

RECENT ADVANCES OF DYNAMIC KINETIC RESOLUTION: DESIGN, ENGINEERING AND OPTIMIZATION

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INTRODUCTION

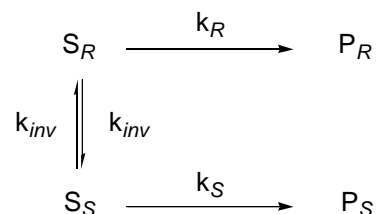
The Concept of Dynamic Kinetic Resolution

Conventional kinetic resolution takes advantage of the fact that enantiomers react at different rates in the presence of a chiral catalyst or a chiral reagent. Given one enantiomer reacts much faster than the other, one could obtain the product derived from the more reactive enantiomer and the unreacted less reactive enantiomer in high enantiomeric excess. Conventional kinetic resolution suffers from an inherent limitation; namely, the highest attainable yield of the product is 50% whereas the other 50% of the undesired enantiomer may not be able to be utilized. This inevitably limits the practicality and efficiency of the synthesis. However, if one envisions that under the reaction conditions, there is a rapid equilibrium between the two enantiomers, obtaining one single product in high yield and high enantiomeric ratio becomes possible. This phenomenon is described as dynamic kinetic resolution.¹ A system of kinetic resolution can be converted to dynamic kinetic resolution by allowing racemic starting material to interconvert in situ. Dynamic kinetic resolution has been done using enzymatic, non-enzymatic methods and the combination of enzymes and metal catalysts.^{1(b), (d)} Recently, dynamic kinetic resolution has attracted much attention and gained much importance due to its advantage over conventional kinetic resolution, and has become an area of active research. This abstract highlights recent advances in dynamic kinetic resolution, illustrating the diversity of modes of racemization, with the focus on the design and optimization of each methodology.

Kinetic Model of Dynamic Kinetic Resolution

A reaction involving two enantiomers in a chiral environment can be represented in a generic scheme (Scheme 1), where k_R and k_S are the rate constants of the conversion of enantiomeric starting materials S_R and S_S to products P_R and P_S , respectively, and k_{inv} is the rate constant of racemization. Based on the assumptions of (1) k_R , k_S and k_{inv} are rate constants of first-order kinetics; (2) S_R and S_S interconvert at the same rate; (3) S_R and S_S convert to P_R and P_S irreversibly, and P_R and P_S are configurationally stable under reaction conditions; (4) S_R is arbitrarily assumed to be the faster reacting enantiomer, i.e. $k_R > k_S$, Noyori and co-workers² showed that the enantio excess of P_R is the highest when it

Scheme 1. Kinetic Scheme of Dynamic Kinetic Resolution.

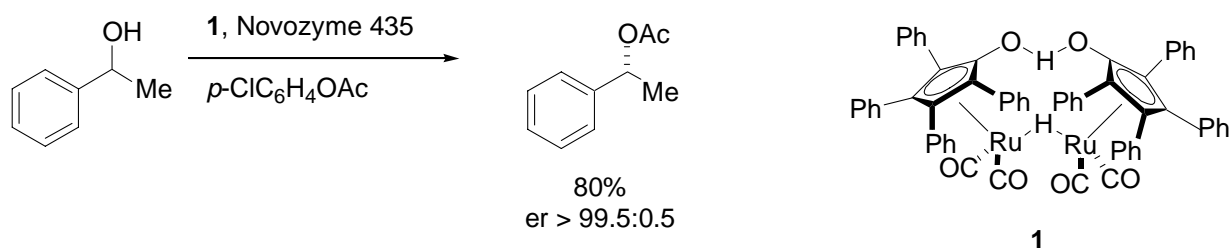


is first formed, and approaches the minimum as the reaction approaches completion. In addition, the dynamic kinetic resolution becomes more efficient as k_R/k_S or k_{inv}/k_R increases. Extending Noyori's concept, Andraos³ pointed out that dynamic kinetic resolution and Curtin-Hammett principle are very closely connected. The more the reaction conditions simulate to Curtin-Hammett limit, the more efficient the dynamic kinetic resolution becomes. He also correlated the enantiomeric excess of the starting material and that of the product: In a very efficient dynamic kinetic resolution, the enantiomeric ratio of the product is virtually independent of that of the starting material, and it is invariably high. These kinetic and energetic considerations allows dynamic kinetic resolution to be quantified and fine tuned, including switching solvents, modifying catalyst, changing catalyst loading and alternatively, adjusting reaction temperatures. For example, if k_R and k_S are similar while racemization is fast (Curtin-Hammett limit), decreasing the temperature can increase the selectivity of the catalyst. Conversely, if k_R and k_S are different enough while racemization is slow (non-Curtin-Hammett limit), increasing the temperature and facilitate racemization and enhance the enantiomeric excess of the product.

DYNAMIC KINETIC RESOLUTION OF SECONDARY ALCOHOLS VIA ACYLATION

Kinetic resolution of secondary alcohols, which are useful chiral building blocks, using lipases is a well established method, in which, *R* enantiomer is selectively acylated.⁴ The origin of enantioselectivity come from the stabilization of the tetrahedral intermediate derived from *R* enantiomer from the histidine residue of the catalytic triad through hydrogen bonding. Modeling studies indicate that this stabilization is absent in the case of *S* enantiomer.⁵ Bäckvall and co-workers envisioned that the enzymatic resolution of secondary alcohols can be converted into a more efficient process of dynamic kinetic resolution by allowing the secondary alcohol substrate to freely racemize. Thus dimeric ruthenium complex **1**, which is known to catalyze hydride transfer reactions is employed for this purpose in tandem with the Novozyme 435 (*Candida Antarctica* lipase B immobilized on resin) to achieve dynamic kinetic resolution (Scheme 2).⁶

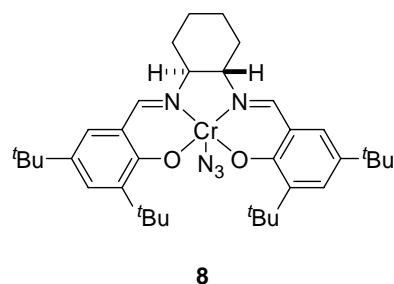
Scheme 2. Dynamic Kinetic Resolution of Secondary Alcohols Using Ru Catalyst and Lipase.



In this system, ruthenium complex **1** oxidized the secondary alcohol to a ketone via hydride transfer from alcohol to ruthenium, and the concomitant reduction, which is another hydride transfer, took place from both faces of the ketone carbonyl group. The net result of this process is racemization of the alcohol. The less reactive *S* enantiomer is able to be converted to the *R* enantiomer through this pathway and be subsequently acylated. The dynamic kinetic resolution of secondary alcohol developed by Bäckvall and co-workers showed a general scope of substrate; both aromatic and alkyl substituted secondary alcohols are resolved in high enantimetric ratio. Functionalization and homologation on the smaller substituents are also tolerated. However, electron-rich aryl alcohols are acylated sluggishly, albeit with high enantiomeric ratio.⁶

ASYMMETRIC RING OPENING OF EPICHLOROHYDRIN

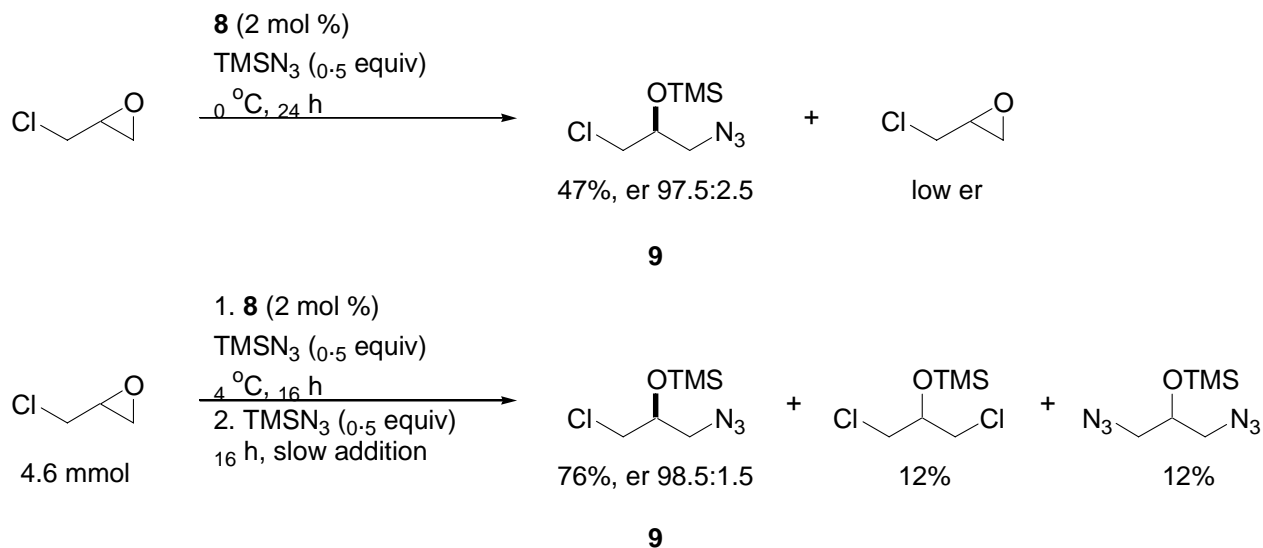
Epichlorohydrin is a useful building block that can be easily prepared at low cost, and its ring opening product is a highly functionalized secondary alcohol derivative that has a lot of synthetic utility.



Jacobsen has described a very efficient kinetic resolution of epichlorohydrin using Cr(salen) complex **8** and TMSN₃.¹³ When half an equivalent of TMSN₃ is used, the ring opening product **9** is obtained in high enantiomeric ratio. However, the starting epichlorohydrin is recovered with eroded enantiopurity (Scheme 3).¹⁴ Jacobsen suggested that the epichlorohydrin is racemized existed, and since the rate of racemization and ring opening are similar, dynamic kinetic resolution

can potentially be achieved. However, treatment of epichlorohydrin with stoichiometric amount of TMSN₃ only resulted in ring opening product **9** with low enantiomeric ratio (er 70:30). The optimized condition is found to be initial employment of kinetic resolution conditions, followed by slow addition of 0.5 equivalent of TMSN₃. In so doing, since the concentration of TMSN₃ is kept very low throughout the period of slow addition of TMSN₃, the rate of racemization would be substantially faster than epoxide ring opening. Consequently, silyl ether **9** is obtained in good yield and excellent enantiomeric ratio (Scheme 3). Silyl ether **9** is a highly functionalized chiral building block and, its synthetic utility is demonstrated by Jacobsen and co-workers in the synthesis of U-100592.¹⁴ Although this is indeed a very efficient process, the formation of achiral dichloride and diazide byproducts is a drawback of this method. It should be noted that, epichlorohydrin is a special case among epoxides. Epichlorohydrin can undergo the process of dynamic kinetic resolution because it can form an achiral intermediate, but this is not the case for other terminal epoxides. Therefore, this method methodology, unfortunately, cannot be applied to other terminal epoxides.

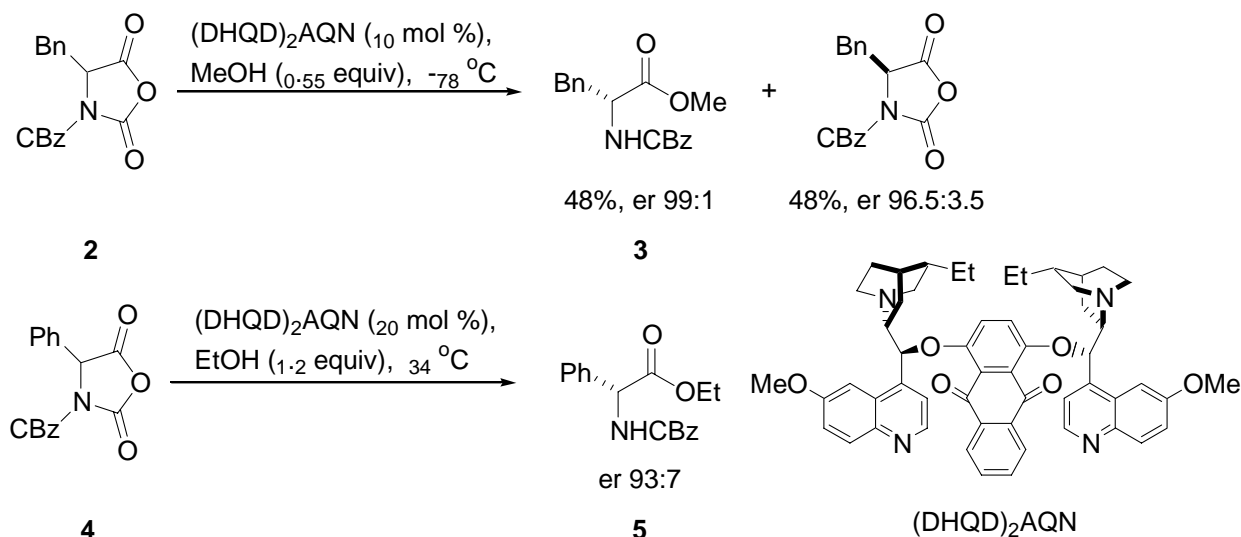
Scheme 3. Ring Opening of Epichlorohydrin in the Presence of Cr(salen) Complex **8**.



DYNAMIC KINETIC RESOLUTION OF α -AMINO ACID *N*-CARBOXYANHYDRIDES

In addition to secondary alcohols, α -amino acids are another class of useful building blocks. Deng and co-workers recently reported that at $-78\text{ }^{\circ}\text{C}$, racemic α -amino acid *N*-carboxyanhydride **2** is resolved using methanol and cinchona alkaloid (DHQD)₂AQN with high enantioselectivity, resulting enantiomerically enriched amino ester **3**.⁷ Deng envisioned that under favorable conditions, the cinchona alkaloid can effectively racemize the starting material by removing the α proton next to the carbonyl group to generate an enolate, followed by the subsequent protonation on both faces of the enolate. Deng and co-workers suggest that alcoholysis catalyzed by a cinchona alkaloid involves a trimolecular transition state.⁷ On the other hand, the mechanism of racemization is likely to be bimolecular. This implies that the entropy of activation of alcoholysis is more negative than that of racemization. Therefore, at higher temperatures, the energy barrier of racemization can be reduced to a greater extent relative to that of alcoholysis. Hence, the rate of racemization can be accelerated and exceed that of alcoholysis simply by raising the reaction temperature, which in turn, makes dynamic kinetic resolution possible. Indeed, at room temperature, racemic α -amino acid *N*-carboxyanhydride **4** reacted with ethanol in the presence of (DHQD)₂AQN and gave alcoholysis product aminoester **5**, in high enantiomeric ratio (Scheme 4).⁸ In contrast, same reaction conducted at $-78\text{ }^{\circ}\text{C}$ is very unselective. This method allows the synthesis of a variety of chiral arylglycinates with high enantiomeric ratio from racemic sources. Deng and co-workers also expanded the scope of the substrate to benzyl substituted α -amino acid *N*-carboxyanhydrides.⁹ Because of the diminished acidity of this class of substrates, more

Scheme 4. Kinetic and Dynamic Kinetic Resolution of α -Amino Acid *N*-Carboxyanhydrides.

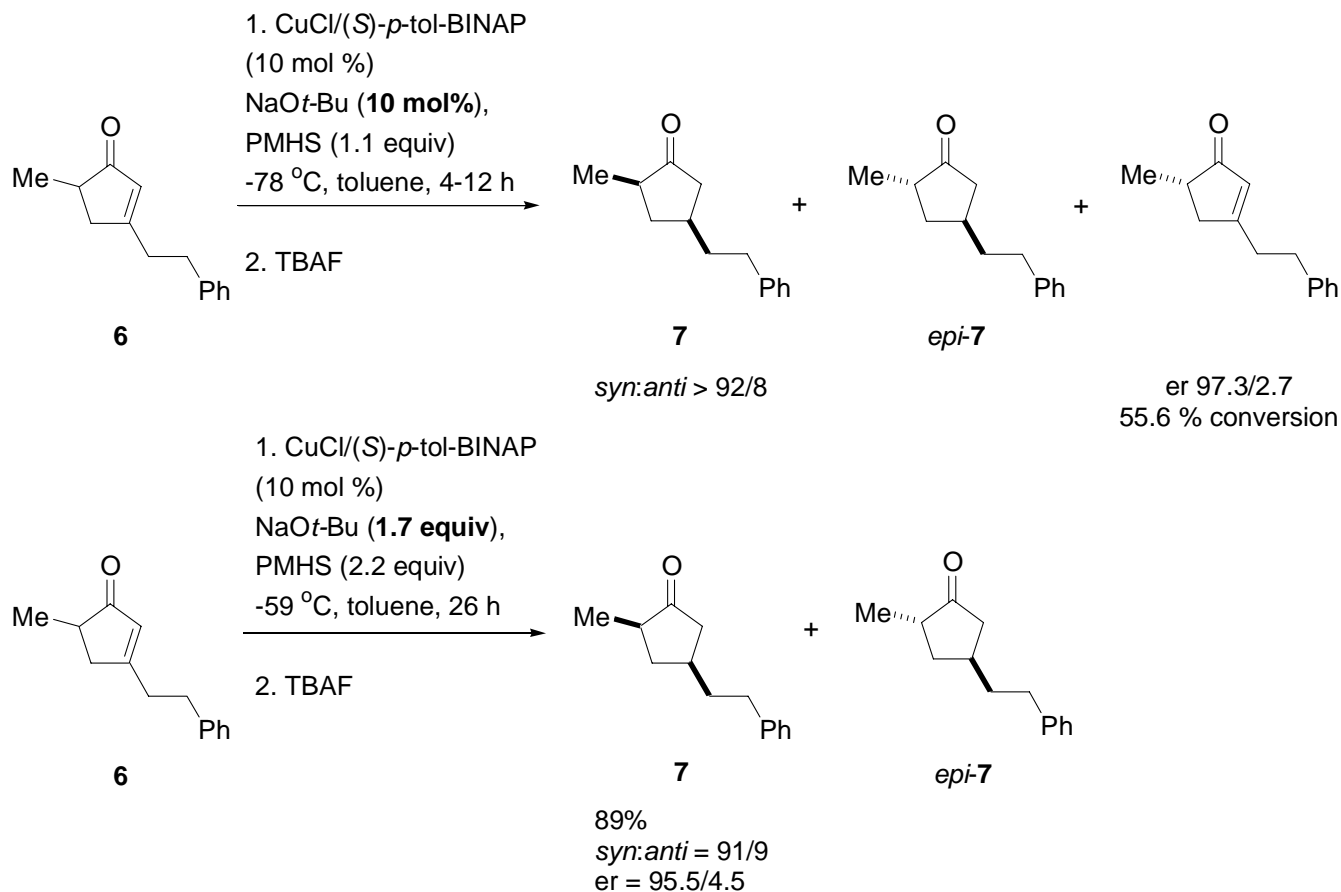


electron-withdrawing protected group on the nitrogen, such as dichloroacetyl group is required to promote cinchona alkaloid-catalyzed racemization and thus obtain a higher enantiomeric ratio. Moreover, Deng and co-workers also developed the dynamic kinetic resolution of dioxolanedione, the oxygen analogue of α -amino acid *N*-carboxyanhydrides, to obtain enantiomerically enriched α -hydroxy esters.¹⁰

COPPERCATALYZED CONJUGATE REDUCTION OF CYCLOPENTENONES

Buchwald and co-workers recently developed a methodology Cu catalyzed asymmetric conjugate reduction of cyclopentenones, using polymethylhydrosiloxane as the hydride source.¹¹ They observed that the *R* enantiomer of 3,5-disubstituted 2-cyclopentenones such as **6**, can be selectively reduced while the unreacted *S* enantiomer is recovered with high enantiomeric ratio (Scheme 5).¹² Unlike all the previous examples, this method allows setting of a two non-adjacent stereocenters in one pot. Buchwald envisioned converting the kinetic resolution into a dynamic kinetic process by exchanging the acidic proton next to the carbonyl group and thereby racemizing cyclopentenone **6**. Indeed, using excess amount of KO^tBu, cyclopentenone **6** is efficiently racemized, and resulted reduction product is obtained in high enantiomeric ratio. Moreover, Buchwald observed that for the substrates with more sterically demanding substituents α to the carbonyl group, higher reaction temperatures are required to promote efficient racemization. The drawback of Buchwald's method is that due to the conformational lability of the cyclopentanone **7**, in the presence of an excess of NaOt-Bu, it is epimerized to give a small amount of *anti* product *epi-7* (Scheme 5).¹²

Scheme 5. Asymmetric Conjugate Reduction of Cyclopentenones.

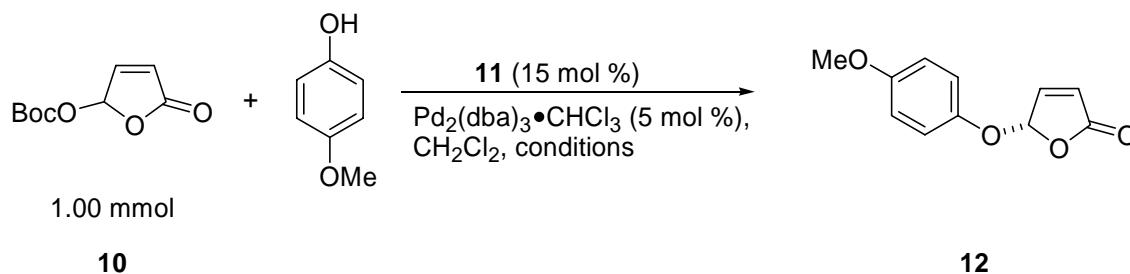


ASYMMETRIC ALLYLIC SUBSTITUTION OF γ -ACETOXYBUTENOLIDES

The kinetic resolution of γ -acetoxybutenolide **10** is done by asymmetric allylic substitution reaction catalyzed by chiral palladium complex.¹⁵ Although the product **12** is isolated in 45% yield and high enantiomeric ratio, unexpectedly, Trost and co-workers observed a deterioration of the enantiopurity of recovered butenolide **10**, and this is rationalized by involving a rapid racemization of **10** under the reaction conditions (Table 1, entry 1). Therefore, this system has the potential to be transformed into dynamic kinetic resolution. The initial trial is done using the above set of conditions with stoichiometric amount of *p*-methoxyphenol, but the enantiomeric excess of product **12** is very moderate (entry 2). Presumably, this is because the rate at which the isomerization of π -allylpalladium intermediates is still not rapid enough with respect to allylic substitution so that the dynamic kinetic resolution of butenolide **10** can be efficient. Subsequently, Trost and co-workers suggest the possibility of opening an alternative pathway of racemization. Therefore, a substoichiometric amount of TBACl

(tetrabutylammonium chloride) employed to promote isomerization,¹⁶ and consequently, the enantiomeric ratio of **12** is increased to substantially (entry 3). This result can be further optimized by carrying out the reaction in the absence of Cs₂CO₃ at 0 °C to attenuate the rate of nucleophilic addition of *p*-methoxyphenol. As a result, although the reaction proceeded somewhat more slowly, the enantiomeric ratio of **12** could be further increased to 87.5:12.5 (entry 4).¹⁵

Table 1. Kinetic and Dynamic Kinetic Resolution of γ -Acetoxybutenolide **10.**



entry	mol % phenol	mol % Pd	mol % ligand	conditions	yield (er)
1	45	0.5	1.5	15% Cs ₂ CO ₃ , rt, 16 h	45% (93.5:6.5-95:5)
2	100	0.5	1.5	15% Cs ₂ CO ₃ , rt, 16 h	80% (74:26)
3	100	2.5	7.5	15% Cs ₂ CO ₃ , 30% TBACl, 0 °C, 12 h	80% (87.5:12.5)
4	100	1.0	3.0	30% TBACl, 0 °C, 12 h	74% (92:8)

CONCLUSION

Dynamic kinetic resolution has the inherent advantage over conventional kinetic resolution as it is more efficient and does not leave behind the undesired enantiomer that may not be easily reutilized. The above examples illustrate that it is possible to convert kinetic resolution to the more efficient dynamic kinetic resolution in high yield and enantiomeric ratio by allowing the enantiomers to interconvert. Different modes of racemization in the above examples further show that a very wide variety of substrates used in kinetic resolution have the potential to be converted to dynamic kinetic resolution. Moreover, one can optimize the dynamic kinetic resolution by accelerating the rate of racemization and enhancing the selectivity. In the near future, one can certainly expect to see many more synthetically useful methodologies of dynamic kinetic resolution being developed.

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