University of Pardubice

Faculty of Chemical Technology

Institute of Organic Chemistry and Technology

Martin Kocúrik

Styrene Copolymers as Selective Sorbents and Catalysts in Flow Systems

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Author: **Ing. Martin Kocúrik**

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

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Abstract

The first part of the dissertation addresses the preparation and characterization of sorbent materials designed for the adsorption of 1-naphthaleneacetic acid (NAA). Molecularly imprinted polymers (MIPs) were prepared using photochemically initiated suspension copolymerization followed by template removal. Two different monomeric derivatives of NAA were utilized to ensure molecular imprinting: 4-vinylbenzyl-2-(naphthalen-1-yl)acetate and *N*-methyl-2-(naphthalen-1-yl)-*N*-((4-vinylbenzoyl)oxy)acetamide. Both types of MIPs were able to capture more than 98% of NAA from an aqueous solution (10^{-3} mol/l) within 10 minutes and subsequently desorb it quantitatively. The prepared MIPs can be used for at least 10 consecutive adsorption/desorption cycles. Additionally, MIPs derived from esters were highly effective in adsorbing NAA in a continuous flow system (10^{-2} mol/l) and demonstrated selective adsorption for NAA from mixtures with anthranilic acid or salicylic acid. The second part of the dissertation focuses on the innovative synthesis and catalytic application of (*S*)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole. A complex of this ligand with $Pd(TFA)_2$ was used as a highly efficient enantioselective catalyst for the addition of arylboronic acids to cyclic *N*-sulfonylketimines. A heterogeneous variant of this catalyst was prepared by covalently anchoring the modified ligand to a commercially available polystyrene copolymer (PS-PEG TentaGel S NH_2). The immobilized catalyst exhibited a slight decrease in enantioselectivity (1 – 3% ee) and a fourfold decrease in reaction rate compared to its homogeneous counterpart. However, it showed remarkable solvolytic stability, allowing for 9 consecutive reaction cycles with only a moderate decrease in yield and enantioselectivity (98%; 90% ee → 90%; 83% ee). In addition to batch reaction setup, a flow reactor was successfully assembled. The continuous reaction showed approximately one-third of the reaction rate (TOF 1.6 h^{-1} → 0.5 h^{-1}), but the TON parameter increased (73) compared to the batch setup (19). The obtained results provide valuable insights for the further development of efficient flow reactors for the continuous synthesis of benzosultams.

Keywords

Molecularly imprinted polymers, Recyclable catalyst, Continuous flow

Abstrakt

Prvá časť dizertačnej práce rieši prípravu a charakterizáciu sorpčných materiálov určených na adsorpciu kyseliny 1-naftalénoctovej (NAA). Molekulárne otlačené polyméry (MIP) boli pripravené fotochemicky iniciovanou suspenznou ko-polymerizáciou a s následným odstránením templátu. Na zaistenie molekulárneho odtlačku boli využité dva rozdielne monomérne deriváty NAA: 4-vinylbenzyl-2-(naftalén-1-yl)acetát a *N*-metyl-2-(naftalén-1-yl)-*N*-((4-vinylbenzoyl)oxy)acetamid. Oba typy MIP boli schopné zachytiť viac ako 98% NAA z vodného roztoku (10^{-3} mol/l) počas 10 minút a následne ju kvantitatívne desorbovať. Pripravené MIP je možné použiť v najmenej 10 po sebe idúcich adsorpčných/desorpčných cykloch. MIP odvodené od esterov boli taktiež vysoko účinné na adsorpciu NAA v kontinuálnom prietokovom systéme (10^{-2} mol/l) a vykazovali selektivitu adsorpcie pre NAA zo zmesi s kyselinou antranilovou alebo salicylovou. Druhá časť dizertačnej práce sa zaoberá vylepšenou syntézou a katalytickým využitím (*S*)-4-(*terc*-butyl)-2-(5-(trifluórmetyl)pyridín-2-yl)-4,5-dihydrooxazolu. Komplex tohto ligandu s $Pd(TFA)_2$ bol využitý ako vysoko účinný enantioselektívny katalyzátor pre adíciu arylboronových kyselín na cyklické *N*-sulfonylketimíny. Heterogénna varianta tohto katalyzátora bola pripravená kovalentným zakotvením modifikovaného ligandu na komerčne dostupný kopolymér styrénu (PS-PEG TentaGel S NH_2). Pripravený imobilizovaný katalyzátor vykazoval mierne zníženie enantioselektivity (1 – 3 % ee) a štvornásobné zníženie reakčnej rýchlosti v porovnaní s homogénnou variantou. Na druhej strane však vykazoval pozoruhodnú solvolytickú stabilitu a umožnil 9 po sebe idúcich reakčných cyklov iba s miernym poklesom výťažku a enantioselektivity (98 %; 90 % ee → 90 %; 83 % ee). Okrem vsádzkového usporiadania reakcie sa podarilo úspešne zostaviť prietokový reaktor. Kontinuálne prevedenie reakcie vykázalo približne tretinové spomalenie reakcie (TOF 1,6 h^{-1} → 0,5 h^{-1}), na druhej strane sa však zvýšil parameter TON (73), v porovnaní so vsádzkovým usporiadaním (19). Získané výsledky poskytujú cenné poznatky pre ďalší vývoj účinných prietokových reaktorov pre kontinuálnu syntézu benzosultámov.

Kľúčové slová

Molekulárne odtlačené polyméry, recyklovateľný katalyzátor, kontinuálne prietokový systém

Abbreviations

AA – anthranilic acid

AIBN – Azobisisobutyronitrile

BAPOs – Phenylbis(2,4,6-trimethylbenzoyl)phosphine oxide

Bn_2O – dibenzyl ether

DBU – 1,8-Diazabicyclo(5.4.0)undec-7-ene

DCC – *N*,*N*'-Dicyclohexylcarbodiimide

DCM – dichloromethane

DMAP – 4-dimethylaminopyridine

DMF - *N*,*N*-dimethylformamide

DVB – divinylbenzene

EDC·HCl – *N*-Ethyl-*N*'-(3-dimethylaminopropyl)carbodiimide hydrochloride

er – enatiomeric ratio

HOBt – Hydroxybenzotriazole

ICP-MS – Inductively coupled plasma mass spectrometry

MeCN – acetonitrile

MIPs – molecularly imprinted polymers

mPEG – methoxy polyethylene glycol

NAA – 1-naphthaleneacetic acid

PhCl – chlorobenzene

PS-PEG – polystyrene polyethylene glycol resin

PVA – polyvinyl alcohol

rt – room temperature

SA – salicylic acid

t-BuNicox – methyl (*S*)-6-(4-(*tert*-butyl)-4,5-dihydrooxazol-2-yl)nicotinate

TEA – triethylamine

TEG – tetraethylene glycol 4-vinylbenzyl ether

TFE – 2,2,2-Trifluoroethanol

THF – tetrahydrofuran

TOF – turnover frequency

TON – turnover number

TsCl – p-Toluenesulfonyl chloride

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1 Introduction

1.1 Molecularly imprinted polymers (MIPs)

The intensive development of human society is intrinsically linked with the increasing contamination of the environment by organic substances. This contamination poses significant challenges in monitoring environmental pollution levels, as the presence of various interfering substances in real samples can affect the accuracy and reliability of the analysis.[1] Addressing this issue is critical for effective environmental management and protection.

One promising solution lies in developing specific sorbents designed to either selectively remove interfering substances from samples prior to analysis or to capture the desired analyte from a solution, desorb it, and then subject it to detailed analysis. Among the innovative approaches for creating such specific sorption materials is the preparation of molecularly imprinted polymers (MIPs).[2,3]

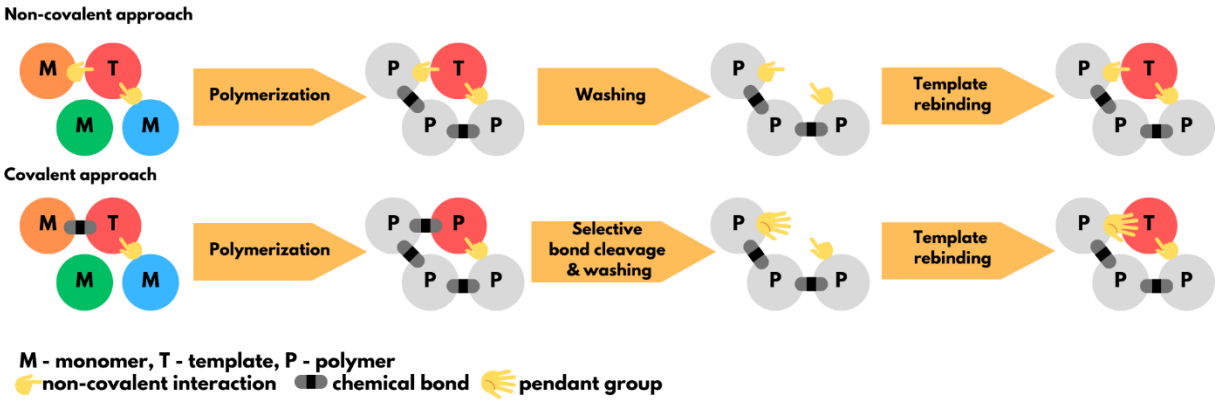


Figure 1 *Schematic representation of MIPs preparation.*

The most numerous molecularly imprinted polymers (MIPs) are prepared using the so-called non-covalent method. In this approach, the target substance (template) is mixed with monomers capable of forming non-covalent interactions with the substance (e.g., hydrogen bonds, van der Waals forces). Following polymerization, the template is washed out from the resulting polymer. The advantage of this method lies in its relative simplicity, although it requires that the template and monomers form non-covalent interactions.[2,3]

A less explored method is the covalent approach, where the template molecule is first modified with polymerizable double bonds through a labile bond. After polymerization, selective cleavage of the covalent bond between the template molecule occurs, and the template is subsequently removed from the polymer matrix. Along with the molecular imprint of the template, a functional group remains on the polymer, which can support the capture of the desired analyte during rebinding.[2,3]

1.2 Immobilized Palladium catalysts in asymmetric synthesis

When developing a contemporary chemical process, it is crucial to carefully evaluate the necessity of employing toxic and non-renewable metal catalysts, as well as to explore the possibilities for their recovery and reuse to reduce environmental pollution. Numerous techniques for the repeated use of catalytic systems are available, and their adoption is necessary for future sustainability.[4,5]

To attain an optimally efficient green chemical process, the design of heterogeneous catalysts should prioritize the use of safer chemicals and incorporate advanced mixing and heating technologies. Methods such as flow reactors, microwave heating, and ultrasound can enhance the recyclability and consistent catalytic performance of these catalysts.[6]

The implementation of a continuous flow system necessitates the use of a suitable solid support. The process of heterogenization typically relies on the intermolecular interactions between the solid support and the active compound, with the characteristics of the solid support significantly affecting the efficiency of the heterogeneous system. These interactions can be classified into three types: covalent bonding, non-covalent bonding, and encapsulation.[7] Immobilization techniques utilizing these interactions have been documented for inorganic materials,[8] organic polymers,[9,10] organic-inorganic hybrid materials,[11] nanomaterials and magnetic nanoparticles.[12,13] Insoluble organic polymers are particularly advantageous as supports for flow system preparation, due to their facile synthesis, chemical inertness, cost-effectiveness, and mechanical stability, which enable them to endure the conditions of flow systems for extended durations.[4]

In asymmetric synthesis utilizing Palladium catalysis, the advancement of immobilized catalysts has proven to be highly valuable. This approach has been effectively employed in a wide range of reactions, such as allylic substitution,[14–20] the Hayashi-Miyaura reaction,[21–24] cross-coupling reactions,[25–28] the Henry reaction,[29,30] and various other transformations involving the formation of C-C or C-X bonds.[31–34]

2 Objectives

- Preparation of covalent molecularly imprinted polymers of 1-naphthaleneacetic acid with different covalent bonding and its testing for rebinding/releasing of NAA

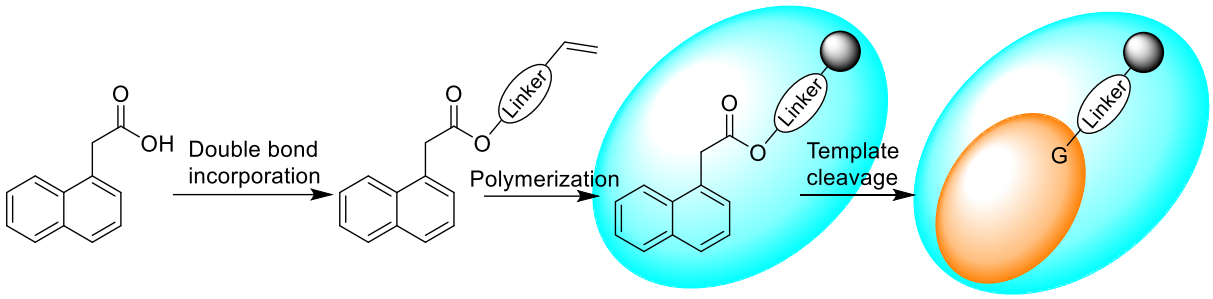
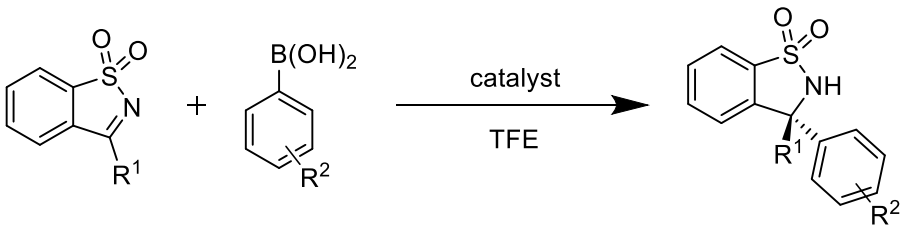


Figure 2 *Schematic preparation of 1-naphthaleneacetic acid MIPs.*

- Evaluating the Palladium(II) trifluoroacetate complex with (*S*)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole as a catalyst for the asymmetric addition of arylboronic acids to cyclic *N*-sulfonylketimines. Immobilizing (*S*)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole to create an efficient heterogeneous catalyst for the development of a continuous flow system.



Scheme 1 *Pd catalysed addition of arylboronic acid to N-sulfonylketimines.*

3 Results and Discussion

3.1 Covalent Molecularly Imprinted Polymers for Selective Adsorption of 1-Naphthylacetic Acid

The utilization of covalent approaches for the synthesis of Molecularly Imprinted Polymers (MIPs) has been relatively underrepresented in the literature, despite their apparent advantages. Although covalent strategies are predominantly employed for templates bearing –OH groups, their application for templates containing –COOH groups has not been extensively described. This gap in research motivated the investigation of covalent methodologies for the preparation of MIPs tailored for the selective adsorption of 1-naphthylacetic acid (NAA).

During the design phase of target molecules, two distinct binding modes for the reverse binding of NAA were considered. The basic model involved the utilization of a template bearing a 4-vinylbenzyl residue attached via an ester bond. This design facilitated the shortest and most cost-effective preparation of MIPs with a residual –OH group. However, it was acknowledged that the final cavity size after template removal would be one atom smaller than NAA itself.

In overcome the limitations of the basic model, an advanced model was designed. This model employed a longer linker, which provided a cavity size matching that of NAA, along with the presence of a residual –COOH group on the MIPs. Computational studies supported the anticipated advantages of the second model, including a higher binding energy of the hydrogen bond between NAA and the -COOH group on the MIPs during subsequent NAA trapping (Figure 3).

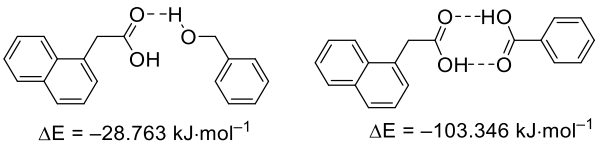
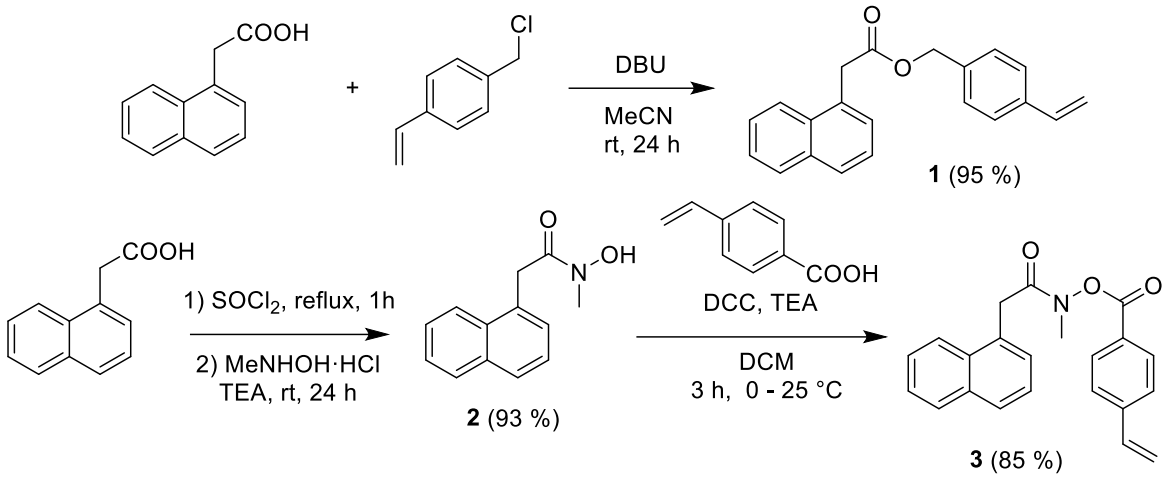


Figure 3 *Bonding energy of H-bond of NAA and pendant group.*

3.1.1 Synthesis of monomers

Monomer **1**, bearing the NAA fragment attached via an ester bond, was prepared by nucleophilic substitution of NAA with 4-vinylbenzyl chloride and the use of DBU as a base (Scheme 2).

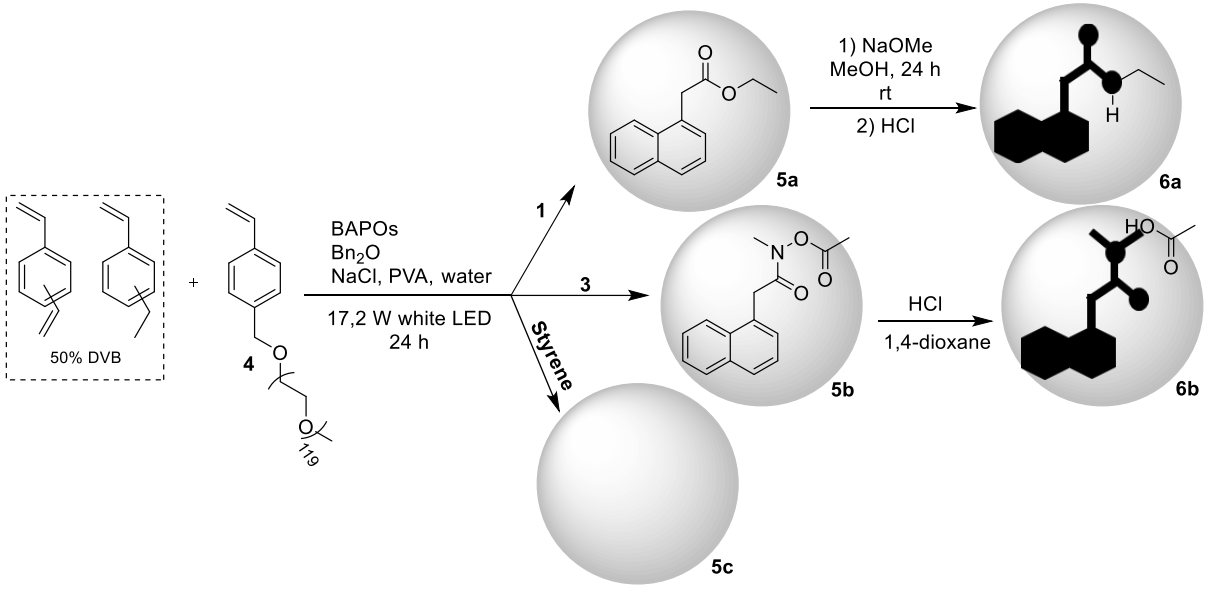
Monomer **3**, bearing an *N*-Me hydroxamate linker, was prepared from NAA, it was first converted to an acyl chloride, then underwent nucleophilic substitution with *N*-Me hydroxylamine to produce intermediate **2**. This intermediate was subsequently converted to the final monomer **3** under carbodiimide coupling conditions with 4-vinylbenzoic acid (Scheme 2).



Scheme 2 Synthesis of Polymerizable Monomers for the Preparation of Covalent MIPs.

3.1.2 Synthesis and Characterization of Copolymers

The monomers **1** and **3** were subjected to suspension copolymerization induced by visible light, utilizing the photoinitiator BAPOs (Scheme 3). Initial experiments revealed that the resulting polymers exhibited very low water wettability. To enhance wettability, 4-vinylbenzyloxy mPEG5000 (4) (5%) was incorporated into the monomer mixture, successfully achieving the desired effect. Further optimizations indicated that polymers with a higher degree of cross-linking (30 mol% DVB compared to 20 mol% DVB) and a greater amount of porogen (1 ml Bn_2O/1g monomers compared to 3 ml Bn_2O/1g monomers) yielded superior results.



Scheme 3 Preparation of MIPs and cleavage of template.

Due to the different nature of the labile bonds used for template capture, distinct conditions were required for their subsequent removal. For compound **5a**, with the template bound via an ester bond, removal was achieved through alcoholysis with MeONa for 16 hours at low temperature. For compound

5b, with the template bound through an *N*-Me hydroxamate linker, acidic hydrolysis using aqueous HCl, conducted under reflux in 1,4-dioxane for 16 hours, was employed.

Template removal was confirmed through FT-IR spectroscopy by the absence of specific vibrational bands and the emergence of new bands corresponding to –OH/–COOH groups (Figure 4). For polymers **6a**, derived from monomer **1**, the carbonyl vibrational bands at wavenumbers 1730 and 1142 cm^{-1}, which were prominent in **1** and **5a**, were no longer present. Additionally, a new vibrational band appeared at 3364 cm^{-1}, indicating the presence of –OH groups. For polymers **6b**, derived from monomer **3b**, the carbonyl vibrational bands from the hydroxamate fragment (1754 and 1675 cm^{-1}), which were prominent in **3b** and **5b**, disappeared. The vibrational band for the –COOH group was very faint, attributed to the rigid nature of the polymer matrix, which hinders the formation of hydrogen bonds.

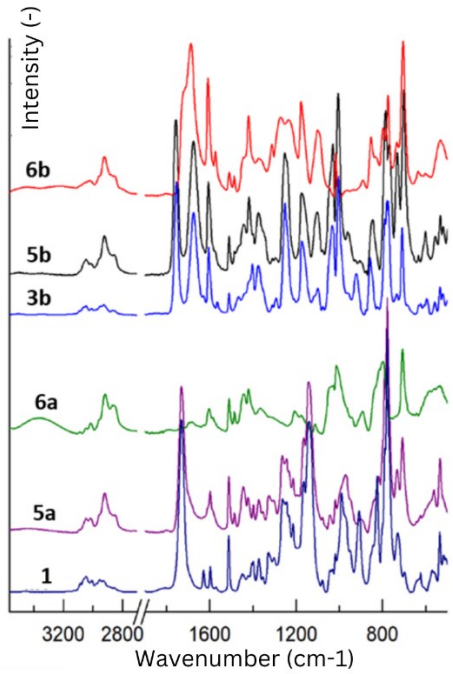


Figure 4 FT-IR spectra of selected monomers and copolymers.

3.1.3 Testing Adsorption Activity

To evaluate the polymer's ability to adsorb NAA, a 10^{-3} $mol \cdot L^{-1}$ NAA solution was used. Since hydrogen bonding with pendant groups (–OH, –COOH) was expected to be the primary binding mechanism, a working solution that suppresses NAA dissociation (pK_a = 4.23 in water) was required. Thus, a glycine-HCl buffer (0.1 $mol \cdot L^{-1}$, pH 2.6) was employed.

During proof testing, significant NAA binding from the stock solution was observed. Polymers **5a**, **5b**, and the non-selective polymer **5c** showed relatively low NAA adsorption. After template removal, polymers **6a** and **6b** exhibited nearly complete NAA capture, suggesting specific binding via molecular imprinting and pendant groups on the polymer surface. Despite expectations, both **6a** and **6b**

demonstrated similar efficiency, contrary to the anticipation that MIP **6b**, with an *N*-methylhydroxamate linker, would be more active due to a larger cavity size matching NAA and stronger binding with its –COOH groups. The finding reveals that the adsorption efficiency of NAA on MIP is primarily influenced by the swelling behaviour of the MIP in the given environment rather than the surface size in its dry state, the cavity size post-template removal, or the type of residual auxiliary group on the MIP surface.

Firstly, the optimal amounts of MIP **6a** and **6b** required for the quantitative capture of NAA were determined. The study determined that 40 mg of MIP **6a** and **6b** is optimal for quantitative NAA capture, whereas the non-selective **5c** achieved only 30% NAA capture even at twice the amount (80 mg) (Table 1).

Table 1 Dependence of adsorbed NAA (%) on the amount (mg) of polymers.

#	**Amount of MIPs** (mg)	**Adsorbed NAA** (%)[1]		
		5c	**6a**	**6b**
1	10	-	91	84
2	20	-	93	95
3	30	22	97	95
4	40	22	>98	>98
5	50	24	98	98
6	60	25	98	93
7	70	25	>98	92
8	80	30	>98	94

0.5 mL solution of 10^{-3} M NAA in 0.1 mol·L^{-1}glycine-HCl buffer at pH = 2.6; 1 h; 20 °C; 2 drops of EtOH.

Further optimization consisted of determining the time required for quantitative NAA uptake. The results show that for **6a** and **6b**, only 10 – 30 minutes is sufficient time.

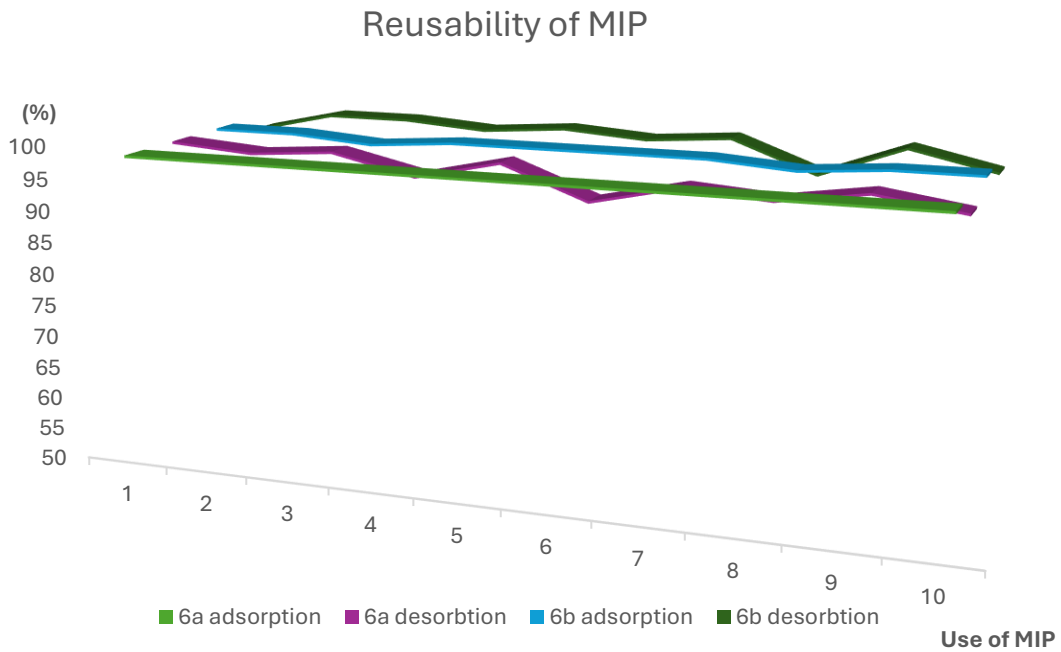
The final evaluation stage of the prepared MIPs involved examining the release and reusability of adsorbed NAA. Initial desorption using aqueous sodium hydroxide at 80 °C released only trace amounts of NAA. However, using ethanol instead of water improved NAA release. Quantitative desorption of adsorbed NAA was achieved within 10 minutes at 50 °C using a 0.1 mol·L^{-1} NaOH solution in a 50% ethanol-water mixture (Table 2).

Table 2 Optimization of NAA desorption procedure.

#	Elution medium	MIP	Time (min)	Temperature (°C)	Desorbed NAA (%)
1	NaOH (1 mol·L^{-1}, water)	**6b**	30	80	<5
2	EtOH	**6b**	5	30	60
3		**6b**	20	30	80
4	NaOH (0.1 mol·L^{-1}, water:ethanol=1:1)	**6b**	5	30	90
5		**6a**/**6b**	10	50	>98

Aparature was placed into an ultrasound bath.

After successfully identifying the elution system, a series of experiments was conducted to verify the reusability of MIPs **6a** and **6b**. The results demonstrated that both MIPs retained their original properties even after 10 cycles of NAA capture and release (Figure 5), indicating the suitability of their preparation in terms of the cross-linking agent used.[35]



Aparature placed into ultrasound bath.; Adsorption: 0.5 mL stock solution (c_{NAA}=10^{-3} mol·L^{-1}, c_{buf}=0.1 mol·L^{-1}, pH_{buf}=2.6), 1 h, 20 °C, 2 drops of EtOH, **6a**: 30 min, **6b**: 10 min. Desorbtion: NaOH (0.1 mol/l, water:ethanol, 1:1), 10 min, 50 °C

Figure 5 Reusability of MIPs.

3.1.4 Real sample analysis

The developed methodology with **6a** polymer was adapted for use in real water samples (tap water, well water) spiked with NAA (10^{-3} mol·L^{-1} NAA). To simplify the procedure, stock solutions of NAA were prepared in water samples that were acidified with HCl to pH < 3. The results show that the developed methodology can be applied to real samples without losing efficiency.

3.1.5 Effectivity evaluation in the flow system

The reusability study demonstrated that MIPs **6a** and **6b** consistently captured NAA from the solution. Given the almost identical results and the easier preparation of **6a**, it was chosen for continuous flow removal of NAA. In a lab-scale experiment, a 30% methanolic NAA solution at 1×10^{-2} mol·L^{-1} and pH 2.8 was used. A polyethylene column packed with 0.81 g of **6a** was fitted with a UV detector. Over ten cycles, the column's capacity stabilized after the first four cycles, absorbing over 99% of NAA from 30 mL of stock solution in each subsequent cycle, with a molar adsorption capacity of 0.373 mmol·g^{-1}. Alkaline regeneration with 30% methanolic NaOH solution resulted in less than 0.25% NAA elution, indicating effective polymer conditioning and minimal loss (Figure 6).

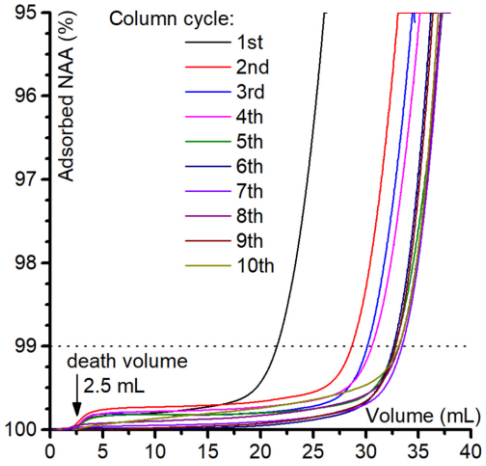


Figure 6 Reusability of MIPs in flow system.

3.1.6 Selectivity evaluation in the flow system

The selective affinity of MIPs for a specific compound from a mixture is a crucial property. To evaluate the selectivity of the prepared MIP **6a**, anthranilic acid (AA) and salicylic acid (SA), common plant growth stimulators, were chosen. The same column packed with **6a** used for adsorption capacity evaluation was connected to a UV-Vis detector with a diode array. The UV-Vis absorption spectra of the respective acids (NAA, AA, SA) were measured, allowing for their quantitative determination using the Lambert-Beer law (Figure 7).

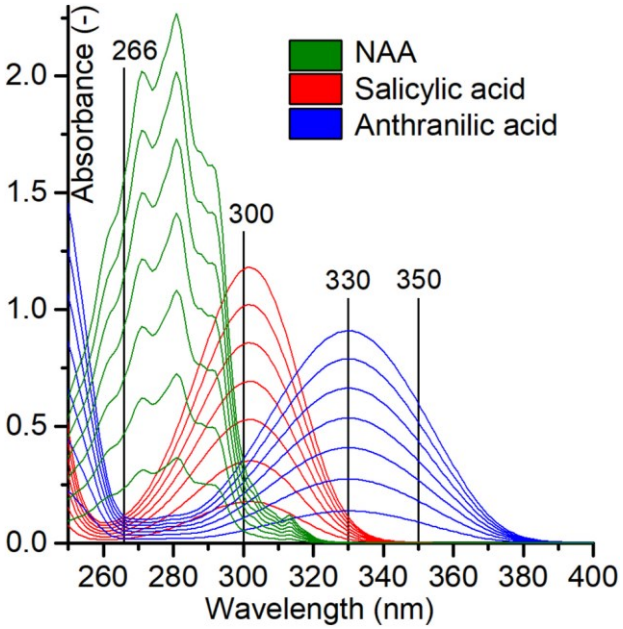


Figure 7 Absorption spectra of NAA, salicylic acid (SA) and anthranilic acid (AA).

Stock solutions of the acids at 5×10^{-3} mol·L^{-1} in 30% aqueous methanol were used to evaluate selectivity. For pure anthranilic acid (AA), MIP **6a** showed minimal affinity, with no retention after 2 column volumes (5 mL). For pure salicylic acid (SA), **6a** displayed greater affinity, retaining SA for 14 column volumes, half the capacity observed for NAA (Figure 6). In binary mixtures (AA+NAA, SA+NAA), the detector was saturated by the acid with a lower sorption capacity. Detailed UV-Vis spectral analysis confirmed the dominance of the acid with lower sorption affinity to **6a** in the eluted mixture (Figure 8).

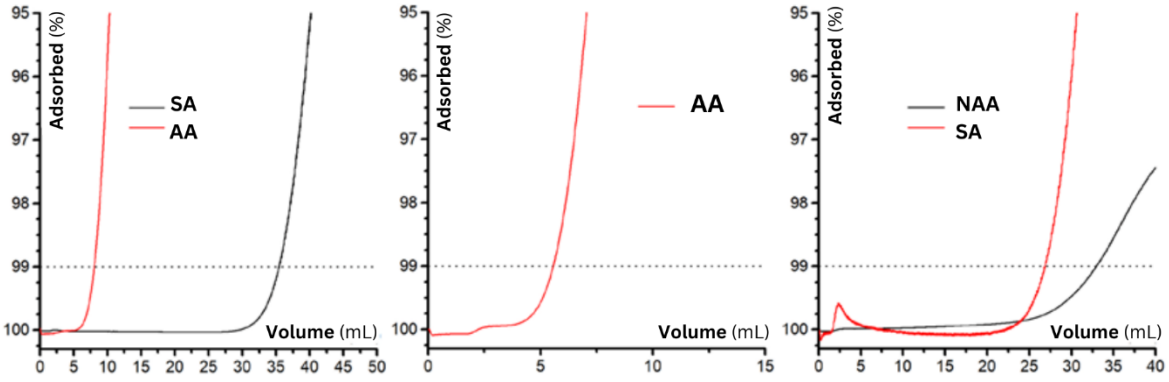
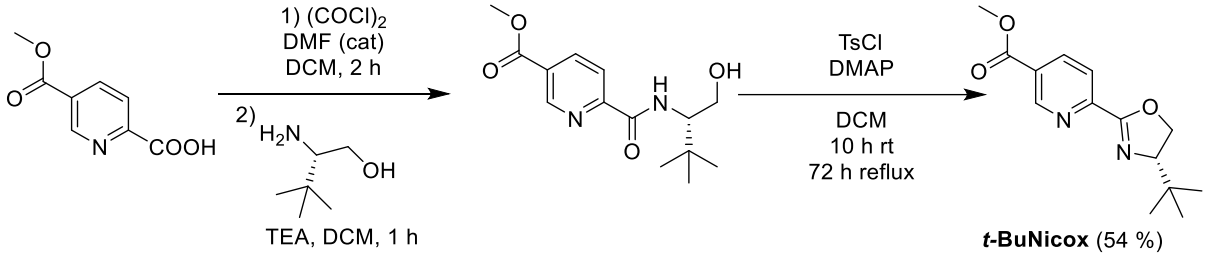


Figure 8 Selectivity evaluation of MIPs in the flow system.

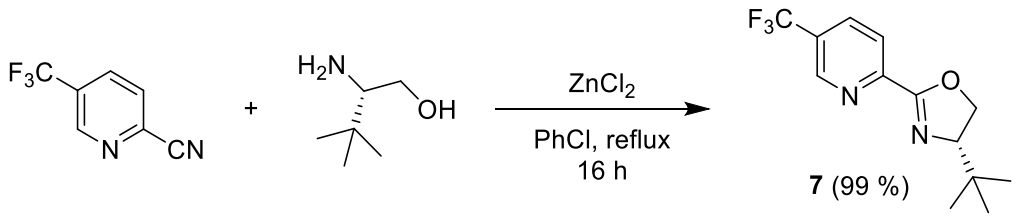
3.2 Heterogeneous Catalyst for Enantioselective Addition of Arylboronic Acids to Cyclic Ketimines

This work builds on Yang's research[36] using homogeneous catalysis with $Pd(TFA)_2$ and the *t*-BuNicox ligand, which yielded optically enriched cyclic sulfonamides with high enantioselectivity and excellent yields. However, the *t*-BuNicox synthesis is a 4-step process with a low yield (54%) (Scheme 4). Consequently, an alternative PyOx-type ligand was proposed, allowing for potential immobilization on a solid support.



Scheme 4 Synthesis of *t*-BuNicox.

Ligand **7** was proposed as an alternative to the *t*-BuNicox ligand used in the original work. The structural modification involved replacing the electron-accepting MeOOC– group at position 5 with an F_3C– group. The precursor for ligand **7** is commercially readily available, making it attractive for industrial-scale synthesis and reducing the risk of ligand degradation through ester group hydrolysis. The preparation of ligand **7** is described in the literature through the condensation of 5-CF_3-picolinonitrile with optically pure L-*tert*-leucinol, catalysed by 20 mol% ZnOTf, yielding 71%. By optimizing reaction conditions and using 300 mol% $ZnCl_2$ instead of 20 mol% ZnOTf, ligand **7** was prepared in quantitative yield without the need for chromatographic purification (Scheme 5).



Scheme 5 Synthesis of ligand **7**.

3.2.1 Homogeneous catalysis

A series of experiments were conducted to verify the ligand's suitability for the addition of arylboronic acids to 3-butylbenzo[d]isothiazole 1,1-dioxide (**15**), under conditions similar to the original protocol. Initial results demonstrated excellent activity of ligand **7**, comparable to the originally used *t*-BuNicox. Consequently, the experiments were extended to explore further the potential of ligand **7** (Figure 9). The conversion of the starting material to the product was monitored using ^1H NMR spectroscopy to determine the precise reaction time required for achieving quantitative conversion.

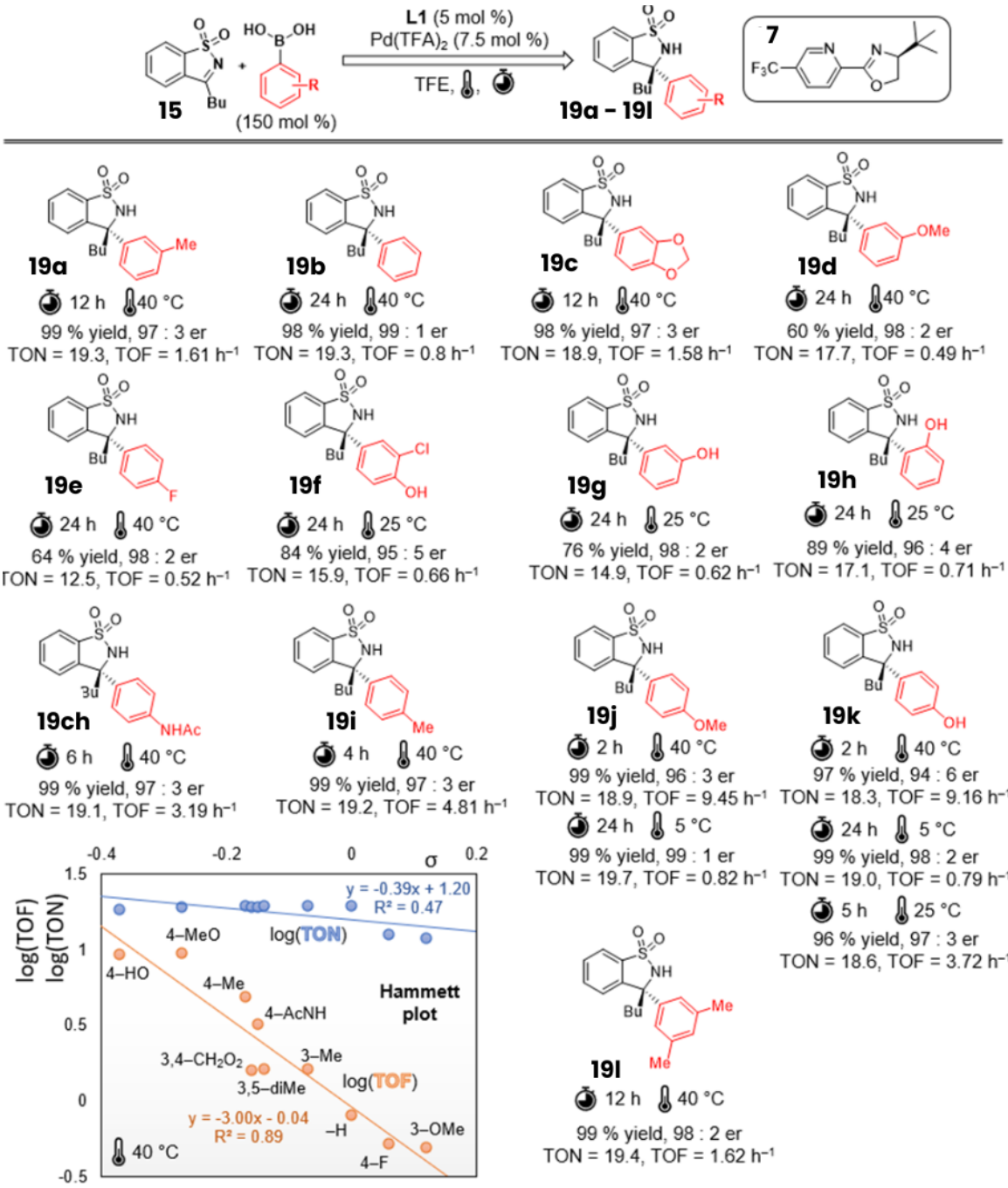


Figure 9 Results of homogeneous catalysis.

The results showed that electron-donating groups on arylboronic acids in the 3– and 4– positions accelerated the reaction, with the highest turnover frequency (TOF) observed for 4-hydroxyphenylboronic acid (**19k**) (Figure 9). However, when we further increased the electron-donating character using 4-(dimethylamino)phenylboronic acid, we observed only minimal conversion (<14%) and the major product was the protodeboronation product *N*,*N*-dimethylaniline within the temperature range of 5 − 40 °C. Boronic acids with electron-withdrawing substituents, such as 3-methoxyphenylboronic acid (**19d**) and 4-fluorophenylboronic acid (**19e**), significantly reduced reactivity.

The negative ρ-value (Figure 9) and the reactivity trend indicated that electron-donating groups stabilize the aryl palladium cation, benefiting the rate-limiting step. These findings align with the proposed mechanism, suggesting that migratory insertion is both the rate-determining and enantioselectivity-determining step.

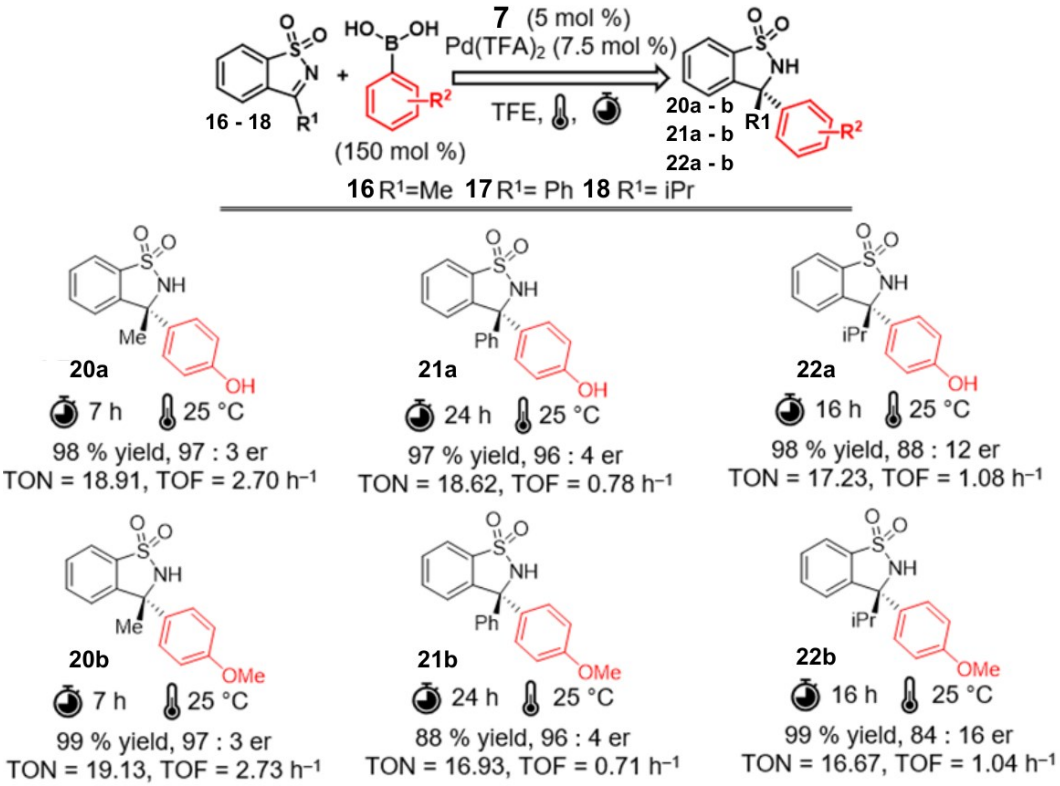
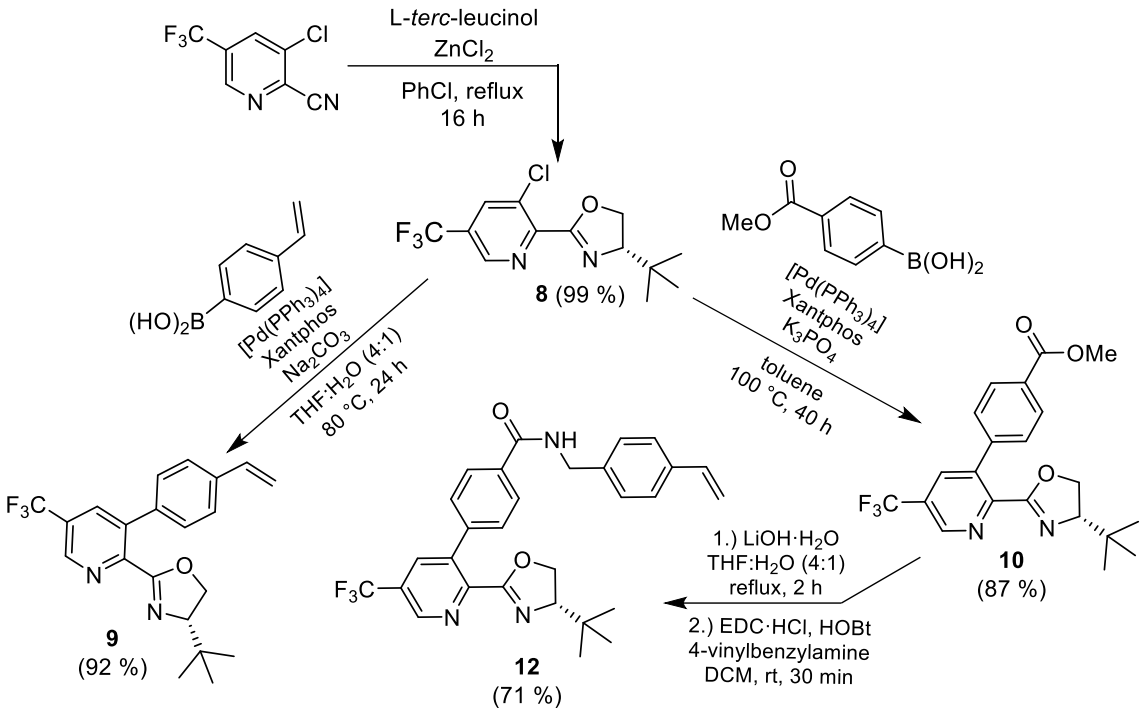


Figure 10 Substrate scope of variously substituted cyclic ketimines.

The series of homogeneous experiments was further expanded to the additions of 4-hydroxyphenylboronic acid and 4-methoxyphenylboronic acid to various substituted cyclic ketimines (**16** – **18**). All substrates yielded addition products under mild conditions (25 °C) with high yields and satisfactory enantiomeric ratios (Figure 10). Notably, the substrate bearing an *i*Pr group decreased in er compared to other substrates (**22a**, **22b**). This reduction in er was attributed to the *i*Pr group's high flexibility and steric bulk, which can negatively impact the reaction's stereochemical pathway.

3.2.2 Copolymers synthesis

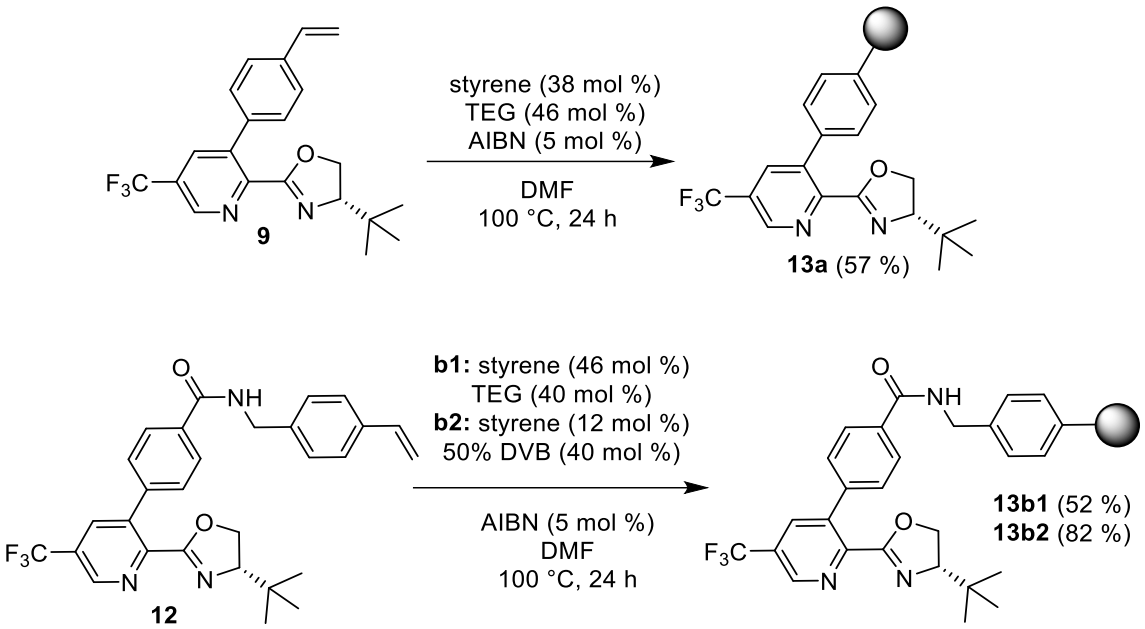
The foundational aspect of the immobilization strategy for ligand **7** was the commercial availability of 3-chloro-5-(trifluoromethyl)-picolinonitrile, commonly used as an industrial precursor for the fungicide fluopicolid. Under optimized conditions, its condensation with L-*tert*-leucinol produced intermediate **8**, which possesses a chlorine atom at the 5-position of the pyridine ring, facilitating subsequent modifications of the core structure.



Scheme 6 Synthesis of polymerizable ligand.

For immobilization, the direct introduction of a styrene fragment onto the pyridine core was explored (Scheme 6). Intermediate **9** was synthesized via the Suzuki-Miyaura reaction of intermediate **8** with 4-vinylphenylboronic acid, yielding a high yield of 92%. Concurrently, efforts were made to create a ligand with an elongated linker to ensure adequate separation between the catalyst and solid support, enhancing accessibility to the reaction center. This involved the Suzuki-Miyaura reaction of intermediate **8** with 4-methoxycarbonylphenylboronic acid under modified, water-free conditions, resulting in the isolation of intermediate **10** in a high yield. Subsequent basic hydrolysis of the ester functional group, followed by carbodiimide coupling with 4-vinylbenzylamine, yielded intermediate **12**, featuring a styrenyl fragment attached via a stable amide bond.

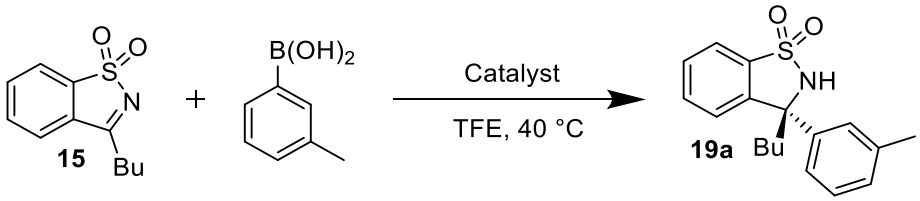
The prepared intermediates **9** and **12** were subsequently polymerized with styrene and bis(4-vinylphenyl)tetraethylene glycol (TEG) or 50% divinylbenzene (DVB) under precipitation polymerization conditions, initiated by AIBN (Scheme 7). Raw polymers were extracted in a Soxhlet extractor, vacuum-dried, and characterized through elemental analysis, FT-IR, and surface area analysis. Custom catalysts were prepared by complexation of polymers **13** with $Pd(TFA)_2$, and the captured Pd content was determined via ICP-MS after sample mineralization.



Scheme 7 Synthesis of copolymers.

3.2.3 Heterogeneous catalysis with copolymers 13

Table 3 Testing of catalytic activity in heterogeneous conditions.



#	Catalyst	mol % cat.	t (h)	Yield (%)	er[1]	TON (-)	TOF (h^{-1})
1	$[Pd(TFA)_2 \cdot \mathbf{7}]_2$	5	12	99	97:3	19.2	1.6
2	[**Pd·13a**]	10	24	25	96:4	2.4	0.1
3	[**Pd·13b1**]	10	24	38	97:3	3.7	0.15
4	[**Pd·13b2**]	10	24	36	97:3	3.5	0.15

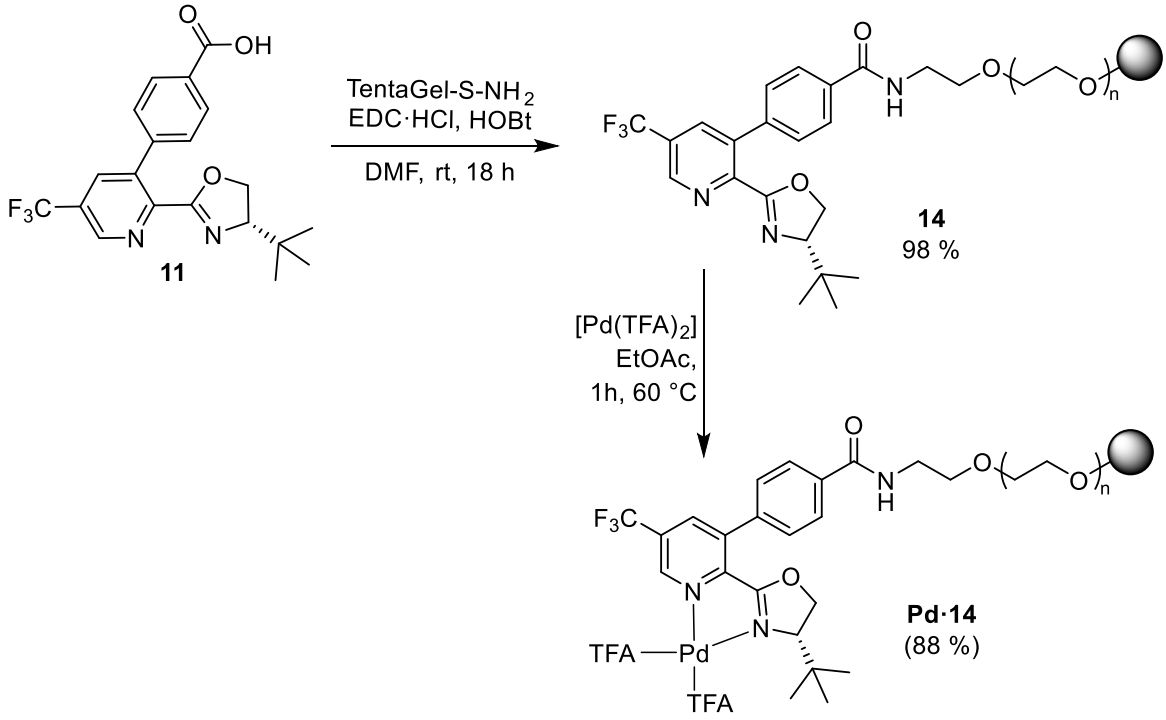
Reaction in 50 mL test tube open to air, [1]Determined by HPLC with chiral stationary phase. [2] Homogeneous conditions

Heterogeneous catalysts were tested for the addition of 3-methylbenzoic acid to ketimine **15** at 40 °C for 24 hours, with catalyst loading increased to 10 mol% as the initial modification (Table 3). Despite the higher loading, a significant reduction in reaction rate compared to the homogeneous system was observed. Notably, **Pd·13a**, located close to the non-polar polymeric matrix, exhibited the lowest conversion rate. **Pd·13b1**, positioned further from the matrix, showed improved reactivity but remained inferior to the homogeneous environment. This diminished reactivity was partly attributed to the limited surface areas of both **Pd·13a** and **Pd·13b1** (13a: 6.9 ± 0.6 m^2/g; 13b: 9.1 ± 1.0 m^2/g). The choice of TEG cross-linker, selected for its polar nature to enhance polymer polarity and facilitate reactant access,

contributed to this limitation. Substituting the cross-linker with DVB yielded **13b2**, with significantly increased surface area (330.4 ± 4.3 m^2/g). However, its Pd complex, **Pd·13b2**, demonstrated activity comparable to **Pd·13b1**. Due to the low activity of the catalytic complexes, no attempts were made to reuse them.

3.2.4 Post-modification strategy of immobilization

Catalysts prepared through copolymerization showed the beneficial impact of distancing the catalytic center from the carrier matrix. Building on this, intermediate **11** was suggested for attachment to commercially available PS-PEG resin (TentaGel S NH_2) via an amide bond (Scheme 8). This resin's advantage lies in its high compatibility, even in highly polar environments like TFE, where the catalytic reaction occurs.



Scheme 8 Immobilization of **11** via post-modification strategy.

The active catalyst was prepared by complexing **14** with $Pd(TFA)_2$ in EtOAc at 60°C, achieving almost complete decolorization within an hour. The precise Pd content was quantified using ICP-MS after the catalyst was filtered, rinsed, and dried to a constant mass.

The prepared **14** was characterized by using FT-IR spectroscopy, microanalysis, and gel-phase ^1H and ^{13}C NMR. The ligand's anchoring is observable in the IR spectra due to the appearance of new amide vibration bands (1660 cm^{-1}). The TentaGel resin's swelling properties allowed for gel-phase NMR measurements, further supporting the structure of **14**. After complexation reaction with $Pd(TFA)_2$, the prepared **Pd·14** was further characterized using FT-IR spectroscopy. A change in the infrared spectra is

particularly noticeable in the signals corresponding to both the C=O (1723 cm^{-1}) and C–F (1195 cm^{-1}) vibrations (Figure 11).

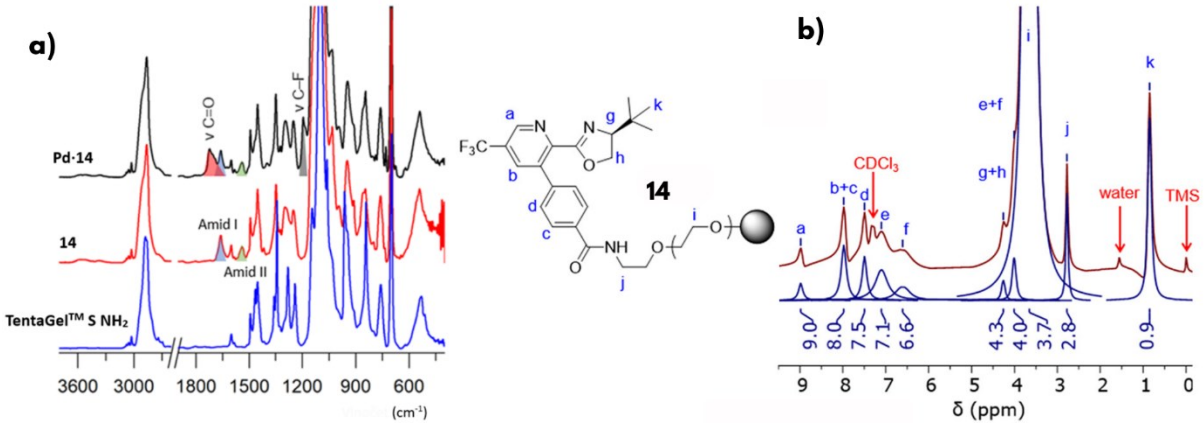


Figure 11 Characterization of ligand **14**.

3.2.5 Testing of catalytic activity of Pd·14 in a batch rearrangement

For evaluating **Pd·14**'s catalytic activity, the addition of 4-methoxyphenylboronic acid to ketimine **15** at 40°C was chosen. Using **Pd·14** at 15 mol% Pd led to a fourfold decrease in reaction rate, requiring an extended 8-hour reaction time to match the yield of homogeneous catalyst 7 (40°C, 2 hours, 99%, er: 96:3). Despite this, the enantioselectivity of product **19j** only slightly decreased compared to the homogeneous catalyst. It was possible to use the catalyst up to 10 times; however, a slight deactivation of the catalyst was observed with continued recycling cycles (Figure 12). This can be explained by Pd leaching, where the Pd content decreased by 10% during the 10 uses compared with the Pd content of the freshly prepared **Pd·14**.

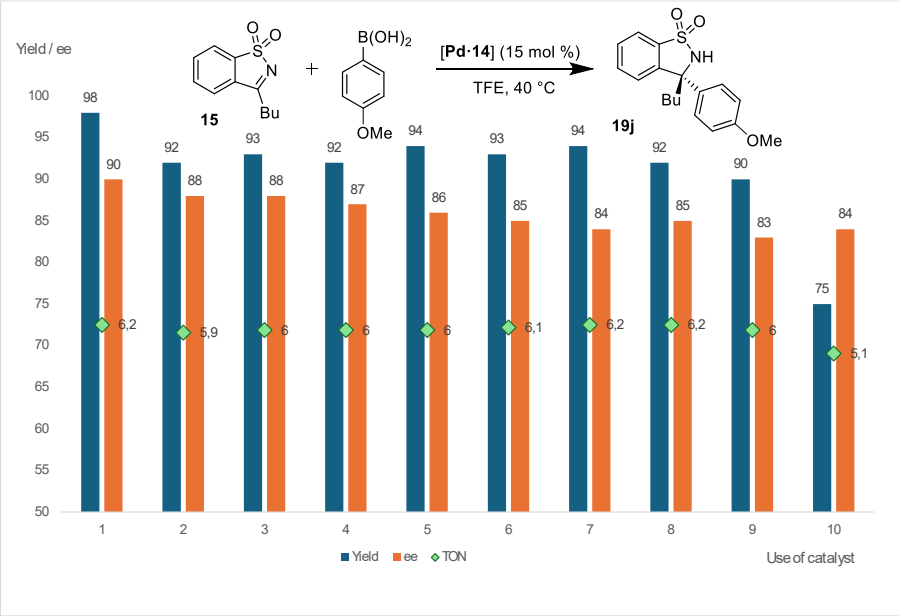
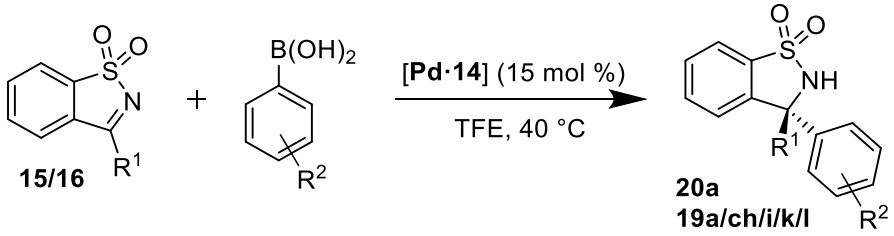


Figure 12 Reusability of **Pd·14**.

The **Pd·14** catalyst was also tested for a series of additions of variously substituted arylboronic acids to ketimines **15** and **16** (Table 4). The same trend was observed throughout these experiments, necessitating a fourfold extension of the reaction time compared to the homogeneous environment to achieve comparable yields. In terms of the enantioselectivity of the resulting products, only minimal decreases were observed compared to the homogeneous environment.

Table 4 Substrate scope with **Pd·14**.



#	R^1	R^2	t (h)	Yield (%)	er^1	TON	TOF (h^{-1})
1	*n*-Bu	3-Me	48	99	96:4	6.4	0.13
2	*n*-Bu	4-NHCOCH$_3$	24	97	95:5	6.1	0.26
3	*n*-Bu	4-Me	16	97	96:4	6.2	0.39
4	*n*-Bu	4-OH	8	99	94:6	6.2	0.78
5	*n*-Bu	3,5-diMe	48	98	97:3	6.3	0.13
6	Me	4-OMe	16	98	95:5	6.2	0.39

Reaction in 50 mL test tube open to air, [1]Determined by HPLC with a chiral stationary phase.

3.2.6 Testing of catalytic activity of Pd·14 in a continuous flow system

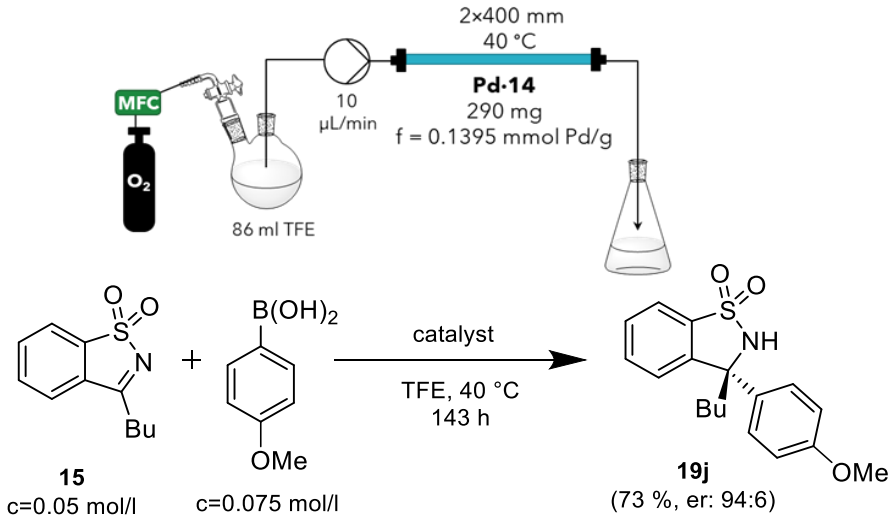


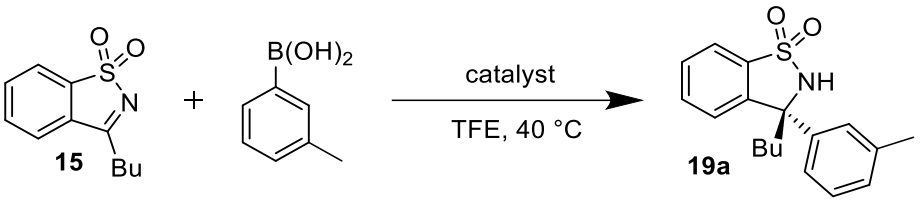
Figure 13 Continuous flow synthesis of **19j**.

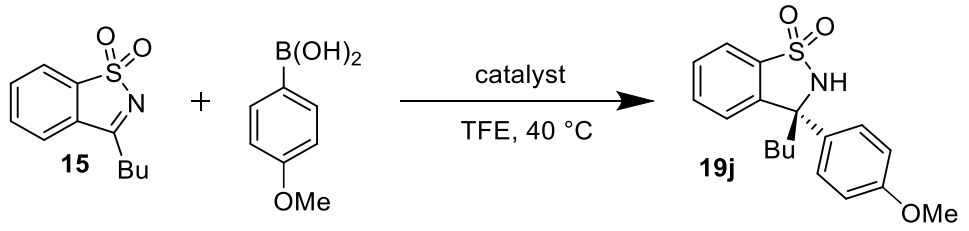
For testing the reactor, the addition of 4-methoxyphenylboronic acid to ketimine **15** was chosen as a model reaction. Flow rate optimization determined a flow rate of 10 µl/min (conc. vl = 50 mmol/l) necessary for >95% conversion. Over 143 hours, the reactor's efficiency was monitored via ^{1}H NMR

spectroscopy, with conversion decreasing after this period, leading to reactor shutdown (Figure 13). During this time, 86 ml of solution of outgoing compounds in TFE passed through the reactor, allowing for the isolation of 1.04 g (73%) of **19j**. Flow setup enhanced process sustainability by reducing TFE consumption, and simple distillation yielded 65% (56 ml) of the original volume with the desired purity.

Comparing the efficiency of the heterogeneous catalysts highlights the importance of using PS-PEG resin for achieving acceptable reactivity in highly polar environments like TFE. This is evident from the unsatisfactory performance of the highly porous catalyst **Pd·13b2**. Increasing the spacer between the polymer matrix and the catalytic center also positively impacts the catalytic reaction. Utilizing TentaGel S NH_2 resin allows for obtaining a competitive heterogeneous catalyst. The highest efficiency of **Pd·14** was observed in a flow setup, showing increased efficiency expressed through TON, albeit with a slight slowdown in reaction rate (TOF) compared to the batch setup (Table 5).

Table 5 Comparison of catalysts for model reaction.



#	Catalyst	er[1]	TON (-)	TOF (h^{-1})
1	[$Pd(TFA)_2$·**7**] (homogeneous system)	97:3	19,2	1,6
2	[**Pd·13a**] (batch rearrangement)	96:4	2,4	0,1
3	[**Pd·13b1**] (batch rearrangement)	97:3	3,7	0,15
4	[**Pd·13b2**] (batch rearrangement	97:3	3,5	0,15
5	[**Pd·14**] (batch rearrangement)	97:4	6,4	0,13
6				
7	[$Pd(TFA)_2$·**7**] (homogeneous system)	96:4	18,9	9,45
8	[**Pd·14**] (batch rearrangement)	93:7	56,56	0,71
9	[**Pd·14**] (continuous flow)	94:6	72.75	0,51

[1]Determined by HPLC with chiral stationary phase.

4 Conclusion

The first part of the dissertation focused on the development of novel sorption materials based on covalently molecularly imprinted polymers for the capturing of 1-naphthylacetic acid (NAA). A new, innovative method of suspension polymerization induced by visible light was employed for polymer preparation. Two different types of polymers were synthesized and tested, differing in the linkage of NAA to the polymer matrix through either an ester or *N*-methylhydroxamate linker. Both types of materials exhibited a high affinity for binding NAA, with the adsorbed NAA being efficiently desorbed and the materials reused up to ten times. Regarding cost-effectiveness and synthetic simplicity, ester-based MIPs are affordable and highly effective sorbents for NAA removal from solutions. The final evaluation involved continuous adsorption of NAA from a solution ($c=10^{-2}$ mol/), which could be repeated at least ten times after saturation and subsequent NAA release from the sorbent. The capacity of the prepared polymer was 69.5 mg NAA per 1 g of polymer. Selectivity testing of the prepared sorption material in a mixture with other plant growth regulators demonstrated a negligible affinity for anthranilic acid and approximately half the capacity for salicylic acid compared to NAA.

The second part of the dissertation introduced an enhanced synthetic route to (*S*)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole. Its utilization as a catalyst for the enantioselective addition of arylboronic acids to cyclic ketimines, showcasing high catalytic activity alongside remarkable enantioselectivity. For the preparation of the heterogeneous catalyst, commercially available PS-PEG resin TentaGel^{TM} S NH_2 were employed, onto which ligand was immobilized via a hydrolytically stable amide linkage. Upon anchoring to the solid support, a fourfold decrease in reaction rate and a slight reduction in enantioselectivity were observed. However, the immobilized catalyst demonstrated notable stability, enabling up to 10 consecutive reaction cycles in a batch system. The successful transition of the reaction to a heterogeneous arrangement facilitated the preparation of a continuous flow reactor, which proved highly advantageous, as the immobilized catalyst achieved even higher turnovers compared to the batch system. These findings provide valuable insights for the development of efficient flow reactors for the continuous synthesis of enantiomerically enriched compounds, such as benzosultams.

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6 List of Students' Published Works

Papers directly related to the presented dissertation thesis

- Kocúrik, M.; Bartáček, J.; Svoboda, J.; Kolská, Z.; Chýlková, J.; & Sedlák, M. Covalent molecularly imprinted polymers for selective adsorption of plant growth stimulator 1-naphthaleneacetic acid. Polymer, 2022, 256, 125189.
- Kocúrik, M.; Bartáček, J.; Drabina, P.; Váňa, J.; Svoboda, J.; Husáková, L.; Finger, V.; Hympánová, M.; Sedlák, M. Immobilization of Trifluoromethyl-Substituted Pyridine-Oxazoline Ligand and Its Application in Asymmetric Continuous Flow Synthesis of Benzosultams. Journal of Organic Chemistry 2023, *88* (21), 15189–15197.

Presented lectures

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- Martin Kocúrik, Jan Bartáček, Jaromíra Chýlková, Martin Vrbický, Miloš Sedlák, Covalent molecularly imprinted polymers for selective adsorption of 1-naphthaleneacetic acid, 11th Barrande-Vltava French-Czech Chemistry Meeting, Dijon, 28 – 30.8. 2022, abstract book p. 53, ISBN: unassigned.
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