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Exploring Supramolecular Gels in Flow-Type Chemistry—Design and Preparation of Stationary Phases

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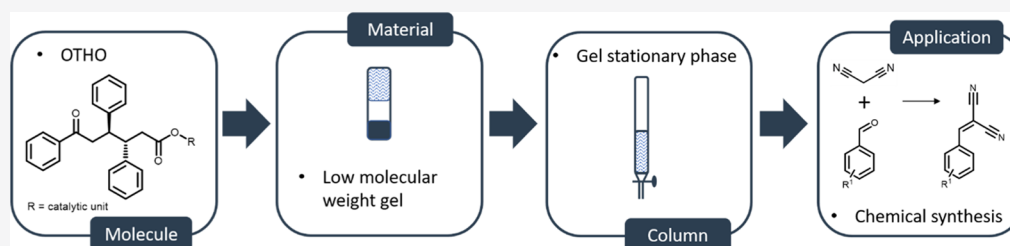
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ABSTRACT: Two major challenges facing chemical synthesis are product isolation and catalyst recovery. One method to overcome these challenges is to perform the synthesis in a flow system with a catalytic stationary phase. However, the polymeric catalytic materials used in flow systems are often laborious to produce. In this study, we investigate a novel supramolecular gel as a catalytic stationary phase material. The gel is based on a modular, easy to synthesize, oxotriphenylhexanoate (OTHO) gelator comprised of a catalytic unit designed to catalyze the Knoevenagel reaction. The catalytic organogel enhances the rate of product formation and can be reused five times. Use of the OTHO to construct catalytic gels is a flexible technique that can be utilized to improve product isolation and reduce wastage of the catalyst.

INTRODUCTION

Much attention has been paid to the field of low-molecular-weight gels (LMWGs) as these versatile materials are highly tunable and responsive to external stimuli. The self-assembly of supramolecular gels is driven by noncovalent interactions such as hydrogen bonding, van der Waals forces, and π - π interactions.¹ Consequently, this makes gels prime material candidates for various future applications such as drug delivery,² waste clean-up,^{3,4} energy storage,⁵ gas storage,⁶ sensing,⁶ and catalysis.^{7,8}

One area of chemistry that has greatly benefitted from solid-phase support is chemical synthesis. Solid supports are used in peptide synthesis⁹ as reagents¹⁰ in natural product synthesis^{11–13} and for the immobilization of expensive metal-based catalysts.¹⁴ In this context, gels are being used to create custom support materials in the catalytic arena. There is a multitude of advantages when using gels for catalysis; these include high surface area, functional tunability, effective oxygen blocking (necessary for some reactions), directional and conformational orientation of the catalytic site, and slow diffusion through immobilized solvent-phase.^{15,16}

The literature reflects the growing number of catalytic hydro-,^{17,18} organo-,^{19–24} and organometallic-^{8,25–32} gels. Gels have been used in a wide range of catalytic reactions including Heck,³¹ Diels–Alder,²⁹ Aldol,^{22–24,30} Suzuki–Miyaura coupling,³¹ N-alkylation,³² and photochemical reactions.¹⁵ Hydro- and organogels differ in the nature of the liquid immobilized; this is either organic solvent (organogels) or water (hydro-

gels). Most organic syntheses are performed in organic solvents. This makes catalytic organogels enticing as they can gelate in a broad range of organic solvents, making them applicable for a wider range of chemical reactions than hydrogels.

Two strategies have been employed to create catalytic gels either by encapsulation of the catalyst by the gel³³ or through synthetic modification of the gelator. In the first method, the catalyst is not covalently bound to the gelator and is free to diffuse through the gel pockets. In the second method, the catalytic unit is covalently bonded to the gelator. Synthesis of a catalytic gelator is often laborious and complex as it is difficult to synthesize a catalyst and guarantee gelation ability.³⁴ Few examples are reflected in the literature for the approach where the catalytic unit is bound to the gelator.^{23,24,32} Furthermore, many catalytic reactions using catalytic gels are studied *in situ* and followed using techniques such as NMR²² and HPLC.²³ In the cases where the product is isolated, the gel is often destroyed making it unsuitable for reuse.³² A solution to overcome these obstacles would be to use supramolecular gels

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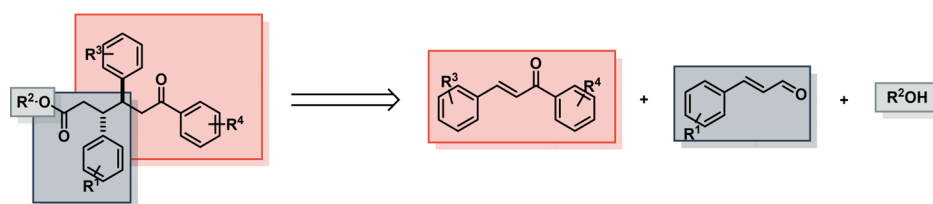


Figure 1. Highly modular OTHO reaction allows for the design and synthesis of a vast array of gelators.

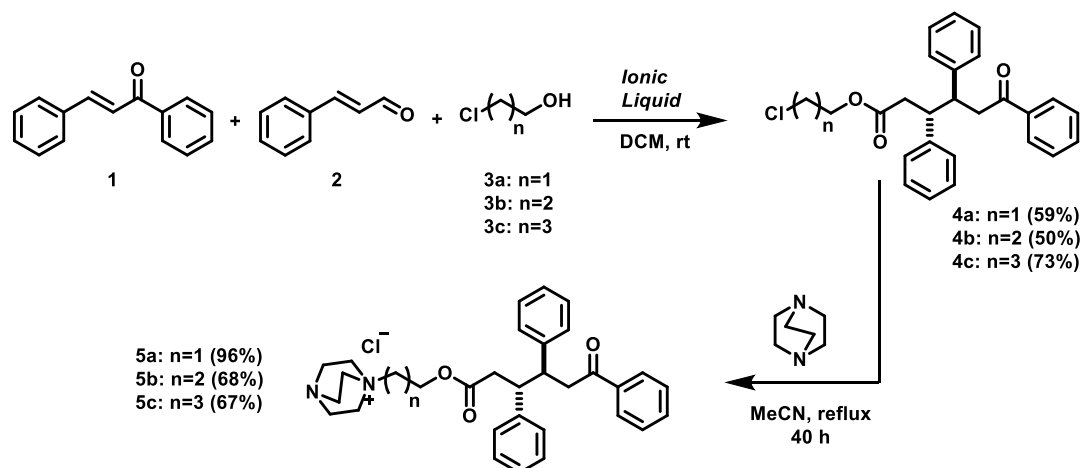


Figure 2. Two-step synthetic pathway for the synthesis of three different OTHO–DABCO compounds (5a, 5b, and 5c) with different length linkers.

in a flow-type system.^{18,35} Flow-type chemistry provides an easy, swift, clean, and efficient separation of the product and the catalyst, as well as a method for catalyst recovery.

It is therefore desirable to create a synthetically flexible gelator that could be assembled in a limited number of steps to enable efficient screening of both gel and catalytic properties.

Oxotriphenylhexanoate (OTHO)^{36–40} is a prime candidate for the development of a catalytic organogel. The synthesis of OTHO is straightforward using readily available starting materials; the compound is easy to purify, and the reaction scales efficiently. In addition, OTHO is synthetically flexible, and the OTHO backbone can be modified with a variety of functional groups that can be used to design a gelator for a desired purpose (Figure 1).

It is advantageous to have a system for catalysis which allows for easy separation of the product and the catalyst, reuse of the catalyst and is compatible with many solvents. It is an added benefit if the synthesis of this catalyst is straightforward. In this work, we design and synthesize a novel catalytic gelator for use in a flow-type system allowing for high reaction efficiency, easy product isolation, and reuse of the gel catalyst.

RESULTS AND DISCUSSION

In order to explore supramolecular gels as a flow-type stationary phase, two different approaches were used. The first involves encapsulating a catalyst in the gel pockets. The second method utilizes synthetic modification of OTHO to create a gelator capable of catalysis. Tertiary amines were identified as the catalytic units of choice as they are known to catalyze a number of reactions^{41–44} that are operationally simple and can be performed at room temperature. The first method was unsuccessful as the catalyst coeluted with the product, making the material unsuitable for reuse (details in Supporting Information). To address this, the catalytic unit

1,4-diazabicyclo[2.2.2]octane (DABCO) was covalently bound to the OTHO.

BUILDING A SUPPORT FOR CATALYSIS

Synthesis of Novel Catalytic Gelator. During the design process, it was decided to attach the DABCO to the ester part of the OTHO via a carbon linker. We postulated that the linker might influence gelation and the catalytic properties of the gel. Thus, three different OTHOs were synthesized, each with a different length carbon linker. The linker lengths were 2-carbon, 3-carbon, and 4-carbon for 5a, 5b, and 5c, respectively (Figure 2).

The two-step gelator synthesis starts with an NHC-catalyzed three-component reaction^{36,37} for the synthesis of alkyl halogen OTHOs 4a–c (Figure 2). *trans*-Chalcone, cinnamaldehyde, and appropriate alcohol were reacted at room temperature in dichloromethane (DCM) in the presence of 1-ethyl-3-methylimidazolium acetate and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The precursor OTHOs were obtained in a pure form as a solid material following a simple precipitation and washing protocol using methanol.

In the final step, the alkyl halogen containing OTHOs (4a–c) were treated with DABCO under refluxing conditions in acetonitrile (MeCN). Following a filtration and washing procedure, the catalytic OTHO–DABCOs (5a–c) were obtained in good yields. Procedure details are described in the Supporting Information.

Gelation of Catalytic OTHO–DABCOs 5a, 5b, and 5c.

There are multiple methods for triggering gelation.^{45–49} We investigated cooling and sonication and found that sonication was the optimal method for triggering gelation. Sonication is a known method for triggering gelation,^{48,49} and a number of explanations for this behavior have been presented.^{50–55}

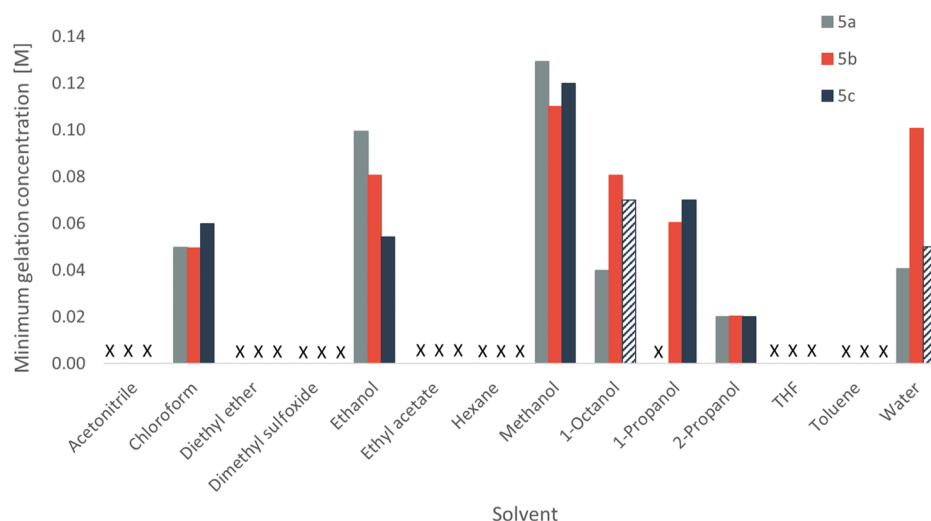


Figure 3. Minimum gelation concentration for each OTHO–DABCO (**5a**, **5b**, and **5c**). The length of the carbon linker influences the gelation. X indicates that gel was not formed. The striped bars represent unstable gels.

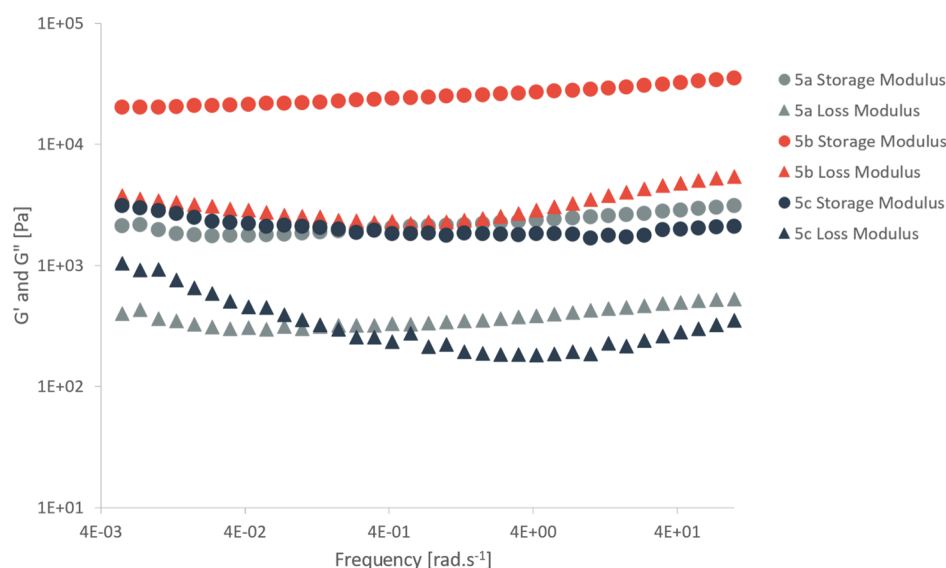


Figure 4. Storage (circle) and loss (triangle) moduli of **5a**, **5b**, and **5c** as a function of frequency. The frequency sweep was performed at a strain of 0.1% and $T = 25\text{ }^{\circ}\text{C}$. All of the gels are made from *i*PrOH and have a concentration of $2 \times 10^{-2}\text{ M}$.

Gelation Study. To test the range of solvents compatible for gelation and to obtain the minimum gelation concentration (MGC) in each solvent, a gelation study was performed. The compound (**5a**, **5b**, or **5c**), starting with an amount of $1 \times 10^{-5}\text{ mol}$, was dissolved in a solvent (1 mL) in a sealed vial using a heat-gun. This solution was sonicated in a benchtop sonicator until either a gel or a precipitate was formed. The temperature of the sonicator water bath was kept between 18 and $23\text{ }^{\circ}\text{C}$. If neither gelation nor precipitation occurred, OTHO–DABCO compound (**5a**, **5b**, or **5c**) was added in $1 \times 10^{-5}\text{ mol}$ portions until gelation or precipitation occurred. The inverted vial test was used to identify gel formation.⁵⁶

The linker length impacts the properties of the compounds, and the three compounds, **5a**, **5b**, and **5c**, behave differently. This is clearly demonstrated by the gelation ability of the series (Figure 3 and Supporting Information Table S2).

During the solvent screening, it was found that **5a–c** form gels in organic solvents such as chloroform and various alcohols. All three compounds were insoluble in diethyl ether,

hexane, and toluene. Precipitate was formed in MeCN and tetrahydrofuran.

All three gelators form hydrogels at varying concentrations. Although **5c** does form a hydrogel, it was unstable and the gel degraded within 30 min. Organic solvent is more useful for organic synthesis, and therefore no further investigation into the hydrogels were performed.

The MGC of **5a** was the most variable, and **5c** forms the least stable gels. The greatest number of stable gels was formed by **5b** indicating that the 3-carbon length linker (**5b**) is the optimal length for gelation. The 3-carbon length linker provides the correct lipophilicity resulting in the desired balance between solubility and insolubility for gel formation.⁵⁷

The most appropriate solvent for comparing the catalytic ability of the gelators is *i*PrOH since all gelators have the same MGC ($2 \times 10^{-2}\text{ M}$), and the resulting gels are stable. Thus, *i*PrOH makes it possible to compare the catalytic ability of the gelators at the same concentration. In order to explore the physical properties of the gels and examine how this may

impact catalysis, characterization of the *i*PrOH gels was performed.

Rheology. Dynamic shear oscillation was used to investigate the rheological properties of the gels. Storage modulus (G') and loss modulus (G'') were measured as a function of frequency and strain. For all three gels, G' is 1 order of magnitude larger than G'' (Figure 4); this is seen in tangled fibrillar networks such as cellulose nanofibrils⁵⁸ and other LMWGs.⁵⁹ The differences in the viscosities can be explained by the differences in the strengths of the interactions within the gel network.

The softest gels are **5a** and **5c**. The softness of **5a** may be attributed to the steric hindrance and electrostatics in combination with the solvent used (*i*PrOH). The steric hindrance is a result of the large, bulky, charged amino groups positioned in such a way (without the freedom of movement the 3-carbon and 4-carbon linkers provide) that they repel each other. The 2-carbon linker does not allow for rotational movement to relieve this strain. Gelator **5c** has a longer, more flexible 4-carbon linker than **5b**, and this may lead to greater conformational freedom of the DABCO functional group, so the network is more flexible, leading to a lower shear viscosity. A similar trend is seen with modified cellulose nanocrystals.⁶⁰ The 3-carbon linker of **5b** appears to provide a balance between the steric hindrance caused by the bulky DABCO group and flexibility and freedom of rotation that results from a longer carbon chain. For this system, a 3-carbon linker is the optimum length to allow for stronger intermolecular forces in *i*PrOH.

Care must be taken when handling the samples before measurement^{61,62} as the gels are often not viscous enough to remain intact during transfer from the sonication vessel to the plate. Because of this, it is difficult to get an exact quantification of the storage and loss moduli. However, the trends observed are reproducible.

Morphology of *i*PrOH Gels. The different linkers result in visually different gels (Figure 5a). Although on a macroscopic scale, the gels were different, SEM images revealed flat, ribbonlike structures in xerogels for all three in *i*PrOH (Figure 5b–d). The least uniform in terms of fiber size, ranging from 0.2 to 1.0 μm , was **5a**. The fibers for **5b** had a size range of 0.3

to 0.6 μm . **5c** had the least broad, most uniform fibers (0.3 μm). All gels exhibited fiberlike morphologies indicating that the solvent did not have an effect on the morphology (Supporting Information Figure S4).

Powder X-ray Diffraction. The powder X-ray diffraction patterns show that the xerogels are semicrystalline, and there are differences in the packing of the molecules in the solid phase (Supporting Information Figure S5). The differences in packing may lead to different arrangements of the active site and hence the catalytic ability of the material.

Catalysis Using Catalytic Gel in Flow-Type System. To evaluate the gelator catalytic performance as a stationary phase, we chose the Knoevenagel reaction as it is known to be catalyzed by tertiary amines.^{63,64}

Control reactions performed in solution required 3 h to reach full conversion. The reaction rate is notably improved when the gel phase was used, and full conversion was reached within an hour (Supporting Information Table S4).

Preparation of Gel Column for Catalysis. The OTHO–DABCO gelator was dissolved in *i*PrOH (4 mL, 2×10^{-2} M) with heating, and the warm solution was poured into a glass column packed with approximately 40 mg of cotton wool. Gelation was triggered via sonication in the column (Supporting Information Figure S7a) using a benchtop sonicator. The resulting gel was washed with *i*PrOH (8 mL) to remove ungelated material from the gel pockets prior to substrate loading. A solution of the substrate was gently added on top of the gel. The tap was closed, and the column stoppered for 60 min. The substrates diffuse through the gel pockets³⁹ where they interact with the catalytic sites and the reaction proceeds. The column was then eluted using 100 mL of EtOAc (Supporting Information Figure S7b). The remaining gel was dissolved in DCM for further analysis by NMR.

The use of a glass column has several advantages including, straightforward removal of the ungelated compound before catalysis with washing and simple separation of the product from the gel phase. In addition, the use of a transparent glass column provides the ability to monitor the reaction visually and detect precipitation and changes in the morphology and color.

Catalysis. The catalytic ability of the three gelators, **5a–c**, were compared (Table 1). For all experiments, the reaction proceeds with quantitative conversion of the starting material. Gelator **5a** was able to catalyze the reaction between benzaldehyde and malononitrile with 100% conversion and crude yield of 94% (Table 1, entry 1). However, a large amount of **5a** was washed out of the gel column during the elution process, indicating that this gel is not very stable. As seen during the gelation study, **5c** was the least stable gel and the gel degrades during the elution of the product (Table 1, entry 3). Gelator **5b** was visibly the most stable gel, and only a small amount of the gelator was present in the product mixture (Table 1, entry 2). Despite having the lowest crude yield, this stability makes this system more attractive than the other two. From the rheological results, **5b** was the strongest gel (Figure 4 and Supporting Information Figure S2–S3). This is a result of the optimal chain length and consequently stronger intermolecular forces within the gel network. Therefore, gelator **5b** was used for further investigation because it has the desirable physical properties, the best isolation of product, and 100% conversion. Irrespective of the system, analysis of

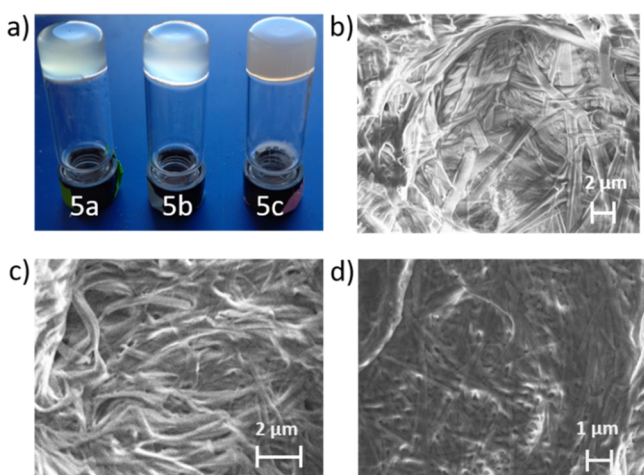
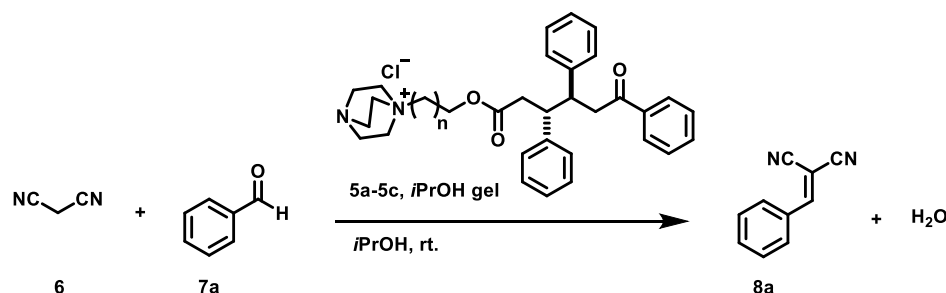
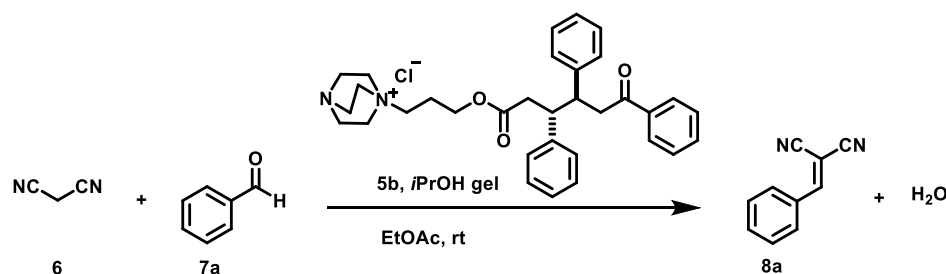


Figure 5. (a) Gels in *i*PrOH **5a**, **5b**, and **5c** (left to right). The gels are visibly different. The compound with the longest linker, **5c**, is the opaquest. SEM images of (b) **5a**, (c) **5b**, and (d) **5c**. All three gels have similar morphologies (all fibers).

Table 1. Comparison of Knoevenagel Reaction between Benzaldehyde and Malononitrile Using *i*PrOH Gels of **5a**, **5b**, and **5c**^a

entry	catalyst	conversion [%]	crude yield [%] ^b	coeluted gelator [%] ^c	product encapsulated in gel [%] ^d
1	5a ($n = 1$)	100	94	15	22
2	5b ($n = 2$)	100	69	6	35
3	5c ($n = 3$)	100	83	13	45

^aFull conversion was reached within 1 h in each instance, and *i*PrOH (100 mL) was used for elution. ^bCalculated using the mass of eluted material after drying. ^cPercentage of **5** coeluted with the product, based on NMR data. ^dPercentage of product trapped in gel portion after elution. Calculated using NMR data collected on the dissolved gel after elution.

Table 2. Study Into the Reuse of the Gel—**5b** Was Used Five Times without Significant Loss of the Gelator^a

run	conversion [%]	crude yield [%] ^b	coeluted gelator [%] ^c	crude mass [mg]
1	100	90	9	47
2	100	77	4	39
3	100	63	trace	32
4	92	36	trace	18
5	80	43	trace	47

^aReactions were carried out on a gel of **5b** (0.8 mmol) from *i*PrOH at room temperature; the starting materials, **6** (0.3 mmol) and **7a** (0.45 mmol), were loaded as an EtOAc (1 mL) solution. ^bCalculated using the mass of eluted material after drying. ^cPercentage of **5b** coeluted with the product, based on NMR data.

the gel after product isolation with NMR reveals that some product always remains trapped in the gel phase.

After testing various solvents, it was found that using EtOAc (100 mL) instead of *i*PrOH resulted in faster elution time, greater product isolation, and less dissolution of the **5b** gel (Supporting Information Figure S8, Table S5–S6).

The number of times the gel could be reused was tested, and at least five successive reactions could be performed on the same gel without large amounts of **5b** washing out (Table 2). There is a sharp decrease in yield after the fourth reaction, and this performance is comparable with the other gel catalyst.²⁵ The trend in the yield can be explained by the amount of product that remains trapped within the gel. After three consecutive uses, the concentration of the product within the gel pockets is high, and as a result access to the catalytic units is blocked. The slight improvement in the yield for the fifth run (36–43%) is most likely due to the product from the previous reactions being eluted. Full conversion is not reached for the fifth reaction. The remaining gel phase is dissolved after the last run, and ¹H NMR revealed that the gel phase was made up of ~50% product.

There are several reasons for the loss in activity including the hindrance of access of the catalytic site. These blockages can be caused by the incomplete removal of the product from the active site, the partial collapse of the gel pocket, or the formation of a stable ion pair between the ammonium ion and the anion of the malonitrile.

To investigate the impact of the gel phase on the catalytic activity, **5b** gel was replaced by **5b** in the solid phase (as a precipitate from EtOAc) and catalysis was carried out in an identical fashion. In this case, only 55% conversion to **8a** was achieved, clearly demonstrating the importance of the gel pocket in efficient catalysis, which allows the substrates to flow through the material and interact with the catalytic sites. In addition, it provides a larger surface area for the reaction.

Examining the gels before and after use via SEM revealed changes to the material. After the catalytic reaction, the fibers shrink and solids could be seen entwined in the fibers (Figure 6). These solids block the catalytic sites and result in lower yields during reuse. NMR analysis of the gel after catalysis showed that only the product and OTHO–DABCO were present, confirming that the large, white structures in the SEM micrographs are the product.

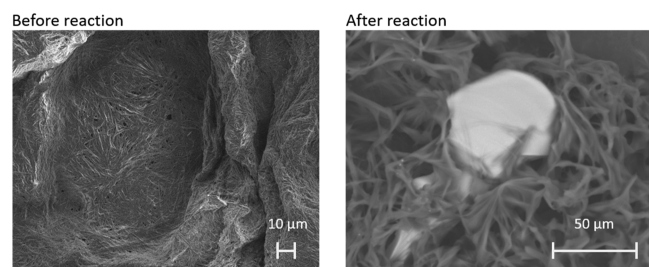


Figure 6. Gel network of **5b** before and after use. Both SEM micrographs have a magnification of 1.45k \times . The precipitated product can be seen entwined in the network. This product blocks catalytic sites and the reaction cannot proceed, resulting in lower yields. NMR shows that only the gelator and the product are present.

Substrate Scope. In order to test the functional group tolerance of the catalytic system as well as how compatible the gel is with different functional groups, the substrate scope was investigated. All reactions performed well with yields ranging from 65 to 69% (Figure 7). For example, halogen substituents are well tolerated and *p*-chloro substituted benzaldehydes can be used as substrates in the reaction affording the corresponding product (**8b**) in 68% yield, revealing that the system is broadly compatible with a variety of substrates, making this a robust material for the Knoevenagel reaction.

In general, the gel network is retained during the reaction for most functional groups present in the benzaldehyde starting material. However, *p*-nitro benzaldehyde appears to disrupt the gel network. As a result, an increased amount of the gelator was washed out during elution, and the product was trapped in the gel (45%) to a greater extent than the other substrates (between 15 and 25%).

CONCLUSIONS

Catalytic supramolecular gels provide an elegant solution for the challenges of separation and catalytic species recovery and reuse. In this study, we show that a catalytic gelator can be designed and synthesized with desirable physical properties for our technique. The OTHO gelator can be converted into a catalytic gel that is operational under flow-type conditions. The catalytic system can be reused at least five times and is compatible with a number of substrates. We were also able to

show that the major contributor to the loss of catalytic activity is accumulation of product in the gel.

We believe that supramolecular gels have the potential to pave the way for new developments of custom catalytic stationary phases as they can be readily designed and prepared from low-molecular-weight gelators. Currently, our group is investigating the challenges associated with robustness, solvent compatibility, and sustained catalytic efficiency in catalysis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.iecr.1c01914>.

General procedure for OTHOs 4a-c preparation; general procedure for OTHO-DABCO synthesis; gelation study; characterization of gels; experimental setup; optimization of conditions for catalysis; and NMR spectra of synthesized OTHOs (PDF)

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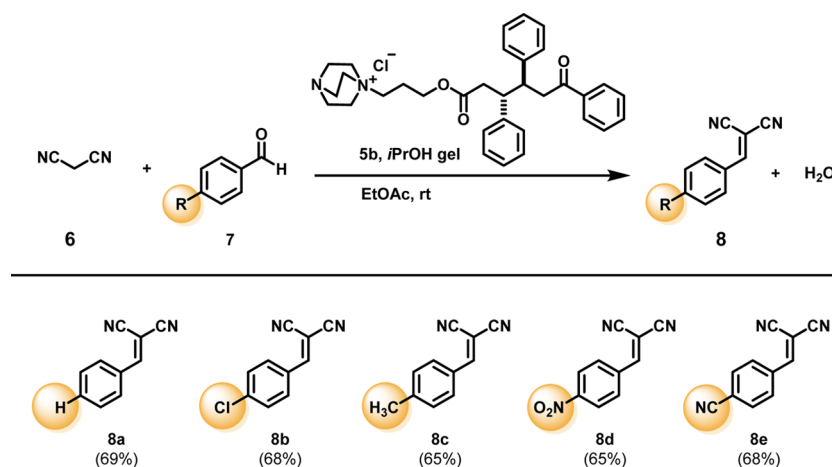


Figure 7. Substrate scope. All reactions reached full conversion within 1 h in the gel. 100 mL of EtOAc was used to elute the product. Isolated yields are given. Reactions were carried out on an *i*PrOH gel of **5b** (0.8 mmol) at room temperature; substrates **6** (0.3 mmol, 1 equiv) and **7** (0.45 mmol, 1.5 equiv) were loaded as an EtOAc (1 mL) solution.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

DCM	dichloromethane
EtOAc	ethyl acetate
iPrOH	2-propanol
PXRD	powder X-ray diffraction
MGC	minimum gelation concentration
OTHO	oxotriphenylhexanoate
THF	tetrahydrofuran

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