PANCHAKOTesSAYS
ISSN : 0976-4968
Vol-13, No.-2, Nov 2022

Review on Direct Asymmetric Aldol Addition Reaction Catalyzed by Strong Chiral Brønsted Acids

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Abstract

Organocatalysis have tremendously progressed in the last two decades and asymmetric organocatalysis gradually become integrated part of research in organic synthesis. After the ground-breaking work of Terada and Akiyama, asymmetric reaction using chiral Brønsted acid attracts great attention. Aldol reactions are comprehensively studied in diverse asymmetric organocatalysis. It is also enriched by the catalysis of various types of chiral weak hydrogen bond donor catalysts to strong Brønsted acid catalysts, known as asymmetric Brønsted acid catalysis. Strong chiral Brønsted acid catalyzed aldol reactions can be performed directly without modification of the substrates or indirectly i.e., Mukaiyama type aldol reaction.

In this review article, asymmetric aldol reactions catalyzed by strong Brønsted acid will be discussed. It is found that this kind of aldol reactions are rarely been studied and needed more attention. Brønsted acid like Weak hydrogen bond donor catalyst will not be considered. This article is organized under the category of (1) Introduction, (2) Asymmetric direct aldol addition reaction (3) Miscellaneous (4) Conclusion. (5) Acknowledgement (6) References.

KEYWORDS: Asymmetric, Direct aldol, Chiral Brønsted acid, Organocatalysis, Enantioselectivity

INTRODUCTION

The aldol reaction is a very important chemical transformation in synthetic chemistry. It has immense application in the synthesis of many important biologically active compounds such as antibiotics, antitumor compounds, antiproliferating, antifungal, and heart disease drugs, etc [1]. The reaction is important in many aspects such as it can generate new carbon-carbon bond with generation of one or more stereogenic centers. Generally, an aldol reaction can be performed under acidic or basic conditions to form β-hydroxy ketone or aldehyde, but the need for the development of environmentally benign process, concept of catalysis was developed. In the catalytic process, a reaction can be accomplished under milder reaction conditions by using very small quantity of catalyst. So, extensive researches are undergoing not only for the development of new catalytic process, but are also to control the absolute stereochemistry of chiral centers over fifty years [2, 3]. Among the various asymmetric

approaches, the most favored one is asymmetric catalysis where sub-stoichiometric amount of asymmetric catalysts are used [4].

The first asymmetric catalytic aldol type reaction was developed by Mukaiyama *et al*. in 1973 with silyl enol ethers using metal catalyst [5]. Since then, enormous studies were carried out to improve the metal catalyzed enantioselective aldol reactions [6, 7] and were used in several valuable syntheses [8]. However, the drawback of this catalysis is that the synthesis of these catalysts required stoichiometric amounts of chiral sources and there are also several limitations in synthetic applications [9]. So, a complementary catalytic approach, coined as organocataysis was developed [10]. In asymmetric organocatalysis, a small amount of pure chiral organic compound is used to induce enantioselectivity and it is completely devoid of metals. Over the last two decades, asymmetric organocatalysis witnesses a tremendous growth with newer concepts [11]. The latest addition was the asymmetric Brønsted acid catalysis which was developed independently by Akiyama and Tereda in 2004 [12, 13]. Since then, the field of asymmetric Brønsted acid catalysis has been extensively studied and chiral Brønsted acids have emerged as efficient enantioselective catalysts for the activation of variety of functional groups such as imines, vinyl ethers, carbonyl group, alkenes and many more [14].

This article will mainly focus on the asymmetric direct aldol addition reaction catalyzed by chiral Brønsted acids. The activation of the substrate can occur via hydrogen bonding or protonation, but, it is often difficult to distinguish between these modes of activation [15].

ASYMMETRIC DIRECT ALDOL ADDITION REACTION

One of the most challenging tasks in catalysis is to perform the aldol reaction in a direct catalytic diasetereo- and enantioselective way [16]. The earliest direct asymmetric aldol reaction was reported by using enzymes as catalysts [17]. Bifunctional chiral metal complexes catalysed direct aldol reaction is also enriched the field [18]. Since the seminal work of List, Lerner and Barbas [19, 20], organo-catalyzed asymmetric direct aldol reaction has shown remarkable progress [21, 22]. The organocatalytic asymmetric direct aldol reaction is mainly governed by aminocatalysis where proline or other organocatalysts with primary or secondary amino groups catalyzed the aldol reaction via an enamine intermediate [23]. Other important organocatalysis that contributed in direct aldol are asymmetric thioureas or weak hydrogen bond donor catalysis and asymmetric cinchona alkaloids catalysis or basic catalysis. Brønsted acid catalyzed direct aldol reaction was the most recent addition in this field and is our interest of discussion in this review.

Terada and coworkers reported an enantioselective direct aldol type reaction of azlactone **2** with vinyl ether **1** in presence of chiral catalyst (*R*)-**4**. They prepared β-hydroxy-α-amino acid derivatives **3** with high enantio- and diastereoselectivities (up to 97% ee of the major *syn* isomer) (Figure 1) [24].

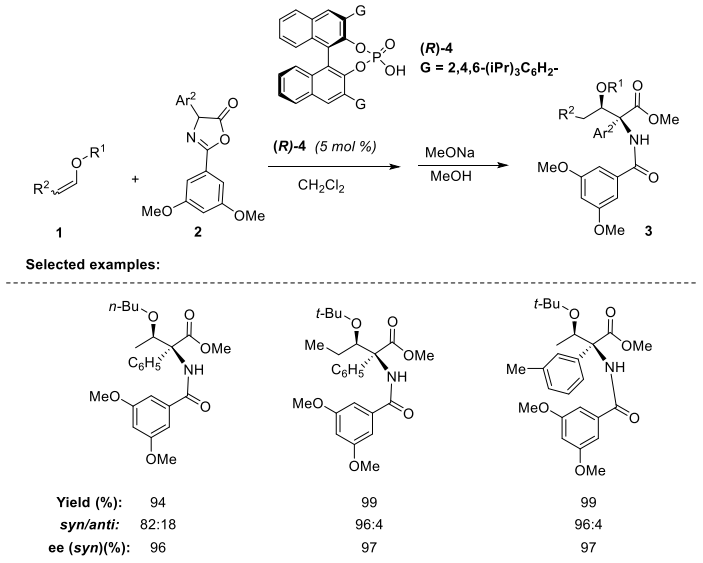

Figure 1: Direct aldol type reaction of azlactone (Terada *et al*., 2009) [24].

The authors proposed a mechanistic pathway involving oxocarbenium ion pair formation from chiral conjugate base (**TS_1**) via protonation of vinyl ether by the Brønsted acid and created an asymmetric environment through C-H···O hydrogen bonding occurred between the acidic proton(s) of oxocarbenium ion and anionic site of the chiral conjugate base of the Brønsted acid [25]. Then, this oxocarbenium ion (**TS_1**) reacted with the azalactones **2** via their oxazole tautomer (**2'**) (Figure 2) [24].

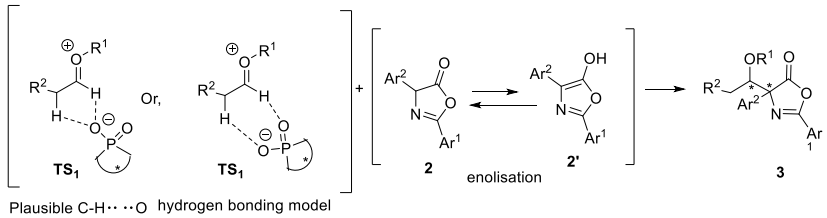

Figure 2: Mechanism Proposed by Terada *et al*., 2009 [24].

Pousse *et al*. reported the first Brønsted acid catalysed asymmetric direct aldol reactions in 2010 [26]. The authors optimized several Brønsted acids (Figure 3) and found H_8BINOL derived phosphoric acid catalyst (***R*)-5a** to afford best enantioselectivities and diastereoselectivities. Interestingly, they observed that

stronger Brønsted acids (*e.g*. PTSA and Rac. **8**, Figure 3) behaved sluggishly, although acidity is very much essential for activation.

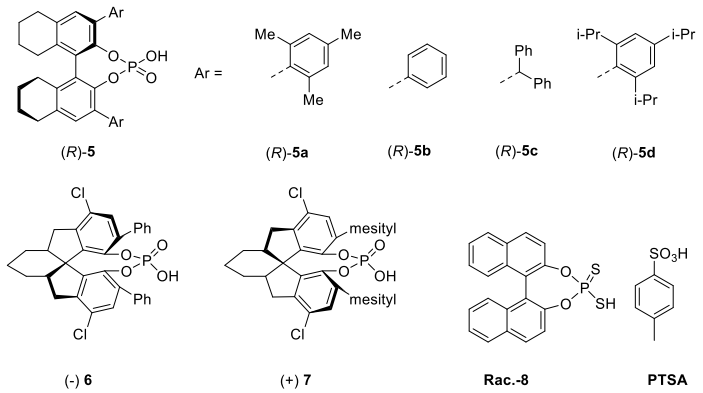

Figure 3: Catalysts for direct aldol reactions (Pousse *et al*., 2010).

They also found that the chiral BINOL backbone of BINOL-derived phosphoric acid are required to be substituted with bulky aromatics on the 3,3′-positions to induce high selectivity in the asymmetric direct aldol reactions [26].

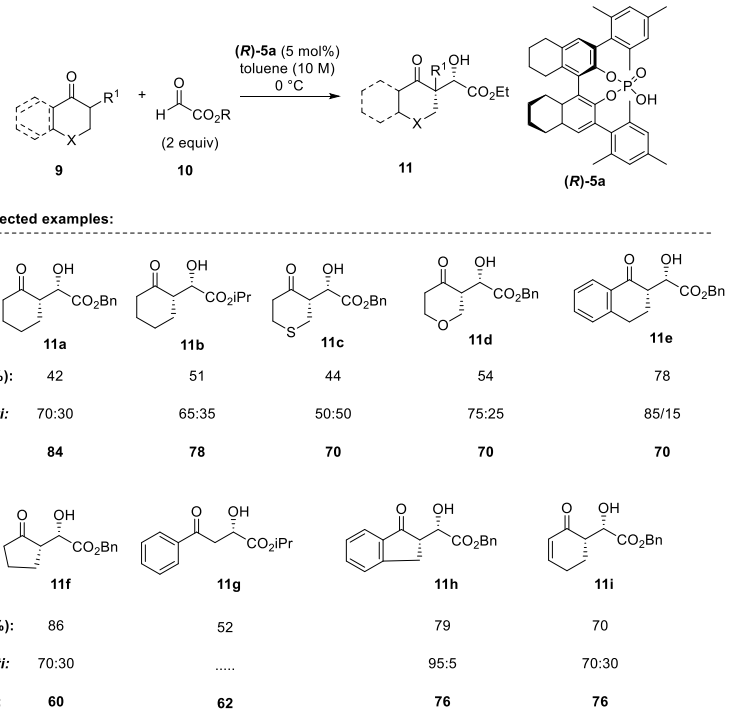

Figure 4: Direct aldol reactions reported by Pousse *et al*., 2010) [26].

Under optimized conditions, cyclic ketones **9** were used with ethyl glyoxalate **10** in presence of H_8BINOL derived phosphoric acid catalyst (***R*)-5a** to afford the aldol

products **11** in good yields and obtained the aldol product **11** mainly as the *syn*-isomer with enantioselectivies up to 84% ee (Figure 4) [26].

Accordingly, it is a complementary approach to enanmine catalysis [26]. This is because the use of enamine based catalysts is limited to only moderately hindered donors such as aldehydes and unsubstituted ketones, while acetophenone and fused cyclic aromatic ketones (e.g., indanone, tetralone) derivatives are little or unknown [27]. Beside, the $\alpha,\beta,$- unsaturated ketones are challenging substrates in amine catalysis due to the probable trap of amine catalysts through an irreversible 1,4-Micheal type addition.

The authors proposed a dual activation of nucleophile i.e. ketone to form an enol in the reaction medium (Figure 5) and this dual controlling effect are thought to be responsible for the observed enantio-and diastereoselectivity.

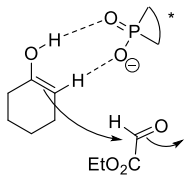

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Figure 5: Proposed transition state for Direct Aldol addition (Pousse *et al*., 2010)

A more detailed mechanistic studies are infact required to dettermine the actual pathways of activation for this reaction. They also found that acetophenone and α,β-unsaturated ketone gave the expected aldol product with good enantioselectivities (upto 84%) and *syn*-diastereoselectivities (upto 95:5) (Figure 4). Interestingly, in case of unsaturaed ketone, they did not observed any expected vinylogous addition product and elimination product. The catalyst was found to be recycleable upto 80% by coloumn chromatography.

Das *et al*. (2011) also reported direct regiospecific enantioselective aldol reaction of enones and dienones using chiral H_8BINOL-derived Brønsted acid **(*R*)-5a** (Figure 6) [28]. After optimisation of several chiral phosphoric acid Catalysts (Figure 3), chiral Brønsted acid **(*R*)-5a** was found to be most efficient to provide good yiled and enantioselectivity. At the optimised conditions, the authors used various Methyl vinyl ketones β-substituted by an aryl or heteroaryl moiety **13** in aldol reaction with Ethyl glyoxalate **10** in presence of the H_8BINOL derived chiral phosphoric acid (***R*)-5a** and obtained the aldol products **14** in very good to high yields with enantiomeric excess up to 82% (Figure 6) [28].

They observed interesting results with acid sensitive substrates like furan and thiophene β-substituted vinyl ketones **13** which also provided the aldol product with good yields and enantioselectivies (products **14e** and **14f** in the Figure 6). When, they used dienones, **15** and **16** which are more vulnerable substarte in any type of catalysis, yields similar results under the same conditions (Figure 7) [28].

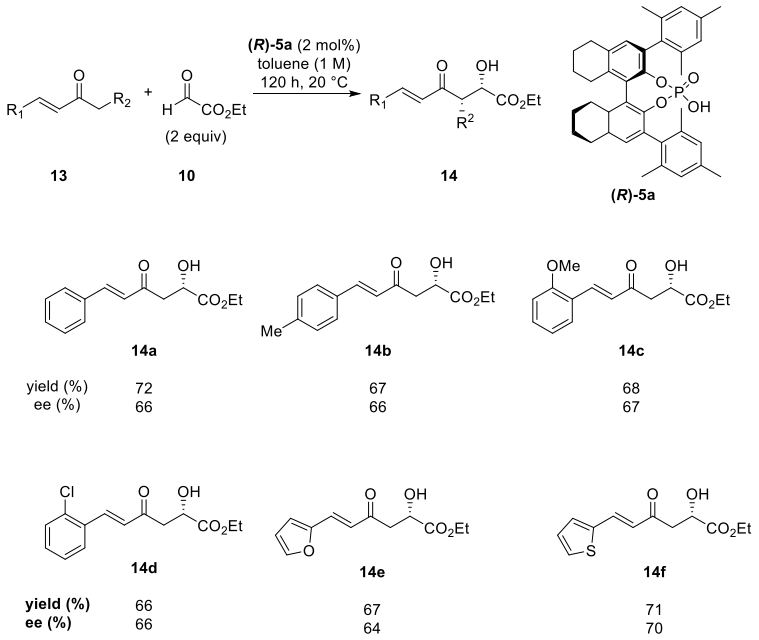

Figure 6: Direct aldol reactions using enones (Das *et al*., 2011).

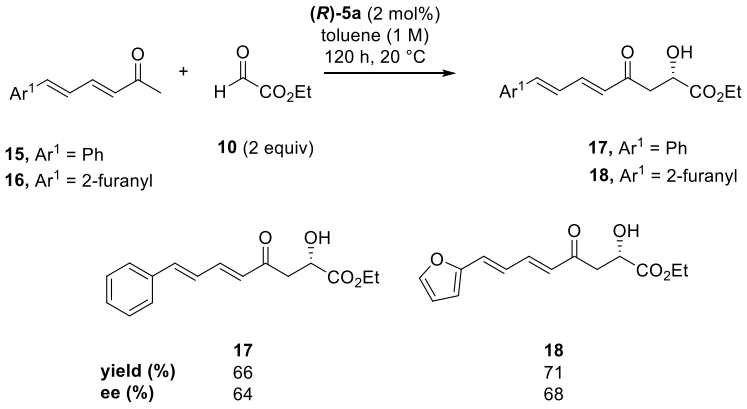

Figure 7: Asymmetric direct Aldol reactions of dienones (Das *et al*., 2011).

MISCELLANEOUS

In 2009, Akiyama group reported an intramolecular aldol addition followed by condensation reaction for kinetic resolution (K.R.) of racemic compound **19** presences

of chiral Brønsted acid catalyst (*R*)-**4** and obtained inspiring result to carry out asymmetric Robinson annulations type reaction (Figure 8) [29].

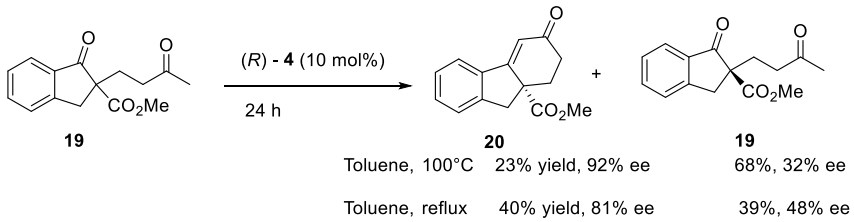

Figure 8: K.R. of **19** through Aldol reaction using **4** (Mori *et al.*, 2009) [29]

The reaction was thought to pass via a chair like cyclic enol transition state in presence of bifunctional catalyst (*R*)-**4** (Figure 9).

In 2012, the same group studied the effect of different strong catalysts as well as substrate structure in the same reaction (Scheme 8). They also investigated the reaction mechanism using DFT calculation which confirmed the enolic transition state described in the figure 9 [30].

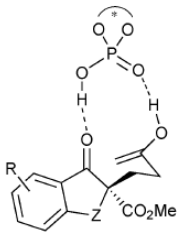

Figure 9: Transition state for K.R. by catalyst (*R*)-**4** [29].

A similar type of reaction was reported for desymmetrization of dienones **21** by Akiyama and coworkers in presence 5 mol% of chiral catalyst (*R*)-**4** in 2009. The authors obtained good to excellent yield of the desymmetrized product **22** (Figure 10) [31]. A theoretical investigation for the reaction mechanism confirmed the above transition state model (Figure 9).

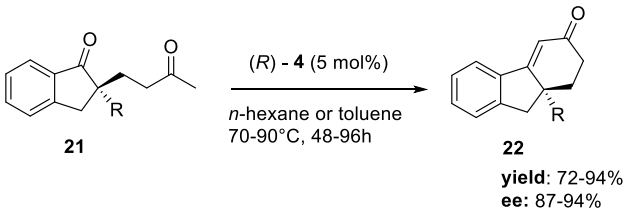

Figure 10: Desymmetrization of *meso*-**21** using (*R*)-**4** [31].

CONCLUSION

In this review article, recent development of Brønsted acid catalyzed asymmetric direct aldol reactions have been summed up. The discovery of asymmetric Brønsted acid catalyzed direct aldol reaction using carbonyl pronucleophiles was a big landmark in history of catalysis as the Brønsted catalysis was initially limited for the activation to the more basic imine groups. Besides, this catalysis was also able to complement some shortness in organocatalysis in context to the challenging substrates like acetophenone, α,β-unsaturated ketones (enones) and dienones as well as it showed new hope for future research regarding activation of more challenging functional groups in Brønsted acid catalysis. But there are still many limiations remains in Brønsted acid catalysed direct aldol reactions like use of organic solvents, high catalysts loading, limited substrate scopes, etc.

ACKNOWLEDGEMENT

I am indebted to Sreegopal Banerjee college, Bagati, for providing softwares, computer facility and internet facilities.

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