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Research review paper

Biocatalysis for desymmetrization and resolution of stereocenters beyond the reactive center: How far is far enough?

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ABSTRACT

The kinetic resolution of racemates and desymmetrization are the most common approaches to the preparation of enantiomerically enriched compounds. These procedures allow the access of high valuable, chiral building blocks for many purposes in academic or industrial R&D endeavors. Nevertheless, the scope of stereochemistry recognition in biotransformations usually occurs at the site of the transformation or when it is close to it (not more than 3 bonds). However, there are a growing number of enzymatic transformations which surpass the limits of stereorecognition of remote chiral (or prochiral) centers. In this account, we would like to present some aspects of biocatalyzed remote resolutions and remote desymmetrizations to call attention for these challenging transformations.

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Introduction

The construction of chiral compounds containing one or more stereocenters is certainly one of the most attractive and important challenges in contemporary synthetic organic chemistry (Hanessian et al., 2013). Currently, many organic chemists have been concerned with developing synthetic methods to provide compounds in enantiomerically pure forms. One reason for the importance to obtain chiral compounds is intimately linked to the relationship between biological activity and stereoisomerism, and therefore the use of chiral drugs in enantiopure form is nowadays a standard requirement (FDA, 2014).

The most common approach to the preparation of enantiomerically enriched compounds is the kinetic resolution of racemates. This procedure consists of transforming both enantiomers of a racemate into the desired products at different rates. An ideal efficient resolution occurs when the reaction rates of the two isomers are different enough that one enantiomer remains virtually unreacted. Various non-enzymatic or enzymatic methods for resolution are known (Pellissier, 2011), and typically the stereocenter to be resolved is close to the reaction center, in the α or β position (Fig. 1).

The existing dilemma in choosing between enzymatic and non-enzymatic methods for kinetic resolution basically involves environmental (metals vs. non-metals) and cost (organocatalysts vs. biocatalysts) issues. However, the possibility of resolution of stereocenters beyond the reactive center, i.e. a remote stereocenter (Fig. 2), has made the use of enzymes more advantageous.

A remote stereocenter is defined by Gröger as a group separated by a moiety of at least three atoms or an aromatic group from the group to be transformed (Blasco and Gröger, 2014). The study of enzymatic remote resolutions can provide valuable information to evaluate if such enzyme shows a broad or strict substrate specificity (often called

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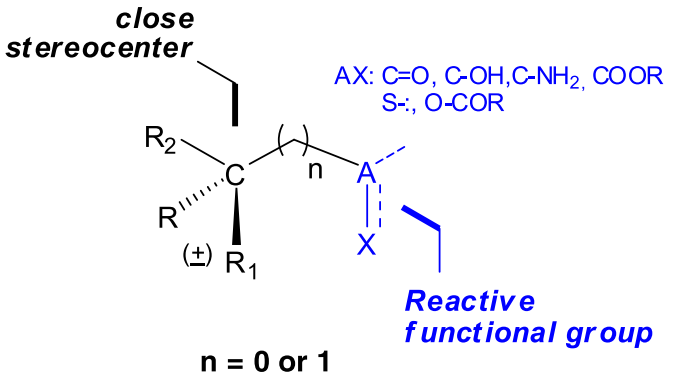

Fig. 1. Racemic compound where the stereocenter is at the α (n = 0) or β-position (n = 1) relative to the reactive group.

enzyme substrate promiscuity) (Hult and Berglund, 2007). Moreover, in organic synthesis, the possibility of solving remote centers allows the organic chemist to use this methodology in any part of the route, whereas in the traditional methods the chiral induction is usually done in the first stages of the synthetic route due to the limitation of the substrate and available methodologies to generate or to induce chirality stepwise. Thus, remote stereocontrol in transformations remains a challenging task for chemical transformations. Remote stereocontrol is limited by the direct communication between the reactive site and the molecule's stereocenter not usually farther than five bonds in length in acyclic systems (Mikami et al., 2001; O'Brien, 2011). This "direct communication" consists in the interactions among these substrates' centers themselves (intramolecular) and also the intermolecular interaction with enzyme's catalytic site when the enzyme–substrate complex is formed. Such interactions govern the stereocenter's preference during the biocatalytic reaction. However, other systems can subdue the intrinsic limitations of acyclic ones such as cyclic structures or other non-usual structures such as rigid molecular systems (Clayden et al., 2004), helicoidal moieties (Johnston and Smith, 2014), or coordination complexes (Clayden, 2011).

During the preparation of this manuscript Blasco and Gröger published a short review on remote resolution that focused on the synthesis of pharmaceuticals, flavors, and vitamins (Blasco and Gröger, 2014). In this review, it is intended to show the remotest enzymatic resolutions (and desymmetrizations) made by enzymes so far. Besides, differently from Blasco's review, some examples using other enzymes than hydrolases for remote resolution are also shown in this work. The subject of remote resolution was covered in two important textbooks of biocatalysis (Bornscheuer and Kazlauskas, 2006; Paravidino et al., 2012) and in a pioneer review of Mizuguchi et al. (1994).

The intention of this manuscript is not to cover thoroughly the literature on this subject but to call the attention for opportunities for the challenging task of resolution of remote stereocenters. Mainly, this review is summarized by cyclic and acyclic substrates submitted to enzymatic reactions and subdivided by the distance from the stereogenic center (or the pro-chiral center) to the group to be biotransformed. For each substrate submitted to remote resolution or desymmetrization, the distance from the (pro)stereogenic center to the reactive group is shown in colors.

Resolution of racemic compounds and desymmetrizations in a remote position to reactive group

Acyclic substrates

According to the literature, one of the first reports about desymmetrization of open-chain substrates containing a remote pro-chiral center was published by Mohr et al. (1983). With pig liver esterase, it was observed that increasing the distance between the pro-chiral methyl group and the ester group from two bonds to three bonds (diester **1**), the enantiomeric excess was decreased from 90% to 10% (Scheme 1). The authors first concluded that high stereoselectivity can be achieved only if the prochiral center from the ester group is restricted to the α- or β-position to the stereogenic center.

Im et al. (2003) tested four enzymes in enzymatic transesterification of primary alcohol **3**. Among them, *Pseudomonas cepacia* (PCL) showed the best enantioselectivity when reacted vinyl acetate, providing (*R*)-alcohol **3** with 99% ee and (*S*)-ester **4** with 52% ee at a conversion of 66% (Scheme 2).

Forró et al. (2011) developed a new enzymatic strategy for the synthesis of 1-(3-hydroxypropyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**5** and **6**) key intermediates for the preparation of enantiomeric crispines A and E, which display high biological activity against the human cancer cell. The first approach was the lipase-catalyzed asymmetric acylation of primary alcohol with a remote stereogenic center. The procedures described in the literature have not been effective. Therefore optimization of enzymes, solvent, acyl donor groups, and temperature was necessary. The best resolution of **5** was obtained by using lipase PS (*Burkholderia cepacia*), vinyl decanoate, and catalytic amounts of Et_3N and Na_2SO_4 in t-BuOMe (Scheme 3).

In the same study, another employed approach was an enzymatic hydrolysis of **6**; the authors found that the side of the acyl moiety had a marked effect on both the enantioselectivity and the reaction rate. The reaction was more selective for R = $(CH_2)_8Me$ than R = Me. The solvent also has influence: the reaction is more reactive and enantioselective in the presence of water than in *t*-BuOMe only. But water did not affect either the enantioselectivity or the conversion when 1 or 4 equivalents were used. The best hydrolysis of racemic

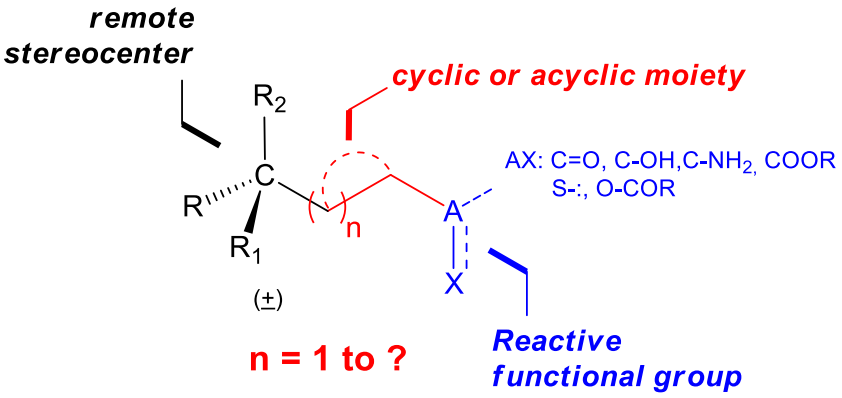

Fig. 2. Compound with stereocenter beyond the reactive center; resolution (and desymmetrizations) with enzymes is possible.

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