

Dynamic Kinetic Resolution: Practical Applications in Synthesis

Introduction

The resolution of racemic mixtures has become an increasingly important field in organic chemistry due to the ease of preparing racemic substrates and the number of transformations that can be exploited to easily change one enantiomer in preference to the other¹. Kinetic resolution has been a tool for chemists for almost 150 years and remains an important transformation for creating enantiopure samples. The one major limitation of this technique is that the maximum theoretical yield is 50% due to the consumption of only one enantiomer. Because of this, the unreacted enantiomer must be racemized and resubmitted to resolution conditions in order to increase this yield. If the racemization can occur concurrently with the kinetic resolution, known as *dynamic* kinetic resolution, then theoretically 100% of the racemic mixture can be converted to one enantiomer².

Dynamic kinetic resolution is an example of a Curtin-Hammett system in which the composition of products is controlled by the free energies of the transition states and not the composition of the starting materials³. In other words, the rates of the competing reactions along with the rate of racemization are extremely important in the overall resolution reaction. Figure 1 is a representation of this type of system where $\Delta\Delta G^\ddagger$ is more important than ΔG . The ideal dynamic kinetic resolution reaction which approaches 100% conversion to a 100% enantiomerically enriched product is one in which $k_{inv} \gg k_R \gg k_S$ (Figure 2)⁴. If k_{inv} were in fact closer to or even slower than k_R , the ee of the product would be lowered because the amount of R in solution would not be produced fast enough to make k_S negligible.

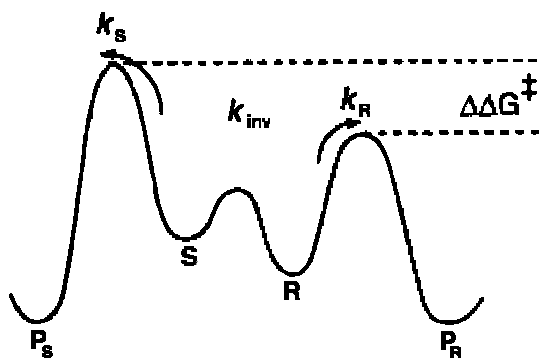


Figure 1. Dynamic Kinetic Resolution

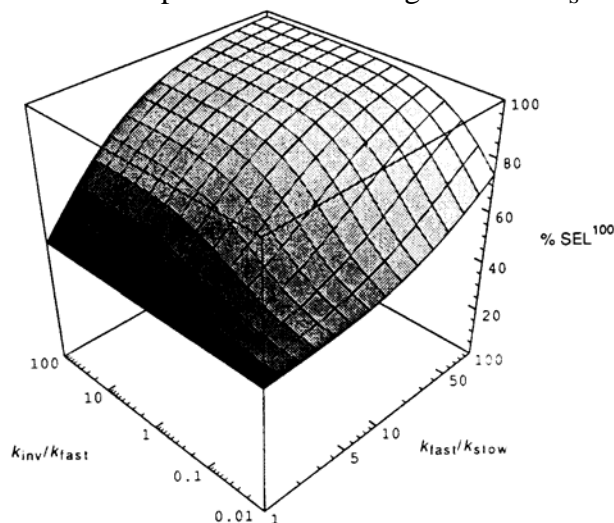
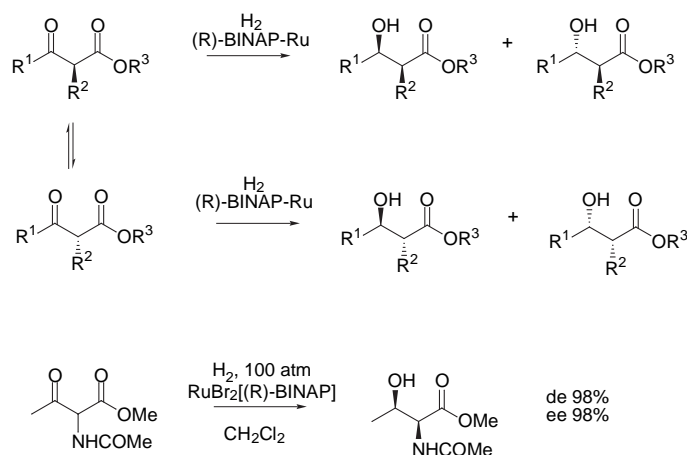


Figure 2. Relationship of k_{inv} , k_R , and k_S

Types of Dynamic Kinetic Resolution

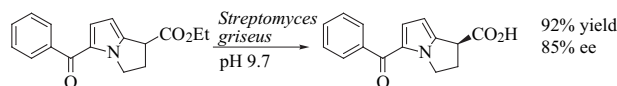
The first reported example of dynamic kinetic resolution by purely chemical means was by Noyori in 1989 with the Ru-BINAP hydrogenation catalyst⁵. β -ketoester **1**, which readily isomerizes between **1 α** and **1 β** via an enol intermediate, is reduced with the Ru-BINAP catalyst to give one of the four diastereomers in high de and ee (Scheme 1). The catalyst not only differentiates between the enantiotopic faces of the ketone, it can also discriminate between enantiomers at the α position. Converting racemic **1**

into **2** with excellent control of two adjacent centers shows the power and importance of diastereomeric dynamic kinetic resolution.



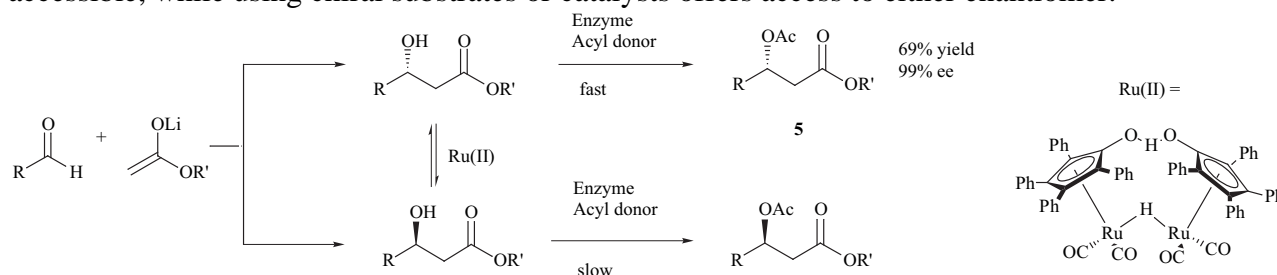
Scheme 1. Noyori System

The widest use of dynamic kinetic resolution is accomplished with enzymes alone or in tandem with a chemical racemization to provide enantiopure secondary alcohols⁶, acetates⁷, carboxylic acids⁸, esters⁹, and β -hydroxy esters¹⁰. Sih has reported the dynamic kinetic resolution of ethyl ester **3** with the protease *Streptomyces griseus* in alkaline solution to produce the corresponding acid **4** in 92% yield and 85% ee¹¹ (Scheme 2). Bäckvall has developed many dynamic kinetic resolution reactions which take advantage of both enzymatic resolution and transition metal mediated isomerization. One such reaction



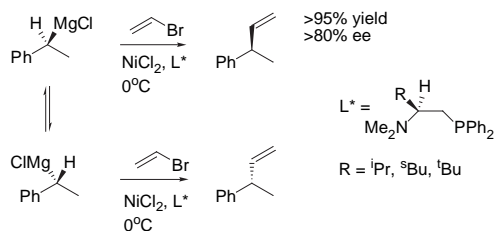
Scheme 2. Enzymatic Resolution

combines an aldol reaction with Ru catalyzed isomerization of the secondary alcohol and lipase mediated acetylation to produce the β -acetoxy ester **5** in 69% yield and 99% ee¹² (Scheme 3). One serious drawback to using enzymes with dynamic kinetic resolution is that only one enantiomer is sometimes accessible, while using chiral substrates or catalysts offers access to either enantiomer.



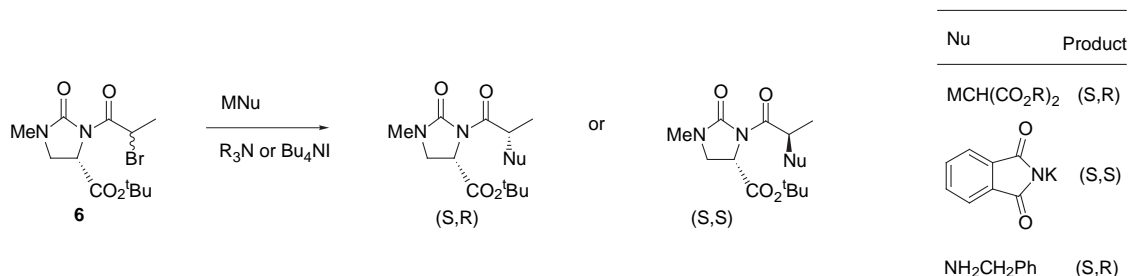
Scheme 3. Enzyme and Transition Metal Dynamic Kinetic Resolution

Using chemical means to accomplish dynamic kinetic resolution greatly expands the scope of this reaction. One such application of resolving enantiomers is the asymmetric Grignard cross coupling reaction¹³ where a racemic Grignard is transmetalated to a nickel catalyst with a chiral ligand (Scheme 4). This now resolved carbon-metal center adds to vinyl bromide with retention to preserve the stereochemistry of the newly formed chiral carbon.



Scheme 4. Transmetalation

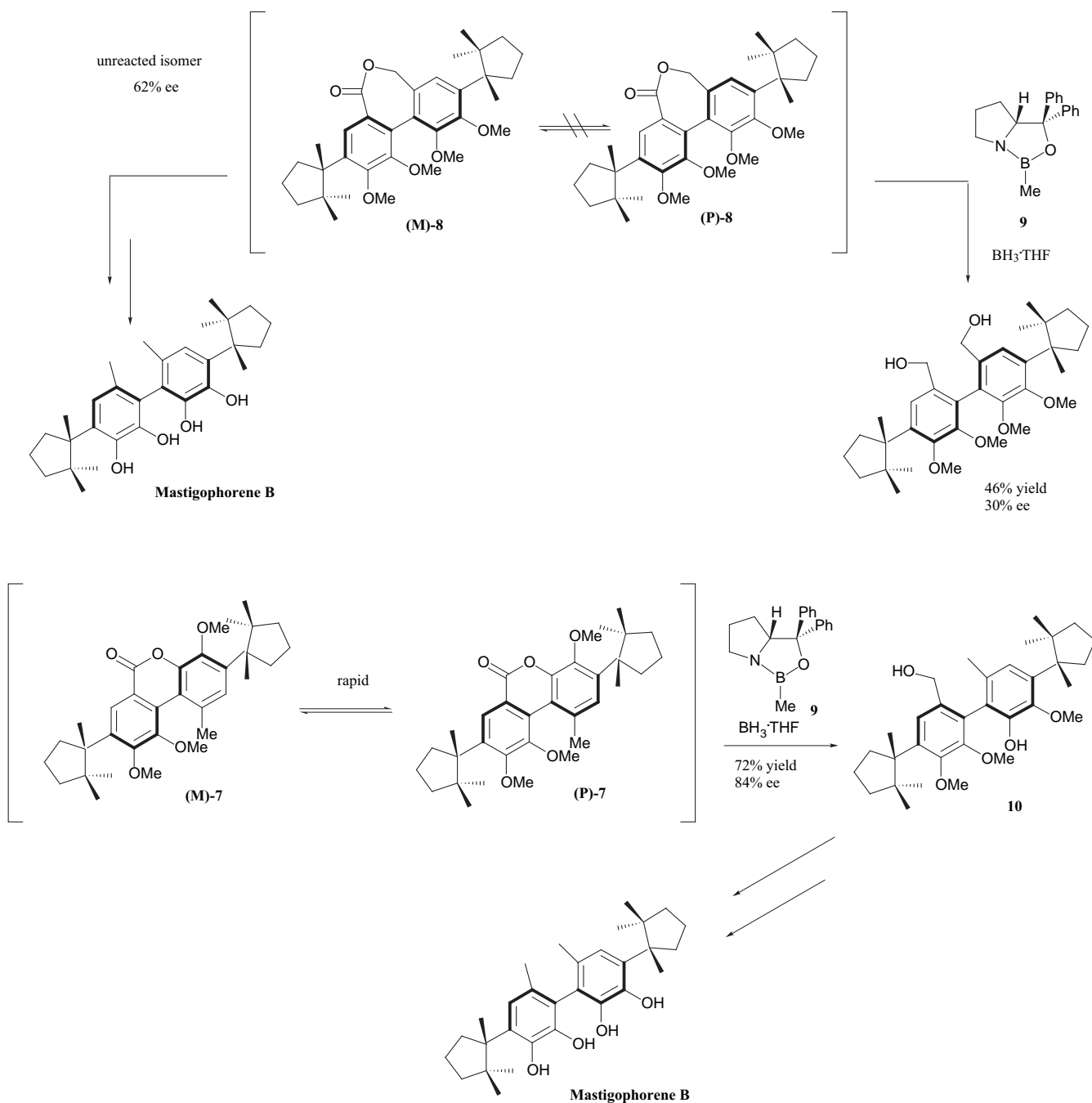
Diastereomers can be resolved by this technique using either reagent or catalyst control for the asymmetric induction. One example of reagent control is the chiral auxiliary developed by Nunami from L-asparagine¹⁴ (Scheme 5). Urea **6** was racemized with either an amine base through the enolate or halide ion via S_N2 and resolved with a wide range of nucleophiles to provide a variety of α -substituted esters and amino acids with the stereochemistry dictated by the *tert*-butyl ester sidechain. One drawback to this technique is that the chiral auxiliary must be removed when the reaction is complete.



Scheme 5. Nunami Chiral Auxiliary System

Kinetic Resolution vs. Dynamic Kinetic Resolution

The total synthesis of Mastigophorene B has been accomplished in two routes, one involving kinetic resolution and the other utilizing dynamic kinetic resolution to set the chiral axis¹⁵. Intermediates **7** and **8** were synthesized in similar ways, but **7** has a six membered lactone and **8** has a seven membered lactone ring (Scheme 6). This difference in ring size makes **8** conformationally stable at room temperature whereas **7** is not. Kinetic resolution of **8** with the Corey-Bakshi-Shibata (CBS) oxazaborolidine **9** gave the unreacted isomer in 62% ee. The opened product was recycled back to the lactone **8** and resubmitted to the resolution conditions. The dynamic kinetic resolution of **7** with the same reaction conditions gave the product **10** in 72% yield with 84% ee. Although the resolution of **7** occurred in one step, the kinetic resolution of **8** was part of a more efficient route because **8** is synthesized from identical monomers and hence shortens the synthesis.



Scheme 6. Mastigophorene B

Conclusion

Chemically mediated dynamic kinetic resolution is becoming an ever increasingly used technique for asymmetric synthesis. The theory of obtaining a 100% yield of one enantiomer or diastereomer from an easily prepared racemic mixture is extremely alluring. The careful control of relative rates in the competing reactions of dynamic kinetic resolution remains a key factor in optimizing these reactions. There is no doubt that dynamic kinetic resolution will become a widely used technique not only in the synthetic lab, but also in industrial production of chiral molecules.

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