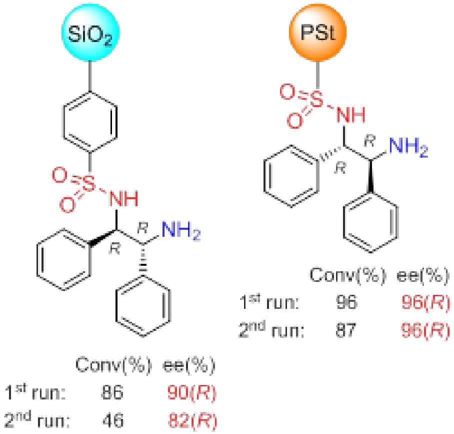

Figure 2. Selected heterogenized chiral catalysts and results obtained in the test reaction.

The success of the immobilization process of the chiral compounds was checked by FT-IR spectroscopy, absorption bands characteristic to the sulfonamide group appeared in the spectra of the materials shown in the figure. The silica-supported catalysts gave lower enantioselectivities and partially lost their activity upon reuse, which we ascribed to the unfavorable effect of the support's surface acidic sites. On the contrary, the chiral catalysts immobilized on polystyrene resins approached the performances of the soluble catalysts, affording the same conversion and only slight decrease in the enantioselectivity. Moreover, the enantiodiscrimination ability of the catalyst was kept in a 2nd run. The small decrease in conversion may be attributed to the small amount of catalyst lost during manipulations. Good results were also obtained with catalysts immobilized on polystyrene resins via thiocarbamides or squaramide groups (not shown in the figure), which will be also presented.

Conclusion

We have studied the asymmetric Michael-addition of aldehydes to maleimides using optically pure 1,2-diamine derivatives resulting in chiral succinimides. We have investigated in detail the effect of variations in the structure of the catalysts and the reactants. Based on the results of these experiments we could deduce the structural elements of the reaction components, which have decisive influence on the stereochemical outcome of these asymmetric reactions. Based on these results we selected the proper catalyst and linker for the immobilization of the chiral catalyst in order to obtain heterogeneous chiral catalysts, which approached the performances of their soluble counterparts. The proper choice of the support allowed the reuse of the solid catalysts without enantioselectivity decrease. Finally, we note that the prepared heterogeneous catalysts are the first, which were designed for the asymmetric Michael-addition of aldehydes to maleimides. Results presented in this work are also promising starting-points of further efforts devoted to apply heterogeneous, environmentally friendly catalysts in the preparation of practically relevant chiral succinimides.

Acknowledgements

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