APPLICATION OF NEW CATALYTIC SYSTEMS IN ASYMMETRIC MICHAEL ADDITIONS TO MALEIMIDES

PHD THESES

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1. INTRODUCTION AND AIMS

Since the most important molecules in living organisms are chiral, the selective production of suitable optical isomers of compounds designed to interact with them, such as drugs, is of paramount importance. In addition, from an environmental point of view, it is also advantageous to carry out their syntheses as efficiently as possible, thus minimising the environmental impact of the processes. Among the enantioselective methods, the asymmetric catalytic reactions are nowadays gaining ground, where the stereoselective incorporation of the chiral centre into the molecule is achieved by the action of optically active catalysts. The advantage of these processes is that small amounts of chiral materials are required to produce large amounts of enantiomerically pure compounds.

Such chiral catalysts are widely used, for example, in C-C coupling reactions such as Michael additions, which are highly efficient processes for coupling small molecules and introducing new chiral centres enantioselectively in organic compounds. In these reactions, a large variety of Michael donors and acceptors can be used, allowing to obtain very diverse products. Among the Michael acceptors, maleimides are prominent, as the resulting chiral succinimides are valuable, optically pure intermediates that can be used in the pharmaceutical industry. The promising results obtained so far also demonstrate that the efficient enantiomerically pure production of these compounds could be important for the healthcare industry. Motivated by this, we have started to develop various catalytic systems for the asymmetric Michael addition of maleimides and carbonyl compounds.

Because of the practical importance of the asymmetric conjugate additions we aimed to synthesize phosphoric acid amides and thiophosphoric acid amides from chiral 1,2-diamines. Due to the low number of publications appeared in the literature on the application of these derivatives, we initially focused our research on the comparison of the performances of the chiral 1,2-diamine derivatives in the Michael addition of *N*-substituted maleimides and isobutanal. Then we have extended our studies to the reaction of other Michael donors and maleimides using the thiophosphoric acid amide derivative of 1,2-diphenylethane-1,2-diamine, which was found to be the most efficient. Mechanistic studies were designed to elucidate the role of the thiophosphoric amide group and explain its performance compared to sulfonic acid amides.

Given the practical importance of heterogeneous catalysis, as well as the economic and environmental considerations, we aimed to develop reusable heterogeneous asymmetric catalytic systems. We designed a method to bond covalently chiral 1,2-diamines on organic and inorganic solid supports. For the same purpose, we wanted to develop a chiral heterogeneous catalyst from natural, inexpensive amino acids and readily available inorganic oxides by surface adsorption. We hoped that the results of our study will open new paths for the development of catalytic systems that can be successfully used in a variety of enantioselective Michael additions.

2. MATERIALS AND METHODS

Measurements were carried out at millimole quantities in screw-top glass reactors by magnetic stirring at room temperature or immersed in an oil bath kept at the appropriate temperature. Some of the reactions with heterogeneous catalysts were carried out using shaker to avoid particle degradation. The product from the mixtures containing homogeneous catalyst was obtained by extraction. Heterogeneous catalysts were separated from the liquid phase by filtration or centrifugation. The products were analysed by gas chromatography using chiral capillary columns. The isolated Michael adducts were obtained by column chromatography or recrystallization and their purity and structure were determined by ^{1}H- and ^{13}C-NMR spectroscopy.

Mechanistic studies with chiral diamine derivatives were carried out by ESI-MS and NMR measurements. The covalent bonding of the chiral diamines to various insoluble supports was verified by FT-IR spectroscopy. The organic content of the heterogeneous catalysts prepared by adsorption was determined by UV-Vis spectroscopy. Further characterizations of chiral solids were performed by FT-IR spectroscopy, Raman spectroscopy, thermogravimetry, XRD and SEM.

3. NEW SCIENTIFIC RESULTS

T1. We prepared (thio)phosphoric amide chiral organocatalysts and used them for the first time in asymmetric Michael additions between isobutanal and *N*-substituted maleimides.

We prepared chiral (thio)phosphoric amide derivatives from C_2-symmetric 1,2-diamines in good yields. Derivatives of 1,2-diphenylethane-1,2-diamines were obtained in a one-step procedure (PO-DPEN and PS-DPEN, **Figure 1**), while the synthesis from cyclohexane-1,2-diamines required three steps.

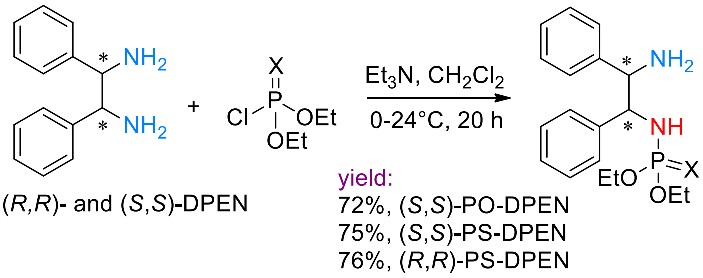

Figure 1 Preparation of (thio)phosphoramides by a one-step process.

In our catalytic studies, the Michael addition between isobutanal and *N*-benzyl maleimide was chosen as a test reaction (**Figure 2**), in which we obtained enantiomerically pure succinimide derivative by complete conversion of the starting maleimide [2]. In the next step, we studied the effect of the Michael acceptor structure by changing the *N*-substituent of the maleimide. After optimization of the reaction conditions, it became possible to obtain optically pure succinimides with near complete conversion from several maleimide derivatives using the (*S*,*S*)-PS-DPEN organocatalyst, which we have employed for the first time in this reaction.

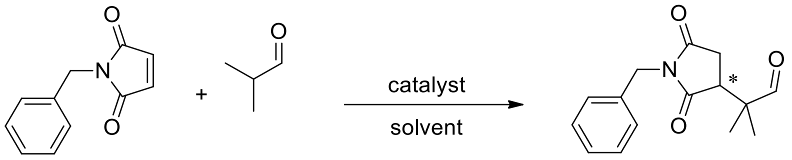

Figure 2 Test reaction: asymmetric Michael addition of *N*-benzylmaleimide and isobutanal.

T2. The use of (*S*,*S*)-PS-DPEN catalyst was extended to the asymmetric Michael addition of maleimides and ketones.

Using aliphatic and cycloaliphatic ketones as nucleophiles, conjugated addition to maleimide derivatives was carried out using (*S*,*S*)-PS-DPEN as the chiral catalyst. Excellent enantiomeric excesses (*ee* 97-99%) and conversions were obtained in these reactions, although longer reaction times were required with cycloaliphatic ketones, which was attributed to the steric hindrance of these rings. The diastereomeric ratio (*dr*) in reactions of cyclopentanone and cyclohexanone reached 85/15 [2].

T3. We used for the first time chiral primary amine - phosphoric or thiophosphoric amides as bifunctional organocatalysts in asymmetric Michael additions of 1,3-dicarbonyl compounds and maleimides.

High stereoselectivities (*dr* and *ee*) and excellent yields were achieved using ethyl 2-fluoroacetoacetate in Michael additions to *N*-substituted maleimides. The results showed that the thiophosphoric amide proved to be a very efficient chiral organocatalyst in the addition of α-fluoro-β-ketoester, but reactions with α-chloro and α-methyl derivatives were slow. Similar success was achieved using cyclic β-ketoesters, which gave the desired adducts with outstanding diastereoselectivities and high optical purities. Further extending the range of the Michael donors, our catalyst was also tested in the addition of a β-diketone, *i.e.* acetylacetone, to *N*-substituted maleimides, in which it was also effective [3].

T4. Instrumental studies have been used to identify the intermediates formed during the additions, thus we have shown for the first time that the reaction of each nucleophiles applied follows an enamine-type mechanism.

The results obtained showed a higher activity of (thio)phosphoric amides in the addition of aldehydes to maleimides compared to the corresponding sulfonamides, which was also associated with the increase of the *ee* values. Our studies suggest that this may be due to the more flexible hydrogen bonding between the thiophosphoric amide and the maleimide allowing a more favourable arrangement of the activated electrophile (**Figure 3**, **A**), resulting in a near enantiomerically pure product, also accompanied by faster product formation.

ESI-MS studies showed that the enamine formed in the reaction of ethyl 2-fluoroacetoacetate with PS-DPEN exhibited a stronger nucleophilic attack to the activated maleimide compared to acetylacetone, as illustrated by the relative amounts of the detected intermediates. The addition of acetylacetone was studied by NMR measurements and it was shown that the nucleophilicity of the enamine determines the rate of C-C bond formation. Intermediates identified by ESI-MS and NMR measurements revealed that the reactions of 1,3-dicarbonyl nucleophiles also occur via enamine formation (**Figure 3**, **B**). This reaction pathway and the absence of a parallel deprotonation pathway assured the high stereoselectivity of these reactions. An important result of our work is the unprecedented use of bifunctional organocatalysts with a primary amine and a hydrogen donor group for the asymmetric Michael addition of 1,3-dicarbonyl compounds to maleimides [2,3].

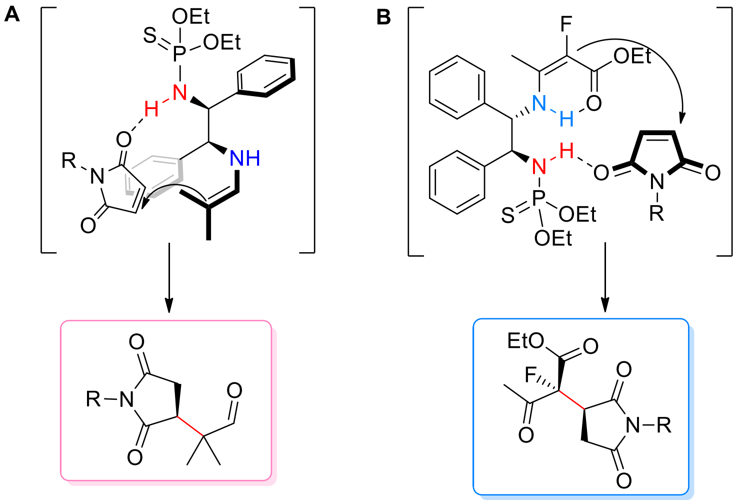

Figure 3. Proposed transition states in reactions of different nucleophiles.

T5. Optically pure 1,2-diamines covalently bonded to functionalized supports have been developed and used for the first time as heterogeneous chiral catalysts in Michael additions to maleimides.

Chiral 1,2-diphenylethane-1,2-diamines were covalently bonded to organic or inorganic supports through sulfonamide groups by a simple procedure, as evidenced by infrared spectroscopy. The performance and reusability of the resulting heterogeneous catalysts were investigated in the reaction of isobutanal with *N*-benzylmaleimide. The resulting chiral solids were found to be active and enantioselective heterogeneous catalysts, approaching the results achievable in homogeneous systems. The catalyst was reusable, retaining its activity in few reactions. These chiral solids, are the first heterogeneous diamine-type enantioselective catalysts used in asymmetric additions between aldehydes and maleimides [1].

T6. By adsorption of natural amino acids on the surface of readily available inorganic oxides, we have prepared the first environmentally friendly hybrid heterogeneous catalysts efficient in Michael additions to maleimides.

We have developed an *in situ* producible, green, environmentally friendly and economical catalytic system, which gave excellent results in Michael additions of various aldehydes to 30 *N*-substituted maleimides. This system was made even more advantageous by the use of renewable solvents, natural chirality sources and the easy preparation of the heterogeneous recyclable catalyst. Several primary α-amino acids proved to be effective chiral catalysts, with the best results obtained with L-phenylalanine, which gave complete conversion and outstanding (up to 99%) enantiomeric excess. Various inorganic materials could be successfully used as supports, such as oxides, cation-exchanger clays or anion-exchanger layered double hydroxides. The reaction conditions were optimized by using two inorganic solids (bentonite and Al_2O_3) and two solvents (diisopropyl ether and ethyl acetate). Our studies have shown that heterogeneous chiral hybrid materials prepared *ex situ* can catalyze these Michael additions as well. The readily recovered chiral catalysts remained active after repeated uses; moreover, the reduction in the number of catalytically active sites did not affect the enantiodifferentiation [4].

T7. The characteristics and behaviour of the inorganic-organic hybrid catalyst has been investigated using a variety of instrumental methods.

UV-Vis spectroscopy, thermogravimetry, XRD, FT-IR, Raman spectroscopy and SEM measurements showed that the amino acid is deposited as surface crystallites or in the interlayer space in the case of bentonite, but the reactions are most likely catalysed by surface adsorbed chiral compounds, as also confirmed by the results obtained with Al_2O_3 (**Figure 4**). Based on the results of the structural studies, it was concluded that the aforementioned amino acid deposits act as a source of chiral organic compound replenishment during the asymmetric reaction [4].

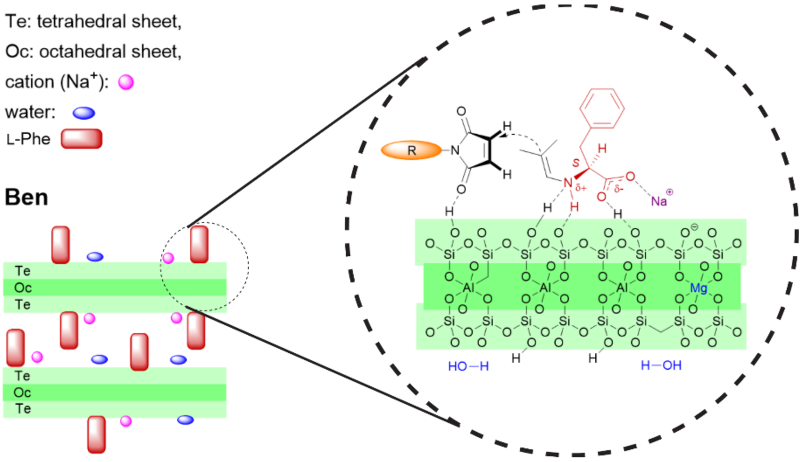

Figure 4 Schematic representation of the structure of the chiral hybrid material formed *in situ* from L-Phe and Ben and that of the proposed surface transition state.

T8. The synthetic value of the developed catalytic systems has been demonstrated by the preparation of several chiral succinimide derivatives on larger scale.

We have tested the applicability of our homogeneous and heterogeneous asymmetric catalytic systems with larger amounts of materials. The synthesized (*S*,*S*)-PS-DPEN catalyst showed high activity in several solution-phase reactions and yielded nearly optically pure product. However, with the most efficient heterogeneous chiral hybrid catalyst prepared *in situ* using bentonite and L-Phe, it was possible to produce succinimide derivatives at gram scale and purify them even by a single recrystallization. The use of both catalytic systems enabled the preparation of a large number of Michael adducts in increased quantities with efficiencies consistent with smaller scale experiments. As a result of our work, we have succeeded in developing practical, green, environmentally friendly and economical catalytic systems for the efficient production of optically pure succinimides [2,4].

4. LIST OF SCIENTIFIC PUBLICATIONS

(MTMT ID: 10065013)

Publications directly related to the doctoral thesis

[1] Gy. Szőllősi, **V. Kozma**
Design of heterogeneous organocatalyst for the asymmetric Michael addition of aldehydes to maleimides
ChemCatChem **2018**, *10*, 4362-4368.
IF: 4,495

[2] **V. Kozma**, F. Fülöp, Gy. Szőllősi
1,2-Diamine-derived (thio)phosphoramide organocatalysts in asymmetric Michael additions
Adv. Synth. Catal. **2020**, *362*, 2444-2458.
IF: 5,837

[3] **V. Kozma**, Gy. Szőllősi
Conjugate addition of 1,3-dicarbonyl compounds to maleimides using bifunctional primary amine–(thio)phosphoramide organocatalysts
Mol. Catal. **2022**, *518*, 112089 (1-13).
IF*: 5,062

[4] **V. Kozma**, Gy. Szőllősi
Enantioselective Michael addition of aldehydes to maleimides catalysed by surface-adsorbed natural amino acids,
Catal. Sci. Technol. **2022**, submitted for publication.
IF*: (6,119)

Cumulated IF: 21,513

* Impact factor of 2020 (IF)

Conference presentations related to the doctoral thesis

Oral presentations

1. V. Kozma, Gy. Szőllősi
Királis szukcinimid-származékok enantioszelektív előállítása homogén és heterogén katalizátorokkal
XL. Kémiai Előadói Napok, **2017**, Szeged.

2. V. Kozma
Aldehidek aszimmetrikus Michael-addíciója maleimidekre, homogén és heterogenizált királis diamin-származékokkal
Országos Tudományos Diákköri Konferencia, **2017**, Miskolc.

3. V. Kozma
Aszimmetrikus Michael-addíciók maleimidekre királis 1,2-diamin vázú katalizátorokkal
Gyógyszerkémiai Munkabizottság és a Magyar Kémikus Egyesülete Csongrád Megyei Csoportjának 17. tudományos előadóülése, **2018**, Szeged.

4. V. Kozma
Aszimmetrikus Michael-addíciók maleimidekre királis 1,2-diamin vázú katalizátorokkal
Országos Tudományos Diákköri Konferencia, **2019**, Budapest.

5. V. Kozma, Gy. Szőllősi
Phosphoramide chiral catalysts for environmentally friendly asymmetric organocatalytic processes
26th International Symposium on Analytical and Environmental Problems, **2020**, Szeged.
Proceedings of the 26th International Symposium on Analytical and Environmental Problems, 35-39.

6. V. Kozma
Királis 1,2-diamin vázú katalizátorok használata aszimmetrikus Michael-addíciókban
Szegedi Ifjú Szerves Kémikusok Támogatásáért Alapítvány, a SZAB Szerves és Gyógyszerkémiai Munkabizottság és a Magyar Kémikus Egyesülete Csongrád Megyei Csoportjának 21. tudományos előadóülése, **2021**, Szeged

Posters

1. V. Kozma, Gy. Szőllősi
Asymmetric Michael-additions using homogeneous and heterogenized chiral 1,2-diamine derivatives
13th European Congress on Catalysis, **2017**, Firenze, P3.63.

2. V. Kozma, Gy. Szőllősi
Aszimmetrikus Michael-addíciók maleimidekre homogén és heterogén királis katalizátorokkal
Magyar Kémikusok Egyesülete, *Vegyészkonferencia*, **2017,** Hajdúszoboszló, P-66.

3. V. Kozma, Gy. Szőllősi
Environmentally benign catalysis: Asymmetric Michael-additions using homogeneous and heterogenized chiral 1,2-diamine derivatives
23th International Symposium on Analytical and Environmental Problems, **2017**, Szeged, P86.

4. V. Kozma, Gy. Szőllősi
Asymmetric Michael additions using heterogenized chiral 1,2-diamine catalysts
14th Pannonian International Symposium on Catalysis, **2018**, Starý Smokovec P-1.1, 118.

5. V. Kozma, Gy. Szőllősi
Asymmetric Michael-additions catalyzed by environmentally benign heterogeneous chiral 1,2-diamine derivatives
25th International Symposium on Analytical and Environmental problems, **2019**, Szeged, P87.
Proceedings of the 25th International Symposium on Analytical and Environmental Problems, 342-344.

6. V. Kozma, Gy. Szőllősi
Natural chiral catalysts on solid surfaces used in Michael addition to maleimides
27th International Symposium on Analytical and Environmental Problems, **2021**
Proceedings of the 27th International Symposium on Analytical and Environmental Problems, 193-197.

Publications not related to the doctoral thesis

[5] Gy. Szőllősi, L. Kovács, **V. Kozma**, V. J. Kolcsár,
Asymmetric Michael addition catalyzed by a cinchona alkaloid derivative non-covalently immobilized on layered inorganic supports
Reac. Kinet. Mech. Cat. **2017**, *121,* 293-306.

IF: 1,515

[6] G. Varga, **V. Kozma**, V. J. Kolcsár, Á. Kukovecz, Z. Kónya, P. Sipos, I. Pálinkó, Gy. Szőllősi,
β-isocupreidinate-CaAl-layered double hydroxide composites-heterogenized catalysts for Michael addition
Mol. Catal. **2020**, *487*, 110675.

IF: 5,062

Cumulated IF: 6,577

Conference presentations not related to the doctoral thesis

Posters

1. Gy. Szőllősi, L. Kovács, **V. Kozma**, V. J. Kolcsár,
Asymmetric Michael-addition catalyzed by a cinchona alkaloid derivative non-covalently immobilized over layered materials
13th Pannonian International Symposium on Catalysis, **2016**, Siófok, P40.

2. Gy. Szőllősi, A. Zs. Mogyorós, D. Gombkötő, B. Fancsali, V. J. Kolcsár, **V. Kozma**, G. Kőhl,
Heterogeneous asymmetric Michael additions catalyzed by proline-inorganic oxide hybrid materials
14th Pannonian International Symposium on Catalysis, **2018,** Starý Smokovec, P-2.16.

3. Gy. Szőllősi, V. J. Kolcsár, **V. Kozma**, B. Fancsali, A. Zs. Mogyorós, D. Gombkötő, G. Kőhl, Heterogeneous asymmetric Michael additions using environmentally friendly catalysis: application of chiral inorganic-organic hybrid materials
25th International Symposium on Analytical and Environmental Problems, **2019**, Szeged, P108.
Proceedings of the 25th International Symposium on Analytical and Environmental Problems, 409-413.

5. TOTAL IMPACT FACTORS

Total impact factor of the publications on which the thesis is based:	**21.513**
Total impact factor of publications not related to the thesis:	**6.577**
Total impact factor of all publications:	**28.090**
Total number of references:	**36**
Total number of references without self-references:	**24**

(MTMT, 05. 05. 2022.)