

UNIVERSITY OF PARDUBICE

FACULTY OF CHEMICAL TECHNOLOGY

Institute of Organic Chemistry and Technology

Jan Bartáček

**Immobilized catalysts for the enantioselective reactions
on activated double bonds**

Theses of the Doctoral Dissertation

Pardubice 2020

Study program: **Organic Chemistry**

Study field: **Organic Chemistry**

Author: **Ing. Jan Bartáček**

Supervisor: **prof. Ing. Miloš Sedlák, DrSc.**

Year of the defence: 2020

References

BARTÁČEK, Jan. Immobilized catalysts for the enantioselective reactions on activated double bonds. Pardubice, 2020. 151 pages. Dissertation thesis (Ph.D.). University of Pardubice, Faculty of Chemical Technology, Institute of Organic Chemistry and technology. Supervisor prof. Ing. Miloš Sedlák, DrSc.

Abstract

Catalytic activity of the prepared swellable pearl-like copolymers of ethyl-(4-vinylbenzyl)-L-tartrate was tested on the model epoxidation of cinnamyl alcohol. Recycling of such catalysts was not possible because of tartrate leaching due to ester bond alcoholysis. On that ground, ethyl-(2*R*,3*R*)-2,3-dihydroxy-4-oxo-5-(4-vinylphenyl)pentanoate and its swellable pearl-like copolymer were designed and prepared. It was possible to use this copolymer with stable-bonded ketoester derived from L-tartaric acid at least 4 times. This was tested on two substrates. The results obtained in term of yields, enantioselectivity and recyclability are superior to all currently known heterogeneous systems and fully comparable with homogeneous conditions. In the second part of this work, a literature review on palladium catalysed asymmetric 1,4-addition of arylboronic acids to conjugated cyclic enones was compiled. Consequently a new monomer (*S*)-4-(*tert*-butyl)-2-(4-(4-vinylphenyl)pyridin-2-yl)-4,5-dihydrooxazole and its swellable pearl-like copolymers with different cross-linkers were designed and prepared. Catalytic activity of palladium(II) complexes of the prepared copolymers was tested on addition of phenylboronic acid to 3-methyl-2-cyclohexenone. The relationship between the structure of the cross-linker and catalytic activity was described. It was possible to use those catalysts at least 6 times and their catalytic activity was comparable with homogenous conditions even for other substrates.

Keywords

Sharpless epoxidation; Michael addition; Recyclable catalyst; Pearl-like copolymer; Enantioselective catalysis

Abstrakt

Byla studována katalytická aktivita připravených botnavých perlových kopolymerů založených na ethyl-(4-vinylbenzyl)-L-tartrátu pro modelovou Sharplesovu epoxidaci skořicového alkoholu. Tyto katalyzátory nebylo možné recyklovat z důvodu alkoholýzy esterové vazby a s tím spojeným vymýváním tartátového fragmentu z matrice polymeru. Proto byl navržen a připraven ethyl-(2*R*,3*R*)-2,3-dihydroxy-4-oxo-5-(4-vinylfenyl)pentanoát a z něho odvozený botnavý perlový kopolymer. Tento kopolymer se stabilně zakotveným ketoesterem odvozeným od kyseliny L-vinné bylo možné recyklovat minimálně 4 ×, což bylo ověřeno na dvou substrátech. Dosažená enantiosektivita, výtěžky a možnosti recyklace jsou nesrovnatelně vyšší ve srovnání s dosud publikovanými heterogenními systémy a jsou zcela srovnatelné s provedením reakce v homogenním prostředí. Ve druhé části práce byla zpracována literární rešerše palladiem katalyzovaných asymetrických 1,4-adic arylboronových kyselin na konjugované cyklické enony. Následně byl navržen a připraven monomer (*S*)-4-(*tert*-butyl)-2-(4-(4-vinylfenyl)pyridin-2-yl)-4,5-dihydrooxazol a z něho byly připraveny botnavé perlové kopolymery s rozdílnými síťovadly. Katalytické vlastnosti palladnatých komplexů, od připravených kopolymerů, byly studovány na adici fenyloboronové kyseliny na 3-methylecyklohex-2-en-1-on. Byl diskutován vliv struktury síťovadla na katalytické vlastnosti. Katalyzátory bylo možné recyklovat až 6× a jejich účinnost byla srovnatelná s homogenním prostředím, a to i pro další modelové substráty.

Klíčová slova

Sharplesova epoxidace; Michaelova adice; Recyklovatelný katalyzátor; Perlový kopolymer; Enantiosektivní katalýza

Abbreviations

(*S*)-*t*BuPyOx – (*S*)-4-(*tert*-butyl)-2-(pyridin-2-yl]-4,5-dihydrooxazole

4 Å MS – 4 Å molecular sieves

Ar – aryl

BVPC12 – 1,12-bis(4-vinylphenyl)dodecane

BVPE – 1,2-bis(4-vinylphenyl)ethane

DCE – 1,2-dichloroethane

DCM – dichloromethane

diMeOPEG – poly(ethylenglykol) dimethylether

DVB – divinylbenzene

ee – enantiomeric excess

HFIP – 1,1,1,3,3,3-hexafluoroisopropylalcohol

L-(+)-DET – (+)-diethyl L-tartrate

Pd(TFA)₂ – palladium(II) trifluoroacetate

PS – polystyrene

PVA – polyvinyl alcohol

PyOx – pyridine-oxazoline

SEM – scanning electron microscopy

TBHP – *tert*-butylhydroperoxide

TFA – trifluoroacetic acid

Table of Contents

| | | |
|------------|---|-----------|
| 1 | INTRODUCTION | 7 |
| 1.1 | Sharpless asymmetric epoxidation..... | 7 |
| 1.2 | Palladium catalysed addition of arylboronic acid to cyclic enones..... | 8 |
| 2 | OBJECTIVES..... | 9 |
| 3 | RESULTS AND DISCUSSION..... | 10 |
| 3.1 | HETEROGENEOUS CATALYSTS FOR SHARPLESS EPOXIDATION | 10 |
| 3.1.1 | Synthesis and characterization of copolymers 3a-d | 10 |
| 3.1.2 | Testing of catalytic activity of copolymers 3a-d | 11 |
| 3.1.3 | Synthesis and characterization of copolymer 4 | 13 |
| 3.1.4 | Testing of catalytic activity of copolymer 4..... | 14 |
| 3.2 | HETEROGENEOUS CATALYSTS FOR ENANTIOSELECTIVE ADDITION OF BORONIC ACIDS TO CONJUGATED CYCLIC ENONES | 17 |
| 3.2.1 | Synthesis and characterization of copolymers 10–12..... | 17 |
| 3.2.2 | Testing of catalytic activity of copolymers 10–12*Pd..... | 19 |
| 4 | CONCLUSION | 22 |
| 5 | LIST OF REFERENCES..... | 24 |
| 6 | LIST OF STUDENTS' PUBLISHED WORKS..... | 27 |

1 Introduction

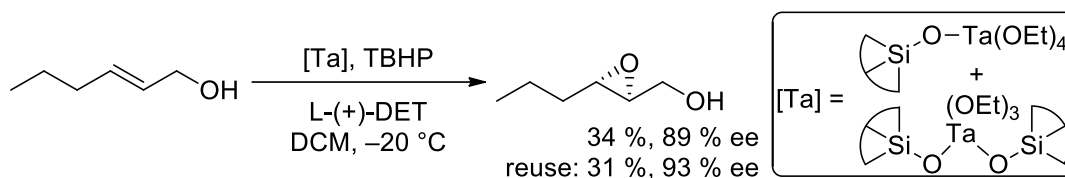
1.1 Sharpless asymmetric epoxidation

In 1980 prof. Sharpless and prof. Katsuki published the first article dealing with newly discovered enantioselective epoxidation of allylic alcohols by organic hydroperoxides catalysed by titanium(IV) complexes of enantiopure esters of tartaric acid (Scheme 1) [1,2].



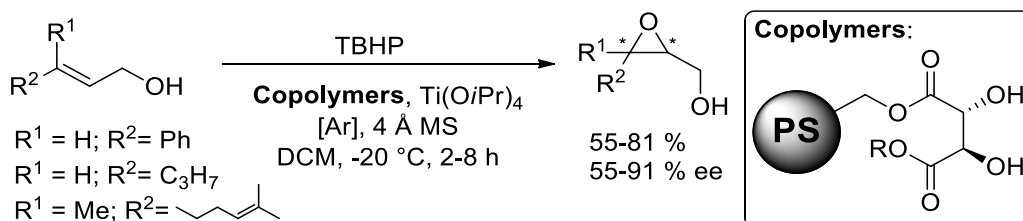
Scheme 1 General scheme of Sharpless epoxidation [1,2].

Great advantages of this reaction are low price of both enantiopure tartaric acid esters and titanium(IV) alkoxides as well as good availability of variously substituted allylic alcohols [2]. This reaction usually provides products with a high degree of enantioselectivity, usually above 90 % ee. The reaction is also compatible with various functional groups (aldehydes, ketones, acetals, esters, nitriles, silylethers...) [2]. Many studies were dealing with immobilization of catalysts for Sharpless epoxidation but recyclization was unsuccessful for most of them [3–9]. Meunier et al. were partially successful on immobilization of tantalum(V) alkoxide onto silica gel (Scheme 2) [10]. They were able to reuse the prepared catalyst although the results obtained are incomparable with homogeneous conditions.



Scheme 2 Immobilized tantalum(V) alkoxide as recyclable catalyst for Sharpless epoxidation [10].

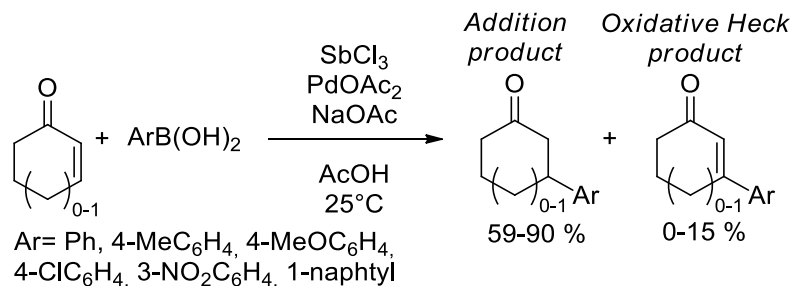
Another partially successful work was done by Suresh et al. with immobilization of tartaric acid esters onto various polystyrenes (Scheme 3) [11]. The results obtained are mediocre but authors state the possibility of reuse such catalysts for three times [11].



Scheme 3 Polystyrene supported tartaric acid esters as recyclable catalyst for Sharpless epoxidation [11].

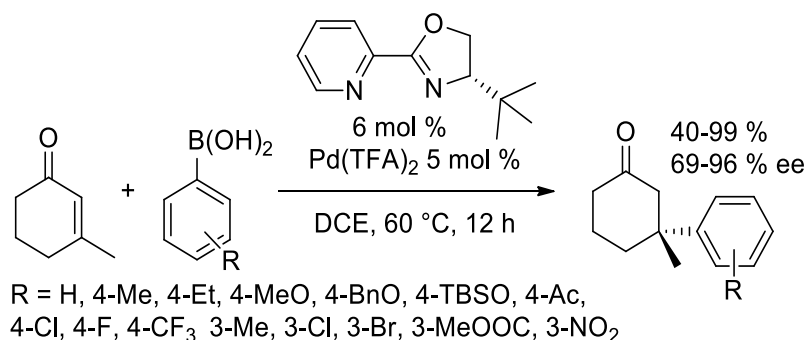
1.2 Palladium catalysed addition of arylboronic acid to cyclic enones

The first palladium catalysed addition of arylboronic acids to cyclic enones was done by Cho et. al. They used Pd(OAc)₂ as catalyst with SbCl₃ as cocatalyst (Scheme 4) [12]. The problem of this reaction is the forming of by-product by oxidative Heck reaction.



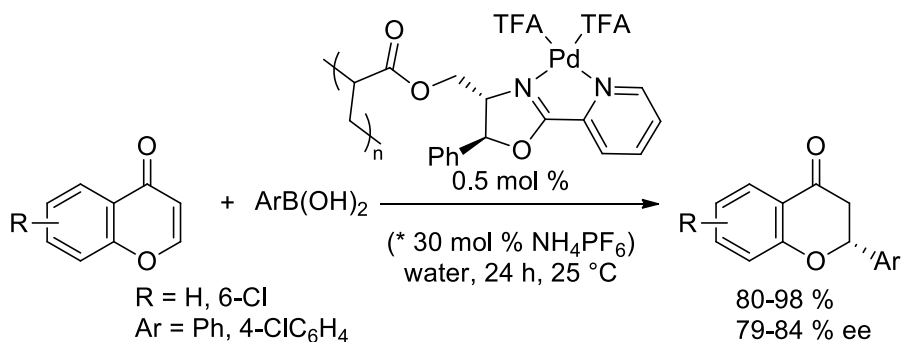
Scheme 4 The first palladium catalysed addition of arylboronic acids to cyclic enones [12].

The most studied asymmetric variant of this reaction was done by Stoltz et. al. They have used Pd(TFA)₂ in combination with chiral pyridine-oxazoline (Scheme 5) [13]. The reaction is moisture and air tolerant and usually provides products in good yields with a high degree of enantioselectivity [13–15].



Scheme 5 Asymmetric addition of arylboronic acids to cyclic enones catalyzed by Pd/PyOx system [13–15].

Immobilization of pyridine-oxazoline was done by O'Reilly et al. [16]. Only addition to chromones were tested and no recyclization was studied (Scheme 6) [16].



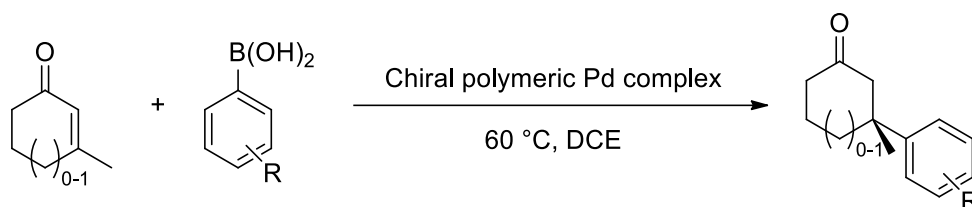
Scheme 6 Immobilized Pd/PyOx catalyst for asymmetric additions of boronic acids to chromones [16].

2 Objectives

- Preparation and testing copolymers of styrene with suitable monomers as recyclable catalysts for Sharpless asymmetric epoxidation.



- Preparation and testing copolymers of styrene with suitable monomers as recyclable catalysts for asymmetric conjugated 1,4-addition of arylboronic acid to 3-substituted conjugated cyclic enones, leading to products bearing all-carbon quaternary stereogenic centre



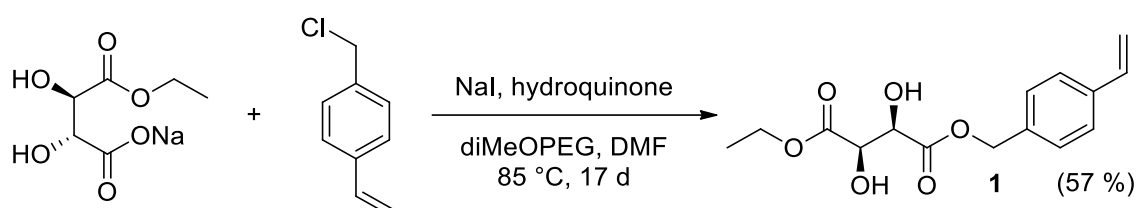
3 Results and Discussion

3.1 HETEROGENEOUS CATALYSTS FOR SHARPLESS EPOXIDATION

In my diploma thesis [17] catalytic activity of copolymer of styrene (49,14 mass %), ligand **1** (49,14 mass %) a tetraethyleneglycol-bis(4-vinylbenzyl)ether (TEG-BVBE) (1,72 mass %) on Sharpless epoxidation was found. This catalytic activity was further studied in order to describe effect of polymeric matrix to Sharpless epoxidation and to prove the possibility of recyclization of copolymers of monomers, mentioned above.

3.1.1 Synthesis and characterization of copolymers 3a-d

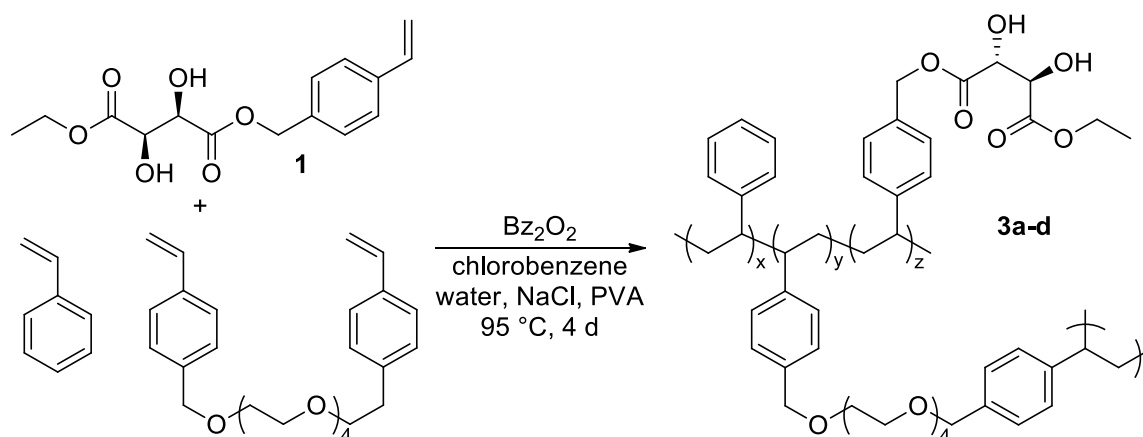
Key monomer **1** was prepared according to my diploma thesis [17] by nucleophilic substitution of sodium ethyl-L-tartrate by 4-vinylbenzyl chloride (Scheme 7).



Scheme 7 Preparation of key monomer **1**.

Monomer **1** was copolymerized with styrene and TEG-BVBE cross-linker (Scheme 8) [18]. Cross-linking agents and its amount (0.75 mol %) were chosen because of chemical stability of ether bond and high swellability of prepared resins (up to 8,7 ml·g⁻¹ in DCM). Swellability is a key parameter for an easy diffusion of reactant to the active centre [19,20].

Following molar ratios styrene/ligand **1** were chosen: **3a** – 56 : 1, **3b** – 11 : 1, **3c** – 3 : 1, **3d** – 0 : 1. The prepared copolymers were characterized by means of optical microscopy, FT-IR spectroscopy and swellability.



Scheme 8 Preparation of copolymers **3a-d**.

3.1.2 Testing of catalytic activity of copolymers 3a-d

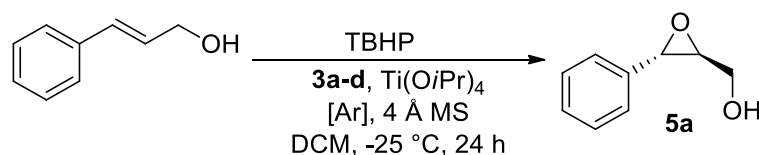
Catalytic activity of copolymers **3a-d** was tested on epoxidation of cinnamyl alcohol by TBHP.

For comparison, catalysis under homogeneous conditions was tested at first (Table 1; Entry 1). From the results obtained it is clear that epoxidation catalysed by copolymers **3a-c** proceeded with great conversion as well as enantioselectivity.

Configuration of the product obtained depends on stoichiometry of the Ti(IV) complex. The monomeric complex $Ti_2(\text{Tartrate})_1(\text{OiPr})_6$ catalyses formation of (2*R*,3*R*)-product and dimeric complex $Ti_2(\text{Tartrate})_2(\text{OiPr})_4$ formation of (2*S*,3*S*)-product [10]. It is clear that in all cases the dimeric complex was the major active species.

The conversions achieved with copolymers **3a-b** were almost quantitative, even higher than in homogeneous conditions, with a high degree enantioselectivity (Table 1; Entry 2–4). In the case of copolymer **3c**, decrease of conversion (81 %) with high enantioselectivity (99 % ee) were observed. The conversion lap could be fixed up to quantitative by using bigger loading of catalyst but for a cost of a lower enantioselectivity (86 % ee) (Table 1; Entry 6).

Table 1 Results overview for copolymers **3a-d**.



| Entry | Tartrate | Tartrate content in copolymer ^d (mmol·g ⁻¹) | Ratio substrate/Ti/ tartrate | Cycle | Conversion ^a (%) | ee ^b (%) |
|-------|---------------------|--|------------------------------------|-----------------|--------------------------------|------------------------|
| 1 | homog. ^c | – | 100:5:10 | 1 st | 81 | 97 |
| 2 | 3a | 0.16 | 100:7.5:15 | 1 st | 99 | 99 |
| 3 | 3b | 0.67 | 100:7.5:15 | 1 st | 99 | 95 |
| 4 | 3c | 1.67 | 100:9:23 | 1 st | 80 | 99 |
| 5 | 3c | 1.67 | 100:9:23 | 2 nd | 36 | 76 |
| 6 | 3c | 1.67 | 100:23:50 | 1 st | 99 | 86 |
| 7 | 3c | 1.67 | 100:23:50 | 2 nd | 70 | 34 |
| 8 | 3d | 3.33 | 100:7.5:15 | 1 st | 32 (72 h) | 9 |

^a The conversion determined after 24 h by ¹H NMR

^b Enantiomeric excess determined by chiral HPLC

^c Benzyl(ethyl)-L-tartrate, results from ref. [17]

^d Estimated from ratio of monomers in their mixture

When the copolymer **3d** was used only very low activity as well as enantioselectivity were observed (Table 1; Entry 8). Copolymer **3d** presumably makes a very dense network of catalytically inactive Ti(IV) complexes [21].

In summary lower content of tartrate in copolymer (5 – 20 %) led to higher both conversion and enantioselectivity. This is in agreement with previously described dilution effect of polymeric matrix [12].

Recyclability of copolymer **3c** was tested. In both cases lower conversion as well as enantioselectivity were observed (Table 1; Entry 4–7). Comparison of FT-IR spectra of fresh copolymer, after 1st and 2nd cycles showed up decreased intensity of valence C=O ester bands (1738 cm⁻¹) as well as valence C–O bands (1086–1260 cm⁻¹) (Figure 1).

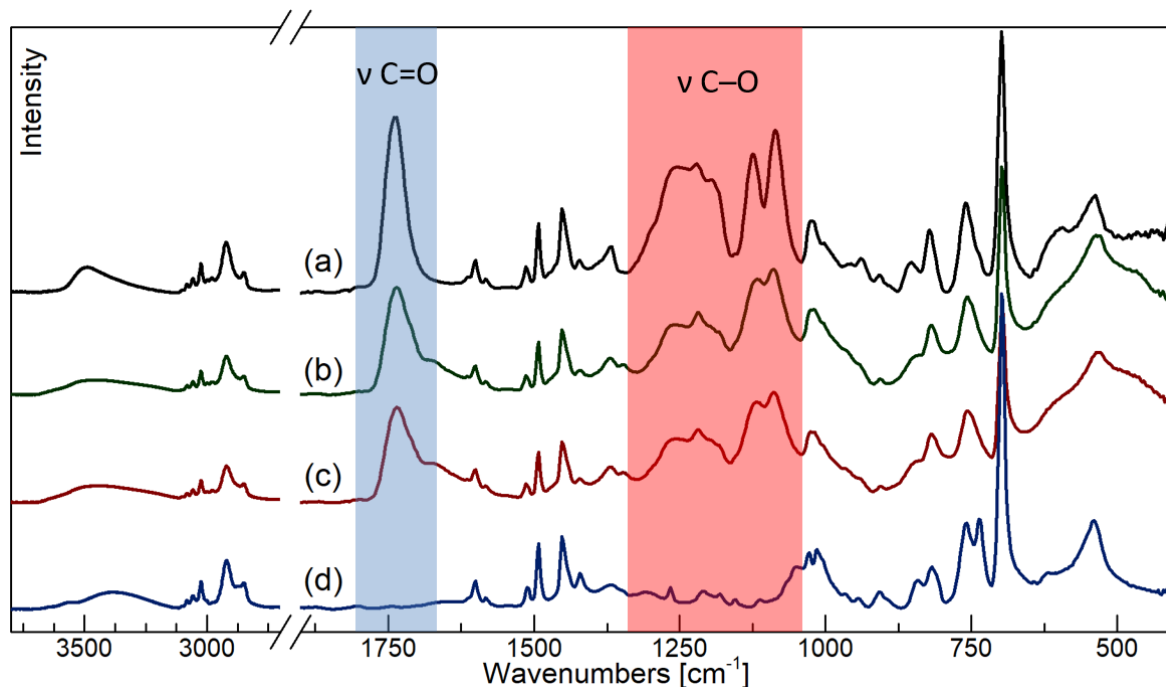
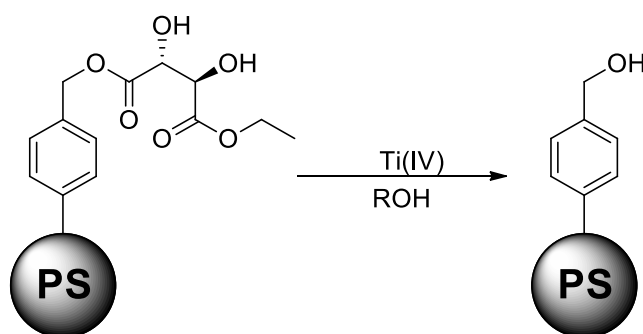


Figure 1 Comparison of FT-IR spectra of fresh copolymer **3c** (a), after 1st (b), 2nd (c) cycle and reference sample after alcoholysis by 1M MeONa (d)

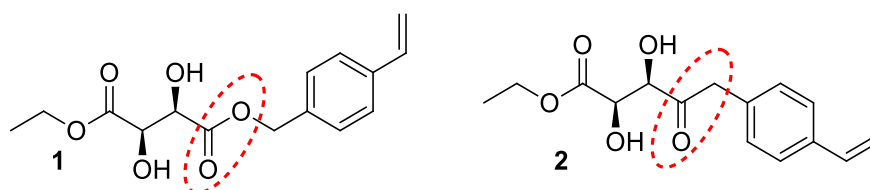
This observation can be explained by Lewis acid-catalysed alcoholysis by alcohols in the reaction mixture. This can lead to leaching of L-tartrate fragment leaving benzyl alcohol fragment on polymeric matrix. (Scheme 9). This fragment can coordinate Ti(IV) originating unreactive or non-selectively catalysing complexes. This unfavourable effect leads to lower conversions as well as enantioselectivities and is the main cause of non-recyclability of ester-based tartrate copolymers.



Scheme 9 Alcoholysis of copolymer **3c**

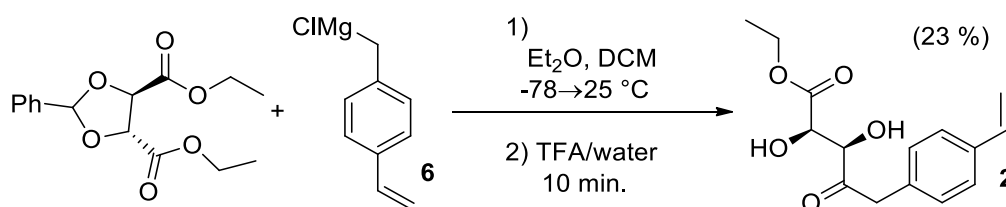
3.1.3 Synthesis and characterization of copolymer 4

Because of impossible recyclization of ester-based tartrate copolymers, a structural modification of monomer 1 was proposed. In monomer 2 the labile ester bond is replaced by a stable ketone C–C bond (Scheme 10).



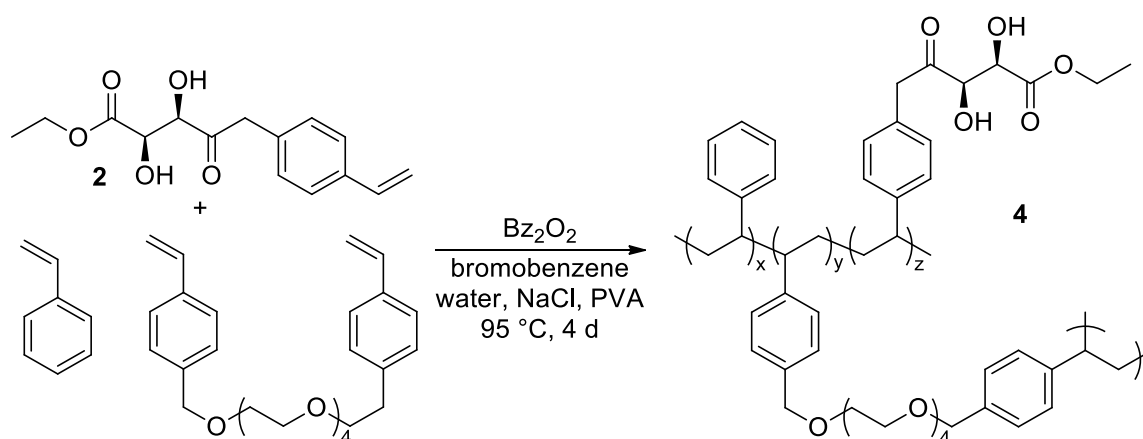
Scheme 10 Structural modification of monomer 1.

Monomer 2 was prepared in 23% yield by addition of Grignard reagent 6 to a (4*R*,5*R*)-diethyl 2-phenyl-1,3-dioxolane-4,5-dicarboxylate. Protecting group of *O,O*-benzylideneacetal was consecutively removed by treating with TFA/water (Scheme 11).



Scheme 11 Preparation of monomer 2.

Monomer 2 was consequently copolymerized with styrene and TEG-BVBE cross-linker (1.4 mol %). According to previous findings on copolymers 3a-d, the molar ratio styrene/ligand 2 was chosen as 12 : 1 (Scheme 12). Copolymer 4 was characterized by means of optical microscopy, SEM microscopy, FT-IR spectroscopy, ¹³C CP/MAS NMR spectroscopy and swellability.

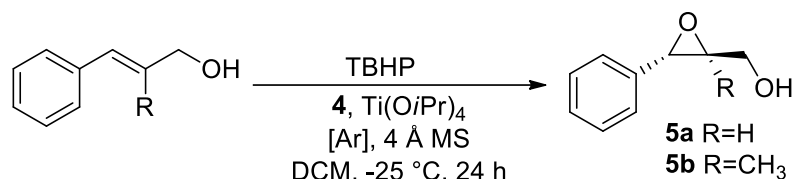


Scheme 12 Preparation of copolymer 4.

3.1.4 Testing of catalytic activity of copolymer 4

Catalytic activity of copolymer 4 was tested on epoxidation of two substrates (cinnamyl alcohol and α -methylcinnamyl alcohol) by TBHP (Table 3).

Table 2 Overview of catalytic experiments with copolymer 4.



Ligand content^d: 0,63 mmol·g⁻¹, Substrate/Ti/ligand ratio - 100:7.5:15

| # | Product | Cycle | Conversion ^a % | % ee ^b (2 <i>S</i> ,3 <i>S</i>) |
|---|---------|-------|---------------------------|---|
| 1 | 5a | 1. | 80 | 97 |
| 2 | 5a | 2. | 90 | 99 |
| 3 | 5a | 3. | 80 | 96 |
| 4 | 5a | 4. | 67 | 97 |
| 5 | 5b | 1. | 99 | 99 |
| 6 | 5b | 2. | 99 | 89 |
| 7 | 5b | 3. | 99 | 82 |
| 8 | 5b | 4. | 99 | 87 |

^a The conversion determined after 24 h by ¹H NMR

^b Enantiomeric excess determined by chiral HPLC

^c Estimated from ratio of monomers in their mixture

From the results obtained it is clear that epoxidation catalysed by Ti(IV) complexes of copolymer 4 proceeded with high conversions as well as enantioselectivities. In contrary to copolymer 3c, recyclization was possible to use and copolymer 4 could be used at least 4 times. After each cycle, copolymer 4 was filtered off, washed and after drying used in the next cycle. During recyclization in epoxidations of cinnamyl alcohol, good conversions (80→90→80→67 %) and excellent enantioselectivities (97–99 % ee) were observed. In case of the more reactive α -methylcinnamyl alcohol, almost quantitative conversions were observed in every cycle, on the other hand a small drop of enantioselectivity was observed (99→89→82→87 % ee) (Table 3). Recycling experiments confirmed the assumption that anchoring of L-tartrate moiety by ketone bond leads to a much better stability in comparison to anchoring by ester bond. This was also supported by measuring of FT-IR spectra of fresh copolymer 4 after the first and fourth cycle. Intensity of bands of valence C=O vibrations (1739 and 1720 cm⁻¹) remains unchanged during recycling (Figure 2). An increase in

overall background and intensity of bands 1630 cm^{-1} and $1200\text{--}1000\text{ cm}^{-1}$ was observed. These bands most likely belong to TiO_2 [23].

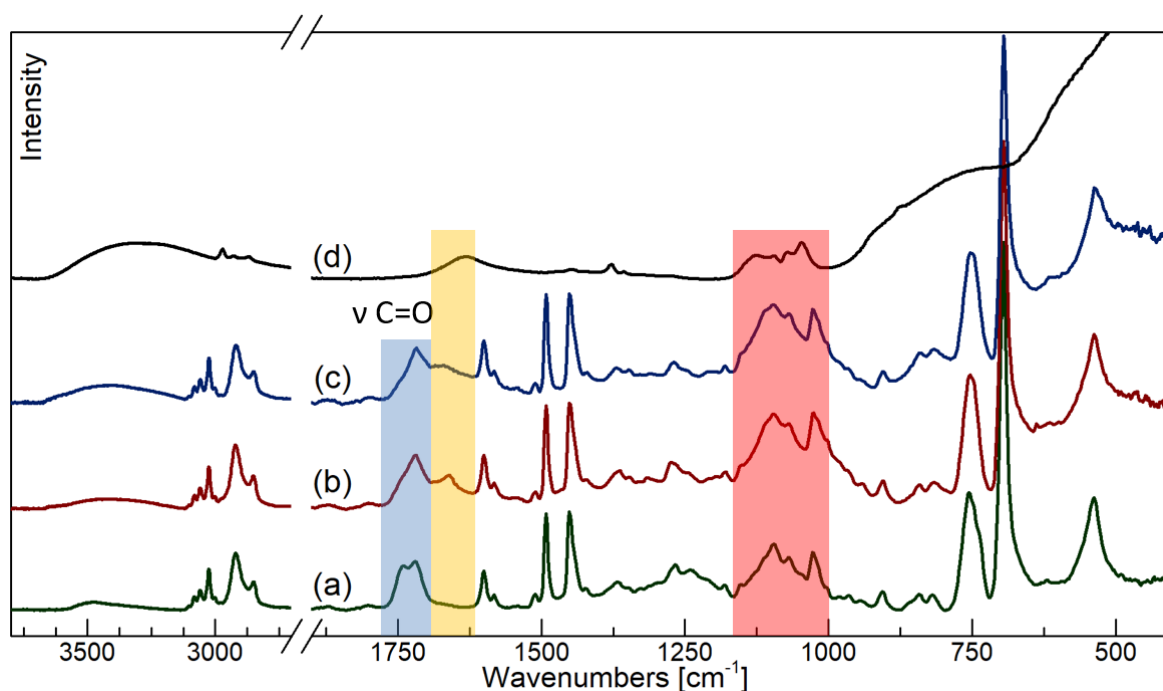
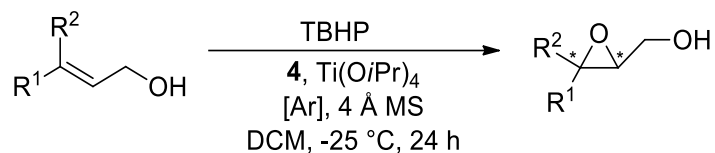


Figure 2 FT-IR spectra of copolymer **4** (a) fresh, (b) after 1st, (c) 4th cycle and (d) TiO_2 .

Ti content in copolymer **4** was studied by EDX analysis. Copolymer **4** after first cycle had 1.5 mass % Ti and after fourth cycle 2.3 mass %. From these results it is clear that an expulsion of TiO_2 occurs. TiO_2 can partially inhibit the catalytic centres in the polymeric matrix. This effect can explain a slight loss of the catalytic activity during recyclization.

Copolymer **4** was also tested for epoxidation of various allylic alcohols. Epoxidation of (*E*)-4-nitrocinnamyl alcohol and (*E*)-4-chlorocinnamyl alcohol proceeded with high conversion and enantioselectivities. On the other hand, epoxidation of 3,3-diphenylallyl alcohol and geraniol proceeded with good conversions but only low enantioselectivities. These differences can be explained by the character of the polymeric matrix, which exhibits high substrate selectivity to (*E*)-cinnamyl alcohols due to its specific microenvironment [19,22].

Table 3 Overview of epoxidations of various allylic alcohols using copolymer **4**.Ligand content^d: 0,63 mmol·g⁻¹, Substrate/Ti/ligand ratio - 100:7.5:15

| Product | Conversion ^a % | % ee ^b |
|---------|---------------------------|---|
| | 98 | 98 (2 <i>S</i> ,3 <i>S</i>) |
| | 99 | >99 (2 <i>S</i> ,3 <i>S</i>) |
| | 84 | 40 (<i>R</i>) |
| | 97 | 52 ^d (2 <i>R</i> ,3 <i>R</i>) |

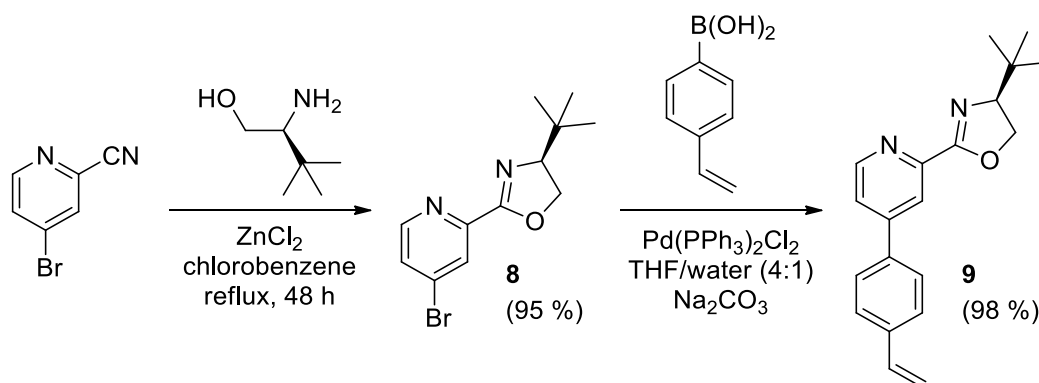
^a The conversion determined after 24 h by ¹H NMR^b Enantiomeric excess determined by chiral HPLC^c Estimated from ratio of monomers in their mixture^d Isolated as benzoate

3.2 HETEROGENEOUS CATALYSTS FOR ENANTIOSELECTIVE ADDITION OF BORONIC ACIDS TO CONJUGATED CYCLIC ENONES

Immobilized catalysts for Rh-catalysed addition of boronic acids to cyclic enones (Hayashi-Miyaura reaction) have been known for some time [24–26]. These systems are suitable for addition to 3-unsubstituted enones, leading to products bearing tertiary chiral centre. For 3-substituted enones, giving products with quaternary chiral centre, systems based on Pd complexes are more suitable. Until now only one heterogeneous system exists, but recyclization has not been done [16]. Based on literary review the most suitable ligand for immobilization is (*S*)-4-(*tert*-butyl)-2-(pyridin-2-yl)-4,5-dihydrooxazole. In combination with Pd(TFA)₂ it is the well-studied catalytic system, giving excellent results for many substrates in terms of both enantioselectivity and yield [13,15]. In comparison with other highly efficient systems [27] the main advantage is chemical stability in reaction media.

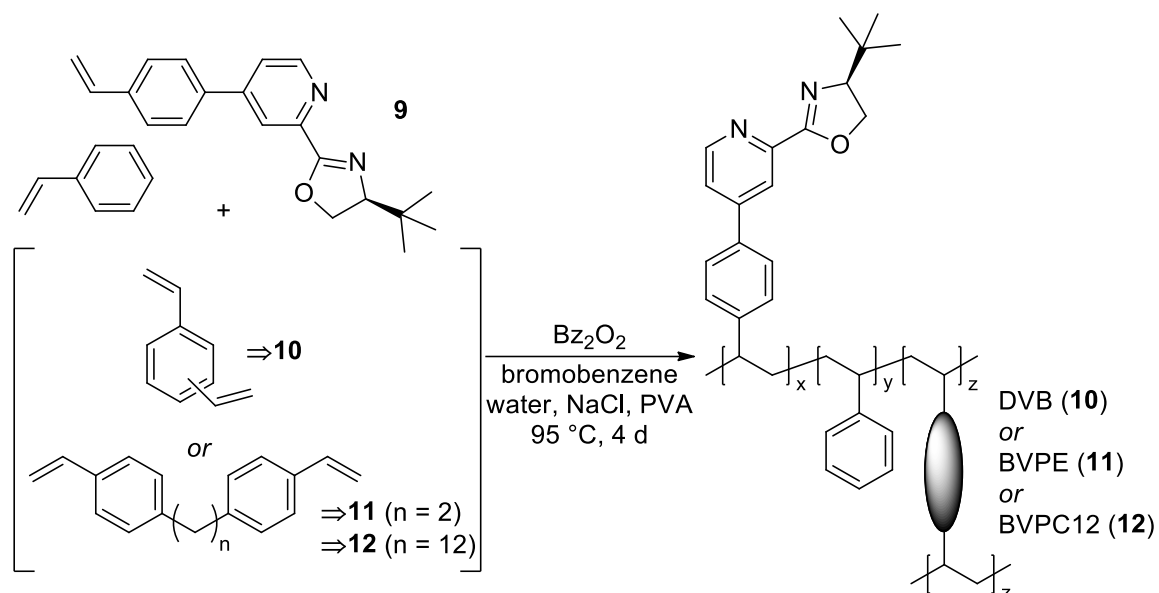
3.2.1 Synthesis and characterization of copolymers 10–12

Suitable monomer (*S*)-4-(*tert*-butyl)-2-(4-(4-vinylphenyl)pyridin-2-yl)-4,5-dihydrooxazole **9** was designed and synthesized by two step reaction with overall yield of 93 % from commercially available compounds (Scheme 13).



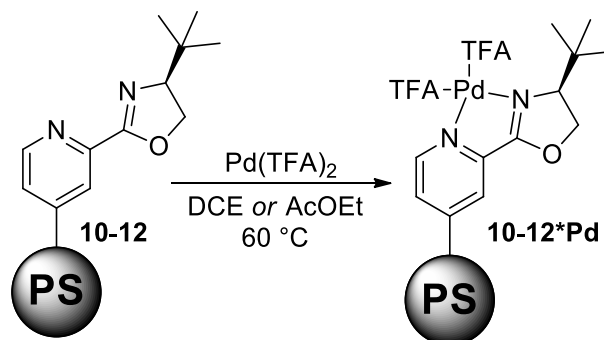
Scheme 13 Preparation of monomer **9**.

Monomer **9** was consequently copolymerized with styrene in molar ratio styrene/monomer **9** approximately 12 : 1 with 0.9 mol % of various cross-linkers. In case of copolymer **10**, divinylbenzene (DVB) was the cross-linker, for **11** 1,2-bis(4-vinylphenyl)ethane (BVPE) and for **12** 1,12-bis(4-vinylphenyl)dodecane (BVPC12) (Scheme 14).



Scheme 14 Preparation of copolymers **10–12**.

Complexation of copolymers **10–12** with $\text{Pd}(\text{TFA})_2$ yielded active catalysts **10–12*Pd** (Scheme 15).



Scheme 15 Preparation of catalysts **10–12*Pd**.

The prepared copolymers **10–12** were characterized using microanalysis, SEM microscopy, FT-IR spectroscopy and by swellability. Copolymer **11** was further characterized by ^{13}C CP/MAS NMR. The prepared Pd(II) complexes **10–12*Pd** were characterized using SEM microscopy and FT-IR spectroscopy.

In swellability the trend of higher swelling capacity of copolymer with increasing distance of vinylic groups in cross-linker is observable (Table 4).

Table 4 Swellability of copolymers **10–12**.

| Copolymer | Cross-linker | Swellability ($\text{ml}\cdot\text{g}^{-1}$) | |
|-----------|--------------|--|-------|
| | | DCE | AcOEt |
| 10 | DVB | 3.8 | 2.3 |
| 11 | BVPE | 5.3 | 2.0 |
| 12 | BVPC12 | 8.8 | 2.7 |

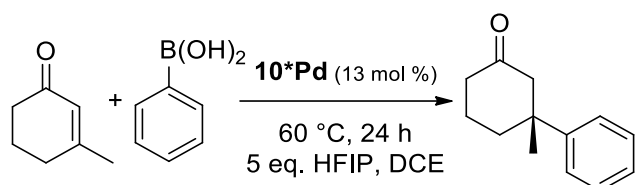
3.2.2 Testing of catalytic activity of copolymers 10–12*Pd

Optimization of reaction conditions required addition of proton source into the reaction mixture. Initial experiments showed that water is not a suitable source of proton because it does not prefer penetration into polymeric matrix. However, 1,1,1,3,3,3-hexafluoroisopropylalcohol (HFIP) was identified as a suitable proton source for reaction with polymeric catalysts 10–12*Pd. Deuteration experiments with HFIP-d₂ also supported its role as proton source.

For the testing of the catalytic activity of the prepared copolymers 10–12*Pd, addition of phenylboronic acid to 3-methyl-2-cyclohexenone at 60 °C with the reference time of 24 h was chosen.

The results of the testing of the catalyst 10*Pd under optimized conditions are summarized in Table 5. For comparison, results from homogenous conditions are given [14]. High conversion (96 %) and enantioselectivity (73 %) were observed. In comparison with homogenous conditions, enantioselectivity was significantly lower with 10*Pd.

Table 5 Overview of catalytic experiments with 10*Pd.



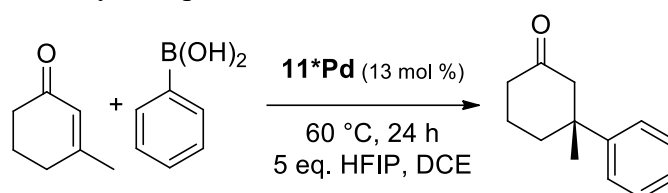
| Cycle | Conversion ^a (%) | ee ^b (%) |
|--------------------------|-----------------------------|---------------------|
| Homogeneous ^c | 99 | 91 |
| 1 st | 96 | 73 |
| 2 nd | 88 | 81 |
| 3 rd * | 77 | 81 |

^a Determined after 24 h by ¹H NMR
^b (*R*); Enantiomeric excess determined by chiral HPLC
^c (*S*)-*t*BuPyOx/Pd(TFA)₂, DCE, 10 eq. H₂O, 12 h, 60 °C [14]
*Reoxidation by *p*-chloranil before catalytic cycle

In the second cycle, a slight increase in enantioselectivity (81 % ee) with a small drop in conversion (88 %) were observed. Deactivation of the catalyst can be caused by many factors such as leaching of Pd [22,28]. Leaching of active catalytic species was excluded by Sheldon's test [28]. Another possibility is reduction of catalytically relevant Pd(II) to Pd(0) [29,30]. From this reason oxidation after the second cycle by 2,3,5,6-tetrachlorocyclohexa-2,5-diene-1,4-dione (*p*-chloranil) was provided. In the next cycle another lowering of conversion was observed with enantioselectivity untouched (77 %; 81 % ee). The expected reason of this observation is the collecting of the products of reactions as well as reoxidizing agents in the polymeric matrix.

Under optimized conditions (13 mol % catalyst, 60 °C, 24 h, 5 eq. HFIP) catalyst **11***Pd was studied. It was prepared from copolymer **11** with higher swelling capacity (5.3 ml·g⁻¹). Ratio of **11** / Pd(TFA)₂ used for preparation of **11***Pd proved to be a crucial parameter for the catalytic activity. While **11** was complexed with an excess of Pd(TFA)₂, high conversions were observed during four catalytic cycles followed by a drop in fifth cycle ((A); Table 6). After catalyst reoxidation by *p*-chloranil, the catalytic activity was restored. In the first cycle only low enantioselectivity was observed (70 % ee). In the second cycle there was an increase in enantioselectivity (80 % ee). This probably corresponds to the rearrangement of the catalytic complex [31].

Table 6 Overview of catalytic experiments with **11***Pd.



Preparation of **11***Pd with ratio **11** / Pd(TFA)₂ (solvent)

| Cycle | (A) 1 : 2 (DCE) | | (B) 2 : 1 (DCE) | | (C) 1.3 : 1 (AcOEt) | |
|-----------------|--------------------------------|------------------------|--------------------------------|------------------------|--------------------------------|------------------------|
| | Conversion ^a (%) | ee ^b (%) | Conversion ^a (%) | ee ^b (%) | Conversion ^a (%) | ee ^b (%) |
| 1 st | 95 | 70 | 93 | 89 | 99 | 73 |
| 2 nd | 95 | 80 | 54 | 90 | 90* | 87 |
| 3 rd | 84 | 82 | - | - | 99* | 88 |
| 4 th | 89 | 82 | - | - | 89* | 89 |
| 5 th | 66 | 83 | - | - | 54* | 89 |
| 6 th | 96* | 83 | - | - | 69* | 87 |

^a Determined after 24 h by ¹H NMR

^b (*R*); Enantiomeric excess determined by chiral HPLC

* Reoxidation by *p*-chloranil before catalytic cycle

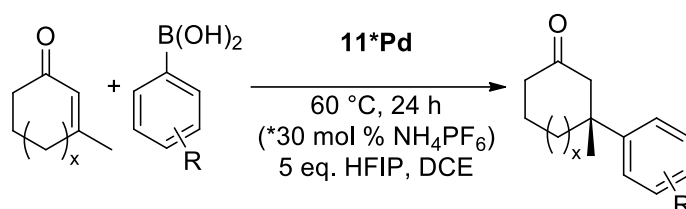
Enantioselectivities were increasing until the sixth cycle to 83 % ee. However, this value is not comparable with homogeneous conditions (91 % ee).

From the mentioned reason catalyst **11***Pd was prepared in a different manner, using ratio **11** / Pd(TFA)₂ 2 : 1. This catalyst showed great conversion and enantioselectivity in the first cycle (93 %, 89 % ee). In the second cycle enantioselectivity remained unchanged but conversion significantly dropped (54 %; 90 % ee) (Table 6). From the results obtained the significant excess of ligand **11** in comparison to the amount of Pd(TFA)₂ is necessary for achieving a high degree of enantioselectivity. On the other hand such a catalyst loses its catalytic activity quickly, presumably by reduction of catalytically relevant Pd(II) to Pd(0) [29,30]. These findings led to the third recycling series where **11***Pd was prepared only by using a slight excess of **11** over Pd(TFA)₂ (1.3 : 1) and complexation was provided in AcOEt as a solvent (due to higher solubility of Pd(TFA)₂ in comparison to DCE, leading to better yields of complexation). Also, reoxidation of the catalyst by *p*-chloranil was done after each cycle. In the first cycle, almost quantitative conversion with low

enantioselectivity (73 % ee) was observed. In the second cycle, enantioselectivity increased to 87 % ee and in the next cycles oscillated around this value. Conversion was high in four cycles, after that it was decreasing ((C); Table 6). A possible explanation is the cumulation of *p*-chloranil reduction products in the polymeric matrix or oxidation on the other place of the macromolecule leading to catalyst deactivation.

Copolymer **11*Pd** was tested as a catalyst in a series of various substrates. To ensure maximal enantioselectivity in the first run, **11*Pd** was prepared by a complexation reaction of **11** with Pd(TFA)₂ in ratio 2 : 1 with AcOEt as a solvent. In the case of low reactivity 30 mol % NH₄PF₆ was added. This salt stabilizes cationic Pd species and has beneficial effect on reaction rate [32]. Comparison of the results obtained with catalyst **11*Pd** with those reported in homogenous shows lower catalytic activity (Table 7). On the other hand, only small decrease in enantioselectivity was observed in most of the cases.

Table 7 Results of addition series of boronic acids to various enones catalysed by **11*Pd**.



| | | Homog. conditions | | Catalyst 11*Pd | |
|---|-------------------|------------------------|---------------------|-----------------------------|---------------------|
| x | R | Yield ^c (%) | ee ^c (%) | Conversion ^a (%) | ee ^b (%) |
| 1 | 4-CH ₃ | 99 | 87 | 94 | 75 |
| 1 | 4-CF ₃ | 99 | 96 | 85* | 91 |
| 1 | 4-Cl | 94 | 95 | 78* | 91 |
| 1 | 4-Ac | 99 | 96 | 52* | 90 |
| 1 | 4-OBn | 96 | 74 | 59* | 58 |
| 0 | H | 84 | 91 | 99 | 79 |
| 0 | 4-CH ₃ | 99 ^d | 77 ^d | 92* (96 h) | 67 |

^a Determined after 24 h by ¹H NMR

^b (*R*); Enantiomeric excess determined by chiral HPLC

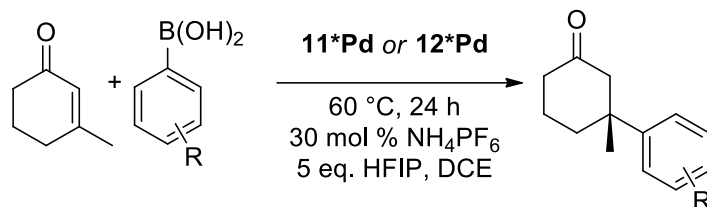
^c Results from ref. [14]

^d Our result: 5 mol % Pd(TFA)₂, 6 mol % (*S*)-*t*Bu-PyOx, 5 eq. H₂O, 60 °C, 24 h, DCE

* Addition of 30 mol % NH₄PF₆

From the results obtained it looks like the lower catalytic activity is related to the steric bulk of substituents on boronic acids. A possible explanation is insufficient diffusion. From this reason copolymer **12** with a higher swelling capacity ($8.8 \text{ ml} \cdot \text{g}^{-1}$) was prepared and its $\text{Pd}(\text{TFA})_2$ complex **12*Pd** was tested as a catalyst for problematic substrates. Unfortunately, in comparison to **11*Pd** similar (or even worse) results were obtained (Table 8).

Table 8 Comparison of catalytic activity of **11*Pd** and **12*Pd**.



| R | Catalyst | |
|----------|-----------------------------------|-----------------------------------|
| | 11*Pd^b | 12*Pd^b |
| | Conversion^a (%) | Conversion^a (%) |
| H | 99 | 89 |
| 4-Ac | 52* | 50* |
| 3-COOMe | 57* | 51* |
| 4-OBn | 59* | 41* |

^a Determined after 24 h by ^1H NMR

^b Prepared by complexation of **11/12** with $\text{Pd}(\text{TFA})_2$ in 2 : 1 ration in AcOEt

To explain these findings, hypotheses about the impact of diffusion on reaction parameters are not sufficient. Further experiments are possible.

4 Conclusion

In the first part of the dissertation thesis, the catalytic activity of the copolymers of ethyl-(4-vinylbenzyl)-L-tartrate with styrene as potential recyclable catalysts for Sharpless epoxidation were tested. Tartrate ligands anchored to the polymeric matrix by ester bond showed great catalytic activity, comparable with homogeneous conditions, although their recyclization was not possible. The reason was the leaching of the tartrate fragment due to ester bond alcoholysis. This led to synthesis of ethyl (2*R*,3*R*)-2,3-dihydroxy-4-oxo-5-(4-vinylphenyl)pentanoate, where the tartrate fragment is bonded by a stable C–C ketone bond. Its copolymer with styrene was prepared and tested as a catalyst for Sharpless epoxidation. The results showed that the structural change led to a stable and recyclable copolymer while reaction parameters (conversion and enantioselectivity) remained unchanged. Catalytic activity was studied on two substrates in four cycles. During recyclization, a small drop in the catalytic activity was observed. This was caused by the unavoidable hydrolysis of Ti(IV) alkoxide to titanium dioxide that precipitated in the polymeric matrix.

In the second part of this thesis, copolymers of styrene with (*S*)-4-(*tert*-butyl)-2-(4-(4-vinylphenyl)pyridin-2-yl)-4,5-dihydrooxazole were prepared. Palladium(II) complexes of such copolymers were tested as potentially recyclable catalysts for Pd-catalysed asymmetric addition of arylboronic acids to five- and six-membered enones. The different cross-linkers were used for the preparation of the copolymers and their impact on the swelling capacity of the prepared copolymers and the catalytic activity were discussed. The crucial parameters for transition to heterogeneous system was the necessity of the addition of HFIP as a proton source and reoxidation of the reduced Pd(0) back to Pd(II) by *p*-chloranil between cycles. Under optimized conditions it is possible to use such catalyst at least six times. For numerous substrates, the parameters (conversion, enantioselectivity) are very similar to those reported in homogeneous conditions.

5 List of References

- [1] Katsuki, T.; Sharpless, K. B. The First Practical Method for Asymmetric Epoxidation. *J. Am. Chem. Soc.* **1980**, *102* (18), 5974–5976
- [2] Heravi, M. M.; Lashaki, T. B.; Poorahmad, N. Applications of Sharpless Asymmetric Epoxidation in Total Synthesis. *Tetrahedron Asymmetry* **2015**, *26* (8), 405–495
- [3] Karjalainen, J. K.; Hormi, O. E. O.; Sherrington, D. C. Highly Efficient Heterogeneous Polymer-Supported Sharpless Alkene Epoxidation Catalysts. *Tetrahedron Asymmetry* **1998**, *9* (9), 1563–1575
- [4] Karjalainen, J. K.; Hormi, O. E. O.; Sherrington, D. C. Efficient Polymer-Supported Sharpless Alkene Epoxidation Catalyst. *Molecules* **1998**, *3* (3), 51–59
- [5] Karjalainen, J. K.; Hormi, O. E. O.; Sherrington, D. C. Heterogeneous Asymmetric Epoxidation of Cis-Allylic Alcohols: Use of Polymer-Supported Ti(IV)-Catalyst. *Tetrahedron Asymmetry* **1998**, *9* (12), 2019–2022
- [6] Karjalainen, J. K.; Hormi, O. E. O.; Sherrington, D. C. An Improved Heterogeneous Asymmetric Epoxidation of Homoallylic Alcohols Using Polymer-Supported Ti(IV) Catalysts. *Tetrahedron Asymmetry* **1998**, *9* (21), 3895–3901
- [7] Zhao, W.; Hao, Z.; Hu, C.; Li, J.; Xu, X. The Epoxidation of Allyl Alcohol on Ti-Complex/MCM-48 Catalyst. *Microporous Mesoporous Mater.* **2008**, *112* (1–3), 133–137
- [8] Xiang, S.; Zhang, Y.; Xin, Q.; Li, C. Asymmetric Epoxidation of Allyl Alcohol on Organic–Inorganic Hybrid Chiral Catalysts Grafted onto the Surface of Silica and in the Mesopores of MCM-41. *Angew. Chem. Int. Ed.* **2002**, *41* (5), 821–824
- [9] Choudary, B. M.; Valli, V. L. K.; Prasad, A. D. An Improved Asymmetric Epoxidation of Allyl Alcohols Using Titanium-Pillared Montmorillonite as a Heterogeneous Catalyst. *J. Chem. Soc. Chem. Commun.* **1990**, *100* (17), 1186
- [10] Meunier, D.; Piechaczyk, A.; de Mallmann, A.; Basset, J.-M. Silica-Supported Tantalum Catalysts for Asymmetric Epoxidations of Allyl Alcohols. *Angew. Chem. Int. Ed.* **1999**, *38* (23), 3540–3542
- [11] Suresh, P. S.; Srinivasan, M.; Pillai, V. N. R. Copolymers of Polystyrene—New Polymer Supports for Asymmetric Epoxidation of Allylic Alcohols. *J. Polym. Sci. Part Polym. Chem.* **2000**, *38* (1), 161–169
- [12] Cho, C. S.; Motofusa, S. I.; Ohe, K.; Uemura, S.; Shim, S. C. A New Catalytic Activity of Antimony(III) Chloride in Palladium(0)-Catalyzed Conjugate Addition of Aromatics to α,β -Unsaturated Ketones and Aldehydes with Sodium Tetraphenylborate and Arylboronic Acids. *J. Org. Chem.* **1995**, *60* (4), 883–888
- [13] Kikushima, K.; Holder, J. C.; Gatti, M.; Stoltz, B. M. Palladium-Catalyzed Asymmetric Conjugate Addition of Arylboronic Acids to Five-, Six-, and Seven-

- Membered β -Substituted Cyclic Enones: Enantioselective Construction of All-Carbon Quaternary Stereocenters. *J. Am. Chem. Soc.* **2011**, *133* (18), 6902–6905
- [14] Holder, J. C.; Goodman, E. D.; Kikushima, K.; Gatti, M.; Marziale, A. N.; Stoltz, B. M. Synthesis of Diverse β -Quaternary Ketones via Palladium-Catalyzed Asymmetric Conjugate Addition of Arylboronic Acids to Cyclic Enones. *Tetrahedron* **2015**, *71* (35), 5781–5792
- [15] Shockley, S. E.; Holder, J. C.; Stoltz, B. M. Palladium-Catalyzed Asymmetric Conjugate Addition of Arylboronic Acids to α,β -Unsaturated Cyclic Electrophiles. *Org. Process Res. Dev.* **2015**, *19* (8), 974–981
- [16] Lestini, E.; Blackman, L. D.; Zammit, C. M.; Chen, T.; Williams, R. J.; Inam, M.; Couturaud, B.; O'Reilly, R. K. Palladium-Polymer Nanoreactors for the Aqueous Asymmetric Synthesis of Therapeutic Flavonoids. *Polym. Chem.* **2018**, *9* (7), 820–823
- [17] Bartáček, J. Preparation and Characterization of Recyclable Catalyst for Enantioselective Epoxidations of Substituted Allylic Alcohols. Diploma thesis, Univerzita Pardubice, 2017
- [18] Wilson, M. E.; Paech, K.; Zhou, W.-J.; Kurth, M. J. Solvent and Reagent Accessibility within Oligo (Ethylene Glycol) Ether [PEG] Cross-Linked Polystyrene Beads. *J. Org. Chem.* **1998**, *63* (15), 5094–5099
- [19] Hodge, P. Polymer-Supported Organic Reactions: What Takes Place in the Beads? *Chem. Soc. Rev.* **1997**, *26* (6), 417
- [20] Bouillon, I.; Soural, M.; Miller, M. J.; Krchňák, V. Resins with Identical Specifications Are Not Identical. Identifying a Useful Solid-Phase Resin. *J. Comb. Chem.* **2009**, *11* (2), 213–215
- [21] Jacobsen, E. N. Transition Metal-Catalyzed Oxidations: Asymmetric Epoxidation. *Compr. Organomet. Chem. II* **1995**, 1097–1135
- [22] Altava, B.; Burguete, M. I.; García-Verdugo, E.; Luis, S. V. *Chiral Catalysts Immobilized on Achiral Polymers: Effect of the Polymer Support on the Performance of the Catalyst*; The Royal Society of Chemistry, 2018; Vol. 47
- [23] Sarker, Md. A. R. Optical Properties of Al- and Zr-Doped Rutile Single Crystals Grown by Tilting-Mirror-Type Floating Zone Method and Study of Structure-Property Relationships by First Principle Calculations. *J. Inorg. Chem.* **2014**, *2014*, 1–11
- [24] Otomaru, Y.; Senda, T.; Hayashi, T. Preparation of an Amphiphilic Resin-Supported BINAP Ligand and Its Use for Rhodium-Catalyzed Asymmetric 1,4-Addition of Phenylboronic Acid in Water. *Org. Lett.* **2004**, *6* (19), 3357–3359
- [25] Shen, G.; Osako, T.; Nagaosa, M.; Uozumi, Y. Aqueous Asymmetric 1,4-Addition of Arylboronic Acids to Enones Catalyzed by an Amphiphilic Resin-Supported Chiral Diene Rhodium Complex under Batch and Continuous-Flow Conditions. *J. Org. Chem.* **2018**, *83* (14), 7380–7387

- [26] Kuremoto, T.; Yasukawa, T.; Kobayashi, S. Heterogeneous Chiral Diene-Rh Complexes for Asymmetric Arylation of α,β -Unsaturated Carbonyl Compounds, Nitroalkenes, and Imines. *Adv. Synth. Catal.* **2019**, *361* (16), 3698–3703
- [27] de Gracia Retamosa, M.; Álvarez-Casao, Y.; Matador, E.; Gómez, Á.; Monge, D.; Fernández, R.; Lassaletta, J. M. Pyridine-Hydrazone Ligands in Asymmetric Palladium-Catalyzed 1,4- and 1,6-Additions of Arylboronic Acids to Cyclic (Di)Enones. *Adv. Synth. Catal.* **2019**, *361* (1), 176–184
- [28] Lempers, H. E. B.; Sheldon, R. A. The Stability of Chromium in CrAPO-5, CrAPO-11, and CrS-1 during Liquid Phase Oxidations. *J. Catal.* **1998**, *175* (1), 62–69
- [29] Lamb, C. J. C.; Vilela, F.; Lee, A.-L. Pd(II)-Catalyzed Enantioselective Desymmetrization of Polycyclic Cyclohexenediones: Conjugate Addition versus Oxidative Heck. *Org. Lett.* **2019**, *21* (21), 8689–8694
- [30] Baek, D.; Ryu, H.; Ryu, J. Y.; Lee, J.; Stoltz, B. M.; Hong, S. Catalytic Enantioselective Synthesis of Tetrasubstituted Chromanones via Palladium-Catalyzed Asymmetric Conjugate Arylation Using Chiral Pyridine-Dihydroisoquinoline Ligands. *Chem. Sci.* **2020**
- [31] Segarra, A. M.; Guerrero, R.; Claver, C.; Fernández, E. How To Turn the Catalytic Asymmetric Hydroboration Reaction of Vinylarenes into a Recyclable Process. *Chem. – Eur. J.* **2003**, *9* (1), 191–200
- [32] Holder, J. C.; Zou, L.; Marziale, A. N.; Liu, P.; Lan, Y.; Gatti, M.; Kikushima, K.; Houk, K. N.; Stoltz, B. M. Mechanism and Enantioselectivity in Palladium-Catalyzed Conjugate Addition of Arylboronic Acids to β -Substituted Cyclic Enones: Insights from Computation and Experiment. *J. Am. Chem. Soc.* **2013**, *135* (40), 14996–15007

6 List of Students' Published Works

Papers directly related to the presented dissertation thesis

Bartáček, J.; Drabina, P.; Váňa, J.; Sedlák, M. Recoverable Polystyrene-Supported Catalysts for Sharpless Allylic Alcohols Epoxidations. *Reactive and Functional Polymers* **2019**, *137*, 123–132.

Bartáček, J.; Váňa, J.; Drabina, P.; Svoboda, J.; Kocúrik, M.; Sedlák, M. Recoverable Polystyrene-Supported Palladium Catalyst for Construction of All-Carbon Quaternary Stereocenters via Asymmetric 1,4-Addition of Arylboronic Acids to Cyclic Enones. *Reactive and Functional Polymers* **2020**, *Accepted manuscript (1. 5. 2020)*.

Presented posters

Jan Bartáček, Pavel Drabina, Jiří Váňa, Miloš Sedlák, Separable Polystyrene-Supported Catalyst for Sharpless Epoxidation, Barrande–Vltava 2018, Strasbourg, France, 27. – 28. 8. 2018.

Jan Bartáček, Pavel Drabina, Jiří Váňa, Miloš Sedlák, POLYSTYRENE-SUPPORTED TARTRATE CATALYST FOR SHARPLESS EPOXIDATION, ORCHEM 2018, Berlin, Germany, 10. – 12. 9. 2018.

Jan Bartáček, Pavel Drabina, Jiří Váňa, Miloš Sedlák, Novel recyclable polystyrene-supported catalyst for Sharpless epoxidation, OMCOS 2019, Heidelberg, Germany, 21.-25.7.2019, page 109, available online <https://www.omcos2019.de/abstractbook/>.

Presented lectures

Jan Bartáček, Jiří Váňa, Pavel Drabina, Miloš Sedlák, POLYSTYRENOVÝ KOPOLYMER JAKO KATALYZÁTOR PRO ENANTIOSELEKTIVNÍ EPOXIDACE ALLYLALKOHOLŮ, *Chémia a technológia pre život*, Bratislava, Slovakia, 9. 11. 2017, pages 296–297, ISBN: 978-80-89579-77-2.

The other papers

Androvič, L.; Bartáček, J.; Sedlák, M. Recent Advances in the Synthesis and Applications of Azo Initiators. *Res Chem Intermed* **2016**, *42* (6), 5133–5145.

Královec, K.; Havelek, R.; Kročová, E.; Kučírková, L.; Hauschke, M.; Bartáček, J.; Palarčík, J.; Sedlák, M. Silica Coated Iron Oxide Nanoparticles-Induced Cytotoxicity, Genotoxicity and Its Underlying Mechanism in Human HK-2 Renal Proximal Tubule Epithelial Cells. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis* **2019**, *844*, 35–45.

Váňa, J.; Bartáček, J.; Hanusek, J.; Roithová, J.; Sedlák, M. C–H Functionalizations by Palladium Carboxylates: The Acid Effect. *J. Org. Chem.* **2019**, *84* (20), 12746–12754.

Janíková, L.; Chýlková, J.; Šelešovská, R.; Sedlák, M.; Váňa, J.; Dušek, L.; Bartáček, J. Electrochemical Behavior of Plant Growth Stimulator 1-Naphthaleneacetic Acid and Its Voltammetric Determination Using Boron Doped Diamond Electrode. *Journal of Electroanalytical Chemistry* **2020**, *859*, 113855.