Dynamic Kinetic Resolution

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Non-Enzymatic Dynamic Kinetic Resolution of Secondary Aryl Alcohols: Planar Chiral Ferrocene and Ruthenium Catalysts in Cooperation**

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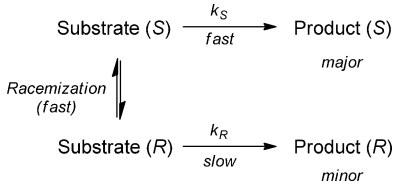
acylation · chiral resolution · kinetic resolution · secondary alcohols

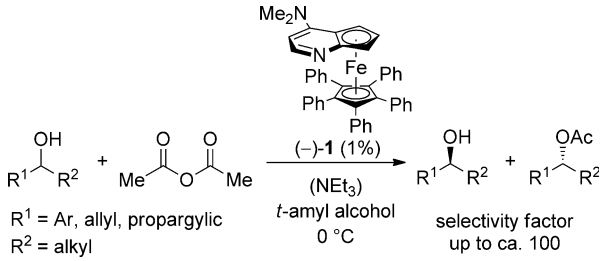
Methods for the synthesis of optically active compounds are important for the preparation of pharmaceuticals, agricultural chemicals, and materials for electronics and optics, and thus, the synthesis of chiral derivatives is an important area of contemporary synthetic organic chemistry.[1] One of the most appealing methodologies to achieve this goal is dynamic kinetic resolution (DKR). This strategy consists of the combination of a selective kinetic resolution and a fast enough racemization process in a one-pot transformation. This approach allows for the conversion of both enantiomers of a racemic substrate into a single enantiomer of the product. Thereby, the limitation of kinetic resolution, which provides a maximum yield of 50% for a particular enantiomer, is overcome (Scheme 1).[2]



Scheme 1. General representation of dynamic kinetic resolution.

A popular approach within DKR is to utilize enzymes, since they often catalyze reactions with high enantio- and regioselectivity, in cooperation with transition-metal complexes.[2] Such combinations have been extensively studied since Williams et al. demonstrated their compatibility.[3] Of particular importance is the development of the combined strategy for the DKR of secondary alcohols, which utilizes an enzymatic kinetic resolution and metal-catalyzed racemization. The best results in terms of activity and enantioselectivity are obtained using an enzymatic kinetic resolution which is performed using CALB (*Candida antarctica* lipase B) together with [C_5Ph_5Ru] complexes as racemization catalysts.[4]

In parallel to the development of enzyme/transition-metal-based DKR, chiral dimethylaminopyridine (DMAP) catalysts have been used in the kinetic resolution of alcohols.[5] In this context, Fu et al. have reported several planar chiral DMAP–ferrocene derivatives as very efficient catalysts for this process using acetic anhydride (Ac_2O) as an acetylating agent. Several racemic secondary alcohols were resolved, providing very high selectivities in *t*-amyl alcohol at 0 °C in the presence of NEt_3 (Scheme 2).[6]



Scheme 2. Kinetic resolution of secondary alcohols.

In this Highlight, we describe the important contribution recently made by Fu et al. on the first non-enzymatic DKR of secondary alcohols (Scheme 3).[7] The non-enzymatic DKR presents the advantage of producing either enantiomer of the product depending on which enantiomer of the catalyst is employed. For many years, the main drawback for the development of non-enzymatic DKR was the incompatibility between the planar chiral DMAP complex and the harsh conditions required for the racemization process. Recently, Bäckvall et al. developed a [C_5Ph_5Ru] catalyst that rapidly racemizes secondary alcohols at room temperature.[8] Fu et al. took advantage of this discovery in their design of a novel non-enzymatic DKR process (Scheme 3). Unfortunately, the tandem ferrocene–ruthenium catalytic system was not compatible in the DKR of racemic 1-phenylethanol by means of acylation with Ac_2O, although the racemization of the optically pure (*R*)-1-phenylethanol proceeded smoothly under the experimental kinetic resolution conditions. After a reaction time of 48 h, the desired acetylated compound was

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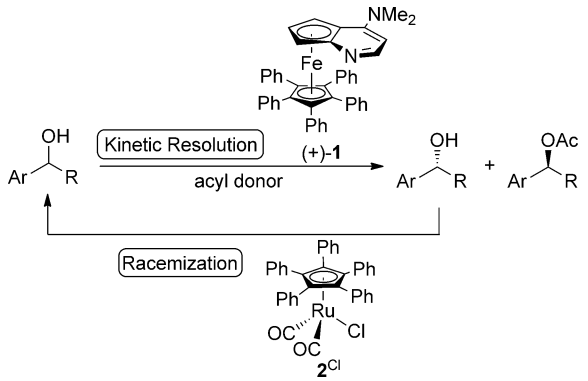
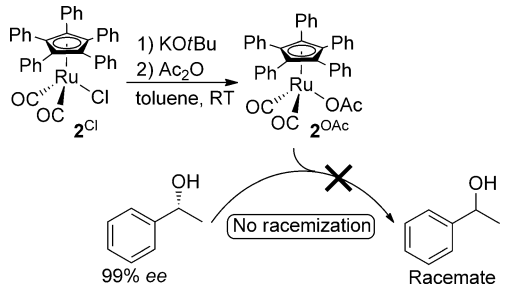


Scheme 3. Non-enzymatic DKR of secondary alcohols.

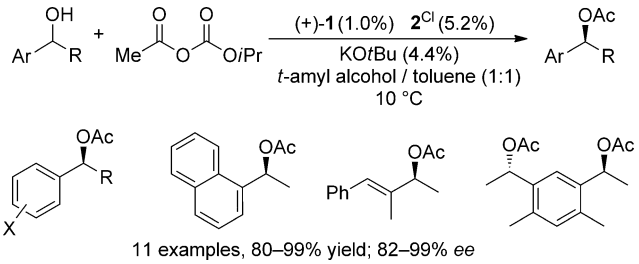
obtained with a selectivity of only 38% *ee*. The reason for this poor enantioselectivity is that Ac_2O deactivates the ruthenium catalyst. The Fu group confirmed this by synthesizing a new ruthenium derivative containing acetate as a ligand and, as expected, this complex did not catalyze the racemization of (*R*)-1-phenylethanol (Scheme 4).



Scheme 4. Deactivation of the racemization catalyst by Ac_2O.

Changing the acylating agent from Ac_2O to the acetyl isopropyl carbonate elegantly solved the problem. Since the acyl carbonates are less electrophilic than the anhydrides, the deactivation of ruthenium catalyst by acetate coordination might be avoided. Indeed, the acyl carbonate did not react with the ruthenium catalyst after 20 h at room temperature. On the other hand, although there are some reports that describe the decarboxylation of acyl carbonates promoted by DMAP,[9] no significant amounts of the corresponding ester were detected, even in the presence of ferrocene–DMAP derivative. Altogether, the authors were able to find the appropriate conditions for the non-enzymatic DKR of secondary alcohols using low catalyst loading (1.0% of (+)-**1**, and 5.2% of $\mathbf{2}^{Cl}$) in *t*-amyl alcohol/toluene (1:1) at 10°C. For example, for the DKR of the model substrate (racemic 1-phenylethanol) the corresponding *S* acetate was obtained in high yield and good *ee* (95% conversion (GC), 87% *ee*).

The scope of the DKR transformation was demonstrated using a variety of racemic secondary arylcarbinols, including those with electron-rich as well as electron-poor substituents in *ortho*, *meta*, and *para* positions of the aromatic ring, and an extended π-system; the corresponding acetates were obtained



Scheme 5. Non-enzymatic DKR of secondary alcohols.

in good yields and around 90% *ee* (Scheme 5). Additionally, the reaction was performed with an aromatic allylic alcohol as the racemic substrate. The alkyl substituent of the carbinol can range in size from a methyl group to a more bulky isopropyl group. Therefore, this methodology complements the corresponding enzymatic DKR, which was only effective when the alkyl group was not branched.[10] The stereoconvergent acylation of a diol was also developed by this procedure and the C_2-symmetric bis(acetate) was obtained in excellent enantioselectivity.

Finally, Fu and co-workers have performed a complete and detailed experimental mechanistic study of this non-enzymatic DKR. They have found that the reaction is first order in the racemic carbinol substrate, in the acylation ferrocene complex, and in the acylating agent, but only when the concentration of the acylating agent is below 0.5 M. The rate law, however, does not depend on the racemization catalyst. This study, together with the NMR experiments developed to characterize the catalytic acylated species, led the authors to propose a reaction mechanism, in which the rate-determining step is the acyl transfer from the catalyst to the alcohol.

In conclusion, this is the first time that the non-enzymatic DKR of secondary alcohols through acylation is described. This is a not only a complementary methodology to the chemoenzymatic DKR, but also the starting point for new developments in this field.

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