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A novel dynamic kinetic resolution system for production of enantiopure aliphatic amines.

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PURPOSE OF THE ABSTRACT

A large part of active pharmaceutical ingredients and agricultural components are best applied as their enantiopure forms, especially since other forms can cause undesired or even toxic (side) effects.[1] Obtaining enantiopure chemicals can be a difficult task, from synthesis to purification, due to the nearly identical physical properties of enantiomers. Separation is currently achievable by interaction with other chiral molecules (to form diastereomers) or with enantioselective catalysts.[2] An example of the latter is kinetic resolution, where a chiral catalyst (often an enzyme) selectively catalyses the conversion of one enantiomer to a product which can be easily separated by conventional methods such as precipitation, distillation or extraction. However, the main drawback of kinetic resolution and other separation methods is often that for every desired (isolated) enantiomer, the same amount of an undesired enantiomer is left over.[2-3]

The addition of a racemization catalyst in a kinetic resolution system has led to the conversion of the undesired enantiomer towards a functionalized, desired product. At the same time as the enzyme selectively functionalizes one enantiomer, the racemization assures that the ratio of the unreacted enantiomers remains the same. As a result, the concentration of the undesired enantiomer decreases, while the desired form can be functionalized to a stable and separable product.

Many dynamic kinetic resolution systems exist for a wide array of substrates.[2-5] However, the dynamic kinetic resolution for aliphatic amines remains an unresolved challenge. Some systems for benzylic amines have had some moderate success on aliphatic substrates; but suffer from long reaction times, enzyme incompatibility, high catalyst loadings (> 5 mol%) and limited substrate scope.[6-8]

Hereby, we wish to present our initial results on a novel dynamic kinetic resolution system for aliphatic amines; studying racemization and kinetic resolution separately and in combination.

First, a suitable racemization catalyst was identified for the consecutive dehydrogenation/hydrogenation of an enantiopure substrate (S-2-aminooctane) ? over an (short-lived) imine intermediate ? by monitoring the enantiomeric excess (ee).[9] Starting with a commercial ruthenium on carbon, a significant drop in ee was noted at higher catalyst loadings (15 mol%). Further development of self-prepared ruthenium catalysts showed improved activity by dispersion of metallic Ru on alkaline spinel supports, in particular, magnesium aluminate. However, the Ru/spinel catalysts still required high catalysts loading. More success was found with zeolite supports. A wide array of zeolite topologies, both with Ru(III) and Ru(0), were screened. Surprisingly, the ionic ruthenium zeolites resulted in higher catalyst activities and thus lower enantiomeric excess.

Next, the kinetic resolution of aliphatic amines with enzymes was evaluated. Candida Antarctica lipase B, a thermostable enzyme, showed a significant difference in stability depending on the polarity of the solvent. Apolar solvents resulted in successful kinetic resolutions, while polar solvents, like DCM and THF were sometimes detrimental to enzyme stability, contrary to previously reported kinetic resolution in those solvents.[10] Furthermore, different resolution agents were investigated, such as esters and carbonates. Depending on the used ester or carbonate, functionalisation of the amine substrate was unselective. Smaller, less hindered agents caused uncatalyzed, unselective conversion and alkylation, while larger resolution agents resulted in a highly selective turnover with minimal side-products.

Combination of both the racemization and the kinetic resolution system resulted in a selective dynamic kinetic

resolution exceeding the kinetic resolution limit of 50%. Reaction conditions will be optimized to achieve the best results, at which point a wide substrate scope will be tested.

FIGURES

FIGURE 1

FIGURE 2

KEYWORDS

amines | enantiopure | resolution | racemization

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