The Application of Nanoparticles Supported Chiral Organocatalysts in Asymmetric Aldol Reactions: a Study on the Recent Advancement

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ABSTRACT

The nanotechnology witnessed a tremendous growth over the last two decades. Various types of nanomaterials were invented and were applied in diverse field. They have also been utilized as supporting agents to immobilize or graft various catalysts to improve their catalytic activity, stabilization, recycling ability etc. Recently nanoparticles have been extensively used as a supporting agent to prepare nano-particles-supported chiral organo-catalysts (NPSCOCs) and evaluated their catalytic activity in various asymmetric organic transformations. Nanoparticles supported chiral catalysts have high stability and generally provide better selectivity. The most importantly, the supported catalysts can easily be recovered and recycled several times. Thus, this improves the catalytic efficiency and turnover number of the catalyst. Besides, the NPSCOCs can work in eco-friendly solvent like water. This article will focus on the application of NPSCOCs in asymmetric aldol reaction in eco-friendly conditions.

Key words: Functionalised nanoparticles, Immobilization, Supported chiral organo-catalyst, Green Chemistry, asymmetric aldol reaction**.**

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I. INTRODUCTION

The development of environmentally benign together with economically favourable chemical method is highly challenging task in synthetic organic chemistry. In this aspect, catalysis is most popular choice as it leads to highly efficient green process producing least amount of waste with accelerated reaction rate. Among the various catalysis the most favoured one is organocatalysis for its unique characteristics like being devoid of heavy metals, easy to prepare or available in the nature, least or no sensitivity towards oxygen and moisture, cost effective, availability of diverse structural feature, etc [1-3]. The incredible potential of asymmetric catalysis for making enantio-enrich organic compounds is well-known. Now-a-days, asymmetric organocatalysis turns into integral part of asymmetric synthesis [4-6]. However, non-recyclability of homogenous organocatalysts and high catalyst loading are major drawbacks [7-9]. These limitations were partly overcome by the invention of various types of supporting agents like polymers, hybrid silica gel, fluorous tags, nanoparticles (NPs), ionic liquids for the synthesis of recoverable supported organocatalysts [10-14]. With the fast advancement of nanotechnology various types of functionalized nano-particles have been developed and used as supporting agent for diverse types of catalysts [15-23]. The retrievable nano-particles supported organocatalysis becomes one of the most widely used process in the various asymmetric transformations due to its simple recoverability and recyclability [24, 25].

Asymmetric Aldol reaction has been extensively studied reaction in diverse unsupported organocatalysis [26, 27]. The chiral organocatalysts that were active in asymmetric aldol reactions were also immobilized using nano-particles and the NPSCOCs were evaluated in asymmetric aldol reaction to find out their recoverability, efficiency as well as to develop eco-friendly better catalytic conditions [28-32]. Several review articles are present in the literature with emphasising the detailed discussion on the preparation of various types of supported nanoparticles, their characterization, chemical properties, etc. [14-17]. This article is going to emphasis on the recent application of retrievable NPSCOCs on asymmetric aldol reactions.

II. DISCUSSION

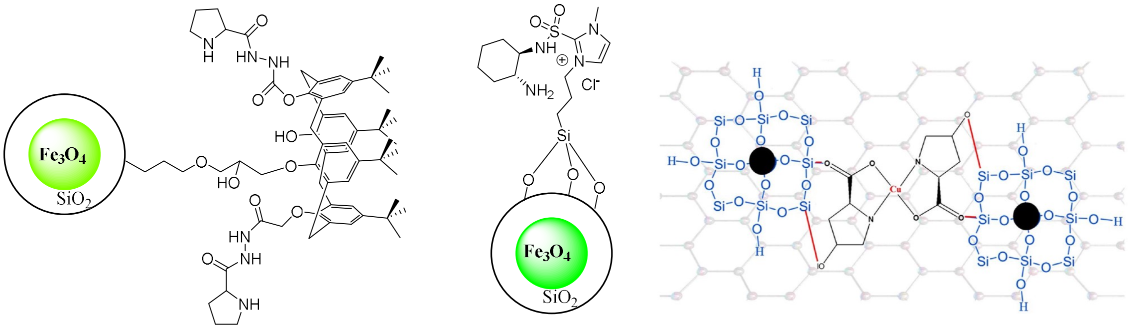
II.a. MAGNETIC NANOPARTICLES (MNPS) AS SUPPORTING AGENT

Among the various nanoparticles used as supporting agents for organocatalyst, MNPs were the most popular choices for chemist. Because the MNPs supported catalysts are cost effective, easy to prepare, highly active like their homogeneous counterparts, etc. [33, 34] Besides these, it can easily be separated using external magnet avoiding monotonous filtration or centrifugation process and can be reused for several times. The quasi-homogeneous nature and high stability of the MNPSCOC plays crucial role to provide highly pure enantio-enrich organic products in environmentally friendly solvents like water [35-40].

There are several brilliant reviews present in literature discussing about the preparation, characterisation and properties of the magnetic nanoparticles supported chiral organo-catalysts (MNPSCOC) [41-43]. This article will focus only on the recent application of MNPSCOC in asymmetric aldol reaction.

II.b. MAGNETIC NANOPARTICLE SUPPORTED ORGANOCATALYSTS IN ASYMMETRIC ALDOL REACTION

In 2015, Yilmaz *et al.* successfully developed a simple methodology to prepare a new type of MNP-supported chiral organocatalysts MNPs-Cat-**1** from calixarene-containing proline **(**Fig. 1**)** for the first time [44].



Calix-pro-MNPs-Cat-1 (Yilmaz *et al.*, 2015)

MNPs-Cat-2 (Xu *et al.*, 2016)

MNPs-Cat-3 (Nasir *et al*, 2019).

Figure 1: MNPSCOCs developed and evaluated in ADA reaction by various groups

The catalyst MNPs-Cat-**1** having spherical dimension was evaluated on asymmetric direct aldol (ADA) reactions between aromatic aldehydes (acceptor **I**) and cyclohexanone (donor **II**) and was found very efficient in affording aldol adduct **III** with good to excellent selectivities [dr (*anti:syn*): up to 97:3 and ee (*anti*): up to 93%] with high yield (Fig. 2).

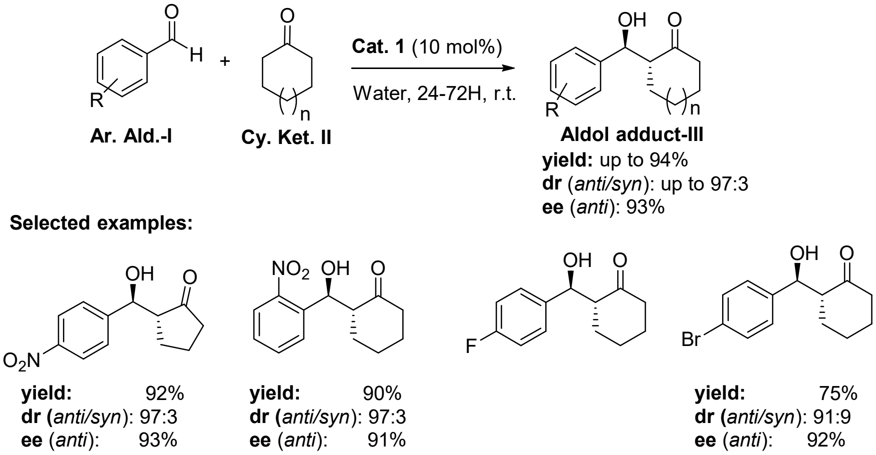


Figure 2: Catalytic performances of MNPs-Cat-1 in ADA reaction, Yilmaz *et al.*, 2015, [44].

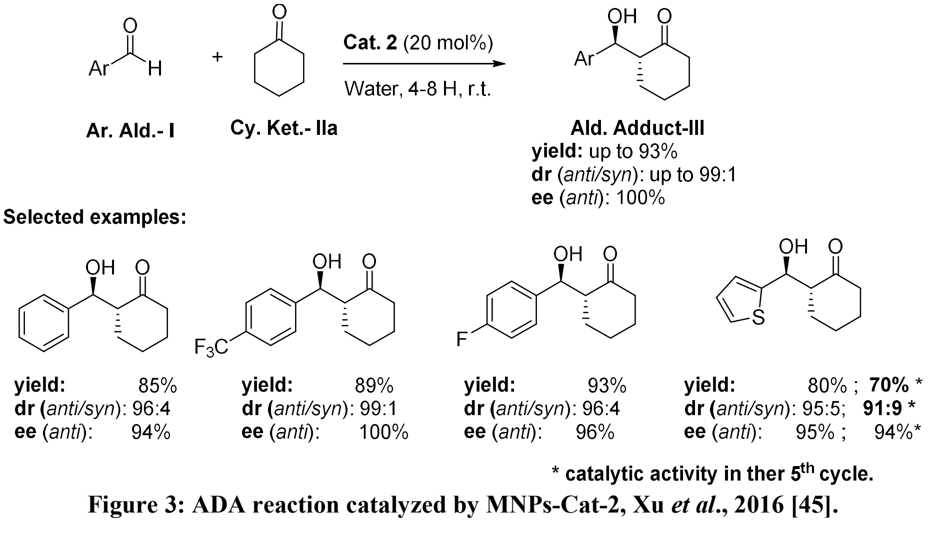
The authors also performed recycling experiment of the Calex-pro- MNPs-Cat-**1** and observed no significant loss of activities and selectivities up to five cycles, but, thereafter, it started to drastically loss both the activities and selectivities (Table 1).

Table 1: Calix-Pro-MNPs-Cat-1 in recycling experiment in ADA reaction (Donor: Cyclohexanone, Acceptor: 4-Nitrobenzaldehyde), Yilmaz *et al.*, 2015, [44].

Cycle	Yield (%)	dr (*anti:syn*)	ee (*anti*)(%)
1	92	97:3	93
3	90	89:11	87
6	82	84:16	79
8	68	73:27	64

In 2016, Xu *et al.* prepared a magnetic nanoparticles-supported chiral aminocyclohexane MNPs-Cat-**2** (Fig. 1) containing an imidazolium ionic liquid moiety. The incorporation of ionic liquid in the MNPSCOCs will provide several advantages like better stability, higher quasi- homogeneousity leading to superior catalytic activity, higher recyclability, etc.

The ionic liquid tagged MNPs-Cat-**2** was successfully evaluated in the ADA reactions between cyclohexanone **II** and aromatic & heteroaromatic aldehydes **I** under a green procedure in water. The synthesized catalyst demonstrated good to high catalytic activity yielding 70–94% aldol addition adduct **III** and excellent stereoselectivity (ee: 92–100%, dr: 91:9–99:1) (Fig. 3). The excellent performance of the catalyst can be explained by the vital role played by the ionic liquid moiety through facilitating the link among reactants and catalytic sites in water medium. The MNPs-Cat-**2** was readily recovered from the reaction medium by applying an external permanent magnet and recycled for five times without any significant loss of catalytic efficiency [45].



*** catalytic activity in ther 5th cycle.**

Figure 3: ADA reaction catalyzed by MNPs-Cat-2, Xu *et al.*, 2016 [45].

In 2019, Nasir *et al.* developed a noble catalyst via immobilization of Cu(proline)$_2$ complex onto the surface of magnetic grapheme, G/MF@SiO$_2$@Cu(proline)$_2$, MNPs-Cat-**3** (Fig. 1). The authors successfully developed a greener catalytic procedure for ADA reaction using the grapheme based MNPs-Cat-**3** under solvent free condition. The prepared nanocatalyst MNPs-Cat-**3** afforded all aldol products in good to excellent yield (up to 98%) with outstanding enantiomeric excess (> 90%) (Fig. 4) [46].

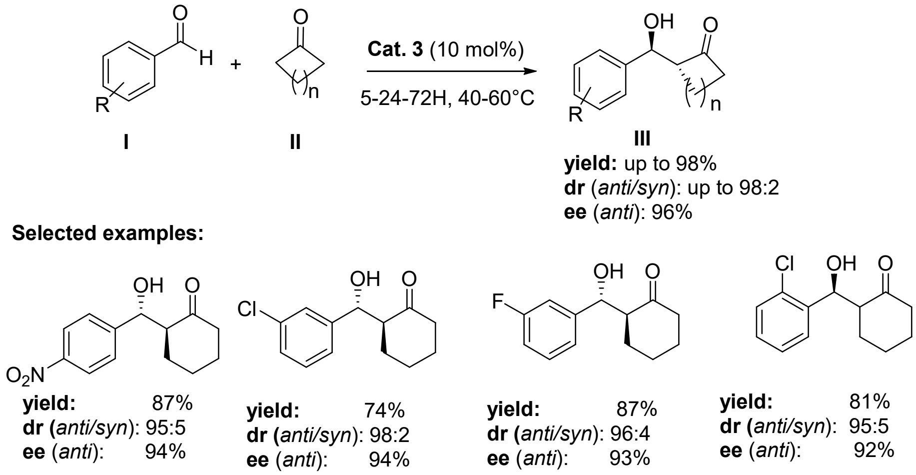


Figure 4: ADA reaction catalyzed by MNPs-Cat-3 under solvent-free condition, Nasir *et al.*, 2019 [46].

The authors also executed a separate experiment of the ADA reaction using various components as catalyst that was used in the synthesised MNPs-Cat-**3** to find out the active components of the designed catalyst and they found that only proline, $CuCl_2$. $2H_2O$, and $Cu(proline)_2$ complex afforded the aldol adduct with lower yield compared with the synthesised catalyst $G/MF@SiO_2@Cu(proline)_2$, Cat-**3** (Table 3). These experiments imply that the catalytic activity of the copper complex, $Cu(proline)_2$ and proline were improved many fold after immobilization onto the surface of magnetic Graphene ($G/MFe@SiO_2$) composite,.

Table 4. Comparative study of various materials in aldol reaction, Nasir *et al.*, 2019 [46].

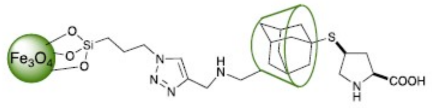
Entry	Nanocatalyst	Yield (%)
1	Graphene	Trace
2	$MnFe_2O_3$	Trace
3	G/MF*	Trace
4	$G/MF@SiO_2$	Trace
5	Proline	59
6	$CuCl_2$, $2H_2O$	60
7	$Cu(Proline)_2$	65
8	MNPs-Cat-**3**	98
* G: Graphene; MF: $MnFe_2O_3$		

As like other MNPs supported catalysts, it can be easily recovered with an external magnet and recycled up to five cycles without any substantial loss of activity with extremely small leaching of the catalyst (Table 3) [46].

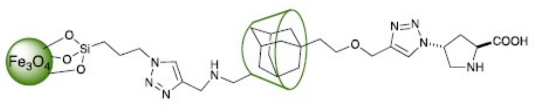
Table 3: Recycling experiments of MNPs-Cat-3 in ADA reaction, Nasir *et al.*, 2019 [46].

Cycle*	Yield (%)	dr (*anti/syn*)	ee (*anti*) (%)
1	98	73:27	89%
2	96	73:27	89%
3	95	73:27	89%
4	93	73:27	89%
5	90	73:27	89%
* Donor: Cyclohexanone, Acceptor: *p*-nitrobenzaldehyde			

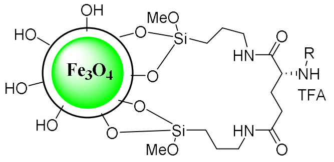
In 2019, Pericàs *et al*. reported very interesting noble type of MNPs supported a supramolecular motif based adamantly substituted proline organocatalysts MNPs-Cat-**4** and MNPs-Cat-**5** (Fig. 5). The designed catalyst can acts as magnetic shuttle where the supramolecular motif containing β-CD acts as a reversible connector between the MNPs and the organocatalyst molecule [47].



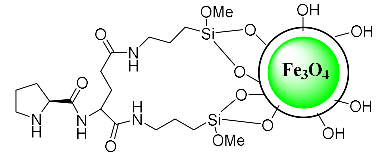
MNPs-Cat-4
(Pericàs *et al.*, 2019)



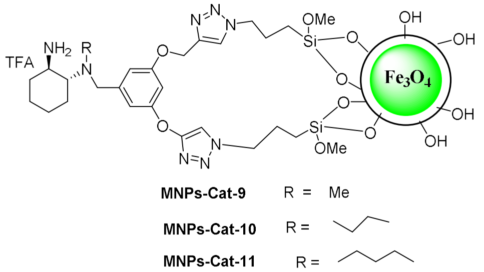
MNPs-Cat-5
(Pericàs *et al.*, 2019)



MNPs-Cat-6 (R = H)
MNPs-Cat-7 (R = CH$_3$)
(Tai *et al,*, 2019)



MNPs-Cat-8
(Tai *et al,*, 2019)



(Tai *et al,*, 2019)

Figure 5: Catalysts developed by Pericàs *et al.*, 2019 for ADA reaction [47].

The authors used the adamantyl-decorated MNPSCOCs with proline as active site**,** MNPs-Cat-**4** & **5** as modular, magnetically recyclable catalysts to develop an environmentally benign procedure on ADA reaction between aromatic aldehydes (acceptor-**I)** and cyclohexanone (donor **IIa**) in water (dr: up to 33:1; ee: up to 99 %) (Fig.- 6) [47].

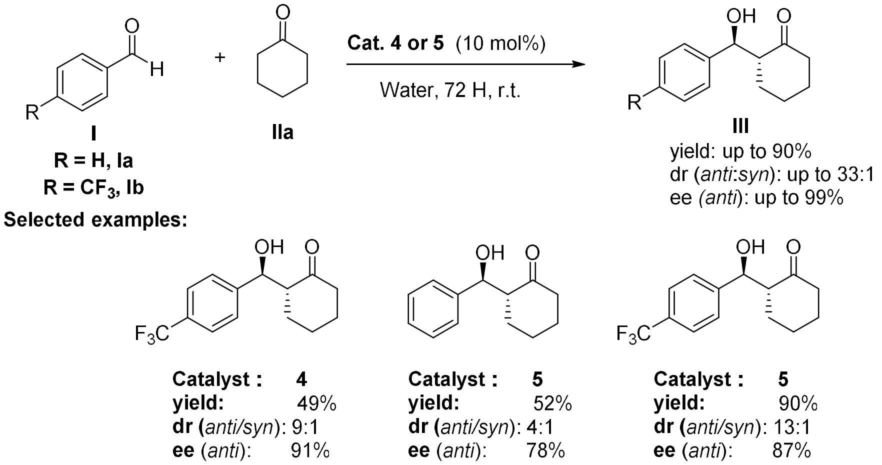


Figure 6: Catalytic activity of MNPs-Cat-4 & 5 in ADA reaction by Pericàs *et al.*, 2019 [47].

Interestingly, the catalytic assemblies can be readily disassembled in organic media, and the authors used recovered nanoparticles as chemical shuttles to re-complex with another substituted catalytic unit. The both catalysts were also recyclable but the catalyst **5** found to be more stable under the reaction as well as work up conditions and remained active up to 3 consecutive cycles without any significant loss of enantioselectivity. (Table 4) [47].

Table 4: Recycling of the catalysts 4 and 5 in the ADA reaction of Ib with IIa [47].

Catalyst	Cycle	Yield (%)	dr (*anti/syn*)	ee (*anti*) (%)
4	1	32	9:1	92
	2	17	9:1	93
	3	traces	6:1	91
	4	traces	6:1	92
5	1	89	14:1	89
	2	57	10:1	87
	3	35	5:1	85

In 2019, Tai *et al.* prepared several silica-coated MNPSCOCs, MNPs-Cat-**6** to **11,** from the derivatives of chiral amine, Pro-Glu or cyclohexyl-1,2-diamine (Fig. 5) and their bifunctional enamine activities were examined in the ADA reaction [48].
They observed that MNPs-Cat-**11** with the largest macrocyclic ring and the longest aliphatic chain provided best selectivities (up to 96% ee) (Fig. 7). The authors explained the results with '*macrocyclic effect'*. The MNPs-Cat-**11** was also found to recyclable up to 3 runs [48].

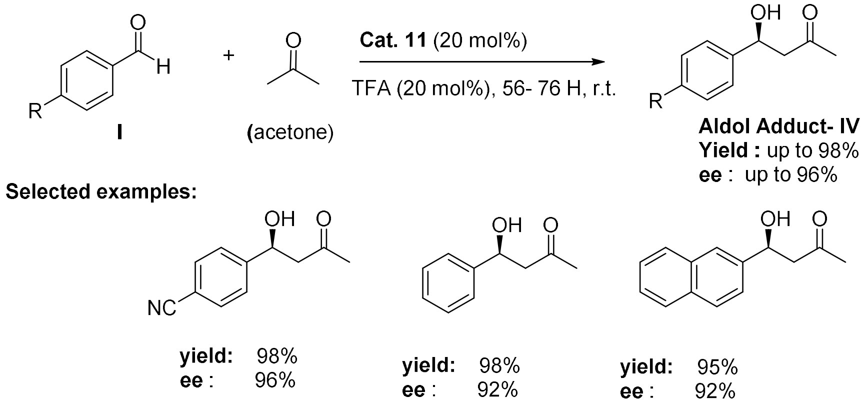


Figure 7: Catalytic performance of MNPs-Cat-11 in ADA reaction, Tai *et al.*, 2019, [48].

In 2020, Dai *et al.* made L-Pro-based thermal and magnetic dual-responsive nano-hybrids supported MNPs-Cat-**12.** The catalyst **12** was synthesised by thiol-ene click chemistry [49]. A synthetic diagram for the preparation of catalyst is represented in Figure 8.

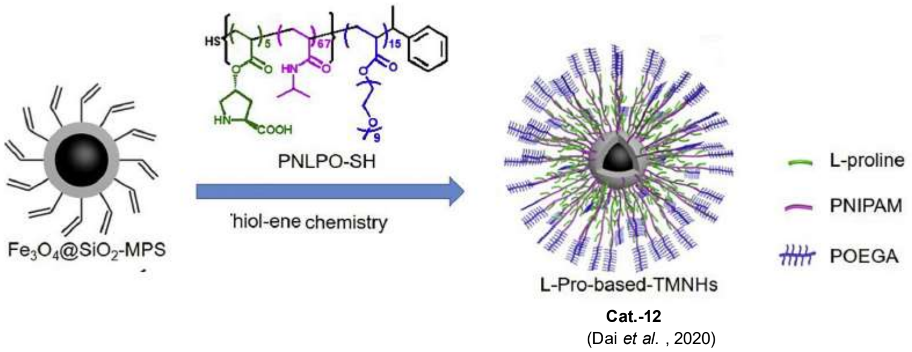


Figure 8: Schematic representation of the synthesis MNPs.Cat.-12 in ADA reaction.[49]

The catalytic activity of the synthesized catalyst was successfully evaluated in ADA reaction between cyclohexanone and 4-nitrobenzaldehyde in aqueous medium. Thermal-responsive L-Pro-based-TMNHs-**cat.-12** shown good catalytic activity and selectivity above LCST (lower critical solution temperature), which was explained by the shaping of hydrophobic aggregates to collect organic reactants and forming a hydrophobic micro-environment for specific organic synthesis [50, 51].

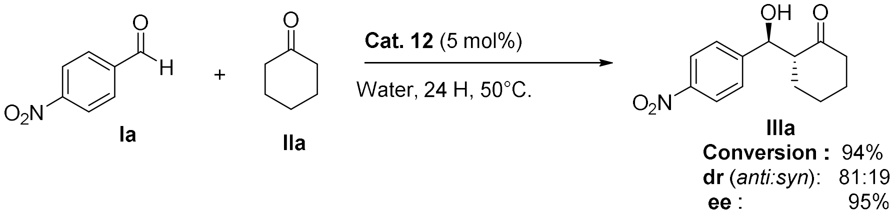
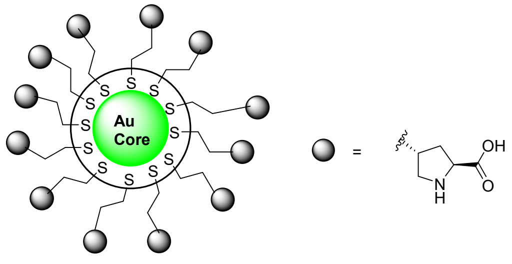


Figure 9: Catalytic performance of the MNPs-Cat-12 in ADA reaction, Dai *et al.* 2020 [49].

The Magnetic responsive L-Pro-based-TMNHs- Cat-**12** was found very efficient even after ten recycling run [52].

II.c. GOLD NANOPARTICLES SUPPORTED CHIRAL ORGANOCATALYSTS (GNPSCOCS) IN ASYMMETRIC ALDOL REACTION

Gold nanoparticles have also been attracted the attention of many chemists for their remarkably efficient catalytic properties [53-56]. It can also be used as supporting agent to prepared various recoverable and recyclable organo-catalyst. There are many examples of the application of GNPSCOCs in diverse organic reactions [57]. These articles will focus only on the recent application of GNPSCOCs in asymmetric aldol reaction.
In 2016, Mase *et al.* prepared a self-assembling gold nanoparticle (GNPs)-supported L-proline derivative **GNPs-Cat-13** through one-phase modified Brust–Schiffrin method from chloroauric acid and 4-hydroxy-L-proline (Fig.10) [58].



GNP- Cat-13

(Mase *et al.*,2016)

Figure 10: GNP-supported L-proline Cat-13 as organocatalysts by Mase *et al.*, 2016 [58].

Catalytic activity of **GNPs-Cat-13** was successfully evaluated in ADA reaction. The catalyst demonstrated high catalytic activity and in most cases, it was observed that the reactions afforded the *anti*-aldol products with high to excellent diastereo- and enantioselectivities. (Yields: up to 99%, dr (*anti:syn*): 91:9 & ee (*anti*): up to 89 (Fig. 11) [58].

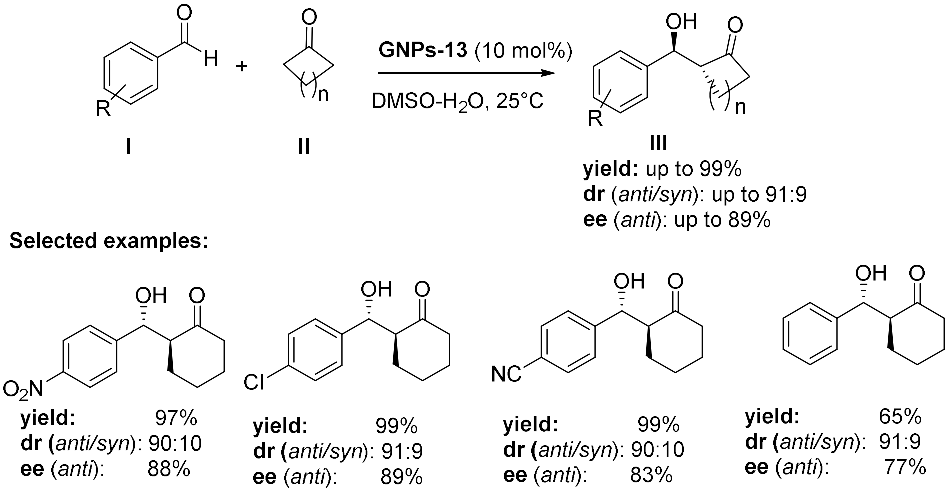


Figure 11: GNPs-Cat-13 catalyzed ADA reaction reported by Mase *et al.*, 2016 [58].

This catalyst, **GNPs-Cat-13** was recycled up to five consecutive cycles maintaining outstanding activity and selectivity. The GNPs catalyst having colloidal properties aggregates on change in dielectric constant of the reaction medium and the reaction mixture turns into heterogeneous. The **GNPs-Cat-13** was easily recovered from the reaction mixture by centrifugation followed by decantation after adding EtOAc in the reaction mixture (Table 5).

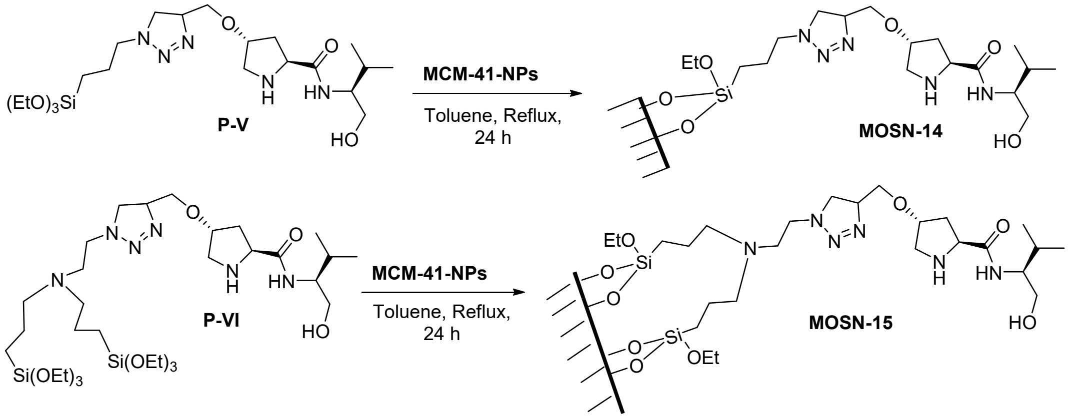
Table 5: Recycling of GNPs-Cat-13 in ADA reaction of p-NBA & Cyclohexanone [58].

Cycle	Yield (%)	dr (*anti/syn*)	ee (*anti*) (%)	Recovery (%)
1	97	90:10	88	>99
2	98	91:9	88	>99
3	98	91:9	88	>99
4	98	92:8	88	>99
5	98	92:8	88	>99

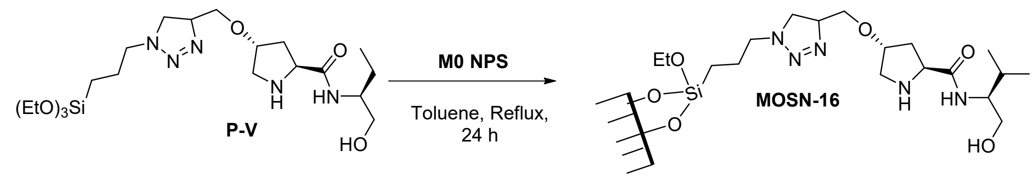
II.d. MESOPOROUS ORGANOSILICA NANOPARTICLES SUPPORTED CHIRAL ORGANOCATALYSTS IN ADA REACTION

In 2019, Pleixats *et al.* prepared several eco-friendly mesoporous organosilica nanoparticles supported chiral organocatalysts **MOSN- 14 - MOSN-19** from mono- and bis-silylated proline-valinol amides (Fig.-12) [59].

Preparation of Organosilica Nanoparticles derived catalyst- MOSN-14 & MOSN -15 :

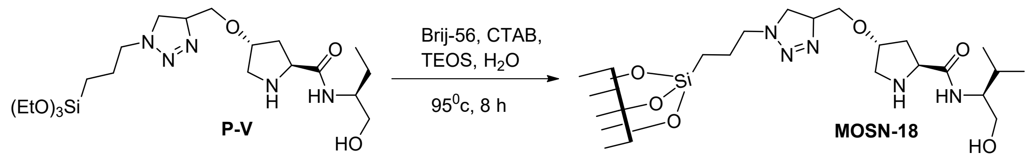


Preparation of Organosilica Nanoparticles derived catalyst- MOSN-16 & MOSN - 17 :



MOSN-17 was prepared in analogous manner from **P-VI.**
(M0 NPS were synthesized in an aqueous buffer solution of pH 7 from a mixture with the following molar ratios: Brij-56:CTAB:TEOS:H_2O = 7:20:160:120 000).

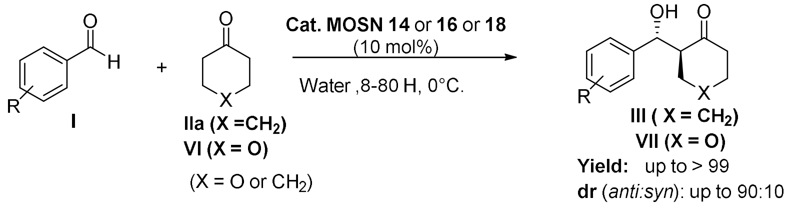
Preparation of Organosilica Nanoparticles derived catalyst- MOSN- 18 & MOSN - 19 :



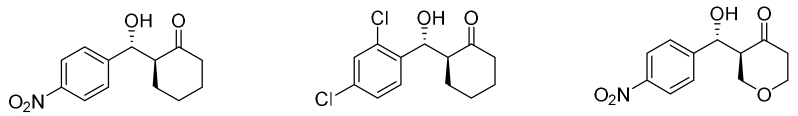
MOSN-19 was prepared in analogous manner from **P-VI.**

Figure 12: Schematic preparation of MOSN-14- MOSN-19 reported by Pleixats *et al.*[59].

The authors examined the catalytic activity of these silica supported nanocatalysts **MOSN-14 to MOSN -19** in the ADA reaction. They found that the organo-nanocatalysts derived from mono silylated precursors were more active than that of bis-silylated one. According to the authors, the chiral moiety present in the bis-silylated derived catalysts **MOSN-15, MOSN-17 and MOSN-19** have less flexibility which limits their catalytic activity and selectivity. The mono silylated precursor derived catalyst **MOSN-14** and **MOSN-18** were found most active in ADA reaction leading to excellent yield and selectivity. Comparative results were summarized in the figure below (Fig. 13).



Selected examples:



Cat. MOSM:	14	16	18	14	16	18	14	16	18
Yield (%):	>99	>99	>99	97	95	98	>99	>99	>99
dr (*anti:syn*):	89:11	85:15	89:11	81:19	83:17	84:16	88:12	90:10	89:11
ee (*anti*):	82	62	84	84	82	90	80	86	90

Figure 13: Catalytic performances of the catalysts MOSN-14, MOSN-16, and MOSN-18 [59].

The **MOSN** catalysts could easily be separated by decantation after centrifugation. The recovered catalysts also showed excellent performances in the ADA reaction between cyclohexanone and *p*-nitrobenzaldehyde up to five recycles (Table 6) [59].

Table 6: Recycling of MOSN 14 in ADA reaction between *p*-NBA and cyclohexanone [59].

Cycle	Yield (%)	dr (*anti/syn*)	ee (*anti*) (%)
1	>99	89/11	82
2	>99	88/12	78
3	>99	89/11	80
4	>99	89/11	82
5	>99	89/11	82

III. CONCLUSION

The application of nanoparticles supported chiral organocatalsysts (NPSCOCs) in asymmetric aldol reaction were discussed throughout the article, In all cases moderate to excellent yields, diastereo-selectivities and enantioselectivities were obtained during the catalytic activity evaluation test of the supported catalyst in ADA reaction. The catalysts were easily separated from the reaction mixture and recycled several times without any major loss in activity or selectivity as well as catalytic efficiency. In some cases, immobilization or grafting of chiral organocatalyst on nanoparticles led to improve catalytic activity. Interestingly, in most cases, a significantly improved eco-friendly procedure was developed. But, there are lots to progress in this field. More vigorous studies are required to develop more competent protocols that can be used in pharmaceutical industry.

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