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Rational design of pseudo-enantiomeric libraries of ligands based on pyranoses for application in asymmetric catalysis

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ABSTRACT

This review deals with the solution given by synthetic chemists to overcome the problem of access to both enantiomers of a given process when carbohydrates are used as ligands. Indeed, although sugars are stereochemically rich compounds, and derived from one of the most abundant renewable material, their use in asymmetric catalysis has been limited by the fact that most of them have D-configuration.

This review explains the concept of pseudo-enantiomeric ligands, and collects examples based on *pyranoses*, by describing their relevant use in asymmetric catalysis.

1. Introduction

It is well known that enantiomers have different biological activity, and that their interaction with living organisms can give rise to distinct responses [1].

Many examples demonstrate how these differences can be expressed. They range from curiosities, such as that relating to limonene (*R*-enantiomer: citrus taste; *S*-enantiomer: turpentine taste), up to shocking cases such as that regarding the well known effects caused by the use of (*S*)-thalidomide.

For this reason, when used as active ingredients, the enantiomers must be regarded as distinct drugs, and current regulations do strongly discourage manufacture and sale of chiral drugs in racemic form, forcing the producers to commercialize the only active enantiomer [1].

In some notable cases, both enantiomers do present wanted properties, and, hence, it is necessary to find convenient methods for their synthesis. For instance, (+*S*,*R*,*R*,*R*)-nebivolol and (−*R*,*S*,*S*,*S*)-nebivolol synergistically act to produce a highly beneficial cardiovascular profile [2].

On this basis, it is nowadays acknowledged the importance of developing convenient methodologies to provide enantiomerically pure products.

Organometallic catalysis is one of the most successful strategies [3]. Since the first example dated 1967 [4] and 1968 [5–7], organometallic catalysts have attracted increasing interest in both academic and industrial contexts, for some clear advantages:

(i) the remarkable activity, which allows the use of high substrate/metal ratios;
(ii) the tunability of the coordination environment, that widens the scope of substrates;
(iii) the tolerance to functional groups, which enhances chemoselectivity, and then reduces the number of purification steps of the products.
(iv) the flexibility of the physical properties, which helps separation and immediate recycle of the catalyst.

It is also recognized that all of these benefits require careful design of the catalyst, and appropriate choice of the chiral ligand [3].

The most common way by which a ligand transfers its chiral information to the substrate is through the steric control, and therefore, it is necessary to predict the three-dimensional structure of the species involved, exercise which becomes particularly complex if the ligand presents many degrees of flexibility, and is conformationally dynamic.

This aspect, combined with the plurality of catalytic reactions under study and application, produces an intense research, aimed to design and evaluate new chiral ligands in catalysis.

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In this frame, a fruitful approach is the appropriate functionalization of common carbohydrates [8–16]. This choice is based on several benefits:

- Many carbohydrates are plentiful, and, therefore, easily available;
- They are "naturally chiral" and this avoids the complicated resolution of racemates;
- Carbohydrates are highly functionalized and their chemistry is extremely developed.

The latter characteristic is particularly attractive because libraries of modular ligands become easily accessible. Consequently, in recent years, excellent results have been obtained using ligands derived from sugars in a wide range of asymmetric reactions [8–16].

Within this large variety of auxiliaries, a key-role is played by those based on the pyranose ring, because of their neat analogy with the ligands (especially the extraordinary *privileged* ligands) derived from *trans*-1,2-disubstituted-cyclohexane [17–19]. Both families show the coordinating functions in adjacent positions of a 6-membered ring (as exemplified in Fig. 1), and, accordingly, it is expected that the catalytic performance of corresponding catalysts is similar.

In addition, the multi-functional sugar scaffold allows to extend the field of application, due to the possibility to modulate finely the physical properties of the catalyst. For example, accessory hydroxyl groups can be used to introduce specific phase-tags [20], or as anchoring groups, or as emilabile coordination sites.

However, a weakness of this strategy is the fact that pyranoses are often available only with one configuration, and therefore it is impractical to prepare the enantiomeric counterparts of the ligands. The immediate consequence is that the obtainment of both enantiomers of a given chiral product can be inaccessible, and this undesirable circumstance is in conflict with the above mentioned premise.

Nevertheless, by assuming that the enantioselectivity of a reaction depends only on the local chirality in close proximity to the active metal center [21], this obstacle can be overcome in an elegant way, that involves the design of *pseudo-enantiomeric ligands* by employing the wide choice of pyranoses, coupled with their intrinsic poly-functionality.

Therefore, in this context, we shall define as *pseudo-enantiomeric* those pyranoses derived ligands that possess the same connectivity within the cyclometallated ring, and, on the basis of a rational design, provide enantiomorphous coordination environment [22].

The expectation is that both enantiomeric products of a given reaction become now easily accessible.

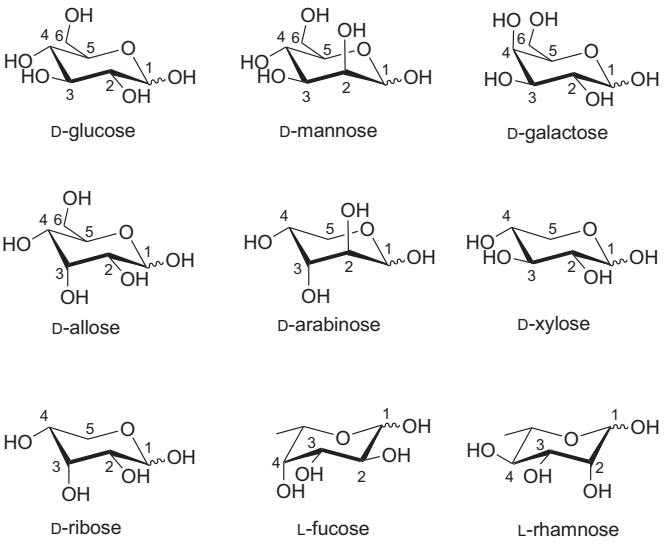

Fig. 2. Common sugars used as building blocks of chiral ligands.

This strategy has proved successful in more than one occasion, and the purpose of this mini-review is to give an overview of significant cases in the literature.

2. General strategy

The choice of the suitable sugar for preparing a chiral ligand is motivated by several factors.

First of all, the price, which must be competitive with other common chiral building blocks, and, of course, is strictly related to its natural abundance and availability.

Second, the geometrical rigidity, that typically relies on the conformational stability of the chair. This feature is highly desirable for ensuring steric control to the chiral catalysts.

At the same time, it is also profitable to take advantage of natural sugars already provided with donor atoms, as in the case of *N*-acetylglucosamine, glucosamine, galactosamine or glucosylamine, respectively functionalized in position 2 or 1.

On this basis, D-glucose, D-mannose, D-galactose and D-allose are highly competitive building blocks (Fig. 2). In other specific cases anhydro- or deoxy-versions are also useful and accessible at competitive prices [23].

Once defined the set of pyranoses useful as building blocks, it is possible to draw some general strategies for the design of pseudo-enantiomeric ligands based on this “bouquet”.

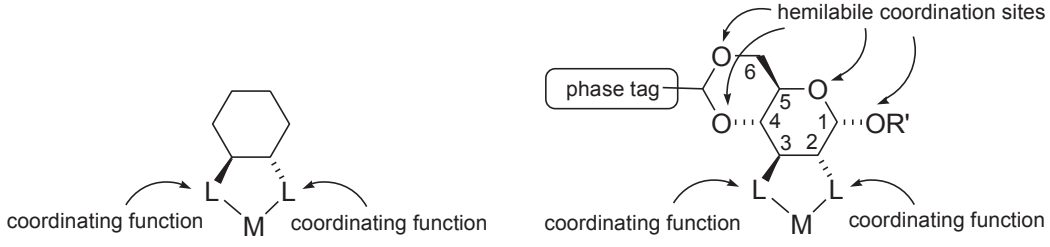

Fig. 1. Comparison between the general structure of privileged ligands based on *trans*-disubstitued cyclohexane and ligands based on pyranoses.