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Recent developments in organocatalytic dynamic kinetic resolution

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1. Introduction

In spite of the important advances achieved in asymmetric synthesis and especially asymmetric catalysis, the resolution of racemic substrates is still the most prominent way to chiral compounds. A simple kinetic resolution is defined as a process where the two enantiomers of a racemate are transformed to products at different rates.[1] If the kinetic resolution is efficient, one of the enantiomers of the racemic mixture is converted into the desired chiral product while the other is recovered unchanged (Fig. 1). However, this methodology presents the limitation of having a maximum theoretical yield of 50%.

The wish of the chemical industry to reduce costs and waste in the production of chiral building blocks led chemists to develop novel resolution procedures of racemic mixtures that proceed

Abbreviations: Ar, aryl; BINOL, 1,1'-bi-2-naphthol; Bn, benzyl; Boc, *tert*-butoxycarbonyl; Bz, benzyl; Cbz, benzyloxycarbonyl; Cy, cyclohexyl; DABCO, 1,4-diazabicyclo[2.2.2]octane; DCE, dichloroethane; de, diastereomeric excess; dkr, dynamic kinetic resolution; DMF, dimethylformamide; Dmpe, 1,2-bis(dimethylphosphino)-ethane; DMSO, dimethylsulfoxide; dr, diastereomeric ratio; ee, enantiomeric excess; HATU, 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*] pyridinium 3-oxid hexafluorophosphate; HBTM, homobenzotetramizole; Hept, heptyl; Hex, hexyl; HIV, human immunodeficiency virus; HMPA, hexamethylphosphoramide; MOM, methoxymethyl; MS, molecular sieves; Naph, naphthyl; NCS, *N*-chlorosuccinimide; NHC, *N*-heterocyclic carbene; Non, nonyl; Oct, octyl; Pent, pentyl; Phth, phthalimido; Piv, pivaloyl; PMB, *p*-methoxybenzyl; r.t., room temperature; TBME, *t*-butyl methyl ether; TBS, *tert*-butyldimethylsilyl; THF, tetrahydrofuran; TIPS, triisopropylsilyl; TMS, trimethylsilyl; Tol, tolyl; Ts, 4-toluenesulfonyl (tosyl).

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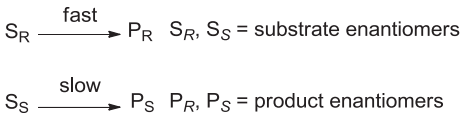

Fig. 1. Classical kinetic resolution.

beyond this 50% limited theoretical yield. Many efforts have been devoted to overcome this limitation which has led to the evolution of classical kinetic resolution into dynamic kinetic resolution in which one can in principle obtain a quantitative yield of one of the enantiomers. Indeed, dynamic kinetic resolution combines the resolution step of kinetic resolution, with an in situ equilibration or racemisation of the chirally-labile substrate (Fig. 2). In this methodology, the enantiomers of a racemic substrate are induced to equilibrate at a rate that is faster than that of the slow-reacting enantiomer in reaction with the chiral reagent (Curtin–Hammett kinetics). If the enantioselectivity is sufficient, then isolation of a highly enriched non-racemic product is possible with a theoretical yield of 100% based on the racemic substrate. However, requirements have to be fulfilled in order to gain the complete set of advantages of dynamic kinetic resolution, such as the irreversibility of the resolution step, and the fact that no product racemisation should occur under the reaction conditions. In order to obtain products with high optical purity, the selectivity (k_{fast}/k_{slow}) of the resolution step should be $\geq$20. Furthermore, the rate constant for the racemisation process (k_{inv}) should be faster than the rate constant of the resolution step (k_{fast}).

In a dynamic kinetic resolution process, all of the substrate can

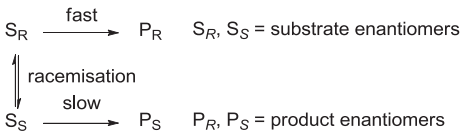

Fig. 2. Dynamic kinetic resolution.

be converted into a single product isomer with a 100% theoretical yield. Racemisation of the substrate can be performed either chemically, biocatalytically or even spontaneously; with conditions chosen to avoid the racemisation of the product. The utility of dynamic kinetic resolution is not limited to a selective synthesis of an enantiomer; when the reaction occurs along with the creation of a new stereogenic centre, an enantioselective synthesis of a diastereoisomer is also possible. This powerful concept has been applied to either enzymatic or non-enzymatic reactions.[2] One of the most important achievements in dynamic kinetic resolution recently developed deals with organocatalysed processes which have considerably expanded the synthetic scope of this methodology. While the end of the last century has been dominated by the use of metal catalysts,[3] a change in perception occurred during the last 15 years when several reports confirmed that relatively simple organic molecules could be highly enantioselective catalysts in a myriad of transformations. This rediscovery has initiated an explosive growth of research activities in organocatalysis.[4] Organocatalysts have several important advantages, since they are usually robust, inexpensive, readily available, and non-toxic.[5,6] Their application in synthesis has permitted the preparation of a number of important chiral products with the exclusion of any trace of hazardous metals and with several advantages from an economical and environmental point of view. In recent years, the first examples of organocatalysed dynamic kinetic resolution processes have been described. Today, a wide number of chiral organocatalysts are available to achieve excellent levels of stereocontrol that could only previously be achieved using biocatalysts. Whilst the use of enzymes for the dynamic kinetic resolution of racemic substrates to afford enantiopure compounds in high enantioselectivities and good yields has emerged as a popular strategy in synthesis,[7] it is only relatively recently that the widespread application of non-enzymatic chiral catalysts for dynamic kinetic resolution has gained popularity within the synthetic community.[1d] The goal of the present review is to cover the advances in organocatalytic reactions evolving through dynamic kinetic resolution reported since the beginning of 2011, since this topic was previously reviewed in 2011.[8] For the reader's convenience, this review is divided into six sections, according to the different types of organocatalytic activation modes employed in these reactions, such as aminocatalysis, *N*-heterocyclic carbene catalysis, hydrogen-bonding catalysis, Brønsted acid catalysis, Brønsted base catalysis, and Lewis base catalysis. It must be noted that multicatalysed dynamic kinetic resolutions involving a combination of an organocatalyst with another catalyst are not included in this review.

2. Aminocatalysis

2.1. Proline-derived catalysts

Asymmetric organocatalysis can follow different modes of activation which can be classified according to the covalent or non-covalent character of the substrate–organocatalyst interaction and to the chemical nature of the catalyst (Lewis base, Lewis acid, Brønsted base, Brønsted acid). Furthermore, a wide range of organocatalysts can, however, interact with the substrate through both covalent and noncovalent interactions and/or display a dual acid/base character (bifunctional organocatalysts). In the area of covalent organocatalysis, the enamine activation catalysis, based on the use of a chiral secondary amine as catalyst, has become one of the most applied organocatalytic modes of activation, allowing the enantioselective α-functionalisation of enolisable aldehydes and ketones with a wide variety of electrophiles. It began with the initial formation of an iminium ion by condensation of the aminocatalyst to the carbonyl group of aldehyde or ketone which evolves into an enamine intermediate that subsequently reacts with an electrophile to give the final product. The most employed catalyst for enamine-type reactions is the cheap, natural, simple, and readily available amino acid, L-proline. It can react with carbonyl groups to form iminium ions or enamines which constitute key synthetic intermediates in a number of asymmetric reactions. The high enantioselectivities generally observed in proline-mediated reactions can be rationalised by the capacity of this molecule to promote the formation of highly organised transition states with extensive hydrogen-bonding networks.[9] There are several reasons why proline has become an important molecule in asymmetric catalysis, e.g., it is an abundant chiral molecule which is inexpensive and available in both enantiomeric forms. Since the first examples of proline-catalysed enantioselective direct intermolecular aldol reactions reported by List et al. in 2000,[10] these reactions have been extensively studied.[11] However, despite the impressive stereoselectivity reached in many examples, a continuing limitation to synthetic applications of these processes has been the rather narrow substrate scope often limited to simple or aromatic aldehydes and few competent ketones. In this context, by extending their early methodology,[12] Ward et al. have developed enantioselective direct aldol reactions of enolisable dioxolan-protected α-substituted β-ketoaldehydes with ketones which employed L-proline as organocatalyst.[13] As shown in Scheme 1, the reactions of dioxolan-protected α-substituted β-ketoaldehydes **2** with cyclic ketones **1** afforded the corresponding aldol products **3** as almost single diastereomers (dr>20:1) in moderate yields (47–66%) and high enantiomeric excesses of 93 to >98% ee. Using an acyclic ketone such as acetone led to a better yield (72%), a good enantioselectivity of 90% ee, albeit a lower diastereoselectivity (dr=10:1). Furthermore, when the reaction conditions were applied

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