1. Title of the project

Understanding Structure-Property Relationships of Metal-Organic Framework Catalysts: A High Throughput Study

2. Abstract

Catalytic reactions offer the opportunity to minimise costs in chemical production by circumventing the use of stoichiometric reagents and diminishing waste management. However, long development times for the discovery and optimisation of catalysts still preclude their application in many cases. In recent years, advances in technology have begun to surmount this issue. A remarkable example is seen in the use of high throughput screening to develop a homogeneous catalyst with high selectivity for the synthesis of Aliskiren (Novartis). Yet, homogeneous catalysts suffer from difficulties in separation and recovery during industrial processes. Heterogeneous catalysts, on the other hand, are much more easily recovered and stable but, until now, finely tuning selectivity and activity of heterogeneous catalysts has been a laborious and time-consuming task.

Metal organic framework (MOFs) catalysts combine the advantages of homogeneous and heterogeneous catalysts. For the first time, the intentional design of solid catalysts, based on ligand immobilisation in confined space is becoming possible and whole libraries of catalytically active MOFs can be quickly synthesised. Currently, no large-scale screening process to evaluate these systems exists. Comprehensive research would, however, enable understanding the relationships between MOF crystal structure, ligand structure and catalytic properties of this material class.

To investigate this connection, I propose an approach to developing high throughput methodology in order to screen metal organic framework libraries based on (chiral) phosphoramidite ligands. Using this approach, firstly a library of organic linker molecules based on phosphoramidite ligands will be synthesised. Secondly, the linkers will be incorporated into a MOF library. Finally, catalytic conversion will be studied in the presented confined space.

3. Applicant(s)

Michael A. Müller
Promotor: Prof. dr. Ben L. Feringa

4. Key Publications of the applicant

N/A

5. FOM research group

N/A

6. Institute

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7. Duration of the project

4 years, starting in 2017

8. Personnel

8.1 - Senior-scientists
B. L. Feringa conceptual guidance 10 %
8.2 - Junior-scientists and technicians
Michael A. Müller executing PhD research 100 %

9. Cost estimates

9.1. Personnel Costs

1 PhD student 4 years k€ 216

9.2. Running budget

Travel and subsistence for experimental PhD student k€ 60

9.3. Equipment

1. BET surface area analysis instrument 30k
(for analysis of MOF library)
2. Liquid handling robotics 60k
(for automated liquid handling)
3. Upgrade for X-Ray diffraction instrument 20k
(enabling automated, sequential analysis)

9.4. Other support

N/A

9.5. Budget summary

Position	2017	2018	2019	2020	2021	TOTAL
Position(s): PhD students	0.25	1	1	1	0.75	4
Personnel (costs in k€):	14	54	54	54	40	216
Running budget	3.75	15	15	15	11.25	60
Equipment	0	60	30	20	0	110
TOTAL(k€)	17.75	99	89	92	51.25	386

10. Research programme

10.1 Introduction and goal of the proposed research

In fine chemical industry, obtaining an enantiomerically enriched target molecule is a major challenge. The presence of the desired (R-) or (S-) configurations at all stereogenic centres is a crucial property. Especially in the pharmaceutical industry, where often one chiral form interacts favourably in physiological environment while the others are inactive or toxic. Consequently, developing catalytic methods to produce single enantiomers is crucial for drug development.

In order to obtain enantiomerically enriched compounds, two major approaches exist. Firstly, enantiomeric resolution, in which one stereo configuration is separated from the other at the end of or during non-stereoselective synthesis. This is expensive and starting from a racemic mixture most often limits the maximum reaction yield of a single stereoconfiguration to 50% and consequently, the other 50% are lost for further synthesis. Secondly, stoichiometric reactions starting from enantioenriched or prochiral compounds. By choosing a stereoselective reaction route, the preferred configuration is formed predominantly. This approach generally produces a higher yield of the desired compound but is chemically more difficult to achieve and expensive, chiral reagents are needed. Additionally, unwanted side products are often generated and have to be disposed of. The resulting costs could be avoided if existing catalytic reactions were applied. That, however, requires optimisation of asymmetric catalysts for individual reactions which are still difficult to do in a for industry relevant time frame.[1]

One example of a successful approach that led to industrial application in recent years is the use of an asymmetric, homogeneous catalyst based on phosphoramidite ligands for a hydrogenation reaction in the total synthesis of aliskiren.[2] The key to success in this example laid in easily modifiable BINOL-based phosphoramidite ligands[3] and the high throughput screening approach.[1] Systematic testing and optimisation, coupled with accurate analysis of products and conditions allow for rapid optimisation of asymmetric catalysts. This approach allows producing enantiopure products in a financially more viable manner. This comprises already an enormous step towards enabling usage of this homogeneous catalytic system in fine chemical industry. While successful in their own right, homogeneous catalysts are often difficult to separate and recover from solution. Consequently, large investments to purify the reaction product and recover the catalyst are necessary. This often is done on industrial scale by expensive chiral high performance liquid chromatography (HPLC). Furthermore, homogeneous catalysts tend to leech toxic

metal ions during synthesis into the product phase. In the majority of cases, heterogeneous catalysts are preferred due to their ease of separation, their stability and higher resistance to ageing processes. Additionally, often, existing industrial facilities for heterogeneous catalytic processes can be repurposed to be used in another. For homogeneous catalytic processes, this is rarely possible. Heterogenization, also called immobilisation, of homogeneous catalysts, is, therefore, a popular approach to making catalytic reactions even more attractive. Phosphoramidite immobilisation on Polystyrene and Merrifield resins has been attempted before by the research groups of Waldmann and Feringa but suffered from substantial loss in enantioselectivity.[4,5] MOFs constitute another approach.

I am currently working on preliminary research for using BINOL-based phosphoramidite ligands as linkers in MOFs. During my current project, I will demonstrate the effectiveness of MOFs based on these versatile ligands in catalysis. Synthesis proceeds analogously to the BINOL MOFs that have been reported in literature. There, BINOL has been incorporated into catalytically active MOFs using Zn^{2+}, Cd^{2+}, Cu^{2+} and Re^{+} as metal centres.[6,7,8] While being based on these systems, our newly developed MOFs surpass them by far in catalytic scope. BINOL-based phosphoramidite MOFs are unknown materials with remarkable prospects in asymmetric catalysis. By exploiting the highly modular synthesis of this well-understood ligand, an extensive library can be easily generated and later converted into MOFs. This property is unprecedented in MOF catalysis.[9,10] In combination with their versatility in homogeneous catalysis,[11] a powerful class of immobilised catalysts can be developed. Immobilisation of ligands for catalysis in MOF structures results in confined space formation, often leading to an increased catalytic activity compared to their homogeneous analogues.[6] How an increase of activity arises is a crucial question in MOF catalysis that is still unanswered. However, it is known that numerous parameters, like crystal morphology, pore size, surface area, etc. constitute the MOF catalytic sites and thereby influence catalytic properties.[12] Engineering the MOF catalytic site using the large parameter space is much more precise than improving any homogeneous system. As a result, the heterogeneous catalyst has the potential to surpass the properties of its homogeneous analogue in both conversion and stereoselectivity. BINOL-based phosphoramidites and already show a remarkable ability to control over catalytic sites in homogeneous catalysts. Using BINOL-based phosphoramidites in MOFs, the exerted control over the catalytic sites is expected to be even more pronounced. Consequently, this ligand class is especially well suited to be used as linkers in MOFs for asymmetric catalysis, compared to many other less adjustable ligands.[9,10,13]

However, for industrial applications, short development times of MOF catalysts are essential. Therefore, a parallelized process to optimise catalytic properties of MOFs is crucial.[14] Automation of the catalyst optimisation incentivises this further by not only saving time but also man-hours and thereby salary costs. The high throughput technology to synthesise phosphoramidite and MOF libraries exist but have never been combined. It is a major step to bring both together and establish a first example for the rapid generation and analysis of MOF-based chiral catalysts for application in fine chemical industry.
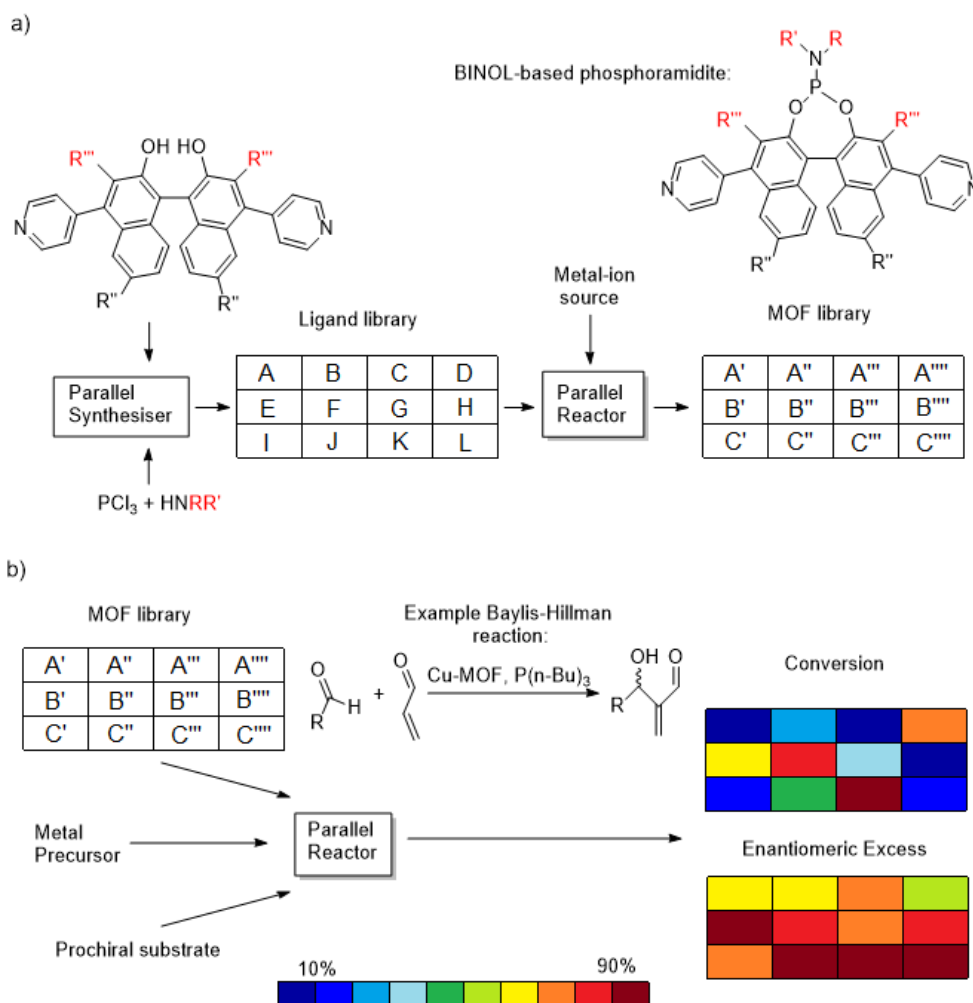
Goal of the proposed research

Figure 1: *a) Based on a BINOL precursor, a ligand library will be synthesised in a parallel synthesiser. The obtained ligands will upon addition of a metal ion source be used as linkers in the synthesis to MOFs. By varying growth conditions, the same linker will be used to create MOFs with different 3D crystal structures. b) Then, the MOFs in the library are used as the catalysts in a reaction, and conversion, as well as enantiomeric excess, will be recorded for each library entry. Structure-property relationships are therefrom observed.*

During the proposed project, I will optimise methods for both BINOL-based phosphoramidite linker and MOF synthesis regarding quality and production time as described in figure 1. Furthermore, I will improve characterization and standardise data analysis in order to establish a high throughput approach. This will be done by developing a sequential process that starts with the synthesis of a BINOL-based organic linker precursor. The ligand parameters that will be screened are the functionality at the amino group and the BINOL's 3,3'-position (marked red in fig. 1) which have proven to greatly influence conversion and enantiomeric excess in the homogeneous analogue of the catalyst.[6] In a first assessment, the differences in catalytic properties between selected homogeneous and heterogeneous catalyst analogues are evaluated. Subsequently, the precursor will be converted to an extensive phosphoramidite library. From this library, by using different growth conditions, a MOF-crystal library will be produced. For this,

I propose to screen temperature, linker concentration, pH, solvent, type and source of metal ions in MOF library synthesis. The phosphoramidite based MOF library will then be used to screen a so-called Baylis-Hillman reaction, a C-C bond formation reaction. Other reactions that will be investigated are asymmetric hydrogenation reactions. In between each step, the reaction products will be purified and analysed. One focus will be investigating industry relevant properties, like re-usability, metal ion leaching, ageing, turnover number, turnover frequency and therewith connected space-time yield. This novel approach connects already existing high throughput methods of both phosphoramidite and MOF screening with the research on immobilising homogeneous ligands in MOFs. From these insights into the connection between MOF morphology and catalysis will be gathered. This will yield, a to this point unprecedented amount of data, elucidating the relationship between MOF structure and its catalytic activity. In principle, the obtained knowledge of structure-property relationships can expand it's scope to other organic ligands as well. This effort will be supported by the team's prior experience with the high throughput screening of homogeneous phosphoramidite and experience in synthesising MOFs.

The remainder of the research program is organised as follows:

Section 10.2 discusses state-of-the-art and the scientific importance;

Section 10.3 introduces the basics of metal organic frameworks as catalysts;

Section 10.4 further introduces the group of phosphoramidites as privileged ligands for catalysis;

Section 10.5 summarizes the status of related research in my team;

Section 10.6 describes the new experiments that I propose here for the high throughput screening;

Section 10.7 ends with some final remarks and an outlook

10.2 State-of-the-art and Scientific Importance

Homogeneous phosphoramidite catalysts have already seen commercial use for years and BINOL-based library generation is well established in literature. Their high throughput screening for homogeneous catalysts is well developed and sold as a service by DSM.[2] Reactions that are catalysed by this remarkably versatile group of catalysts are for example C-C bond formation reactions and asymmetric hydrogenation.[11] An application for phosphoramidites that has not been investigated is their use as linkers in MOFs. However, BINOL itself has been incorporated into MOFs via carboxyl and pyridine functional groups. In these MOFs assemblies with Cu-, Zn-, Re- and Cd-Ions have been reported in literature.[6,7] MOFs, in general, have been in development for several decades. Their research focus lied mostly on gas storage and separation. Some MOF types are even produced on industrial scale (BASF). Compared to that, MOFs as asymmetric catalysts is a young field which has seen a massive rise in interest in the last decade.[8,15,16] Yet, to the best of my knowledge, no commercialization of a MOF catalyst has been realised yet. One reason is their thermal stability which is, with decomposition temperatures typically around 200-300°C, relatively low compared to the more widely applied zeolites. Currently, the main employer of catalysts is the bulk chemical industry where processes need higher thermal stability. Consequently, many simple MOFs cannot be used in catalysis for this
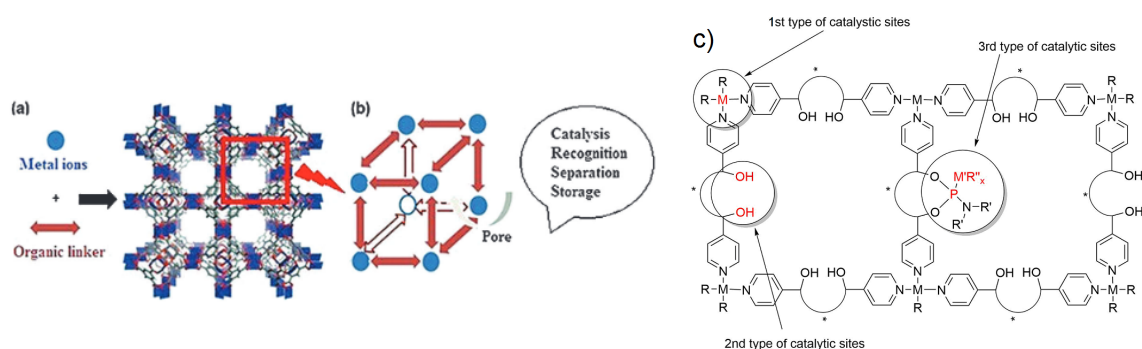
Figure 2: *a) The structure of a typical MOF. b) simplified illustration of a MOF c) The three types of catalytic sites in a metal-organic framework: the connecting metal centre, the organic linker, the post-synthetically modified organic linker, i.e. an immobilised homogeneous catalyst.*[13]

reason. This might change, however, as the development of secondary building units in recent years increased MOF stability significantly. An increase in decomposition temperatures of individual MOFs up to 500 or even 600°C can be achieved. Another reason for the not yet realised commercialization is the time needed to research catalysts for the fine chemical industry. There, research time replaced lower thermal stabilities as limiting factor since many processes are performed below 200 or even 100°C.

10.3 Metal-Organic Frameworks as catalysts

Metal organic frameworks are sometimes called designer solids due to the ease with which their properties can be modulated. In this material class, organic linker molecules are connected networks by coordination bonds with metals via functionalized end groups, such as carboxylic groups or pyridines. By building numerous coordination bonds an extended network forms a porous crystal. An example can be seen in figure 2a. The limitless choice of organic linker molecules leads to a limitless amount of possible MOFs. By choosing metal salt, organic linker and crystal growth conditions correctly, in principle, a porous solid-state material with precisely engineered properties can be produced. Consequently, research on MOFs as catalysts and MOFs in general and has been growing steadily in the last years. The sheer amount of possible permutations, however, is its own weakness. Initial results are promising, but optimising MOFs proves a challenge due to their enormous structural variability. In certain fields like gas storage, this can be overcome by employing in-silico screening. The MOF is synthesised only after the MOF structure with wanted properties (crystal structure, organic linker and metal ion) has been calculated. Due to the needed computational power, this approach can only be used for simple systems.

Consequently, in catalysis, this approach proves difficult due to the matter's complexity. Dynamics and precise molecular interactions are still too demanding to compute precisely. A promising alternative is to find catalysts by high throughput screening. So far literature knows no fully automated process from synthesis to analysis in this field.

In catalysis, literature focuses on individual MOFs. In summarising reviews, a direct com-

parison is difficult due to differences in research focus of different research groups and the exemplary character of observed properties. The proposed research enables to make statements about general characteristics and connections between metal ions choice, organic linker properties and different crystal morphologies. Currently, research focuses on 3 major ways in which MOFs catalyse reactions. The numbered types of catalytic sites can be seen in Figure 2b.

1) The metal centre that connects the organic linker is unsaturated and thereby reactive. The type of linker plays only a minor role. 2) The organic linker directly catalyses the reaction without much influence of the metal ion, except for a modulation of energy levels. 3) The organic linker is used as ligand for a homogeneous catalyst that is thereby immobilised in the MOF pores.[13]

The third catalysis type will be used in the proposed research. However, all types of MOF catalysts can in principle be investigated by this approach. By adapting technology from MOF high throughput screening of growth conditions to other fields, an immense increase in investigated MOFs per time is made possible. MOFs are generally grown in a solvothermal process and characterised by X-ray diffraction (XRD) experiments, as well as Brunauer–Emmett–Teller (BET) theory gas adsorption experiments and scanning electron microscopy (SEM).

10.4 Phosphoramidites as Privileged Ligands

Phosphoramidites are monodentate ligands, synthesised by the reaction of two hydroxyl groups with phosphorus trichloride and any primary or secondary amine. Therefore, the reaction is highly modular and it is easy to generate a ligand library.[17] Consequently, this type of ligand is especially suitable for high throughput screening of homogeneous catalysts. One of the most researched phosphoramidites is based on BINOL (Fig. 3) which is cheap compared to many alternative enantiopure starting materials. Furthermore, steric effects of the naphthalene backbone constitute an asymmetric environment suited to the formation of a particular stereoconfiguration. Phosphoramidites as a ligand class in homogeneous catalysis are well established.[2] Often two phosphoramidite ligands per coordination complex are used. These two can be the same phosphoramidite or have different amino groups.[2] However, also homogeneous complexes with only one phosphoramidite have been reported in the literature where other achiral ligands in the catalyst improved enantioselectivity.[14] This ligand class is used in asymmetric hydrogenation and carbon-carbon bond formation.[11] The relations between structure, electronic properties and their catalytic behaviour is well understood. In BINOL-based ligands especially the 3,3'-substitution pattern influences enantiomeric excess drastically for hydrogenation reactions.[6] Their wide use is evident by the screening service of 96 phosphoramidites for hydrogenation reactions offered by DSM.[2]

In earlier research by Feringa and Waldmann,[4,5] the immobilisation resulted in the decrease of enantiomeric excess from above 95% to 84% at best. This result is typical for the immobilisation via functional groups to surfaces since interactions with the substrate lead the catalytic sites to become less well-defined. The immobilisation in MOFs, in contrast, has shown the potential to enhance enantiomeric excess in several cases.[6] The rigidity of the organic linkers in this material contributes to uniform catalytic sites, as observed in homogeneous catalysts. To the
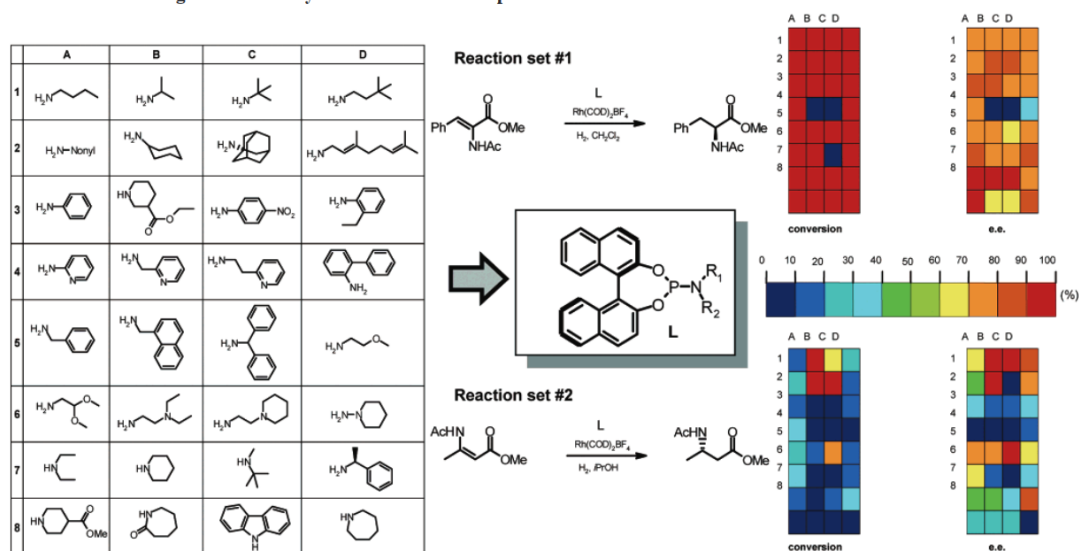
Figure 3: *The principle behind the priorly developed homogeneous screening process. In the left box the used amine substitution is given while on the right the conversion and enantiomeric excess for the associated reaction is indicated.[2]*

best of my knowledge, a MOF has never before been intentionally designed to increase enantiomeric excess for a preselected reaction. While improvement of enantiomeric excess does not always occur, the understanding behind the process responsible for its enhancement is of major interest for the catalytic community. Enantiomeric excess results will be obtained by chiral gas-liquid chromatography (GLC) while phosphoramidites will be characterised by [1]H-nuclear magnetic resonance (NMR) spectroscopy.

10.5 Status of Research in Group

The group has been actively involved in the development of BINOL-based phosphoramidites. After reporting decreased enantioselectivity when immobilising phosphoramidites on polymer beads an alternative route is now investigated. New MOFs using BINOL-based phosphoramidites as linkers are currently researched. The expertise of which has been developed in the context of the group's smart materials subgroup. Linker synthesis is ongoing and, supported by the group's experience, progressing smoothly. The next step comprises, the first reported growth of BINOL-based phosphoramidite MOFs. Afterwards, their potential in stereoselective, catalytic C-C bond formation at the hand of a so-called chiral Baylis-Hillman reaction is investigated. Additionally, their use in asymmetric hydrogenation will be explored. The goal of the research is to compare selected phosphoramidite linker molecules in heterogeneous and homogeneous phase regarding yield and stereoselectivity, as well as characterising the used MOFs. Surface area, metal ion leaching, 3D structure are investigated. At this moment, the synthesis of the linker molecule has been almost achieved. This is the most time-consuming step. Approximately, the midway point of the preliminary studies demonstrating the feasibility of our designed linkers in MOF catalysis has been reached.

10.6 Time Line

To optimize the high throughput screening, methods that a) can be utilized in a high throughput approach, b) yield the information we need to continue with the next step, c) yield the information that is interesting to industry, d) take the least amount of time and e) are cost effective, are investigated. Throughout the first two years, more general properties like thermal stability and surface area are measured and compared to other MOFs. Further effects of a) functional groups and b) MOF formation conditions on these properties will be investigated.

In the first year, the PhD student will establish the organic linker library by reaction of various primary and secondary amines with the synthesised precursor. Their catalytic properties in homogeneous phase will be characterised for later comparison.

The second year is dedicated to using various phosphoramidite linkers to synthesise an extended MOF library and to measure general properties of the latter. For this, methods like thermogravimetric analysis, XRD and scanning electron microscopy will be used. Then experiences from high-throughput experimentation in literature will be transferred to establish the high-throughput synthesis of phosphoramidites and MOFs.

In the third year, the obtained MOF framework library is taken and used to catalyse different asymmetric Baylis-Hillman and hydrogenation reactions. For this in the group existing high throughput reaction vessels will be used to independently vary pressure, temperature and catalyst/substrate concentration. Chiral GLC will then be used to investigate conversion and enantiomeric excess. This, coupled with prior XRD studies, will yield information on structure-property relations.

In the fourth year, potential commercialization of the process will be investigated. Processes are standardised that are used for analysis, once a "hit" on a specific catalyst is observed. Industry relevant properties, like re-usability, metal ion leaching, ageing, turnover number, turnover frequency and therewith connected space time yield will be measured.

10.7 Final Remarks and Outlook

1) How phosphoramidites can be incorporated into MOFs is still investigated. It may seem early to propose the next step already. However, existing literature suggests the success of the fundamental approach. The BINOL linker has been synthesised and incorporated into MOFs. Consequently, it was possible to use post modification to convert the BINOL group. Whether the presence of phosphoramidites will influence MOF growth has still to be investigated. How and if the pyridine group that is linked to the naphthalene subgroup effects the synthesis of phosphoramidites is equally unknown. How addition of the pyridine affects homogeneous catalysis will be investigated. Since the position of pyridine is at the 4,4' position, no major influence on catalytic properties is expected. Type 3 catalytic MOFs have been reported in the literature. Phosphorous atoms are unlikely to interfere with the MOF formation process. No MOF growth based on phosphorous-metal centre interactions has been reported in literature.

2) Upon success of this research, commercial use of the developed technology will be investigated. The development and production of specially engineered heterogeneous catalysts for

the fine chemical industry is a promising market. Existing applications of homogeneous phosphoramidites in the industry indicate a potential market for their heterogeneous analogues. If analysis of a business venture is deemed financially sound, a spin-off of the university of Groningen could follow.

11. Infrastructure and collaborations

11.1 Host group

The group of Ben Feringa at the University of Groningen has performed cutting-edge research for years. Next, to the renowned work on molecular motors, catalysis is the second backbone of the group. Their work on phosphoramidites represents a major contribution to the field. In recent years, exploiting fundamental knowledge in these fields to investigate functional (nano-)materials has become another focus. In this context, the group developed expertise in the synthesis and analysis of MOFs. The proposed research continues a program in confined space catalysis and extends a prior project. Our novel work on incorporating phosphoramidites into MOFs makes us leading experts on this industrially, relevant topic.

11.2 Sample Materials

Currently, synthesis of the organic linker is performed and optimisation of the last step is proceeding. The first MOF is expected to be obtained in spring of 2017. Afterwards, the synthesis will be optimised and extensive sample characterization by XRD, TGA, catalytic studies, etc will be conducted. Findings will be published in the summer of 2017.

11.3 Instruments

The host group possesses instruments for TGA, GLC, high-throughput catalysis (Biotage 8 vessel Endeavor multi-reactor), and other common analyses (FT-IR, UV/Vis, NMR, MS, HPLC, elemental analysis). However, instruments have to be upgraded to be compatible for high throughput screening. Currently, BET surface area measurement equipment, automated liquid handling infrastructure and an application to enable high throughput XRD measurements are necessary investments, as described in section 9.3 cost estimates for equipment.

11.4 Other facilities and existing resources

From collaborations within the Zernike and Stratingh Institute, instruments including XRD, SEM and Raman spectroscopy are accessible.

11.5 Relevant collaborations

N/A

12. Application perspective in industry, other disciplines or society

The implications of this research are affecting catalytic research and applications at large. Fine chemical companies can use the developed MOFs to screen catalysts for their syntheses. The approach is quick, cheap and circumvents costs encountered in stoichiometric chemistry as the alternative. Using the developed high-throughput methodology for catalyst optimisation, catalysts with high selectivity and activity can be found quickly. Expensive chiral reagents or waste management are no longer needed since more atom economic reactions become accessible. Less environmental pollution is the result. Upon initial success, even incorporating two different ligands into the same MOFs becomes conceivable. These can potentially catalyse different reactions while exploiting the close proximity of catalytic sites for efficient cascade reactions. For example, C-C bond formation reactions can be coupled to asymmetric hydrogenation. Further, the proposed research has the potential to affect the field of porous organic networks. The high throughput approach can be modified to synthesise various covalent organic frameworks (COFs). Currently, it is still difficult to discover new COFs. An integrated high-throughput approach from synthesis to study of catalytic properties would constitute a major assistance in developing this field. These materials are generally more stable than MOFs. Consequently, they are interesting for applications in bulk chemical industry, where the instability of MOFs poses their major limitation. Moreover, the high-throughput approach can be adapted to other fields of heterogeneous catalysis research. Rapid screening of relations between nanoparticles properties like size, morphology, etc. and enantiomeric excess, as well as activity, becomes possible. For example, systematic screening of industrially relevant catalyst poisoning followed by subsequent reactivation experiments becomes more efficient. In all of the above applications, automation and parallelization of a large portion of the research reduce the number of researchers needed to conduct the experiments. Therefore reducing the costs of research institutes.

13. Data Mangement

All reported syntheses will be reproducible and general trends observed in MOF catalysis will be transferable to other systems. Furthermore, MOF samples will be stored and can be reused at the University of Groningen. During the project, digital data will be stored locally (national level) at the university Y-drive. The data will be stored as read-only. Nothing will be deleted and raw data will be saved with analysing documents. Physical data will be stored in the group's cooling room. Furthermore, lab journals on experimental procedure will be kept in paper form in the corresponding office of the PhD student. Longterm, the data will be saved in the same way. Access lies with Prof. Ben Feringa, and, in the case of Prof. Feringa's retirement, the director of the Stratingh institute. Access to the data during the project will be administered by Prof. Ben Feringa, and, in the case of his retirement, the director of the Stratingh institute. All facilities for data storage are available.

14. FOM Subfield classification

NANO

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