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Review on the Recent Development of Asymmetric Aldol Reaction using Polymer Supported Chiral Organocatalysts

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Abstract

Asymmetric organocatalysts have been comprehensively studied from the early 2000's as alternatives to transition-metal catalysts. The remarkable potential of asymmetric organocatalysis for preparing enantiopure compounds is well-recognized. However, non-recyclability of organocatalysts and high catalyst loading in organocatalysis were big problem. Immobilization of chiral organocatalysts on polymer supports leads to easy recyclability of the catalysts and trouble-free purification of the product after competition of a reaction. These also confirm from the recent reports that describe the advantages of using polymer as supporting agent for organocatalysts. Asymmetric Aldol reactions which were widely studied in asymmetric organocatalysis using non-supported organocatalysts have been reviewed in this article to emphasize the potential of polymer supported organocatalyts.

KEYWORDS: Asymmetric Aldol reaction, Chiral Organocatalysts, Polymer supported, Stereoselectivity

INTRODUCTION

Organocatalysis is tremendously growing area in the stereoselective organic synthesis. It is the most useful tool for the synthesis of valuable enantio-enrich compounds.[1] It is a metal-free substitute to the commonly used organometallic catalysts. Generally, organocatalysts are stable towards moisture and oxygen, easy to handle, easily accessible and cost-effective compounds. But, it has some disadvantages, such as the high catalyst loadings (up to 30 mol %) is required and difficulty to recover the catalysts from reaction mixture.

One feasible approach to solve these problems would be the heterogenization of organocatalysts. In fact, the immobilization of asymmetric transition metal catalysts and enzymes catalyst have been widely explored to improve their practicability and applicability. Likewise, the immobilization of organocatalyst has also been frequently attempted prior to its renaissance in the early 2000.[2] The immobilization of organocatalyst can be achieved either using solid support for heterogeneous system or using non-solid support for homogeneous system. Interestingly, polymer can be used as support to prepare both heterogeneous and homogeneous type immobilized organocatalysts. Therefore, polymer supported organocatalysts have been widely prepared to facilitate recoverability and reusability of the catalyst.

Insoluble cross-linking polystyrene derived polymeric supports remains insoluble throughout a reaction. The so synthesized supported catalysts can be separated by a simple filtration or decantation after the reaction. However, the insolubility of such supports may create other problems like difficult in catalyst characterization and reduction in catalyst reactivity.[3-7] In contrary, soluble polymer-bound organocatalysts can be easily characterized by solution-state spectroscopy and it can demonstrate the same reactivity as their low-molecular-weight analogs. But, soluble polymer-supported organocatalysts generally remain in the solution of product and it have to be separated other ways. For example, separations of a soluble polymer-supported catalysts and a low molecular-weight product can be achieved using permselective membranes based on their molecular size.[8] However, this technique is not popularly used for recovery of the soluble polymer supported catalysts. The most commonly used technique is making the solution into biphasic mixture followed by gravity separation [9] or precipitating the polymer supported catalysts using excess volume of poor solvent followed by filtration or centrifugation.

Aldol reaction is enormously used to prepare various derivatives in pharmaceutical chemistry. So, asymmetric aldol reaction becomes very important in this area. The study on the organocatalyzed asymmetric aldol reaction has been tremendously progressed.[10] Hence, the focus of this review article is to highlight the recent progress on the application of polymer supported chiral organocatalyst (PSCOC) in asymmetric aldol reaction.

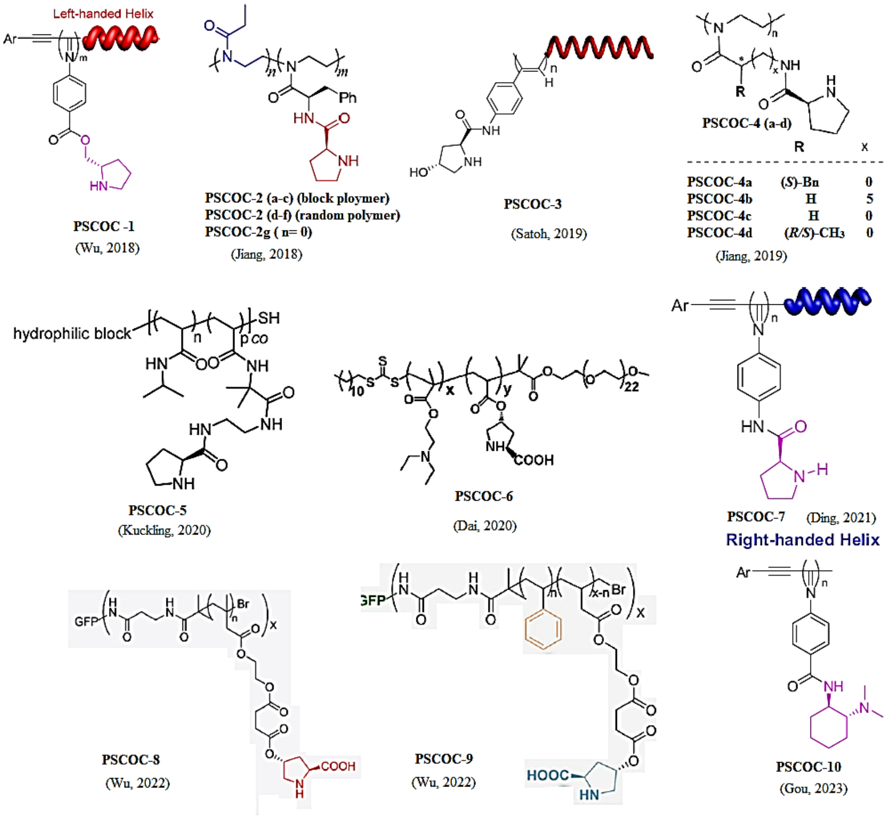
Discussions on Polymer Supported Chiral Organocatalysts (PSCOCs) in Asymmetric Aldol Reactions

The use of polymer as supporting agent gradually became very popular in wide verities of catalysts to improve their efficiency through recycling and reusing process in catalysis.[11] The prospective economic as well as green chemistry advantages of this approach have led to many reports describing the activity of polymer-supported organocatalysts in asymmetric aldol reaction. But, this review article will focus only those reports that have been published only last five years.

In 2018, Wu *et al*. developed a series of helical polyisocyanide-based supported L-prolinol ester containing active catalysts (Figure 1).[12] Interestingly, the left-handed helical polymer showed amplification property in the designed supported chiral organocatalyst (COC). The supported catalysts showed higher stereoselectivity compared to the active small chiral organocatalysts in asymmetric Micheal addition reaction and showed excellent stereoselectivity and activity. The polyisocycanide based static helical polymer supported organoatalyst **PSCOC-1** also has better environmental stability with the ability to maintain its helicity in various solvents even at an elevated temperature. The catalyst **PSCOC-1**, which was mainly evaluated in Michael addition reaction, also afforded high stereoselectivity in asymmetric direct aldol (ADA) reaction between *p*-cyanobenzaldehyde (*p*-CBA) and cyclohexanone (CyH) (yield: 83%, ee: 99%, dr: 99/1) (Table 1). The polymer supported catalyst **PSCOC-1** found to be easily recoverable and reusable more than five times without any significant loss in stereoselectivity and its activity.

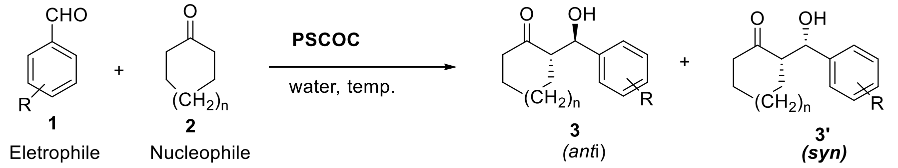
In the mean time, Jiang *et al*. reported a series of amphiphilic polymer supported catalysts **PSCOC-2(a-g)** derived from poly(2-oxazoline) derivatives containing a L-prolinamide pendant (Figure 1).[13] The catalysts were synthesized through a controlled cationic ring-opening polymerization followed by post-modification strategy. Among the synthesized amphiphilic catalysts, the block copolymer supported catalyst **PSCOC-2c** showed best activity (yield up to 99%) and stereoselectivity (90/10 dr, 86% ee) in ADA reaction (Table 1), which was explained by micellar effect of the catalysts.

Figure 1: Polymer supported catalysts evaluated in ADA reactions (2018-2023)



In 2019, Satoh *et al.* developed a new water-soluble one-handed helical poly(phenylacetylene) **PSCOC-3** containing L-hydroxyproline pendants (Figure 1). The authors found that the Cotton effect patterns of the polymer varies significantly depending on the solvent composition.[14] The catalyst **PSCOC-3** was evaluated on asymmetric aldol reaction between *p*-nitrobenzaldehyde (*p*-NBA) and cyclohexanone (CyH) at various conditions and showed outstanding stereoselectivity (ee (*anti*): 99%, dr (*anti:syn*):99:1) with moderate activity (yield: up to 54%) in an eco-friendly aqueous media (Table 1). Noticeably, one handed helical polymer catalyst **PSCOC-3** showed better selectivity than the monomer analogue at the same reaction conditions. The improved results were explained by a *synergistic effect* of the macromolecular helicity with L-hydroxyproline pendants in the catalyst **PSCOC-3** in aqueous media.

Table 1: Asymmetric aldol reaction catalyzed by various polymer supported chiral organocatalyst (PSCOC).

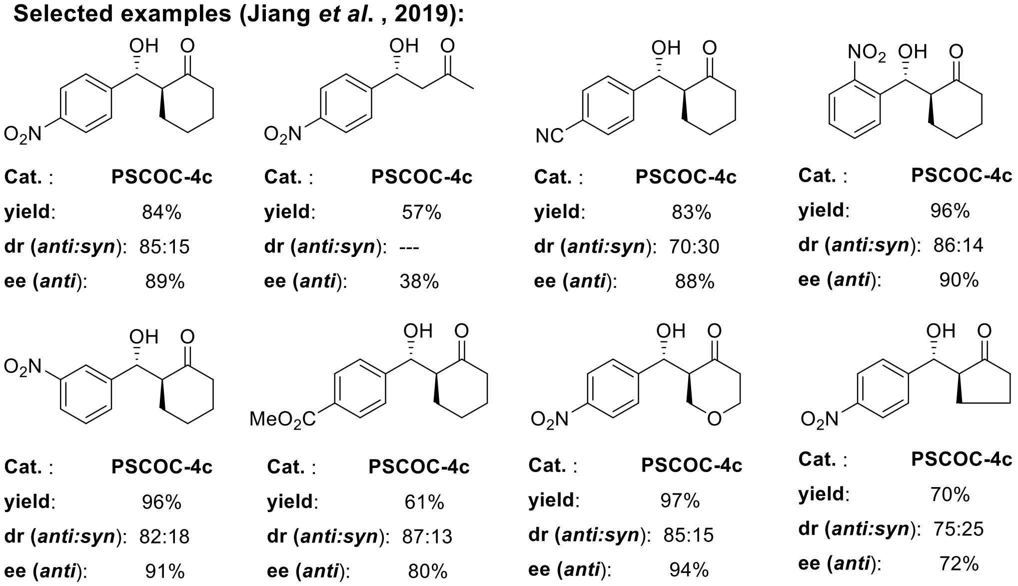


Sl. No.	Catalyst (PSCOC)	Acceptor*	Donor*	Yield (%)	dr (*anti:syn*)	ee (*anti*) (%)	Ref.*
1	**1**	*p*-CBA	CyH	83	99:1	99	12
2	**2c**	*p*-NBA	CyH	96	9:1	86	13
3	**3**	*p*-NBA	CyH	54	99:1	99	14
4	**5**	*p*-NBA	CyH	up to 83	up to 85:15	up to 82	16
5	**6**	*p*-NBA	CyH	up to 91	up to 92:8	up to 96	17

**p*-CBA- *p*-cyanobenzaldehyde; *p*-NBA- *p*-nitrobenzaldehyde; CyH-Cyclohexanone; Ref. -Reference

At the same time, Jiang et al. reported a series of poly(2-oxazoline) derivative supported organocatalyst PSCOC-4(a-d) bearing prolinamide as pendant (Figure 1).[15] The catalysts were assessed in ADA reaction between various aromatic aldehydes (electrophile) and cyclic ketones/acetone in aqueous solution. The authors observed that the catalytic activities of the catalysts were highly influenced by the length of the alkyl linker and its substituents. Among the supported prolinamide catalysts, PSCOC-4c with short alkyl chain demonstrated best catalytic activity and stereoselectivity (Figure 2). The PSCOC-4c could be recovered from the reaction mixture by precipitation in ether and recycled up to five consecutive cycles providing reproducible stereoselectivities in the model ADA reaction between p-NBA and Cyclohexanone (Table-2).

Figure 2: Performances of PSCOC-4c in ADA reaction by Jiang *et al.,*2019. [15]


Selected examples (Jiang *et al.* , 2019):

Cat. :	**PSCOC-4c**	**Cat.** :	**PSCOC-4c**	**Cat.** :	**PSCOC-4c**	**Cat.** :	**PSCOC-4c**
yield:	84%	**yield**:	57%	**yield**:	83%	**yield**:	96%
dr (***anti:syn***):	85:15	**dr** (***anti:syn***):	---	**dr** (***anti:syn***):	70:30	**dr** (***anti:syn***):	86:14
ee (***anti***):	89%	**ee** (***anti***):	38%	**ee** (***anti***):	88%	**ee** (***anti***):	90%
Cat. :	**PSCOC-4c**	**Cat.** :	**PSCOC-4c**	**Cat.** :	**PSCOC-4c**	**Cat.** :	**PSCOC-4c**
yield:	96%	**yield**:	61%	**yield**:	97%	**yield**:	70%
dr (***anti:syn***):	82:18	**dr** (***anti:syn***):	87:13	**dr** (***anti:syn***):	85:15	**dr** (***anti:syn***):	75:25
ee (***anti***):	91%	**ee** (***anti***):	80%	**ee** (***anti***):	94%	**ee** (***anti***):	72%

Table 2: Recycling experiment of PSCOC-4c in ADA reaction. [15]

Acceptor	Donor	Cycle	Yield (%)	dr (*anti:syn*)	ee(%)
P-NBA	CyH	1	86	76:24	88
		2	85	80:20	90
		3	85	81:19	91
		4	82	84:16	89
		5	79	87:13	92

In 2020, Kuckling *et al.* developed three different polymer supported L-prolinamide catalysts, **PSCOC-5**, using thermo-responsive block copolymer (TBC) based hydrophilic blocks (Figure 1).[16] Theses catalysts were successfully evaluated on ADA reactions between *p*-NBA and CyH in aqueous media. The TBC based catalysts exhibited poor to moderate activity and selectivity (Table 1).

In the same period, Dai *et al*. prepared a series of pH-responsive polymer supported L-proline catalysts **PSCOC-6** via RAFT polymerization process (Figure 1).[17] The catalysts were successfully tested on ADA reaction and showed best catalytic activity at pH 7 at an optimized hydrophilic to hydrophobic composition ratio of the catalyst (dr (*anti:syn*): 92:8); ee (*anti*): up to 96%, yield: up to 91%) (Table 1). All the newly designed polymer supported catalysts showed better activity and selectivities compared to 4-hydroxy-L-proline at pH 7. Interestingly, the catalyst was also maintained high stereoselectivity even after five recycling process (Table 3).

Table 3: Recycling experiment with PSCOC-6 by Dai *et al.*, 2020. [17]

Acceptor	Donor	Cycle	Conversion (%)	dr (*anti:syn*)	ee (*anti*) (%)
p-NBA	CyH	1	92	92:8	96
		2	85	89:11	93
		3	79	91:9	96
		4	61	90:10	95

In 2021, Ding *et al*. reported a series of right-handed helical poly(phenyl isocyanide)-supported chiral organocatalyst **PSCOC-7** bearing L-proline pendants (Figure 1).[18] Helical polymer catalysts **PSCOC-7** exhibited superior stereoselectivity in ADA reaction compared to the non-supported L-proline catalyst under the optimized conditions in brine. The supported catalyst **PSCOC-7** showed very good catalytic activity and high stereoselectivity in ADA reaction between cyclohexanone and various aromatic aldehydes (dr (*anti:syn*) – up to > 20:1 and ee (*anti*): up to 90%) (Figure 3). The catalyst **PSCOC-7** can effortlessly be recovered and reused for at least five cycles without drastic change in reactivity and selectivity (Table 4).

Figure 3: Reported results of selected aldol adducts by Ding *et al.*, 2021. [18]

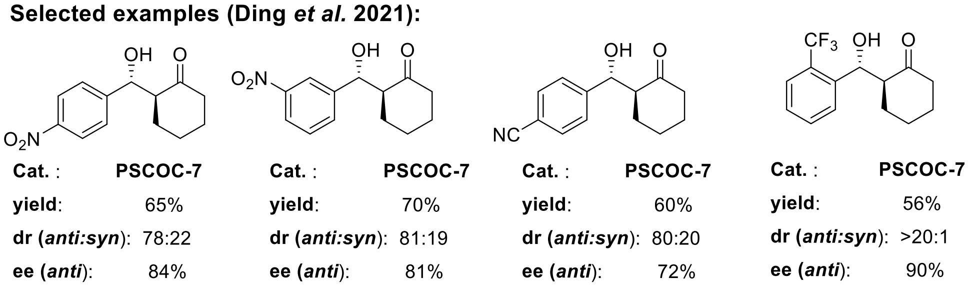
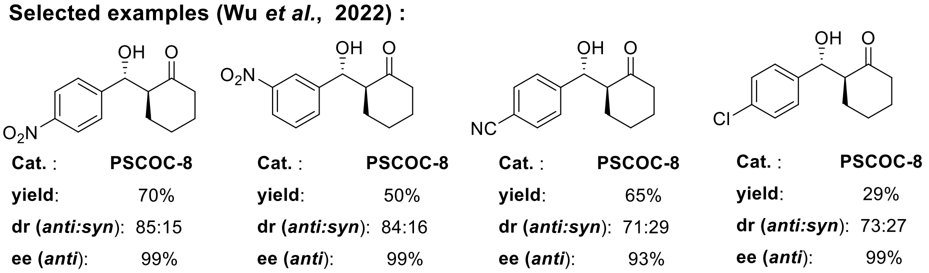


Table 4: Recycling experiment with PSCOC-7 by Ding *et al.*, 2021.[18]

Electrophile	Nucleophile	Cycle	Yield (%)	dr (*anti:syn*)	ee(%)
p-Nitrobenzaldehyde	Cyclohexanone	1	65	78:22	84
		2	64	75:25	84
		3	65	80:20	83
		4	63	79:21	83
		5	63	77:23	82

In 2022, Wu *et al*. prepared an interesting polymer supported catalyst **PSCOC-8** that can mimic enzymes. They developed an artificial enzymes type catalysts by combining polymers of proline and proteins (Figure 1).[19]

Figure 4: Results of some Aldol adducts reported by Wu *et al.*, 2022 .[19]



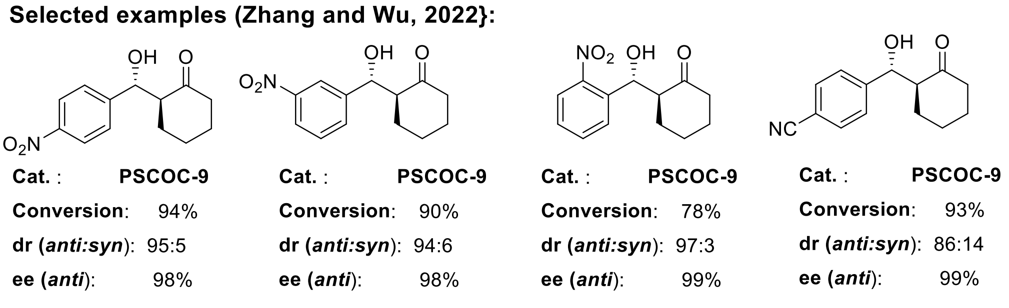
Selected examples (Wu *et al.*, 2022) :

Cat. : **PSCOC-8**	**Cat.** : **PSCOC-8**	**Cat.** : **PSCOC-8**	**Cat.** : **PSCOC-8**
yield: 70%	**yield**: 50%	**yield**: 65%	**yield**: 29%
dr (*anti:syn*): 85:15	**dr (*anti:syn*)**: 84:16	**dr (*anti:syn*)**: 71:29	**dr (*anti:syn*)**: 73:27
ee (*anti*): 99%	**ee (*anti*)**: 99%	**ee (*anti*)**: 93%	**ee (*anti*)**: 99%

This artificial polyenzyme **PSCOC-8** was fairly water soluble and exhibited acceptable activity with good to excellent stereselectivity in ADA reaction of various aromatic aldehydes and cyclohexanone (dr (*anti:syn*): up to 88:12, ee(*anti*): up to 99%) (Figure 4).[19]

In the mean time, the authors extended the concept to prepare a better artificial aldolase and developed a tailored protein polymer conjugate, **PSCOC 9** (Figure 1).[20] As expected, the synthesized tailored conjugate catalyst **PSCOC 9** were more active than the previously developed **PSCOC 8**. The catalytic activity of the derived catalyst increased many fold and promoted the conversion in the ADA reaction up to 94% with excellent enantioselectivity (Figure 5) and the **PSCOC 9** was recyclable up to four cycles keeping the performance intact. Besides these, the newly designed artificial aldolase exhibited wide pH range tolerance against extreme conditions (high temperature).

Figure 5: Important aldol adducts reported by Zhang and Wu, 2022. [20]

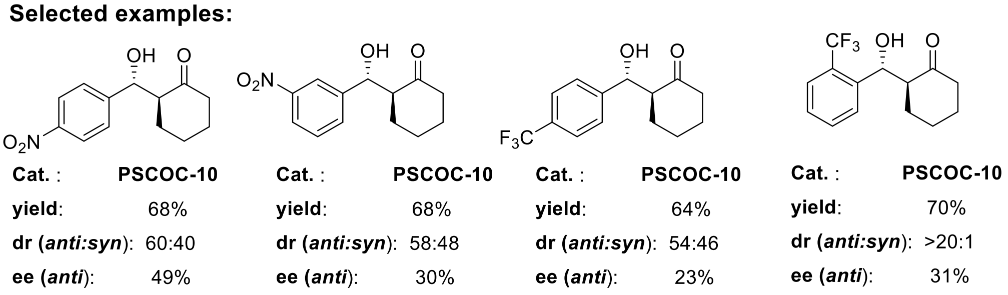


Selected examples (Zhang and Wu, 2022}:

Cat. : **PSCOC-9**	**Cat.** : **PSCOC-9**	**Cat.** : **PSCOC-9**	**Cat.** : **PSCOC-9**
Conversion: 94%	**Conversion**: 90%	**Conversion**: 78%	**Conversion**: 93%
dr (*anti:syn*): 95:5	**dr (*anti:syn*)**: 94:6	**dr (*anti:syn*)**: 97:3	**dr (*anti:syn*)**: 86:14
ee (*anti*): 98%	**ee (*anti*)**: 98%	**ee (*anti*)**: 99%	**ee (*anti*)**: 99%

Very recently, in July, 2023, Gou *et al*. developed few novel helical poly(phenylisocyanide) derived polymer supported catalyst **PSCOC-10** bearing chiral (1*R*,2*R*)-1,2-cyclohexanediamine pendant (Figure 1).[21] The Chiral cyclohexanediamine polymer supported catalysts **PSCOC-10** demonstrated good catalytic activity with moderate stereoselectivity in ADA reaction between various aldehydes and cyclohexanone (dr (*anti:syn*): up to >20:1 and ee (*anti*): 49%) (Figure 6). The catalysts showed excellent performances in Asymmetric Michael addition reaction also.

Figure 6: Enantio-enrich Aldol adducts reported by Gou *et al.*, 2023 [21]



CONCLUSION

This article revisits the recent reported literature regarding polymer supported organocatalysts catalyzed ADA reaction. Most of the discussed catalysts are more active as well as better stereoselective compared to the non-supported chiral organocatalysts. Most importantly, the supported catalysts can be recycled and reused up to five times suggesting that the strategies partially fulfill the demand in respect of easy catalysts separation, reusability and development of environmentally benign conditions. But, a lot of improvement is required in the recoverability, stability of the supported catalyst in drastic conditions, need to decrease in catalyst loading, increase in turnover number, etc. Besides, new type of reactions should also be evaluated using the newly designed polymer supported organocatalysts.

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