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## Chiral zinc catalysts for asymmetric synthesis



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## 1. Introduction

Stereoselective processes continue to attract a great deal of attention, particularly in context of searching for new, efficient, selective, cheap and environmentally benign catalysts. Although, a number of organic reactions can be carried out under asymmetric control, most transformations require the application of toxic and expensive precious metals such as rhodium, ruthenium, palladium or iridium as catalysts.<sup>1</sup> Over time, these noble metals were successively replaced by less expensive ones, such as zinc,<sup>2</sup> iron<sup>3</sup> and copper.<sup>4</sup> In spite of the really low price of zinc compounds, especially inorganic salts like chloride, triflate or acetate, the asymmetric organic reactions catalysed by zinc complexes are relatively underdeveloped compared to their iron and copper counterparts.<sup>3,4</sup> This report collectively discusses a selection of recent contributions about catalytic applications of zinc compounds in various areas of asymmetric synthesis.

There are five stable isotopes of zinc (Zn) in nature that make up about 0.0075% of the Earth's crust, making zinc the 24th most abundant element.<sup>5</sup> As a metal, zinc is found in many important applications in industry. The major application of metallic zinc is its use in plating iron materials in order to prevent corrosion processes.<sup>6</sup> It is also used in many cells and batteries such as in Daniell, Clarc, Bunsen, Leclanché models and many others.<sup>7</sup> In most chemical compounds, zinc is found primarily in the +II oxidation state, but some examples of a +I oxidation state are also known.<sup>8</sup> Organozinc compounds, in which the zinc occurs at zero oxidation state, are relatively a much smaller group.

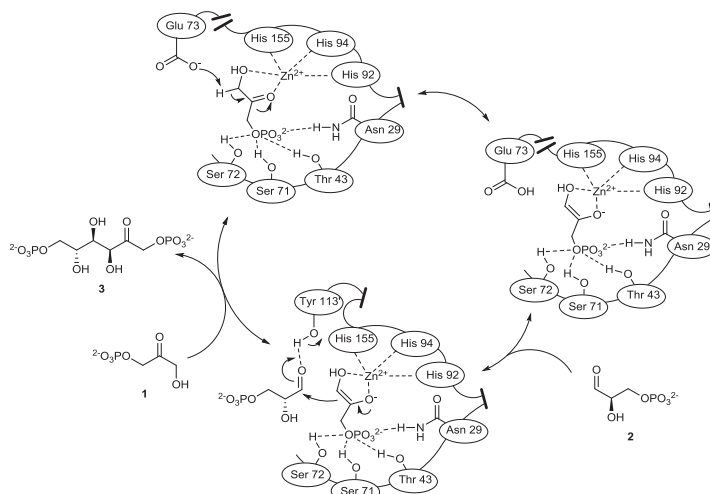
Zinc occurs in trace amounts in living organisms, for example, the typical human body mass contains just 33 ppm. Nevertheless, it is an essential element since it plays very important roles in various biochemical processes.<sup>5</sup> A deficiency of this microelement, for example, causes many health problems such as anaemia, slow growth, birth defects, poor wound healing, psoriasisform skin lesions, dermatitis and hair loss, poor glucose tolerance, diarrhoea and loss of appetite.<sup>9</sup> Zinc is also an integral part of many enzymes and proteins, such as DNA and RNA binding proteins. In the latter case, zinc creates zinc finger domains and is directly involved in

binding the protein to a nucleic acid.<sup>10</sup> Enzymes, which rely on zinc catalyse a number of biochemical reactions in living systems, greatly accelerating both the rate and specificity of metabolic processes. The first enzyme in which zinc was found to be an intrinsic cofactor is *Carbonic anhydrase*, making it the first recognised metalloenzyme.<sup>11</sup> It was discovered in 1932,<sup>12</sup> and the essential role of zinc in its catalytic interconversion of carbon dioxide and water to bicarbonate and protons, and vice versa, was proven in 1940.<sup>11</sup> Nowadays, it is known that zinc-containing enzymes belong to all six major classes of enzymes, i.e., *hydrolases, isomerases, ligases, lyases, oxidoreductases* and *transferases*, inspiring chemists to design similarly efficient artificial chiral catalysts based on central Zn ions. This report highlights a selection of important applications of Zn-based chiral catalysts and discusses only few prominent examples of stoichiometric application of zinc compounds for asymmetric synthesis.

## 2. C–C bond formation

### 2.1. Direct catalytic aldol reaction

It is instructive to start this chapter by discussing how aldolases' mode of action is the inspiration for the synthesis of artificial Zn complexes and for designing catalysts for direct asymmetric aldol reactions. In nature, asymmetric aldol reactions are performed by aldolases that belong to lyases, the enzymes responsible for various bond formations by means other than hydrolysis and oxidation reactions. Type II aldolases represent a group of metal-based, and mostly zinc-containing enzymes. The Zn<sup>2+</sup> cation is coordinated to imidazolium rings of three histidine residues in the active site (His-92, His-94 and His-155, [Scheme 1](#)). These enzymes synthesise carbohydrates from dihydroxyacetone-3-phosphate **1** (DHAP) and appropriate aldehydes, e.g., glyceraldehyde 3-phosphate **2**. DHAP, in its enolate form, is bound to a Zn<sup>2+</sup> cofactor in the enzyme active site, and the phosphate moiety of glyceraldehyde is hydrogen bonded within the hydrophilic pocket formed by tyrosine, glycine and asparagine and two serine residues. The proposed mechanism of catalytic activity of type II aldolase is shown in [Scheme 1](#). In



**Scheme 1.** Reaction of glyceraldehyde 3-phosphate and dihydroxyacetone-3-phosphate (DHAP) catalysed by class II aldolase (Zn<sup>2+</sup> cofactor acts as a Lewis acid).

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