



-Striving for Sustainable Organocatalysis-

Design and Characterization of Silica Monolith Supports and
Application of Chitosan as a Solid Catalyst

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"Indeed, in the creation of the heavens and the earth, and the alternation of the night and day, and the [great] ships which sail through the sea with that which benefits people, and what Allah has sent down from the sky of rain, giving life thereby to the earth after its lifelessness and dispersing therein every [kind of] moving creature, and [His] directing of the winds and clouds controlled between the heaven and the earth, are signs for a people who use reason."

Al Quran (2:164)

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Abstract

Sustainable organocatalysis requires heterogeneous catalytic systems that are efficient, reusable, and aligned with the principles of sustainability. This thesis explores two complementary materials aimed at achieving this balance: the rational engineering of hierarchically porous silica monolith support and the utilization of renewable chitosan biopolymers as solid catalysts. Together, these studies illustrate how rational control over material structure and intrinsic functionality can be harnessed to simultaneously enhance catalytic performance and align with environmental sustainability.

In **Publication 1**, the focus was on the structural evolution of mesoporosity in hierarchically porous silica monoliths prepared by the Nakanishi method. The study placed particular emphasis on advanced physisorption analyses using argon (87 K) and nitrogen (77 K), complemented by hysteresis scanning, to unravel the development of the mesoporous network under varying hydrothermal treatment temperatures (HTTs). These analyses revealed a systematic expansion of mesopores (8 to 25 nm) while maintaining constant pore volume, indicating a dissolution-reprecipitation mechanism that governs mesopore formation and connectivity. The work provided fundamental insights into how hydrothermal conditions shape mesoporous network, diffusion, and accessibility, establishing design principles for tailoring monoliths for catalytic and separation applications.

In **Publication 2**, chitosan was studied as a renewable heterogeneous organocatalyst for Knoevenagel condensations among various benzaldehydes and ethyl cyanoacetate. High yields were achieved under mild conditions, with efficient catalyst and solvent reuse across multiple cycles. Importantly, the study demonstrated that renewability alone is not enough; optimization of overall process through mild conditions, energy efficiency, and recyclability can make a genuine impact on sustainable synthesis. The approach was successfully optimized to the gram-scale synthesis of an Atorvastatin intermediate, underlining its practical relevance.

Together, these publications highlight two distinct but complementary strategies: the controlled engineering of pore structures in silica monoliths for applications such as continuous-flow catalysis and the dynamic functionality of chitosan as a green catalyst. Both approaches contribute to the broader goal of developing efficient, robust, and truly sustainable organocatalytic systems.

Zusammenfassung

Nachhaltige heterogene Organokatalyse erfordert Katalysatorsysteme, die effizient, wiederverwendbar und im Einklang mit den Prinzipien der grünen Chemie sind. Diese Arbeit untersucht zwei komplementäre Materialien, die darauf abzielen, dieses Gleichgewicht zu erreichen: die systematische Gestaltung von hierarchisch porösen Trägermaterialien aus Silikamonolithen und die Nutzung erneuerbarer Chitosan-Biopolymere als Feststoffkatalysatoren. Zusammen veranschaulichen diese Studien, wie eine gezielte Kontrolle über Materialstruktur und intrinsische Funktionalität genutzt werden kann, um sowohl die katalytische Leistung zu verbessern, als auch die Umweltverträglichkeit zu gewährleisten.

Publikation 1 legt den Fokus auf die strukturelle Entwicklung der Mesoporosität in hierarchisch porösen Silika-Monolithen, die nach der Nakanishi-Methode hergestellt wurden. Die Studie legt besonderen Wert auf fortgeschrittene Physisorptionsanalysen mit Argon (87 K) und Stickstoff (77 K), ergänzt durch Hysteresescans, um die Entwicklung des mesoporösen Netzwerks unter verschiedenen hydrothermalen Behandlungstemperaturen (HTTs) zu entschlüsseln. Diese Analysen zeigen eine systematische Erweiterung der Mesoporen von 8 auf 25 nm bei gleichbleibendem Porenvolumen, was auf einen Auflösungs-Ausfällungs-Mechanismus hinweist, der die Bildung und Konnektivität der Mesoporen steuert. Die Arbeit liefert grundlegende Einblicke, wie hydrothermale Bedingungen das mesoporöse Netzwerk, die Diffusion und die Zugänglichkeit beeinflussen, und etabliert Designprinzipien zur Anpassung von Monolithen für katalytische und Trennungsanwendungen.

In **Publikation 2** wurde Chitosan als erneuerbarer heterogener Organokatalysator für Knoevenagel-Kondensationen zwischen verschiedenen Benzaldehyden und Ethylecyanoacetat untersucht. Unter milden Bedingungen wurden hohe Ausbeuten erzielt, wobei Katalysator und Lösungsmittel über mehrere Zyklen effizient wiederverwendet werden konnten. Wichtig ist, dass die Erneuerbarkeit allein nicht ausreicht; die Optimierung des Gesamtprozesses durch milde Bedingungen, Energieeffizienz und Recyclingfähigkeit kann einen echten Beitrag zu nachhaltiger Synthese leisten. Die Synthese eines Atorvastatin-Intermediats wurde erfolgreich im Grammmaßstab optimiert, was seine praktische Relevanz unterstreicht.

Zusammen heben diese Veröffentlichungen zwei unterschiedliche, aber komplementäre Strategien hervor: die kontrollierte Gestaltung der Porenstruktur in Silika-Monolithen für Anwendungen wie

die kontinuierliche Flusskatalyse und die dynamische Funktionalität von Chitosan als grünen Katalysator. Beide Ansätze tragen zum übergeordneten Ziel bei, effiziente, robuste und nachhaltige organokatalytische Systeme zu entwickeln.

Publications

Publication 1:

Ali, U., Meinus, R., Turke, K., Schreiner, P.R. and Smarsly, B.M., Tuning the Mesopore Network in Meso-Macroporous Silica Monoliths by Hydrothermal Treatment—A Physisorption Study. *Langmuir*. **2025**, 41, 22, 13845 - 13859

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Publication 2:

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Introduction

The increasing global emphasis on sustainability has placed chemical research at a crucial intersection, where efficiency, innovation, and environmental responsibility must be coordinated.¹ In this regard, the framework of green chemistry, first formalized by Anastas and Warner in 1998, provides guiding principles for designing chemical processes and products that minimize or eliminate hazardous substances. The 12 Principles of Green Chemistry involve strategies such as prevention of waste, atom economy, less hazardous chemical syntheses, designing safer chemicals, safer solvents and auxiliaries, energy efficiency, use of renewable feedstocks, reduction of derivatives, catalysis, design for degradation, real-time analysis for pollution prevention, and inherently safer chemistry for accident prevention.² Among these, catalysis holds a particularly central role. Catalysis, the acceleration of a chemical reaction by a substance that is not consumed during the process,³ is fundamental to nearly all areas of modern life. It is estimated that around 85 to 90 % of all chemical processes are catalyzed, and approximately 85 percent of all manufactured products involve catalysis at some stage of their production chain. The economic and societal impact is immense, with catalytic technologies contributing an estimated 30 to 40 percent of global GDP.⁴ By lowering activation barriers and steering reaction pathways, catalytic processes enable efficient and selective transformations under milder, more resource-conscious conditions, addressing several principles of green chemistry simultaneously. However, as sustainability becomes a defining criterion in chemical innovation, catalysis must evolve beyond efficiency alone, integrating renewability, safety, and environmental compatibility into its design and application. Thus, development of sustainable catalysis requires balancing efficiency with broader considerations such as catalyst origin, toxicity, reusability, and environmental impact.^{5, 6}

Homogeneous catalysts, typically dissolved in the reaction medium, offer well-defined active sites and excellent selectivity. However, their practical drawbacks, such as difficulties in separation, potential contamination of products, and the frequent use of toxic solvents limit large-scale applicability. By contrast, heterogeneous catalysts, in which the active phase is distinct from the reaction medium, provide operational simplicity, easy recovery, and compatibility with continuous-flow technologies.⁷⁻¹⁰ For decades, metal-based catalysts have dominated both categories. Transition metals such as palladium¹¹, platinum¹², rhodium¹³, and nickel¹⁴ have enabled key reactions ranging from hydrogenation¹⁵ to cross-coupling¹⁶, profoundly shaping synthetic chemistry and industrial practice. However, reliance on scarce or precious metals, concerns about

toxicity, and the energy-intensive nature of their extraction and purification pose significant sustainability challenges. These drawbacks highlight the need for alternative catalytic models that balance performance with environmental compatibility.

In this context, organocatalysis has emerged as a particularly promising approach. Small, metal-free organic molecules, often derived from natural or renewable sources can promote a wide array of synthetically relevant reactions.¹⁷⁻²⁶ The acknowledgement of this field with the 2021 Nobel Prize in Chemistry highlighted its growing importance.^{27, 28} However, the reality of industrial deployment for organocatalysts is more complex. Most organocatalysts are employed homogeneously, which complicates recovery and necessitates relatively high loadings (often in the 10-30 mol% range).^{2, 19, 20, 29} This increases costs, reduces atom efficiency, and reduces process sustainability.

To address the limitations of homogeneous organocatalysts, increasing attention has been directed toward immobilization strategies, where the catalyst is either anchored onto or incorporated within a support material. Immobilization combines the molecular precision of homogeneous systems with the operational advantages of heterogeneous catalysis, enabling easier recovery, improved reusability, and often enhanced stability under reaction conditions.^{30, 31} In such systems, the design of the support material becomes just as critical as the catalyst itself: surface chemistry dictates anchoring interactions and potential cooperative effects, and mechanical robustness ensures durability. Mesoporous materials such as silica have been widely employed for these purposes, as their tunable pore networks can be optimized to balance catalyst loading with substrate diffusion qualities particularly valuable in advanced applications like flow chemistry.³²⁻³⁵ Nevertheless, designing such a catalytic system that match the activity and selectivity of their homogeneous counterparts remains an ongoing challenge. While synthetic supports like porous silica offer structural control, biopolymers with functionalizable surface groups offers more sustainable alternatives that combine functionality with environmental compatibility.³⁶⁻³⁸ Renewable biopolymers such as chitosan exemplify this trend, providing not only a stable support framework but also intrinsic catalytic activity through amine functional group.³⁹⁻⁴³ This dual functionality promotes the use of renewable feedstocks, safer chemical syntheses by avoiding toxic metals, and waste prevention through reuse, thereby simultaneously addressing multiple principles of green chemistry and highlighting the integration of material design with sustainable catalysis.

This study is therefore structured around two complementary material systems: engineered silica monoliths, which provide the highly porous scaffolds necessary to fundamentally optimize mass transfer in continuous-flow catalytic systems; and the biopolymer chitosan, which brings a highly active, reusable, and non-toxic solid support and/or organocatalyst. In this context, **Publication 1** focuses on the tuning of the mesopore network in meso-macroporous silica monoliths through adjusting the hydrothermal treatment temperature (HTT) and understanding its effects using physisorption studies to reveal the mesopore size and connectivity. The latter is crucial for achieving an optimal balance between high surface area for catalyst loading, efficient mass transfer, and substrate accessibility, while simultaneously minimizing diffusion limitations and pore blocking - a principle that is equally vital in chromatography to ensure sharp peaks and effective analyte interactions. Silica monoliths were synthesized via the K. Nakanishi method, which combines sol-gel chemistry with phase separation to produce hierarchically porous columns, and a range of HTTs (80 to 110 °C) was explored to systematically alter mesopore dimensions and connectivity. Physisorption using Ar (87 K) and N₂ (77 K), complemented by advanced hysteresis scanning provided detailed insights into the effects of HTT on mesopore size, connectivity, and network architecture. Overall, this study provides a rational framework for tailoring silica monoliths for optimized diffusion characteristics for catalytic and separation applications. **Publication 2** focuses on the utilization of chitosan as a sustainable heterogeneous organocatalyst. This study was driven by the broader question of whether renewability alone ensures sustainability in catalysis, or whether a truly sustainable process must also integrate the principles of green chemistry. To address this, raw chitosan was employed as a base catalyst for one-pot Knoevenagel condensations between various benzaldehydes and ethyl cyanoacetate. The reaction parameters were optimized to fulfilled several principles of green chemistry, employing non-toxic solvents, low reaction temperatures, and efficient recovery of both catalyst and solvent. Furthermore, the approach was successfully extended to the gram-scale synthesis of a key Atorvastatin intermediate [4-methyl-3-oxo-N-phenyl-2-(phenylmethylene)-pentanamide], demonstrating the industrial relevance of catalytic system. The study also investigated the dynamic structural behavior of chitosan, revealing that its water-binding and swelling properties significantly enhance catalytic activity by removing water by-products and increasing access to active sites.

Accordingly, in this thesis, I discuss two complementary material systems. The first consists of synthetically engineered supports, exemplified by hierarchically porous silica monoliths, with

emphasis on their synthesis mechanisms and the in-depth characterization of their porous structures using state-of-the-art physisorption techniques. The second involves bio-derived polymeric systems, represented by chitosan, where the discussion focuses on its chemical nature, its role as a support material, and its intrinsic catalytic activity. Together, these examples illustrate how a deep understanding of material design can be strategically employed to bridge structural control with environmental compatibility in the development of sustainable catalytic systems.

1. Background

2.1 Support Materials for Heterogeneous Organocatalysis

A support in heterogeneous organocatalysis refers to a material that provides a stable, structured environment for the immobilization or incorporation of organocatalytic species. It serves as a physical matrix that anchors the active organic catalyst, ensuring its spatial separation from the reaction medium while maintaining accessibility to reactants. The design and selection of a support material is of prime importance when used for hosting organocatalytic species. A good support material should not compromise on catalytic activity and selectivity. The selection of a catalytic support plays a key role in determining not only the stability and reusability of catalyst but also its accessibility, diffusion behavior and compatibility with various media. To achieve these properties, it is important to integrate material science with molecular catalyst design, enabling the development of tailored catalytic systems optimized for specific synthetic tasks. Support materials for heterogeneous organocatalysts can be broadly classified based on their chemical nature and origin, including materials like porous silica³², zeolites^{44, 45}, carbon-based supports⁴⁶, synthetic polymers such as polystyrene and polyacrylates⁴⁷, and naturally derived biopolymers like cellulose⁴⁸, chitosan⁴⁹, alginates⁵⁰, lignin⁵¹, and starch⁵² etc. While these classes offer diverse surface properties, stability, and functionalization options, they can be broadly categorized in terms of sustainability into two major types: synthetically engineered supports, which provide high surface area, tunable porosity, and chemical robustness but depend on non-renewable resources, and biopolymer-based supports, derived from renewable natural sources, which offer abundant functional groups, biocompatibility, and a lower environmental impact. Nevertheless, natural biopolymers also present certain limitations when used as supports for organocatalysts, including low surface area, limited mechanical and thermal stability, and batch-to-batch variability arising from the diversity of natural sources.

2.2 Synthetically Engineered Support Materials

Synthetically engineered supports are materials deliberately designed and synthesized to possess well-defined structural properties. By precisely controlling reaction parameters during their preparation, such as temperature, pH, solvent composition, and aging or treatment conditions, the morphology, porosity, and surface functionality of these supports can be finely tuned. These supports include porous silica (e.g., Mobile Composition of Matter No.41 or MCM-41, Santa Barbara Amorphous-15 or SBA-15, silica particles, and silica monoliths)^{35, 53-55}; polymers (such as polystyrene, polyethylene glycol, and polyacrylamide)^{56, 57}; zeolites (like BEA-type, ZSM-5, Y-zeolite, and mordenite)^{58, 59}; metal organic framework (MOFs)^{60, 61}; and carbon-based materials such as activated carbon, carbon nanotubes, carbon nitride, and graphene oxide (see [Figure 1](#)).^{62, 63} Each of these material offers unique structural and chemical properties for functionalization. For example, polymers offer considerable functional flexibility and can be chemically modified to immobilize a wide range of organic catalytic moieties⁵⁶; most of zeolites used for catalytic applications provide molecular selectivity and strong acidity due to their crystalline microporous structures⁴⁵; and carbon-based materials exhibit high thermal stability and tunable surface properties⁶³. Additionally, some materials display intrinsic catalytic activity owing to their surface functionalities, such as zeolites⁶⁴, MOFs⁶⁵, and carbon nitrides.⁶⁶ Despite these strengths, such materials may face challenges regarding stability, pore size constraints, or complex synthesis. For example, polymeric resins can suffer from swelling, limited thermal and chemical stability or carbon-based materials and zeolites having complex and often energy-intensive synthesis can limit tunability.^{58, 63, 67} Among these materials, porous silica supports are widely used due to their high surface area, mechanical robustness, and surface silanol groups that enable facile functionalization, making them favorable among common support materials for their tunable structural properties and relatively straightforward synthesis.^{33, 68-71}

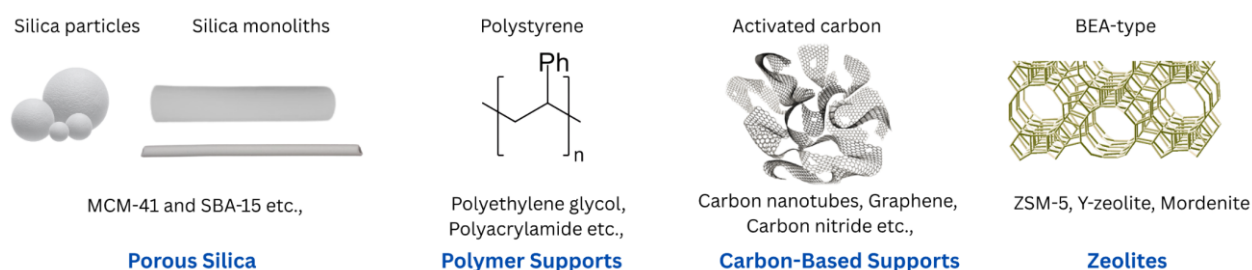


Figure 1. Examples of widely used synthetically engineered support materials for organocatalysts.

Porous Silica

Porous silica refers to a form of silicon dioxide (SiO_2) characterized by a network of interconnected pores that span the micro- (< 2 nm), meso- (2-50 nm), or macroporous (> 50 nm) scale. Its high surface area, tunable pore size, and chemical stability make it an ideal material for adsorption, separation, and catalysis.^{33, 72} The porous architecture facilitates controlled mass transport and provides abundant surface silanol groups that can be functionalized to anchor active species or modify surface polarity. Depending on synthesis conditions, porous silica can be tailored to exhibit specific textural and structural properties, enabling its use as a versatile support material in heterogeneous catalysis and related applications.^{32, 73, 74} Leveraging these properties, functionalization of porous silica with organocatalysts has been one of the most widely explored strategies in the past decades for developing heterogeneous catalytic systems (see Figure 2).^{33, 34, 53, 54, 68, 70, 75-94} Furthermore, silica based support also excel in both batch and advanced continuous-flow catalysis due to their efficient mass-transfer and diffusion properties. Altogether, the tunable architecture, chemical robustness, and ease of functionalization make porous silica a model, cost-effective, and environmentally benign support for enhancing catalytic performance in heterogeneous systems.³⁰ MCM-41, MCM-48, SBA-15, SBA-16, silica gel, fumed silica, spherical silica particles, and hierarchically porous silica monoliths are examples of porous silica materials that have been widely studied as solid support.^{68, 76, 78} Each of these silica materials offering distinct surface area, pore architecture and functionalization potential. For example, MCM-41 offers a

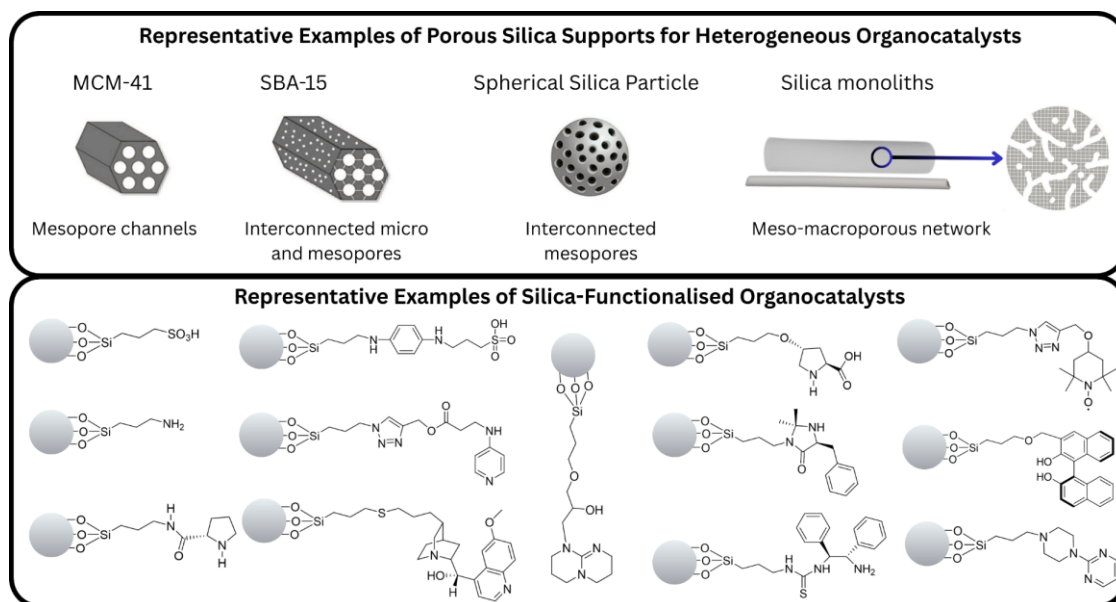


Figure 2. Representative examples of porous silica support and silica functionalized organocatalysts.

mesopore range of 2-5 nm with ordered hexagonal mesopores and a surface area of more than 1000 m²g⁻¹; these particles are excellent for small-molecule catalysis, but are limited by poor mechanical stability and restricted diffusion for bulky substrates.^{53, 95, 96} SBA-15 provides a larger mesopore range of 5-30 nm, also with ordered hexagonal mesopores and a high surface area between 600-800 m²g⁻¹, enabling efficient diffusion of larger molecules, although particle aggregation in liquid media can hinder interparticle mass transfer.^{54, 97, 98} Spherical silica particles like LiChrospher[®] exhibit broader pore size distributions (PSDs) of 2-50 nm, with surface areas of 100-600 m²g⁻¹, offering flexibility for immobilizing catalysts of different sizes. However, their limited mechanical strength can sometimes lead to diffusion constraints and structural instability.⁹⁹⁻¹⁰¹ In contrast, silica monoliths integrate a hierarchical meso-macroporous network (<2 nm to 5 μm) with surface areas of 100–600 m²g⁻¹, offering continuous diffusion pathways ideally suited for catalytic applications under dynamic conditions. These unique properties make silica monoliths particularly attractive as support materials for continuous-flow catalysis, where efficient mass transport and mechanical robustness are critical for achieving high catalytic productivity and long-term stability.¹⁰²⁻¹⁰⁴

Monolithic Silica Support for Continuous-flow Catalysis

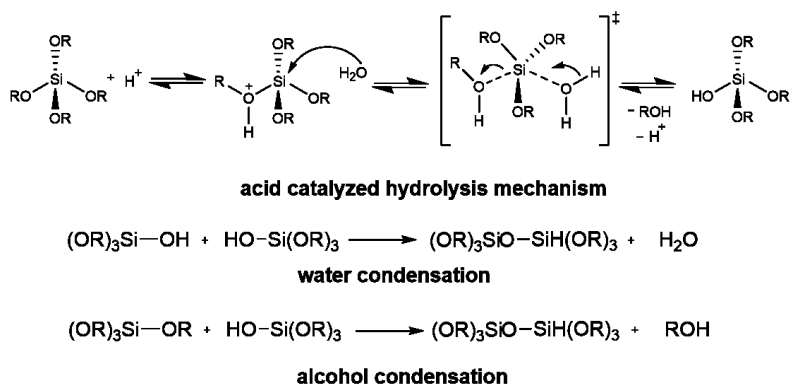
The transition from traditional batch processes to continuous-flow catalysis, where reactants are continuously fed and products simultaneously collected, represents a significant step toward sustainable and more efficient organic synthesis.¹⁰⁵ Flow systems provide enhanced control of reaction parameters, superior heat and mass transfer, improved safety, and easier scalability, all of which align with the principles of green chemistry.^{106, 107} In this context, silica-based materials have become indispensable solid supports. Traditional packed-bed reactors employing mesoporous silica powders such as MCM-41, SBA-15 or spherical LiChrospher[®] particles have been widely explored; these materials offer well-defined mesopores for catalyst immobilization but often suffer from high back pressure, particle aggregation, and uneven flow distribution that limit long-term performance.^{90, 98, 108-110} In contrast, silica monoliths, first synthesized by Nakanishi and co-workers, overcome these drawbacks through their hierarchically interconnected meso-macroporous architecture. These structures combine large, continuous macropores that enable convective flow with mesopores that provide abundant surface area for catalyst anchoring and molecular diffusion.¹¹¹ Furthermore, silica monoliths exhibit a high hydraulic permeability of approximately 1.0 x 10⁻¹³ m², resulting from their interconnected macropore network and large

mesoporous surface area. Their total porosity ($\approx 86\%$) surpasses that of packed-particle beds ($\approx 80\%$), which display much lower hydraulic permeability ($\sim 6 \times 10^{-15} \text{ m}^2$). This structural advantage yields superior flow characteristics and reduced pressure drops, enabling stable, continuous operation. Additionally, the open pore network minimizes co-product accumulation that can inhibit catalytic activity in particulate beds.¹¹²⁻¹¹⁴ Anne Galarneau and co-workers were among the first to demonstrate the practical use of functionalized silica monolithic flow reactors.¹¹⁵⁻¹¹⁸ Our group (Bernd Smarsly and co-workers) further advanced the understanding of hierarchical porosity in silica monoliths and their implementation in continuous-flow catalysis through the development of poly(ether ether ketone) (PEEK)-cladded silica monolithic reactors.^{34, 35, 55, 70, 90, 92, 103, 109, 119, 120} Multiple studies demonstrated the superior mass transport and pressure stability for monolithic reactors compared to particulate systems. These investigations have consistently shown that mesopore size and connectivity play a decisive role in determining performance, governing not only the immobilization of catalytic species within the pore structure but also the diffusion of reactants and efficient access to active sites during catalysis. Within this context, **Publication 1** of this thesis provides a mechanistic understanding of how mesopore networks evolve during hydrothermal treatment, offering crucial insights for tailoring silica monoliths with optimized transport characteristics for high-performance catalytic applications.

For tailoring porosity in silica monoliths, a detailed understanding of the underlying synthetic mechanisms is essential to develop an optimized pore system with enhanced diffusion properties. The sol–gel and phase-separation processes involved in Nakanishi-type syntheses are highly sensitive to even minor variations in parameters such as precursor composition, pH, temperature, and solvent ratios. While this sensitivity can pose challenges, it also provides a unique opportunity to tailor the hierarchical pore structure of the monoliths with remarkable precision when the synthetic conditions are carefully controlled.

Synthetic Mechanism of Silica monoliths

The preparation of monolithic silica using the well-established Nakanishi sol-gel method, or its variations, is widely used in both industrial applications and academic research.¹¹¹ Preparation begins with the initial **hydrolysis** and **condensation** of alkoxysilanes in an acidic medium, typically an aqueous solution of acetic acid, carried out at $0\text{ }^{\circ}\text{C}$ to room temperature. Common alkoxysilane precursors include tetraethyl orthosilicate (TEOS), and tetramethyl orthosilicate (TMOS) (see [Scheme 1](#)). The hydrolysis of these inorganic precursors in aqueous media leads to



Scheme 1. Mechanism of hydrolysis and condensation reactions leading to gelation during silica monolith synthesis.

the formation of a sol, which then transforms into a gel through condensation reactions. **Gelation** is the transition from a sol to a gel, involving the growth and cross-linking of hydrolyzed and condensed species into a three-dimensional macromolecular network. Initially, condensation forms dimers, trimers, and oligomers, resulting in a colloidal sol with suspended nanoparticles. These particles aggregate into short chains, which continue growing into a three-dimensional network as more sol particles attach. Eventually, microgel regions form and connect into a continuous gel structure at the gel point, where viscosity increases sharply. Finally, all gel phases connect to form a continuous network. The point at which the last bond is formed is known as the **gel point**, where viscosity rises sharply, resulting in a rigid gel. In general, any structural change in the gel caused by the liquid within its pores is considered **gel aging**. During aging, three processes occur simultaneously: **polycondensation**, **syneresis**, and **Ostwald ripening** or **coarsening**. Polycondensation refers to the continued cross-linking of hydroxyl groups on the gel surface, which increases the connectivity and strength of the network. Syneresis is a consequence of polycondensation, where the gel network contracts and expels liquid from the pores. Ostwald ripening involves the dissolution and re-deposition of material based on surface curvature: material dissolves from convex (positively curved) surfaces and re-deposits onto concave (negatively curved) surfaces (see Figure 3). This process increases the contact area between aggregated particles, enhancing the stability of the gel network. All three processes are influenced by **pH**, and **temperature** that collectively lead to **phase separation** through **spinodal decomposition**.^{121, 122} As a result of these combined phenomena, chemical spinodal decomposition occurs, leading to the separation of a homogeneous mixture into two coexisting phases: a water-rich phase and a silica/polymer-rich phase (see Figure 4.a). This phase separation is a kinetic process in which both phases evolve simultaneously. The morphology of the resulting porous network is determined by

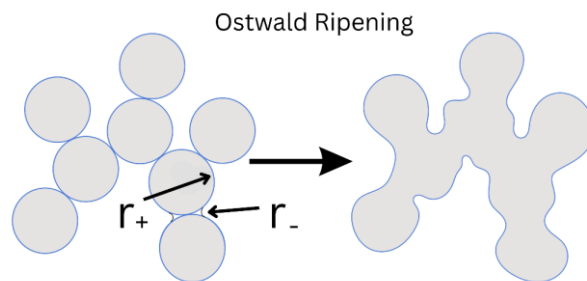


Figure 3. Illustration of Ostwald ripening during the synthesis of silica monoliths.

this phase separation. The shape and size of the water-rich phase govern the macropore size and structure, while the topology and dimensions of the silica/polymer-rich phase define the skeletal framework of the silica monolith. The rate of condensation, which directly influences pore formation during gelation, is strongly dependent on temperature. Therefore, even a small variation in temperature lead to changes in the macroporous structure of the silica monolith. For example, Meinus *et al.* (2017) noted that lowering the temperature by just 1.5 °C during the gelation step can result in a twofold increase in mean size of macropores.¹¹⁹ In our study (**Publication 1**), the gelation temperature was carefully maintained at 22.5 °C for 20 h to ensure identical macroporosity across all monoliths, as the primary objective was to investigate the evolution of mesoporosity. Notably, the organic polymers are also added during sol preparation that plays a key role in inducing phase separation by interacting with the polar silica surface while orienting its hydrophobic backbone (e.g., $-\text{CH}_2-\text{CH}_2-$ in polyethylene oxide) toward the solvent phase, thereby facilitating phase segregation.

The pH and temperature dependence of the overall process makes it possible to adjust these parameters to control the structural properties of the material. To achieve this, a hydrothermal treatment (HT) step is introduced after gelation, during which a basic pH and controlled temperatures are applied to stiffen the silica skeleton and enlarge micropores (or small mesopores) into mesopores (see [Figure 4.b-c](#)). The basic pH enhances the solubility of silica, allowing control over mesopore size. Specific mesopore dimensions can be tuned based on the concentration of OH^- ions released by basic precursors such as urea in water. Temperature also affects the concentration of OH^- ions during HT, making it a key parameter in regulating mesopore size. However, overly harsh conditions can lead to excessive silica dissolution, resulting in the loss of a stable silica network. Several factors are influenced by the temperature during HT: (i) the concentration of OH^- ions depending on the decomposition rate of urea or other basic precursors, (ii) the rate of base dif-

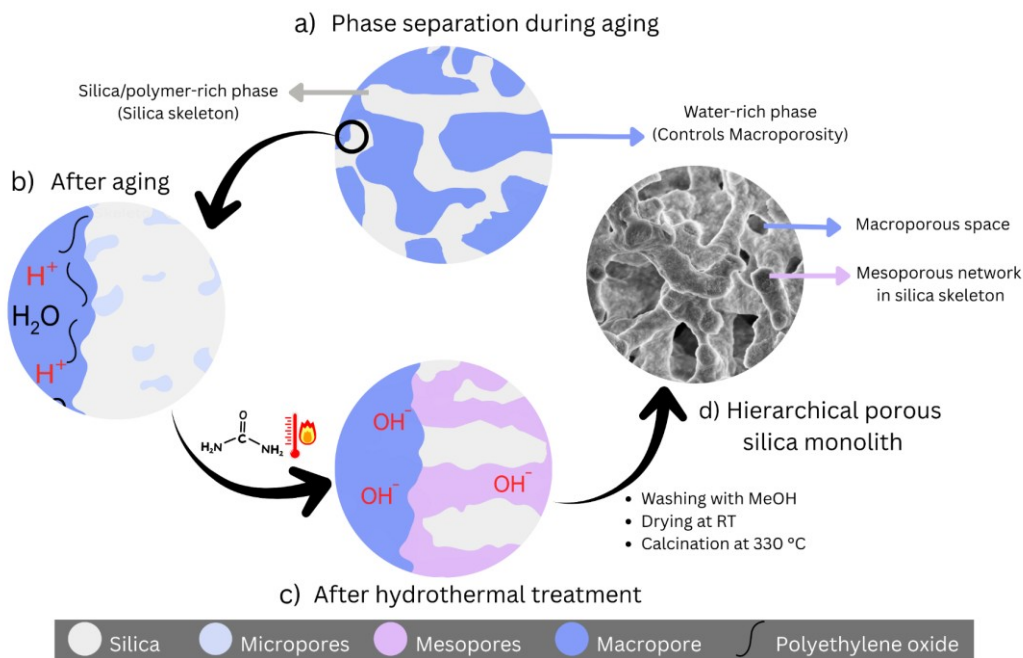


Figure 4. Illustration of porosity evolution during silica monolith synthesis: (a) phase separation during aging separates a water-rich phase (resulting macropore space) and silica-rich gel (resulting silica skeleton), (b) after aging, macropores and randomly distributed micropores in silica skeleton, (c) hydrothermal/base treatment expands micropores into a mesoporous network, and (d) SEM image of meso-macroporous silica monolith skeleton.

-fusion into the silica skeleton, (iii) the rate of silica dissolution, and (iv) the internal vapor pressure inside the treatment vessel. While the first three factors clearly correlate with temperature and affect the PSD, the exact role of internal vapor pressure in influencing mesoporosity remains unclear. Notably, while the aging step plays a critical role in determining the stability of the silica network and the mesopore size, the macropore size is negligibly affected by the HT.^{112, 119, 123, 124} Our study systematically investigated HTTs from 80 to 110 °C. Systematic increments of 3 °C (80-95 °C) were utilized to meticulously track the transformation from a restricted to an open pore network. Above 95 °C, 5 °C increments (95-110 °C) continued to characterize the development of the open pore network.

After the generation of mesoporosity during HT, the next critical step is the drying of silica monoliths. This step is essential for preparing stable, crack-free structures because strong capillary forces generated during solvent evaporation can induce stress within the monolithic network, leading to crack formation, especially if the gel body is unstable or if an unsuitable drying method is used. In the Nakanishi method, after HT, a solvent exchange is performed in which the aqueous pore-liquid in the synthesized monolith is replaced with methanol. The monolith is placed in a sealed tube filled with methanol and shaken for 24 hours. This process is repeated over three days

to ensure thorough exchange. Solvent exchange with lower surface tension solvents like methanol or ethanol is used to minimize capillary stress during evaporation, which helps prevent cracking by reducing the forces acting on the pore walls as the liquid dries. Afterward, the material is dried overnight under ambient conditions in a fume hood.^{125, 126}

After drying, the calcination step is performed where the organic polymer used for polymer-induced phase separation is thermally decomposed to preserve inorganic framework. In case of Nakanishi method, to break down PEO, a calcine temperature of 330 °C is used to remove organic matter for about 20 to 30 hours. The texture of the monoliths is not affected during this process.¹¹¹

Characterization of Hierarchically Porous Silica Monoliths

As mentioned earlier, silica monoliths typically possess a hierarchical pore structure comprising of micro- meso- and macropores, all integrated within a single material. To analyze micro- and mesopores in silica monoliths, gas physisorption, also known as physical gas adsorption analysis is commonly performed using nitrogen or argon at their respective boiling points (77 K for nitrogen and 87 K for argon). In this technique, data are collected in the form of sorption isotherm, which represent the amount of gas adsorbed as a function of pressure at a constant temperature. The isotherms are typically plotted as the amount of adsorbate versus the relative pressure (p/p_0), where p is the equilibrium pressure of the adsorbate and p_0 is its saturation vapor pressure. The shape of an adsorption isotherm (or physisorption isotherms) reflects the structural properties of a material, determined by the balance between fluid-solid (adsorbate-adsorbent) and fluid-fluid (adsorbate-adsorbate) interactions, as well as the confinement effects imposed by the pore architecture. In this context, the IUPAC has classified physisorption isotherms into eight distinct types (see [Figure 5.a](#)): I(a), I(b), II, III, IV(a), IV(b), V, and VI, each representing characteristic adsorption behaviors and corresponding porous/nonporous structure.¹²⁷ From these isotherms, several key structural parameters can be derived, including the specific surface area (BET, $\text{m}^2 \text{g}^{-1}$), PSD (nm), cumulative pore volume (mL g^{-1}), and insights into pore connectivity and network effects. During the physisorption analysis of silica monoliths, micropores are typically filled at very low relative pressures, usually below $0.15 p/p_0$. Once the micropores are saturated, increasing the relative pressure leads to the gradual formation of multilayers of adsorbed gas on the walls of mesopores. As the pressure continues to rise, the mesopores eventually undergo capillary condensation, a process where the gas condenses into a liquid-like state within the pores in a sudden, step-like manner. This behavior represents a shifted vapor-liquid phase transition, driven by the confined

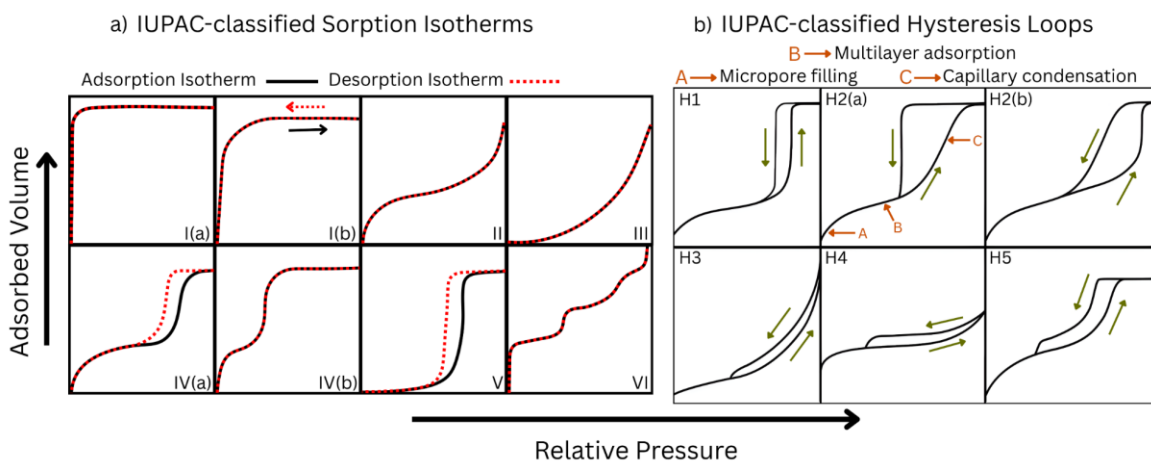


Figure 5.(a) Illustrate IUPAC classification of physisorption isotherms and (b) illustrate IUPAC classification of hysteresis loops.

geometry of the mesopores. After the mesoporous network is fully filled, typically around a relative pressure closer to 1.0, desorption begins as the relative pressure is gradually reduced. During this process, capillary evaporation first empties the pores, followed by a gradual thinning of the remaining adsorbed multilayer resulting type IV(a) isotherm (see Figure 5.a)^{128, 129}

In mesoporous materials, condensation and evaporation usually happen at different relative pressures, resulting in a characteristic hysteresis loop on the adsorption isotherm. This happens because condensation generally occurs at a higher pressure than evaporation. The shape of this loop depends on several factors, not only the structure of the pore network (such as restricted access or pore blocking due to narrow neck width of pores), but also by initiated condensation caused by reduced nucleation barriers.¹³⁰ These barriers are especially noticeable in materials with well-separated, independent pores, such as silica MCM-41, KIT-6, or silica monoliths treated at higher HTT (>100 °C) that develop independent pore network.^{131, 132} According to IUPAC classification, hysteresis loops are grouped into types H1, H2(a), H2(b), H3, H4 and H5 based on their shapes (see Figure 5.b). These shapes are largely influenced by how evaporation happens, which in turn is controlled by the pore network structure and the stability of the liquid inside the pores.^{127, 132-134} In the case of silica monoliths, we observed hysteresis loops of type H2(a), a mix of H1 and H2(a), or pure H1, due to heterogeneity in PSD's and connectivity, influenced by HTT.

To determine the PSD of silica monoliths, the Non-Local Density Functional Theory (NLDFT) method is commonly applied. This method, based on statistical mechanics, gives a more accurate description of how fluids behave in confined pores, making it reliable for both micro- and mesopore analysis.^{135, 136} PSD can be calculated by applying NLDFT kernels to adsorption and desorption

branches of the isotherm. Comparing the two gives insight into the structure of the pore network. Advanced pore network analysis involves not just comparing PSDs from both branches, but also using two different adsorptive gases, such as nitrogen (77 K) and argon (87 K).^{130, 131} These gases show different thermodynamic behavior in confined spaces due to difference in molecular weight, polarity, and critical temperature, helping to identify the type of pore network effects present, such as pore blocking or cavitation. If the PSDs from both adsorption and desorption match closely (Figure 6.a), this suggests an independent pore network. However, if the PSDs shift between the two branches (Figure 6.b), it indicates presence of restricted pores. Specifically, a matching PSDs from desorption with both gases (Figure 6.c) suggests pore blocking (pore blocking: access to pores due to narrower connecting pathways), while a shift between nitrogen and argon desorption PSDs points to cavitation (cavitation: pore cavity empty through neck below critical size $\sim 4\text{--}5$ nm for nitrogen at 77 K) as the cause of evaporation (Figure 6.d).^{136, 137} We observed in our study that in silica monoliths, pore network effects primarily manifest as pore blocking due to a broad distribution of neck sizes, while cavitation is generally not a dominant mechanism during pore evaporation.

In addition to comparing pore size distributions obtained with different adsorptive, desorption hysteresis scanning represents a further advancement in gas sorption analysis, enabling a more comprehensive understanding of the evaporation mechanisms within mesoporous networks at varying pressures.^{138, 139} This technique not only confirms and differentiates the pore network effects but also provides additional insight into how fractions of small and large mesopores undergo evaporation within interconnected structures. To resolve the overall desorption process into finer details, partial adsorption-desorption cycles are conducted within the main hysteresis loop at selected relative pressure points, allowing identification of distinct evaporation events.

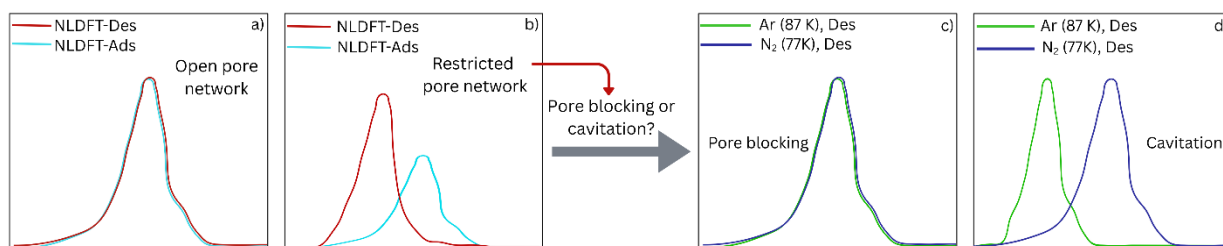


Figure 6. Illustration of an advanced pore network analysis approach: (a) comparing adsorption and desorption branches to assess pore connectivity (open or blocked); (b) if blocked pores are detected, (c) using two different adsorbates, such as argon and nitrogen, to distinguish between pore blocking or d) cavitation effects.

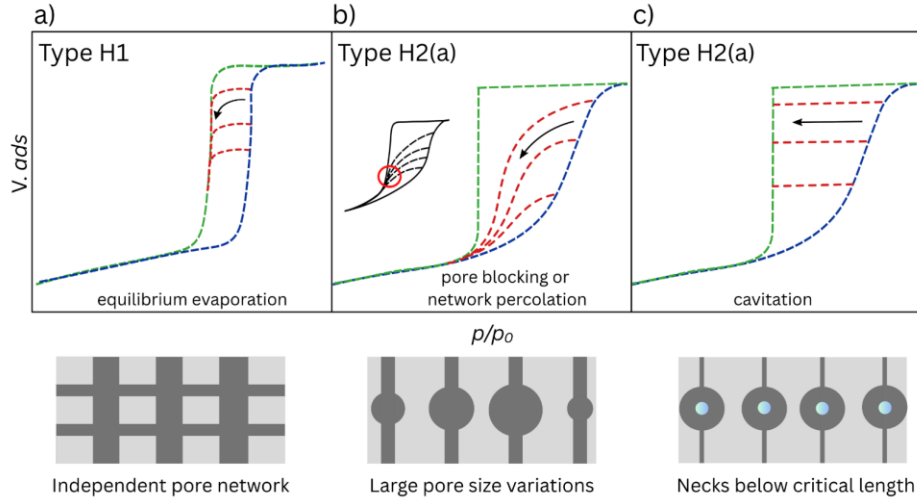


Figure 7. Schematic of hysteresis scanning of desorption isotherms, where the shape and merging of hysteresis lines into the main desorption curve indicate different types of pore connectivity in the mesoporous network.

These scanning lines reveal how pores empty during desorption, either through a rapid bending and merging into the main loop or by retaining the characteristic shape of the primary hysteresis loop. This pattern and steepness of the hysteresis lines within the main loop indicate different evaporation mechanisms. For instance, when the desorption lines gradually and independently merge into the main hysteresis loop with a small bend at the end, it suggests an independent pore network, commonly observed in H1-type hysteresis (see Figure 7.a). In contrast, when the lines merge collectively toward the lower end of the loop, it indicates restricted pore networks with pore blocking, known as network percolation, typical of H2(a)-type hysteresis (see Figure 7.b). A sharp, horizontal crossover of the hysteresis lines into the main H2(a) loop shows cavitation, where pores suddenly empty at lower relative pressures due to vapor instability (see Figure 7.c).^{136, 139, 140}

In silica monoliths, pores empty either independently or by network percolation, depending on the size and connectivity of the mesopores. Additionally, these monoliths often exhibit spatial heterogeneity or spatial pore gradient effect, where different regions within the material may have varied PSD and connectivity that empty the pores within the network in different ways. This can result in scanning hysteresis lines that merge into the main loop at higher relative pressures rather than at the loop's lower closure point (see inset in Figure 7.b). Kube *et al.* (2020) initially studied this effect by in situ-small-angle X-ray scattering (SAXS)-physisorption experiments that revealed pore gradient effect in disordered pore network of silica monolith.¹²⁰

For the analysis of macropores, techniques such as contact porosimetry, capillary flow porometry,

and mercury intrusion porosimetry (MIP) have been recommended by IUPAC.¹⁴¹ Among these methods, MIP is considered the state-of-the-art technique for the characterization of macroporosity, not only in general porous materials but also specifically in silica monoliths. The main advantage of MIP over other techniques lies in its broad measurement range, allowing the determination of pore diameters from approximately 4 nm up to more than 400 μm . However, while MIP offers extensive pore size coverage, the entrapment of mercury in small or blocked mesopores can make it less reliable for pores at the lower end of this range. During MIP analysis, mercury does not spontaneously penetrate pores because of its high surface tension. At atmospheric pressure, mercury remains outside the pores, and hydraulic pressure (up to 400 MPa) is gradually applied to force the mercury into the pore network. As the pressure increases, mercury first intrudes into macropores and, at higher pressures, into mesopores. During the extrusion phase, mercury starts to leave the pores at lower pressures, though a slight delay is observed due to the metastable state, resulting in a hysteresis loop. Initially, this hysteresis was attributed to mercury entrapment in small or blocked pores. However, after performing multiple intrusion-extrusion cycles, it was observed that although trapped mercury could be largely removed, hysteresis persisted. Later studies demonstrated that this behavior arises from nucleation barriers associated with the formation of a vapor-liquid interface during extrusion, similar to the desorption branch of a sorption isotherm.¹⁴²⁻¹⁴⁴ After acquiring the MIP isotherm, the PSD is calculated based on the Washburn equation, which assumes cylindrical pore geometry and relates the pore radius (r) to the applied pressure (P).^{136, 145}

$$P = - \frac{2 \gamma \cos\theta}{r} \quad (i)$$

- P applied pressure,
- γ surface tension of Hg ($\sim 480 \text{ mN/m}$)
- θ contact angle ($\sim 140^\circ$ for mercury on most solids),
- r pore radius.

In our study, we performed a single cycle of mercury intrusion and extrusion measurements for the silica monoliths. During this first cycle, the effects of pore blocking influenced the entrapment of mercury, and consequently, the extrusion isotherm did not coincide with the intrusion isotherm even at very low pressure (see [Figure 8.a](#)). Our primary objective was to analyze and confirm the macropore dimensions, since the synthesis of the silica monoliths was deliberately designed to maintain consistent macropore sizes. Therefore, the entrapment of mercury in mesopores does not

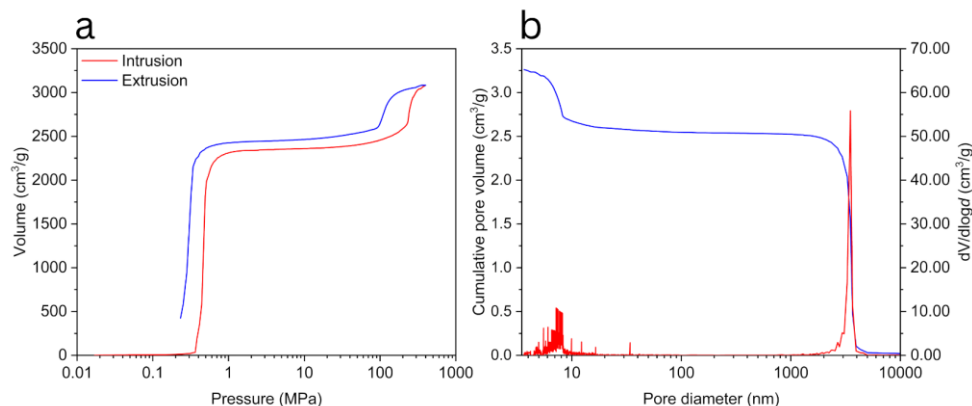


Figure 8. Graphical representation of a MIP data for a silica monolith, (a) MIP isotherm with a single cycle of intrusion and extrusion of mercury, (b) PSD and cumulative pore volume calculated from MIP isotherm.

significantly affect the determination of macropore size and volume, as these parameters are derived from the intrusion isotherm. The volume of mercury intruded was recorded at each pressure step. The total intruded volume represents the cumulative pore volume, and differentiation of this data yields the PSD (see Figure 8.b).

To summarize, this study provides detailed synthetic and analytical insights into the evolution of the mesoporous network in silica monoliths. **Publication 1** comprehensively investigates the hydrothermal treatment step, revealing its crucial role in establishing reproducible and optimized mesopore structures. The research offers a rational framework for understanding the underlying mechanism of mesoporous network evolution, emphasizing the dissolution-reprecipitation process driven by basic pH under elevated temperatures. This mechanistic understanding, supported by advanced physisorption analyses, not only elucidates pore dimensions but also unravels the complexities of pore connectivity and network accessibility.

While silica monoliths exemplify the success of synthetic control in achieving structural precision, sustainability in catalysis can also be explored in materials that originate from renewable sources and possess inherent functionality. As an alternative and complementary strategy, biopolymer-based supports offer a pathway toward greener catalytic system. Among these, chitosan stands out for its natural abundance, biodegradability, and intrinsic catalytic activity through its amino and hydroxyl functional groups.¹⁴⁶ These attributes make it an ideal model to explore how renewable materials can serve not only as robust supports but also as active participants in catalysis-extending the design principles of hierarchical silica frameworks into the domain of bio-derived, dual-function catalytic systems.

2.3 Biopolymers as Dual-Function Support Materials

Biopolymers as dual-function supports are renewable macromolecular materials that simultaneously provide structural support and intrinsic catalytic functionality for sustainable heterogeneous catalysis.¹⁴⁷⁻¹⁵⁰ Within heterogeneous catalysis, the most widespread application of biopolymers has historically been as supports for metal catalysts. Their abundance of modifiable functional groups ($-\text{OH}$, $-\text{NH}_2$, $-\text{COOH}$, phenolic units) provides strong anchoring points for metal ions and complexes, facilitating stable immobilization and efficient turnover for reactions.¹⁵¹⁻¹⁵⁵ This explains why biopolymer-metal hybrids are more frequently reported than purely organocatalytic systems. However, in the context of sustainable organocatalysis, growing attention is being directed toward the intrinsic catalytic roles of biopolymers or their use as supports for immobilized organic catalysts. Derived from renewable resources, the materials which are widely explored for the catalytic application include cellulose (the most abundant biopolymer from plant cell walls)¹⁵⁶, chitosan (obtained by the deacetylation of chitin which is main component in exoskeleton of crustaceans)¹⁵⁷, alginate (from brown algae)¹⁵⁸, and starch (commonly found in food crops) (see Figure 9).¹⁵⁹ In addition to these, other biopolymers have also been explored as catalytic materials or as supports to some extent. For example, lignin (isolated from secondary cell walls of vascular plants) provides aromatic hydroxyl groups and a rigid, phenolic-rich framework^{160, 161}, pectin (component of plants cell walls) offers galacturonic acid residues for acid catalysis or immobilisation,¹⁶² and protein-derived systems such as gelatin and silk fibroin have also been adapted as renewable catalytic matrices.¹⁶³ While their catalytic application is less developed compared to cellulose or chitosan, these examples highlight the possibilities for designing biopolymer-based supports. Their functional groups versatility not only allows surface modification and catalyst immobilization but also enable these materials to participate directly in catalysis, thereby functioning as dual-role platforms that can act as both support and catalytic site.

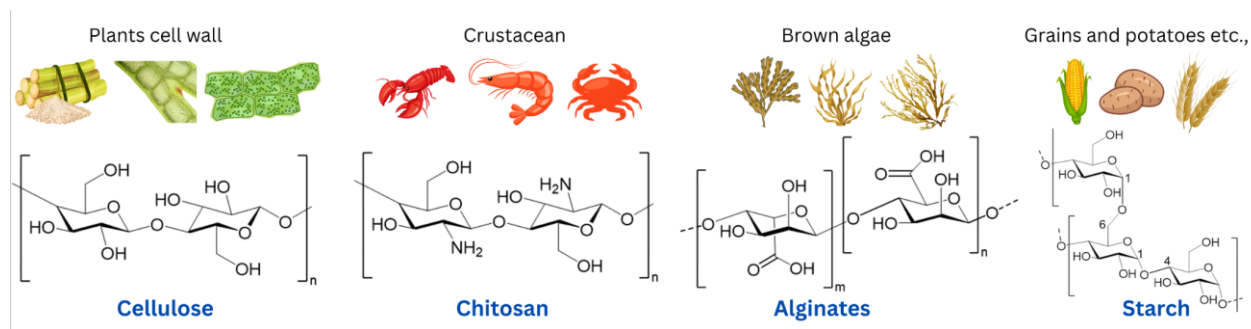


Figure 9. Examples of biopolymer reported as catalyst and/or support for organocatalysis.

Chitosan

Chitosan is one of the most prominent natural polysaccharides in catalysis research, distinguished by the presence of reactive amino groups along its polymer backbone. Its chemical structure consists primarily of β -(1 $\rightarrow$ 4)-linked D-glucosamine units, with varying amounts of N-acetyl-D-glucosamine depending on the degree of deacetylation. The combination of hydroxyl and amino groups provides chitosan with a unique reactivity profile compared to cellulose or starch, which contain only hydroxyl groups. It is largely derived from chitin (poly-N-acetyl-glucosamine), the second most abundant natural polymer after cellulose. Chitin is a structural component in the exoskeletons of crustaceans (e.g., shrimp, lobsters, crabs), insects, and in the cell walls of fungi. Through a multistep process, starting from crustaceans exoskeleton, chitin can be converted into chitosan with varying degrees of deacetylation (DDA), depending on the applied conditions.¹⁶⁴ The physicochemical properties of chitosan are largely determined by its DDA and molecular weight. For instance, chitosan is generally soluble in acidic media due to protonation of its amino groups, while low-molecular-weight oligomers dissolve across a broader pH range. In contrast, high-molecular-weight chitosan remains insoluble under neutral or basic conditions. Due to its unique physicochemical nature, chitosan widely known for its applications in water treatment, pharmaceuticals, biomedicine, cosmetics, and the food industry.¹⁶⁵⁻¹⁶⁷

Chitin to Chitosan

The extraction of chitin and its successive conversion into chitosan has been extensively reported in the literature, with marine sources such as crustacean shells representing the dominant feedstock. The conventional approach relies primarily on chemical extraction, although biological methods employing enzymes or microorganisms have also been described in some studies.¹⁶⁸ The chemical process typically involves three sequential steps: (i) demineralization, where minerals like carbonates are removed from the shells using acid treatment; (ii) deproteinization, which removes proteins and other organic components under alkaline conditions; and (iii) deacetylation, in which chitin is converted into chitosan by treatment with concentrated alkali at elevated temperature. The exact choice of reagents and conditions varies among reports, often depending on the degree of mineralization and the organic component of the source material. For demineralization, treatment with 10% (w/v) HCl for 2-3 h is most commonly employed to dissolve CaCO₃. Deproteinization is typically carried out using aqueous NaOH solutions in the range of 1-10% (w/w), applied at 65-100 °C for 1-12 h. Finally, deacetylation is achieved by exposing chitin to 40-50% (w/w) NaOH

solution at elevated temperatures, resulting in the cleavage of acetyl groups and the generation of free amino functionalities.¹⁶⁹⁻¹⁷⁴ Two key parameters that are closely monitored and controlled during chitosan production are its molecular weight and DDA. These characteristics largely determine the physicochemical properties of the polymer; such as solubility, crystallinity, and charge density, and consequently influence its suitability for different applications. In **publication 1**, we employed low-molecular-weight chitosan obtained from a commercial supplier with a DDA of approximately 75%, reportedly derived from shrimp shells.

Chemistry of Chitosan

The chemistry of chitosan is defined by the presence of multiple reactive functional groups along its polymer backbone. Each repeating unit contains a primary amino group at the C2 position, a primary hydroxyl group at C3, and a secondary hydroxyl group at C6, while the glycosidic linkage between C1 and C5 also contributes to its reactivity (see [Figure 10](#)). This diversity of functional groups enables extensive derivatization of chitosan, allowing the design of polymers with tailored physicochemical properties and novel catalytic behaviors. With the aim of improving chitosan or adapting it for specific applications, a wide range of derivatives have been developed. For instance, modifications such as deacetylation, depolymerization, or quaternization mainly applied as a biodegradable solid acid catalyst and proton-conductive material, whereas alkanoylated and acylated chitosan is used to tune hydrophobicity for applications in drug delivery, coatings, cosmetics, and diabetic wound healing.¹⁷⁵⁻¹⁷⁸ Chemically crosslinked chitosan is widely applied to improve mechanical stability, swelling resistance, and reusability in catalysis, adsorption, and biomedical scaffolds.^{179, 180} Graft polymerization of chitosan enables the introduction of tailored side chains, enhancing solubility, functionality, and compatibility for applications in drug delivery,

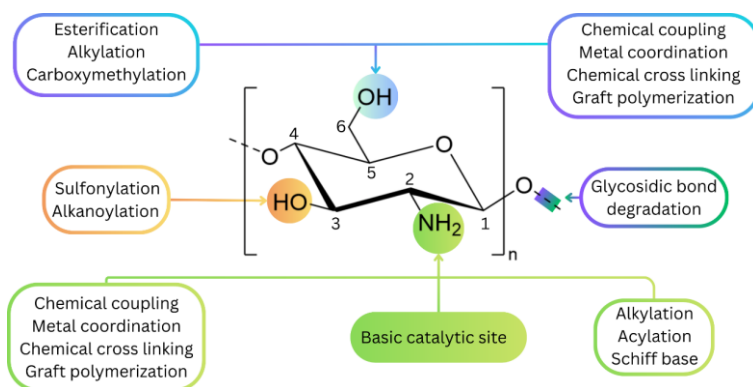


Figure 10. Overview of functional groups in chitosan that can be modified or act as active sites in catalysis.

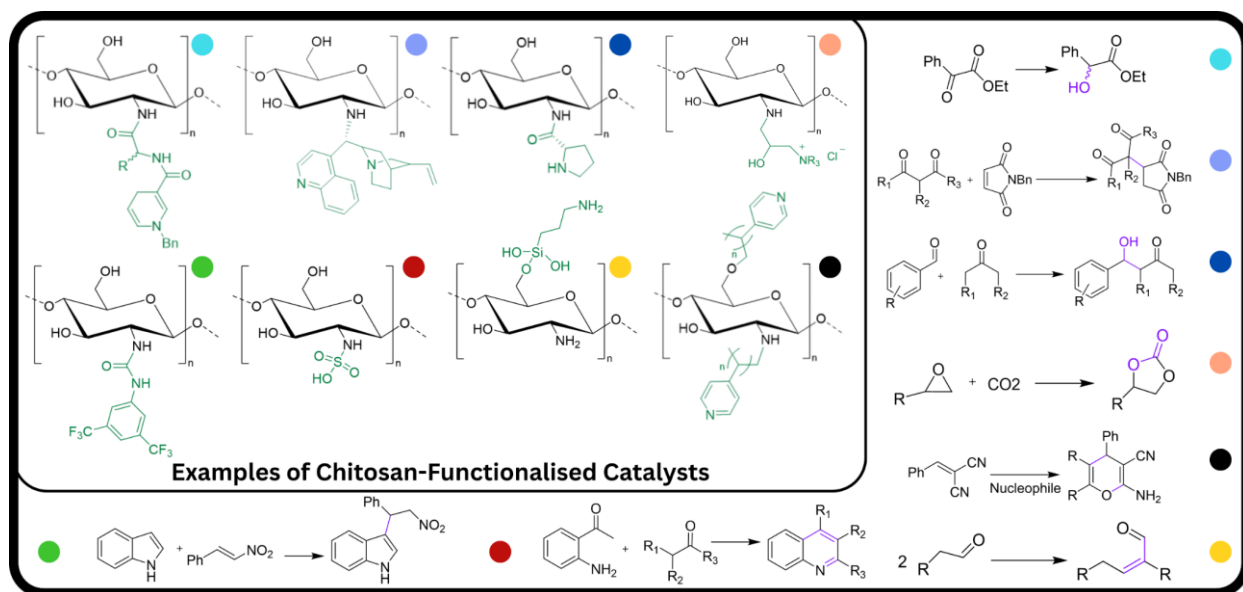
water treatment, and catalytic supports.^{181, 182}

The large number of amine groups also makes chitosan an excellent sustainable support material for diverse metal catalysts.¹⁸³⁻¹⁸⁵ In this context, chitosan has been extensively employed to immobilize palladium, nickel, and copper species, among others, for organic transformations such as Suzuki-Miyaura¹⁸⁶, Heck¹⁸⁷, Sonogashira¹⁸⁸, and hydrogenation reactions.^{189, 190} The strong coordination ability of amino and hydroxyl groups provides stable binding sites, while the biopolymeric framework ensures heterogeneity and reusability, making chitosan-metal hybrids attractive for sustainable catalytic applications.

Chitosan as a Support for Organocatalysts

Beyond its role in coordinating metal species, chitosan has also been explored as a sustainable platform for the immobilization of purely organic catalysts. The abundance of amino and hydroxyl groups along the polymer backbone allows covalent attachment with organocatalytic moieties, thereby creating heterogeneous systems that combine the reactivity of small-molecule catalysts with the sustainability, stability and recyclability of a solid support (see [Scheme 2](#)). In this way, chitosan functions not only as a passive carrier but also as a cooperative matrix that can contribute secondary interactions to the catalytic process. Most reported functionalization strategies target the primary amine at the C2 position or in few cases secondary hydroxyl group at C6. For instance, Zhang *et al.* (2009) grafted L-proline onto the amino groups of chitosan via acyl chloride chemistry and employed the resulting material to catalyze aldol reactions between aromatic aldehydes and ketones.¹⁹¹ In a related study, Jose *et al.* (2010) immobilized (3-aminopropyl)trimethoxysilane (APTMS) on the hydroxyl groups of chitosan, enabling catalytic activity in self-aldolization reactions among aliphatic aldehydes. Interestingly, they observed no such reactivity with pristine chitosan.⁴⁰ Furthermore, pyridine-functionalized chitosan has been reported to promote Michael addition reactions in heterocyclic synthesis. For example, poly(4-vinylpyridine) was immobilized on chitosan beads to catalyze Michael additions between benzylidenemalonitrile and various nucleophiles, with the catalyst reused over four cycles without significant loss of activity.¹⁹²

Similarly, Liu *et al.* (2012) immobilized cinchona alkaloids such as quinine and cinchonine onto chitosan and demonstrated comparable catalytic performance in Michael additions to that of the free alkaloids.¹⁹³ In a further advancement, Mahe *et al.* (2015) investigated the role of spacers in



Scheme 2. Overview of chitosan supported organocatalysts applied for sustainable heterogeneous organocatalysis; corresponding colors denote the catalysts associated with each transformation.

the grafting of dihydronicotinamide motifs onto chitosan. In the reduction of ethyl benzoylformate to ethyl mandelate, they observed a clear improvement in yield (from 33% to 79%) when a spacer was introduced.³⁸ In addition to base-type modifications, acid catalysts have also been developed on chitosan. Chitosan-supported sulfonic acid has been applied in Friedländer annulations¹⁹⁴, while chitosan-supported urea derivatives have been reported as catalysts for Friedel-Crafts alkylations.⁴¹ Moreover, several chitosan-supported ammonium salts have been designed for the cycloaddition of carbon dioxide to epoxides, followed by further transformation of the resulting cyclic carbonates into dimethyl carbonate.¹⁹⁵⁻¹⁹⁷ In summary successful functionalization and decent catalytic performances of these organocatalysts demonstrating the versatility of chitosan as a sustainable platform for different organocatalytic transformations.

Chitosan as Heterogeneous Organocatalyst

Chitosan is an inherently functional biopolymer whose amino and hydroxyl groups impart both basic and nucleophilic catalytic activity.¹⁹⁸ By using as a solid catalyst, chitosan offers multiple advantages: it is non-toxic, biodegradable, inexpensive, and readily separable from reaction mixtures, thereby reducing waste and simplifying purification. The average pK_a of chitosan in water is approximately 6.5, though it can vary depending on the degree of deacetylation (DDA), crystallinity, and molecular weight.¹⁹⁹ However, solid chitosan particles typically exhibits a low intrinsic surface area, generally in the range of 10-20 m^2g^{-1} , which limits accessibility to its

catalytically active amino groups.^{200, 201} To overcome this, many studies have focused on modifying chitosan into structured forms such as hydrogels, aerogels, and cross-linked beads with higher surface areas (up to 100-250 m²/g).²⁰²⁻²⁰⁴ While these materials improve mass transfer and catalytic turnover, their preparation often involves energy-intensive processes or hazardous reagents. Consequently, using unmodified chitosan directly as a catalyst represents a simpler and more sustainable alternative.

Although only a few studies have explored raw chitosan for catalytic applications, primarily in condensation reactions, they have consistently demonstrated notable activity and excellent reusability.^{43, 205-209} However, systematic optimization of such catalytic systems within the broader framework of green chemistry remains limited. In this context, **Publication 2** examines the potential of solid chitosan as a sustainable heterogeneous catalyst for the one-pot Knoevenagel condensation, with particular emphasis on optimizing reaction parameters to improve sustainability of overall process. The reaction was optimized not only for the model transformation between various benzaldehydes and ethyl cyanoacetate but also extended to the gram-scale synthesis of an important Atorvastatin intermediate [4-methyl-3-oxo-N-phenyl-2-(phenylmethylene)pentanamide], demonstrating the practical relevance of this sustainable catalytic approach. Notably, the solvent-binding and swelling capacities of chitosan in the employed solvents were found to play a significant role in facilitating efficient catalysis by enhancing active-site accessibility.

Solvent-Binding and Swelling Capacities of Chitosan

The catalytic performance of chitosan is closely governed by its swelling and solvent-binding behavior, particularly in protic media. Solvent molecules can penetrate the polymer network, leading to chain expansion and enhanced hydrogen bonding, which in turn expose additional amino and hydroxyl groups responsible for catalytic activity. This behavior effectively transforms chitosan into a hydrogel-like material with significantly increased surface area and improved mass transfer properties. For instance, Cho *et al.* (1998) reported water-binding capacities ranging from 458% to 805%, depending on the DDA and bulk density of chitosan.²¹⁰ In our study, water vapor sorption analysis also revealed a dynamic surface area of chitosan approximately 150 m²g⁻¹, which is comparable to that of hydrogels. We further quantified water and ethanol binding capacities of 520% and 104%, respectively, alongside swelling capacities of 607% in water and 171% in ethanol. Such expansion not only facilitates efficient reactant diffusion but also enables adsorption of water

generated during condensation reactions, thereby driving the equilibrium toward product formation.

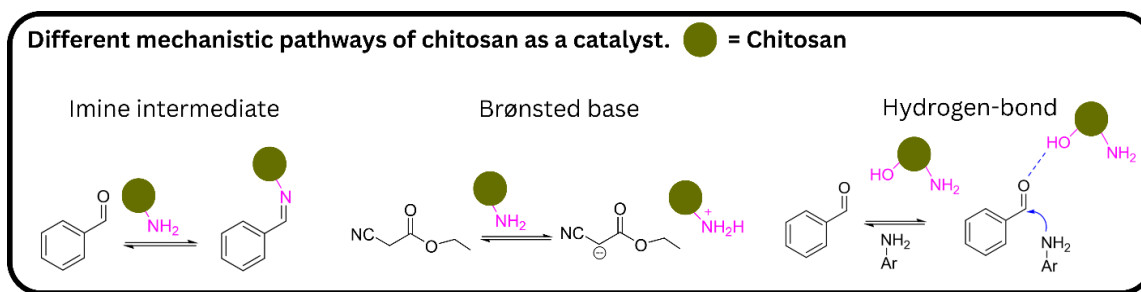
Conversely, in aprotic or non-swelling media, limited solvent-polymer interactions restrict access to catalytic sites and reduce activity. However, catalytic performance can still be maintained under such conditions by adjusting parameters such as catalyst loading or reaction time. For example, in **Publication 2**, synthesis of Atorvastatin intermediate was successfully performed in acetone, a solvent in which chitosan does not swell - achieving over 95% yield simply by doubling the chitosan amount from 50 mg to 100 mg, under mild, room-temperature conditions. Remarkably, this was accomplished without the addition of acetic acid or the use of a Dean–Stark trap for water removal, as commonly reported in other studies.²¹¹⁻²¹⁵ This finding suggests that chitosan's high water-binding capacity may not only eliminate the need for such external measures but could also mimic the cooperative catalytic role of acetic acid - an observation inferred from practical results, though the exact mechanistic explanation remains to be confirmed.

Collectively, this discussion underscores the dual functionality of chitosan - acting both as a solid catalyst and as a dynamic, solvent-responsive matrix whose physical adaptability directly enhances catalytic efficiency. Combined with its renewability, reusability, and benign nature, these attributes establish raw chitosan as a powerful and sustainable platform for metal-free heterogeneous organocatalysis.

Mechanistic Pathways of Chitosan as a Catalyst

Available reports demonstrate that the versatile chemistry of chitosan, bearing both amino and hydroxyl groups, can promote organic reactions through different mechanistic pathways depending on the transformation under study (see [Scheme 3](#)). The free -NH_2 groups can act as Brønsted bases, abstracting protons from activated methylene compounds to generate carbanions that subsequently attack electrophilic substrates such as aldehydes or ketones. Alternatively, the amino groups may engage in covalent activation via formation of imine (Schiff base) intermediates with carbonyl compounds; in such cases, the resulting imine species serve as activated electrophiles that undergo C–C bond formation. In addition, chitosan can function as a hydrogen-bonding catalyst, wherein both -OH and -NH_2 functionalities establish multiple hydrogen bonds with substrates, lowering activation barriers by stabilizing transition states.^{39, 216}

Initially, the distinction between these mechanistic modes was unclear, and before 2015 most



Scheme 3. Different catalytic pathways adopted by chitosan as a catalyst.

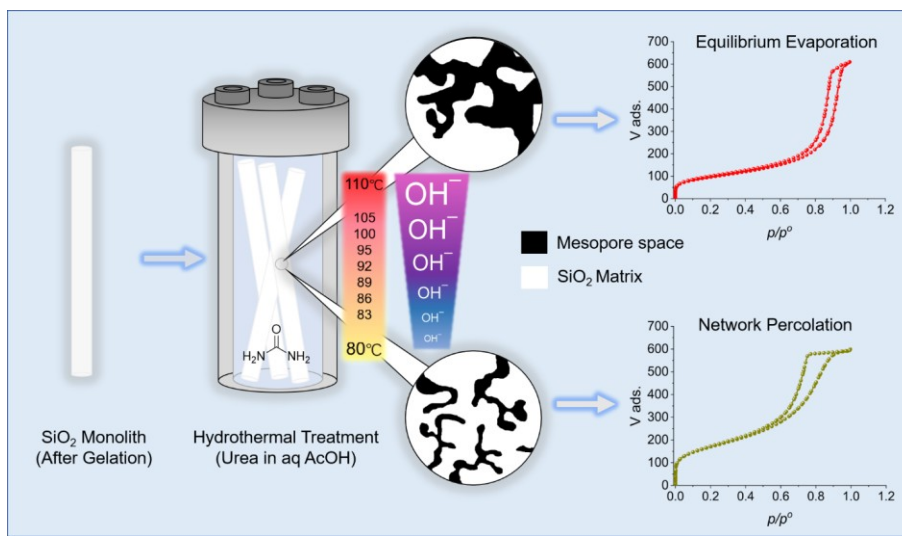
studies attributed the activity of chitosan hydrogels in Knoevenagel, Aldol, and Henry reactions primarily to Brønsted base catalysis.^{42, 217-219} In 2016, however, Franconetti *et al.* combined NMR and density functional theory (DFT) analyses to demonstrate that Knoevenagel condensations catalyzed by chitosan hydrogels proceed via an imine intermediate pathway.²²⁰ Later, in 2018, Rani *et al.* reported that Knoevenagel condensations of ethyl acetoacetate and dimethylmalonate with aryl aldehydes follow the imine-mediated pathway in aqueous media.²⁰⁷ Notably, mechanistic studies using spectroscopic or computational methods have so far been conducted mainly on chitosan hydrogels, where the large water content in gel beads may significantly influence the reaction pathway. For pristine (raw) chitosan powder, no NMR- or DFT-based mechanistic investigations have yet been reported in the context of Knoevenagel or aldol reactions. Instead, available studies generally assume that catalysis proceeds either through imine pathway for carbonyl compounds and/or through Brønsted base-driven generation of carbanions, though this remains to be experimentally verified for the raw chitosan.^{43, 208, 209, 221} Additionally, one can also argue that water released as condensation product can assist the reaction same like in hydrogels. Beyond this, Strecker reactions catalyzed by raw chitosan have been proposed to follow a hydrogen-bonding mechanism, similar to those typically associated with thiourea-based organocatalysts.²²² In this case, the hydroxyl groups of chitosan act as poly-hydrogen-bond donors to activate reaction between carbonyl compound, amine, and cyanide.²¹⁶

In summary, these discussions establish chitosan as more than a biodegradable support material; it is a multimodal heterogeneous organocatalyst. Through its combination of abundant, tunable active sites, adaptability to solvent environments, and recyclability, chitosan offers a promising route to sustainable catalysis. Future progress will likely depend on balancing the gains in activity achieved through structural modifications with the environmental costs of their preparation, ensuring that the applications of this biopolymer remains aligned with the principles of green chemistry.

2. Publications

Publication 1

Tuning the Mesopore Network in Meso-Macroporous Silica Monoliths by Hydrothermal Treatment—A Physisorption Study



DOI: [10.1021/acs.langmuir.5c00572](https://doi.org/10.1021/acs.langmuir.5c00572)

Reference:

Ali, U., Meinus, R., Turke, K., Schreiner, P.R. and Smarsly, B.M., Tuning the Mesopore Network in Meso-Macroporous Silica Monoliths by Hydrothermal Treatment—A Physisorption Study. *Langmuir*. **2025**, 41, 22, 13845–13859

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Tuning the Mesopore Network in Meso-Macroporous Silica Monoliths by Hydrothermal Treatment – A Physisorption Study

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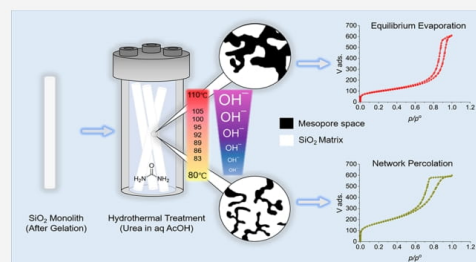
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ABSTRACT: Macro-mesoporous silica monolith columns, prepared by a sol–gel procedure developed by K. Nakanishi, show beneficial flow and separation properties due to their 3D-interconnected macropores in combination with mesopores, providing a high surface area. Building on this, they are routinely used in analytical liquid chromatography. Within the synthetic process, fine-tuning of the mesopore dimension and interconnection is achieved by an etching step involving hydrothermal treatment under basic conditions, typically in the range of 80 °C–100 °C. The present study aims to unravel details of this harsh procedure by a comprehensive analysis of the resulting mesoporous network. Thus, a series of silica monoliths was prepared across a range of hydrothermal treatment temperatures (HTT) between 80 and 110 °C, thereby tuning the mesoporosity. Mercury intrusion porosimetry confirmed that enhanced HTT does not alter the macropore dimension and only affects the mesopore space. The study employed state-of-the-art physisorption analysis applying two adsorptives, Ar (87 K) and N₂ (77 K), to identify changes in the mesopore size and network connectivity as a function of HTT. Also, advanced hysteresis scanning was performed on the same materials, providing independent insights into pore network effects. These analyses indicate that increasing HTT systematically enhances the average mesopore size from 8 nm (80 °C) to approximately 25 nm (110 °C) and widens the pore size distribution, pointing to pronounced dissolution of SiO₂ at higher HTT. Surprisingly, the total mesopore volume remains constant upon increasing the HTT, implying a dissolution-precipitation mechanism for SiO₂, rather than mere etching. Importantly, the in-depth porosity analysis reveals an increase in the size of necks, which reduces restrictions in the mesopore network connectivity. Furthermore, the data are in line with a recently proposed spatial mesopore size gradient in monoliths, which we find to be relevant at lower HTT and to systematically diminish toward higher HTT.



INTRODUCTION

Complex meso-macroporous structures have become an important field of materials science in recent years, and major progress has been achieved for different materials such as silica, zeolites, carbons, ceramics, cellulose, clays, and metal–organic frameworks (MOFs), etc.^{1–8} The attention dedicated to meso-macroporous materials is certainly spurred by their commercialized applications in the fields of adsorption, separation science, and catalysis. Still, researchers continuously succeed in elucidating and overcoming limitations related to diffusion, accessibility, and mass transport of these materials through analytical and synthetic methods.^{9–11} These properties can be improved by finely modifying the macro- and mesoporous network.^{12–18}

Hierarchical silica monoliths containing both meso- and macroporosity have emerged as particularly suitable materials due to their enhanced mass transfer properties, large surface area, well-defined macroporous skeleton, and standardized sol-gel-type synthesis based on readily available starting compounds.^{12,19,20} The special type of silica monoliths introduced by Nakanishi et al., possessing tunable meso- and

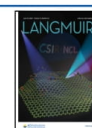
macropore sizes and high surface area, are highly useful for various flow applications in heterogeneous catalysis, separation or adsorption, high-performance liquid chromatography (HPLC), super thermal insulators, and applications requiring self-standing bodies.^{20–27} They are particularly advantageous with regard to uniform hydraulic flow and access to active sites compared to other porous materials used for similar applications, such as organic polymer monoliths and particle-based fixed beds.^{28–30} Specifically, SiO₂ monoliths potentially allow for optimizing the mobile phase velocity (contact time), reaction and adsorption selectivity, mass and heat transfer (efficiency), and specific surface area (loading capacity) in a distinct fashion.^{13,31} Owing to these features, these materials

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are commercially used in HPLC as a stationary phase, typically clad with steel or a specific polymer.^{32–35}

However, adapting these hierarchically porous silica monoliths to specific needs still faces fundamental challenges related to the synthesis: aside from the macropore space, potential problems may arise due to (I) the presence of micropores and (II) potential restrictions in mesopore connectivity.^{29,30,34} These two phenomena might lead to potentially poor connections between and access to the mesopores, causing, e.g., pore blocking and potentially resulting in limitations for certain liquid-phase applications. Such hindered connectivity (a) limits the accessibility of guest species to the active sites, (b) causes poor diffusion and mass transfer, and (c) creates steric limitations for larger organic molecules, which are relevant issues, especially in organocatalysis.^{36–39} To overcome these limitations, an in-depth understanding of the pore-generating synthetic steps is required, thus enabling fine-tuning of mesopore size and connectivity.

Hence, in the following, a brief description of the synthesis of meso-macroporous SiO₂ monoliths, based on the “Nakanishi process”, is given. The macropore network originates from phase separation during hydrolysis and condensation reactions of silicon alkoxides and the simultaneous induction of phase separation by spinodal decomposition of an organic polymer in an acidic environment. The next step involves hydrothermal treatment in the presence of urea at elevated temperatures (in the range of 80 °C and above), resulting in a pH increase, which, in turn, causes dissolution and reprecipitation of SiO₂. For instance, hydrothermal treatment is typically performed at 95 °C, yielding an average mesopore diameter of approximately 13 nm, which is typically used in the HPLC application of these monoliths.²³ This hydrothermal treatment widens pristine micropores into mesopores and thus determines the final mesopore space with regard to the mesopore size distribution and their mutual connection. The wide use of this route is based on its straightforward synthetic steps that lead to a specific meso- and macropore structure and surface area, with high reproducibility.⁴⁰ By controlling different parameters during synthesis, one can tune the meso- and macropores at different steps of synthesis as per application demands.^{41,42}

While the hydrothermal treatment has been extensively studied for its impact on the final transport properties, the mechanistic details of structural and chemical changes, their impact on the final mesopore size distribution, and the connectivity of mesopores are still a matter of research, especially regarding their dependence on the treatment temperature. In previous studies, the temperature applied during the hydrothermal treatment was quite high, but covering a broader temperature range is expected to provide additional insights.^{43–50}

Thus, to further elucidate the generation of mesoporosity and the influence of hydrothermal treatment on the connectivity of mesopores, we studied silica monoliths treated over a range of HTTs between 80 and 110 °C.

The advancements in state-of-the-art physisorption analysis and the interpretation of data are mainly based on density functional theory (DFT), allowing for the evaluation of consistent and meaningful pore size distributions (PSDs) over a broad range of micro- and mesopores. For advanced pore network analysis, we performed physisorption studies of the samples using two different adsorptives, argon (87 K) and

N₂ (77 K), and compared the PSD data to interpret pore networking effects (pore blocking, cavitation, or independent pore networks) in silica monoliths. This analysis applied the methodology for pore network analysis first reported in 2006 by Thommes et al.⁵¹ The use of both nitrogen and argon is essential for accurate pore network analysis due to their differing thermodynamic states and adsorption behaviors. Using nitrogen (77 K) for pore analysis has limitations, especially for micropores, due to its specific interactions with surface groups that affect pore filling pressure and diffusion. In contrast, physisorption using argon at 87 K is more suitable for several reasons. By comparing desorption pore size distributions obtained with both gases, one can distinguish between pore blocking and cavitation mechanisms, providing a clearer understanding of pore connectivity and behavior.⁵²

Hysteresis scanning is another advancement in physisorption science that reveals the correlation between the pore network, its connectivity, pore shape, and PSD. In hysteresis scans, the variation in gas pressure during the process of adsorption and desorption generates partial filling and emptying of pores in the range of relative pressure where hysteresis occurs. This leads to hysteresis lines originating in the region of the hysteresis envelope, and their shape provides insight into the connectivity of the mesopores, for instance, in terms of an equilibrium evaporation transition, network percolation (pore blocking), or cavitation. In the past few years, a lot of work has been devoted to scanning hysteresis lines starting from the desorption branch, but far fewer studies address the scanning of adsorption isotherms.^{53–57} In 2012, Cimino et al. worked on studying the scanning of adsorption and desorption isotherms of materials possessing different kinds of pore networks. They introduced percolation models and partial correlation models for network effects in mesoporous materials. They also developed a computational method for calculating the distribution of pore and neck sizes as well as the network coordination number.⁵⁴ Svidrytski et al. studied the hysteresis scans of both adsorption and desorption isotherms using different kinds of mesoporous silica materials spanning ordered (SBA-15, KIT-6) to disordered (random silica with restricted mesopores) mesopore networks. Their work found good agreement between modeling and experimental isotherms for materials exhibiting type IV(a) isotherms with a H1 hysteresis loop (for ordered mesopores) and a H2 hysteresis loop (for random silica).⁵⁵ Thus, we used desorption hysteresis scanning experiments to elucidate fine differences in mesopore connectivity as a function of the HTTs.

In summary, variations in the HTT alter the rate of chemical changes during the process, which, in turn, might affect the evolution of the mesopore network. This study is an attempt to understand these changes by state-of-the-art physisorption analysis using an advanced pore network analysis approach over a range of samples treated at different HTT and thus to improve the overall understanding of the mesopore networks of this important class of silica monoliths. Moreover, mercury intrusion porosimetry and SEM analysis were carried out to identify possible changes in the macropore structure induced by elevated HTT.

MATERIALS AND METHODS

Tetramethoxysilane (TMOS, 98%) was purchased from Thermo Scientific, acetic acid (100%) from Carl Roth, urea from Sigma-Aldrich, and poly(ethylene oxide) (PEO, $M_n = 10\,000$ g/mol) from Fluka Analytical.

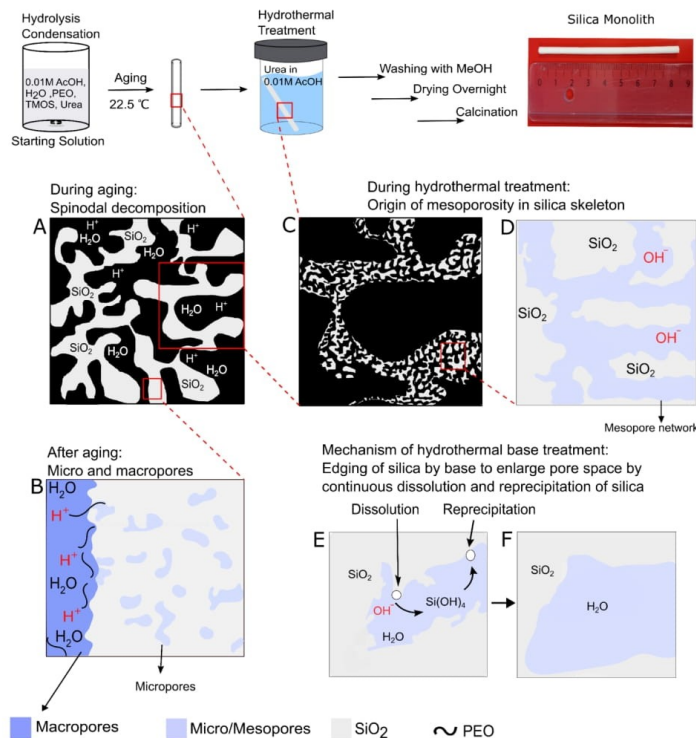


Figure 1. Schematic synthesis of silica monoliths by the “Nakanishi route”, and origin of porosity at different steps of synthesis: (A) origin of micro- and macropores during aging at 22.5 °C that separates the water-rich phase (macropores) and silica-rich phase after spinodal decomposition; (B) generation of micropores inside the silica skeleton during gelation, which enlarge into mesopores during hydrothermal treatment; (C, D) emergence of mesopores during hydrothermal treatment in basic pH that dissolves silica into soluble siliceous species and enlarges the micropores into a mesoporous network; dissolution (E) and reprecipitation (F) of silica during hydrothermal treatment.

Characterizations. SEM: A Smart SEM MERLIN (Carl Zeiss) scanning electron microscope was used for scanning electron microscopy with an acceleration voltage of 1 kV. Samples were sputtered with platinum for 60 s before analysis.

Mercury Intrusion Porosimetry: The morphology of the macropores was analyzed using a mercury porosimeter (Pascal 140/440, Thermo Fisher Scientific, Rodano, Italy) with a pressure range of 0–400 MPa. Washburn’s equation was used to analyze the data, supported by the instrument software (Sol.I.D). A surface tension of 0.48 N/m and a contact angle of 140° were assumed for the intruded mercury.

Physisorption: Physisorption studies using Ar (87 K) and N₂ (77 K) were carried out using an automated gas adsorption station (Autosorb iQ2, Quantachrome Corp., Boynton Beach, FL). For the measurements, a small piece of each silica monolith sample (20 mg) was placed into a glass tube with a cylindrical end measuring 9 mm in diameter. Each sample was degassed at 120 °C for 12 h before starting the physisorption experiment. For Ar (87 K) physisorption measurements, the samples were kept at 87 K using liquid Ar. The surface areas were calculated by the Brunauer–Emmett–Teller (BET) model, while pore size distributions (PSD) were determined using the NLDFT-Kernel (Ar at 87 K, zeolite/silica cylindrical pores) applied to both the adsorption and desorption branches. The BET model approach was also used to calculate the surface areas for N₂ (77 K) physisorption, while pore size distributions were determined using the NLDFT-Kernel (N₂ at 77 K on silica cylindrical pores) for both the adsorption and desorption branches. Cumulative pore volume and cumulative surface area distributions were also calculated for

comparison. All these calculations were performed by the ASiQvin software, version 5.21. To elucidate the porous structure in different samples, hysteresis scanning was measured for both the adsorption and desorption branches of all samples. For the hysteresis scanning, four data points were selected from the isotherms, which were then used for the desorption hysteresis scan.

Synthesis of Silica Monoliths. A modified Nakanishi route was used to synthesize silica monoliths. 1.21 g of poly(ethylene oxide) (PEO, $M_n = 10\,000$ g/mol) and 0.9 g of urea were dissolved in 10 mL of 0.01 M acetic acid, and the solution was magnetically stirred at room temperature until all the particles dissolved in the aqueous acidic solution. The clear solution was then shifted to an ice bath for 20 min, after which 5.6 mL of tetramethyl orthosilicate (tetramethoxysilane or “TMOS”) was added and stirred for an additional 20 min at 0 °C. The ice bath was then removed, and the solution was stirred at room temperature for the final 10 min. For the next step, i.e., gelation, we used stainless-steel tubes with an inner diameter of 3.8 mm and a length of 15 cm. The tubes had already been immersed in a thermostat (Julabo F26, Julabo GmbH, Germany) set to maintain a precise constant temperature of 22.5 °C. The ends of the tubes were sealed with plastic caps wrapped with parafilm, and 1.2 mL of the solution was added into each tube using a syringe. After 20 h of gelation at 22.5 °C, the silica monoliths were removed from the stainless-steel tubes and transferred into centrifuge vessels containing 45 mL of an aqueous solution of urea and acetic acid for hydrothermal treatment (9 g of urea dissolved in 100 mL of 0.01

are commercially used in HPLC as a stationary phase, typically clad with steel or a specific polymer.^{32–35}

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M acetic acid). See Figure 1 for the mechanism and a schematic illustration of the Nakanishi-type synthesis.

Hydrothermal Treatment Conditions. For hydrothermal treatment, the centrifuge vessels containing silica monoliths in 45 mL of solution (9 g of urea dissolved in 100 mL of 0.01 M acetic acid) were tightly closed, wrapped with parafilm, and then placed into an oven. An autoclave was used for those monoliths that were hydrothermally treated at temperatures of 100 °C and above. Table 1 shows the

Table 1. Parameters for the Hydrothermal Treatment of Silica Monoliths

Sample name	Hydrothermal treatment temperature (HTT) (°C)	Temperature ramp (h)	Holding time (h)
SiO ₂ -80	80	10	10
SiO ₂ -83	83	10	10
SiO ₂ -86	86	10	10
SiO ₂ -89	89	10	10
SiO ₂ -92	92	10	10
SiO ₂ -95	95	10	10
SiO ₂ -100-1	100	10	10
SiO ₂ -100	100	13	15
SiO ₂ -105	105	10	10
SiO ₂ -110	110	10	10

temperature and timing parameters used for the hydrothermal treatment of different samples. From 80 to 95 °C, the hydrothermal temperature was systematically increased in steps of 3 °C, and by 5 °C

from 95 to 100 °C to match the boiling point of water, then to 105 and 110 °C. The temperature ramp and holding time for every hydrothermal treatment were kept at 10 h each, so the total time for each hydrothermal treatment was 20 h, except SiO₂-100 for which a temperature ramp lasting 13 h and a holding time of 15 h were applied to observe the impact of increased hydrothermal treatment timing on PSD. The names of the samples reflect the temperature at which they were treated hydrothermally (for example, SiO₂-80 was treated at a HTT of 80 °C).

Sensitivity of Synthetic Route for Silica Monoliths. The synthetic route for silica monoliths is highly sensitive to even the slightest change in any of the parameters, including the concentration of polymers, variations in pH, contamination, pressure changes, or, most importantly, slight changes in temperature and timing. Even a slight change in any parameter can lead to differences in the size, shape, and connectivity of pores in silica monoliths. To tailor and control the porosity, it is important to have profound insight into the individual steps involved in the generation of micro-, macro-, and mesopores.⁵⁸

During gelation, chemical spinodal decomposition occurs that separates two coexisting phases, namely, a solvent-rich phase and a silica/polymer-rich phase. Spinodal decomposition is a kinetic process in which two phases grow simultaneously, accompanied by the condensation of silica oligomers. The shape and size of the water-rich phase control the size and shape of the final macropore network, while the topology and size of the silica-rich phase determine the topology and dimension of the silica monolith skeleton (Figure 1A,B). The rate of condensation is controlled by temperature, which ultimately governs the mean macropore size during the gelation step.^{12,14,41,59,60}

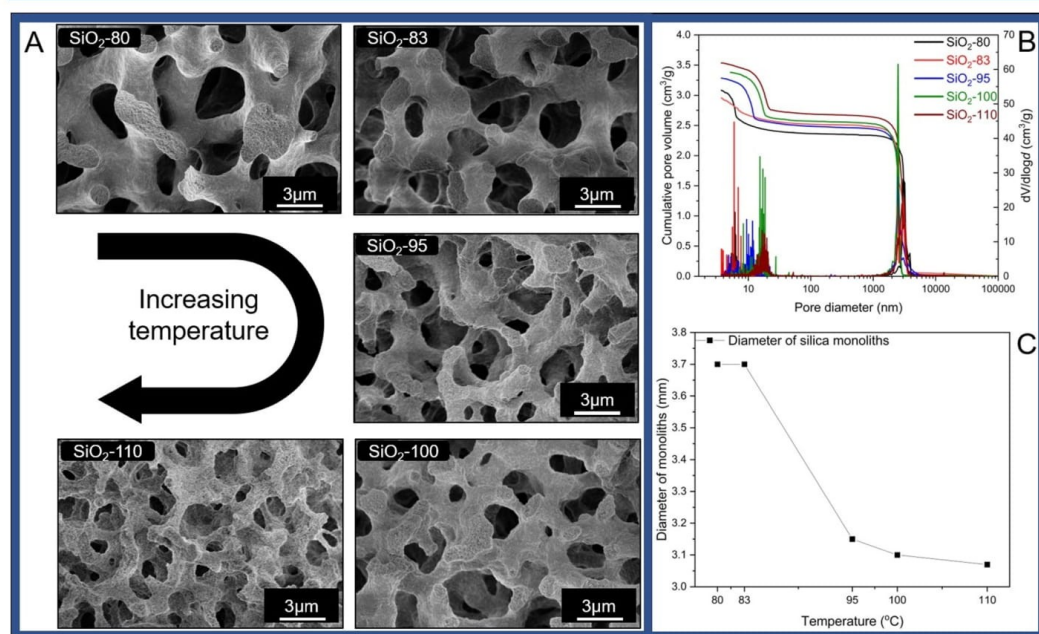


Figure 2. SEM images (A) of silica monoliths prepared at different HTT. The name of the samples indicates the HTT. An identical magnification was used for the SEM micrographs to ensure comparability of the skeleton morphology. With increasing HTT, it can be seen that the skeleton of silica monoliths become more irregular in shape due to strong etching effects. Furthermore, with increasing temperature silica reprecipitates on the outer surface rendering the skeleton surface coarser in appearance. (B) Mercury intrusion porosimetry data for silica monoliths showing good agreement in macropore sizes among all samples, which is due to the identical gelation temperature during the course of synthesis of monoliths that controls the size of macropores. The diameter of silica monoliths (C) gradually decreases as result of corrosion of silica with base from the outer surface and shrinkage due to vapor pressure exerted on outer surface during high HTTs.

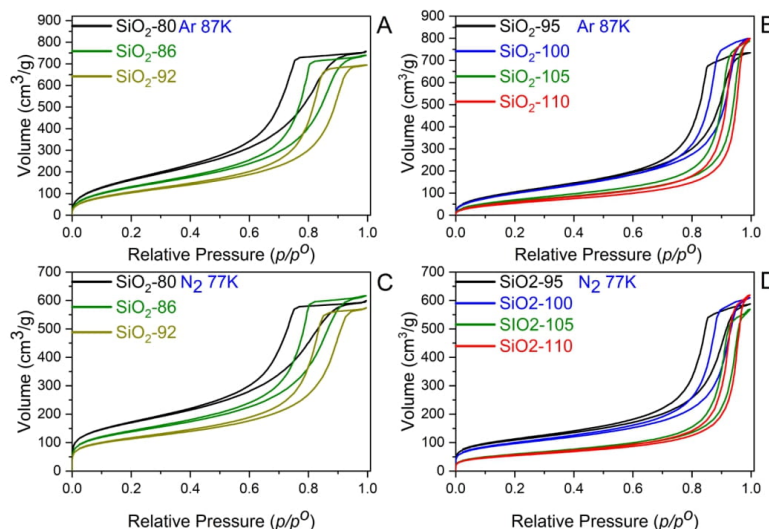


Figure 3. (A,B) Ar (87 K) and (C,D) N₂ (77 K) physisorption isotherms of silica monoliths treated at different hydrothermal temperatures. The name of samples reflects the temperature at which they were treated hydrothermally (for example, SiO₂-80 was treated at 80 °C). As the HTT increases, the condensation step shifts toward higher p/p^0 due to an increase in mesopore size, and the shape of isotherms changes from type H2 to mixture of H2 and H1, and finally to type H1 at higher temperatures. Only selected isotherms are shown here for better visualization. All of the isotherms of a total of nine samples can be seen in the Figure S1A–D.

Recently, Meunier et al. published a study on the influence of temperature changes during the gelation step, concluding that even a slight increase or decrease in temperature by only 1.5 °C leads to changes in the macropore size by a factor of 2.⁶¹

Hydrothermal Treatment. The gelation step is followed by hydrothermal treatment of the silica monoliths in a solution of urea and acetic acid. This step is responsible for tailoring mesopores inside the monolithic silica skeleton, using basic media generated by the decomposition of urea into aqueous ammonia at elevated temperatures (Figure 1C,D). The hydrothermal treatment causes the widening of micropores and also etching (dissolution) of silica from a silica-rich phase into small dissolved siliceous species (formally Si(OH)₄) creating micro- and mesoporosity, and concurrently involving reprecipitation at nearby concave surfaces (Figure 1E,F). The etching of micropores and the rate of dissolution and reprecipitation depend on the HTT, which can thus be used to control the mesopore size. The hydrothermal step might be viewed as a process similar to Ostwald ripening or coarsening, during which silica dissolution occurs at convex surfaces while reprecipitation occurs at concave surfaces, thereby decreasing the overall curvature on the mesoscale. Increasing the temperature during hydrothermal treatment results in the broadening of the pore size distribution as well as the enlargement of mesopores.^{44,62–66}

After the hydrothermal treatment was completed, the silica monoliths were removed from the oven and allowed to cool to room temperature. They were then immersed in 45 mL of HPLC-grade methanol, ensuring complete submersion for solvent exchange. This process was repeated every 24 h for three consecutive days to facilitate thorough removal of residual species.

Following solvent exchange, the monoliths were dried overnight in a fume hood and subsequently subjected to calcination at 330 °C. The calcination process involved a controlled heating ramp from room temperature to 330 °C under air over 15 h, followed by a 10-h holding time to ensure complete decomposition of residual organic polymer (PEO). Predrying overnight and using a slow heating ramp prevent cracking in the monoliths by reducing capillary forces during the calcination process. After calcination, the monoliths were

characterized in detail to assess their meso- and macroporous structures.

RESULTS AND DISCUSSION

The synthesis follows previously reported protocols and yields the typical meso-macroporous makeup, with the macropores forming a continuous network of micrometer-dimensioned pores, while the mesopores are located in the skeleton separating the macropores.^{40,61} SEM analysis (Figure 2A) reveals that at lower HTT (SiO₂-80, SiO₂-83) the silica skeleton exhibits a well-defined shape with a uniform diameter of the strands. The mesopores inside the skeleton are visible on the broken silica arms. As the temperature increases, (SiO₂-95, SiO₂-100, SiO₂-110) the skeleton appears more irregularly spread, which is a result of heterogeneity in the redeposition of dissolved silica on the skeleton surface, enhanced by the elevated temperature in the autoclave during hydrothermal treatment. At high HTT, the rate of silica dissolution increases and enlarges the mesopore size by trimming silica under more basic conditions and then randomly redepositing it onto the outer surface. SEM images further show no visible effect on the size of macropores during hydrothermal treatment, which is confirmed by mercury intrusion analysis in Figure 2B indicating an almost identical macropore diameter for all samples. This finding is expected because of the uniform temperature conditions during the gelation step. Yet, a significant difference in mesopore volume is observed in the pore size distributions (Figure 2B), revealing that the mesopore volume increases with an increase in HTT. This difference is due to (i) mesopores smaller than 3.5 nm, which are nonintrudable by mercury, and (ii) pore blocking of large mesopores connected by smaller ones. These effects are present in samples SiO₂-80, SiO₂-83, and SiO₂-95 confirmed

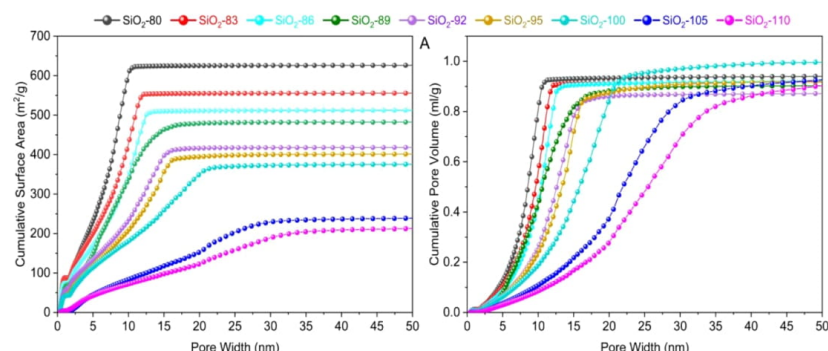


Figure 4. Cumulative surface area (A) and cumulative pore volume (B) obtained from desorption branches of Ar (87 K) physisorption isotherms by using an NLDFT cylindrical pore model.

by physisorption data (see below). By contrast, the larger, independent open mesopores in SiO₂-100 and SiO₂-110 do not exhibit such hindrance of intrusion. A prominent effect is observable in the diameter of silica monoliths (Figure 2C), which decreases with increasing treatment temperature. This decline is due to corrosion of silica from the outer surface of the monolith by the base, which dissolves silica into aqueous solution, and shrinkage caused by vapor pressure exerted on the monolith surface. However, it remains difficult to determine which of these effects is the dominant contributor.

To elucidate the influence of hydrothermal temperature on the mesoporous structure, especially with regard to mesopore connectivity, the monolithic silica rods were analyzed by Ar (87 K) and N₂ (77 K) physisorption analysis.

Figure 3 reveals that all of the physisorption isotherms are of type IV(a), while the hysteresis loops vary as the HTT increases. Taking SiO₂-80 as a reference, the position of the condensation step shifts to higher relative pressures, implying that the mesopore size increases with an increase in HTT. Silica rods treated at lower HTT (SiO₂-80 to SiO₂-89) show a mixture of H2(a) and H1 hysteresis loops (SiO₂-83 and SiO₂-89 isotherms in Figure S1), the latter being typical of silica monoliths that are well-known for their well-connected mesoporous network. A contribution of a H2(a) hysteresis loop appears as a steeper step in the desorption branches and thus indicates hindered emptying from filled mesopores, caused by “pore blocking” or “cavitation”. In either case, the cavity remains filled until the neck evaporates at lower relative pressure p/p^0 . We would like to note that the incline in the desorption branch can possibly be influenced additionally by the size distribution of mesopores and the necks connecting them. While the Ar (87 K) and N₂ (77 K) isotherms of SiO₂-80 to SiO₂-89 exhibit a major contribution of a H2(a) hysteresis loop, with higher HTT the shape of the isotherms shows continuously increasing contributions of H1 hysteresis, accompanied by an increase in mesopore size (see below). A more drastic change can be seen when silica rods are hydrothermally treated at 92 °C and above. For the highest HTTs (SiO₂-100, SiO₂-105, SiO₂-110) almost ideal H1 hysteresis loops were observed as a result of well-connected and accessible mesopores. Such a systematic change in the shape of isotherms with moderate steps in the applied HTT offers the opportunity for fine-tuning mesopore diameters and connectivity. The differentiation between the different possible

mesopore connectivity scenarios was performed on the basis of NLDFT-based pore-size distributions, see below.

Influence of Hydrothermal Temperature Treatment on Cumulative Surface Area and Cumulative Pore Volume. Cumulative (Figure 4) and differential pore size distributions (PSDs) (Figure 6) were evaluated from physisorption data for Ar (87 K) and N₂ (77 K) isotherms. The NLDFT cylindrical pore model was used to calculate the PSDs, which is known to provide accurate pore size distributions for silica materials of this type.^{51,67} For comparison, the NLDFT model of cylindrical and spherical pores was also applied to two samples. The results (Figure S2) showed negligible differences in PSDs with both models for SiO₂-80 and SiO₂-100 with argon; however, for nitrogen, where the NLDFT cylindrical-spherical kernel is only available for the desorption branch, the PSDs appeared low in volume but overestimated in size, which is not consistent with data from the cylindrical kernel of argon and nitrogen (Figure 5).

Thus, using the NLDFT kernel for cylindrical pores, the samples up to SiO₂-100 showed a small micropore volume, which disappears upon increasing the HTT. Since the changes in the PSD are most prominent in the range of 5–20 nm, we conclude that micropores and small mesopores are converted into larger mesopores, confirming the general view on the impact of such hydrothermal exposure. Concomitantly, the overall surface area continuously decreases (Figure 4A and Table 2), from almost 560 m²/g (SiO₂-80) to 350 m²/g (SiO₂-100), and finally 200 m²/g (SiO₂-110) upon enhancing the temperature in the hydrothermal treatment, as a result of small micro- and mesopores merging into larger mesopores. Quite interestingly, the overall cumulative pore volume is almost unaffected by varying the HTT (Figure 4B and Table 2), despite the marked change in the PSD. In the samples treated at hydrothermal temperatures between 80 and 90 °C with steps of 3 °C, the major contribution to the total pore volume results from mesopores in the range of 2 to 15 nm. Notably, increasing the hydrothermal treatment time for SiO₂-100 from 20 to 28 h does not alter the PSD but leads to a slight increase in cumulative pore volume (Figure S3). For temperatures above 100 °C, mesopores larger than approximately 15 nm dominate the contribution to the mesopore volume (Figure 4B). Note that the gelation temperature and time were carefully kept uniform for the synthesis of all silica monoliths to avoid any effects of gelation conditions on mesoporosity,

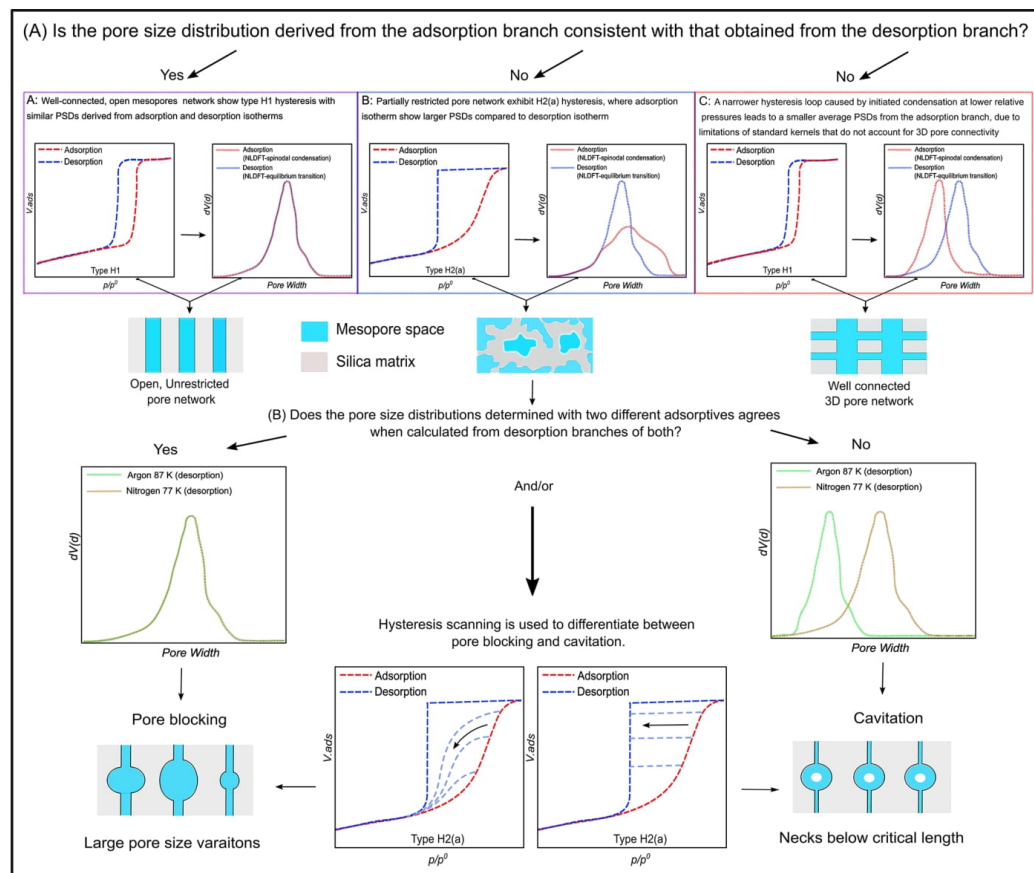


Figure 5. The advance pore network analysis approach used in this study (reported in detail by Schlumberger et al. 2021),⁵² where the use of two different adsorptives help to determine the pore network effects due to different thermodynamic behaviors of Ar (87 K) and N₂ (77K) in confined mesopore space. (A) Comparing pore size distributions from adsorption and desorption branches using NLDFT adsorption branch kernels and NLDFT equilibrium desorption branch kernels, respectively, to check for the presence of restricted pores. (B) If restricted pores are found, comparing results from different adsorptive gases can help to understand the desorption process. Differences in the pore size distributions from nitrogen (N₂) and argon (Ar) desorption branches suggest cavitation. (C) A narrow H1-type hysteresis loop due to condensation starting at low relative pressure. This shifts the pore size distribution from the adsorption branch to smaller values because standard models (kernels) do not consider the 3D connectivity of pores. Desorption hysteresis scanning is also a useful method for probing pore network effects, where the shape and closure behavior of hysteresis branches help distinguish between pore blocking and cavitation mechanisms.

ensuring that the observed variations in PSDs can be attributed solely to the hydrothermal conditions. The influence of pores larger than 50 nm on cumulative surface area and cumulative pore size is shown in Figure S4. Hence, these systematic trends in the PSD, surface area, and pore volume indicate a widening and fusion of micropores and small mesopores upon dissolution of siliceous species, which do not remain in the solution but are deposited within the sample. It is well-established that an increase in hydrothermal temperature decomposes urea in aqueous solution into ammonia, raising the pH value. This increase in pH along with increased temperature, enhances the rate of dissolution of silica into Si(OH)₄ creating wider mesopores in monolithic rods.⁶⁸ The constant overall cumulative pore volume also suggests that the

rate of dissolution is similar to the rate of reprecipitation for all of the applied temperatures. From these physisorption experiments alone, however, it is impossible to conclude the whereabouts of this dissolved-deposited SiO₂ material.

MESOPORE CONNECTIVITY

For deeper insight into the progressive changes in the mesopore space, especially with regard to connectivity and dependence on the HTT, we calculated PSDs from both the desorption and adsorption branches of the isotherms (Figure 3).^{69,70} Following the advanced pore network analysis approach developed by Thommes et al.^{51,52} (Figure 5), network effects, and particularly possible pore emptying hindrance in the form of “pore blocking” or “cavitation”, can

Table 2. Variation in Surface Area, Average Pore Size, and Pore Volume of Silica Rods Treated at Different Hydrothermal Temperatures, Determined by Ar Physisorption (87 K)

Sample	BET surface area (m ² /g)	Average pore size (nm)	Total pore volume (mL/g)
SiO ₂ -80	560	9	0.94
SiO ₂ -83	480	11	0.92
SiO ₂ -86	440	12	0.93
SiO ₂ -89	420	13	0.93
SiO ₂ -92	350	14	0.88
SiO ₂ -95	360	15	0.93
SiO ₂ -100-1	335	19	0.95
SiO ₂ -100	350	19	ca. 1
SiO ₂ -105	230	23	ca. 1
SiO ₂ -110	200	27	ca. 1

be identified and distinguished from one another by comparing PSDs determined from the adsorption and desorption branches in cases where pronounced hysteresis is observed. This analysis is based on the isotherms of two different adsorptives, namely Ar (87 K) and N₂ (77 K). These two adsorptives have different thermodynamic states inside the mesopores, enabling a straightforward procedure for identifying possibly restricted pore emptying from the state of liquid fluid based on the desorption-based PSDs: If the PSDs obtained for Ar (87 K) and N₂ (77 K) measurements are identical, then pore blocking is the dominant phenomenon. On the other hand, if the PSDs evaluated from Ar (87 K) isotherms are shifted compared to the N₂ (77 K) analysis, then desorption is governed by cavitation.

The PSDs determined from the adsorption and desorption branches of the Ar (87 K) and N₂ (77 K) isotherms exhibit interesting features (Figures 6 and S5), especially as a function of the HTT:

1. Comparing the two different adsorptives, Ar (87 K) vs N₂ (77 K), the respective desorption-based PSDs are practically identical for one particular HTT, implying the absence of cavitation as a pore emptying mechanism. Also, the adsorption-based PSDs are almost identical for the two adsorptives, suggesting that the absolute values obtained for the PSDs are reliable.⁵²
2. For HTT up to 92 °C, the PSDs obtained from the adsorption branch are different from the desorption-based PSDs for both adsorptives, Ar (87 K) and N₂ (77 K), in two features: first, the desorption-based PSDs are sharper and level off at smaller diameters (approximately 14–16 nm) than the adsorption-based PSDs (>20 nm). Second, the adsorption-based PSDs indicate a larger fraction of mesopores in the range of 4–7 nm compared to the desorption-based PSDs. Interestingly, the mode value for the average pore diameter is larger for the desorption-based analysis compared to the adsorption-based PSD. These peculiarities point to two structural properties of the mesopore space: on the one hand, it can be described as an interconnected pore network rather than independent mesopores. The filling of small connecting pores generates menisci, which may reduce the nucleation barrier for condensation in the empty pores. Thus, condensation will occur at pressures slightly below the pressure commonly predicted for delayed condensation, and the average pore diameter determined

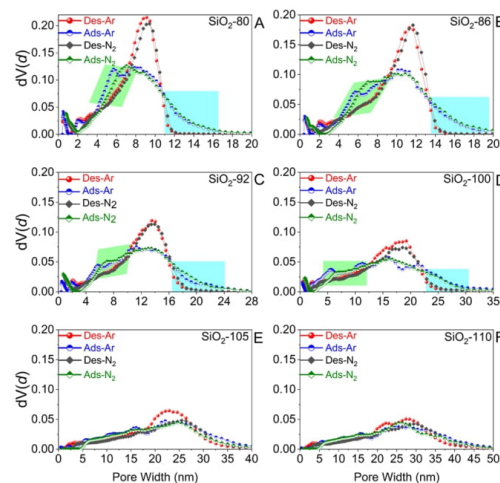


Figure 6. (A–F) NLDFT pore size distributions calculated from Ar (87 K) and N₂ (77 K) adsorption and desorption branches of physisorption isotherms of silica monoliths, as a function of the HTT. The areas displayed in green color highlight the shift of the PSD toward smaller pores calculated from adsorption isotherms, indicating the pore network effects. The bluish areas highlight those larger mesopores being connected by small-size mesopores. These larger-size mesopores thus do not appear in desorption-derived PSDs calculated from desorption branch due to pore blocking.

from the adsorption branch will appear slightly smaller. Note that a shift of the adsorption branch to smaller pore sizes, compared to desorption-based PSDs, has also been reported for such monoliths, which is accounted for as “initiated condensation”.⁷¹ Such a shift is attributed to a mismatch in the assumed connectivity of pores in the applied adsorption kernels, which describe adsorption in well-accessible and independent cylindrical pores, thereby not taking into account three-dimensional connectivity (Figure S5, case C). This effect was, for instance, described by the Kleitz group for physisorption on KIT-6 silica.⁷²

On the other hand, a fraction of larger mesopores (>ca. 12 nm) is surrounded by necks of smaller diameters, resulting in the “pore-blocking” phenomenon.

For all HTTs above 92 °C, the PSDs exhibit increased pore diameters and lie almost on top of each other (Figures 6 and S5), while the overall pore dimensions increase with rising HTT. This similarity of all PSDs points to the absence of narrow connecting pores and, thus, the absence of pore blocking or cavitation.

To quantitatively assess pore network effects, the mesopore volumes were calculated from the cumulative pore volumes of all samples. Notably, comparing these distributions, calculated from NLDFT adsorption (Figure 7A) and NLDFT desorption branches (Figure 7B), reveals how variations in pore volume fractions across different mesopores’ size ranges correlated with changes in pore network connectivity. As shown in both parts of Figure 7, only a tiny volume fraction of micropores is present, which disappears above 100 °C, probably due to the merging of smaller pores. Similarly, the volume fraction of

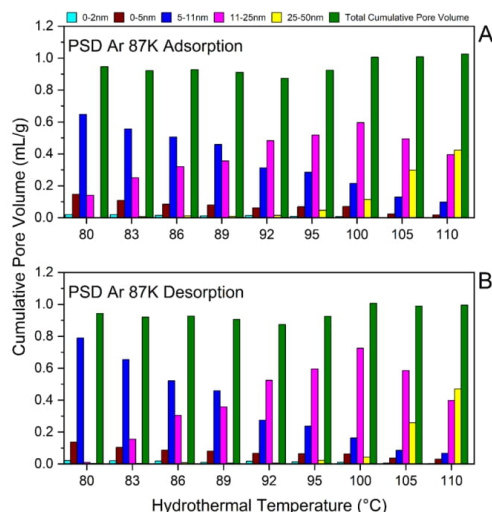


Figure 7. (A,B) Cumulative pore volume distributions in different ranges of mesopores, calculated by applying the NLDFT method on adsorption and desorption branches (Ar 87 K).

mesopores ≤ 5 nm decreases consistently for both adsorption and desorption branches across all samples. Additionally, the volume of 5–11 nm mesopores (blue line) declines upon increasing treatment temperature; however, the volume for this range of mesopores (5–11 nm) derived from the adsorption branch differs from those calculated from the desorption branch.

This shift in volume fractions of the 5–11 nm mesopores is particularly prominent in monoliths treated at 80 °C, 83 °C, and 86 °C. For instance, in the case of SiO₂-80 the volume of 5–11 nm mesopores is almost 0.8 mL/g from desorption, compared to 0.67 mL/g for the adsorption branch. This difference (0.13 mL/g) matches the difference in pore volumes of the 11–25 nm population (pink line) as calculated from the adsorption and desorption branches. This apparent redistribution of mesopore volume from the 11–25 nm range (adsorption) to the 5–11 nm range (desorption) suggests that 0.13 mL/g of 11–25 nm mesopores are connected by necks in the 5–11 nm range, leading to pore blocking. Through this analysis, the mesopore volume fraction differences and redistribution in smaller ranges enable the determination of:

- which range of mesopores is restricted,
- the volume of restricted mesopores,
- and which neck sizes are responsible for pore restrictions.

Based on this interpretation, the 11–25 nm mesopores are restricted due to pore blocking rather than cavitation, as the neck sizes responsible for the restriction exceed the critical neck width w_c (5–7 nm) responsible for cavitation.^{51,73,74} From SiO₂-95 onward, the emergence of 25–50 nm mesopores becomes apparent, with their contribution to total pore volume increasing progressively. By SiO₂-100, the 11–25 nm mesopore population begins to decline, transitioning into the 25–50 nm population, which dominates the cumulative

pore volume at 110 °C under extreme hydrothermal treatment conditions.

Desorption Hysteresis Scanning for Advanced Interpretation of Pore Network Effects and Heterogeneity in the Mesoporous Space. For further understanding the pore connectivity and elucidating the type of pore network effects after hydrothermal treatments, desorption hysteresis scans were performed on specifically chosen samples, according to their distinct hysteresis loops. Argon at 87 K was used for the analysis, and four segments of desorption isotherms were recorded for each sample. In “desorption hysteresis scanning” experiments, multiple cycles of adsorption and desorption were performed: the relative pressure, at which desorption is initiated, was reduced in a stepwise fashion, and a desorption scan was measured. From the contours of these desorption branches the underlying desorption mechanism can be inferred.^{54,71} Thus, desorption starts from different filling states of the mesopores depending on the p/p^0 value. Sorption cycles were conducted at different, representative p/p^0 , and the desorption mechanisms were determined using the IUPAC classification, (Figure S7; a GIF is available as animated explanation of desorption scanning mechanism in the Supporting Information), which contains three different types of hysteresis loops and pore evaporation mechanisms. Figure 8B–D shows hysteresis scans of different samples having distinct boundary loops and related desorption segments that reveal the influence of HTT on the mesopore connectivity. Hysteresis isotherms along with their complete adsorption and desorption segments are illustrated by Figure S6. The sample SiO₂-83, treated at the lowest HTT (Figure 8B), exhibits a boundary loop with an H2(a)-type hysteresis loop,⁷¹ such shape already indicating a pore network effect. All four segments of the desorption scans bend sharply and meet at the same point at lower p/p^0 , revealing that evaporation is dependent on the neighboring pores. The overall evaporation from the pore network takes place by network percolation,⁷¹ so that all desorption segments merge together at the same lower p/p^0 value. Note that the desorption segments do not coincide at the lower closure point of the boundary loop but at a higher p/p^0 . Thus, the desorption patterns are not straightforward and, importantly, cannot be attributed to one of the general types of hysteresis patterns. Recently, it was suggested that such desorption scanning features might be due to spatial mesopore size gradients within this type of silica monoliths. Such kind of effect was first reported by Meinusch et al. in 2017 postulating that the mesopores toward the outer surface of the skeleton are larger compared to the core of the skeleton.⁶¹ In 2020 Kube and Turke et al. used small-angle X-ray scattering (SAXS) coupled *in situ* with physisorption to further elucidate this pore size gradient effect in such silica monoliths. Their work indeed revealed a gradient in mesopore size, getting smaller while moving into the center of monolith. It was proposed that such potential spatial heterogeneity of mesopores cannot be elucidated by conventional isotherm analysis, but only scanning desorption lines expose such a phenomenon. Also, in the study of Kube et al., the scanning hysteresis lines merged into a main desorption isotherm before the closing point of the hysteresis loop, as compared to “pore blocking” effects where all the desorption scanning lines coincide at the lower closure point of the hysteresis loop.⁷¹ Thus, the shape of hysteresis lines reflects the pore blocking phenomenon, but additionally we propose that the merging of lines before the closure point of the hysteresis loop is

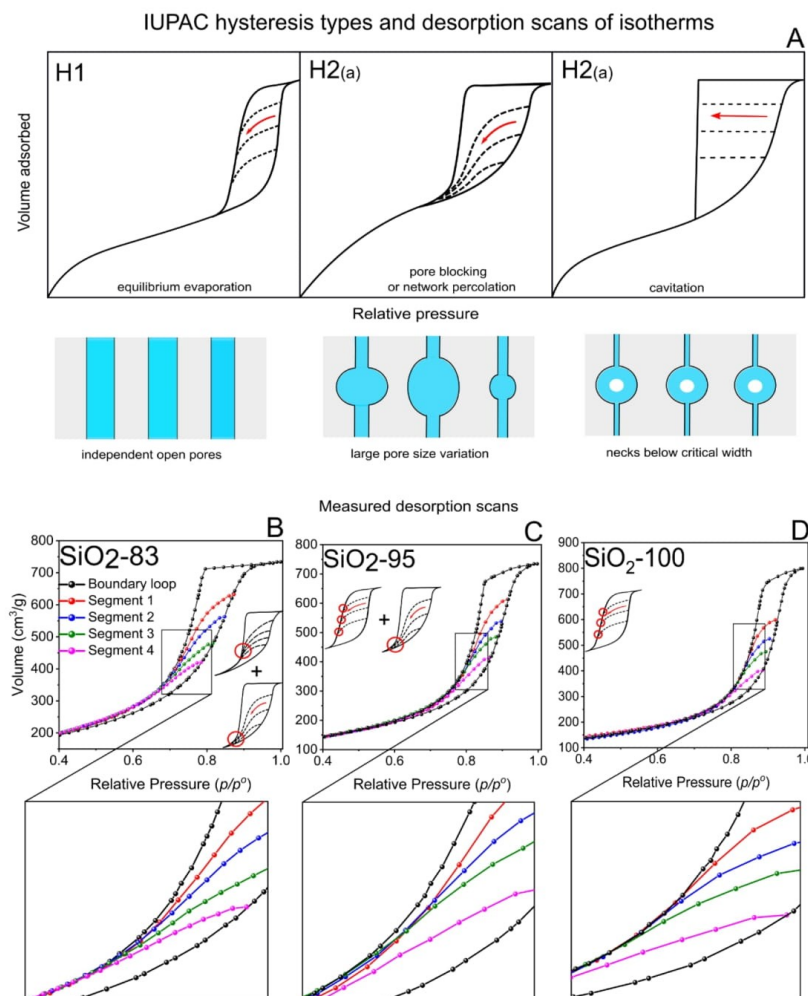


Figure 8. (A) Overview of IUPAC hysteresis types and related desorption hysteresis scans of mesoporous materials with different pore network. Reproduced from Kube and Turke et al. Copyright 2020 American Chemical Society. (B–D) Hysteresis loops of three samples treated at different HTTs having four desorption scanning isotherms each (Ar 87K). (B) (SiO₂-83) exhibits a H2(a) type hysteresis loop, C (SiO₂-95) exhibits a mixture of H2(a) and H1, while (D) (SiO₂-100) reflects the H1 hysteresis loop. For visual clearance, the hysteresis lines are zoomed-in in separate graphs. The insets in (B), (C), and (D) illustrate the fundamental types of IUPAC hysteresis loops and desorption scanning lines.

influenced by spatial pore size gradient effect resulting in a mixture of hysteresis types (small hysteresis models as in Figure 8B). In sample SiO₂-95 (Figure 8C), the boundary loop can be interpreted as a mixture of H2(a) and H1-type hysteresis loops. The first three desorption segments bend sharply until merging together first and then meeting the boundary loop at higher p/p^0 values compared to sample SiO₂-83. By contrast, the fourth desorption segment intersects the boundary loop independently of the other three at the lower closure point. This kind of desorption mechanism reveals that the evaporation, especially of the larger mesopores, still depends on the connecting pores (network percolation) and is, in addition, possibly affected by a gradient in the mesopore

diameter, so that the first three segments evaporate at higher p/p^0 values. The sample SiO₂-100 (Figure 8D) possesses a typical H1-type boundary hysteresis loop, revealing an independent open mesopore network. Therefore, the desorption segments merge into the boundary loop independently, which is in agreement with the conclusions drawn from the PSDs and previous studies.^{55,72} Despite these findings, the exact mechanism behind the heterogeneity in pore size distribution (PSD) across the monolith remains debated. It is unclear whether this is due to variations in pH and diffusion across the monolith's width or if it is primarily influenced by internal vapor pressure during hydrothermal treatment.

Thus, based on desorption hysteresis scans, the following additional insights into the evaporation mechanisms of different pore networks can be extracted:

- The shape of the boundary loops does not allow for unambiguously determining the evaporation mechanism, but desorption scanning analysis provides further insight.
- Evidence of network percolation can be deduced from desorption hysteresis lines if all lines converge at the same p/p^0 value.
- Desorption scans help to possibly identify spatial heterogeneity in PSD's or spatial pore size gradient effects.⁷¹

Based on the interpretation that the merging of desorption scanning isotherms at higher values of the hysteresis loop reflects the heterogeneity of the pore network, the evaporation mechanism in such a porous system is illustrated in Figure 9a.

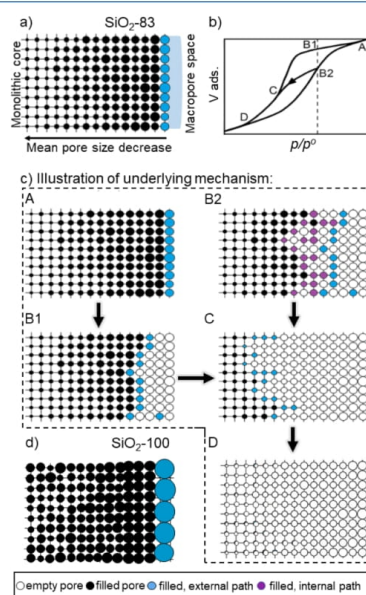


Figure 9. Anticipated model for the spatial heterogeneity of the mesopore space in silica monoliths in the form of a pore size gradient. Reproduced from Kube and Turke et al.⁷¹ (copyright 2020 American Chemical Society). (a) A schematic illustrating the mesopore space in SiO₂-83 with heterogeneously distributed mesopores; (b) isotherm and desorption hysteresis line for a pore network that exhibits a pore size gradient; (c) illustration of the mechanism of evaporation according to the isotherm and hysteresis line in Figure 9b; (d) model illustrating the large-size mesopore space in sample SiO₂-100: in spite of a possible gradient, the mesopores can be regarded as independent pores in terms of the physisorption behavior.

This translates the experimental data into a model for a possible pore network present in sample SiO₂-83 that illustrates the spatial pore size gradient effects as suggested by the desorption scanning isotherms in Figure 8B. In the underlying model, all the pores are connected to their neighboring pores in three dimensions. The mean pore size decreases toward the core of the monolith, while the largest

mesopores open into the macropore space. The main desorption isotherm in Figure 9b evaporates in the sequence A–B1–C–D (Figure 9c), where at point A, all the pores are filled, and at point D, the hysteresis loop closes. In comparison, the desorption scanning isotherm (Figure 9b) starts at point B2, where the majority of larger mesopores have already emptied, and the pore size gradient creates three regions within the pore network: i.e. (i) the dense core (smallest pores) with all the filled pores, (ii) the semi-dense shell farther outward having only a fraction of filled pores, and (iii) the larger pores toward the outer surface that are empty. This desorption scanning branch merges into the main isotherm at point C, where all the pores from the semi dense regions are vacant. The pores evaporate by both external and internal evaporation depending on the state of neighboring pores. At point C, the empty state of the pores is identical to the main desorption isotherm, thus the scanning desorption isotherm merges at this point. From point C–D, the entire pore network continues to empty, so the pores only evaporate into larger mesopores and then into external space (macropores) until point D, where all the mesopores are empty. A possible schematic for the open mesopore network of sample SiO₂-100 is presented in Figure 9d as a reflection of the desorption scanning isotherms from Figure 8D.

CONCLUSIONS

This study aimed to elucidate details in the synthesis of meso-macroporous SiO₂ monoliths generated by the widespread synthetic strategy established by Nakanishi et al. These materials are distributed as commercial products and are routinely used as stationary phases in liquid chromatography, especially in the pharmaceutical industry and research. Their usage is based on a well-defined and optimized macropore and mesopore space, which combines excellent flow and separation properties. However, the underlying synthetic steps are delicate, possibly impeding reproducible synthesis. In general, the synthetic process is quite sensitive to slight changes in temperature during the two relevant steps in the synthesis: within the initial gelation step, spinodal decomposition occurs between the siliceous phase and the polymer-containing phases, which ultimately creates the macropores (Figure 1). In our previous publication, we showed that this step is quite sensitive even to small temperature variations on the order of 1 K, allowing for tuning the macropore dimension.⁵⁸

Here, we focus on the subsequent harsh hydrothermal treatment step (Figures 1 and 10), which involves the release of NH_{3,aq} from urea, and the basic environment widens small cavities (micropores) into the desired mesoporous network. While this synthesis is well established and yields materials used as commercial stationary phases in HPLC, here we attempted to examine the relationship between the hydrothermal treatment step and the concomitant final mesopore space.

In the synthesis, tuning of the mesoporosity is typically achieved by applying different hydrothermal temperatures. Here, we synthesized SiO₂ monoliths by applying HTT between 80 and 110 °C, which resulted in a systematic change in the mesopore dimension and the connectivity between the mesopores. State-of-the-art physisorption analysis, using Ar (87 K) and N₂ (77 K) as adsorptives, revealed that a 3 °C increment in HTT (from 83 to 95 °C) led to an approximately 1 nm increase in the average mesopore diameter, ranging from 11 to 15 nm. Thus, modifying the HTT enables a precise

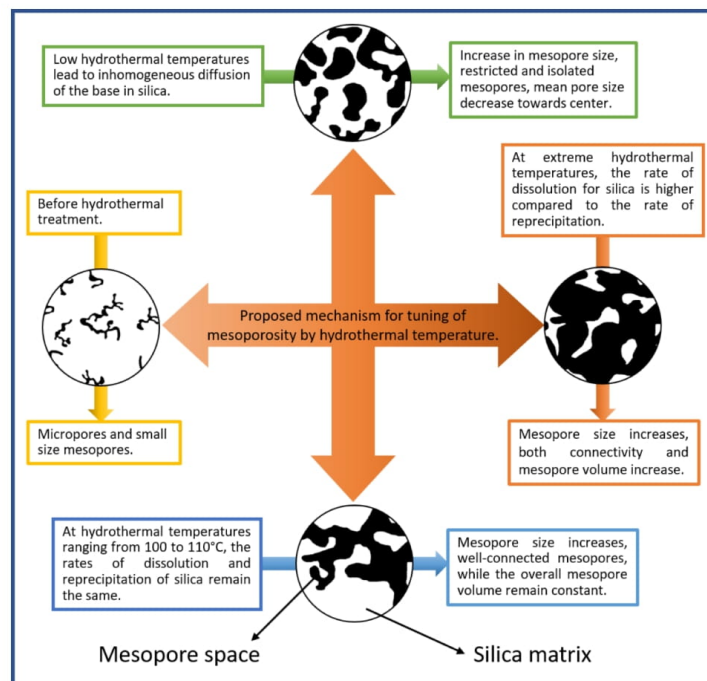


Figure 10. Proposed mechanism of hydrothermal treatment that controls the size of mesopores, pore network effects, and the spatial gradient in pore size distribution across the width of silica monoliths by changing the rate of silica dissolution of silica by base diffusion.

variation of the mesopore dimension. In the range of 95 to 110 °C, with every 5 °C change in HTT, a more pronounced increase of 4 nm is observed, yielding tunable average mesopore sizes from 15 to 27 nm. The influence of the base treatment and HTT on the mesopore space is summarized in Figure 10.

The most relevant insight of this study was obtained regarding the connection between the mesopores, which is a significant structural feature with respect to the separation properties in HPLC. Possible hindrance in the mutual connection, e.g., in the form of bottlenecks (see Figure 8), can potentially impede diffusion in the mesopore space. Thus, desorption hysteresis scanning analysis was performed on selectively chosen samples and revealed the evaporation mechanism and, consequently, the connection within the mesoporous network. The desorption scanning isotherms of samples SiO₂-83 and SiO₂-95 with type H2(a) hysteresis revealed pore blocking. Additionally, we interpret the merging of hysteresis lines at higher p/p^0 as an indication of the presence of spatial pore size gradient effects within the silica monoliths, confirming recent *in situ* physisorption SAXS studies. However, with an increase in HTT to finally 100 °C, the mesopore size distribution broadened, accompanied by the evolution of a well-connected mesoporous network without hindrance in connection. Despite these findings, the exact mechanism behind the heterogeneity in pore size distribution (PSD) across the monolith remains debated. It is unclear whether this is due to variations in pH and diffusion

across the monolith's width or if it is primarily influenced by internal vapor pressure during hydrothermal treatment.

From our analyses, we conclude that within the hydrothermal treatment, the rate of diffusion of the base within the material not only controls the size of mesopores but also affects the spatial distribution of mesopores of different sizes. Lower HTT involves a smaller concentration of OH⁻ ions and may not be sufficient to overcome energetic barriers. This may result in a spatial pore size gradient across the diameter of a strand, confirming recent *in situ* physisorption SAXS studies on monoliths.⁶⁸

The previous studies on hydrothermal treatment for tuning mesoporosity in silica monoliths focused mainly on the application perspective, particularly in HPLC.^{43–50} Our present study complements these studies and contributes to a better understanding of the relevant hydrothermal synthetic step. The insights might allow for advanced control of the mesopore size and pore network connectivity effects via hydrothermal treatment, which could help improve the properties of these monoliths for applications in separation and heterogeneous catalysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.langmuir.5c00572>.

Figure S1: Nitrogen and argon isotherms for all samples;
Figure S2: Comparison of PSD using different kernels;
Figure S3: Isotherms and PSD for SiO₂-100-1 and SiO₂-

100; Figure S4: Total cumulative surface area and cumulative pore volume; Figure S5: PSD for samples SiO₂—83, 89, and 95; Figure S6: Complete cycles of adsorption hysteresis scanning; Figure S7: GIF related to the mechanism of desorption hysteresis scanning (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

- (1) Roth, W. J.; Gil, B.; Makowski, W.; Marszalek, B.; Eliášová, P. Layer like porous materials with hierarchical structure. *Chem. Soc. Rev.* **2016**, *45* (12), 3400–3438.
- (2) Millini, R.; Bellussi, G. Hybrid organic–inorganic zeolites: status and perspectives. *Catal. Sci. Technol.* **2016**, *6* (8), 2502–2527.
- (3) Parker, R. M.; Guidetti, G.; Williams, C. A.; Zhao, T.; Narkevicius, A.; Vignolini, S.; Frka-Petecic, B. The self-assembly of cellulose nanocrystals: Hierarchical design of visual appearance. *Adv. Mater. Interfaces* **2018**, *30* (19), 1704477.
- (4) Xu, R.; Mao, J.; Peng, N.; Luo, X.; Chang, C. Chitin/clay microspheres with hierarchical architecture for highly efficient removal of organic dyes. *Carbohydr. Polym.* **2018**, *188*, 143–150.
- (5) Cychoz, K. A.; Guillet-Nicolas, R.; Garcia-Martinez, J.; Thommes, M. Recent advances in the textural characterization of hierarchically structured nanoporous materials. *Chem. Soc. Rev.* **2017**, *46* (2), 389–414.
- (6) Bi, Y.; Zhang, H.; Wang, H.; Jia, Q.; Zhang, S. Facile preparation of reduced GO modified porous ceramics with hierarchical pore structure as a highly efficient and durable sorbent material. *J. Phys. Chem. C* **2020**, *40* (5), 2106–2112.
- (7) Lorignon, F.; Gossard, A.; Carboni, M. Hierarchically porous monolithic MOFs: An ongoing challenge for industrial-scale effluent treatment. *Chem. Eng. J.* **2020**, *393*, 124765.
- (8) Singh, S. K.; Akhtar, M. J.; Kar, K. K. Hierarchical carbon nanotube-coated carbon fiber: ultra lightweight, thin, and highly efficient microwave absorber. *ACS Appl. Mater. Interfaces* **2018**, *10* (29), 24816–24828.
- (9) Schneider, D.; Mehlhorn, D.; Zeigermann, P.; Kärger, J.; Valiullin, R. Transport properties of hierarchical micro–mesoporous materials. *Chem. Soc. Rev.* **2016**, *45* (12), 3439–3467.
- (10) Bai, P.; Haldoupis, E.; Dauenhauer, P. J.; Tsapatsis, M.; Siepmann, J. I. Understanding diffusion in hierarchical zeolites with house-of-cards nanosheets. *ACS Nano* **2016**, *10* (8), 7612–7618.
- (11) Hartmann, M.; Schwieger, W. Hierarchically-structured porous materials: from basic understanding to applications. *Chem. Soc. Rev.* **2016**, *45* (12), 3311–3312.
- (12) Triantafillidis, C.; Elsaesser, M. S.; Hüsing, N. Chemical phase separation strategies towards silica monoliths with hierarchical porosity. *Chem. Soc. Rev.* **2013**, *42* (9), 3833–3846.
- (13) Enke, D.; Glaeser, R.; Tallarek, U. Sol-Gel and Porous Glass-Based Silica Monoliths with Hierarchical Pore Structure for Solid-Liquid Catalysis. *Chem. Ing. Technol.* **2016**, *88* (11), 1561–1585.
- (14) Sachse, A.; Galarneau, A.; Fajula, F.; Di Renzo, F.; Creux, P.; Coq, B. Functional silica monoliths with hierarchical uniform porosity as continuous flow catalytic reactors. *Microporous Mesoporous Mater.* **2011**, *140* (1–3), 58–68.
- (15) Li, F.; Wang, Z.; Ergang, N. S.; Fyfe, C. A.; Stein, A. Controlling the shape and alignment of mesopores by confinement in colloidal crystals: Designer pathways to silica monoliths with hierarchical porosity. *Langmuir* **2007**, *23* (7), 3996–4004.
- (16) Drisko, G. L.; Zelcer, A.; Caruso, R. A.; de AA Soler-Illia, G. J. One-pot synthesis of silica monoliths with hierarchically porous structure. *Microporous Mesoporous Mater.* **2012**, *148* (1), 137–144.
- (17) Putz, F.; Waag, A.; Balzer, C.; Braxmeier, S.; Elsaesser, M. S.; Ludescher, L.; Paris, O.; Malfait, W. J.; Reichenauer, G.; Hüsing, N. The influence of drying and calcination on surface chemistry, pore structure and mechanical properties of hierarchically organized porous silica monoliths. *Microporous Mesoporous Mater.* **2019**, *288*, 109578.
- (18) Guo, X.; Wang, R.; Yu, H.; Zhu, Y.; Nakanishi, K.; Kanamori, K.; Yang, H. Spontaneous preparation of hierarchically porous silica monoliths with uniform spherical mesopores confined in a well-defined macroporous framework. *Dalton Trans.* **2015**, *44* (30), 13592–13601.
- (19) Kato, M.; Sakai-Kato, K.; Toyo'oka, T. Silica sol-gel monolithic materials and their use in a variety of applications. *J. Sep. Sci.* **2005**, *28* (15), 1893–1908.
- (20) Galarneau, A.; Sachse, A.; Said, B.; Pelisson, C.-H.; Boscaro, P.; Brun, N.; Courtheoux, L.; Olivi-Tran, N.; Coasne, B.; Fajula, F. Hierarchical porous silica monoliths: A novel class of microreactors for process intensification in catalysis and adsorption. *C. R. Chim.* **2016**, *19* (1–2), 231–247.
- (21) Staniak, M.; Wójcik, M.; Sowa, I.; Tyszczyk-Rotko, K.; Strzemiński, M.; Dresler, S.; Myśliński, W. Silica-Based Monolithic Columns as a Tool in HPLC—An Overview of Application in Analysis of Active Compounds in Biological Samples. *Molecules* **2020**, *25* (14), 3149.
- (22) Majors, R. HPLC and UHPLC Columns: Then, Now, Next. *LC-GC. North Am.* **2018**, *36* (2), 128–132.
- (23) Turke, K.; Meinusch, R.; Cop, P.; Prates da Costa, E.; Brand, R. D.; Henss, A.; Schreiner, P. R.; Smarsly, B. M. Amine-Functionalized Nanoporous Silica Monoliths for Heterogeneous Catalysis of the Knoevenagel Condensation in Flow. *ACS Omega* **2021**, *6* (1), 425–437.
- (24) Zhu, J.; Hu, J.; Jiang, C.; Liu, S.; Li, Y. Ultralight, hydrophobic, monolithic konjac glucomannan-silica composite aerogel with thermal insulation and mechanical properties. *Carbohydr. Polym.* **2019**, *207*, 246–255.

- (25) Fajula, F.; Galarneau, A. Combining phase separation with pseudomorphic transformation for the control of the pore architecture of functional materials: a review. *Pet. Chem.* **2019**, *59* (8), 761–769.
- (26) Hwang, S.-W.; Jung, H.-H.; Hyun, S.-H.; Ahn, Y.-S. Effective preparation of crack-free silica aerogels via ambient drying. *J. Sol-Gel Sci. Technol.* **2007**, *41* (2), 139–146.
- (27) Belmoujahid, Y.; Bonne, M.; Scudeller, Y.; Schleich, D.; Grohens, Y.; Lebeau, B. Thermal conductivity of monolithic assemblies of SBA-15 ordered mesoporous silica particles. *Microporous Mesoporous Mater.* **2015**, *201*, 124–133.
- (28) Ibrahim, A. E.; Elhenawee, M.; Saleh, H.; Sebaiy, M. M. Overview on liquid chromatography and its greener chemistry application. *Ann. Adv. Chem.* **2021**, *5* (1), 004–012.
- (29) Unger, K. K.; Skudas, R.; Schulte, M. M. Particle packed columns and monolithic columns in high-performance liquid chromatography-comparison and critical appraisal. *J. Chromatogr. A* **2008**, *1184* (1–2), 393–415.
- (30) Walsh, Z.; Paull, B.; Macka, M. Inorganic monoliths in separation science: a review. *Anal. Chim. Acta* **2012**, *750*, 28–47.
- (31) Kirschning, A.; Solodenko, W.; Mennecke, K. Combining enabling techniques in organic synthesis: continuous flow processes with heterogenized catalysts. *Chem. Eur. J.* **2006**, *12* (23), 5972–5990.
- (32) Altmaier, S.; Cabrera, K. Structure and performance of silica-based monolithic HPLC columns. *J. Sep. Sci.* **2008**, *31* (14), 2551–2559.
- (33) Cabrera, K. Applications of silica-based monolithic HPLC columns. *J. Sep. Sci.* **2004**, *27* (10–11), 843–852.
- (34) Guiochon, G. Monolithic columns in high-performance liquid chromatography. *J. Chromatogr. A* **2007**, *1168*, 101–168.
- (35) Schachtschneider, A.; Wessig, M.; Spitzbarth, M.; Donner, A.; Fischer, C.; Drescher, M.; Polarz, S. Directional materials—nanoporous organosilica monoliths with multiple gradients prepared using click chemistry. *Angew. Chem., Int. Ed.* **2015**, *54* (36), 10465–10469.
- (36) Schulze, J. S.; Brand, R. D.; Hering, J. G.; Riegger, L. M.; Schreiner, P. R.; Smarsly, B. M. DMAP immobilized on porous silica particles and monoliths for the esterification of phenylethanol in continuous flow. *ChemCatChem* **2022**, *14* (8), No. e202101845.
- (37) Sachse, A.; Galarneau, A.; Coq, B.; Fajula, F. Monolithic flow microreactors improve fine chemicals synthesis. *New J. Chem.* **2011**, *35* (2), 259–264.
- (38) Sachse, A.; Hulea, V.; Finiels, A.; Coq, B.; Fajula, F.; Galarneau, A. Alumina-grafted macro-/mesoporous silica monoliths as continuous flow microreactors for the Diels–Alder reaction. *J. Catal.* **2012**, *287*, 62–67.
- (39) Sachse, A.; Linares, N.; Barbaro, P.; Fajula, F.; Galarneau, A. Selective hydrogenation over Pd nanoparticles supported on a pore-flow-through silica monolith microreactor with hierarchical porosity. *Dalton Trans.* **2013**, *42* (5), 1378–1384.
- (40) Nakanishi, K.; Soga, N. Phase separation in gelling silica–organic polymer solution: systems containing poly (sodium styrenesulfonate). *J. Am. Ceram. Soc.* **1991**, *74* (10), 2518–2530.
- (41) Nakanishi, K. Pore structure control of silica gels based on phase separation. *J. Porous Mater.* **1997**, *4* (2), 67–112.
- (42) Nakanishi, K.; Soga, N. Phase separation in silica sol–gel system containing poly (ethylene oxide) II. Effects of molecular weight and temperature. *Bull. Chem. Soc. Jpn.* **1997**, *70* (3), 587–592.
- (43) Puy, G.; Roux, R.; Demesmay, C.; Rocca, J.-L.; Iapichella, J.; Galarneau, A.; Brunel, D. Influence of the hydrothermal treatment on the chromatographic properties of monolithic silica capillaries for nano-liquid chromatography or capillary electrochromatography. *J. Chromatogr. A* **2007**, *1160* (1–2), 150–159.
- (44) Hara, T.; Mascotto, S.; Weidmann, C.; Smarsly, B. M. The effect of hydrothermal treatment on column performance for monolithic silica capillary columns. *J. Chromatogr. A* **2011**, *1218* (23), 3624–3635.
- (45) Inayat, A.; Reinhardt, B.; Uhlig, H.; Einicke, W.-D.; Enke, D. Silica monoliths with hierarchical porosity obtained from porous glasses. *Chem. Soc. Rev.* **2013**, *42* (9), 3753–3764.
- (46) Moukhalhal, K.; Le, N. H.; Bonne, M.; Toufaily, J.; Hamieh, T.; Daou, T. J.; Lebeau, B. Controlled crystallization of hierarchical monoliths composed of nanozeolites. *Cryst. Growth Des.* **2020**, *20* (8), 5413–5423.
- (47) Lei, J.-H.; Liu, D.; Guo, L.-P.; Yan, X.-M.; Tong, H. Fabrication and characterization of hexagonal mesoporous silica monolith via post-synthesized hydrothermal process. *J. Sol-Gel Sci. Technol.* **2006**, *39* (2), 169–174.
- (48) Mrowiec-Białoń, J.; Jarzębski, A. Fabrication and properties of silica monoliths with ultra large mesopores. *Microporous Mesoporous Mater.* **2008**, *109* (1–3), 429–435.
- (49) Yang, P.; Wang, W.; Xiao, X.; Jia, L. Hydrothermal preparation of hybrid carbon/silica monolithic capillary column for liquid chromatography. *J. Sep. Sci.* **2014**, *37* (15), 1911–1918.
- (50) Yu, L.; Brun, N.; Sakaushi, K.; Eckert, J.; Titirici, M. M. Hydrothermal nanocasting: Synthesis of hierarchically porous carbon monoliths and their application in lithium–sulfur batteries. *Carbon* **2013**, *61*, 245–253.
- (51) Thommes, M.; Smarsly, B.; Groenewolt, M.; Ravikovitch, P. I.; Neimark, A. V. Adsorption hysteresis of nitrogen and argon in pore networks and characterization of novel micro- and mesoporous silicas. *Langmuir* **2006**, *22* (2), 756–764.
- (52) Schlumberger, C.; Thommes, M. Characterization of hierarchically ordered porous materials by physisorption and mercury porosimetry—a tutorial review. *Adv. Mater. Interfaces* **2021**, *8* (4), 2002181.
- (53) Klomkang, N.; Do, D.; Nicholson, D. Hysteresis loop and scanning curves for argon adsorbed in mesopore arrays composed of two cavities and three necks. *J. Phys. Chem. C* **2015**, *119* (17), 9355–9363.
- (54) Cimino, R.; Cychosz, K. A.; Thommes, M.; Neimark, A. V. Experimental and theoretical studies of scanning adsorption–desorption isotherms. *Colloids Surf., A* **2013**, *437*, 76–89.
- (55) Svidrytski, A.; Hlushkou, D.; Thommes, M.; Monson, P. A.; Tallarek, U. Modeling the impact of mesoporous silica microstructures on the adsorption hysteresis loop. *J. Phys. Chem. C* **2020**, *124* (39), 21646–21655.
- (56) Tompsett, G.; Krogh, L.; Griffin, D.; Conner, W. Hysteresis and scanning behavior of mesoporous molecular sieves. *Langmuir* **2005**, *21* (18), 8214–8225.
- (57) Barsotti, E.; Tan, S. P.; Piri, M.; Chen, J.-H. Capillary-condensation hysteresis in naturally-occurring nanoporous media. *Fuel* **2020**, *263*, 116441.
- (58) Nakanishi, K. Sol–gel process of oxides accompanied by phase separation. *Bull. Chem. Soc. Jpn.* **2006**, *79* (5), 673–691.
- (59) Babin, J.; Iapichella, J.; Lefèvre, B.; Biolley, C.; Bellat, J.-P.; Fajula, F.; Galarneau, A. MCM-41 silica monoliths with independent control of meso- and macroporosity. *New J. Chem.* **2007**, *31* (11), 1907–1917.
- (60) El Kadib, A.; Chimenton, R.; Sachse, A.; Fajula, F.; Galarneau, A.; Coq, B. Functionalized inorganic monolithic microreactors for high productivity in fine chemicals catalytic synthesis. *Angew. Chem., Int. Ed.* **2009**, *48* (27), 4969–4972.
- (61) Meinsch, R.; Ellinghaus, R.; Hormann, K.; Tallarek, U.; Smarsly, B. M. On the underestimated impact of the gelation temperature on macro- and mesoporosity in monolithic silica. *Phys. Chem. Chem. Phys.* **2017**, *19* (22), 14821–14834.
- (62) Takahashi, R.; Nakanishi, K.; Soga, N. Small-angle X-ray scattering study of nanopore evolution of macroporous silica gel by solvent exchange. *Faraday Discuss.* **1995**, *101*, 249–263.
- (63) Ishizuka, N.; Minakuchi, H.; Nakanishi, K.; Hirao, K.; Tanaka, N. Chromatographic characterization of macroporous monolithic silica prepared via sol-gel process. *Colloids Surf., A* **2001**, *187*, 273–279.
- (64) Nakanishi, K.; Takahashi, R.; Nagakane, T.; Kitayama, K.; Koheiya, N.; Shikata, H.; Soga, N. Formation of hierarchical pore structure in silica gel. *J. Sol-Gel Sci. Technol.* **2000**, *17* (3), 191–210.
- (65) Galarneau, A.; Iapichella, J.; Brunel, D.; Fajula, F.; Bayram-Hahn, Z.; Unger, K.; Puy, G.; Demesmay, C.; Rocca, J. L. Spherical

ordered mesoporous silicas and silica monoliths as stationary phases for liquid chromatography. *J. Sep. Sci.* **2006**, *29* (6), 844–855.

(66) Finsy, R. On the critical radius in Ostwald ripening. *Langmuir* **2004**, *20*, 2975–2976.

(67) von der Lehr, M.; Ellinghaus, R.; Smarsly, B. M. Hierarchically porous monolithic silica with varying porosity using bis (trimethoxysilyl) arenes as precursors. *New J. Chem.* **2016**, *40* (5), 4455–4463.

(68) Boehm, H.-P. The Chemistry of Silica. Solubility, Polymerization, Colloid and Surface Properties, and Biochemistry. *Angew. Chem., Int. Ed.* **1980**, *92* (4), 328–328.

(69) Monson, P. A. Understanding adsorption/desorption hysteresis for fluids in mesoporous materials using simple molecular models and classical density functional theory. *Microporous Mesoporous Mater.* **2012**, *160*, 47–66.

(70) Landers, J.; Gor, G. Y.; Neimark, A. V. Density functional theory methods for characterization of porous materials. *Colloids Surf., A* **2013**, *437*, 3–32.

(71) Kube, S. A.; Turke, K.; Ellinghaus, R. D.; Wallacher, D.; Thommes, M.; Smarsly, B. M. Pore size gradient effect in monolithic silica mesopore networks revealed by in-situ SAXS physisorption. *Langmuir* **2020**, *36* (40), 11996–12009.

(72) Kleitz, F.; Berube, F.; Guillet-Nicolas, R.; Yang, C.-M.; Thommes, M. Probing adsorption, pore condensation, and hysteresis behavior of pure fluids in three-dimensional cubic mesoporous KIT-6 silica. *J. Phys. Chem. C* **2010**, *114* (20), 9344–9355.

(73) Ravikovitch, P. I.; Neimark, A. V. Density functional theory of adsorption in spherical cavities and pore size characterization of templated nanoporous silicas with cubic and three-dimensional hexagonal structures. *Langmuir* **2002**, *18* (5), 1550–1560.

(74) Ravikovitch, P. I.; Neimark, A. V. Experimental confirmation of different mechanisms of evaporation from ink-bottle type pores: equilibrium, pore blocking, and cavitation. *Langmuir* **2002**, *18* (25), 9830–9837.

Tuning the Mesopore Network in Meso- Macroporous Silica Monoliths by Hydrothermal Treatment – a Physisorption Study

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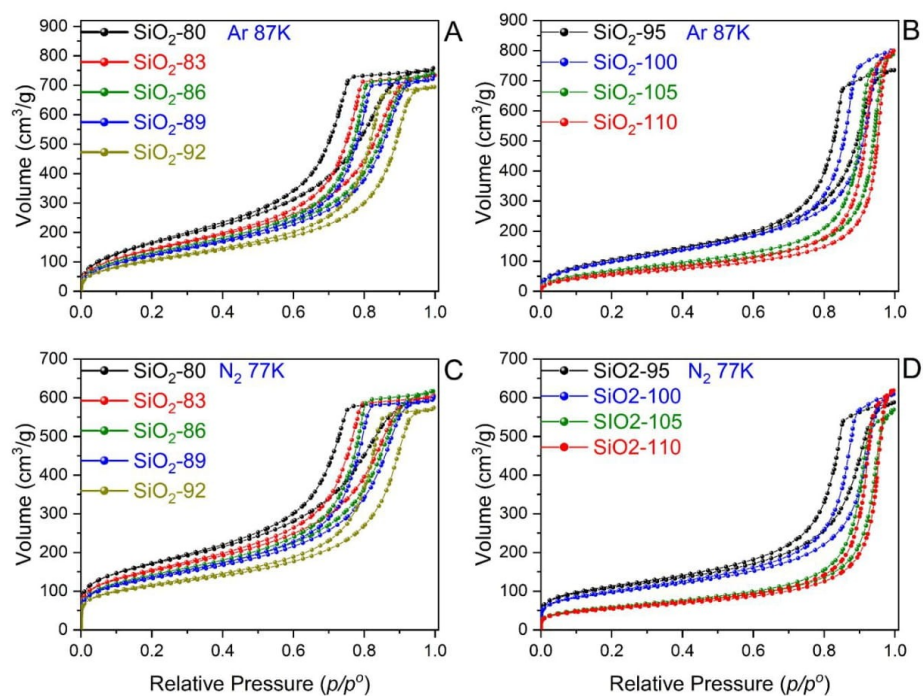


Figure S 1. A-D Physorption isotherms for silica monoliths measured by two different adsorptives (Ar at 87 K and N₂ at 77 K).

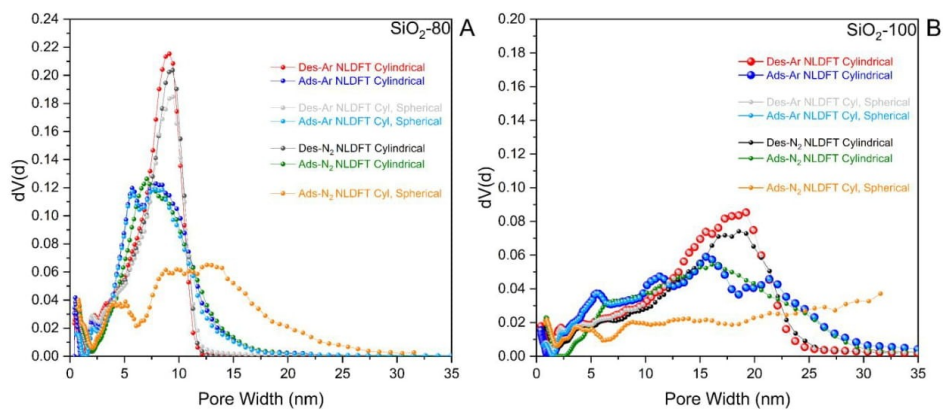


Figure S 2. AB Comparison of PSDs calculated from NLDFT cylindrical kernel for Argon 87 K and Nitrogen 77 K with NLDFT cylindrical and spherical kernel for Argon 87 K and Nitrogen 77 K.

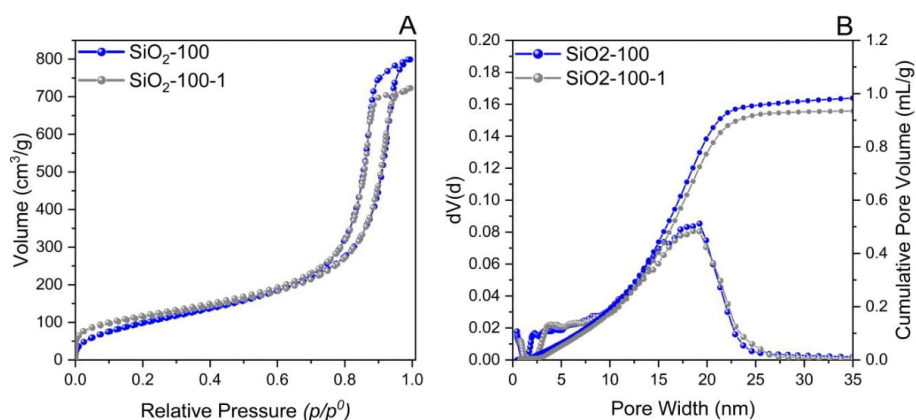


Figure S 3. (A) Ar 87 K physisorption isotherms for two silica monolithic samples treated at the same hydrothermal temperature but different treatment time: SiO₂-100 for 28 hours and SiO₂-100-1 for 20 hours. **(B)** Comparison of PSD calculated from NLDFT desorption isotherms for silica. Both figures indicate that different hydrothermal treatment times result in no significant difference in the isotherms and pore size distribution (PSD). However, the cumulative pore volume of SiO₂-100 is slightly higher than that of SiO₂-100-1 due to the longer hydrothermal treatment time. SiO₂-100 underwent a total of 28 hours of treatment (13 hours heating ramp plus 15 hours holding), while SiO₂-100-1 was treated for 20 hours (10 hours heating ramp plus 10 hours holding).

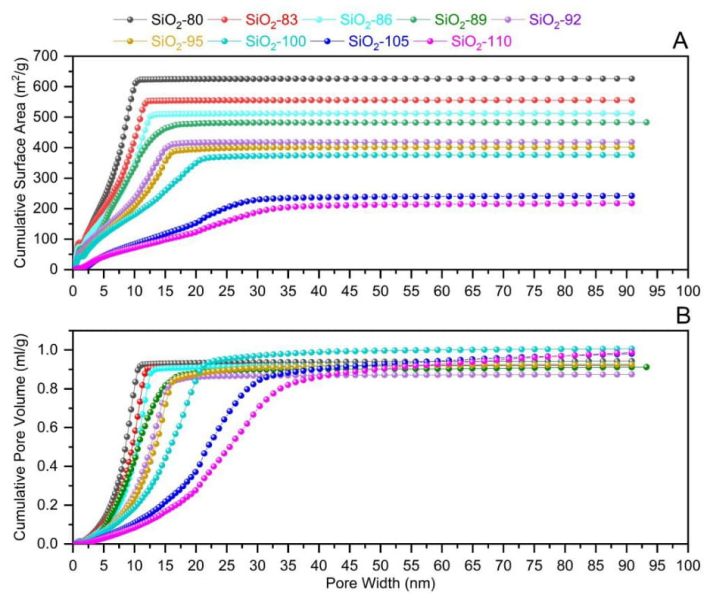


Figure S 4. A and B show the cumulative surface area and cumulative pore volume distributions contributed by the range of mesopores size and pores larger than 50 nm.

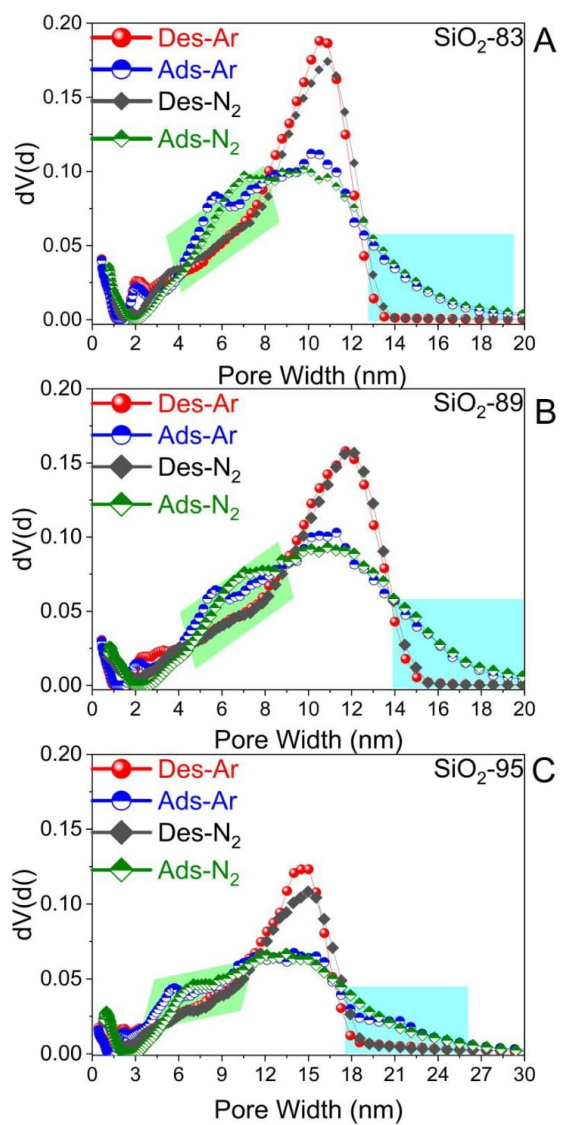


Figure S 5. A-C Pore size distributions calculated from Ar (87 K) and N₂ (77 K) adsorption and desorption branches of physisorption isotherms using NLDFT method for cylindrical pores.

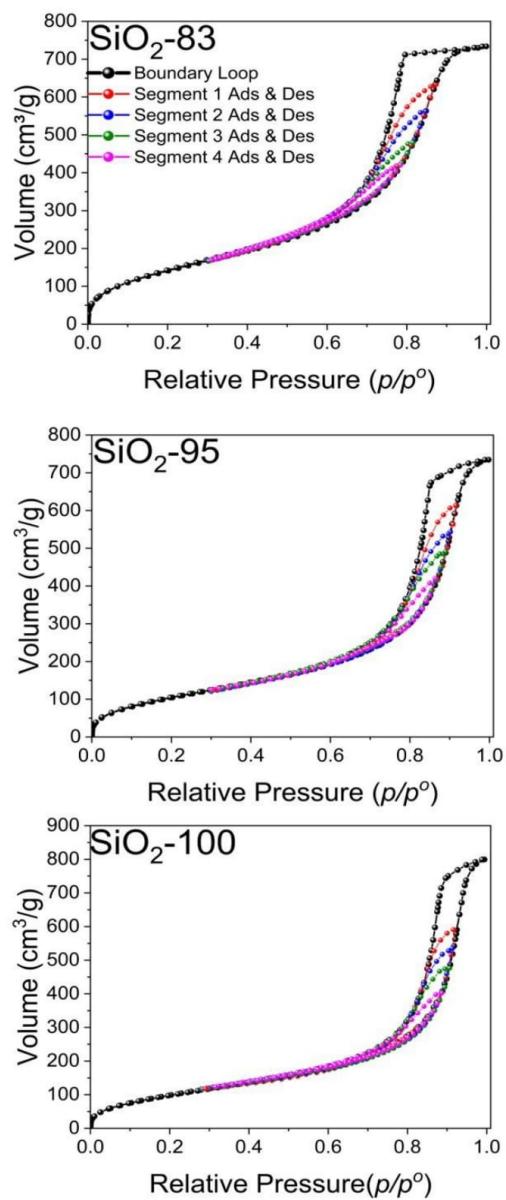


Figure S 6. Hysteresis isotherms along with their complete adsorption and desorption segments showing the complete mechanism of hysteresis scanning measured with Ar ($T = 87$ K).

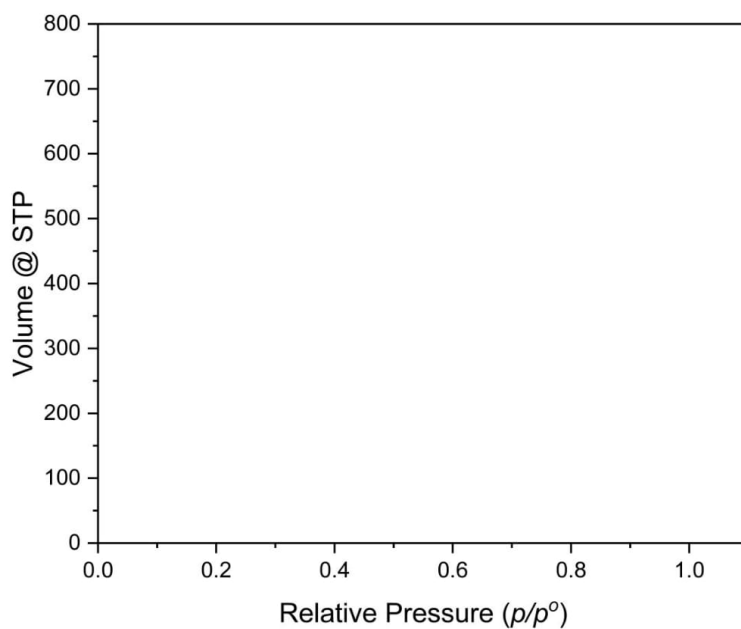
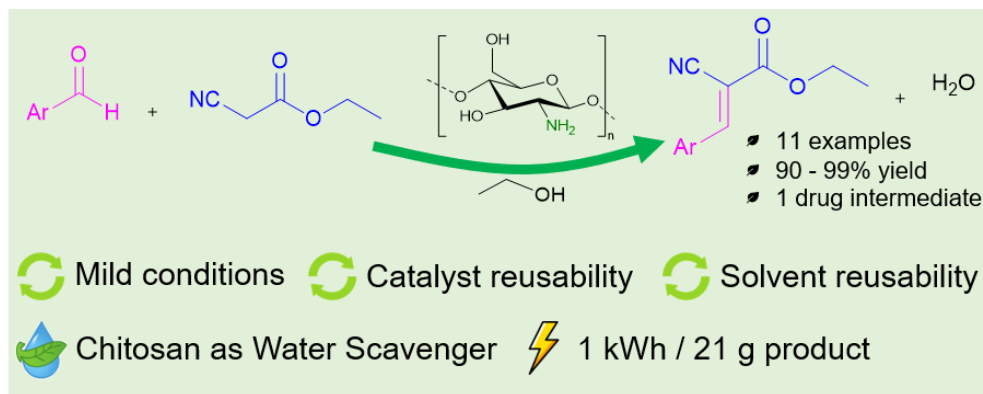


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Publication 2

Chitosan as a solid catalyst for the one-pot Knoevenagel condensation in the context of sustainable chemistry



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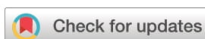
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Chitosan as a solid catalyst for the one-pot Knoevenagel condensation in the context of sustainable chemistry

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 Paul P. Debes, ^{ac} Jaime Gallego, ^{ac} Peter R. Schreiner ^{*bc} and
 Bernd M. Smarsly ^{*ac}

We employed chitosan to catalyse the Knoevenagel condensation between various benzaldehydes and ethyl cyanoacetate. Chitosan exhibited excellent reusability, maintaining catalytic efficiency over six reaction cycles with yields consistently between 95% and 98%, for benzaldehyde and *p*-tolualdehyde. Furthermore, we were able to recycle the used solvent (ethanol), enhancing overall sustainability. Expanding the application of chitosan, we synthesised 4-methyl-3-oxo-*N*-phenyl-2-(phenylmethylene)-pentanamide, a key intermediate of the statin drug Atorvastatin synthesis on gram-scale with 96% yield. This demonstrates the use of chitosan as a catalyst for the synthesis of fine chemicals with improved sustainability; notably, the chitosan-catalysed process aligns with several key principles of sustainability. The employed chitosan exhibited a high water-binding capacity of about 520%, which enhances product formation by capturing water as the reaction byproduct. The high yields in the repeated use originated from the catalytic action of a large number of amino groups and the extraordinary and reversible swelling and binding capacity for polar solvents. We propose that such a swellable, insoluble, abundant catalyst material that is able to bind large amounts of water, constitutes a promising concept in organocatalysis. Analytical techniques such as scanning electron microscopy, mercury intrusion porosimetry, diffuse reflectance infrared Fourier transform spectroscopy, and X-ray diffraction analysis verified the catalyst's integrity, showing no significant physical or chemical degradation after multiple uses. Thus, chitosan emerges as a sustainable catalyst for organic synthesis with promising implications for Knoevenagel reactions.

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Introduction

Natural biopolymers are increasingly explored as supports or active components in the design of sustainable heterogeneous catalysts for organic synthesis.^{1–3} The underlying principles include the development of environmentally friendly processes that reduce waste, minimize energy consumption, and utilise renewable resources.^{4,5} A sustainable heterogeneous catalyst for organic synthesis must exhibit high catalytic efficiency, stability, reusability, and ideally biodegradability. For example, mesoporous silica-supported catalysts and polymer-supported organocatalysts are known for their high efficacies and selectivities, but immobilization of organocatalysts on different

supports frequently involves hazardous solvents, acids, or bases.^{6–10} The use of natural biomolecules and biopolymers as organocatalysts for organic reactions can be considered a particularly appealing concept for sustainable organic transformations due to their abundance, biocompatibility, chiral backbones, and biodegradability.^{2,11}

Chitosan is such an example, composed of poly-*D*-glucosamine, and it is abundantly available in living organisms.¹² Technically, chitosan is obtained by deacetylation of chitin, which is a poly-*N*-acetylglucosamine extracted from the exoskeleton of shrimp, crabs, and a few molluscs (Fig. 1).^{13,14} The unique features of chitosan as a solid heterogeneous catalyst, among others, are its natural abundance, biocompatibility, and enormous number of amino groups in the backbone.^{15–17} Amino groups act as catalytic sites for base-catalysed organic reactions, but can also be transformed into other functional groups. For instance, the chitosan amino groups can be converted into imines by reaction with aldehydes, to use them, for example, as anchoring sites of metal complexes.^{18,19}

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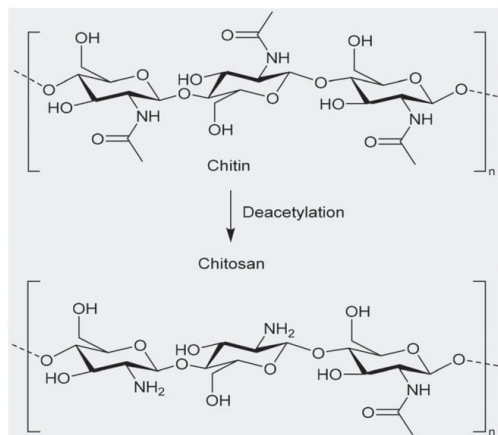


Fig. 1 Deacetylation of poly-*N*-acetylglucosamine (chitin) to poly-*D*-glucosamine (chitosan).

So far, materials widely used as a heterogeneous catalyst for base-catalysed organic reactions are porous silica materials, zeolites, and metal organic frameworks (MOFs) containing amino groups.^{6,20–23} Among amino-functionalized silica, zeolites, or MOFs, chitosan is considered to be superior in terms of sustainability and natural availability, as it is derived from chitin, which is the second most abundant biopolymer after cellulose.^{24–27} Typical uses of chitosan as a basic heterogeneous catalyst or as a support for anchoring metals concern micro- and nano-scaled particles, flakes, fibres, sponges, gel beads, and membranes.^{28–33}

In 2017, Sakthivel *et al.* first reported the use of pristine chitosan as a solid base catalyst for the Knoevenagel condensation to synthesize benzylidenemalononitriles. They achieved high yields with different benzaldehydes and malononitrile under mild conditions (40 °C, ethanol, solvent) and demonstrated chitosan's reusability for up to four cycles without significant loss in activity.²⁸

In 2020, Anbu *et al.* expanded on this by using chitosan for the Knoevenagel–Doebner condensation to synthesize α,β -unsaturated carboxylic acids. They conducted reactions at 70 °C, testing various solvents, and found no loss in catalytic activity over five cycles, together with no significant structural changes in chitosan as confirmed by XRD and SEM analysis.²⁶ Later in 2020, Anbu *et al.* extended their work to Knoevenagel condensations of benzaldehydes with cyanoacetamide, once again showing stable catalytic performance over five cycles with no structural and changes in chitosan.²⁵

While the general mechanism of the Knoevenagel reactions, involving aldehydes and NH_2 groups as catalyst, is well known, a few studies addressed mechanistic details and revealed the relevance of the stability of the imine intermediate for the product formation, using DFT calculations and suitable NMR experiments.^{34,35}

Despite these promising results, several challenges persist. Previous studies relied on hazardous solvents such as DMF, DMSO, or DCM, which are incompatible with green chemistry

standards. Additionally, high reaction temperatures (*e.g.*, 70 °C) and the absence of solvent recycling reduce the overall sustainability of the processes. Moreover, research on gram-scale synthesis and applications in industrially relevant reactions particularly for drugs preparations *etc.* have not been reported. The sustainability claim is limited to the use of solid chitosan or chitosan derivatives as sustainable catalyst, while the broader principles of green chemistry are not consistently applied throughout the process.^{25,26,35,36} To address these challenges, we focused on the use of solid chitosan as a catalyst for Knoevenagel condensations, discussing potential industrial relevance. While previous studies demonstrated chitosan-catalysed Knoevenagel condensations, *e.g.*, using malononitrile ($\text{p}K_{\text{a}} \approx 11.0$ in DMSO at 25 °C) and cyanoacetamide ($\text{p}K_{\text{a}} \approx 9.0$),^{25,26} our study uses ethyl cyanoacetate ($\text{p}K_{\text{a}} \approx 13.1$), a less acidic and sterically more demanding substrate.³⁷ Thus, ethyl cyanoacetate is used to clarify if chitosan shows promising catalytic performance also for a compound with lower C–H acidity under mild conditions, especially room temperature. In particular, after exploring the reaction of benzaldehydes with ethyl cyanoacetate as a model and we extend our study to the synthesis of an Atorvastatin intermediate [4-methyl-3-oxo-*N*-phenyl-2-(phenylmethylene)pentanamide] with improved sustainability with respect to several criteria. Atorvastatin is a widely used statin drug for preventing cardiovascular diseases, and its efficient synthesis is of significant pharmaceutical relevance.^{38–41}

Compared to previous studies on chitosan used for the Knoevenagel reaction, our study focuses on “green chemistry” principles by utilizing eco-friendly solvents like ethanol and acetone, employing conditions near room temperature, and facilitating catalyst and solvent recovery to minimize waste.

Additionally, chitosan's remarkable affinity for water is studied by water-binding capacity (WBC) and water vapour sorption studies. This unique property enables chitosan to capture the water produced in the Knoevenagel condensation, effectively driving the reaction toward condensation. Moreover, chitosan's significant swelling capacity for the employed solvent ethanol is believed to enhance the accessibility of catalytic sites, highlighting its adaptability as catalytic systems.

To assess the robustness of the catalyst, we conducted detailed analyses using scanning electron microscopy (SEM), mercury intrusion porosimetry (MIP), diffuse reflectance infrared Fourier transform spectroscopy (DRIFT), and X-ray diffraction (XRD).

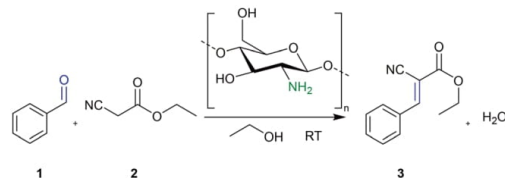
Thus, our study addresses and discusses the sustainable use of chitosan as a solid base catalyst for fine chemical synthesis. By aligning with green chemistry principles, our study is intended to contribute to the development of eco-friendly and more efficient organocatalytic processes.

Results and discussions

Efficiency of chitosan as solid catalyst for Knoevenagel condensations

Here, we focus on the Knoevenagel reaction between benzaldehydes and ethyl cyanoacetate (Scheme 1) as our standard





Scheme 1 Knoevenagel condensation of benzaldehyde with ethyl cyanoacetate at room temperature using solid chitosan as catalyst in ethanol.

Table 1 Optimization of reaction parameters for the reaction between benzaldehyde (1) and ethyl cyanoacetate (2) at room temperature^a

Entry	Chitosan ^b (mg)	Time (h)	Yield (%)
1	0	72	<1 ^c
2	0 ^d	48	<3
3	25	24	45
4	50 1st run	24	93
5	50 2nd run	24	95
6	50 3rd run	24	95
7	50 4th run	24	96
8	50 5th run	24	96
9	50 6th run	24	96
10 ^e	50	13	94
11	100	20	95

^a Reaction conditions: 2 mmol benzaldehyde and 2 mmol ethyl cyanoacetate in 2.5 mL EtOH at 25 °C. ^b 50 mg of chitosan reused six times, no loss in catalytic activity observed. ^c Blank reaction analysed with GC.

^d 50 mg of chitin used instead of chitosan to analyse the influence of the macromolecular structure in the absence of amino groups. ^e The reaction conducted at 40 °C yielded 94% product after 13 hours.

reaction to explore the catalytic efficiency of chitosan and, as an application case, the synthesis of a drug intermediate synthesis.

A blank control reaction (Table 1, entry 1) between benzaldehyde (1, 2 mmol) and ethyl cyanoacetate (2, 2.1 mmol) in ethanol at room-temperature delivers only traces of product after 72 h, as confirmed by gas chromatography (GC). The reaction (Table 1, entry 2) using 25 mg chitin as the catalyst (the untreated polysaccharide bearing no amino groups) yielded less than 3% of product after 48 h. In stark contrast the same amount of chitosan gave 45% product yield, and 50 mg of chitosan gave 93% yield after 24 h (Table 1, entries 3 and 4). This comparison clearly confirms that the amino groups are responsible for the high yields, acting as catalyst.

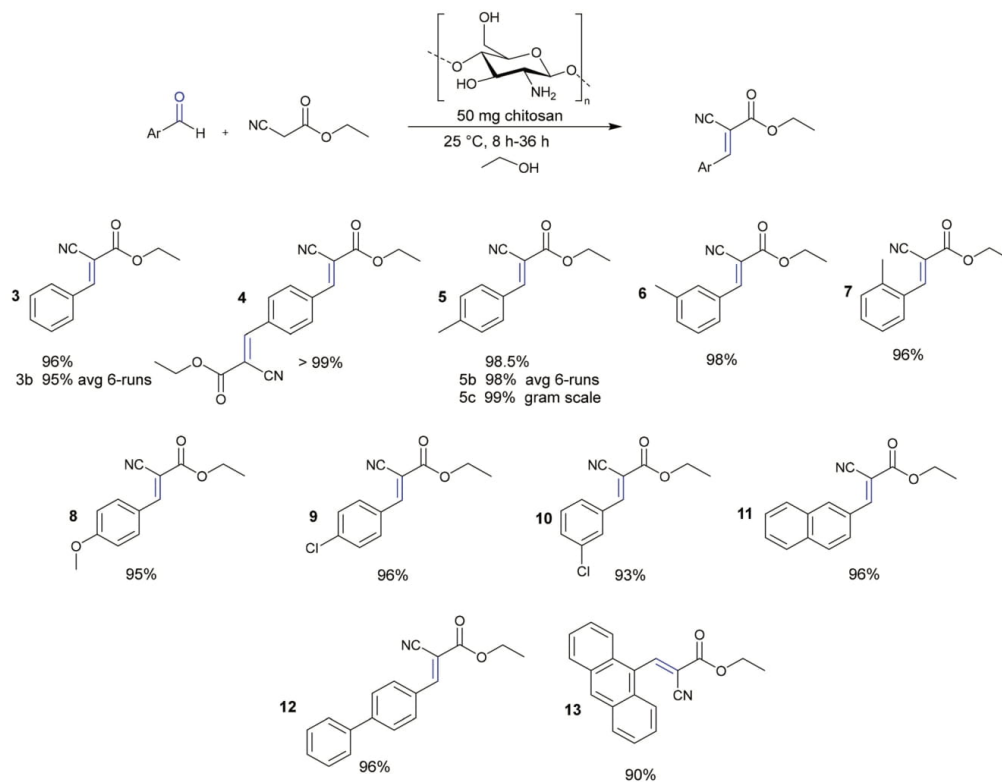
The product yield and purity were confirmed by GC, electrospray ionization high-resolution mass spectrometry (ESI-HRMS), ¹H NMR, and ¹³C-NMR (see SI for details). Room temperature (RT) and ethanol were kept to match sustainable chemistry standards. To investigate the catalytic efficiency and reusability of chitosan, the reaction was repeated six times after filtering and drying pre-used chitosan at 40 °C under reduced pressure for 2 h (Table 1, entries 4–9). All six reaction cycles produced high yields without loss of catalytic activity. Additionally, not only chitosan was recovered and reused after each cycle, but also ethanol, by using a rotary evaporator. The recovered ethanol (2.5 mL) was mixed with additional 0.5 mL from ethanol recovered from washing

chitosan. Also, a total of approximately 2.3 g of product 3 (Scheme 1) was produced by using 50 mg of chitosan as catalyst and using 6 mL of ethanol for six reactions cycles. Additionally, when the reaction was conducted at 40 °C, a 94% yield was achieved in just 13 h however, this came at the cost of a 10% increase in energy consumption due to the elevated temperature (entry 10). Furthermore, increasing the catalyst mass to 100 mg slightly reduced the reaction time to 20 h with a yield of 95% (entry 11). However, such increased catalyst amount required additional solvent to maintain proper dispersion, more solvent for catalyst washing, and longer drying time after the reaction cycle, all of which increased the energy and resource demands. Overall, a total electrical energy of ca. 0.2 kWh was determined for a complete reaction cycle in this case, yielding ca. 1.9 mmol of products, which varies depending on timing and conditions (*vide infra*).

Notably, quantifying the molar percentage of active amino groups in chitosan particles presents a significant challenge due to their large particle sizes and the presence of potentially inaccessible amino groups. According to the supplier, the chitosan material used in this study is 75% deacetylated, and elemental analysis indicates approximately 0.55 mmol g⁻¹ of nitrogen, suggesting an expected content of 0.41 mmol g⁻¹ of amino groups. Based on this, 50 mg of chitosan contain 0.0205 mmol of amino groups. However, the actual number of surface-active amino groups is likely much lower. Attempts to confirm this value *via* the Kaiser test proved difficult, as the bulky reagents were probably unable to access the hindered amino groups within the macromolecular network. Similarly, acid-base titration was unsuitable due to chitosan's solubility in acidic media, while for the catalytic reaction chitosan is present as a solid, undissolved particles. As a result, as catalyst quantity we give the mass of chitosan (in mg) rather than an exact molar percentage of amino groups.

The reaction was further subjected to different substrates that resulted in similarly high yields (Scheme 2, 3–13). In most cases, reactants were fully converted into their condensation products after 24 h. With terephthalaldehyde, the reaction was completed after already 8 h leading to the appearance of the ethanol-insoluble solid product (product 4, Scheme 2), while 2-naphthaldehyde and 9-anthracenecarboxaldehyde required 30 and 36 h for full conversion to 11 and 13 respectively. Given the nearly complete conversion and high selectivity, the products were characterized after drying at room temperature without further purification (except 13). The yield and purity of all products was checked by electrospray ionization high-resolution mass spectrometry (ESI-HRMS), ¹H NMR, and ¹³C NMR spectroscopy (all mass and NMR spectra are provided in the SI file). The MS data showed no signals corresponding to side products, while trace impurities were detected that were attributed to common silicon grease contamination from the glassware. On average a yield of 96% was obtained throughout all reactions based on the final weight of solid products. All products exhibited the thermodynamically favoured *E* isomer, as determined by ¹H-NMR, except for 13 which shows 93% *E* isomer. The spectra were compared and found to be





Scheme 2 Substrate scope of substituted benzaldehydes reacting with ethyl cyanoacetate using chitosan as catalyst under optimized conditions^{a-d}. ^a 2 mmol benzaldehyde derivative, 2 mmol ethyl cyanoacetate. ^b Ethanol used as solvent for all the reactions except for 13 where a 1 : 2 mixture of ethanol and toluene (in volume) was used because of solubility issues. ^c General reaction time of 24 h except entries 4, 11, and 13 with 8 h, 30 h and 36 h, respectively. All reactions carried out at 25 °C except for 13 which was carried out at 40 °C to increase solubility. For gram-scale synthesis **5c**, a reaction time 48 h and 40 °C were used, and 99% of product was achieved. ^d Products **3b** and **5b** correspond to the reusability tests of products **3** and **5**, respectively, where each reaction was repeated six times using the same 50 mg portion of chitosan across all cycles; for entry **5c**, 300 mg recycled chitosan was reused for gram-scale synthesis. For product 13, 100 mg of chitosan was used.

consistent with those previously reported in the literature (shown in the SI file). For **5b**, the reaction was run six times by reusing 50 mg chitosan as catalyst, resulting in 98% yield on average, and no loss in catalytic activity was observed. Before reusing in a subsequent run, chitosan was dried at 40 °C under reduced pressure oven for 2 h to evaporate ethanol and traces of water, so that after 2 h another reaction was ready to run (see Fig. 6 for the synthetic process). With the goal to investigate for upscaled synthesis using chitosan as catalyst, a gram-scale synthesis of **5** was carried out (**5c**, Scheme 2) using 300 mg of already used chitosan that yielded 4.30 g (99%) of product after 48 h. This result shows that gram-scale synthesis performs equally well. Overall, the straightforward nature of the process helped to minimise product loss.

To assess the energy demand of the one-pot synthesis, the energy consumption was calculated at every step by using an electricity meter. The total electric energy consumption for the

synthesis was 0.212 kWh encompassing the entire synthesis chain (26.5 h), for the synthesis of *ca.* 2.0 mmol of products. For comparison, this amount of energy is approximately what a typical laptop (≈ 60 W) would consume if operated for about 3.5 h. Overall, stirring for 24 h at room temperature consumed 0.136 kWh, suction filtration took 5 min and 0.022 kWh, the rotary evaporator used 0.048 kWh in 20 min, and drying in a vacuum oven for 2 h required 0.006 kWh. The energy cost may vary based on stirring time and temperature adjustments, of course. Yet, the mild conditions and one-pot synthesis thus made the overall process quite energy-efficient. As chitosan was purchased from suppliers, the energy consumption during conversion of the shrimp's exoskeleton to chitosan is not included in these calculations. However, it is expected not to be high as the process involves chemical extraction of chitosan at a maximum temperature of 100 °C for 3 h.⁴² In summary, the total energy consumption of this process is still low on an

Table 2 Comparison of different catalytic systems, for the Knoevenagel condensation between benzaldehyde and ethyl cyanoacetate, with the present study

No#	Catalyst	Temperature (°C)	Time (h)	Yield (%)	Catalyst reusability	Ref.	Price ^f
1	Au(OCH ₂ CF ₃)(PPh ₃)	50	97	93	NR	43	400–450 US\$ per g
2	Fly ash supported CaO ^a	90	2	83	3	50	300–500 US\$ per g
3	Carbon Nitride	Microwaves	0.2	87	5	45	Ca. 1–10 US\$ per g
4	UMCM-1-NH ₂ ^b	40	2.2	73	3	46	500–3000 US\$ per g
5	AP-SiO ₂ @Fe ₃ O ₄ ^c	RT	1.5	90	5	44	550 US\$ per 10 mL g ⁻¹
6	Na-A-PW9 ^d	RT	6	83	6	47	54–104 US\$ per g
7	MCM-41-APTMS ^e	80	4	95	4 ^f	48	60–105 US\$ per g
8	Silica monolith-APTMS ^g	RT	Flow	87	NR ^g	6	650–1400 US\$ per column
9	PgBd-porous organic polymer ^h	60	24	96	6	49	60–125 US\$ per g
10	Chitosan	RT	24	96	6	This study	6 US\$ per g

^a Catalyst was reactivated at 700 °C for 2 h before use. ^b UMCM-1-NH₂ = University of Michigan crystalline material-1-amine. ^c AP = aminopropyl. ^d Tri-lacunary polyoxometalates of Na₈H[A-PW₉O₃₄]. ^e APTMS = (3-aminopropyl)triethoxysilane. ^f Catalytic activity gradually decreased to 50% at 4th cycle. ^g Flow catalysis by connecting APTMS-silica monolithic column to an HPLC pump, 30% loss in catalytic activity after 65 h of continuous use. ^h PgBd = phloroglucinol and benzidine. ⁱ Prices are estimated from multiple suppliers (lowest to highest); unavailable prices were approximated for respective precursors of catalysts as of 25 Jun 2025 with help of ChatGPT.

absolute scale, largely owing to the efficiency of the one-pot synthetic approach.

To have a critical and comparative analysis of our work in terms of sustainability, we compared our study to already reported protocols for the synthesis of **3**. Table 2 compares chitosan with different solid heterogeneous basic catalysts used to catalyse the reaction between benzaldehyde and ethyl cyanoacetate, comparing relevant sustainability parameters. Apparently, chitosan stands out as a significantly more cost-effective option, and an environmentally friendly and sustainable choice for this reaction compared to other catalysts. All alternative catalysts are either metal-based^{43,44} and/or they are prepared through multistep syntheses partially involving hazardous reagents.^{6,43–49} A meaningful comparison of energy consumption is challenging, as the synthesis of these catalytic systems often involves multiple steps, the energy consumption of which not being reported, including the functionalization of organic catalysts onto support materials in some cases (Table 2 entries 4 to 8). The yields are significantly lower for these catalysts, and the reusability is substandard as compared to chitosan. Some of these catalysts gradually degrade upon continuous re-use,^{5,46,48} and some of them require higher temperatures for reactivation.⁵⁰ Thus, a comparison of these ten catalysts already indicates good compatibility of chitosan as catalyst with certain principles of sustainable chemistry, which is scrutinised below (Table 4).

As solid chitosan showcased remarkable efficiency as basic catalyst for the Knoevenagel condensation and high reusability, we studied its use in the synthesis of an industrially produced drug, namely an intermediate in the synthesis of Atorvastatin.³⁹

Pfizer's Atorvastatin synthesis route is summarized in Scheme 4.³⁹ Intermediates **19** and **20** (highlighted in blue boxes) are synthesised separately and then undergo a reaction to the target molecule Atorvastatin **22** after two additional steps. Most Atorvastatin-related syntheses focus on intermediate **20**. For the synthesis of intermediate **18**, 4-methyl-3-oxo-*N*-phenyl-2-(phenylmethylene)pentanamide (highlighted in the green box, Scheme 4) only a handful of studies are available (Table 3). In contrast, most reported synthetic routes toward

Table 3 Comparison of already reported synthetic conditions for Atorvastatin intermediate **18** with the conditions used in the present study

No#	Catalyst	Temperature °C	Time (h)	Yield %	Ref.
1	Piperidine/AcOH	84	3	80	40
2	β-alanine/AcOH	61	21	NR	53
3	4-Aminophenol/AcOH	69	24	93	55
4	MNPs-IT-PA	80	4	84	54
5	DABCO-PDO/AcOH	RT	3	83	56
6	DMAP/HCOOH	120	Flow	36	57
7	Chitosan	RT	26	> 96	This study

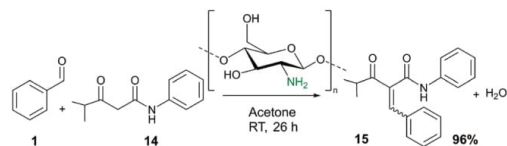
Atorvastatin start either from **18** or, in most cases, from intermediate **19**.^{40,51–54} Frequently, new reported total synthetic approaches rely on a previously established route for the synthesis of **18** where β-alanine and acetic acid are used as catalysts applying an energy intensive Dean–Stark trap step.⁵³ Here, we present a facile and sustainable synthesis for **18**, performed at room temperature, utilizing chitosan as the catalyst in acetone, without additives, resulting in an excellent yield of 96% after 26 h (Scheme 3). The synthetic process is described in detail in the “Experimental section”.

The high yield was confirmed by ESI-HRMS, ¹H-NMR and ¹³C-NMR spectroscopy (spectra given in the SI file). Although the ¹H-NMR spectrum shows an *E* and *Z* isomer mixture, this is irrelevant for the subsequent step of **19** as it involves the addition of *para*-fluorobenzaldehyde to the double bond of **18** to form racemic **19**. By utilization of solid chitosan as a catalyst, along with acetone as solvent at room temperature, this synthesis stands out as sustainable and cost-effective. As two equivalents of benzaldehyde were used for the synthesis of **18**, removal of excess benzaldehyde was accomplished by a silica column using hexane and ethyl acetate 30 : 1. Evidently, the use of hexane is undesired, but was inevitable for purification. Future work might find less harmful procedures for this step.

Table 3 provides a comparison of well-known reported syntheses for **18** with the approach presented in this study. Our method not only achieves higher yields but also stands out



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Scheme 3 Synthesis of 4-methyl-3-oxo-N-phenyl-2-(phenylmethylene)pentanamide using solid chitosan as catalyst in acetone at room temperature.

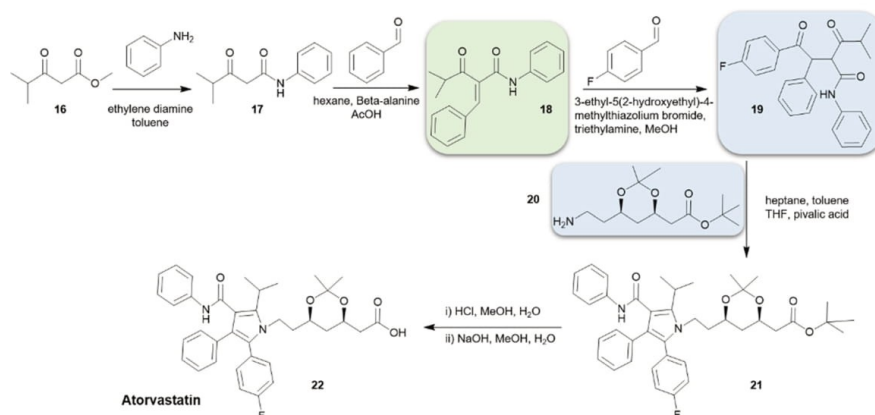
due to a one-pot synthetic approach without additives (e.g., absence of acid), room-temperature conditions, and the ability to reuse the catalyst. Contrarily, entries 1 to 6 in Table 3 lack catalyst reusability, except for entry 4 where a heterogeneous catalyst (propylamine modified with imidazolium ions on magnetic nanoparticles) can be reused multiple times. Entry 6 represents a recent study using a continuous-flow approach. However, the homogeneous catalyst DMAP poses potential hazards owing to toxicity. Overall, the use of unsustainable solvents and catalysts, and high-temperature conditions in all reported methods renders them incompatible with several principles a “green”/sustainable chemistry.

Furthermore, using chitosan as a catalyst offers the distinct advantage of avoiding a procedure to remove water in the synthesis of **18**. The effectiveness of chitosan in this context arises from its peculiar macromolecular structure, which is rich in amino and hydroxyl groups. These groups result in a marked binding capacities and swelling capacity ($S_{\%}$) in protic solvents.⁵⁸ Cho *et al.* reported WBC values ranging from 458% to 805% for chitosan, extracted from shrimp shells; the values depend on the degree of deacetylation (DD) and bulk density.⁵⁹ In our study, the WBC of chitosan was determined using the method developed by Wang and Kinsella.⁶⁰ The chitosan material employed as catalyst was 75% deacetylated and exhibited a WBC value of 520%. This value is 29-fold higher than the amount of water (1 mmol or 18 mg) released during

the condensation reaction for synthesizing **18** with our standard procedure (using 213 mg benzaldehyde). Additionally, the ethanol-binding capacity (EBC), measured using the same method, was found to be 104%. These high binding capacities for protic solvents facilitate the rearrangement of chitosan's polymer chains, presumably exposing more catalytic sites, which can be further understood through a swelling experiment, providing the percentage of solvent kept after the swelling experiment ($S_{\%}$). The $S_{\%}$ values were determined using the method developed by Gupta *et al.*⁶¹ resulting in values of 607% for chitosan in water and 171% in ethanol. These results highlight a crucial property of chitosan in protic solvents—its ability to swell, thereby increasing the surface area and exposing more catalytic sites, ultimately enhancing its catalytic efficiency. Fig. 2 illustrates the swelling of chitosan in a polar solvent, making hindered catalytic sites (amino groups) available for reactants in polar solvents. In our study, vigorous stirring probably further promoted the swelling in ethanol. Furthermore, the high WBC efficiently removes water from the reaction. This dual functionality, namely acting as both a catalyst and an efficient water-binding agent, can explain the high yields in repeated runs. These features represent a distinct property of chitosan, simplifies the reaction setup and process, and thereby provides a sustainable alternative to traditional methods.

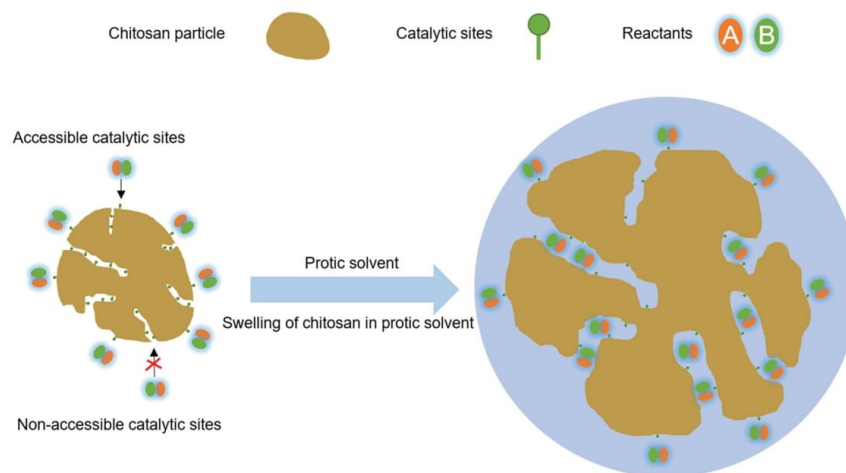
To further investigate water–vapour interaction at the molecular and structural levels, water vapour sorption of chitosan and chitin was measured at two different temperatures (Fig. 3). The water vapour sorption isotherms for chitosan (blue curves in Fig. 3A) indicate pronounced water vapour uptake values of $493 \text{ cm}^3 \text{ g}^{-1}$ and $436 \text{ cm}^3 \text{ g}^{-1}$ at 25°C and 80°C , respectively, compared to chitin (black curves), which shows water uptake values of $237 \text{ cm}^3 \text{ g}^{-1}$ and $269 \text{ cm}^3 \text{ g}^{-1}$ at the maximum achievable relative pressure ($p/p_0 = 0.97$).

As relative humidity increases, the volume adsorbed by both chitosan and chitin rises, reaching maximum levels at full saturation. To illustrate the magnitude of the water vapour



Scheme 4 Synthesis of Atorvastatin followed by Pfizer at the commercial level.





Swelling of chitosan in protic solvents like ethanol due to interactions with hydroxyl and amine groups enhances exposure of catalytic sites for reaction, while its hydrophilicity aids in water capture, facilitating reactions requiring water removal.

Fig. 2 Swelling of chitosan in protic solvents due to interaction with hydroxyl and amino groups of chitosan.

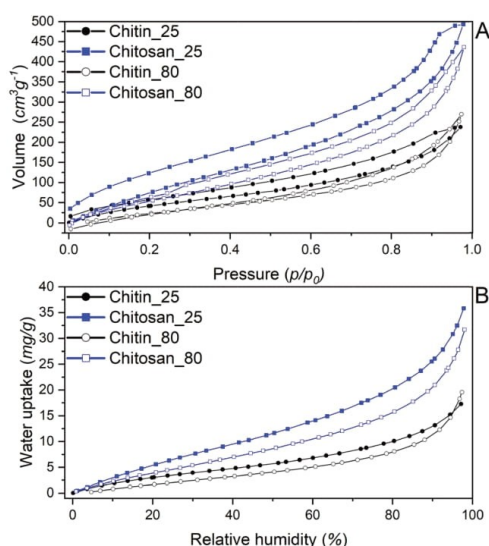


Fig. 3 Water vapour sorption analysis of chitin and chitosan at 25 and 80 °C. (A) Water vapour sorption isotherms showing adsorb volume of vapours per gram of chitosan at maximum $p/p_0 = 0.97$. (B) amount of water vapour sorption in milligram as function of relative humidity.

uptake, these sorption isotherms were converted into a more comprehensive form (Fig. 3B), *i.e.*, by calculating the relative increase in mass *vs.* relative humidity. This representation reveals that at maximum relative humidity, chitosan adsorbs 36 and 31 mg g⁻¹ of water vapour at 25 and 80 °C, respectively,

whereas chitin adsorbs only 17 and 19 mg g⁻¹. The higher adsorption capability of chitosan is attributed to its amine and -OH groups, and a significantly larger BET surface area is estimated from water sorption (150 m² g⁻¹ for chitosan compared to 50 m² g⁻¹ for chitin). Notably, in protic media or under high humidity, chitosan undergoes structural rearrangement due to an acid-base reaction, its strong solvent-binding capacity, and swelling behaviour. As a result, its effective surface area varies significantly depending on the environmental conditions—whether in dry powder form, in water, or in ethanol.

The temperature-dependent differences in the adsorption behaviour give further insight into the water uptake: as seen in Fig. 3 the chitosan water vapour uptake is smaller for the higher temperatures (80 °C) at all pressures. This marked difference is due to the strongly exothermic interaction of water with amino and hydroxy groups. The water vapour isotherms even allow for estimating the isosteric adsorption enthalpy ΔH_{ads} . In essence, ΔH_{ads} can be evaluated from the data shown in Fig. 3 A by using the pressures measured for different temperatures, for the same coverage ϑ , in the range of surface binding. For the two available temperatures we used the two-point approximation

$$\left\{ \frac{\Delta \ln(p)}{\Delta \left(\frac{1}{T} \right)} \right\}_{\vartheta} = \frac{\Delta H_{\text{ads}}}{R}$$

Taking several volumes in the low-pressure range, corresponding to the adsorption of water molecules to the chitosan surface, rather than to condensation of water, we obtain ΔH_{ads} values of *ca.* 10 kJ mol⁻¹. Such values are in sound agreement with the typical values for hydrogen bonds, *i.e.*, can be interpreted as the interaction of water molecules with amino and



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hydroxy groups of chitosan. Hence, the data confirm strong binding of water to chitosan, which further supports the view that water as reaction product is removed from the reaction mixture, thus leading to high yields. In summary, chitosan exhibits superior water uptake compared to chitin, driven by molecular and structural differences that enhance its interaction with water vapour.

Stability of solid chitosan as catalyst

Chitosan exhibited high stability with respect to the catalytic action after being used repeatedly as a catalyst and being subsequently recovered. To analyse physical and chemical changes, chitosan was characterized using various techniques for comparisons after multiple reaction cycles. Fig. 4 shows SEM images of chitosan prior to and after six-fold use as catalyst. At first glance, no structural changes between fresh (Fig. 4A) and used chitosan (Fig. 4C) are visible. Higher magnification reveals some structural alteration, in that the initially smooth surface (Fig. 4B) is not preserved but appears patchy after multiple use (Fig. 4D). However, these scratches could just be a result of vigorous stirring during the reaction which apparently does not affect the catalytic performance.

Fig. 5A shows a mercury intrusion porosimetry (MIP) analysis that was carried out to analyse structural changes possibly leading to creation or closure of meso/macropores after using chitosan as catalyst, *e.g.*, introduced by vigorous stirring. Essentially, MIP data show no significant difference in the porosity in pristine and used chitosan. The population of large macropores is assigned to interparticle voids which slightly change after the reaction, probably because of stirring. The absence of nanopores in MIP seems to be at variance with the marked nanoporosity detected in water sorption, yet the latter is based on strong chemical interaction and swelling.

Diffuse reflectance infrared Fourier transform spectroscopy (DRIFT) analysis of chitosan before and after catalysis (Fig. 5B) does not indicate any changes of the organic functionalities.

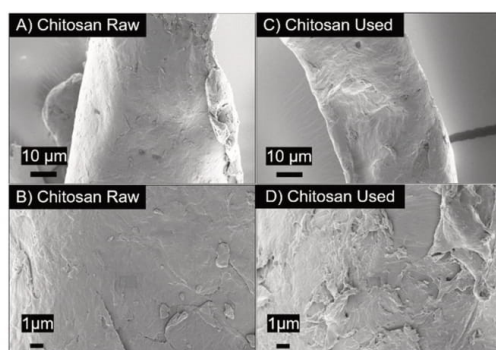


Fig. 4 SEM images of chitosan (A) & (B) before and after six time use as a catalyst (C) & (D) shows that the surface of chitosan is not changed as chitosan is quite stable in organic solvents. Only image (D) shows that the surface of chitosan is scratched due to aggressive stirring during the course of reaction.

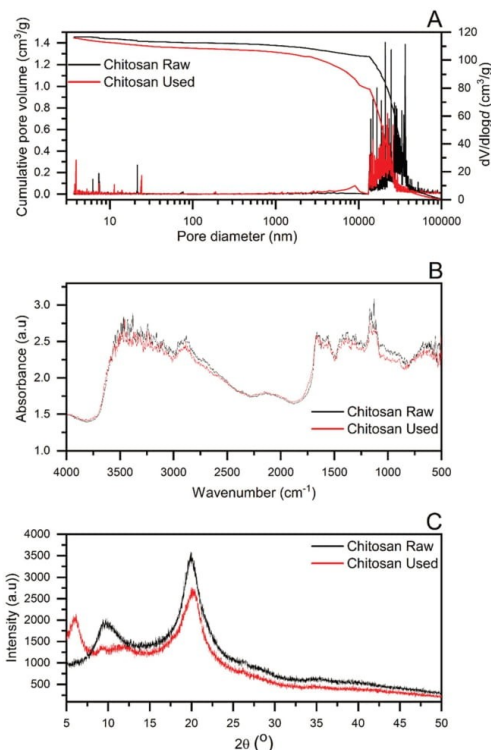


Fig. 5 (A) Mercury intrusion porosimetry data show the emergence of a small mesopore volume after six-fold use of chitosan that are possible slits created by intensive stirring of chitosan while the population of macropores is due to interparticle voids, (B) DRIFT spectrum of pristine chitosan and after six-fold use showing no differences, (C) the XRD analysis of pristine and used chitosan showing no significant difference in the crystallinity, which is seen by the prominent signal at $2\theta = 20^\circ$. The change at smaller diffraction angles might be due to a part of the chains being rearrangement.

To further investigate possible changes on the atomic level, both pristine and used chitosan were subjected to powder XRD analysis (Fig. 5C), exhibiting two prominent signals at *ca.* $2\theta = 10^\circ$ and 20° . These broad signals are characteristic of chitosan, highlighting its amorphous nature.²⁶ However, formally using the Bragg equation, the signals correspond to a repeating dimension of 0.9 nm and 0.4 nm, respectively, which can be qualitatively attributed to the average distance of the polysaccharide chains. After six reaction cycles, the signal at $2\theta = 10^\circ$ disappears, and a signal at $2\theta = 6^\circ$ is observed, likely due to the rearrangement of polymer chains during chitosan swelling in ethanol under rigorous stirring or by repeated heat treatment during drying after each reaction cycle. Yet, the signal at $2\theta = 20^\circ$, being attributable to the arrangement of chains themselves, is unchanged, confirming the structural integrity of the material on the atomic level.



Table 4 Comparison of the present study with the 12 principles of green chemistry

#	"12 Principles of green chemistry"	Present work alignment with principles of green chemistry	Sustainability parameters
1	Waste prevention	Focus on recovery and reuse of catalyst and solvents to reduce waste.	Six reuses of catalyst, Six reuses of ethanol
2	Atom economy	Only water is eliminated, >95% average yield.	Atom economy = 93% Effective atom economy = 89%
3	Less hazardous chemicals synthesis	Simple one-pot synthesis, mostly pure products, eco-compatible solvents.	Chitosan = biopolymer, nontoxic, edible Ethanol, acetone = Eco-friendly solvent Ethyl acetate = problematic Hexane = hazardous
4	Designing efficient but safer products	Eco-friendly solvents, biodegradable, and efficient catalysts, and energy-efficient, one-pot synthesis of condensation products.	Sustainable method, efficient catalyst, and safe.
5	Eco-friendly solvents and reagents	Exclusive use of eco-friendly ethanol and acetone for reaction solution, biopolymer chitosan as catalyst.	Chitosan = biodegradable Ethanol, acetone = eco-friendly solvents Ethyl acetate = problematic Hexane = hazardous
6	Design for energy efficiency	Room temperature for all reactions, 40 °C for only one entry.	0.348 kWh utilised for synthesis of 4.3 g of product (3c, Table 5)
7	Use of renewable feedstock	Source of chitosan is the shrimp exoskeleton (chitin), which is otherwise wasted	Chitosan source = shrimp exoskeleton
8	Reduce derivatives	Highly selective reactions, mostly no purification. Only solvent evaporation to collect pure product.	Overall chemoselectivity => 96%
9	Catalyst	Green catalyst with high selectivity, efficiency, and reusability	Overall chemo-selectivity => 96% Reusability = six reaction cycles, no loss in activity
10	Design for degradation	Chitosan, ethanol, and acetone are biodegradable and nontoxic.	Process = reusable apparatus and auxiliaries, catalyst and solvents biodegradable
11	Real-time analysis for pollution prevention	During product formation, no gases released, only water is eliminated, solvents were reused.	Acetone evaporated during separation of products on rotary evaporator
12	Safer chemistry and processes	One-pot synthesis, only stirring required, mostly no purification step needed.	Major steps = stirring, evaporation of solvent from products, washing of chitosan to reuse.

Comparative analysis of present study to the principles of green chemistry

To evaluate the overall sustainability systematically, we relate the present work to the twelve principles of green chemistry stated by Anastas and Warner in 1998.⁶² Table 4 shows a comparative analysis of the present study with these principles of green chemistry and calculated green factor values.

Conclusions

We demonstrate high catalytic performance and sustainability of chitosan in the Knoevenagel condensation between benzaldehyde derivatives and ethyl cyanoacetate. Chitosan gave high yields (90–99%) across various substrates. Optimising the catalyst amount to 50 mg for *ca.* 212 mg of benzaldehyde resulted in an average yield exceeding 95%, as confirmed by GC, ESI-HRMS, ¹H-NMR and ¹³C-NMR spectroscopy. The catalyst exhibited excellent reusability, maintaining its catalytic efficiency over six reaction cycles with yields consistently between 95% and 98% for different substrates. Additionally, the recovery and reuse of the solvent ethanol, further highlights the sustainable features of this process. The one-pot synthesis approach renders the synthetic process simple and straightforward.

Broadening the scope of chitosan's application for the synthesis of important drug intermediates, we demonstrated its efficacy as catalyst in the one-pot synthesis of an Atorvastatin intermediate, 4-methyl-3-oxo-*N*-phenyl-2-(phenylmethylene)

pentanamide, achieving a yield of 96% at room temperature. Note that the reaction mixture contains only the reactants, solvent, and chitosan, *i.e.*, making the process particularly promising in terms of separating products, solvents and catalyst without the need for elaborate processes. This method outperforms other reported approaches in terms of yield, simplicity, and environmental impact. The gram-scale synthesis of the Atorvastatin intermediate further confirmed the viability of chitosan as a catalyst for the sustainable synthesis of other fine chemicals.

The high water and ethanol-binding capacities of chitosan (WBC = 520%, EBC = 104%) highlight its dynamic structural behaviour in protic solvents and is one of the reasons for the high yields. On one hand, its high-water uptake ability captures water released during the reaction, thus shifting the composition towards the product side. On the other hand, its significant sponge-like swelling in ethanol (171%) enhances the accessibility of catalytic sites, further boosting performance. This dual functionality underscores chitosan's adaptability and effectiveness as a catalyst in water-releasing reactions. Yet, our studies on the solvent uptake also show the need for in-depth studies on the state of water and solvent insight the chitosan gel, and also to which extent a chitosan particle is infiltrated by the solvent. SEM, MIP, DRIFT, and XRD analyses validated the chemical and morphological stability of chitosan, showing no significant degradation after multiple uses, thus ensuring its potential for recyclable application. Our method performs promisingly compared to reported approaches in terms of yield, simplicity, costs and environmental impact, suggesting



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chitosan's potential in pharmaceutical syntheses. Moreover, the reactions featured nearly complete conversion (~100%) and high selectivity (~96%). ESI-HRMS revealed the absence of impurities for most of the synthesized compounds. Thus, the products were characterized without further purification, although additional purification may be applied for pharmaceutical applications where removal of trace impurities is critical.

In comparison to catalysts from 15 other studies, chitosan provided competitive or superior yields and sustainability. Many conventional catalysts demonstrated lower reusability and higher environmental impact, whereas chitosan's biodegradable and non-toxic nature aligns well with "green chemistry" principles, rendering it a promising alternative. Note that the high yields achieved in our study are certainly partially due to the relatively high amount of catalyst used, in relation to the reactants. These high yields are indeed due to the catalytic action of the amino groups and not only by the high WBC, as chitin exhibits low yields, whilst possessing a high WBC, too. However, because of the abundance, facile separation, and reusability of chitosan here the amount and costs of the catalyst are not critical factors. Thus, the chitosan-catalysed process aligns well with several principles of sustainability: high yields, eco-friendly solvents (ethanol and acetone), energy efficiency (room-temperature reactions), and minimal waste generation.

Based on our findings, we propose that chitosan points to an attractive general concept in organocatalysis: using a solid abundant, non-toxic catalyst material, containing a large number of catalytic motifs, and at the same binding to – thereby deactivating – a condensation by-product might be applicable in the synthesis of other relevant fine chemicals.

Future research should therefore focus on exploring chitosan's catalytic potential in other synthetic processes, including base catalysis or by modifying the surface to obtain a different catalytic motif.

Experimental section

Chemical and materials

Chitosan was purchased from Sigma-Aldrich with a reported degree of 75% deacetylation, starting from Chitin (exoskeleton of shrimp as source), Chitin (Sigma-Aldrich, exoskeleton of shrimp as source), ethyl cyanoacetate (Sigma-Aldrich >98%), benzaldehyde (Sigma-Aldrich >99%), *p*-tolualdehyde (Sigma-Aldrich 99%), *m*-tolualdehyde (BLD Pharma 99.72%), *o*-tolualdehyde (BLD Pharma 99%), *p*-anisaldehyde (TCI >99%), 4-chlorobenzaldehyde (Sigma-Aldrich 97%), 3-chlorobenzaldehyde (TCI 98%), terephthalaldehyde (TCI >98%), 2-naphthalaldehyde (Fisher Scientific 98%), 4-biphenylcarboxaldehyde (Fisher Scientific 99%), 9-anthracenecarboxaldehyde (Sigma-Aldrich 97%), 4-methyl-3-oxo-*N*-phenylpentanamide (BLD Pharma 99.5%), absolute ethanol (Fisher Scientific 99.8%), hexane (Sigma-Aldrich, HPLC grade), ethyl acetate (Sigma-Aldrich, HPLC grade), toluene (thermo scientific 99.85%)

and acetone (Sigma-Aldrich 99.5%). All the chemicals were used without further purification.

Methods for analysis

Mass spectrometry (MS). Mass spectrometry was performed by using Bruker Impact II (ESI-HRMS) by using methanol as the carrier.

Nuclear magnetic resonance spectroscopy (NMR). ¹H NMR and ¹³C NMR spectra were measured with a 400 MHz spectrometer (Bruker Avance III HD, Bruker BioSpin GmbH, Rheinstetten, Germany) at 25 °C. CDCl₃ and DMSO-*d*₆ were used as solvent.

Water and ethanol-binding capacity. WBC of chitosan was assessed by placing 0.5 g of chitosan sample into a pre-weighed centrifuge tube. Next, 10 mL of distilled water was added, and the sample was mixed using a vortex for 1 min to ensure proper dispersion. The mixture was allowed to rest at room temperature for 30 min, with alternating shaking for 5 s every 10 min. Following this, the sample was centrifuged at 3200 rpm for 25 min. After carefully removing the supernatant, the tubes were weighed again. The WBC (%) was determined using the following eqn (1). The same method was used to measure the ethanol-binding capacity of chitosan.

$$\text{WBC (\%)} = \frac{(\text{Water bound (g)})}{(\text{Initial sample weight (g)})} \times 100 \quad (1)$$

Swelling. To determine the swelling properties, 0.5 g of dry chitosan was immersed in 15 mL of either deionized water or absolute ethanol. The samples were allowed to swell for 24 h at room temperature. After swelling, chitosan was removed, excess liquid was drained, and the swollen sample was weighed. The swelling percentage was calculated using the eqn (2),

$$S_{\%} = \frac{W_s - W_d}{W_d} \times 100 \quad (2)$$

where W_s is the mass of swollen chitosan, W_d is the mass of dry chitosan.

Water vapour sorption analysis. Water vapour sorption analysis was performed by using a vapour sorption volumetric gas sorption analyser VSTAR (Quantachrom). The samples were degassed at 80 °C for 12 h before analysis. Two temperatures (25 °C and 80 °C) were used for comparative analysis of chitin and chitosan.

Scanning electron microscopy (SEM). Smart SEM MERLIN (Carl Zeiss) scanning electron microscope was used for scanning electron microscopy with acceleration voltage of 1 kV. Chitosan was sputtered with platinum for 60 s before analysis to increase conductivity of the samples.

Mercury intrusion porosimetry (MIP). For porosity analysis a mercury porosimeter Pascal 140/440 (Thermo Fisher Scientific, Rodano, Italy) with a pressure range of 0–400 MPA was used. Washburn equation was applied to analyse the data, using the instrument's software (Sol.I.D). A surface tension of 0.48 N m^{−1} and contact angle 140° were assumed for intruded mercury.



Diffuse reflectance infrared Fourier transform spectroscopy (DRIFT). IR spectra of chitosan were measured using a DRIFT instrument (Alpha II, Bruker Optik, Ettlingen Germany). Dried samples were analysed with a resolution of 4 cm^{-1} and using 80 scans.

XRD. X-ray diffractometry of chitosan samples was measured on an XRDynamic 500 diffractometer by Anton Paar in a 2θ range of $5\text{--}50^\circ$.

One pot synthesis of Knoevenagel condensation products. The method employed for synthesis of the chitosan-catalysed Knoevenagel condensation products from benzaldehydes and ethyl cyanoacetate was simple and straightforward. The one-pot synthesis of all products was carried out without using extreme conditions and complex purification steps. A practical view of the synthetic process can be seen in Fig. 6. A 5 mL one-neck round-bottom flask was utilised for the synthesis of all the products, except for the gram-scale product, where a 25 mL round-bottom flask was used. A 1 cm long magnetic stirrer was used for stirring at 800 rpm, in a flask sealed with a glass plug wrapped in paraffin film. Ethanol was used as the primary solvent for the majority of the products, while toluene was additionally added for the better solubility of 9-anthracenecarboxaldehyde (Table 5, entry 11). The synthesis was mainly conducted at 25°C , with a maximum temperature of 40°C selectively used for better solubility of 9-anthracenecarboxaldehyde (Table 5, entry 11). Reactions were monitored by thin-layer chromatography (TLC). In most cases, after 24 h

reactants were fully converted into products. For terephthalaldehyde (Table 5, entry 2) a solid product appeared after 8 h, while entry 10 and 11 took 30 and 36 h, respectively, for full conversion. After reaction completion, chitosan was separated by suction filtration, while ethanol and acetone (5 mL, 1:1) were used to wash solid chitosan. The separated dissolved products were then transferred to a rotary evaporator, and solvents were evaporated at 40°C while the pressure was gradually reduced to 10 mbar. The solid products were collected after solvent evaporation. The products were then characterized *via* ESI-HRMS, and NMR. The used chitosan was dried at 40°C for two h under reduced pressure and reused for the next reaction. For product 3 and 5, ethanol from both the reaction mixture and the washing of chitosan was recovered by rotary evaporation, condensed in the collecting flask, and subsequently reused in the same reactions. In contrast, acetone used for washing chitosan was completely evaporated during the product separation step under reduced pressure due to its low boiling point. No purification steps were used for the products except for the product of 9-anthracenecarboxaldehyde (Table 5, entry 11). This product was isolated after running the product through a short silica column using hexane and ethyl acetate (30:1) as the mobile phase. After collecting the dissolved product, the solvents were evaporated at 40°C with gradually decreasing pressure to 10 mbar.

For gram-scale synthesis of entry 3c in Table 5, 20 mmol of *p*-tolualdehyde and 20 mmol of ethyl cyanoacetate were added

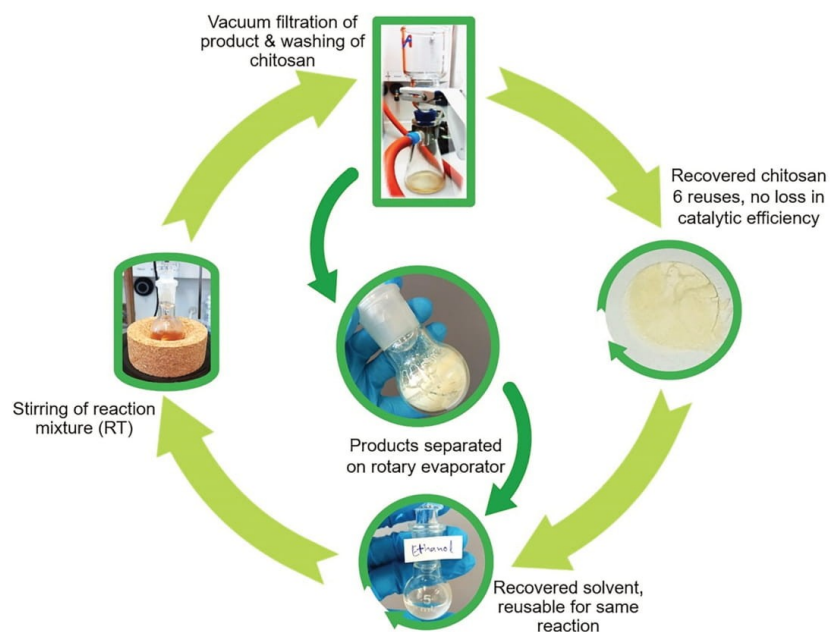


Fig. 6 Practical view for one pot synthesis of Knoevenagel condensation products using chitosan as heterogeneous catalyst.

Table 5 Reaction parameters for the Knoevenagel condensation of benzaldehydes with ethyl cyanoacetate

Entry	Substrates	Scale/mmol	Solvent	Time	Temperature	Chitosan	Yield (%)
1	Benzaldehyde	2 mmol	Ethanol 2.5 mL	24 h	RT	50 mg	96
1b	Six repetitions of reaction	2 mmol	six reuses	24 h	RT	50 mg (reused)	95
2	Terephthalaldehyde	2 mmol	Ethanol 2.5 mL	8 h	RT	50 mg	> 99
3	<i>p</i> -Tolualdehyde	2 mmol	Ethanol 2.5 mL	24 h	RT	50 mg	98.5
3b	Six repetitions of reaction	2 mmol	six reuses	24 h	RT	Six reuses	98
3c	Gram-scaled	20 mmol	Ethanol 12 mL	48 h	40 °C	300 mg (recovered)	99
4	<i>m</i> -Tolualdehyde	2 mmol	Ethanol 2.5 mL	24 h	RT	50 mg	98
5	<i>o</i> -Tolualdehyde	2 mmol	Ethanol 2.5 mL	24 h	RT	50 mg	96
6	<i>p</i> -Anisaldehyde	2 mmol	Ethanol 2.5 mL	24 h	RT	50 mg	95
7	4-Chlorobenzaldehyde	2 mmol	Ethanol 2.5 mL	24 h	RT	50 mg	96
8	3-Chlorobenzaldehyde	2 mmol	Ethanol 2.5 mL	24 h	RT	50 mg	93
9	4-Biphenoxycarboxaldehyde	2 mmol	Ethanol 2.5 mL	24 h	RT	50 mg	96
10	2-Naphthaldehyde	2 mmol	Ethanol 2.5 mL	30 h	RT	50 mg	96
11	9-Anthracenecarboxaldehyde	2 mmol	Ethanol/Toluene 1:2, 6 mL	36 h	40 °C	100 mg	90

into 12 mL of ethanol taken in a 25 mL round-bottom flask. 300 mg of recovered chitosan from different reactions was added as catalyst, and the reaction mixture was stirred at 800 rpm and 40 °C. After 48 h, chitosan and product were separated by the same protocol used for other products, and 4.3 g (quantitative yield) of cream-white solid product was collected.

All the reaction conditions and parameters for synthesis of all the products are shown in Table 5. The conditions were selected to achieve sustainability to maximum extent throughout the synthesis processes.

Synthesis of 4-methyl-3-oxo-*N*-phenyl-2-(phenylmethylene)-pentanamide. For the synthesis of the Atorvastatin intermediate [4-methyl-3-oxo-*N*-phenyl-2-(phenylmethylene)pentanamide], 100 mg of dry chitosan particles were placed in a 5 mL round-bottom flask. Subsequently, 3 mL of dried acetone, 1 mmol (206 mg) of 4-methyl-3-oxo-*N*-phenylpentanamide, and 1.5 mmol (213 mg) of benzaldehyde were added, and the mixture was stirred at room temperature. The reaction was monitored by TLC, and after 26 h, chitosan was separated by suction filtration. The crude product was collected by evaporating the solvent using a rotary evaporator. Due to the high boiling point of benzaldehyde, an additional purification step was necessary. Therefore, column chromatography was used to separate the product from benzaldehyde. Thus, benzaldehyde was first isolated from the main product by adding hexane and ethyl acetate (30:1), and then pure ethyl acetate was added in column to collect the purified product. An off-white solid was collected after evaporating the solvents at 50 °C and 20 mbar pressure using a rotary evaporator.

For the gram-scale synthesis of the Atorvastatin intermediate [4-methyl-3-oxo-*N*-phenyl-2-(phenylmethylene)pentanamide], 400 mg of recovered chitosan was placed in a 50 mL round bottom flask. Then, 15 mmol (3.09 g) of 4-methyl-3-oxo-*N*-phenylpentanamide and 1.5 equivalents of benzaldehyde (22.5 mmol, 2.27 mL or 2.4 g) were dissolved in 15 mL of dried acetone and stirred at room temperature. The reaction progress was monitored with TLC. Upon completion of the reaction in 48 h, chitosan was separated by filtration under reduced pressure. The dissolved residue was transferred to a rotary evaporator, where acetone was evaporated at 40 °C under a pressure of 10 mbar. After evaporating the acetone, a dense

dark brown liquid was collected and purified using silica column to remove benzaldehyde. Initially, hexane and ethyl acetate (30:1) were used to remove benzaldehyde, followed by the collection of the product using pure ethyl acetate. The solvent was removed by rotary evaporation at 50 °C and 20 mbar pressure. The product was then further dried in a vacuum oven at 40 °C overnight. A total of 4.2 g of off-white solid product was obtained, yielding above 95%.

Author contributions

U. A. data curation, investigation, methodology, visualization and writing original draft. F. D. data curation, investigation. L. Q. W. data curation, investigation. P. P. D. data curation, investigation. J. G. data curation, investigation. P. R. S. conceptualisation, funding acquisition, methodology, supervision, and manuscript editing. B. M. S. conceptualisation, funding acquisition, methodology, supervision, manuscript writing and editing. All authors contributed to and agreed on the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article are available upon request.

Supplementary information: For mass spectrometry, ¹H NMR and ¹³C-NMR data. See DOI: <https://doi.org/10.1039/d5nj02915e>.

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References

- 1 Y. Musa and I. B. Bwatanglang, *Sustainable Nanocellulose and Nanohydrogels from Natural Sources*, Elsevier, 2020, pp. 131–154.
- 2 C. P. Jiménez-Gómez and J. A. Cecilia, *Molecules*, 2020, **25**, 3981.
- 3 S. Kamel and T. A. Khattab, *Cellulose*, 2021, **28**, 4545–4574.
- 4 K. Basavaraju, S. Sharma, A. K. Singh, D. J. Im and D. P. Kim, *ChemSusChem*, 2014, **7**, 1864–1869.
- 5 W. Zhang and B. W. Cue, *Green techniques for organic synthesis and medicinal chemistry*, John Wiley & Sons, Oxford, 2018.
- 6 K. Turke, R. Meinusch, P. Cop, E. Prates da Costa, R. D. Brand, A. Henss, P. R. Schreiner and B. M. Smarsly, *ACS Omega*, 2020, **6**, 425–437.
- 7 J. S. Schulze, R. D. Brand, J. G. Hering, L. M. Riegger, P. R. Schreiner and B. M. Smarsly, *ChemCatChem*, 2022, **14**, e202101845.
- 8 J. S. Schulze, J. Migenda, M. Becker, S. M. Schuler, R. C. Wende, P. R. Schreiner and B. M. Smarsly, *J. Mater. Chem. A*, 2020, **8**, 4107–4117.
- 9 X. Yu and C. T. Williams, *Catal. Sci. Technol.*, 2022, **12**, 5765–5794.
- 10 A. Trommer, J. Hessling, P. R. Schreiner, M. Schönhoff and B. M. Smarsly, *ACS Appl. Mater. Interfaces*, 2025, **17**, 24283–24299.
- 11 M. Nasrollahzadeh, N. Shafiei, Z. Nezafat, N. S. S. Bidgoli and F. Soleimani, *Carbohydr. Polym.*, 2020, **241**, 116353.
- 12 T. Chandy and C. P. Sharma, *Biomater. Artif. Cells Artif. Organs*, 1990, **18**, 1–24.
- 13 M. N. R. Kumar, *React. Funct. Polym.*, 2000, **46**, 1–27.
- 14 V. P. Santos, N. S. Marques, P. C. Maia, M. A. B. D. Lima, L. D. O. Franco and G. M. D. Campos-Takaki, *Int. J. Mol. Sci.*, 2020, **21**, 4290.
- 15 D. J. Macquarrie and J. J. Hardy, *Ind. Eng. Chem. Res.*, 2005, **44**, 8499–8520.
- 16 H. Zhang, H. Li, C. C. Xu and S. Yang, *ACS Catal.*, 2019, **9**, 10990–11029.
- 17 E. Guibal, *Prog. Polym. Sci.*, 2005, **30**, 71–109.
- 18 T. F. Jiao, J. Zhou, J. Zhou, L. Gao, Y. Xing and X. Li, *Iran. Polym. J.*, 2011, **20**, 123–136.
- 19 Á. Molnár, *Coord. Chem. Rev.*, 2019, **388**, 126–171.
- 20 Y. Lin, C. Kong and L. Chen, *RSC Adv.*, 2016, **6**, 32598–32614.
- 21 G. Anilur, E. Sert, E. Yilmaz and F. S. Atalay, *J. Solid State Chem.*, 2020, **283**, 121138.
- 22 J. Qiao, B. Zhang, X. Yu, X. Zou, X. Liu, L. Zhang and Y. Liu, *Inorg. Chem.*, 2022, **61**, 3708–3715.
- 23 I. W. Zapelini and D. Cardoso, *Microporous Mesoporous Mater.*, 2021, **324**, 111270.
- 24 M. Kostag and O. A. El Seoud, *Carbohydr. Polym. Technol. Appl.*, 2021, **2**, 100079.
- 25 N. Anbu, R. Maheswari, V. Elamathi, P. Varalakshmi and A. Dhakshinamoorthy, *Catal. Commun.*, 2020, **138**, 105954.
- 26 N. Anbu, S. Hariharan and A. Dhakshinamoorthy, *Mol. Catal.*, 2020, **484**, 110744.
- 27 S. M. Joseph, S. Krishnamoorthy, R. Paranthaman, J. Moses and C. Anandharamkrishnan, *Carbohydr. Polym. Technol. Appl.*, 2021, **2**, 100036.
- 28 B. Sakthivel and A. Dhakshinamoorthy, *J. Colloid Interface Sci.*, 2017, **485**, 75–80.
- 29 S. Zahedi, J. S. Ghomi and H. Shahbazi-Alavi, *Ultrason. Sonochem.*, 2018, **40**, 260–264.
- 30 V. K. Singh, K. Kumar, S. Rai, A. Chaudhary, K. Tungala and A. Das, *J. Environ. Chem. Eng.*, 2023, **11**, 110632.
- 31 L. Liang, L. Nie, M. Jiang, F. Bie, L. Shao, C. Qi, X. M. Zhang and X. Liu, *New J. Chem.*, 2018, **42**, 11023–11030.
- 32 H. Kayser, C. R. Müller, C. A. García-González, I. Smirnova, W. Leitner and P. D. de María, *Appl. Catal., A*, 2012, **445**, 180–186.
- 33 S. Deng, Y. Huang, E. Hu, L.-J. Ning, R. Xie, K. Yu, F. Lu, G. Lan and B. Lu, *Carbohydr. Polym.*, 2023, **321**, 121340.
- 34 D. Rani, P. Singla and J. Agarwal, *Carbohydr. Polym.*, 2018, **202**, 355–364.
- 35 A. Franconetti, P. Domínguez-Rodríguez, D. Lara-García, R. Prado-Gotor and F. Cabrera-Escribano, *Appl. Catal., A*, 2016, **517**, 176–186.
- 36 K. Rajender Reddy, K. Rajgopal, C. Uma Maheswari and M. Lakshmi Kantam, *New J. Chem.*, 2006, **30**, 1549–1552.
- 37 F. G. Bordwel and H. E. Fried, *J. Org. Chem.*, 1981, **46**, 4327–4331.
- 38 S. I. van Leuven and J. J. Kastelein, *Expert Opin. Pharmacother.*, 2005, **6**, 1191–1203.
- 39 B. D. Roth, *Prog. Med. Chem.*, 2002, **40**, 1–22.
- 40 B. D. Roth, C. Blankley, A. Chucholowski, E. Ferguson, M. Hoefle, D. Ortwine, R. Newton, C. Sekerke, D. Sliskovic and M. Wilson, *J. Med. Chem.*, 1991, **34**, 357–366.
- 41 ClinCalc DrugStats Database <https://clincalc.com/DrugStats/Top300Drugs.aspx> (accessed July 2024).
- 42 H. Bonfante-Alvarez, G. De Avila-Montiel, A. Herrera-Barros, M. Torrenegra-Alarcon and A. D. Gonzalez-Delgado, *Chem. Eng. Trans.*, 2018, **70**, 1969–1974.
- 43 S. Komiya, T. Sone, Y. Usui, M. Hirano and A. Fukuoka, *Gold Bull.*, 1996, **29**, 131–136.
- 44 S. Liu, Y. Ni, J. Yang, H. Hu, A. Ying and S. Xu, *Chin. J. Chem.*, 2014, **32**, 343–348.
- 45 M. B. Ansari, H. Jin, M. N. Parvin and S.-E. Park, *Catal. Today*, 2012, **185**, 211–216.
- 46 A. R. Burgoyne and R. Meijboom, *Catal. Lett.*, 2013, **143**, 563–571.
- 47 S. Zhao, Y. Chen and Y.-F. Song, *Appl. Catal., A*, 2014, **475**, 140–146.
- 48 A. Erigoni, M. C. Hernández-Soto, F. Rey, C. Segarra and U. Díaz, *Catal. Today*, 2020, **345**, 227–236.
- 49 T. F. Machado, A. J. Valente, M. E. S. Serra and D. Murtinho, *Microporous Mesoporous Mater.*, 2023, **355**, 112561.
- 50 D. Jain, C. Khatri and A. Rani, *Fuel Process. Technol.*, 2010, **91**, 1015–1021.



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- 51 S. K. Ma, J. Gruber, C. Davis, L. Newman, D. Gray, A. Wang, J. Grate, G. W. Huisman and R. A. Sheldon, *Green Chem.*, 2010, **12**, 81–86.
- 52 N. Andrushko, V. Andrushko, V. Tararov, A. Korostylev, G. König and A. Börner, *Chirality*, 2010, **22**, 534–541.
- 53 P. W. Woo, J. Hartman, Y. Huang, T. Nanninga, K. Bauman, D. E. Butler, J. R. Rubin, H. T. Lee and C. C. Huang, *J. Labelled Compd. Radiopharm.*, 1999, **42**, 121–127.
- 54 A. Ying, F. Qiu, C. Wu, H. Hu and J. Yang, *RSC Adv.*, 2014, **4**, 33175–33183.
- 55 WO2012145808, 2012.
- 56 A. Ying, Y. Ni, S. Xu, S. Liu, J. Yang and R. Li, *Ind. Eng. Chem. Res.*, 2014, **53**, 5678–5682.
- 57 Y. He, M. Li, L. Peng, T. Yang, D. Zhang and Y. Zhang, *ChemistrySelect*, 2024, **9**, e202304182.
- 58 K. C. Gupta and F. H. Jabrail, *Carbohydr. Polym.*, 2006, **66**, 43–54.
- 59 Y. I. Cho, H. K. No and S. P. Meyers, *J. Agric. Food Chem.*, 1998, **46**, 3839–3843.
- 60 J. Wang and J. Kinsella, *J. Food Sci.*, 1976, **41**, 286–292.
- 61 K. C. Gupta and M. R. Kumar, *Biomaterials*, 2000, **21**, 1115–1119.
- 62 P. T. Anastas and J. C. Warner, *Green Chem.*, 1998, **29**, 14821–14842.



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SUPPORTING INFORMATION

Chitosan as a solid catalyst for one-pot Knoevenagel condensation in the context of sustainable chemistry

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Spectrometry and Spectroscopy

Mass spectrometry: HRMS was performed on a Bruker Mikro-TOF or Bruker Impact II (ESI-HRMS) by using methanol as the carrier.

All products were analysed without any additional purification.

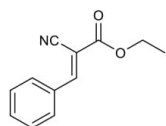
Weak signals at m/z 139.0736, 197.1156, 353.2673, 381.2978 and 388.3949 were detected in the HRMS spectra. These signals show a pattern consistent in almost all samples and coming from

common laboratory contaminants (silicone grease/PDMS and/or PEG/plasticizers). Therefore, they are attributed to background contamination and not to reaction-derived impurities.

Nuclear Magnetic Resonance Spectroscopy: ^1H -NMR (400 MHz) and ^{13}C -NMR (101 MHz) spectral measurements were carried out using a Bruker AV 400 or Bruker AV 400 HD spectrometer at 298 K. Chemical shifts (δ) are given in parts per million (ppm) relative to the respective residual protium or carbon resonances of the deuterated solvent (CDCl_3 : $\delta = 7.26$ and 77.16 ppm; $\text{DMSO}-d_6$: $\delta = 2.50$) Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, or combinations thereof), coupling constants (Hz), integration. All spectral data are reported based on appearance. Citations are provided at the end of the spectral data to facilitate comparison with previously reported spectra of the same compound. Products 13 and 18 were purified using column chromatography prior to NMR analysis.

Analytical Data

Ethyl (2E)-2-cyano-3-phenyl-2-propenoate

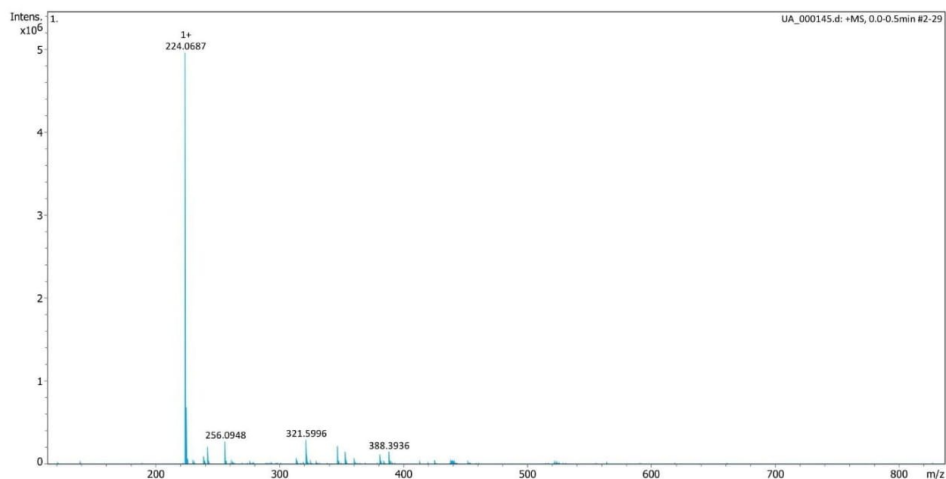


White solid

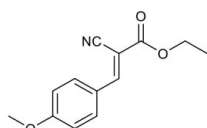
Yield: 0.386 g, 96%.

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ /ppm = 8.26 (s, 1H), 8.02 – 7.97 (m, 2H), 7.59 – 7.48 (m, 3H), 4.39 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ /ppm = 162.6, 155.2, 133.4, 131.6, 131.2, 129.4, 115.6, 103.2, 62.9, 14.3.¹

HRMS (ESI): m/z = 224.0687 $[\text{M}+\text{Na}]^-$, 256.0948 $[\text{M}+\text{Na}+\text{Solvent}]^-$, 201.0795 $[\text{M}-\text{Na}]^-$, (calc. for $\text{C}_{12}\text{H}_{11}\text{NO}_2^-$ m/z = 201.0790).



Ethyl (2E)-2-cyano-3-(4-methoxyphenyl)-2-propenoate

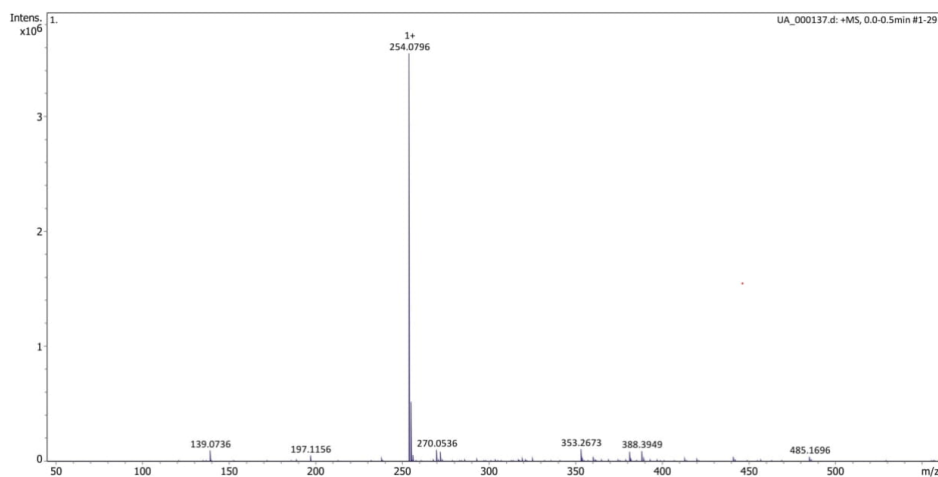


Pale white solid

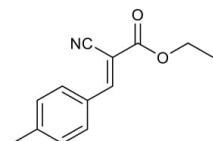
Yield: 0.453 g, 98%.

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ /ppm = 8.17 (s, 1H), 8.04 – 7.98 (m, 2H), 7.02 – 6.97 (m, 2H), 4.37 (q, J = 7.1 Hz, 2H), 3.89 (s, 3H), 1.39 (t, J = 7.1 Hz, 3H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ /ppm = 163.9, 163.3, 154.6, 133.8, 124.5, 116.4, 114.9, 99.5, 62.6, 55.8, 14.4.¹

HRMS (ESI): m/z = 254.0796 $[\text{M}+\text{Na}]^-$, 270.0536 $[\text{M}+\text{K}]^-$, 485.1696 $[\text{2M}+\text{Na}]^-$, 231.0904 $[\text{M}-\text{Na}]^-$, (calc. for $\text{C}_{13}\text{H}_{13}\text{NO}_3^-$ m/z = 231.0895).



Ethyl (2E)-2-cyano-3-(4-methylphenyl)-2-propenoate



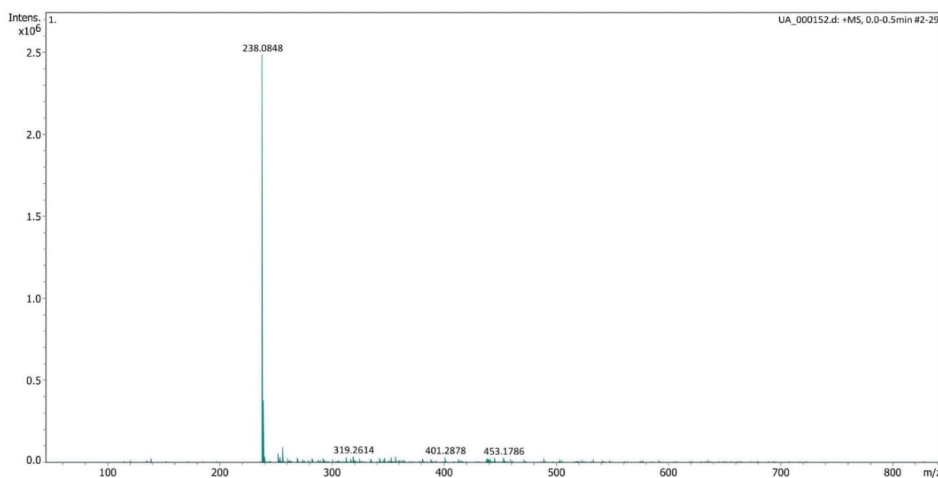
Cream white solid

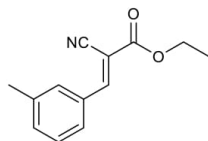
Yield: 0.424 g, 98.5%.

¹H NMR (400 MHz, CDCl₃) δ/ppm = 8.21 (s, 1H), 7.93 – 7.88 (m, 2H), 7.32 – 7.28 (m, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 2.43 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ/ppm = 162.9, 155.1, 144.8, 131.4, 130.2, 129.0, 115.9, 101.8, 62.7, 22.0, 14.3.²

HRMS (ESI): *m/z* = 328.0848 [M+Na]⁺, 453.1786 [2M+Na]⁺, 215.0956 [M–Na]⁺ (calc. for C₁₃H₁₃NO₂⁺ *m/z* = 215.0946)



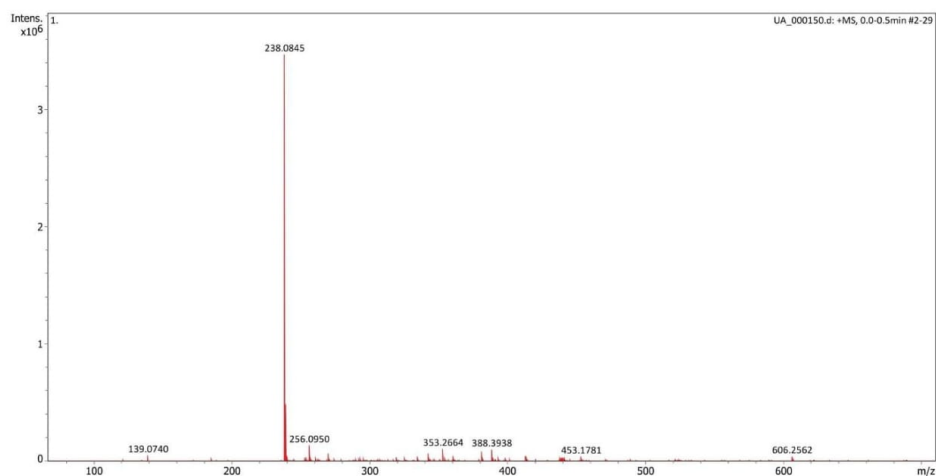
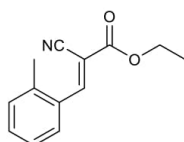
Ethyl (2E)-2-cyano-3-(3-methylphenyl)-2-propenoate

Cream white solid

Yield: 0.422 g, 98%.

¹H NMR (400 MHz, CDCl₃) δ/ppm = 8.22 (s, 1H), 7.84 – 7.80 (m, 1H), 7.79 – 7.76 (m, 1H), 7.42 – 7.35 (m, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 2.42 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ/ppm = 62.8, 155.4, 139.3, 134.4, 131.8, 131.6, 129.3, 128.4, 115.7, 102.8, 62.8, 21.5, 14.3.³

HRMS (ESI): *m/z* = 238.0845 [M+Na]⁺, 453.1781 [2M+Na]⁺, 215.0953 [M-H]⁻ (calc. for C₁₃H₁₃NO₂⁻ *m/z* = 215.0946).

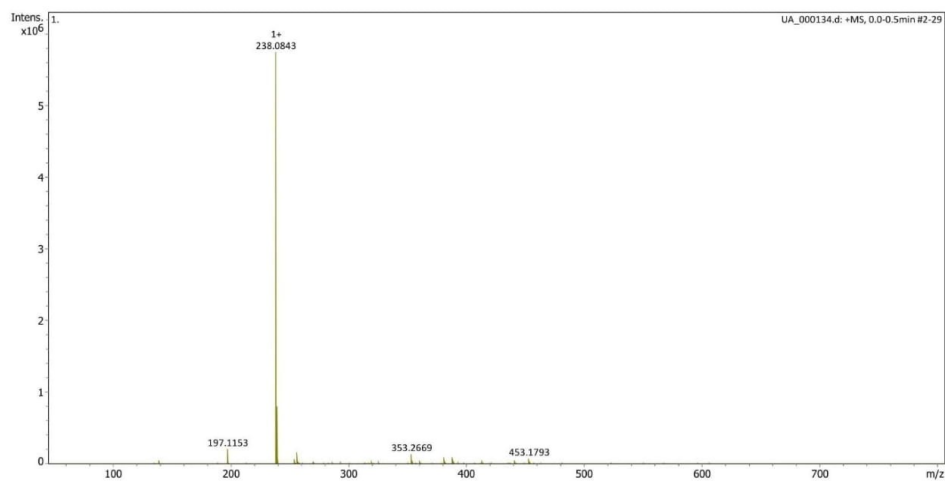
**Ethyl (2E)-2-cyano-3-(2-methylphenyl)-2-propenoate**

Cream white solid

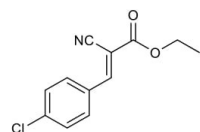
Yield: 0.414 g, 96%.

¹H NMR (400 MHz, CDCl₃) δ/ppm = 8.57 (s, 1H), 8.16 – 8.11 (m, 1H), 7.42 (td, *J* = 7.5, 1.4 Hz, 1H), 7.35 – 7.27 (m, 2H), 4.39 (q, *J* = 7.2 Hz, 2H), 2.45 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ/ppm = 162.6, 153.5, 139.8, 132.9, 131.1, 130.7, 128.7, 126.8, 115.5, 104.6, 62.9, 20.0, 14.3.^{4, 5}

HRMS (ESI): *m/z* = 238.0843 [M+Na]⁺, 453.1793 [2M+Na]⁺, 215.0951 [M-Na]⁻ (calc. for C₁₃H₁₃NO₂⁻ *m/z* = 215.0946).



Ethyl (2E)-2-cyano-3-(4-chlorophenyl)-2-propenoate

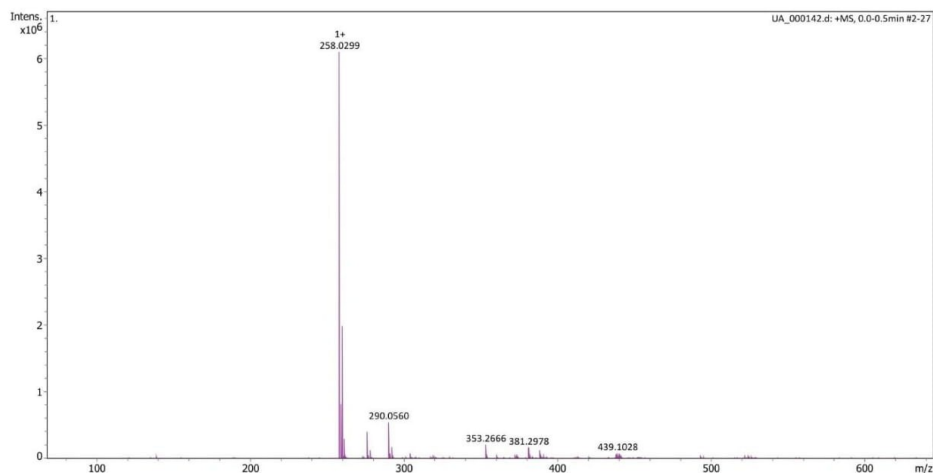


Cream white solid

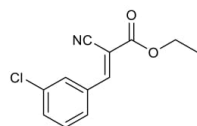
Yield: 0.452 g, 96%.

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ /ppm = 8.20 (s, 1H), 7.96 – 7.91 (m, 2H), 7.52 – 7.44 (m, 2H), 4.39 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ /ppm = 162.4, 153.5, 139.8, 132.4, 129.8, 115.4, 103.7, 63.0, 14.3.²

HRMS (ESI): m/z = 258.0299 $[\text{M}+\text{Na}]^-$, 276.0404 $[\text{M}+\text{Na}+\text{H}_2\text{O}]^-$, 290.0560 $[\text{M}+\text{Na}+\text{Solvent}]^-$, 235.0407 $[\text{M}-\text{Na}]^-$, (calc. for $\text{C}_{12}\text{H}_{10}\text{ClNO}_2$ m/z = 235.0400).



Ethyl (2E)-2-cyano-3-(3-chlorophenyl)-2-propenoate

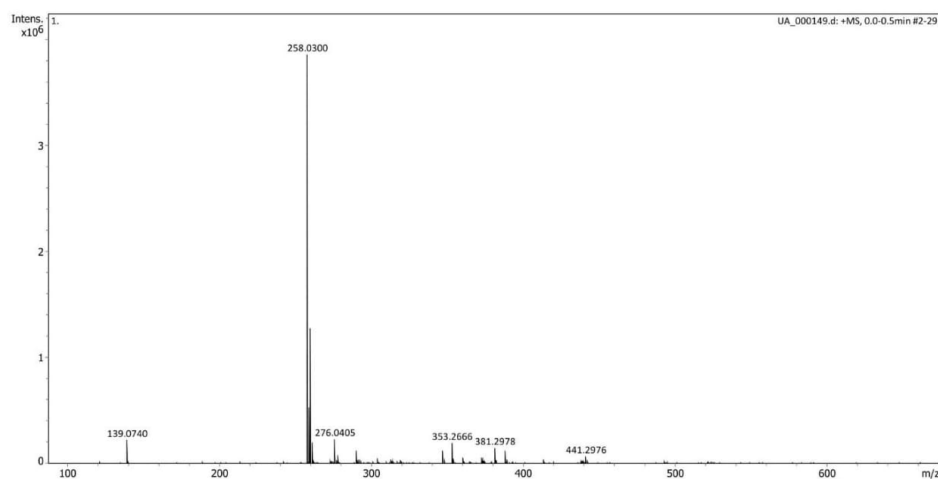


Cream white solid

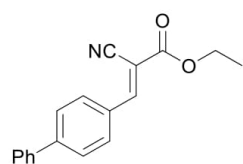
Yield: 0.448 g, 93%.

¹H NMR (400 MHz, CDCl₃) δ/ppm = 8.18 (s, 1H), 7.96 – 7.88 (m, 2H), 7.53 (ddd, *J* = 8.1, 2.0, 1.1 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ/ppm = 162.2, 153.4, 135.5, 133.2, 131.0, 130.7, 128.8, 115.1, 104.8, 63.1, 14.3.⁶

HRMS (ESI): *m/z* = 258.0300 [M+Na]⁺, 276.0405 [M+Na+H₂O]⁺, 290.0560 [M+Na+Solvent]⁺, 235.0408 [M-Na]⁺, (calc. for C₁₂H₁₀ClNO₂ *m/z* = 235.0400).



Ethyl (2E)-3-([1,1'-biphenyl]-4-yl)-2-cyanoprop-2-enoate



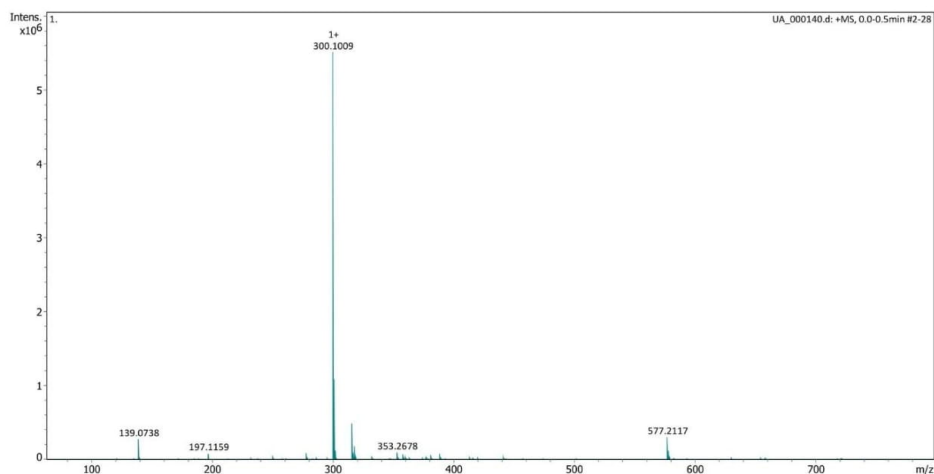
Pale white solid

Yield: 0.532 g, 96%.

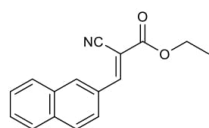
¹H NMR (400 MHz, CDCl₃) δ/ppm = 8.28 (s, 1H), 8.12 – 8.06 (m, 2H), 7.76 – 7.72 (m, 2H), 7.67 – 7.62 (m, 2H), 7.52 – 7.46 (m, 2H), 7.45 – 7.39 (m, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ/ppm = 162.8, 154.6, 146.2, 139.6, 131.9, 130.5, 129.2, 128.7, 127.9, 127.4, 115.9, 102.6, 62.9, 14.3. (NR)

HRMS (ESI): *m/z* = 300.1009 [M+Na]⁺, 316.0748 [M+K]⁺, 577.2117 [2M+Na]⁺, 277.1117 [M-Na]⁺, (calc. for C₁₃H₁₃NO₂ *m/z* = 277.1103).



Ethyl (2E)-2-cyano-3-(2-naphthalenyl)-2-propenoate



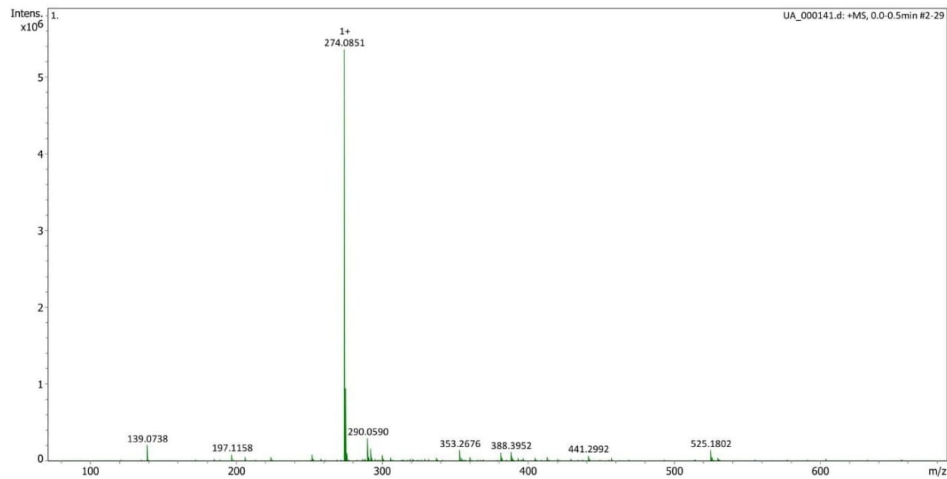
Pale white solid

Yield: 0.481 g, 96%.

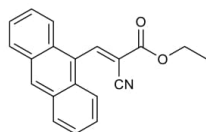
¹H NMR (400 MHz, CDCl₃) δ /ppm = 8.31 (s, 1H), 8.30 – 8.28 (m, 1H), 8.09 (dd, J = 8.7, 1.8 Hz, 1H), 7.84 (t, J = 7.8 Hz, 2H), 7.79 (d, J = 8.2 Hz, 1H), 7.56 – 7.45 (m, 2H), 4.32 (q, J = 7.2 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H).⁷

¹³C NMR (101 MHz, CDCl₃) δ /ppm = 162.8, 155.1, 135.6, 134.3, 133.0, 129.6, 129.3, 129.3, 129.2, 128.0, 127.4, 125.5, 115.9, 102.9, 62.9, 14.3. (NR)

HRMS (ESI): m/z = 274.0851 [M+Na]⁺, 290.0590 [M+K]⁺, 525.1802 [2M+Na]⁺, 251.0959 [M-Na]⁺, (calc. for C₁₆H₁₃NO₂⁺ m/z = 251.0946).



Ethyl 3-(9-anthracenyl)-2-cyano-2-propenoate



Soil color solid

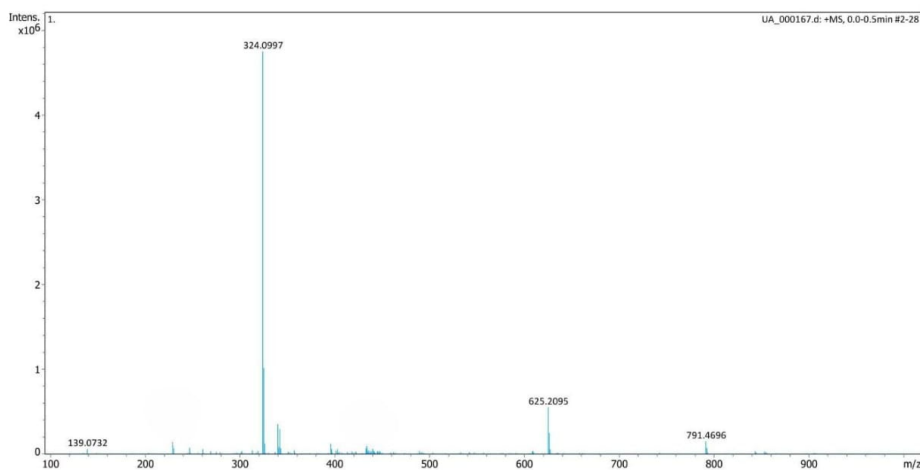
Yield: 0.541 g, 90%.

E/Z = 93%

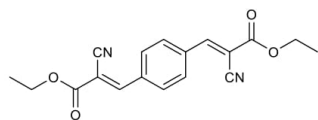
¹H NMR (400 MHz, DMSO-*d*₆) δ /ppm = 9.34 (d, *J* = 1.0 Hz, 1H), 8.85 – 8.80 (m, 1H), 8.24 – 8.11 (m, 2H), 8.09 – 8.00 (m, 2H), 7.70 – 7.60 (m, 4H), 4.43 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H). (**NR**)

¹³C NMR (101 MHz, DMSO-*d*₆) δ /ppm = 160.7, 155.4, 130.5, 130.0, 129.0, 128.2, 127.4, 125.9, 125.7, 124.9, 114.4, 113.5, 62.5, 14.0. (**NR**)

HRMS (ESI): *m/z* = 229.0626 [Substrate+Na]⁺, 324.0997 [M+Na]⁺, 340.0740 [M+K]⁺, 625.2095 [2M+Na]⁺, 301.1104 [M-H][−] (calc. for C₂₀H₁₅NO₂[−] *m/z* = 301.1103).



1,1'-Diethyl (2*E*,2'*E*)-3,3'-(1,4-phenylene)bis[2-cyano-2-propenoate]



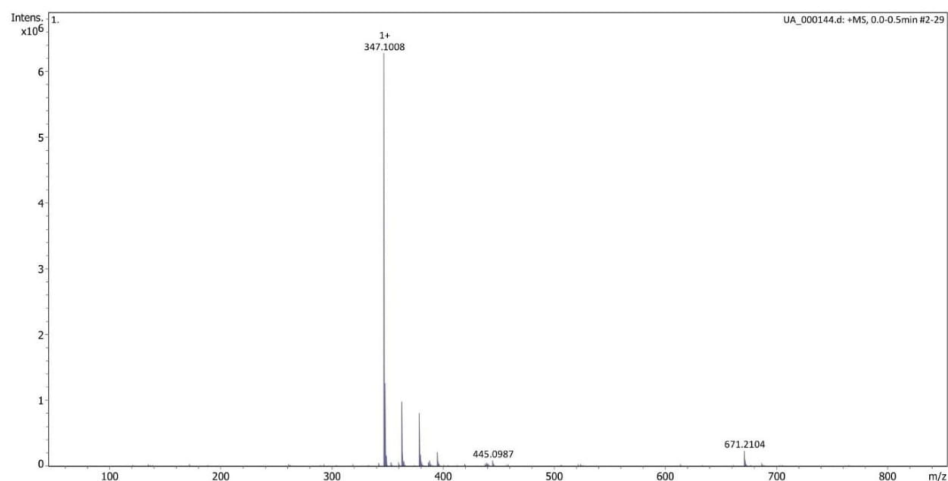
Light yellow solid

Yield: 0.665 g, >99%.

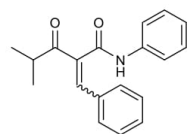
¹H NMR (400 MHz, CDCl₃) δ /ppm = 8.26 (s, 2H), 8.09 (s, 4H), 4.41 (q, *J* = 7.1 Hz, 4H), 1.41 (t, *J* = 7.1 Hz, 6H). ⁸

¹³C NMR (101 MHz, CDCl₃) δ /ppm = 162.0, 152.9, 135.3, 131.5, 115.1, 105.9, 63.3, 14.3. (**NR**)

HRMS (ESI): *m/z* = 347.1008 [M+Na]⁺, 363.0746 [M+K]⁺, 379.1269 [M+Na+Solvent]⁺, 671.2104 [2M+Na]⁺, 324.1116 [M-Na]⁺, (calc. for C₁₈H₁₆N₂O₄[−] *m/z* = 324.1110).



4-Methyl-3-oxo-N-phenyl-2-(phenylmethylene)pentanamide



Off white solid

Yield: 4.2 g, > 95%.

Diastereomer 1:

^1H NMR (400 MHz, CDCl_3) δ /ppm = 9.06 (br s, 1H), 8.15 (s, 1H), 7.64 – 7.60 (m, 2H), 7.44 – 7.39 (m, 2H), 7.38 – 7.28 (m, 5H), 7.18 – 7.11 (m, 1H), 2.62 (hept, J = 6.9 Hz, 1H), 1.03 (d, J = 6.9 Hz, 6H).

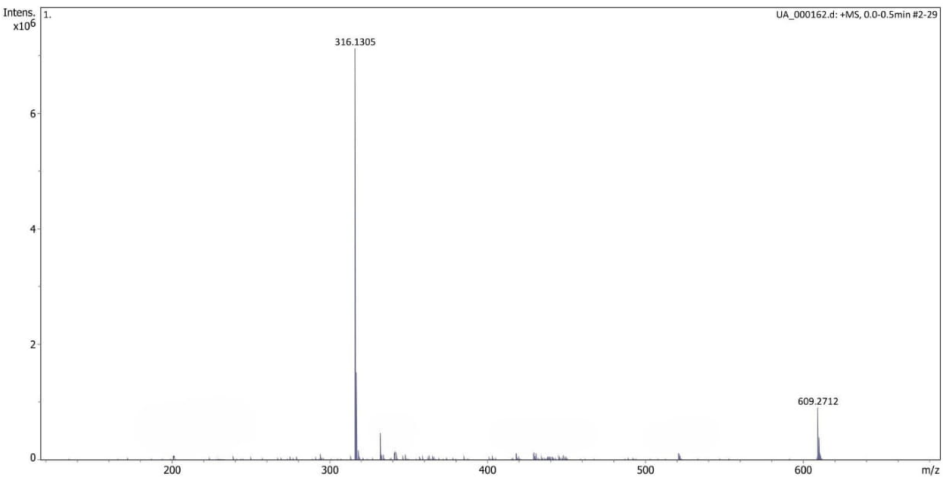
^{13}C NMR (101 MHz, CDCl_3) δ /ppm = 214.7, 161.2, 143.5, 137.8, 136.4, 134.2, 130.4, 129.6, 129.1, 129.0, 124.7, 120.3, 42.0, 18.8.

Diastereomer 2:

^1H NMR (400 MHz, CDCl_3) δ /ppm = 7.81 (br s, 1H), 7.64 – 7.60 (m, 1H), 7.58 – 7.55 (m, 2H), 7.52 – 7.48 (m, 2H), 7.44 – 7.39 (m, 2H), 7.37 – 7.28 (m, 3H), 7.18 – 7.11 (m, 1H), 3.35 (hept, J = 6.8 Hz, 1H), 1.21 (d, J = 6.8 Hz, 6H).

^{13}C NMR (101 MHz, CDCl_3) δ /ppm = 202.6, 165.7, 140.8, 137.5, 136.2, 133.1, 130.8, 130.1, 129.2, 129.1, 125.1, 120.4, 36.8, 19.2.⁹

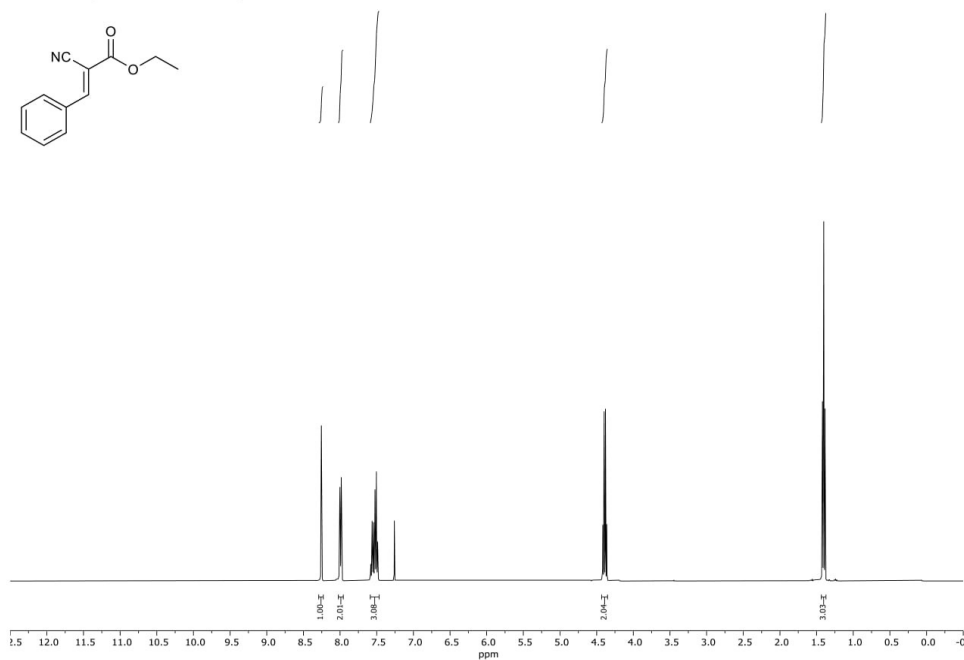
HRMS (ESI): m/z = 316.1305 $[\text{M}+\text{Na}]^-$, 332.1053 $[\text{M}+\text{K}]^-$, 609.2712 $[2\text{M}+\text{Na}]^-$, 293.1413 $[\text{M}-\text{Na}]^-$ (calc. for $\text{C}_{19}\text{H}_{19}\text{NO}_2^-$ m/z = 293.1416).



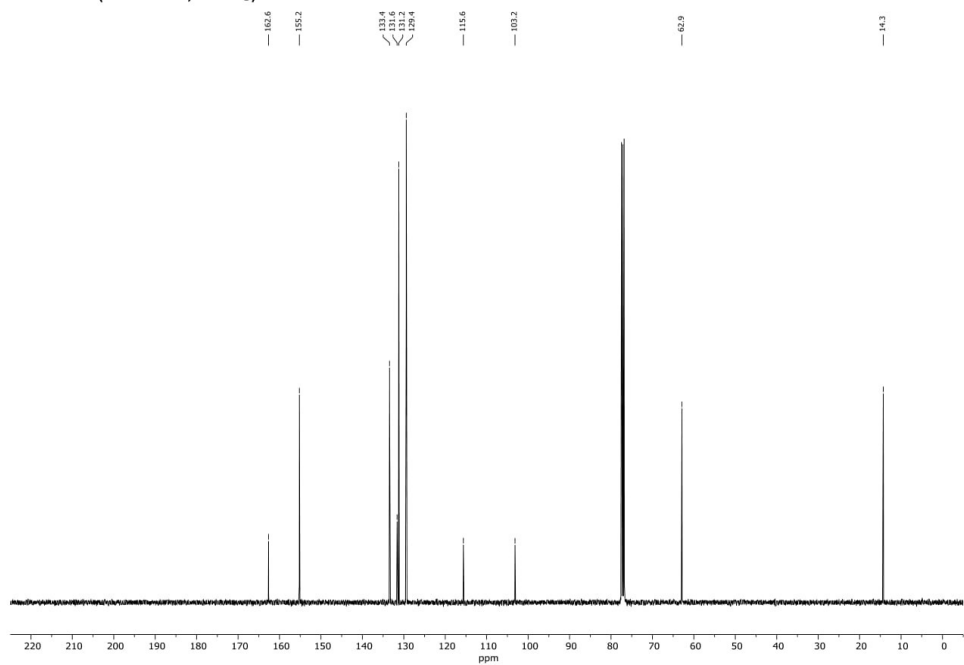
NMR Spectra

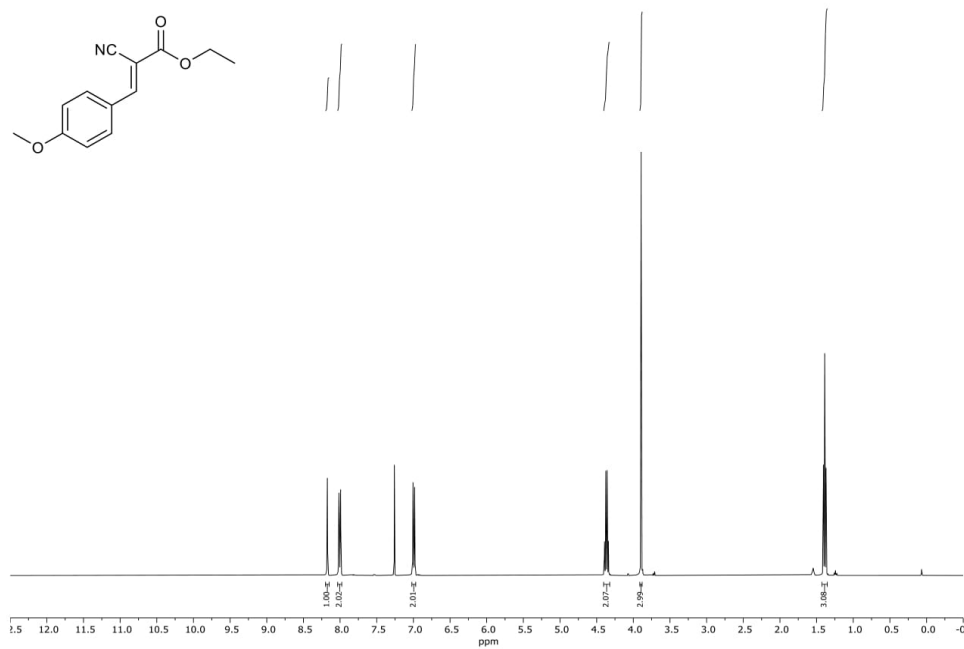
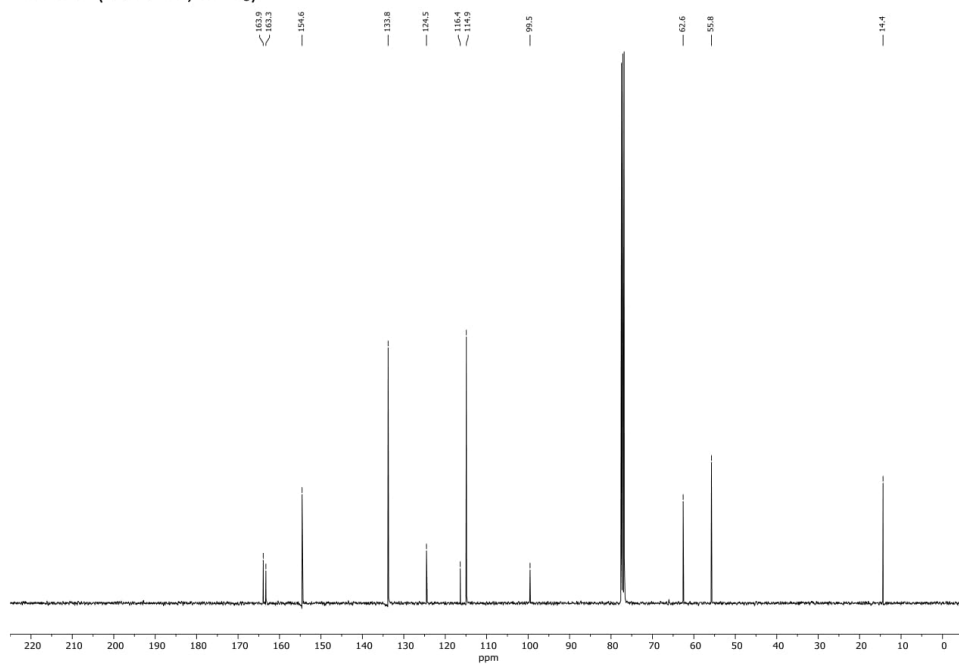
Ethyl (2E)-2-cyano-3-phenyl-2-propenoate

¹H-NMR (400 MHz CDCl₃)



¹³C-NMR (101 MHz, CDCl₃)

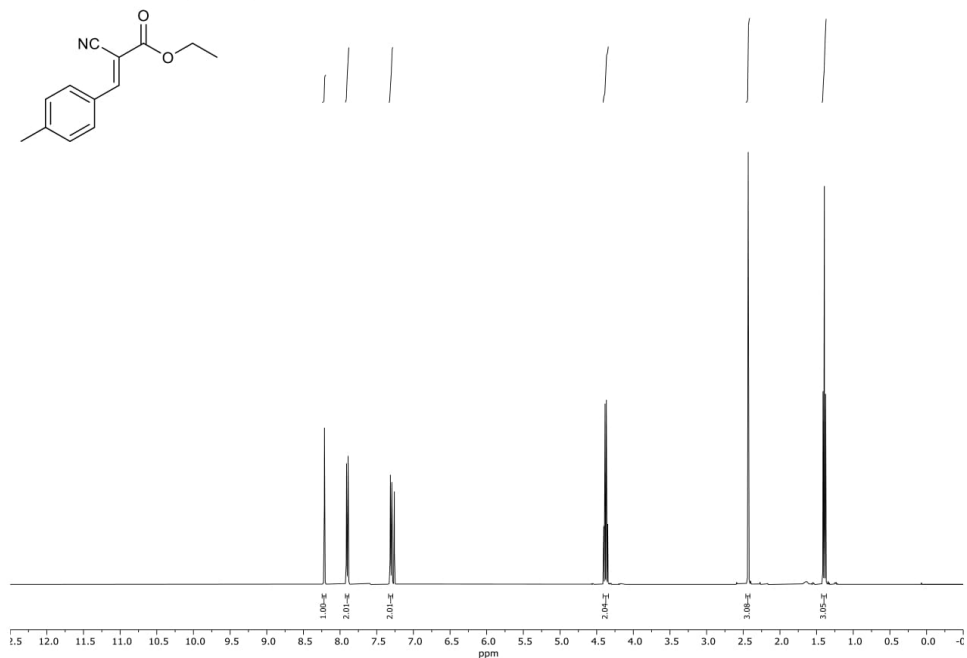


Ethyl (2E)-2-cyano-3-(4-methoxyphenyl)-2-propenoate¹H-NMR (400 MHz, CDCl₃)¹³C-NMR (101 MHz, CDCl₃)

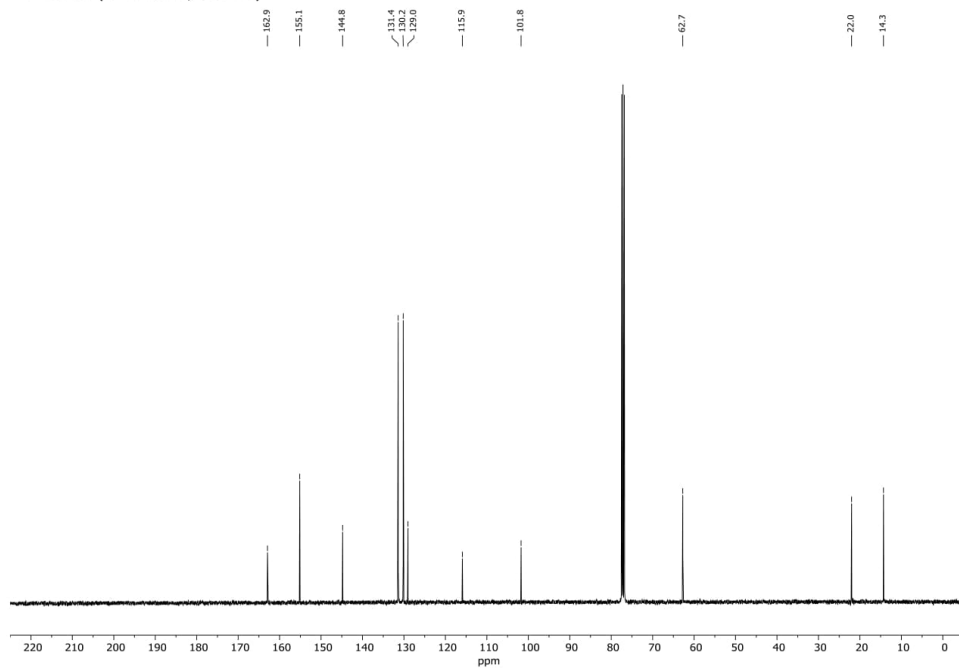
S13

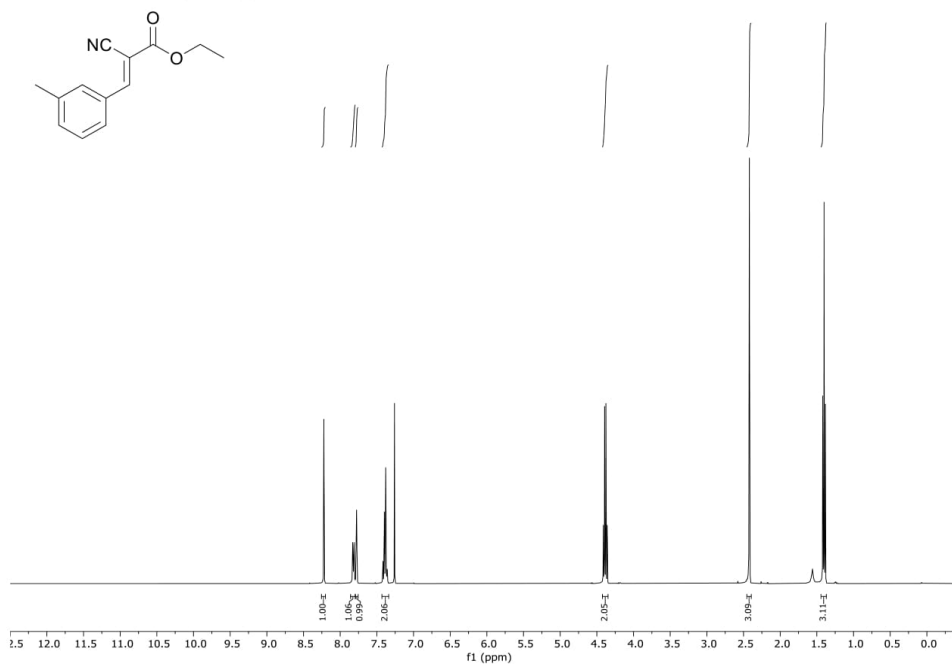
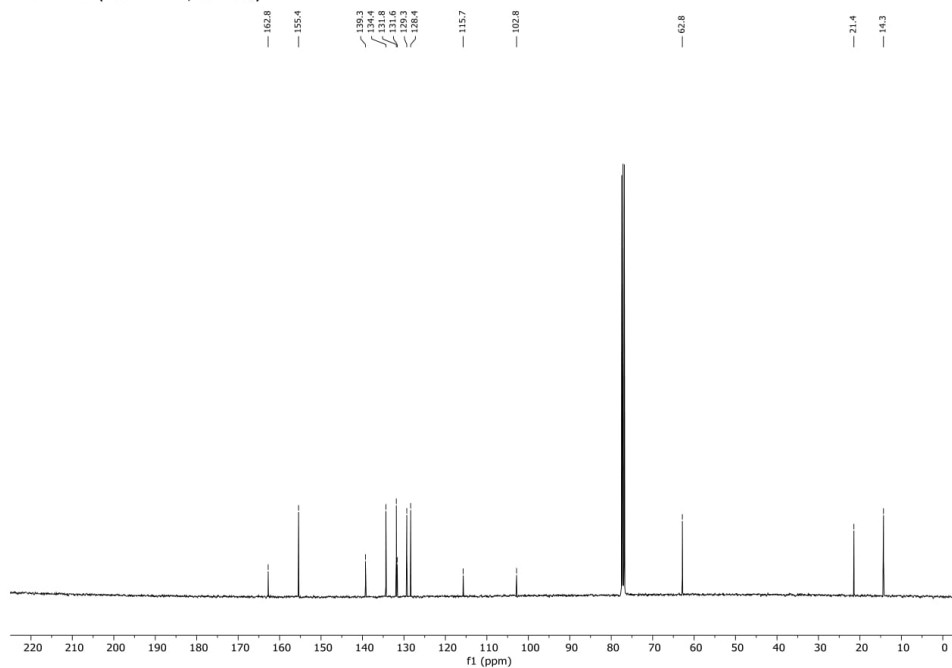
Ethyl (2E)-2-cyano-3-(4-methylphenyl)-2-propenoate

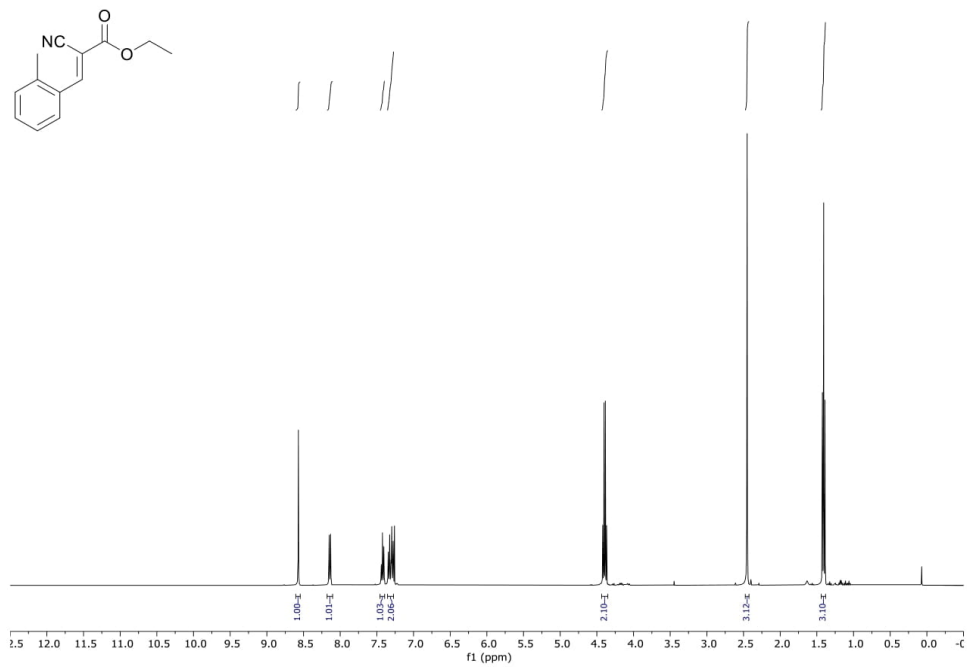
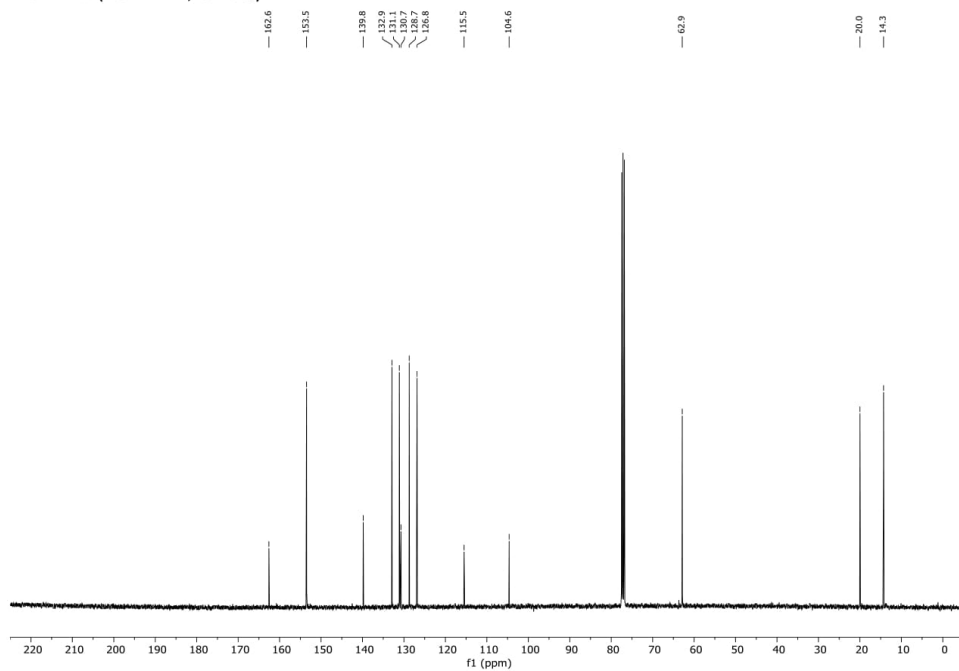
¹H-NMR (400 MHz, CDCl₃)



¹³C-NMR (101 MHz, CDCl₃)

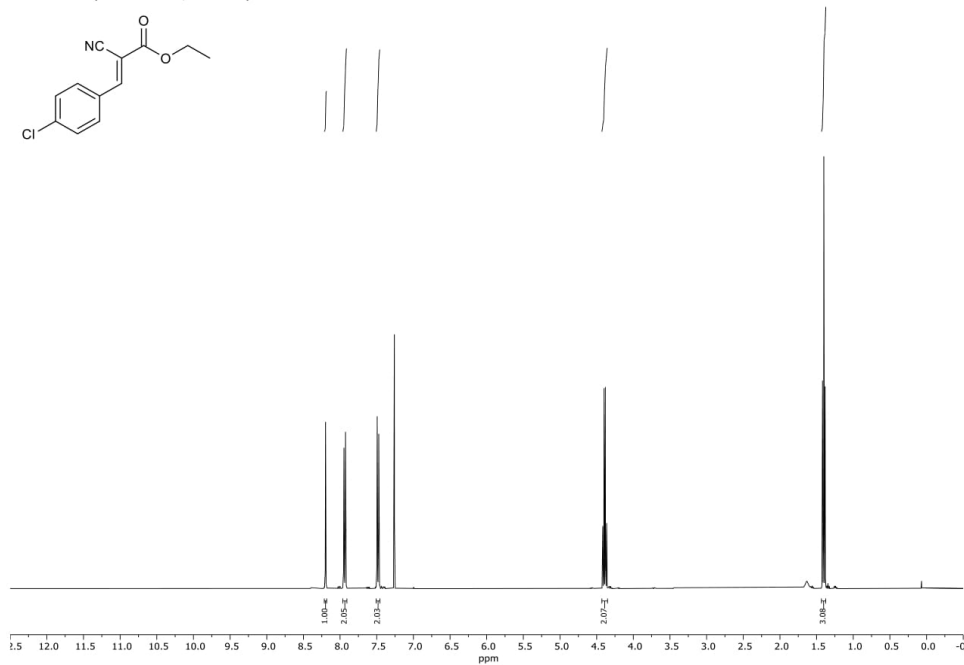


Ethyl (2E)-2-cyano-3-(3-methylphenyl)-2-propenoate¹H-NMR (400 MHz, CDCl₃)¹³C-NMR (101 MHz, CDCl₃)

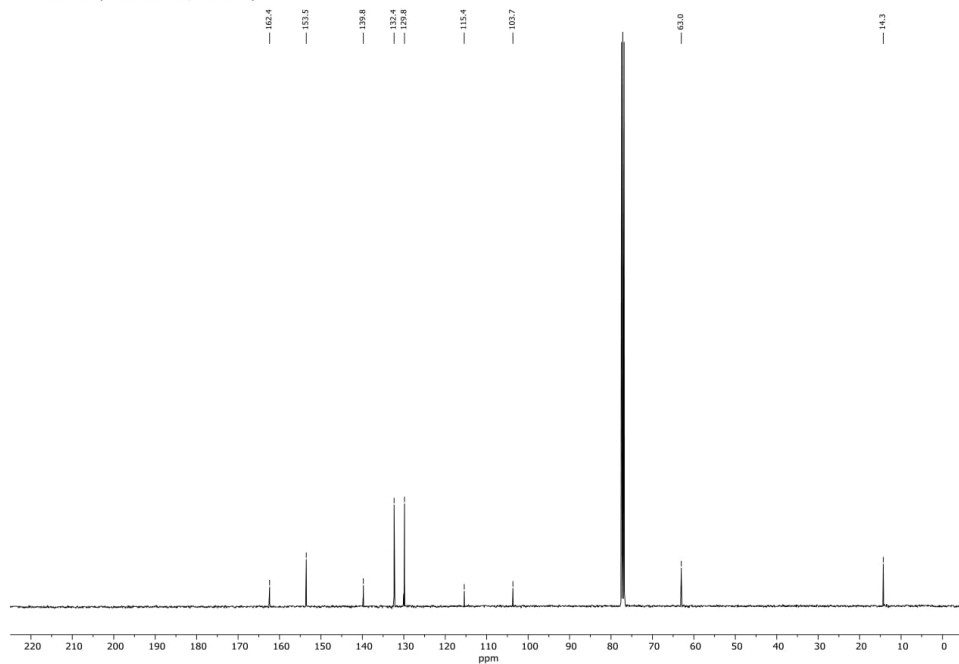
Ethyl (2E)-2-cyano-3-(2-methylphenyl)-2-propenoate¹H-NMR (400 MHz, CDCl₃)¹³C-NMR (101 MHz, CDCl₃)

Ethyl (2E)-2-cyano-3-(4-chlorophenyl)-2-propenoate

¹H-NMR (400 MHz, CDCl₃)

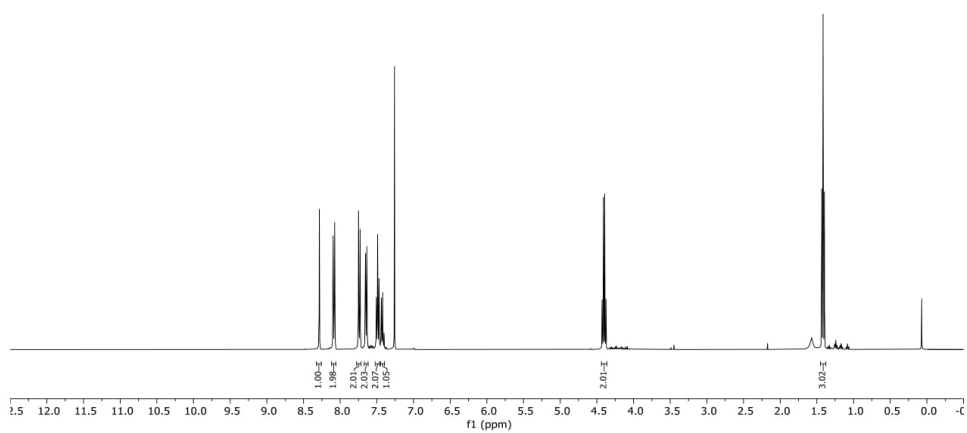
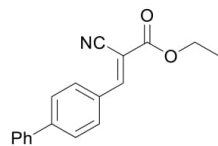


¹³C-NMR (101 MHz, CDCl₃)

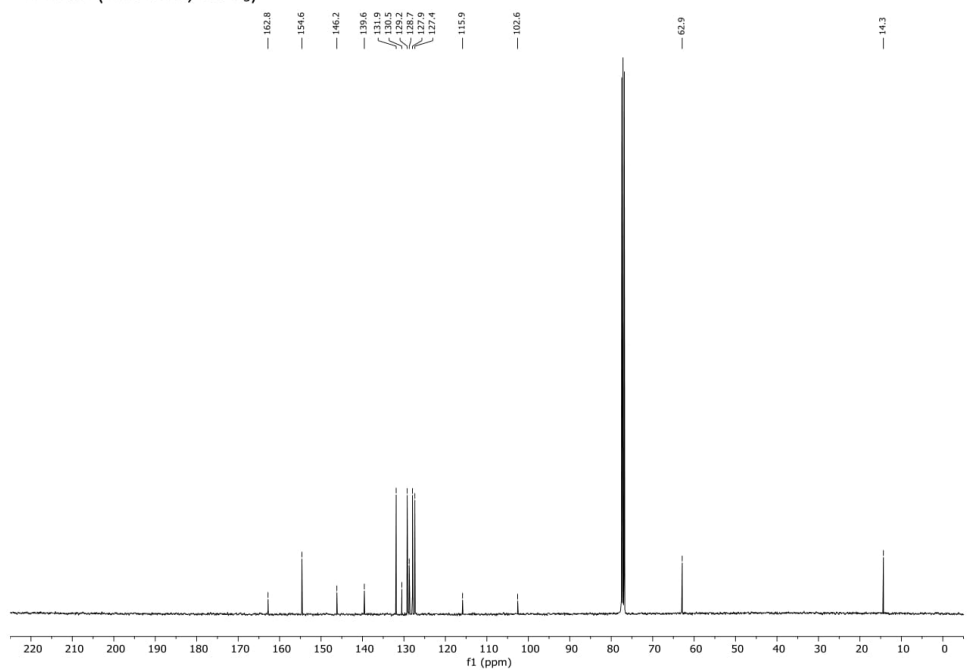


Ethyl (2E)-3-([1,1'-biphenyl]-4-yl)-2-cyanoprop-2-enoate

¹H-NMR (400 MHz, CDCl₃)

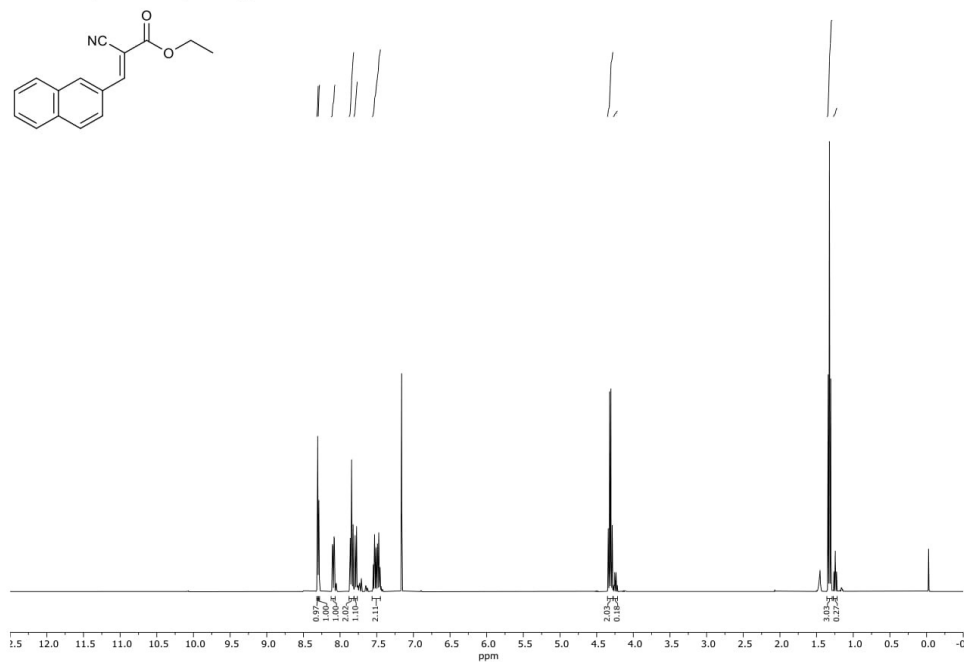


¹³C-NMR (101 MHz, CDCl₃)

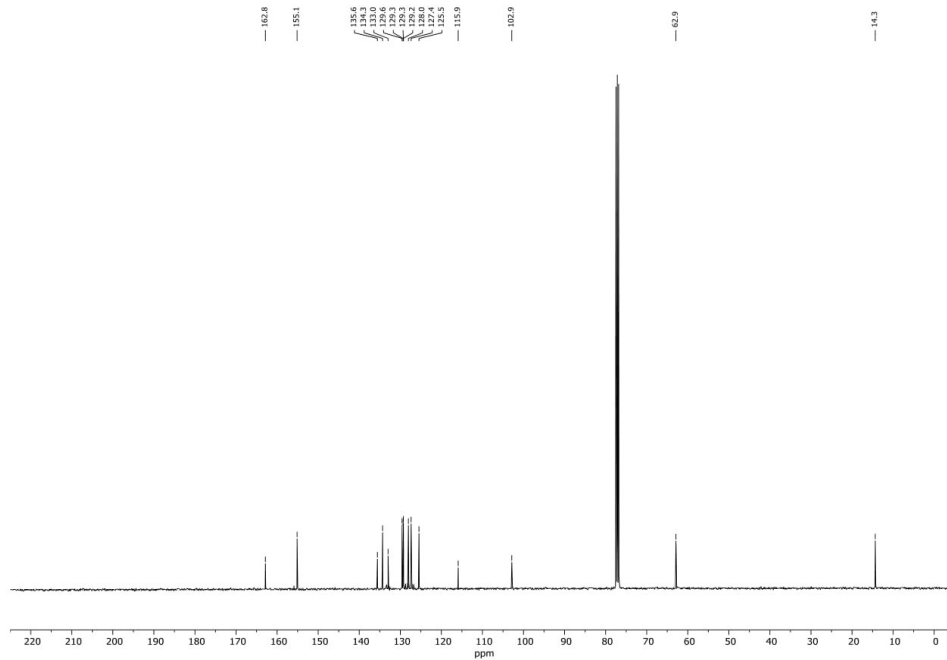


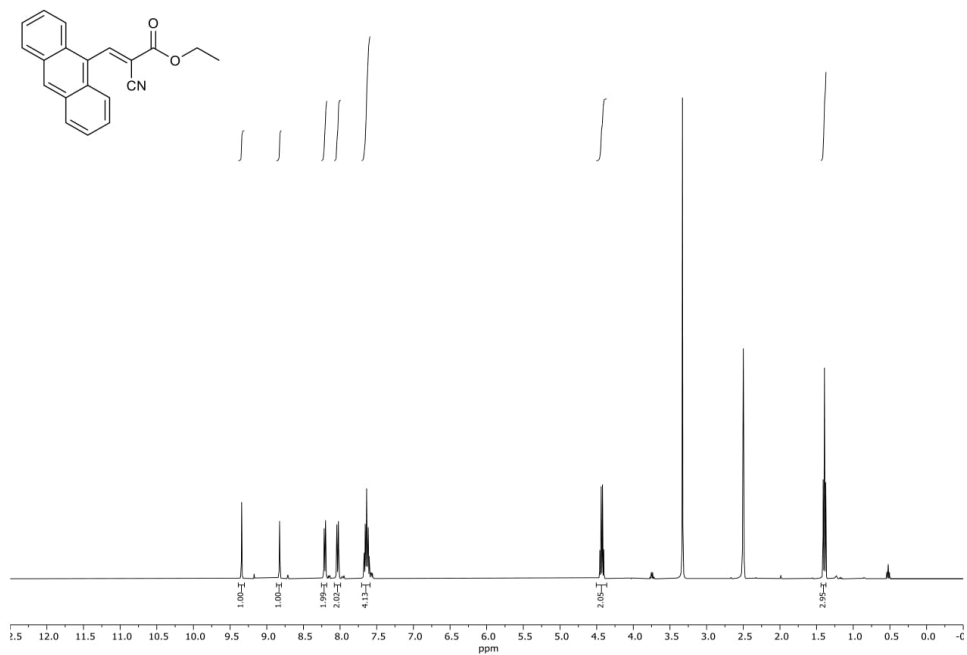
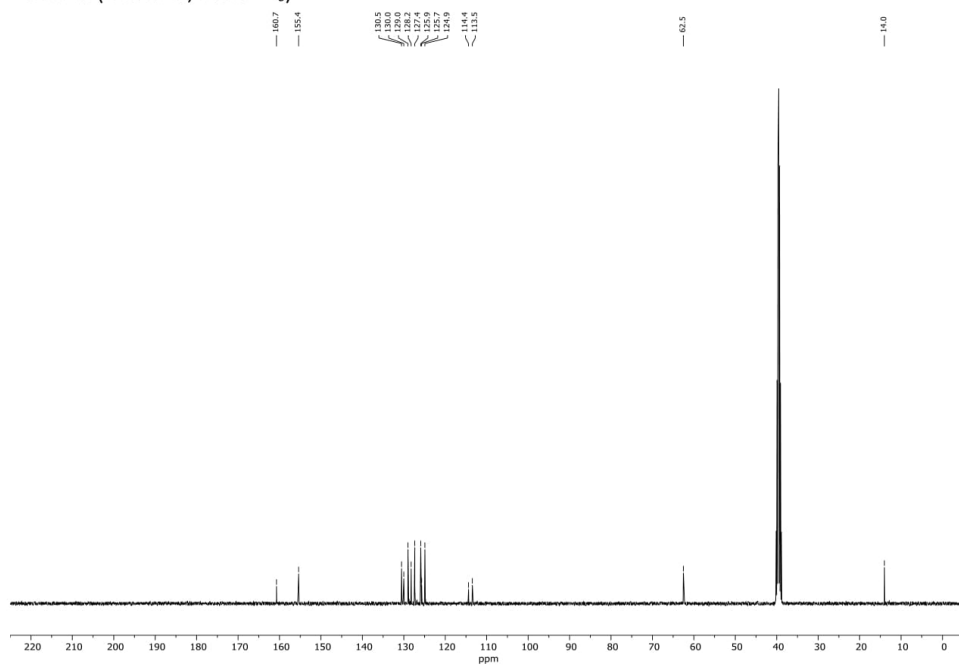
Ethyl (2*E*)-2-cyano-3-(2-naphthalenyl)-2-propenoate

¹H-NMR (400 MHz, CDCl₃)



¹³C-NMR (101 MHz, CDCl₃)



Ethyl 3-(9-anthracenyl)-2-cyano-2-propenoate¹H-NMR (400 MHz, DMSO-*d*₆)¹³C-NMR (101 MHz, DMSO-*d*₆)

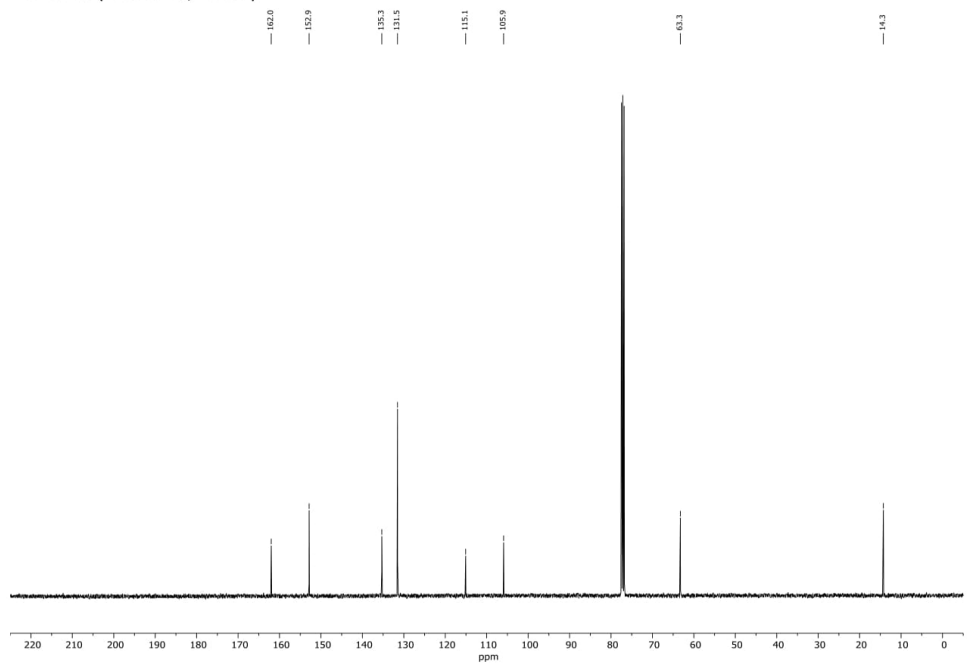
S20

1,1'-Diethyl (2*E*,2'*E*)-3,3'-(1,4-phenylene)bis[2-cyano-2-propenoate]

¹H-NMR (400 MHz, CDCl₃)



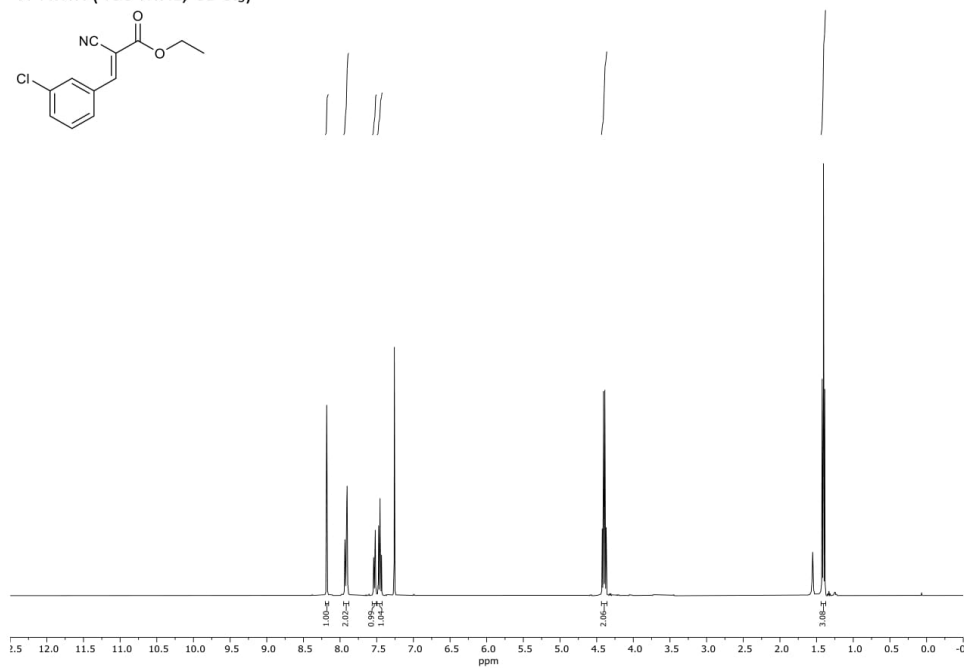
¹³C-NMR (101 MHz, CDCl₃)



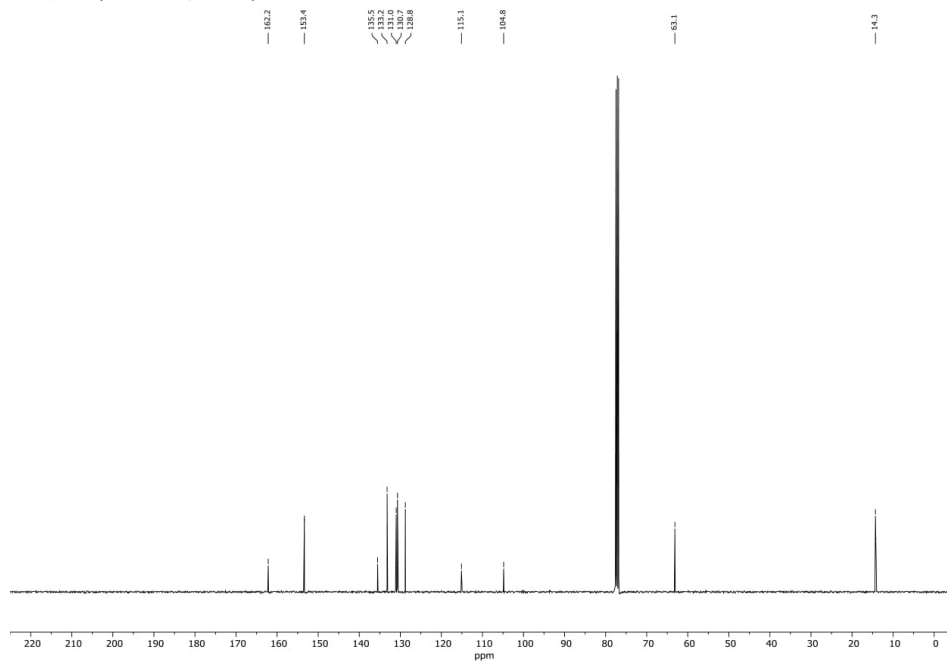
S21

Ethyl (2E)-2-cyano-3-(3-chlorophenyl)-2-propenoate

¹H-NMR (400 MHz, CDCl₃)

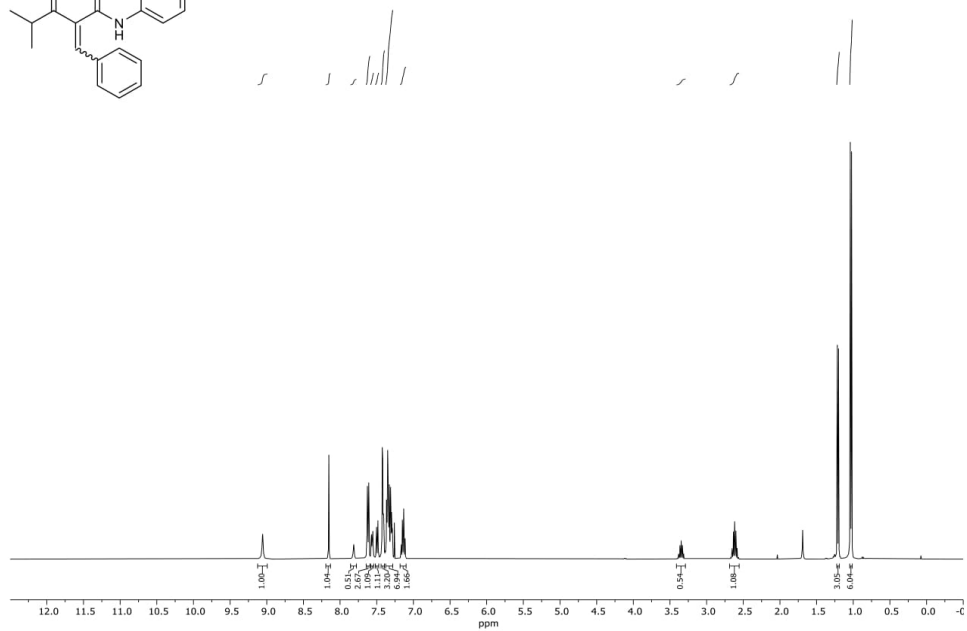
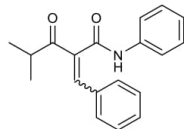


¹³C-NMR (101 MHz, CDCl₃)

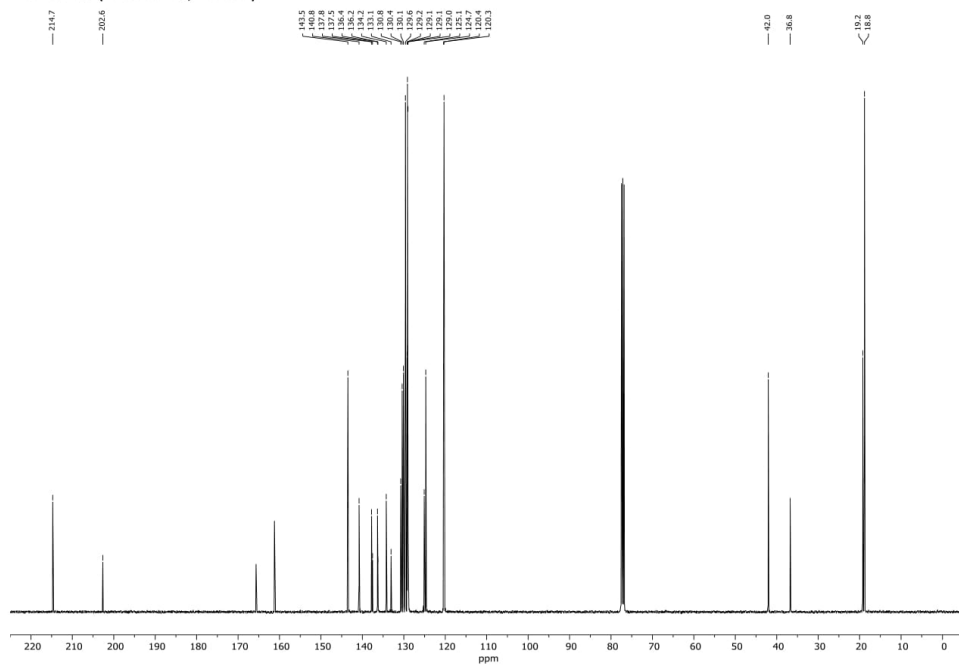


4-Methyl-3-oxo-N-phenyl-2-(phenylmethylene)pentanamide

¹H-NMR (400 MHz, CDCl₃)



¹³C-NMR (101 MHz, CDCl₃)



References

1. G. Li, J. Xiao and W. Zhang, *Green Chem.*, 2012, **14**, 2234-2242.
2. D. Khan, S. Mukhtar, M. A. Alsharif, M. I. Alahmdi and N. Ahmed, *Tetrahedron Lett.*, 2017, **58**, 3183-3187.
3. R. J. Kalbasi, M. Kolahdoozan, A. Massah and K. Shahabian, *Bull. Korean Chem. Soc.*, 2010, **31**, 2618-2626.
4. K. Shiba, K. Ogawa, K. Ishiwata, K. Yajima and H. Mori, *Bioorg. Med. Chem.*, 2006, **14**, 2620-2626.
5. B. Y. Killam, R. T. Barkauskas, D. P. Dembiec, R. S. Farrell, M. A. Gallego, K. A. Kaiser, M. L. Keeling, K. Y. Kang, G. R. Verdoorn and G. Kharas, unpublished work.
6. B. Y. Killam, R. J. Amend, M. A. Budz, A. B. Collins, S. M. Hinz, A. C. Johnson, L. N. Kibler, S. Z. Salem, B. A. Scott and I. Skukan, unpublished work.
7. K. K. Senapati, C. Borgohain and P. Phukan, *J. Mol. Catal. A: Chem.*, 2011, **339**, 24-31.
8. D. Meng, Y. Qiao, X. Wang, W. Wen and S. Zhao, *RSC Adv.*, 2018, **8**, 30180-30185.
9. A. Ying, L. Wang, F. Qiu, H. Hu and J. Yang, *C. R. Chim.*, 2015, **18**, 223-232.

3. Conclusion and Outlook

This cumulative thesis explored two complementary material design strategies aimed at advancing sustainable heterogeneous organocatalysis. The first study focused on hierarchically porous silica monoliths synthesized via the Nakanishi sol-gel method and systematically modified by HT. The aim was to elucidate how mesopore size and connectivity evolve under controlled HT conditions. Advanced physisorption analyses revealed that pore diameters can be precisely tuned from 8 to 25 nm - a critical range governing molecular accessibility to catalytic sites. The study established how HT conditions influence pore network connectivity and diffusion pathways, offering design principles for tailoring silica monoliths with optimized permeability and surface area for catalytic and chromatographic applications. It also underscored that even minor variations in synthesis parameters can induce significant structural differences, providing mechanistic insights essential for the reproducible fabrication of high-performance monolithic supports. The second study examined raw chitosan as a renewable heterogeneous organocatalyst for the Knoevenagel condensation. The aim was to evaluate whether a natural polymer could efficiently catalyze reactions under mild and recyclable conditions consistent with green chemistry principles. Using the condensation of benzaldehydes with ethyl cyanoacetate as a model reaction, chitosan demonstrated high catalytic efficiency (90-99% yields), excellent reusability over multiple cycles, and compatibility with green solvents such as ethanol and acetone. The study revealed that catalytic activity is governed not only by the amino groups but also by the polymer's swelling and water-binding capacities, which enhance accessibility and drive the reaction equilibrium toward product formation. Extension of the approach to the gram-scale synthesis of an Atorvastatin intermediate further underlined its practical and industrial relevance. Collectively, these findings highlight chitosan's dual functionality, both a solid catalyst and a dynamic solvent-responsive matrix demonstrating how renewable materials can fulfil the principles of green chemistry when process parameters are carefully optimized.

Together, these studies provide complementary perspectives: silica monoliths exemplify the rational engineering of pore structures for optimized diffusion, while chitosan illustrates the catalytic potential of renewable biopolymers under sustainable reaction conditions. Importantly, relying solely on solid supports or renewable feedstocks does not automatically guarantee a truly sustainable catalytic process. Achieving genuine alignment with the principles of green chemistry

requires a holistic assessment of the entire synthesis pathway, from catalyst preparation to product isolation, where parameters such as solvent selection, temperature, energy consumption, recyclability, and waste generation are optimized collectively.

Extending the findings of Publication 1, we have recently completed a study in which silica monoliths with systematically varied mesoporosity were applied in continuous-flow catalysis using functionalized monoliths with immobilized organocatalysts. The results indicate that both pore size and network connectivity critically influence catalyst immobilization and turnover frequency, highlighting the practical role of mesostructural features in controlling catalytic performance.

While Publication 1 detailed mesopore evolution across various hydrothermal conditions, the role of internal vapor pressure during hydrothermal treatment remains unclear. It may contribute to heterogeneity in pore size and connectivity by inducing uneven compression of the silica framework, leading to non-uniform dissolution and reprecipitation. Future studies should investigate this phenomenon through in-situ monitoring of internal vapor pressure under different hydrothermal regimes to better correlate pressure dynamics with pore uniformity.

For chitosan, future work should address both opportunities and limitations. Enhancing its accessible surface area through porous structuring could expand its applicability in continuous-flow catalysis, while functionalization with designed organocatalytic motifs may broaden its reactivity profile. Nonetheless, its limited swelling and accessibility in non-protic solvents remain key challenges. These may be overcome through mild crosslinking or hybridization with environmentally benign additives that preserve sustainability while improving performance. In ongoing research, we are also investigating whether hydroxyl groups in chitin and chitosan can be functionalized analogously to silanol sites in silica, offering a sustainable route toward tailored heterogeneous organocatalysts.

Overall, this thesis demonstrates that both the controlled engineering of hierarchical pore networks in silica monoliths and the functional adaptability of chitosan provide distinct yet complementary strategies for advancing sustainable heterogeneous organocatalysis. By uniting structural precision in inorganic materials with renewable functionality in biopolymers, future research can further develop catalytic systems that are not only efficient and robust but also genuinely aligned with the principles of green chemistry.

4. Literature

1. Zimmerman, J. B.; Anastas, P. T.; Erythropel, H. C.; Leitner, W., Designing for a green chemistry future. *Science* **2020**, 367 (6476), 397-400.
2. Anastas, P. T.; Warner, J. C., *Principles of green chemistry*. Oxford University Press: Oxford **1998**; Vol. 29.
3. Steinfeld, J. I.; Francisco, J. S.; Hase, W. L., *Chemical kinetics and dynamics*. Prentice Hall Upper Saddle River, NJ: **1999**; Vol. 2.
4. Catalysis. <https://www.chem.ox.ac.uk/catalysis> (accessed 12.11.2025).
5. Dunn, P. J.; Hii, K. M.; Krische, M. J.; Williams, M. T., *Sustainable catalysis: challenges and practices for the pharmaceutical and fine chemical industries*. Wiley: **2013**.
6. Kate, A.; Sahu, L. K.; Pandey, J.; Mishra, M.; Sharma, P. K., Green catalysis for chemical transformation: The need for the sustainable development. *Curr. Res. Green Sustain. Chem.* **2022**, 5, 100248.
7. Su, D. S.; Zhang, J.; Frank, B.; Thomas, A.; Wang, X.; Paraknowitsch, J.; Schlögl, R., Metal-free heterogeneous catalysis for sustainable chemistry. *ChemSusChem* **2010**, 3 (2), 169-180.
8. Schlögl, R., Heterogeneous catalysis. *Angew. Chem., Int. Ed.* **2015**, 54 (11), 3465-3520.
9. Friend, C. M.; Xu, B., Heterogeneous catalysis: a central science for a sustainable future. *Acc. Chem. Res.* **2017**, 50 (3), 517-521.
10. Lakhani, P.; Bhandari, D.; Modi, C. K., Support materials impact on green synthesis and sustainable processing via heterogeneous catalysis. *Discov Catal.* **2024**, 1 (1), 2.
11. Sehnal, P.; Taylor, R. J.; Fairlamb, I. J., Emergence of palladium (IV) chemistry in synthesis and catalysis. *Chem. Rev.* **2010**, 110 (2), 824-889.
12. Fürstner, A., Gold and platinum catalysis—a convenient tool for generating molecular complexity. *Chem.Soc. Rev.* **2009**, 38 (11), 3208-3221.
13. Fagnou, K.; Lautens, M., Rhodium-catalyzed carbon–carbon bond forming reactions of organometallic compounds. *Chem. Rev.* **2003**, 103 (1), 169-196.
14. Tasker, S. Z.; Standley, E. A.; Jamison, T. F., Recent advances in homogeneous nickel catalysis. *Nature* **2014**, 509 (7500), 299-309.
15. Chen, Q.-A.; Ye, Z.-S.; Duan, Y.; Zhou, Y.-G., Homogeneous palladium-catalyzed asymmetric hydrogenation. *Chem. Soc. Rev.* **2013**, 42 (2), 497-511.
16. Johansson Seechurn, C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V., Palladium-catalyzed cross-coupling: a historical contextual perspective to the 2010 Nobel Prize. *Angew. Chem., Int. Ed.* **2012**, 51 (21), 5062-5085.
17. Trost, B. M., Atom economy—a challenge for organic synthesis: homogeneous catalysis leads the way. *Angew. Chem., Int. Ed.* **1995**, 34 (3), 259-281.
18. Dalko, P. I.; Moisan, L., In the golden age of organocatalysis. *Angew. Chem., Int. Ed.* **2004**, 43 (39), 5138-5175.
19. List, B., Introduction: organocatalysis. *Chem Rev.* **2007**, 107 (12), 5413-5415.
20. Reetz, M.; List, B.; Jaroch, S.; Weinmann, H., *Organocatalysis*. Springer Science & Business Media: **2008**.
21. Buckley, B. R., Organocatalysis. *Annual Reports Section "B"(Organic Chemistry)* **2009**, 105, 113-128.
22. Bertelsen, S.; Jørgensen, K. A., Organocatalysis—after the gold rush. *Chem. Soc. Rev.* **2009**, 38 (8), 2178-2189.
23. Buckley, B. R.; Kimber, M. C.; Slater, N. H., Organocatalysis. *Annual Reports Section "B"(Organic Chemistry)* **2012**, 108, 98-109.

24. Lohar, S.; Mitra, P.; Majhi, S., Current applications of organocatalysis in total synthesis of natural products at room temperature. *Curr. Green Chem.* **2025**, *12* (3), 215-233.
25. Schmid, S. P.; Schlosser, L.; Glorius, F.; Jorner, K., Catalysing (organo-) catalysis: Trends in the application of machine learning to enantioselective organocatalysis. *Beilstein J. Org. Chem.* **2024**, *20* (1), 2280-2304.
26. Jacobsen, E. N.; MacMillan, D. W., Organocatalysis. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107* (48), 20618-20619.
27. List, B., Proline-catalyzed asymmetric reactions. *Tetrahedron* **2002**, *58* (28), 5573-5590.
28. The Nobel Prize in Chemistry 2021. NobelPrize.org. <https://www.nobelprize.org/prizes/chemistry/2021/summary/> (accessed 21.09.2025).
29. Giacalone, F.; Gruttadauria, M.; Agrigento, P.; Noto, R., Low-loading asymmetric organocatalysis. *Chem. Soc. Rev.* **2012**, *41* (6), 2406-2447.
30. Cozzi, F., Immobilization of organic catalysts: when, why, and how. *Adv. Synth. Catal.* **2006**, *348* (12-13), 1367-1390.
31. Shaikh, I. R., Organocatalysis: key trends in green synthetic chemistry, challenges, scope towards heterogenization, and importance from research and industrial point of view. *J. Catal.* **2014**, *2014* (1), 402860.
32. Rostamnia, S.; Doustkhah, E., Nanoporous silica-supported organocatalyst: a heterogeneous and green hybrid catalyst for organic transformations. *RSC Adv.* **2014**, *4* (54), 28238-28248.
33. Corma, A.; Garcia, H., Silica-bound homogenous catalysts as recoverable and reusable catalysts in organic synthesis. *Adv. Synth. Catal.* **2006**, *348* (12-13), 1391-1412.
34. Turke, K.; Meinus, R.; Cop, P.; Prates da Costa, E.; Brand, R. D.; Henss, A.; Schreiner, P. R.; Smarsly, B. M., Amine-functionalized nanoporous silica monoliths for heterogeneous catalysis of the Knoevenagel condensation in flow. *ACS omega* **2020**, *6* (1), 425-437.
35. Trommer, A.; Hessling, J.; Schreiner, P. R.; Schönhoff, M.; Smarsly, B. M., Influence of the Mesoporosity of Silica Carrier Materials on the Performance of an Immobilized Organocatalyst in Heterogeneous Catalysis. *ACS Appl. Mater. Interfaces* **2025**, *17* (16), 24283-24299.
36. Meninno, S., Valorization of waste: Sustainable organocatalysts from renewable resources. *ChemSusChem* **2020**, *13* (3), 439-468.
37. Ellebracht, N. C.; Jones, C. W., Optimized cellulose nanocrystal organocatalysts outperform silica-supported analogues: Cooperativity, selectivity, and bifunctionality in acid-base aldol condensation reactions. *ACS Catal.* **2019**, *9* (4), 3266-3277.
38. Mahé, O.; Brière, J. F.; Dez, I., Chitosan: An upgraded polysaccharide waste for organocatalysis. *Eur. J. Org. Chem.* **2015**, (12), 2559-2578.
39. El Kadib, A., Chitosan as a sustainable organocatalyst: a concise overview. *ChemSusChem* **2015**, *8* (2), 217-244.
40. Jose, T.; Sudheesh, N.; Shukla, R. S., Amino functionalized chitosan as a catalyst for selective solvent-free self-condensation of linear aldehydes. *J. Mol. Catal., A* **2010**, *333* (1-2), 158-166.
41. de Gonzalo, G.; Franconetti, A.; Fernández, R.; Lassaletta, J. M.; Cabrera-Escribano, F., Preparation of chitosan-supported urea materials and their application in some organocatalytic procedures. *Carbohydr. Polym.* **2018**, *199*, 365-374.
42. Reddy, K. R.; Rajgopal, K.; Maheswari, C. U.; Kantam, M. L., Chitosan hydrogel: A green and recyclable biopolymer catalyst for aldol and Knoevenagel reactions. *New J. Chem.* **2006**, *30* (11), 1549-1552.

43. Anbu, N.; Hariharan, S.; Dhakshinamoorthy, A., Knoevenagel-Doebner condensation promoted by chitosan as a reusable solid base catalyst. *Mol. Catal.* **2020**, *484*, 110744.
44. Liu, C.; Zhang, L.; Tan, L.; Liu, Y.; Tian, W.; Ma, L., Immobilized crosslinked pectinase preparation on porous ZSM-5 zeolites as reusable biocatalysts for ultra-efficient hydrolysis of β -glycosidic bonds. *Front. Chem.* **2021**, *9*, 677868.
45. Weitkamp, J.; Puppe, L., *Catalysis and zeolites: fundamentals and applications*. Springer Science & Business Media: **2013**.
46. Antonietti, M.; Lopez-Salas, N.; Primo, A., Adjusting the Structure and Electronic Properties of Carbons for Metal-Free Carbocatalysis of Organic Transformations. *Adv. Mater.* **2019**, *31* (13), 1805719.
47. Kristensen, T. E.; Hansen, T., Polymer-supported chiral organocatalysts: synthetic strategies for the road towards affordable polymeric immobilization. *Eur. J. Org. Chem.* **2010**, *2010* (17), 3179-3204.
48. Deng, W.; Zhang, Q.; Wang, Y., Catalytic transformations of cellulose and cellulose-derived carbohydrates into organic acids. *Catalysis Today* **2014**, *234*, 31-41.
49. Jiménez-Gómez, C. P.; Cecilia, J. A., Chitosan: a natural biopolymer with a wide and varied range of applications. *Molecules* **2020**, *25* (17), 3981.
50. Murakishi, M.; Nakanishi, S.; Sogawa, H.; Sanda, F., Alginate-and κ -carrageenan-supported asymmetric organocatalysts: preparation, characterization, and catalytic activity for Friedel-Crafts alkylation. *RSC Adv.* **2025**, *15* (37), 30865.
51. Guo, L.; Dou, R.; Wu, Y.; Zhang, R.; Wang, L.; Wang, Y.; Gong, Z.; Chen, J.; Wu, X., From lignin waste to efficient catalyst: Illuminating the impact of lignin structure on catalytic activity of cycloaddition reaction. *ACS Sustainable Chem. Eng.* **2019**, *7* (19), 16585-16594.
52. Doi, S.; Clark, J. H.; Macquarrie, D. J.; Milkowski, K., New materials based on renewable resources: chemically modified expanded corn starches as catalysts for liquid phase organic reactions. *Chem. Commun.* **2002**, (22), 2632-2633.
53. Pasricha, S.; Gahlot, P.; Mittal, K.; Rai, D.; Avasthi, N.; Kaur, H.; Rai, S., Functionalized MCM-41: Versatile Catalysts for Organic Transformations. *ChemistrySelect* **2022**, *7* (7), e202103674.
54. Ziarani, G. M.; Roshankar, S.; Mohajer, F.; Badiei, A., The synthesis and application of functionalized mesoporous silica SBA-15 as heterogeneous catalyst in organic synthesis. *Curr. Org. Chem.* **2021**, *25* (3), 361-387.
55. Brand, R. D.; Schulze, J. S.; Henss, A.; Smarsly, B. M., Time-of-Flight Secondary Ion Mass Spectrometry Revealing the Organocatalyst Distribution in Functionalized Silica Monoliths. *ChemistryOpen* **2024**, *13* (11), e202400199.
56. Khokhar, D.; Kour, M.; Phul, R.; Sharma, A. K.; Jadoun, S., *Polystyrene-supported Catalysts*. CRC Press: **2024**; p 89-100.
57. Verma, S.; Jain, S. L.; Sain, B., PEG-embedded thiourea dioxide (PEG. TUD) as a novel organocatalyst for the highly efficient synthesis of 3, 4-dihydropyrimidinones. *Tetrahedron Lett.* **2010**, *51* (52), 6897-6900.
58. Davis, R. J., New perspectives on basic zeolites as catalysts and catalyst supports. *J. Catal.* **2003**, *216* (1-2), 396-405.
59. Gong, X.; Caglayan, M.; Ye, Y.; Liu, K.; Gascon, J.; Dutta Chowdhury, A., First-generation organic reaction intermediates in zeolite chemistry and catalysis. *Chem. Rev.* **2022**, *122* (18), 14275-14345.
60. Daliran, S.; Oveisi, A. R.; Peng, Y.; López-Magano, A.; Khajeh, M.; Mas-Ballesté, R.; Alemán, J.; Luque, R.; Garcia, H., Metal-organic framework (MOF)-, covalent-organic

framework (COF)-, and porous-organic polymers (POP)-catalyzed selective C–H bond activation and functionalization reactions. *Chem. Soc. Rev.* **2022**, *51* (18), 7810-7882.

61. Yang, D.; Gates, B. C., Catalysis by metal organic frameworks: perspective and suggestions for future research. *ACS Catal.* **2019**, *9* (3), 1779-1798.
62. Liu, X.; Dai, L., Carbon-based metal-free catalysts. *Nat. Rev. Mater.* **2016**, *1* (11), 1-12.
63. Bahuguna, A.; Kumar, A.; Krishnan, V., Carbon-support-based heterogeneous nanocatalysts: synthesis and applications in organic reactions. *Asian J. Org. Chem.* **2019**, *8* (8), 1263-1305.
64. Perot, G.; Guisnet, M., Advantages and disadvantages of zeolites as catalysts in organic chemistry. *J. Mol. Catal., A* **1990**, *61* (2), 173-196.
65. Chughtai, A. H.; Ahmad, N.; Younus, H. A.; Laypkov, A.; Verpoort, F., Metal–organic frameworks: versatile heterogeneous catalysts for efficient catalytic organic transformations. *Chem. Soc. Rev.* **2015**, *44* (19), 6804-6849.
66. Wang, Y.; Wang, X.; Antonietti, M., Polymeric graphitic carbon nitride as a heterogeneous organocatalyst: from photochemistry to multipurpose catalysis to sustainable chemistry. *Angew. Chem., Int. Ed.* **2012**, *51* (1), 68-89.
67. Lu, J.; Toy, P. H., Organic polymer supports for synthesis and for reagent and catalyst immobilization. *Chem. Rev.* **2009**, *109* (2), 815-838.
68. Ferré, M.; Pleixats, R.; Man, M. W. C.; Cattoën, X., Recyclable organocatalysts based on hybrid silicas. *Green Chem.* **2016**, *18* (4), 881-922.
69. Martínez-Edo, G.; Balmori, A.; Pontón, I.; Marti del Rio, A.; Sánchez-García, D., Functionalized ordered mesoporous silicas (MCM-41): Synthesis and applications in catalysis. *Catalysts* **2018**, *8* (12), 617.
70. Brand, R. D.; Maass, M.; Grebenyuk, A. G.; Golub, A. A.; Smarsly, B. M., Commercial silica materials functionalized with a versatile organocatalyst for the catalysis of acylation reactions in liquid media. *ChemPhysChem* **2025**, *26* (5), e202400936.
71. Margelefsky, E. L.; Zeidan, R. K.; Davis, M. E., Cooperative catalysis by silica-supported organic functional groups. *Chem. Soc. Rev.* **2008**, *37* (6), 1118-1126.
72. Zamboulis, A.; Moitra, N.; Moreau, J. J.; Cattoën, X.; Man, M. W. C., Hybrid materials: versatile matrices for supporting homogeneous catalysts. *J. Mater. Chem.* **2010**, *20* (42), 9322-9338.
73. Ngo, H. L.; Hu, A.; Lin, W., Molecular building block approaches to chiral porous zirconium phosphonates for asymmetric catalysis. *J. Mol. Catal., A* **2004**, *215* (1-2), 177-186.
74. Li, C.; Zhang, H.; Jiang, D.; Yang, Q., Chiral catalysis in nanopores of mesoporous materials. *Chem. Commun.* **2007**, (6), 547-558.
75. Shukla, M. S.; Hande, P. E.; Chandra, S., Porous Silica Support for Immobilizing Chiral Metal Catalyst: Unravelling the Activity of Catalyst on Asymmetric Organic Transformations. *ChemistrySelect* **2022**, *7* (23), e202200549.
76. Erigoni, A.; Diaz, U., Porous silica-based organic-inorganic hybrid catalysts: A review. *Catalysts* **2021**, *11* (1), 79.
77. Yadav, R.; Baskaran, T.; Kaiprathu, A.; Ahmed, M.; Bhosale, S. V.; Joseph, S.; Al-Muhtaseb, A. a. H.; Singh, G.; Sakthivel, A.; Vinu, A., Recent advances in the preparation and applications of organo-functionalized porous materials. *Chem.–Asian J.* **2020**, *15* (17), 2588-2621.
78. Shinde, P. S.; Suryawanshi, P. S.; Patil, K. K.; Belekar, V. M.; Sankpal, S. A.; Delekar, S. D.; Jadhav, S. A., A brief overview of recent progress in porous silica as catalyst supports. *J. Compos. Sci.* **2021**, *5* (3), 75.

79. Rác, B.; Hegyes, P.; Forgo, P.; Molnár, Á., Sulfonic acid-functionalized phenylene-bridged periodic mesoporous organosilicas as catalyst materials. *Appl. Catal., A* **2006**, *299*, 193-201.
80. Bossaert, W. D.; De Vos, D. E.; Van Rhijn, W. M.; Bullen, J.; Grobet, P. J.; Jacobs, P. A., Mesoporous sulfonic acids as selective heterogeneous catalysts for the synthesis of monoglycerides. *J. Catal.* **1999**, *182* (1), 156-164.
81. Van Rhijn, W.; De Vos, D.; Sels, B.; Bossaert, W., Sulfonic acid functionalised ordered mesoporous materials as catalysts for condensation and esterification reactions. *Chem. Commun.* **1998**, (3), 317-318.
82. MacQuarrie, D. J., Modified mesoporous materials as acid and base catalysts. In *Nanoporous Mater.: Sci. Eng.*, World Scientific: **2004**; pp 553-595.
83. Kubota, Y.; Yamaguchi, H.; Yamada, T.; Inagaki, S.; Sugi, Y.; Tatsumi, T., Further investigations on the promoting effect of mesoporous silica on base-catalyzed aldol reaction. *Topics in Catal.* **2010**, *53* (7), 492-499.
84. Kandel, K.; Althaus, S. M.; Peeraphatdit, C.; Kobayashi, T.; Trewyn, B. G.; Pruski, M.; Slowing, I. I., Substrate inhibition in the heterogeneous catalyzed aldol condensation: A mechanistic study of supported organocatalysts. *J. Catal.* **2012**, *291*, 63-68.
85. Rao, Y. V. S.; De Vos, D. E.; Jacobs, P. A., 1, 5, 7-Triazabicyclo [4.4. 0] dec-5-ene Immobilized in MCM-41: A Strongly Basic Porous Catalyst. *Angew. Chem., Int. Ed.* **1997**, *36* (23), 2661-2663.
86. Adam, F.; Kueh, C.-W., Heterogeneous para-phenylamino sulfonic acid ligand functionalized on MCM-41 derived from rice husk ash: Selective mono-alkylated products of tert-butylation of phenol. *Appl. Catal., A* **2015**, *489*, 162-170.
87. Zamboulis, A.; Rahier, N. J.; Gehringer, M.; Cattoën, X.; Niel, G.; Bied, C.; Moreau, J. J.; Man, M. W. C., Silica-supported l-proline organocatalysts for asymmetric aldolisation. *Tetrahedron: Asymmetry* **2009**, *20* (24), 2880-2885.
88. Prasetyanto, E. A.; Jeong, S.-M.; Park, S.-E., Asymmetric catalysis in confined space provided by l-proline functionalized mesoporous silica with plugs in the pore. *Topics in Catal.* **2010**, *53* (3), 192-199.
89. Chen, Q.; Xin, C.; Lou, L.-L.; Yu, K.; Ding, F.; Liu, S., Mesoporous SBA-15 with short mesochannels immobilized natural quinine for asymmetric Michael addition of chalcones. *Catal. Lett.* **2011**, *141* (9), 1378-1383.
90. Schulze, J. S.; Migenda, J.; Becker, M.; Schuler, S. M.; Wende, R. C.; Schreiner, P. R.; Smarsly, B. M., TEMPO-functionalized mesoporous silica particles as heterogeneous oxidation catalysts in flow. *J. Mater. Chem. A* **2020**, *8* (7), 4107-4117.
91. Gök, Y.; Gök, H. Z., Synthesis, characterization and catalytic performance in enantioselective reactions by mesoporous silica materials functionalized with chiral thiourea-amine ligand. *Research on Chem. Intermed.* **2021**, *47* (2), 853-874.
92. Schulze, J. S.; Brand, R. D.; Hering, J. G.; Riegger, L. M.; Schreiner, P. R.; Smarsly, B. M., DMAP immobilized on porous silica particles and monoliths for the esterification of phenylethanol in continuous flow. *ChemCatChem* **2022**, *14* (8), e202101845.
93. Zhang, T.; Li, B.; Zhang, X.; Wang, J.; Wei, L.; Zhao, B.; Li, B., 4-Dimethylaminopyridine grafted on MCM-41 as an efficient and highly stable catalyst for the production of α -tocopherol acetate. *J. Porous Mater.* **2020**, *27* (6), 1639-1648.
94. De Risi, C.; Bortolini, O.; Brandolese, A.; Di Carmine, G.; Ragno, D.; Massi, A., Recent advances in continuous-flow organocatalysis for process intensification. *Reaction Chem. Eng.* **2020**, *5* (6), 1017-1052.

95. Eslami, M.; Dekamin, M. G.; Motlagh, L.; Maleki, A., MCM-41 mesoporous silica: a highly efficient and recoverable catalyst for rapid synthesis of α -aminonitriles and imines. *Green Chem. Lett. Rev.* **2018**, *11* (1), 36-46.
96. Bhattacharyya, S.; Lelong, G.; Sabounji, M.-L., Recent progress in the synthesis and selected applications of MCM-41: a short review. *J. Exp. Nanosci.* **2006**, *1* (3), 375-395.
97. Kruk, M.; Jaroniec, M.; Ko, C. H.; Ryoo, R., Characterization of the porous structure of SBA-15. *Chem. Mater.* **2000**, *12* (7), 1961-1968.
98. Verma, P.; Kuwahara, Y.; Mori, K.; Raja, R.; Yamashita, H., Functionalized mesoporous SBA-15 silica: recent trends and catalytic applications. *Nanoscale* **2020**, *12* (21), 11333-11363.
99. Iskandar, F.; Mikrajuddin; Okuyama, K., Controllability of pore size and porosity on self-organized porous silica particles. *Nano Lett.* **2002**, *2* (4), 389-392.
100. DeStefano, J.; Langlois, T.; Kirkland, J., Characteristics of superficially-porous silica particles for fast HPLC: some performance comparisons with sub-2- μ m particles. *J. Chromatogr. Sci.* **2008**, *46* (3), 254-260.
101. Beltrán-Osuna, Á. A.; Perilla, J. E., Colloidal and spherical mesoporous silica particles: synthesis and new technologies for delivery applications. *J. Sol-Gel Sci. Technol.* **2016**, *77* (2), 480-496.
102. Rieux, L.; Niederländer, H.; Verpoorte, E.; Bischoff, R., Silica monolithic columns: Synthesis, characterisation and applications to the analysis of biological molecules. *J. Sep. Sci.* **2005**, *28* (14), 1628-1641.
103. Meinus, R.; Hormann, K.; Hakim, R.; Tallarek, U.; Smarsly, B. M., Synthesis and morphological characterization of phenyl-modified macroporous-mesoporous hybrid silica monoliths. *RSC Adv.* **2015**, *5* (26), 20283-20294.
104. Stoeckel, D.; Kübel, C.; Loeh, M. O.; Smarsly, B. M.; Tallarek, U., Morphological analysis of physically reconstructed silica monoliths with submicrometer macropores: effect of decreasing domain size on structural homogeneity. *Langmuir* **2015**, *31* (26), 7391-7400.
105. Colella, M.; Carlucci, C.; Luisi, R., Supported catalysts for continuous flow synthesis. *Acc. Chem. Res.* **2018**, 29-65.
106. Ishitani, H.; Saito, Y.; Laroche, B.; Rao, X.; Kobayashi, S., *Recent perspectives in catalysis under continuous flow*. Royal Society of Chemistry: **2019**.
107. Munirathinam, R.; Huskens, J.; Verboom, W., Supported catalysis in continuous-flow microreactors. *Adv. Synth. Catal.* **2015**, *357* (6), 1093-1123.
108. Kurdyukov, D. A.; Eurov, D. A.; Kirilenko, D. A.; Kukushkina, J. A.; Sokolov, V. V.; Yagovkina, M. A.; Golubev, V. G., High-surface area spherical micro-mesoporous silica particles. *Microporous Mesoporous Mater.* **2016**, *223*, 225-229.
109. Brand, R. D.; Busche, S. A.; Börner, H. G.; Smarsly, B. M., Peptide-based Organocatalyst on Stage: Functionalizing Mesoporous Silica by Tetrazine-Norbornene Ligation. *ChemCatChem* **2023**, *15* (19), e202300778.
110. Tucker, M. H.; Crisci, A. J.; Wigington, B. N.; Phadke, N.; Alamillo, R.; Zhang, J.; Scott, S. L.; Dumesic, J. A., Acid-functionalized SBA-15-type periodic mesoporous organosilicas and their use in the continuous production of 5-hydroxymethylfurfural. *ACS Catal.* **2012**, *2* (9), 1865-1876.
111. Nakanishi, K., *Synthesis concepts and preparation of silica monoliths*. Wiley-VCH: **2011**; p 9-33.
112. Nakanishi, K.; Shikata, H.; Ishizuka, N.; Koheiya, N.; Soga, N., Tailoring mesopores in monolithic macroporous silica for HPLC. *J. High Resolut. Chromatogr.* **2000**, *23* (1), 106-110.

113. Galarneau, A.; Sachse, A.; Said, B.; Pelisson, C.-H.; Boscaro, P.; Brun, N.; Courtheoux, L.; Olivi-Tran, N.; Coasne, B.; Fajula, F., Hierarchical porous silica monoliths: A novel class of microreactors for process intensification in catalysis and adsorption. *Comptes Rendus. Chimie* **2016**, *19* (1-2), 231-247.
114. Ahmed, A.; Clowes, R.; Myers, P.; Zhang, H., Hierarchically porous silica monoliths with tuneable morphology, porosity, and mechanical stability. *J. Mater. Chem.* **2011**, *21* (15), 5753-5763.
115. El Kadib, A.; Chimenton, R.; Sachse, A.; Fajula, F.; Galarneau, A.; Coq, B., Functionalized inorganic monolithic microreactors for high productivity in fine chemicals catalytic synthesis. *Angew. Chem., Int. Ed.* **2009**, *48* (27), 4969-4972.
116. Sachse, A.; Galarneau, A.; Fajula, F.; Di Renzo, F.; Creux, P.; Coq, B., Functional silica monoliths with hierarchical uniform porosity as continuous flow catalytic reactors. *Microporous Mesoporous Mater.* **2011**, *140* (1-3), 58-68.
117. Sachse, A.; Galarneau, A.; Coq, B.; Fajula, F., Monolithic flow microreactors improve fine chemicals synthesis. *New J. Chem.* **2011**, *35* (2), 259-264.
118. Galarneau, A.; Sachse, A.; Said, B.; Pelisson, C.-H.; Boscaro, P.; Brun, N.; Courtheoux, L.; Olivi-Tran, N.; Coasne, B.; Fajula, F., Hierarchical porous silica monoliths: A novel class of microreactors for process intensification in catalysis and adsorption. *C. R. Chim.* **2016**, *19* (1-2), 231-247.
119. Meinius, R.; Ellinghaus, R.; Hormann, K.; Tallarek, U.; Smarsly, B. M., On the underestimated impact of the gelation temperature on macro-and mesoporosity in monolithic silica. *Phys. Chem. Chem. Phys.* **2017**, *19* (22), 14821-14834.
120. Kube, S. A.; Turke, K.; Ellinghaus, R. d.; Wallacher, D.; Thommes, M.; Smarsly, B. M., Pore size gradient effect in monolithic silica mesopore networks revealed by in-situ SAXS physisorption. *Langmuir* **2020**, *36* (40), 11996-12009.
121. Nakanishi, K., Pore structure control of silica gels based on phase separation. *J. Porous Mater.* **1997**, *4* (2), 67-112.
122. Finsy, R., On the critical radius in Ostwald ripening. *Langmuir* **2004**, *20* (7), 2975-2976.
123. Abreu, J. S.; Costa, L. M.; Ferreira, L. D. L.; de Oliveira, R. K. F. G.; de Souza, T. d. C. C.; Nunes, E. H. M.; Houmard, M., Hydrothermal treatment as a tool to tailor the mesoporous structure of sol-gel silica. *J. Non-Cryst. Solids* **2023**, *610*, 122323.
124. Kohns, R. Understanding sol-gel processing: Hierarchical silica monoliths towards applications in chemical reaction engineering. Philips University Marburg, **2020**.
125. Hayase, G.; Kugimiya, K.; Ogawa, M.; Kodera, Y.; Kanamori, K.; Nakanishi, K., The thermal conductivity of polymethylsilsesquioxane aerogels and xerogels with varied pore sizes for practical application as thermal superinsulators. *J. Mater. Chem. A* **2014**, *2* (18), 6525-6531.
126. Kanamori, K.; Aizawa, M.; Nakanishi, K.; Hanada, T., Elastic organic-inorganic hybrid aerogels and xerogels. *J. Sol-Gel Sci. Technol.* **2008**, *48* (1), 172-181.
127. Thommes, M.; Kaneko, K.; Neimark, A. V.; Olivier, J. P.; Rodriguez-Reinoso, F.; Rouquerol, J.; Sing, K. S., Physisorption of gases, with special reference to the evaluation of surface area and pore size distribution (IUPAC Technical Report). *Pure Appl. Chem.* **2015**, *87* (9-10), 1051-1069.
128. Rouquerol, J.; Rouquerol, F.; Llewellyn, P.; Maurin, G.; Sing, K., *Adsorption by powders and porous solids: principles, methodology and applications*. Academic press: **2013**.
129. Lowell, S.; Shields, J. E.; Thomas, M. A.; Thommes, M., *Characterization of porous solids and powders: surface area, pore size and density*. Springer Science & Business Media: **2012**; Vol. 16.

130. Cychosz, K. A.; Guillet-Nicolas, R.; García-Martínez, J.; Thommes, M., Recent advances in the textural characterization of hierarchically structured nanoporous materials. *Chem. Soc. Rev.* **2017**, *46* (2), 389-414.
131. Thommes, M.; Smarsly, B.; Groenewolt, M.; Ravikovitch, P. I.; Neimark, A. V., Adsorption hysteresis of nitrogen and argon in pore networks and characterization of novel micro- and mesoporous silicas. *Langmuir* **2006**, *22* (2), 756-764.
132. Kleitz, F.; Berube, F.; Guillet-Nicolas, R.; Yang, C.-M.; Thommes, M., Probing adsorption, pore condensation, and hysteresis behavior of pure fluids in three-dimensional cubic mesoporous KIT-6 silica. *J. Phys. Chem. C* **2010**, *114* (20), 9344-9355.
133. Cychosz, K. A.; Guo, X.; Fan, W.; Cimino, R.; Gor, G. Y.; Tsapatsis, M.; Neimark, A. V.; Thommes, M., Characterization of the pore structure of three-dimensionally ordered mesoporous carbons using high resolution gas sorption. *Langmuir* **2012**, *28* (34), 12647-12654.
134. Söllner, J.; Neimark, A. V.; Thommes, M., Development and application of an advanced percolation model for pore network characterization by physical adsorption. *Langmuir* **2024**, *40* (44), 23146-23168.
135. Landers, J.; Gor, G. Y.; Neimark, A. V., Density functional theory methods for characterization of porous materials. *Colloids Surf., A* **2013**, *437*, 3-32.
136. Schlumberger, C.; Thommes, M., Characterization of hierarchically ordered porous materials by physisorption and mercury porosimetry—a tutorial review. *Adv. Mater. Interfaces* **2021**, *8* (4), 2002181.
137. Morishige, K.; Tateishi, N., Adsorption hysteresis in ink-bottle pore. *J. Chem. Phys.* **2003**, *119* (4), 2301-2306.
138. Cimino, R.; Cychosz, K. A.; Thommes, M.; Neimark, A. V., Experimental and theoretical studies of scanning adsorption-desorption isotherms. *Colloids Surf., A* **2013**, *437*, 76-89.
139. Svidrytski, A.; Hlushkou, D.; Thommes, M.; Monson, P. A.; Tallarek, U., Modeling the impact of mesoporous silica microstructures on the adsorption hysteresis loop. *J. Phys. Chem. C* **2020**, *124* (39), 21646-21655.
140. Thommes, M.; Schlumberger, C., Characterization of nanoporous materials. *Annu. Rev. Chem. Biomol. Eng.* **2021**, *12* (1), 137-162.
141. Rouquerol, J.; Baron, G.; Denoyel, R.; Giesche, H.; Groen, J.; Klobes, P.; Levitz, P.; Neimark, A. V.; Rigby, S.; Skudas, R., Liquid intrusion and alternative methods for the characterization of macroporous materials (IUPAC Technical Report). *Pure Appl. Chem.* **2012**, *84* (1), 107-136.
142. Porcheron, F.; Monson, P.; Thommes, M., Modeling mercury porosimetry using statistical mechanics. *Langmuir* **2004**, *20* (15), 6482-6489.
143. Guillet-Nicolas, R.; Ahmad, R.; Cychosz, K. A.; Kleitz, F.; Thommes, M., Insights into the pore structure of KIT-6 and SBA-15 ordered mesoporous silica—recent advances by combining physical adsorption with mercury porosimetry. *New J. Chem.* **2016**, *40* (5), 4351-4360.
144. Porcheron, F.; Thommes, M.; Ahmad, R.; Monson, P., Mercury porosimetry in mesoporous glasses: a comparison of experiments with results from a molecular model. *Langmuir* **2007**, *23* (6), 3372-3380.
145. y Leon, C. A. L., New perspectives in mercury porosimetry. *Adv. Colloid Interface Sci.* **1998**, *76*, 341-372.
146. Aranaz, I.; Harris, R.; Heras, A., Chitosan amphiphilic derivatives. Chemistry and applications. *Curr. Org. Chem.* **2010**, *14* (3), 308-330.
147. Musa, Y.; Bwatanglang, I. B., *Current role and future developments of biopolymers in green and sustainable chemistry and catalysis*. Elsevier: **2020**; p 131-154.

148. Aguilera, D. A.; Tanchoux, N.; Fochi, M.; Bernardi, L., Blue Chemistry. Marine polysaccharide biopolymers in asymmetric catalysis: challenges and opportunities. *Eur. J. Org. Chem.* **2020**, 2020 (25), 3779-3795.
149. Cheng, H.; Gross, R. A., *Green Polymer Chemistry: New Products, Processes, and Applications*. ACS Publications: **2010**; p 1-14.
150. Guibal, E.; Vincent, T.; Blondet, F. P., Biopolymers as supports for heterogeneous catalysis: focus on chitosan, a promising aminopolysaccharide. In *Ion Exchange and Solvent Extraction*, CRC Press: **2007**; pp 151-292.
151. Chafran, L.; Matias, A. E.; Silva, L. P., Green Catalysts in the Synthesis of Biopolymers and Biomaterials. *ChemistrySelect* **2022**, 7 (28), e202201276.
152. Kaushik, M.; Moores, A., Nanocelluloses as versatile supports for metal nanoparticles and their applications in catalysis. *Green Chem.* **2016**, 18 (3), 622-637.
153. Anchan, H. N.; Bhat, N. S.; Vinod, N.; Prabhakar, P. S.; Dutta, S., Catalytic conversion of glucose and its biopolymers into renewable compounds by inducing C–C bond scission and formation. *Biomass Convers. Biorefin.* **2024**, 14 (9), 9915-9948.
154. Campelo, J. M.; Luna, D.; Luque, R.; Marinas, J. M.; Romero, A. A., Sustainable preparation of supported metal nanoparticles and their applications in catalysis. *ChemSusChem* **2009**, 2 (1), 18-45.
155. Guibal, E., Heterogeneous catalysis on chitosan-based materials: a review. *Prog. Polym. Sci.* **2005**, 30 (1), 71-109.
156. Klemm, D.; Heublein, B.; Fink, H. P.; Bohn, A., Cellulose: fascinating biopolymer and sustainable raw material. *Angew. Chem., Int. Ed.* **2005**, 44 (22), 3358-3393.
157. Wang, J.; Zhuang, S., Chitosan-based materials: Preparation, modification and application. *J. Cleaner Prod.* **2022**, 355, 131825.
158. Draget, K. I.; Skjåk-Bræk, G.; Smidsrød, O., Alginate based new materials. *Int. J. Biol. Macromol.* **1997**, 21 (1-2), 47-55.
159. Agarwal, S.; Singhal, S.; Godiya, C. B.; Kumar, S., Prospects and applications of starch based biopolymers. *Int. J. Environ. Anal. Chem.* **2023**, 103 (18), 6907-6926.
160. Ayyachamy, M.; Cliffe, F. E.; Coyne, J. M.; Collier, J.; Tuohy, M. G., Lignin: untapped biopolymers in biomass conversion technologies. *Biomass Convers. Biorefin.* **2013**, 3 (3), 255-269.
161. Martín, C. d. M. G.; García, J. I. H.; Bonardd, S.; Díaz, D. D., Lignin-based catalysts for C–C bond-forming reactions. *Molecules* **2023**, 28 (8), 3513.
162. Khazaei, A.; Khazaei, M.; Rahmati, S., A green method for the synthesis of gelatin/pectin stabilized palladium nano-particles as efficient heterogeneous catalyst for solvent-free Mizoroki–Heck reaction. *J. Mol. Catal., A* **2015**, 398, 241-247.
163. Labus, K.; Drozd, A.; Trusek-Holownia, A., Preparation and characterisation of gelatine hydrogels predisposed to use as matrices for effective immobilisation of biocatalystst. *Chemical Papers* **2016**, 70 (5), 523-530.
164. Kou, S. G.; Peters, L. M.; Mucalo, M. R., Chitosan: A review of sources and preparation methods. *Int. J. Biol. Macromol.* **2021**, 169, 85-94.
165. Aranaz, I.; Alcántara, A. R.; Civera, M. C.; Arias, C.; Elorza, B.; Heras Caballero, A.; Acosta, N., Chitosan: An overview of its properties and applications. *Polymers* **2021**, 13 (19), 3256.
166. Kumar, M. R.; Muzzarelli, R. A.; Muzzarelli, C.; Sashiwa, H.; Domb, A., Chitosan chemistry and pharmaceutical perspectives. *Chem. Rev.* **2004**, 104 (12), 6017-6084.
167. Mourya, V.; Inamdar, N. N., Chitosan-modifications and applications: Opportunities galore. *React. Funct. Polym.* **2008**, 68 (6), 1013-1051.

168. Younes, I.; Rinaudo, M., Chitin and chitosan preparation from marine sources. Structure, properties and applications. *Marine drugs* **2015**, *13* (3), 1133-1174.
169. Kim, S.-K., *Chitin, chitosan, oligosaccharides and their derivatives: biological activities and applications*. CRC Press: **2010**.
170. Yao, K.; Li, J.; Yao, F.; Yin, Y., *Chitosan-based hydrogels*. CRC Press **2011**.
171. Arbia, W.; Arbia, L.; Adour, L.; Amrane, A., Pregled bioloških metoda ekstrakcije hitina iz oklopa rakova. *Food Technol. Biotechnol.* **2013**, *51* (1), 12-25.
172. Synowiecki, J.; Al-Khateeb, N. A., Production, properties, and some new applications of chitin and its derivatives. *Crit. Rev. Food Sci. Nutr.* **2010**, (2), 157-171.
173. Gao, M.; Tang, H.; Zhu, H., Advances in extraction, utilization, and development of chitin/chitosan and its derivatives from shrimp shell waste. *Compr. Rev. Food Sci. Food Saf.* **2024**, *23* (5), e70008.
174. Ma, J.; Chu, D.; Rakhimovna, V. N.; Wang, P.; Zhu, S.; Xie, H.; Liu, Q.; Yin, H., Efficient and green extraction of chitin from mantis shrimp shell using deep eutectic solvents at room temperature. *Bioresour. Technol.* **2025**, 132888.
175. Akram, A.; Iqbal, M.; Yasin, A.; Zhang, K.; Li, J., Sulfonated molecules and their latest applications in the field of biomaterials: a review. *Coatings* **2024**, *14* (2), 243.
176. Niu, C.; Liu, Y.; Yang, Y.; Wang, R.; Li, T., Advances in sulfonated modification and bioactivity of polysaccharides. *Int. J. Biol. Macromol.* **2023**, *253*, 126400.
177. Sharma, S.; Kishen, A., Bioarchitectural design of bioactive biopolymers: Structure–function paradigm for diabetic wound healing. *Biomimetics* **2024**, *9* (5), 275.
178. Chin, K. M.; Sung Ting, S.; Ong, H. L.; Omar, M., Surface functionalized nanocellulose as a veritable inclusionary material in contemporary bioinspired applications: A review. *J. Appl. Polym. Sci.* **2018**, *135* (13), 46065.
179. Crini, G.; Torri, G.; Lichtfouse, E.; Kyzas, G. Z.; Wilson, L. D.; Morin-Crini, N., Dye removal by biosorption using cross-linked chitosan-based hydrogels. *Environ. Chem. Lett.* **2019**, *17* (4), 1645-1666.
180. Muzzarelli, R. A., Genipin-crosslinked chitosan hydrogels as biomedical and pharmaceutical aids. *Carbohydr. Polym.* **2009**, *77* (1), 1-9.
181. Bhavsar, C.; Momin, M.; Gharat, S.; Omri, A., Functionalized and graft copolymers of chitosan and its pharmaceutical applications. *Expert Opin. Drug Deliv.* **2017**, *14* (10), 1189-1204.
182. Sanchez-Salvador, J. L.; Balea, A.; Monte, M. C.; Negro, C.; Blanco, A., Chitosan grafted/cross-linked with biodegradable polymers: a review. *Int. J. Biol. Macromol.* **2021**, *178*, 325-343.
183. Lee, M.; Chen, B.-Y.; Den, W., Chitosan as a natural polymer for heterogeneous catalysts support: a short review on its applications. *Appl. Sci.* **2015**, *5* (4), 1272-1283.
184. Rafiee, F., Recent advances in the application of chitosan and chitosan derivatives as bio supported catalyst in the cross coupling reactions. *Curr. Org. Chem.* **2019**, *23* (4), 390-408.
185. Kaur, M.; Bharti, D.; Verma, P. K.; Kumar, V.; Kumar, R., Chitosan-derived materials as heterogeneous catalysts in A3-coupling and click reaction: A comprehensive review. *Int. J. Biol. Macromol.* **2025**, 146389.
186. Wolfson, A.; Levy-Ontman, O., Recent developments in the immobilization of palladium complexes on renewable polysaccharides for Suzuki–Miyaura cross-coupling of halobenzenes and phenylboronic acids. *Catalysts* **2020**, *10* (1), 136.
187. Fakhri, A.; Naghipour, A., Chitosan-Pd (II) complex-decorated Fe₃O₄ nanoparticle as the highly effective and magnetically recyclable catalyst for Suzuki and Heck coupling reactions. *Comments Inorg. Chem.* **2017**, *37* (4), 201-218.

188. Akhtar, R.; Zahoor, A. F.; Parveen, B.; Suleman, M., Development of environmental friendly synthetic strategies for Sonogashira cross coupling reaction: An update. *Synth. Commun.* **2019**, *49* (2), 167-192.
189. Vincent, T.; Guibal, E., Chitosan-supported palladium catalyst. 5. Nitrophenol degradation using palladium supported on hollow chitosan fibers. *Environ. Sci. Technol.* **2004**, *38* (15), 4233-4240.
190. Schübler, S.; Blaubach, N.; Stolle, A.; Cravotto, G.; Ondruschka, B., Application of a cross-linked Pd–chitosan catalyst in liquid-phase-hydrogenation using molecular hydrogen. *Appl. Catal., A* **2012**, *445*, 231-238.
191. Zhang, H.; Zhao, W.; Zou, J.; Liu, Y.; Li, R.; Cui, Y., Aldol reaction catalyzed by a hydrophilic catalyst in aqueous micelle as an enzyme mimic system. *Chirality* **2009**, *21* (5), 492-496.
192. Khalil, K. D.; Al-Matar, H. M., Chitosan based heterogeneous catalyses: Chitosan-grafted-poly (4-vinylpyridine) as an efficient catalyst for michael additions and alkylpyridazinyl carbonitrile oxidation. *Molecules* **2013**, *18* (5), 5288-5305.
193. Liu, P.; Yu, S.; Xiao, S., Research progress on two-dimensional (2D) halide organic–inorganic hybrid perovskites. *Sustainable Energy Fuels* **2021**, *5* (16), 3950-3978.
194. Reddy, B. S.; Venkateswarlu, A.; Reddy, G. N.; Reddy, Y. R., Chitosan-SO₃H: an efficient, biodegradable, and recyclable solid acid for the synthesis of quinoline derivatives via Friedländer annulation. *Tetrahedron Lett.* **2013**, *54* (43), 5767-5770.
195. Zhao, Y.; Tian, J.-S.; Qi, X.-H.; Han, Z.-N.; Zhuang, Y.-Y.; He, L.-N., Quaternary ammonium salt-functionalized chitosan: An easily recyclable catalyst for efficient synthesis of cyclic carbonates from epoxides and carbon dioxide. *J. Mol. Catal., A* **2007**, *271* (1-2), 284-289.
196. Zhao, Y.; He, L. N.; Zhuang, Y. Y.; Wang, J. Q., Dimethyl carbonate synthesis via transesterification catalyzed by quaternary ammonium salt functionalized chitosan. *Chinese Chem. Lett.* **2008**, *19* (3), 286-290.
197. Sun, J.; Wang, J.; Cheng, W.; Zhang, J.; Li, X.; Zhang, S.; She, Y., Chitosan functionalized ionic liquid as a recyclable biopolymer-supported catalyst for cycloaddition of CO₂. *Green Chem.* **2012**, *14* (3), 654-660.
198. Wang, Q. Z.; Chen, X. G.; Liu, N.; Wang, S. X.; Liu, C. S.; Meng, X. H.; Liu, C. G., Protonation constants of chitosan with different molecular weight and degree of deacetylation. *Carbohydr. Polym.* **2006**, *65* (2), 194-201.
199. de Alvarenga, E. S., Characterization and properties of chitosan. *Biotechnol. Biopolym.* **2011**, *91*, 48-53.
200. Ngamsurach, P.; Namwongsa, N.; Praipipat, P., Synthesis of powdered and beaded chitosan materials modified with ZnO for removing lead (II) ions. *Sci. Rep.* **2022**, *12* (1), 17184.
201. Jamka, Z. N.; Mohammed, W. T., Assessment of the feasibility of modified chitosan beads for the adsorption of nitrate from an aqueous solution. *J. Ecol. Eng.* **2023**, *24* (2).
202. Valentin, R.; Molvinger, K.; Quignard, F.; Brunel, D., Supercritical CO₂ dried chitosan: An efficient intrinsic heterogeneous catalyst in fine chemistry. *New J. Chem.* **2003**, *27* (12), 1690-1692.
203. Fu, J.; Yang, F.; Guo, Z., The chitosan hydrogels: From structure to function. *New J. Chem.* **2018**, *42* (21), 17162-17180.
204. Takeshita, S.; Zhao, S.; Malfait, W. J.; Koebel, M. M., Chemistry of chitosan aerogels: three-dimensional pore control for tailored applications. *Angew. Chem., Int. Ed.* **2021**, *60* (18), 9828-9851.

205. Sakthivel, B.; Dhakshinamoorthy, A., Chitosan as a reusable solid base catalyst for Knoevenagel condensation reaction. *J. Colloid Interface Sci.* **2017**, *485*, 75-80.
206. Anbu, N.; Maheswari, R.; Elamathi, V.; Varalakshmi, P.; Dhakshinamoorthy, A., Chitosan as a biodegradable heterogeneous catalyst for Knoevenagel condensation between benzaldehydes and cyanoacetamide. *Catal. Commun.* **2020**, *138*, 105954.
207. Rani, D.; Singla, P.; Agarwal, J., 'Chitosan in water' as an eco-friendly and efficient catalytic system for Knoevenagel condensation reaction. *Carbohydr. Polym.* **2018**, *202*, 355-364.
208. Hirayama, Y.; Kanomata, K.; Hatakeyama, M.; Kitaoka, T., Chitosan nanofiber-catalyzed highly selective Knoevenagel condensation in aqueous methanol. *RSC Adv.* **2020**, *10* (45), 26771-26776.
209. Appaturi, J. N.; Ratti, R.; Phoon, B. L.; Batagarawa, S. M.; Din, I. U.; Selvaraj, M.; Ramalingam, R. J., A review of the recent progress on heterogeneous catalysts for Knoevenagel condensation. *Dalton Trans.* **2021**, *50* (13), 4445-4469.
210. Cho, Y. I.; No, H. K.; Meyers, S. P., Physicochemical characteristics and functional properties of various commercial chitin and chitosan products. *J. Agric. Food Chem.* **1998**, *46* (9), 3839-3843.
211. Roth, B. D.; Blankley, C.; Chucholowski, A.; Ferguson, E.; Hoefle, M.; Ortwine, D.; Newton, R.; Sekerke, C.; Sliskovic, D.; Wilson, M., Inhibitors of cholesterol biosynthesis. 3. Tetrahydro-4-hydroxy-6-[2-(1H-pyrrol-1-yl) ethyl]-2H-pyran 2-one inhibitors of HMG-CoA reductase. 2. Effects of introducing substituents at positions three and four of the pyrrole nucleus. *J. Med. Chem.* **1991**, *34* (1), 357-366.
212. Woo, P. W.; Hartman, J.; Huang, Y.; Nanninga, T.; Bauman, K.; Butler, D. E.; Rubin, J. R.; Lee, H. T.; Huang, C. C., Atorvastatin, an HMG-COA reductase inhibitor and efficient lipid-regulating agent. Part I. Synthesis of ring-labeled [¹⁴C₆] atorvastatin. *J. Labelled Compd. Radiopharm.* **1999**, *42* (2), 121-127.
213. Ying, A.; Qiu, F.; Wu, C.; Hu, H.; Yang, J., Ionic tagged amine supported on magnetic nanoparticles: synthesis and application for versatile catalytic Knoevenagel condensation in water. *RSC Adv.* **2014**, *4* (63), 33175-33183.
214. Ying, A.; Ni, Y.; Xu, S.; Liu, S.; Yang, J.; Li, R., Novel DABCO based ionic liquids: green and efficient catalysts with dual catalytic roles for aqueous Knoevenagel condensation. *Ind. Eng. Chem. Res.* **2014**, *53* (14), 5678-5682.
215. He, Y.; Li, M.; Peng, L.; Yang, T.; Zhang, D.; Zhang, Y., Continuous Flow Synthesis of 4-methyl-3-oxo-n-phenyl-pentanamide. *ChemistrySelect* **2024**, *9* (3), e202304182.
216. Dekamin, M. G.; Azimoshan, M.; Ramezani, L., Chitosan: a highly efficient renewable and recoverable bio-polymer catalyst for the expeditious synthesis of α -amino nitriles and imines under mild conditions. *Green Chem.* **2013**, *15* (3), 811-820.
217. Rajender Reddy, K.; Rajgopal, K.; Uma Maheswari, C.; Lakshmi Kantam, M., Chitosan hydrogel: A green and recyclable biopolymer catalyst for aldol and Knoevenagel reactions. *New J. Chem.* **2006**, *30* (11), 1549-1552.
218. Kühbeck, D.; Saidulu, G.; Reddy, K. R.; Díaz, D. D., Critical assessment of the efficiency of chitosan biohydrogel beads as recyclable and heterogeneous organocatalyst for C-C bond formation. *Green Chem.* **2012**, *14* (2), 378-392.
219. CUI, Y.-C.; ZHANG, H.-F.; LI, R.-T.; LIU, Y.; XU, C., Asymmetric Henry reaction catalyzed by chitosan and its l-proline derivative. *Chinese J. Org. Chem.* **2010**, *30* (05), 707.
220. Franconetti, A.; Domínguez-Rodríguez, P.; Lara-García, D.; Prado-Gotor, R.; Cabrera-Escribano, F., Native and modified chitosan-based hydrogels as green heterogeneous

-
- organocatalysts for imine-mediated Knoevenagel condensation. *Appl. Catal., A* **2016**, *517*, 176-186.
221. Rachitha, S.; Yadav, A. K.; Kamali, M.; Sudarsanam, P.; Dutta, S., Mechanochemical synthesis of Knoevenagel condensation products from biorenewable furaldehydes using crustacean waste-derived chitosan as a sustainable organocatalyst. *RSC Adv.* **2025**, *15* (25), 19687-19695.
222. Doyle, A. G.; Jacobsen, E. N., Small-molecule H-bond donors in asymmetric catalysis. *Chem. Rev.* **2007**, *107* (12), 5713-5743.