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Review on the Application of Covalently Linked Ionic Liquid supported chiral Organocatalysts in Aldol Reactions

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Abstract

Asymmetric organocatalysis becomes indispensible part for asymmetric synthesis. The tremendous potential of asymmetric organocatalysis for preparing enantiopure compounds is well-known. However, non-recyclability of organocatalysts was a big issue. Different types of immobilized organocatalysts including ionic liquid supported (ILS) immobilized organocatalysts provided some advantages. Homogeneous ILS organocatalystswere synthesized from varieties of chiral organic compounds and utilized in diverse type of asymmetric reactions. Asymmetric Aldol reactions which were extensively studied in diverse unsupported organocatalysis were also tested in asymmetric aldol reactions using chiral ionic liquid supported homogeneous organocatalysts. This review highlights on the advancement of asymmetric aldol reactions using covalently linked ionic liquid supported recyclable organocatalysts.

KEYWORDS: Asymmetric organocatalysis, Homogenous, Supported Ionic liquid, Recyclable, Aldol reaction

INTRODUCTION

Asymmetric organocatalysis is massively growing area over the last twenty two years.[1] It has been successfully explored in various types of asymmetric reactions such as aldol [2], aza-Henry [3], Michael [4], Henry [5], Diels-Alder [6], Povarov [7], Friedel-Crafts [8] reactionsand manymore. Since, this catalysis is completely devoid of metal, it is an attractive choice for the preparation of medicinal ingredients in pharmaceutical industry. Besides, organocatalysts are easy to prepare, stable towards oxygen and moistures, easy to use and environmentally benign. However, a major disadvantages of asymmetric organocatalysis is low effectiveness of the catalysts as most of the cases high catalyst loading (Generally, 10-30 mol%) is required [9]. Non-recyclability of organocatalysts is another important drawback in asymmetric organocatalysis. So, keeping the cost of the catalysts in mind and possible agglomeration and aggregation in the reactions, concept of immobilization of catalysts and reusable catalysts preparation have been grown up to recycle catalysts with the development of new catalysts for the stereoselective synthesis.

The recyclability of catalysts can be accomplished 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 media by simple filtration; but it may slower the reaction rate. However, a soluble support may or may not change the reaction rate, but it requires an additional step to be recovered. There are various types of supported materials such as, magnetic, silica, ionic resin, gold, polymer and fluorous supports for immobilized reusable organocatalysts.

After discovery of ionic liquid in 1914 [10], it progressively becomes an indispensible part of chemistry in different ways [11]. Ionic liquids (ILs) can be defined as organic salts which have melting points normally below 100ºC, though ILs can also have melting point as much as 200ºC [11]. So, it is widely used as environmentally friendly solvent in various organic reactions [11].

Over the preceding two decades, ILs have also been employed as supporting agent to prepare homogenous organocatalysts for chemical transformation [12]. Generally, ionic liquid supported organocatalystsare utilized in homogenous catalysis to induce organic transformations in polar solvents. After completion of each reaction, the products are extracted using less polar solvents like diethyl ether and the ionic liquid supported organocatalyst remains in the reaction medium due to its high polarity and thus, IL based immobilizedorganocatalyst can be reused and recycled for several times [12].

Asymmetric Aldol reaction has great attention in pharmaceutical chemistry as the aldol moiety is present in numerous biologically active compounds [13]. 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 [14]. Recently, several reviews on immobilized organocatalysts with IL have been published with emphasizing on the synthesis and general applications [11, 12]. But, there is no reported review literature on the use of covalently linked ionic liquid supported (CILS) organocatalysts on asymmetric aldol reaction. Here, this review will focus on the progress of the covalently linked ionic liquid-supported (CILS) reusable chiral organocatalysts and their applications on asymmetric aldol reactions.

COVALENTLY LINKED IONIC LIQUID IMMOBILIZED CHIRAL ORGANOCATALYSTS IN STEREOSELECTIVE ALDOL REACTIONS

Ionic liquids have various distinctive properties like non-flammability, having very low vapor pressure, superior chemical and thermal stabilities, high density, etc.

which makes them ideal polar environmentally friendly solvents for various chemical transformations [11, 12].

Besides, their characteristics can be easily regulated by changing structures of their anions and cations. These properties make them easily separable from aqueous media as well as organic phase. This distinctive properties make them good choice as a soluble supporting agents for immobilization of organocatalysts. There exist countless research articles involving utilizations of ionic liquids as reaction media or chiral ILs as additives, media or catalysts for asymmetric aldol reactions [11, 12]. The strategy of this review article relies on asymmetric aldol reactions using covalently linked ionic liquid supported (CILS) organocatalysts.

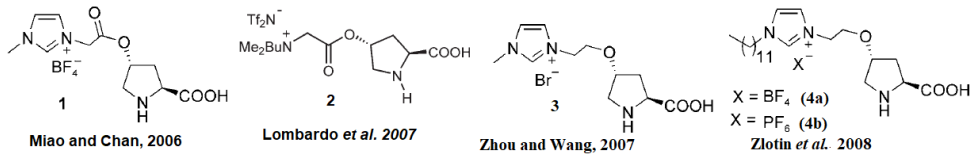
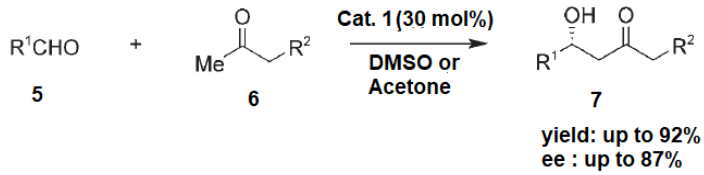


Figure 1: Covalently linked ILS proline catalysts 1-4 [15-18]

In 2006, Miao and Chan synthesized two ionic liquid supported (ILS) proline derivatives and evaluated them in asymmetric aldol reactions (Scheme 1). They observed that supported catalyst **1** (Figure 1) was very efficient to provide better yield and stereoselectivies under neat conditions than in DMSO Catalyst **1** was also found to give superior results than unsupported proline catalyst. It could also be recycled and reused for the same reaction up to four times without significant deviation of enantioselectivities [15].

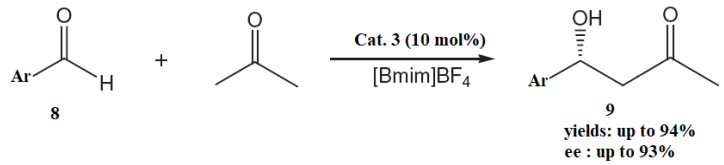


Scheme 1: CILS catalyst 1 catalyzed aldol reaction.

In 2007, Lombardo et al. reported few highly efficient “onium ion tagged proline” derivatives and evaluated them in asymmetric cross aldol reactions. Catalyst **2** was the most active and stereoselective (Figure 1).But, itwas very difficult to recover and was also not very efficient in recycled phase [16].

In the same year, Zhou and Wang synthesized ILS catalyst **3** from proline derivative connected through an ether linkage with the ionic liquid support imidazolium moiety (Figure 1). This catalyst was recyclable and found to afford good to excellent selectivities (ee up to 93%) in aldol reaction of acetone with a variety of aromatic

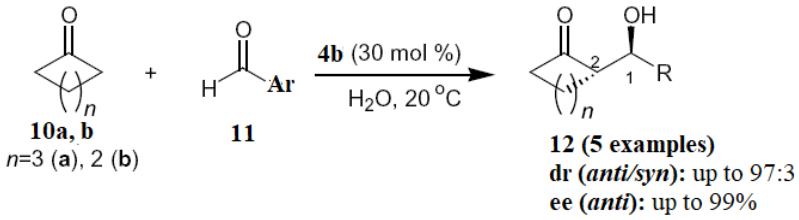
aldehydes (Scheme 2) [17]. The catalyst **3**was recovered and reused up to 6 times without significant deviation of enantioselectivities.



Scheme 2: Catalysts 3 catalyzed asymmetric aldol reaction

In same year, Luo and Cheng reported several covalently bonded ILS pyrrolidineorganocatalysts and evaluated them in asymmetric direct aldol reactions. But the catalysts were ineffective to provide good seteroselectivities [18].

Zlotin*et al*. used long chain hydrocarbon containing ionic liquid as supporting agent to immobilize proline derivatives, **4a-b** in 2008, (Figure 1). The amphiphilic catalysts **4a** and **4b** can efficiently accelerate asymmetric aldol reaction of various aromatic aldehydes with cyclic ketones in green solvent, water and gave high diastereoselectivities and enantioselectivities in presence of 30 mol% of catalysts (Scheme 3) [19]. The catalyst **4b** can be recycled up to 5 times without any deviation of stereoselectivities.



Scheme 3: CILS proline catalyst 4b in direct aldol addition reaction [19]

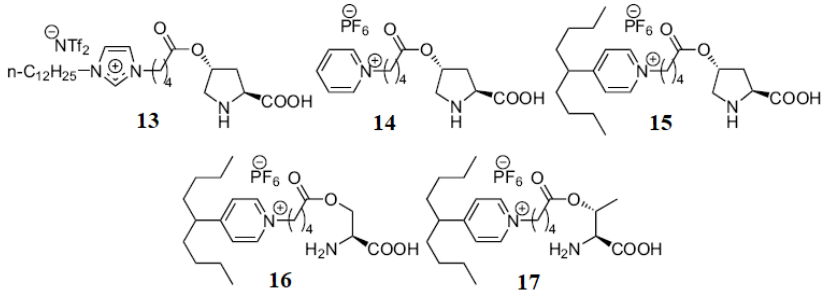
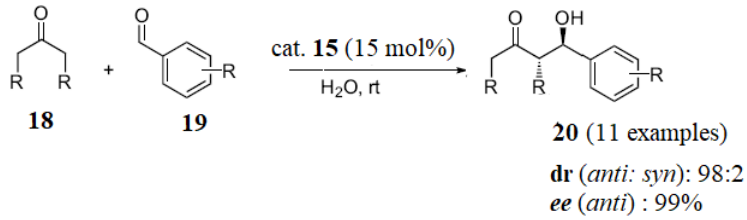


Figure 2: α-amino acids in CILS amphiphilic catalysts13-17, Zlotin*et al*. 2009 [20]

In 2009, the same group synthesized new ILS organocatalysts from proline, threonine, or serine derivatives, **13-17** (Figure 2), which were explored as eco-friendly organocatalysts for asymmetric aldol reactions of aromatic aldehydes with different ketones in aqueous solvent. The authors observed that catalyst **13** and **15**

(Figure 2) were more effective for both stereoselectivities (*dr*: up to 98:2; *ee*: up to >99%) and recyclability (Recycling: cat. **13** - two times and. cat. **15** - eight times without any loss of activities and stereoselectivities) [20].



Scheme 4: Asymmetric catalysis by CILS cat. 15, Zlotin*et al.*, 2009 [20].

Zlotin and coworkers also reported a number of new covalently linked ILS immobilized homogenous organocatalysts**20-28** (Figure 3) from 2010-2017. The majority of the chiral catalysts catalyzed aldol reaction with high activity in eco-friendly solvent, water, mimicking type I aldolese and provided excellent regioselectivities, stereoselectivities

(Table 1, entry 1-8).

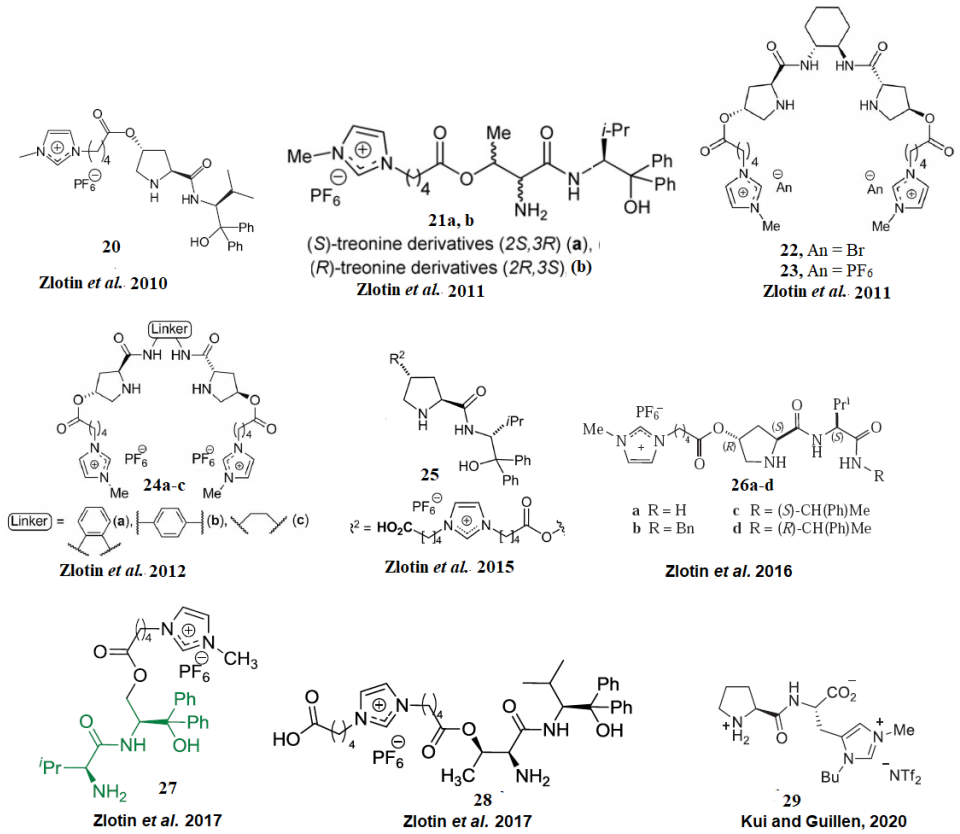


Figure 3: ILS organocatalysts reported by Zlotin*et al.* [21-28]

In 2010, ILS catalyst **20** was derived from prolinamide derivatives (Figure – 3) by Zlotin*et al*. and was found to be more efficient than catalysts having free carboxylic acid group, it demonstrated better yields, higher regioselectivities, diastereoselectivities (*anti:syn*– up to 99:1), enantioselectivities (ee (*anti*): up to 99%) and recyclability (up to 4 times with slightly poorer activity) in an eco-friendly water medium (Table 1, entry -1) [21].

In 2011, same authors prepared ILS novel recyclable catalysts **21a-b** (Figure – 3) from *α,α-(S*)-diphenylvalinol and (*S*)-threonine derivatives and utilized them for direct *syn*-aldol reactions of *α*-Hydroxyketones donors with aromatic aldehydes in toluene (Table 1, entry 2). The catalyst **21a** afforded *syn* aldol adducts with excellent yields and seteroselectivities (*syn/anti*- up to 97:3; ee (*syn*)- up to 99% ee). The catalyst showed drastically reduced activity during recycling (3 times) [22].

Table 1: Asymmetric Direct aldol reactions by ILS cat. 20-28, Zlotin*et al.*

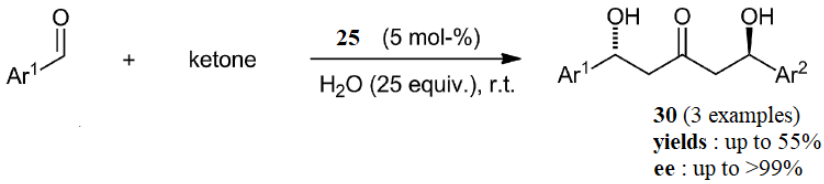
S. No.	Cat. (mol%)	Solv.	Carbonyl donors	Carbonyl acceptors	Conv. (%)	dr (*anti/syn*)	ee (%)	Recy. (No.)	Ref.
1	**20** (1)	H_2O	Cycloalk.	Ar. Ald..	96**	99:1	99 (*anti*)	4	21
2	**21a** (15)	Ph-Me	α-Hydroxyket.	Ar. Ald.	99**	3:97	99 (*syn*)	3	22
3	**23** (10)	H_2O	Cycloalk.&alk.	Ar. Ald	>99	93:7	99 (*anti*)	10	23
4	**24b** (10)	H_2O	Cycloalk.&alk.	Ar. Ald.	99	95:5	98 (*anti*)	15	24
5	**25** (5)	H_2O	Cycloalk.&alk.	Ar. Ald.	99**	96:4	> 99 (*anti)*	10	25
6	**26a, c** (10)	H_2O	Cycloalk.&alk.	Ar. Ald.	99	> 99:1	98(*anti)*	9	26
7	**27** (15)	Ph-Me	α-Hydroxyket.	Ar. Ald.	99	4:96	99 (*syn*)	9	27
8	**28** (15)	Ph-Me	α-Hydroxyket.	Ar. Ald.	99	4:96	99 (*syn*)	5	28

*Ar. - Aromatic Ald. – Aldehydes, Ket. – Ketones, alk. – alkanones Ref. – References, Cat. – Catalysts, Solv. – Solvent, Conv. – Conversions, Max. – Maximum, **isolated yield

In same year, the same authors reported a C_2-symmetric ILS organocatalysts**22** & **23** (Figure 3) from (1*R*, 2*R*)-bis[(*S*)-prolinamido]cyclohexane derivatives containing two

imidazolium cations for evaluating asymmetric aldol reactions [23]. They observed excellent stereoselectivities (*anti*/*syn*- up to 99:1 and ee (*anti*)- up to 99%) for a wide variety of cyclic or linear ketones to various aromatic aldehydes in presence of 10 mol% of catalyst **23** in water (Table 1, entry 3). Interestingly, the catalyst demonstrated outstanding performances up to 10 catalytic cycles with no reactivation [23].

In 2012, Zlotin*et al*. reported dicationicimidazolium supported C_2-symmetric prolinamide catalysts **24a-c** without chiral diamine units as linker (Figure 3) for stereoselective aldol reactions of diverse ketone donors aromatic aldehydes including heteroaromatic aldehyde acceptors in water. The catalyst **24a-c** demonstrated excellent catalytic activities and were more effective in term of recyclability (recycling: up to 14 times with similar d.r. and ee). They were less expensive compare to the similar reported catalysts (Table 1, entry 4) [24].



Scheme 5: CILS organocatalyst 25 catalyzed asymmetric *bis*-aldol reaction [25]

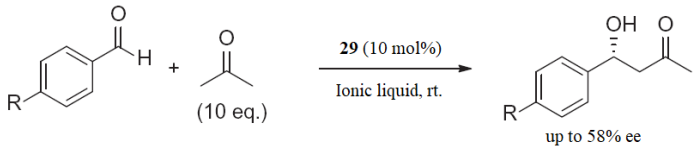
ILS organocatalysts**25** was synthesized from prolinamide derivatives by the same group in 2015 (Figure 3). It showed excellent performance in *mono*-and *bis*-direct aldol reactions (Scheme 5) of cycloalkanone as well as linear ketone donors with diverse aromatic aldehydes in aqueous medium (Table 1, entry 5). The catalyst **25** provided same stereoselectivities with slightly diminished activity up to 10 catalytic cycles [25].

In 2016, ILS catalyst **26a-d** were derived from (4*R*)-HO-(2*S*)-Pro-(*S*)-Val dipeptides (Figure 3) and tested on asymmetric direct aldol reactions of cyloalkanones and aromatic aldehyde acceptors (Table 1, entry 6) by Zlotin*et al*.. The authors found that catalysts **26a** and **26c** were more effective than the others in environmental friendly solvent, water. When conducted recycling experiment, the catalyst **26c**demonstreddrastrically reduced potential for conversion while keeping similar stereoselectivities up to 9 catalytic cycles [26].

In 2017, ILS immobilized catalyst **27** and **28** were synthesized from amino-amide derivatives and carboxylated threonine amide derivatives respectively by the same group (Figure 3). Both the catalysts were evaluated in the asymmetric aldol reactions of unmodified α-hydroxy ketone donors with diverse aromatic aldehyde acceptors [27, 28]. They delivered *syn* aldol adducts with high diastereoselectivities (*syn:anti*:

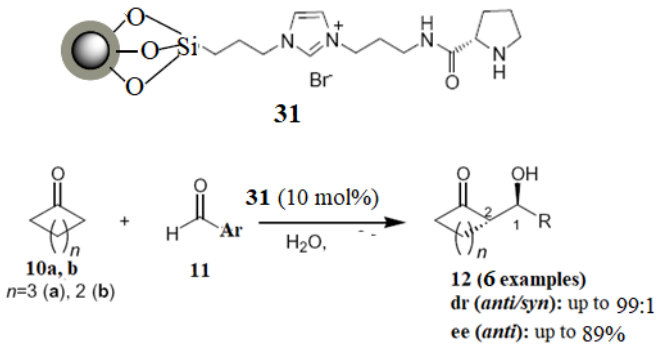
up to 94:6) with excellent enantioselectivities (ee (*syn*) – up to 99%) (Table 1, entry 7 & 8). Catalyst **27** could be recycled up to 9 times without any effect on stereo-induction [27] while catalyst **28** could be recycled up to 5 times with significant reduced activity [28].

In 2020, Kui and Guillen reported ILS organocatalyst**29** (Figure 3) derived from histidine-based salts for asymmetric aldol reactions of acetone and aromatic aldehyde acceptors in ionic liquid (Scheme 6) [29].



Scheme 6: ILS cat. 29 in direct aldol reaction, Kui and Guillen, 2020 [29]

In 2013, Yin *et al*. developed a new type magnetically recoverable immobilized L-proline derivative catalyst **31** using grafting process onto IL-modified Magnetical nanoparticle supports (MNPs) (Scheme 7) [30].



Scheme 7: IL-modified MNPs prolinamide catalyst 31 for Asymmetric aldol reaction, Yin *et al,* 2013 [30].

The activity of this catalyst was compared with IL free similar catalyst ((L-proline-NH_2-SiO_2@Fe_3O_4) in direct stereoselective aldol reactions of diverse cyclic/liner ketone donors with aromatic aldehyde acceptors in aqueous media. They observed better catalytic activity of **31** over its counterpart. Catalyst **31** can be smoothly recovered from the reaction medium using permanent magnet and reused after washing with water for several times without effecting yield and stereoselectivities [30].

CONCLUSION:

This review article gives a brief outlook on the development and the application of covalently linked ILS chiral organocatalysts in stereoselective aldol reactions. The ILS catalysts demonstrated similar activity or better performance compared to

unsupported chiral organocatalysts. Several catalysts showed outstanding recyclability fulfilling the purpose of the supporting. It is expected that we will obtain more advantageous, highly active with recyclable homogeneous ILS organocatalysts in future.

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