

# RECENT PROGRESSES ON THE USE OF RECYCLABLE MESOPOROUS SILICA SUPPORTED ORGANOCATALYSTS IN ASYMMETRIC ALDOL REACTION

## Abstract

Asymmetric Organocatalysis is one of the tremendously growing green approaches in the synthetic organic chemistry to produce enantio-enrich products. However, high catalysts loading, low and tedious recovery of catalyst, use of organic solvents, etc. render their applications in industrial chemistry. The search for 'greener' recoverable and cost effective catalysts for the chemical transformation leads to the development of new types of supported catalysts. Mesoporous silicas (MS) supported heterogeneous chiral organocatalysts attract attention for their interesting physicochemical properties as well as their easy recyclability and handling. The objective of this article is to give brief spotlight on the recent progresses on asymmetric aldol reactions using silica bound immobilized chiral organocatalysts as aldol reaction is predominantly studied chemical transformation in homogenous organocatalysis.

**Keywords:** Heterogeneous organocatalyst, Mesoporous silica, Immobilized, Asymmetric aldol reaction.

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## I. INTRODUCTION

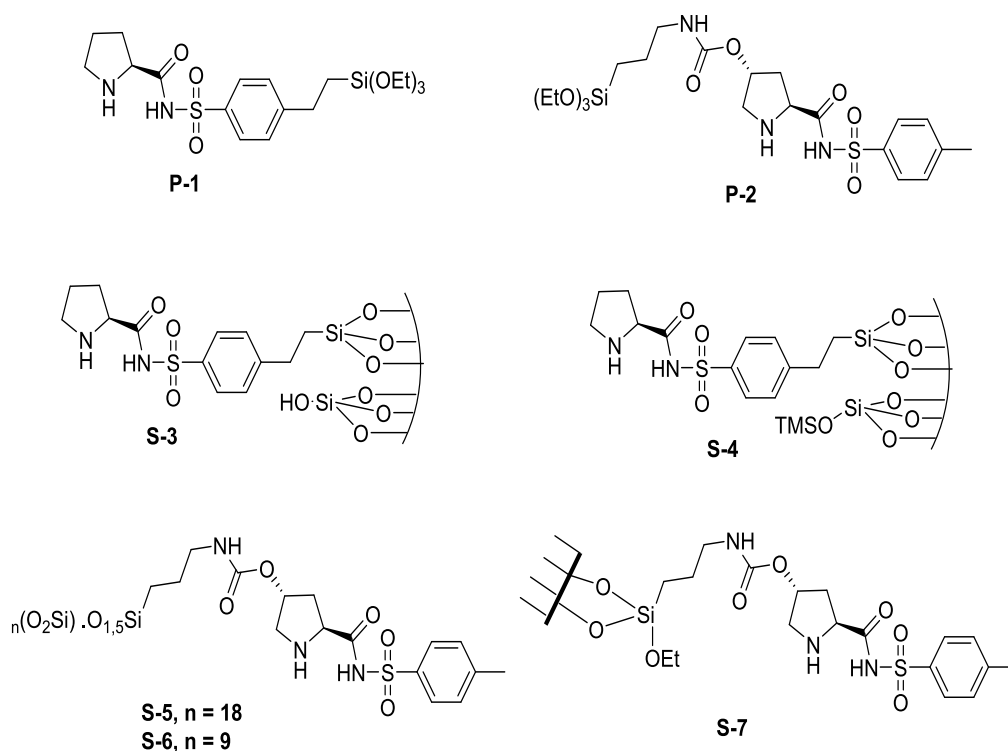
One of the majorly studied reactions in the synthetic chemistry is Aldol reaction as aldol moiety is present in numerous biologically active compounds such as antiproliferating, antibiotics, antitumor compounds, heart diseases and antifungal drugs, etc [1-3]. In this reaction, one or more stereogenic centres are generated during the new carbon-carbon bond formation. Various catalytic processes were developed to control the absolute stereochemistry of the chiral centres over 50 years [4-7]. Among the diverse asymmetric catalytic approaches, organocatalysis become gradually the most favourable one in the preceding two decades, because of its metal-free, environmental-friendly, non-toxic, robust, inert towards moistures and air, easily available nature. Besides, most of the organocatalysts are inexpensive, easy to prepare and easy to handle also [8-11]. Numerous studies of organocatalytic processes have been explored in many different kinds of reactions like Michael [11–13], aldol [14–16], Henry [17–20], Diels-Alder [21–23], aza-Henry [24–26], Povarov [27, 28], Friedel-Crafts [29–31], decarboxylative Doebner-Knoevenagel [32, 33], reactions and many more. Again, asymmetric organocatalysis is exceptionally popular and easy process to synthesize enantiomerically enriched compounds [34], although it has some drawbacks also. The main drawback is high catalyst loading, up to 20-30 mol% catalyst loading is also reported [35, 36]. So, keeping the cost of the catalysts in mind and possible agglomeration and aggregation in the reactions, concept of immobilization of catalyst and reusable catalyst preparation has been grown up to recycle catalysts with the designing of novel catalysts for the stereoselective synthesis. The recyclability of catalysts can be achieved by using a solid support either attaching an insoluble part or a soluble part. In general, an insoluble support makes a heterogeneous catalyst which can be easily recovered from the reaction medium by simple filtration; but it may slower the reaction rate. On the other hand, a soluble support may or may not change the reaction rate, but it requires an extra step to recover the catalyst. The immobilized reusable organocatalysts can also be applied in different kinds of reaction set up like flow chemistry [37, 38]. Various types of supported materials are utilized for the immobilization of organocatalysts, such as magnetic, silica, ionic resin, gold, polymer and fluoruous supporting agent. Various kinds of silica are most commonly used to prepare supported organocatalysts. Among them, the most popular one is hybrid MS like SBA-15, MCM-41, etc. Preparation of immobilized heterogeneous organocatalysts with hybrid silicas yields numerous advantages e.g. chemical inertness, high surface area, exceptional mechanical & thermal stability and effortless recyclability. Silica-supported catalysts are commonly prepared by the surfactant-assisted sol-gel process and grafting methods [39]. Since the inception of the concept of supported catalysts preparation, many silicas supported organocatalysts have been prepared and evaluated in various types of reaction [40–43]. As the Aldol reaction is the most commonly studied reactions in asymmetric organocatalysis, here, this article will focus on the silica-supported reusable chiral organocatalysts and their applications on asymmetric aldol reactions.

## II. SILICA SUPPORTED ORGANOCATALYSTS IN ASYMMETRIC ALDOL REACTIONS

Over the preceding two decades, silica-based materials become very popular as the supporting agent for organocatalysts as it produces cheap and eco-friendly heterogenous recyclable catalysts for organic transformations. Recently, several reviews on immobilized organocatalysts with meso-porous silica have been published with emphasizing on the

synthesis and general applications of silica supported organocatalysts. A few literature surveys have been reported on asymmetric aldol reactions using mesoporous silica (MS) supported organocatalysts before 2016. This article will mainly focus on the recent progresses of asymmetric Aldol reactions catalyzed by meso-porous silica supported immobilized organocatalysts [43, 44].

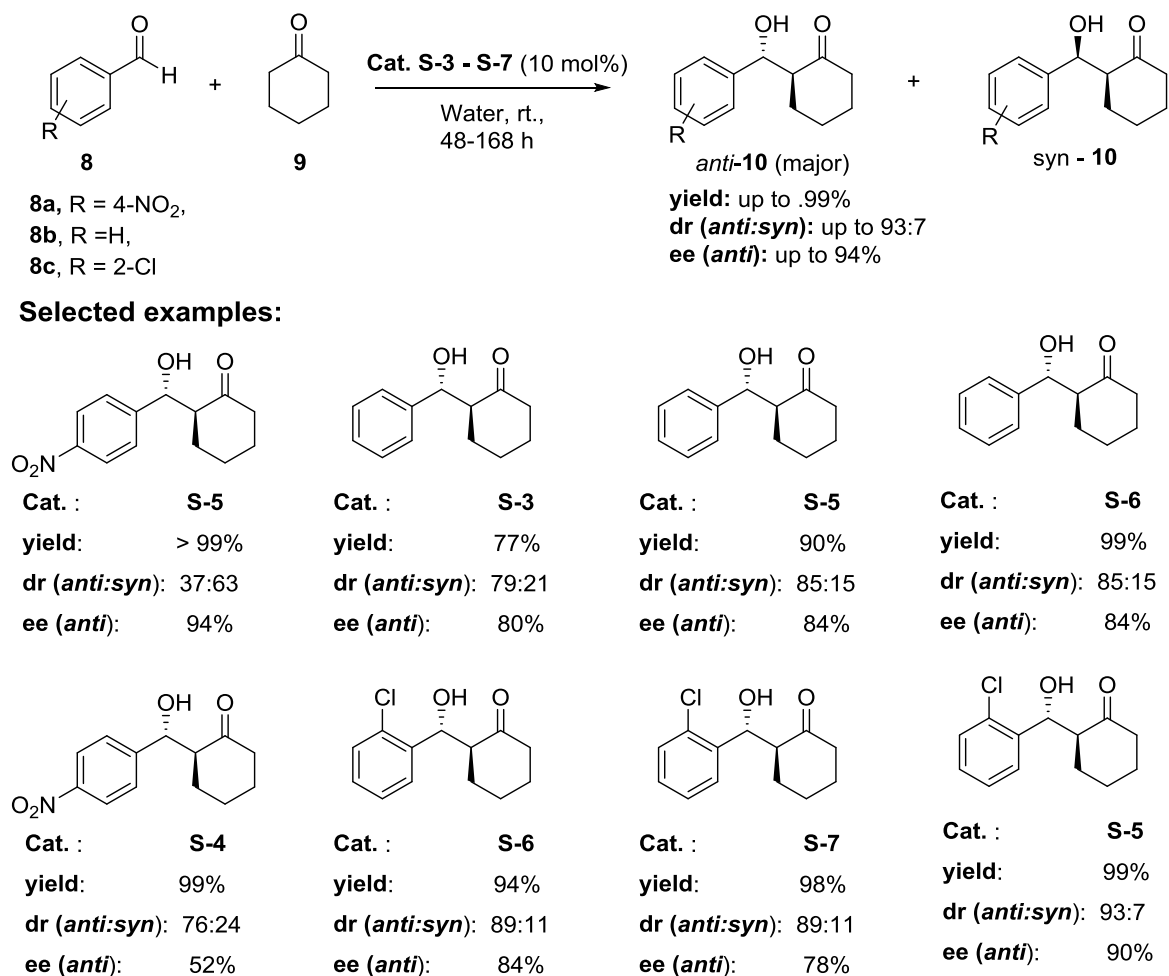
In 2016, Pleixats *et al.* prepared five different types of silica supported organocatalysts **S-3** –**S-7** from two different monosilylated chiral proline sulphonamide precursors **P-1** & **P-2** by sol-gel and grafting methods (Fig. 1). The efficiency, activity and recyclability of all the catalysts were evaluated under green conditions in asymmetric direct aldol (ADA) reaction between cyclohexanone **9** and Aromatic aldehydes **8** in eco-friendly water medium (Fig. 2) [45].



**Figure 1:** Hybrid silica supported catalyst reported by Pleixats *et al.*, 2016 [45]

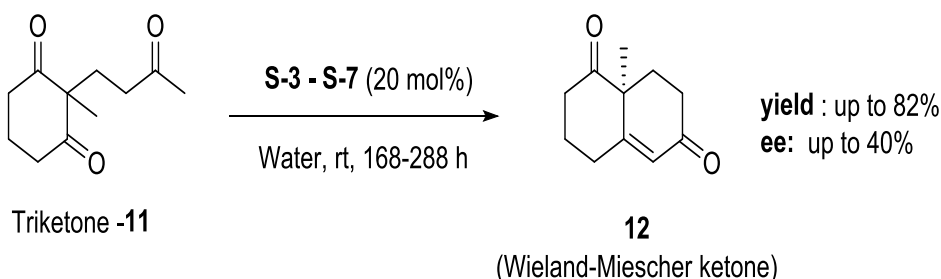
The authors observed good yields (up to 99%) and moderate to excellent diastereo selectivities as well as enantio selectivities (dr: up to 9:1 & ee: up to 94%) using 10-20 mol% of the catalysts, **S-3** – **S-7** without using any co-catalysts (Fig. 2). The results were slightly inferior compared to the homogenous proline sulphonamide catalyst tested under similar reaction conditions (dr - 99:1 & ee - 96%). The catalysts can be recovered with simple filtration. The authors reassessed all the recovered catalysts up to second run. Interestingly, they observed minimal or no loss catalytic activity or selectivities and sometimes obtained better selectivity's. Among the five different supported organocatalysts, **S-5**, **S-6** and **S-7** demonstrated better catalytic activities and stereoselectivities.

RECENT PROGRESSES ON THE USE OF RECYCLABLE MESOPOROUS SILICA SUPPORTED ORGANOCATALYSTS IN ASYMMETRIC ALDOL REACTION



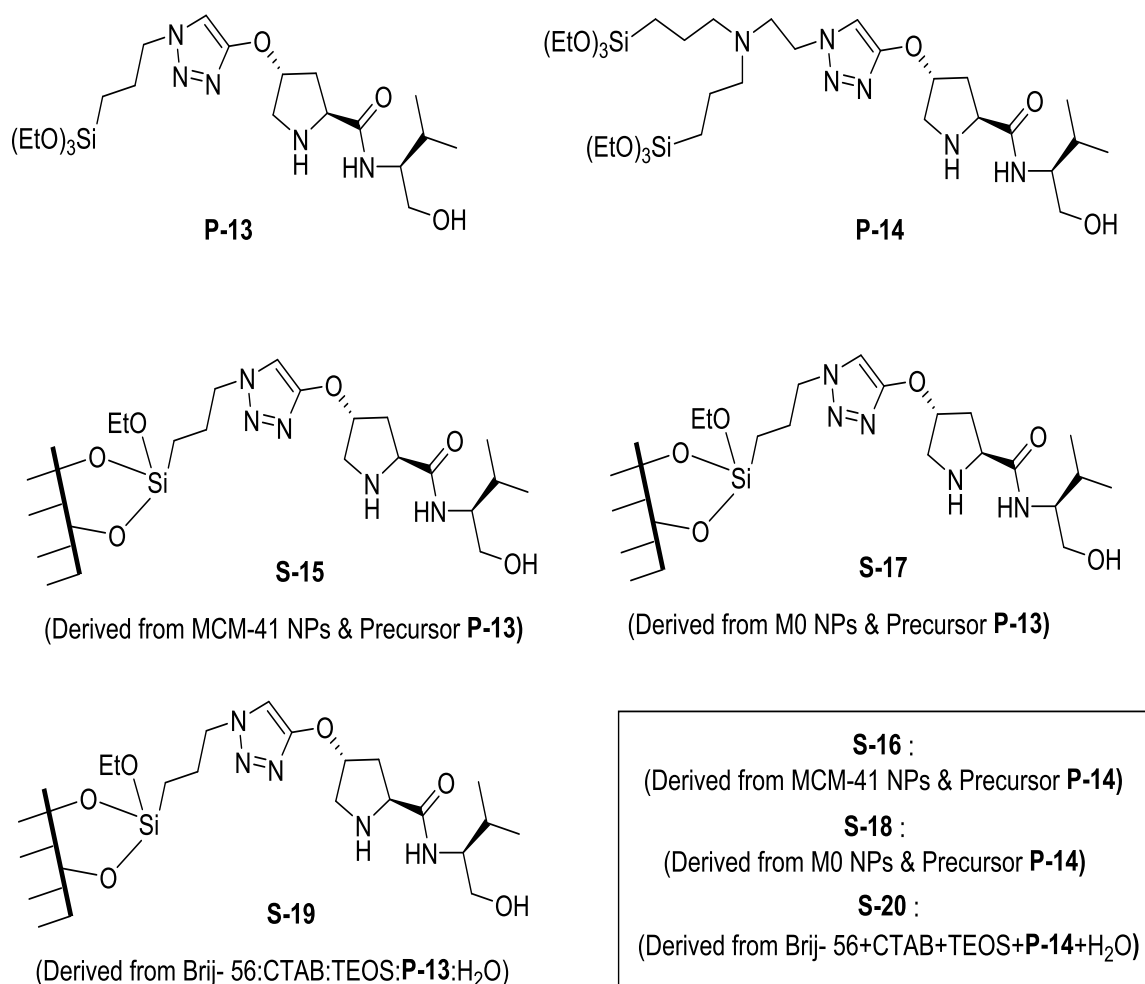
**Figure 2:** Direct aldol reaction explored by different silica supported catalysts by Pleixats *et al.* [45]

They also investigated the activities of the synthesized catalysts **S-3 – S-7** in intramolecular ADA reaction under similar conditions in Robinson type annulation of ketone **11** and obtained the adduct **12** in good yields and moderate enantioselectivity (up to 40%) (Fig. 3).



**Figure 3:** Intramolecular ADA reaction of triketone -11 [45]

In 2019, the same group synthesized another six different supported catalysts **S-15 - S-20** from the mother homogeneous organocatalysts proline-valinol amides based on the mesoporous silica nanoparticles (MSNs) (Fig. 4). The MSNs supported catalysts **S-15**, **S-17** and **S-19** were derived from the monosilylated precursor **P-13** while **S-16**, **S-18** and **S-20** were prepared from bis-silylated precursor **P-14** by co-condensation process [46].

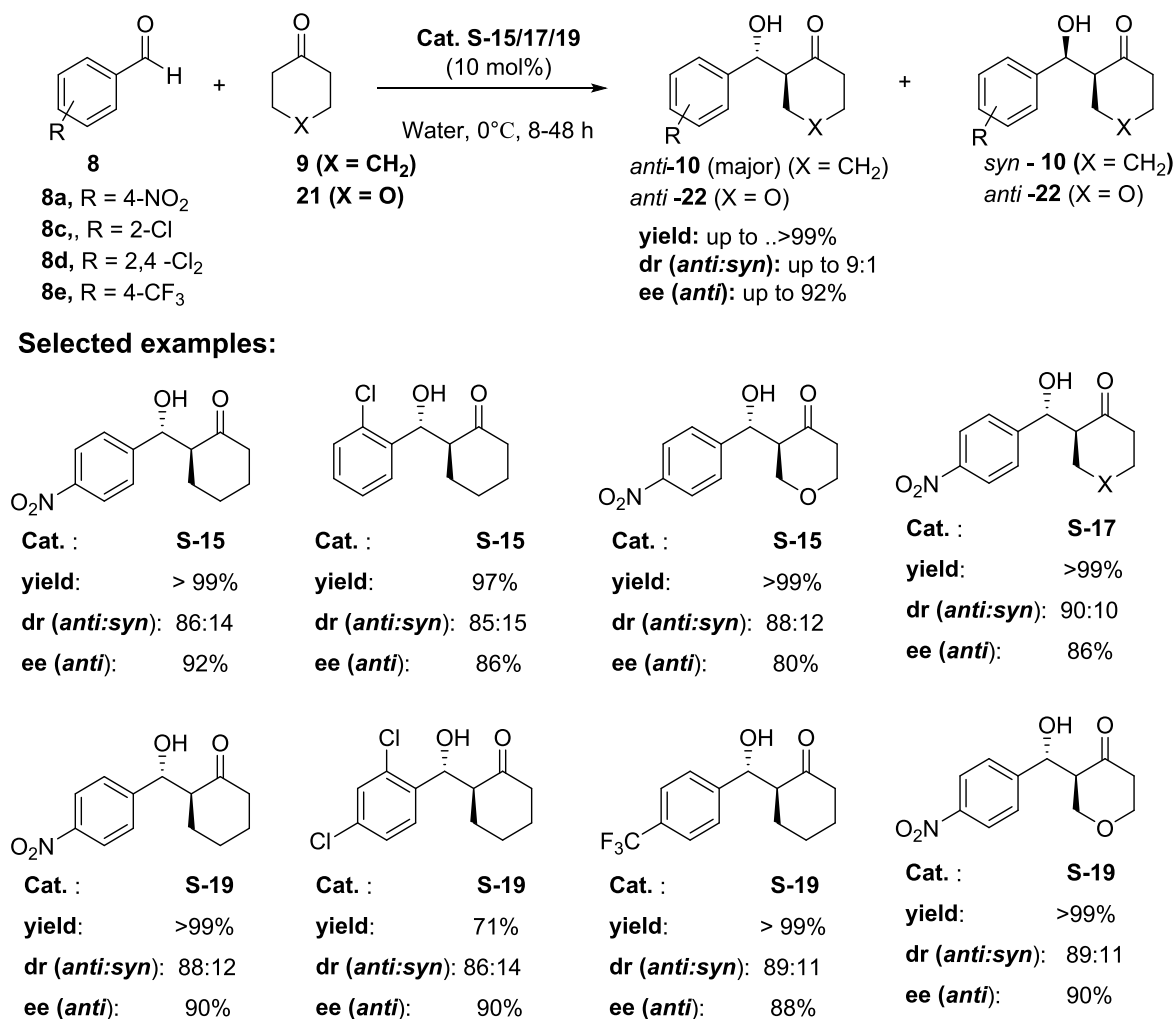


**Figure 4:** MSNs supported catalysts reported by Pleixats *et al.*, 2019 [46]

The authors investigated the efficiency of all the catalysts **S-15-S-20** in ADA reaction between various electrophiles **8** and cyclic ketones **9** (Fig. 5). They found that **S-15**, **S-17** and **S-19** afforded better results in case of both stereoselectivity and yields compare to bis-silylated precursor derived catalysts **S-16**, **S-18**, **S-20** [46].

They observed that the use of MSNs assists to reduce few issues coming out from the diffusion and the sluggish reaction rates yielded from the utilization of bulk organo-silica. Under the optimized environmentally benign conditions, they obtained 74-92% ee with excellent yields (up to > 99%) and up to 9:1 diastereomeric ratios (d.r.) using catalysts **S-15-S-20** (Fig. 5). The catalyst can be recovered easily by centrifugation and decantation. Interestingly, the catalytic activity and stereoselectivities were found to conserve up to five successive cycles (Table 1).

RECENT PROGRESSES ON THE USE OF RECYCLABLE MESOPOROUS SILICA SUPPORTED ORGANOCATALYSTS IN ASYMMETRIC ALDOL REACTION

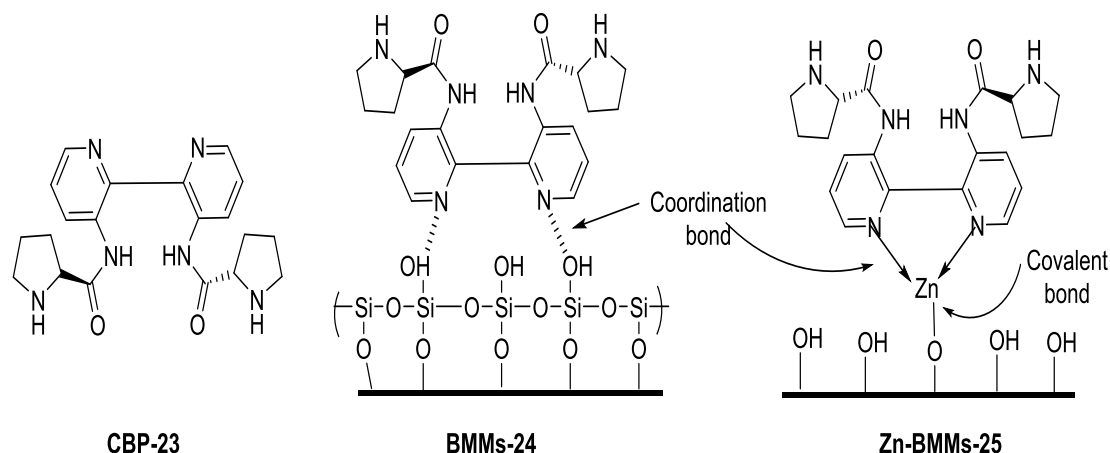


**Figure 5:** ADA reaction catalyzed by MSNs immobilized catalysts S-15-20 by Pleixats *et al.*, 2019 [46]

**Table 1:** Recycling of S-15 in ADA reaction between 4-Nitrobenzaldehyde **8a** and cyclohexanone **9** in water.

Cycle	Yield (%)	dr(anti:syn)	ee (anti) (%)
1	>99	89/11	82
3	>99	89/11	80
5	>99	89/11	82

In 2018, Sun *et al.* prepared bimodal mesoporous silicas (BMMs) supported Chiral Bipyridine-proline (CBP) **23** immobilized catalyst **BMMs-24** via co-ordination bond through grafting process (Fig. 6). The authors prepared several supported **BMMs-24** material with varied amount of CBP-**23** loading to investigate luminescent behaviors of **BMMs-24** and all of them were evaluated in ADA reaction between 4-nitrobenzaldehyde **8a** (acceptor) and cyclohexanone **9** (donor) [47].



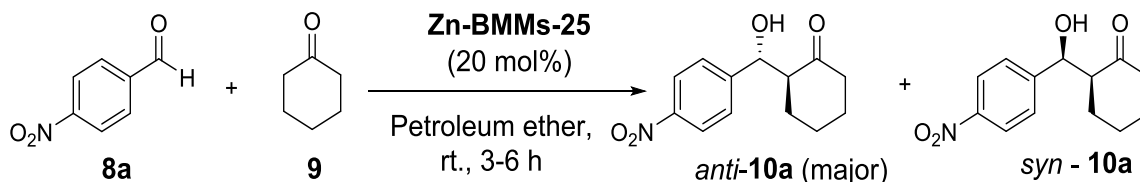
**Figure 6:** CBP-23 immobilized on BMMs catalysts by Sun et al. [47, 48]

They obtained good yields (up to 82%) and good to high stereoselectivities (dr (*anti:syn*): up to 96:4 and ee (*anti*) - up to 86%). (cf. CBP – dr- 94:6, ee (*anti*) - 88%) adding TFA as co-catalyst in DMSO. The catalyst can be reused after recovering by filtration, but it showed drastic catalytic deactivation from the second run (Cycle 2 results: yield- 10%, dr<sub>*anti/syn*</sub>- 85:15, ee *anti*-68%).

In 2019, the authors also prepared **Zn-BMMs-25** (Fig. 6) by grafting **CBP-23** on Zn-modified BMMs (Zn-BMMs) via covalent bond and examined their stability as well as catalytic performances in ADA reaction [48]. The authors optimized various parameters for the synthesis and characterized the catalysts **Zn-BMMs-25** using UV-Vis, XRD patterns, FT-IR spectra, SEM images, N<sub>2</sub> sorption isotherms, and SAXS patterns. They found various fractal features in **Zn-BMMs-25** from the SAXS patterns data analysis.

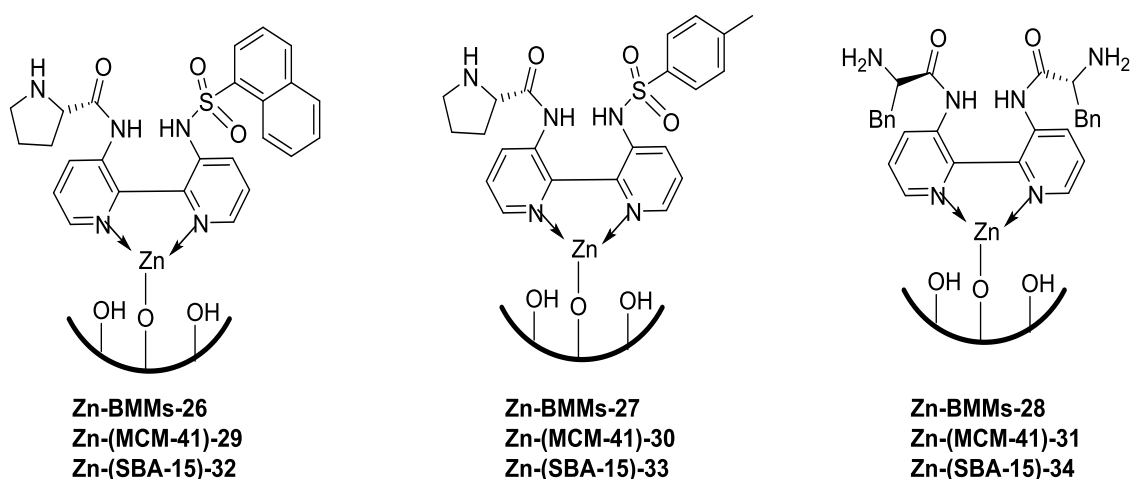
The heterogeneous catalyst **Zn-BMMs-25** exhibited high catalytic efficiency in ADA reaction between the donor cyclohexanone **9** and acceptor 4-nitrobenzaldehyde **8a** providing aldol adduct **10a** with > 92% yields and good stereoselectivities (dr (*anti: syn*): 82:18 & ee (*anti*): 68%) in the fresh condition (Table 2). The Zn-modified catalyst **Zn-BMMs-25** showed better performance than the previously developed non-modified **BMMs-24** in terms of recyclability (recycled up to 6 times) although the stereoselectivities drastically started to diminish from the third cycles and catalytic activity after fourth cycles in petroleum ether (Table -2). The authors investigated the cause of catalytic deactivation of the reused catalyst **Zn-BMMs-25** using XRD patterns. Accordingly, they concluded that the active chiral catalyst **CBP-23** might be gradually agglomerated or unequally disseminated in mesoporous channel of **Zn-BMMs-25**. The most probable causes of catalytic deactivation might be the accumulation of organic products which resulted difficulty in adsorption as well as diffusion of reactant substances of ADA reaction [49].

**Table 2: Recycling of Zn-BMMs-25 in ADA reaction between 4-Nitrobenzaldehyde **8a** and cyclohexanone **9** in petroleum ether.**



Entry	Cycle	Time (h)	yield (%)	dr ( <i>anti</i> / <i>syn</i> )	ee ( <i>anti</i> ) (%)
1	Fresh	3	92.10	82:18	68
2	Second	4	91.50	81:19	67
3	Third	4	80.00	75:25	53
4	Fourth	5	74.60	66:34	40
6	Sixth	6	40.26	52:48	18

In 2022, Sun *et al.* also developed three more analogous supported catalysts **Zn-BMMs-26-28** using Zn-modified BMMs from three bipyridine-based chiral ligands following covalent - coordination attachment methods (Fig. 7) and explored their catalytic performances corresponding to the fractal features of the catalysts materials and to the molar ratio of chiral ligand loading in the ADA reaction between *p*-nitrobenzaldehyde **8a** and cyclohexanone **9** [49].



**Figure 7: Zn-modified MS immobilized catalysts reported by Sun *et al.*, 2022 [50, 51]**

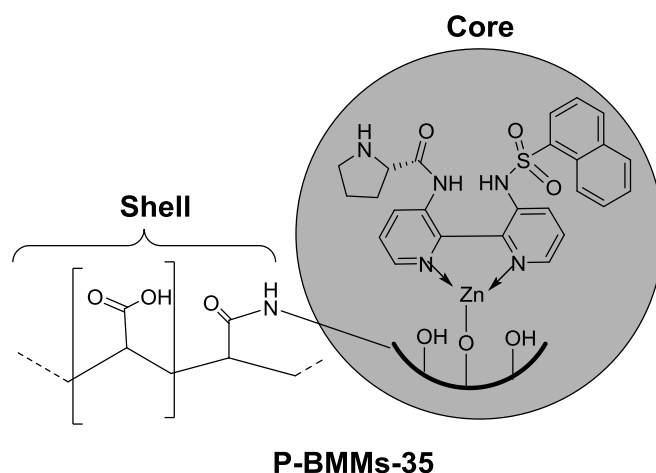
They observed that the yield of aldol adduct (up to 96%) as well as stereoselectivities (dr: up to 72:28, ee (*anti*): up to 55%) increase with the increase of molar ratio of chiral bipyridyl ligand (BL) to Zn (**BL/ Zn**) to an extent of 100% in the immobilized catalysts. However, the stereoselectivities decrease slightly (ee : 52%) while the same ratio was enhanced to 200%. The authors also observed a positive relation between catalytic performances (yield and stereoselectivities) and the fractal features of the catalyst. The



catalyst, **Zn-BMMs-26** also demonstrated better activity and selectivity than the homogenous catalysts in the same conditions.

In the same period, this group also unveiled the fractal features comparisons among the catalysts derived from Zn-modified diverse MS (mesoporous silicas), like, BMMs, MCM-41 and SBA-15 using SAXS method [51]. They prepared BMMs supported **Zn-BMMs-26-28**, MCM-41 supported **Zn-(MCM-41)-29-31** and SBA-15 supported **Zn-(SBA-15)-32-34** catalysts of BL/Zn molar ratio of 100% (Fig. 7) and studied the relation of their fractal features in the catalytic performances of ADA reactions between electrophiles **8a** and cyclohexanone **9**. They observed that BMMs-derived catalysts having short range mesoporous channels (2-3 nm) showed both surface and mass fractal characteristics while highly ordered long range mesoporous silicas (MS), MCM-41 as well as SBA-15-supported catalysts only demonstrated surface fractal aspects [51].

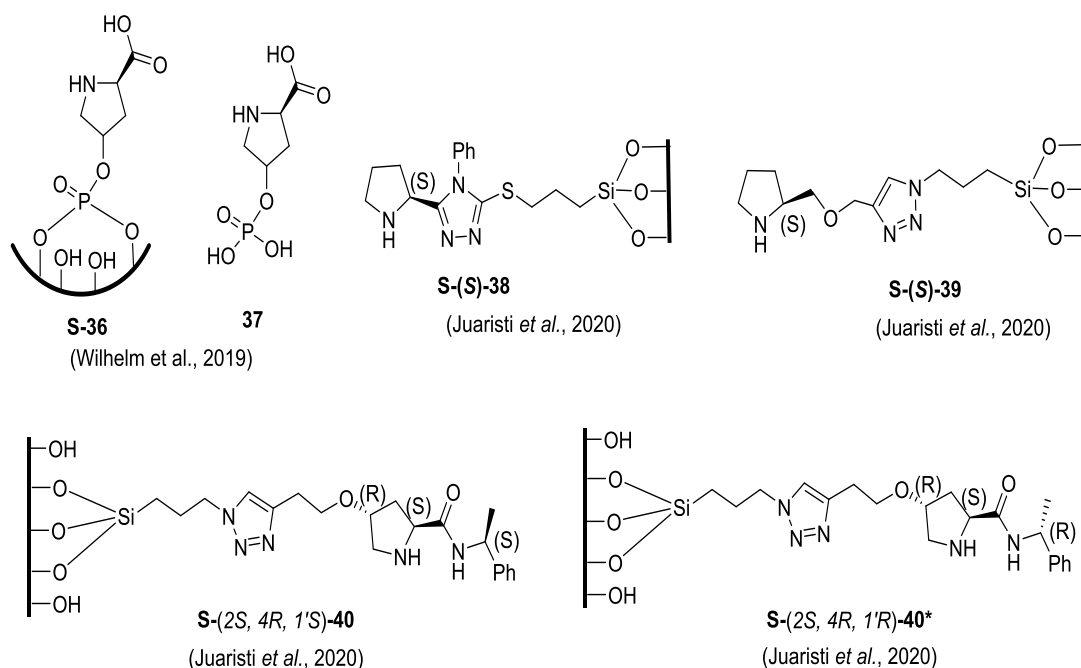
Recently, in 2023, Sun *et al.* prepared a novel pH-sensitive BMMs-supported CBP catalyst **P-BMMs-35** having BMMs in the core structure and Poly(acrylic acid) (PAA) attached with BMMs like a shell (Fig. 8) and evaluated it as a pH-tunable catalyst in ADA reaction between 4-nitrobenzaldehyde **8a** and cyclohexanone **9**. They characterized the catalysts using various instrumental and spectroscopic methods. SAXS patterns analysis confirmed the different types of fractal features presents in the catalyst [52]. The catalytic activity of catalyst **P-BMMs-35** was found very much sensitive towards pH. At pH = 1.5, the catalyst was completely inactive while high catalytic activity was observed from pH = 7.25 - 10.18 (yield: up to 85.68%), However the catalyst **P-BMMs-35** was completely inefficient to provide stereoselectivity (dr (*anti:syn*): up to 54:46 and ee (*anti*): up to 3%) .



**Figure 8:** PAA-BMMs supported CBP catalyst reported by Sun *et al.*, 2023 [52]

In 2019, Wilhelm *et al.* used various MS materials for the immobilization of phosphoric acid esters and **phosphonic** acids. They synthesized immobilized proline catalyst **S-36** in two different MS, LiChrosorb SI 100 and SBA-15 form (*4R*)-4-phosphonoxy-L-proline **37** (Fig. 9).

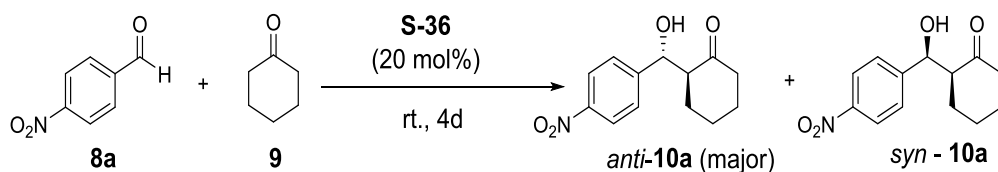
RECENT PROGRESSES ON THE USE OF RECYCLABLE MESOPOROUS SILICA SUPPORTED ORGANOCATALYSTS IN ASYMMETRIC ALDOL REACTION



**Figure 9:** MS based supported catalyst **S-36** by Wilhelm *et al.*, 2019 [53] & **S-38-40\*** by Juaristi *et al.*, 2020 [54].

The authors tested their catalytic activities in ADA reaction between 4-nitrobenzaldehyde **8a** and cyclohexanone **9** using 20 mol% of the functionalized organo-silica catalyst **S-36** and observed slightly lower yields but better enantio- and diastereoselectivities compared to the non-supported catalysts **37** (Table 3) [53]. However, recycling of the **S-36** (from SBA-15) catalyst was not possible as the active component **37** detached from the silica material under work up condition due to hydrolysis.

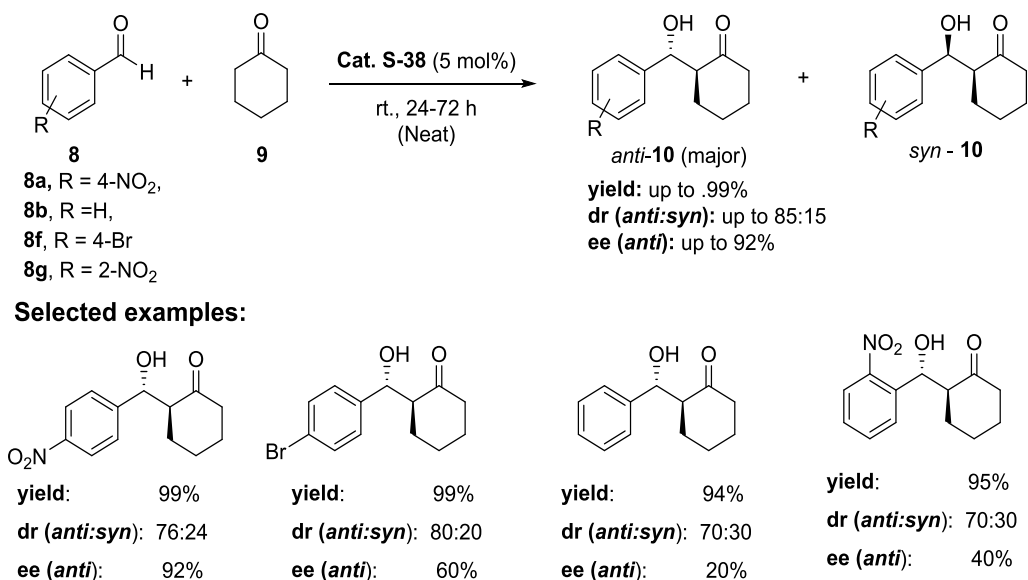
**Table 3:** Comparative results of ADA reactions reported by Wilhelm *et al.*, 2019 [53]



Catalyst	loading (mmol.g <sub>SiO<sub>2</sub></sub> <sup>-1</sup> )	yield (%)	dr ( <i>anti</i> / <i>syn</i> )	ee ( <i>anti</i> ) (%)
Pure- <b>37</b>	-	62	93:7	96
<b>S-36 @LiChrosorb</b>	1.234	53	95:5	97
<b>S-36 @SBA-15</b>	1.162	47	92:8	97

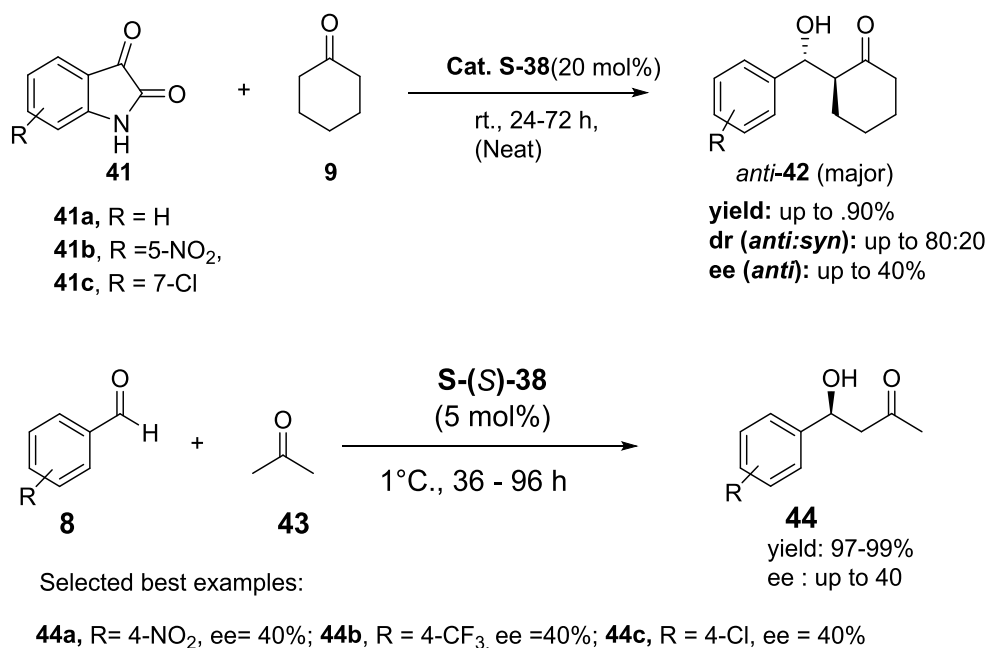
In 2020, Juaristi *et al.* prepared four Nobel mesoporous silica (MS) supported organocatalysts **S-38**, **39**, **40**, **40\*** (Fig. 9) from (*S*)-Proline derivative and explored their catalytic activities in ADA reaction between 4-nitro benzaldehyde **8a** and cyclohexanone **9**. The authors observed catalyst **S-(S)-38** to show the best catalytic activity.

The catalyst **S-(S)-38** delivered excellent yields (up to 99%) and up to 92% ee with moderate diastereoselectivities in ADA reaction between electrophiles **8** and cyclohexanone **9** (Fig. 10). Catalyst **S-(S)-39** was also found to provide comparable results as **S-(S)-38** [54].



**Figure 10:** Activity in ADA reaction of the catalyst S-38 [54].

The activity of catalyst **S-(S)-38** was also explored in the ADA reaction involving cyclohexanone **9** and isatin derivatives **41** as electrophiles (dr up to 4:1 and ee (max.) 40%) & aromatic aldehydes **8** as electrophiles and acetone **43** as donors (yields: 97-99%, ee (max.): 40%) (Fig. 11) [54].



**Figure 11:** ADA reactions reported by Juaristi *et al.*, 2020 [54]

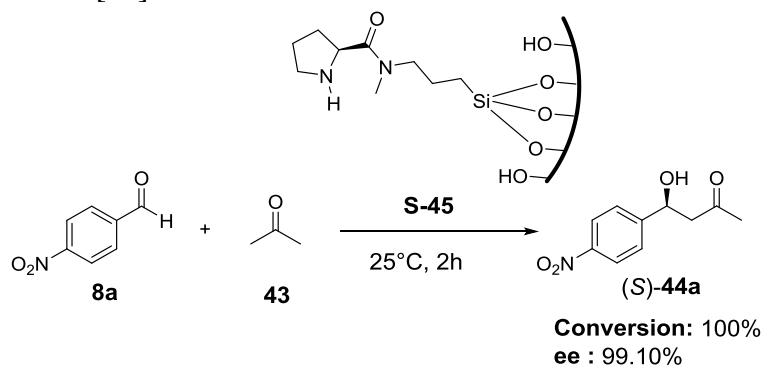
The recyclability of the catalyst **S-(S)-38** was evaluated on ADA reaction between acetone **43** and *p*-nitro benzaldehyde **8a** (Table 4). They carried out up to 15 cycles using catalyst **S-(S)-38** and observed to drop the enantiomeric ratio 40 to 20% while the isolated yields remained almost constant (>96%) (Table 4) [54].

**Table 4:** Catalytic activity and recyclability of the silica supported catalyst **S-(S)-38** by Juaristi et al. [54].

**Cycle**                      **yield (%) of 44a**                      **ee (%) of 44a**

1	98	40
8	99	30
9	98	20
15	96	20

Modi and Lakhani developed silica matrix supported L-proline **S-45** catalyst namely “L-proline-(3<sup>o</sup> amine)-*f*-SiO<sub>2</sub>” in 2022 (Fig. 12). The catalyst **S-45** was synthesized following spick and span protocol [55].

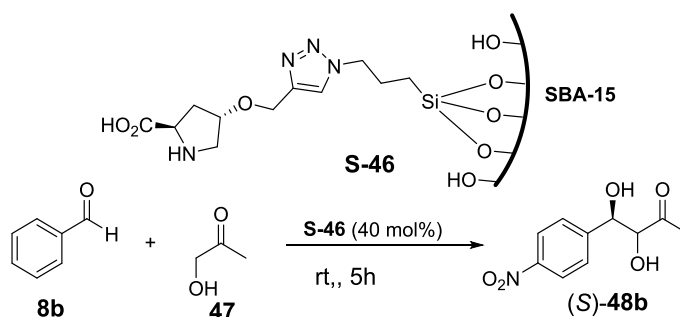


**Figure 12:** Activity of Silica matrix supported **S-45** in ADA reaction by Modi and Lakhani [55].

The synthesized material **S-45** was subjected to ADA reaction at 25°C without any organic solvent between acetone **43** and electrophile 4-nitro benzaldehyde **8a**. The authors observed outstanding selectivity (ee > 99%) with 100% conversion and obtained predominantly *S*-isomer of aldol adduct (**S-44a**) (Fig. 12).

The high activity and stereoselectivity of the catalyst **S-45** was also observed during recycling stages where it showed magnificent activity up to seven successive times (conversion- 100%) and minimal loss of stereoselectivity (ee -99.10% drops to 97.26% after 7<sup>th</sup> cycle) (Fig. 12).

In 2022, D'Agostino *et al.* investigated the consequence of immobilization of L-proline on solid matrix and the solvent effect on reactivity and stereoselectivities (dr & ee) on the heterogenised catalysts **S-46** in comparison with homogenous catalyst L-proline in ADA reaction between hydroxyacetone **47** (donor) and benzaldehyde **8b** (acceptor) via NMR relaxation method. The authors found NMR relaxation method very convenient and fast technique for screening solvents [56]. They carried out the study with previously reported supported L-proline catalysts on SBA-15, **S-46** (Fig. 13) [57].



Solvent Screening table of **S-46**:

Solvent	dr (dr for L-Pro)	ee (%) (ee for -L-Pro)
Neat	1:1.3 (1:2)	Rac (18)
DMSO	1:2 (1:2)	76 (72)
H <sub>2</sub> O	1:1.3 (n.r)	Rac. (n.r.)
EtOH	1:1.3 (n.r.)	Rac. (n.r.)
DMF	1:1.8 (1:2.3)	60 (62)
DCM	1:1 (1:1.5)	Rac.(36)
THF	1:2 (1:3.5)	23 (76)
Cy. Hex	1:1.3 (1:2)	Rac.(28)

**Figure 13:** Solvent screening for ADA reaction by NMR relaxation method [56]

They observed that the surface affinity of the solvents is very crucial to determine the reactivity. According to their results, solvents having higher surface affinity of silica matrix reduce the reactivity. This was explained by the unavailability of the active sites to access by the reactant. Interestingly, the ADA reaction can be carried out in green solvents like water and ethanol in presence of immobilized organocatalyst which is completely opposite behavior to the homogenous counterpart. This implies that immobilization significantly improves the various aspects of a reaction from environmental benignity to easy separation as well as recyclability (leads to higher TON).

### III. CONCLUSION

This article has presented the catalytic activities of mesoporous Silicas (MS) supported chiral organocatalysts on asymmetric aldol reactions. All the supported catalysts

reported here is proline or proline derivatives and were evaluated on bench mark ADA reaction only. There are no reported examples of Mukaiyama type indirect aldol reaction or any novel challenging aldol reactions using silica supported organocatalysts. Though, it is also desirable that the newly designed supported catalyst will be assessed on those asymmetric aldol reactions that have been found extremely challenging in the homogenous conditions. Interestingly, MS supported heterogeneous chiral catalysts showed closely comparable activity to their homogeneous counterpart. Besides, the supported catalysts successfully fulfill the aim of recoverability as well as reusability. Moreover, most of them were highly active in green solvent, water or solvent less (neat) conditions i.e. after heterogenisation, the organocatalysts become environmentally more benign in nature.

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