Practical Considerations in Kinetic Resolution Reactions

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Abstract: This review provides a critical analysis of catalytic kinetic resolution reactions from a practical perspective, asking the question of when, if ever, is kinetic resolution the best option for the synthesis of an optically active target. A series of crucial conditions are identified, and it is postulated that if all of them are met, then indeed kinetic resolution can be highly practical. A variety of catalytic kinetic resolution processes are evaluated in the context of these criteria, with particular emphasis on catalyst availability, substrate scope, availability of the racemic substrate and of alternative methods for accessing enantiopure substrate or product, and key experimental considerations. It is found that several catalytic systems have been developed that offer almost unbeatable methods for the preparation of useful chiral building blocks.

Keywords: asymmetric catalysis; catalysts; chiral resolution; enantiomeric resolution; epoxidations; homogeneous catalysis

1 Introduction

The goal of asymmetric synthesis – whether it is done in an academic or an industrial setting – is to prepare stereochemically-enriched compounds in the most efficient and practical manner possible. However, the choice of strategy is rarely simple, because the ways in which efficiency and practicality are defined can depend on a large number of factors. These can include scale, reagent costs, time allotted and required, number of steps/manipulations, potential hazards, waste generation, specifications for product purity, volumetric productivity and/or throughput, availability of appropriate equipment, and even the scientific background of the synthetic chemists involved. In selecting a method for the preparation of an enantioenriched compound, one must therefore consider the different alternatives. There are three fundamentally different approaches,[1] and these can be defined as follows:

- *Chiral pool*: use of enantiopure starting materials provided by Nature.
- *Resolution*: separation of enantiomers by chemical or physical means.
- *Enantioselective synthesis*: preparation from achiral precursors using chiral reagents or catalysts.

There are numerous instances where the chiral pool approach is unbeatable, either because the requisite starting material is produced by Nature in great abundance or because the target is itself a complex natural product and laboratory syntheses are very expensive relative to isolation from natural sources. Unfortunately, the range of compounds provided by Nature is limited with respect to structure and stereochemistry, and for this reason resolution and asymmetric synthesis will certainly always be vitally important strategies for accessing enantiopure compounds.

Resolution strategies have always played a central role in the preparation of optically active compounds.[2] However, and particularly recently, great effort has been directed toward avoiding such approaches due to what is perceived to be their inherent inelegance and inefficiency. This is due to the fact that, except in those rare cases where both enantiomers can be employed productively, resolutions have a maximum yield of 50% based on racemic starting material. In that respect, they can be seen as displaying inherently poor "atom economy".[3]

Enormous advances have made over the past several years in asymmetric synthesis,[4] with particular emphasis having been placed on the development of enantioselective catalytic reactions.[5] The advantages associated with enantioselective synthesis are well-recognized, and can include: a) access to either enantiomer of product based on which enantiomer of reagent/auxiliary/catalyst is employed; b) use of a readily-available achiral substrate; and c) minimization of waste typically associated with resolution processes.

Different factors influence the practicality of an asymmetric reaction. A list of the features

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John Keith was born in Miami, Florida in 1969. He studied chemistry at the University of South Florida, graduating in 1992. He did his Ph.D. work under the tutelage of Professor Bruce Lipshutz at the University of California Santa Barbara, devoting most of his effort to diastereoselective biaryl couplings related to the korupensamines. After graduating in 1998, he moved to his current position as a post-doctoral associate with Eric Jacobsen at Harvard University. His research there involves the development of methods for the asymmetric hydrocyanation of hydrazones and nitrones.

Jay Larrow was born in 1967 in Holyoke, Massachusetts. He earned his B.S. degree from Worcester Polytechnic Institute in 1989. After working in industry for three years, he joined the Jacobsen group and received his Ph.D. from Harvard University in 1998. He then moved to the University of California, Irvine as an American Cancer Society Postdoctoral Fellow under the direction of Larry Overman. In 1999, he joined ChiRex (now Rhodia ChiRex) as a senior scientist, where his work is focused on the development and application of new asymmetric catalytic technologies. He and his wife Allison welcomed the arrival of their first child in September, 2000.

Eric Jacobsen was born in 1960 in New York City. He carried out his undergraduate studies at N.Y.U. and his Ph.D. work at the University of California, Berkeley with Bob Bergman. After an NIH Postdoctoral Fellowship at MIT with Barry Sharpless, he began his independent career at the University of Illinois at Urbana-Champaign in 1988. In 1993 he moved to his current position as full professor at Harvard University. His research is focused on methodology, synthesis, and mechanism, particularly in the context of asymmetric catalysis. His work has been recognized by the Fluka Reagent of the Year Prize, the Thieme-IUPAC Prize, the Baekeland Medal, and the ACS Award for Creativity in Synthetic Organic Chemistry.

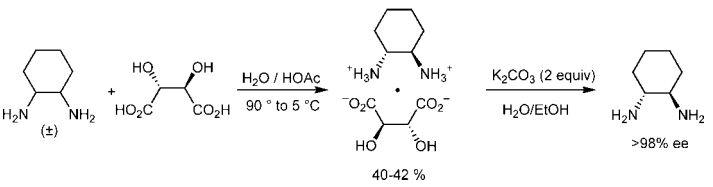
that would describe the ideal enantioselective transformation is necessarily subjective, but it could include:

- Products are obtained in quantitative yield.
- Reaction provides product in 100% enantiomeric excess (ee).
- Starting materials are inexpensive.
- Reaction times are short.
- Large amounts of product can be obtained with available glassware/equipment (high volumetric throughput).
- The chiral catalyst, reagent, or auxiliary is inexpensive and available, and does not contribute to the overall cost.
- Products are easily isolated, with little-or-no purification necessary.
- There is minimal generation of byproducts and waste.
- The reaction can be applied reliably and reproducibly on any scale.
- The reaction displays broad substrate scope, including high functional group compatibility.
- There is no better way to make the product in question.

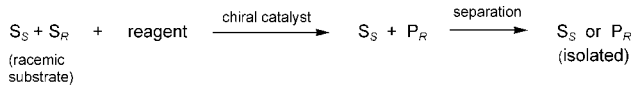
Arguably no reactions discovered to date meet all of these criteria. Indeed, if a new asymmetric catalytic reaction comes close to meeting the first two alone, this can justify its publication in a premier journal. To the extent that no enantioselective process is perfect, it is interesting to compare asymmetric reactions to the best methods for synthesizing the corresponding products in racemic form. In a few cases, e.g., for the laboratory synthesis of 1,2-diols, epoxy alcohols, and certain hydrogenation products, asymmetric catalytic methodologies do in fact exist that make it as easy to prepare highly enantioenriched materials as it is to prepare racemic mixtures. However, in a far greater number of cases, it is still much easier and less expensive to access racemates. As a result, despite what they might lack in "elegance", resolution strategies must always be evaluated carefully against any asymmetric process.[6]

Resolutions fall broadly into three classes. *Classical resolutions* involve the use of a stoichiometric amount of a chiral resolving agent.[7] The resolving agent is associated to the substrate, either covalently or non-covalently, to generate a pair of diastereomers. The diastereomers are separated and, through a separate chemical transformation, the substrate is released from the resolving agent. This approach has proven to be especially useful if salt formation is straightforward, as in the case of amines and carboxylic acids (e.g., Scheme 1[8]). *Chiral chromatography* generally relies on the use of a chiral stationary phase to resolve enantiomers contained in a mobile phase, and in principle it can be carried out on analytical or preparative scale. In reality, the large solvent volumes, long separation times, and relatively high costs of chiral chromatography supports often limit the scale at which chromatographic separations can be carried out. *Kinetic resolution* involves using a chiral catalyst or reagent to promote selective reaction of one enantiomer over the other giving a mixture of enantioenriched starting materi-

al and product, and the desired component is then isolated (Scheme 2).[9]



Scheme 1. Classical resolution of *trans*-1,2-cyclohexanediamine



Scheme 2. Catalytic kinetic resolution

As noted above, the theoretical yields for such resolutions are usually 50%. If the "undesired" resolution byproduct can be racemized or otherwise converted back to the desired enantiomer, then this can improve the yield, and therefore the practicality, of the resolution process, provided the additional cost in time and materials does not eclipse the cost of the initial resolution. In some special circumstances, it is possible to induce substrate racemization under the conditions of resolution. It then becomes possible in principle to convert essentially 100% of the racemate to the desired product (see Section 2.2). Such processes constitute a very special subclass of kinetic resolution reactions known as dynamic kinetic resolutions.

For the most part, however, racemization is not readily effected and the issue of a maximum yield of 50% holds. This applies equally to parallel kinetic resolutions, an additional subclass of kinetic resolution reactions (see Section 2.2). However, given that racemates can often be much less than half as expensive than their enantiopure counterparts, it is clearly simplistic to consider resolutions as being inherently inelegant or impractical. Indeed, the fact that resolution remains so widely used is probably the best evidence that it can in fact be the most attractive option for accessing enantioenriched compounds. Catalytic kinetic resolutions are particularly attractive, at least in principle, because of the need for only small amounts of chiral "resolving agent". However, kinetic resolution has been used very little in a commercial context compared to classical or even chromatographic resolution. The question must therefore be asked, "can kinetic resolutions ever be practical?" We propose that the answer to this question is most certainly "yes", and that the practical potential of kinetic resolution is in fact very significant. However, the following conditions must be met:

- The racemate is cheap and no good enantioselective, chiral pool, or classical resolution route to the product exists.
- The catalyst is highly selective for one enantiomer and is effective at low loadings.
- The catalyst is inexpensive or it can be recycled efficiently.
- The reaction is economical and safe (i.e., inexpensive stoichiometric reagents, no undue dangers associated with the reagents, high volumetric throughput, and a minimum of waste generated).
- The resolved starting material and converted product are easily separated.
- In the ideal case, both the product and the resolved substrate are valuable and recoverable in highly enantioenriched form.

The goal of this review is to provide an analysis of selected catalytic kinetic resolution reactions in the context of the criteria outlined above. As might be expected, there are as yet no perfect kinetic resolutions, just as there are no perfect enantioselective reactions. Nonetheless, it will be shown that there are clear examples where kinetic resolutions provide extremely practical methods for the preparation of useful chiral building-blocks that are otherwise not easily accessed in enantiopure form.

2 Theoretical Considerations

2.1 Standard Kinetic Resolutions

In kinetic resolutions, enantiomers of a racemic substrate (S) react at different rates to form a product (P) that may or may not be chiral (Figure 1). In a catalytic kinetic resolution, the relative rates of reaction for the substrate enantiomers, typically expressed as s or $k_{rel} = k_{fast}/k_{slow}$, are dictated by the magnitude of $\Delta\Delta G^{\ddagger}$. This corresponds to the difference in energies between the diastereomeric transition states in the selectivity-determining step of the catalytic reaction (Eq. 1). Thus, k_{rel} in a kinetic resolution is related to $\Delta\Delta G^{\ddagger}$ in the same manner as it is in an enantioselective reaction of a prochiral substrate.

$$k_{rel} = s = k_{fast}/k_{slow} = e^{\Delta\Delta G^{\ddagger}/RT} \qquad (1)$$

Although the selectivities observed for both kinetic resolution and enantioselective reactions of prochiral substrates reflect the magnitude of $\Delta\Delta G^{\ddagger}$, there is also an important

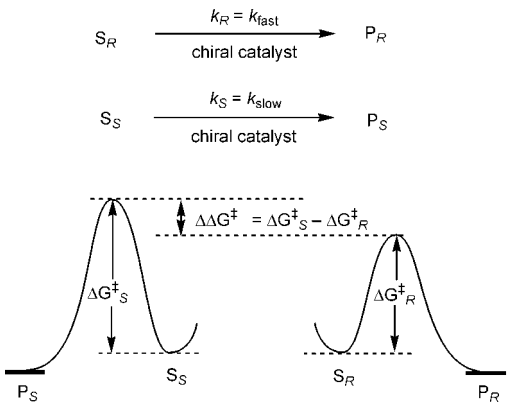


Figure 1. Relative rate constants in kinetic resolutions

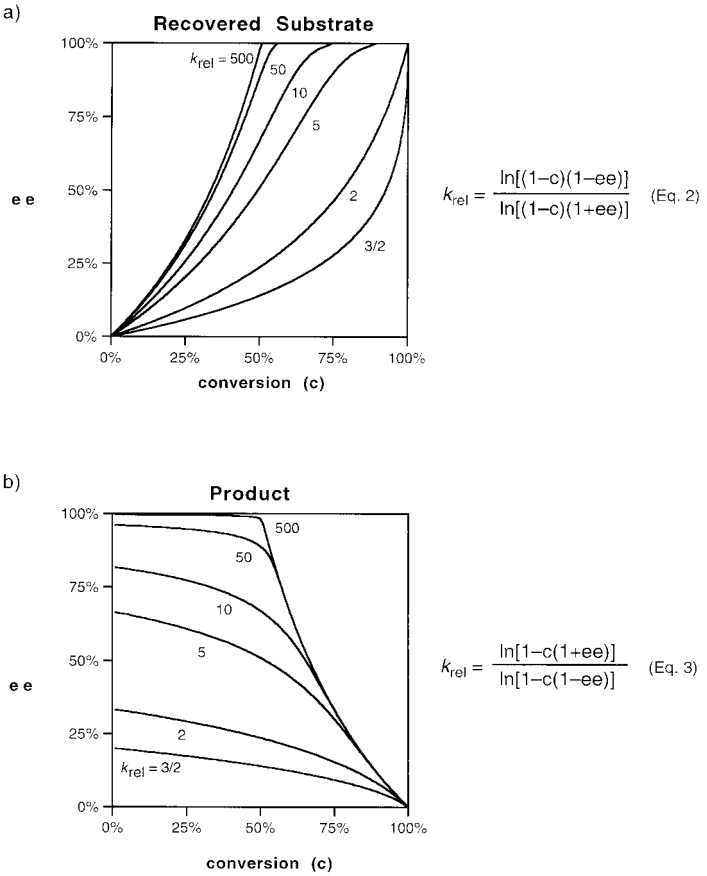


Figure 2. Plots of ee vs. conversion as a function of k_{rel} for **a**) recovered substrate and **b**) product. Curves were calculated using Eqs. 2 and 3.

practical difference between the two. While under normal conditions, enantioselective reactions of prochiral substrates yield product of constant ee,[10] the ee obtained in a kinetic resolution changes as a function of conversion (Figure 2 a). From the perspective of preparative synthesis, certainly the most attractive aspect of kinetic resolutions is that unreacted substrate can be recovered in high ee (e. g. > 99%) even if the k_{rel} is not especially high, simply by carrying the reaction to high enough conversion. Table 1 lists a series of representative values of k_{rel} with corresponding values of $\Delta\Delta G^{\ddagger}$, along with the extent of conversion required to obtain recovered unreacted substrate in 90, 98 and > 99% ee. As is evident from these hypothetical values, the k_{rel} value determines the extent of substrate conversion necessary to attain a target ee, but even a selectivity factor as low as 10 theoretically allows the isolation of unreacted substrate in 98% ee with a quite reasonable 30% recovery.

In contrast, high selectivity factors are necessary in order to obtain high ee product from kinetic resolution. The enantiomeric ratios (er) in the first cycles of the reaction correspond directly to k_{rel} (e. g., $k_{rel} = 10$, er ≈ 10, ee ≈ 82%), but as the reaction proceeds, the ee of the product decreases. As reflected by the plot in Figure 2 b, k_{rel}

Table 1. Representative k_{rel} and $\Delta\Delta G^{\ddagger}$ values, along with the conversions required to attain recovered substrates in 90, 98, and > 99% ee

k_{rel}	$\Delta\Delta G^{\ddagger}$ (kcal/mol)	Conversion (%) required to attain: 90% ee	98% ee	>99% ee
1.5	0.24	99.9	99.99	>99.999
2	0.41	97.2	99.5	>99.7
5	0.95	74.8	84.0	>86.6
10	1.35	62.1	69.7	>72.1
50	2.31	50.4	54.0	>54.9
100	2.72	48.9	51.8	>52.4
500	3.66	47.7	50.0	>50.3

values in excess of 50 are generally required if product of high enantiomeric purity is to be obtained in useful yield.

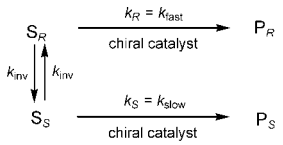
Because ee's change as a function of conversion in standard kinetic resolution reactions, k_{rel} values are generally considered to be more useful for evaluation – and especially comparison – of the efficacy of kinetic resolution catalysts. However, while it is certainly a simple matter to calculate k_{rel} values from conversion and ee data using Eqs. 2 and 3 (Figure 2), it is by no means a straightforward matter to determine k_{rel} values accurately. Indeed, it is likely that most values that are reported in the literature are in fact inaccurate. The curves plotted in Figure 2 assume a first-order kinetic dependence on substrate in the reaction, but different ee vs. conversion curves are obtained in kinetic resolutions displaying other kinetic dependencies on substrate.[11] In fact, the rate laws for synthetically useful kinetic resolutions are almost never determined, but it is generally just assumed that the reactions are first order in substrate and that Eqs. 2 and 3 are applicable. In reality, it is not at all unlikely that the kinetic dependence on substrate can change during the course of the resolution,[12] rendering very difficult any accurate estimation of k_{rel}. Indeed, in our own group's experience studying kinetic resolutions, we often find that k_{rel} values calculated using Eqs. 2 and 3 vary significantly with conversion.[13]

Because of the issues noted above, we will avoid description of reactions in terms of k_{rel} values and present them instead in terms of recovered substrate or product yields and ee's.[14] This seems especially appropriate given that this review seeks to emphasize practical aspects of kinetic resolution reactions, and the practical concern in these or any other asymmetric transformations is not in selectivity factors but rather in how much product can be obtained and in what ee.

2.2 Dynamic and Parallel Kinetic Resolutions

Dynamic and parallel kinetic resolutions also rely on differential reactivity of substrate enantiomers toward a chiral catalyst, however they are also quite different from

standard kinetic resolutions because in principle the catalyst is always encountering a racemic or nearly racemic substrate. In a dynamic kinetic resolution, the substrate undergoes racemization at a rate greater than that of its transformation to product (Scheme 3).[15] Under such circumstances, the product of the resolution reaction can theoretically be isolated in 100% yield with an ee determined by the magnitude of k_{rel}. In a parallel kinetic resolution, both enantiomers undergo reaction at comparable rates to give different products.[16] In this case, as with standard kinetic resolutions described above, the maximum yield is 50% for each product. However, the ee of the products is much less dependent on the degree of conversion. In fact, in the extreme case wherein the two product-forming pathways occur at the same rate, the ee is constant throughout the reaction.



Scheme 3. Dynamic kinetic resolution

Parallel kinetic resolutions were recognized only recently, but their importance as a synthetic strategy is growing. In contrast, several very useful examples of dynamic kinetic resolution reactions have already been identified, and these processes can have enormous practical utility.[17] However, to the extent that they are not subject to the yield constraints inherent in typical kinetic resolutions, they are effectively similar to enantioselective reactions of prochiral substrates, and will not be considered in the context of this review.

3 Selected Kinetic Resolution Reactions

3.1 Acylative/Deacylative Resolutions

Acyl transfer reactions have several inherently practical features that render them attractive in the context of kinetic resolution. In general, the reagents employed are inexpensive (e. g., H_2O for deacylative reactions, and simple acylating reagents such as acetic anhydride or vinyl acetate for the reverse processes), the racemic substrates are readily available, and the products are easily separated from the resolved substrates by extractive methods. A wide range of effective biocatalysts and, more recently, chiral synthetic catalysts has been identified for acyl transfer reactions.

3.1.1 Enzymatic Processes

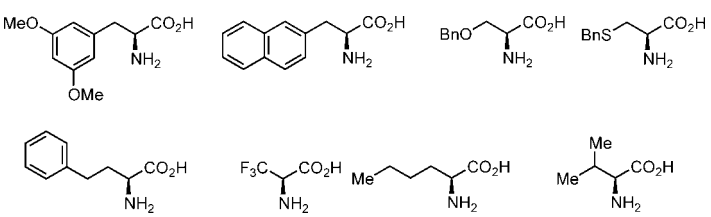
By virtually any analysis, enzymes are the most important catalysts for kinetic resolution, and among these, acylative enzymes (amidases, proteases, esterases, lipases) have seen the greatest application in a synthetic context. They have been applied in a kinetic resolution context to the preparation of a wide variety of amino acids and amides, alcohols, and esters. Many of the requisite enzymes are commercially available, either in pure form or as crude extracts, and in fact enzyme "kits" can now be purchased to facilitate screening and optimization. As a result, these catalysts are being exploited with ever-increasing frequency.

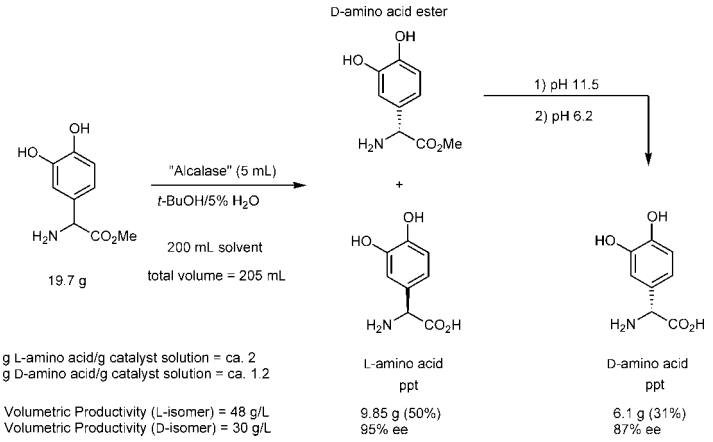
Acylases have been applied successfully in a variety of commercial syntheses, including the resolution of *trans*-methyl phenylglycidate (a precursor to the cardiovascular drug diltiazem),[18] glycidyl butyrate,[19] and a variety of amino acids.[20] Numerous applications have also been uncovered for the preparation of highly enantioenriched alcohols and carboxylic acid derivatives on a laboratory scale. An exhaustive survey of reported applications of acylases in organic synthesis is beyond the scope of this review, and the reader is referred to recent reviews and monographs on this topic.[21] We will focus instead on a small number of examples that illustrate key practical considerations.

Degussa's commercial scale use of acylases for the resolution of *N*-acetylamino acids is especially noteworthy.[22] The racemic substrates are accessed inexpensively via Strecker synthesis. It was established that porcine kidney acylase is effective for resolving straight chain substrates, whereas an enzyme obtained from the mold *Aspergillus oryzae* is optimal for kinetic resolution of substrates bearing branched or functionalized side chains. The reactions are run in a membrane reactor with product and starting material separated via ion exchange. The unreacted starting material is racemized and resubjected to the enzymatic reaction while the hydrolysis product is treated with charcoal and isolated by crystallization. Overall, yields of highly enantioenriched free amino acid are typically 85–90% factoring in recycling of starting material. Table 2 lists some of the amino acids available commercially by this process.

Another interesting application of acylative enzymes for the preparation of amino acids employs the crude subtilisin "Alcalase".[20,23] The substrates for this catalyst are amino acid esters (Scheme 4). The resolution is performed in a 95:5 *tert*-butyl alcohol/water mixture at 0.5 M concentration and at pH 8.2, requiring between 18 minutes to 4 hours to reach completion. The amino acid product is isolated by simple filtration in nearly quantitative yield and the enantiomer is obtained by saponification of the unreacted amino acid ester left in the filtrate.

Table 2. Examples of amino acids resolved effectively *via* Degussa's enzymatic kinetic resolution





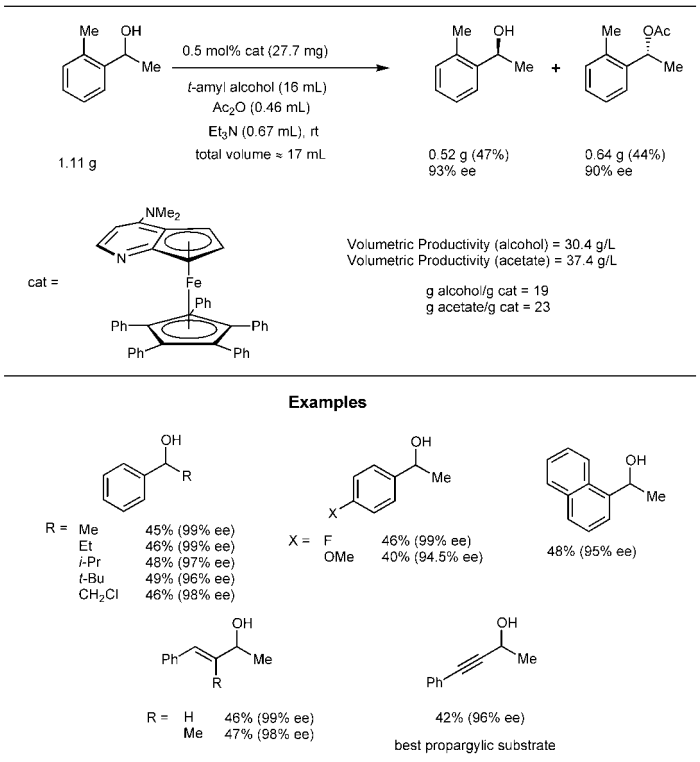
Scheme 4. Alcalase-catalyzed kinetic resolution of amino acid esters

Overview of Acylase Resolutions

Catalyst availability	Many acylases are commercially available and inexpensive
Substrate scope	Lipases and esterases display remarkably broad substrate scope compared to most enzymes. Kinetic resolution of a previously unstudied substrate may require the screening of many enzymes, but enzyme kits are available to facilitate this. Unlike most enzymatic reactions, it is frequently possible to find complementary catalysts that give opposite enantioselectivity.
Availability of racemate	Typically very high. Racemic alcohols, carboxylic acids, and amino acids can be accessed by a variety of general methods.
Alternative methods for accessing enantiopure substrate/product	Lipase resolutions are often the best, and sometimes the only good method available for accessing simple secondary alcohols in highly enantioenriched form. Recent advances in asymmetric catalytic methods have made available competitive (and sometimes superior) approaches to the synthesis of arylcarbinols and α-amino acids.
General experimental considerations	• Acylase-catalyzed reactions can often be run at high concentrations, sometimes even neat. • The stoichiometric reagents are inexpensive (e. g., H_2O). • Separation of unreacted starting material from product can often be effected by simple extraction or filtration. • Immobilizing or crosslinking enzymes has been effected successfully with corresponding increases in the stability and recyclability of the catalysts. • Unlike many other enzymes, acylases do not require cofactors, and are easily applied even by non-specialists.

3.1.2 *Synthetic Catalysts for Kinetic Resolution via Acylation*

Despite all of the attractive practical features of lipases noted above, there has been intensive research activity devoted recently to the discovery of synthetic asymmetric acylation catalysts.[24] This effort is driven by the goal of identifying general small-molecule catalysts for kinetic resolution of alcohols or carboxylic acid derivatives, but it also has been inspired by a more fundamental interest in elucidating principles for catalyst design. The work of the Fu group is particularly noteworthy in that regard. In 1996, they unveiled a new class of nucleophilic catalysts with a ferrocene substructure and planar chirality elements.[25] A carefully-designed DMAP analogue proved to be most effective for the catalytic acylation of certain racemic secondary aryl alcohols with good enantiodescrimination (Scheme 5).[26,27] Upon changing the solvent from ether to *tert*-amyl alcohol, a large increase in both rate and selectivity was observed.[28]



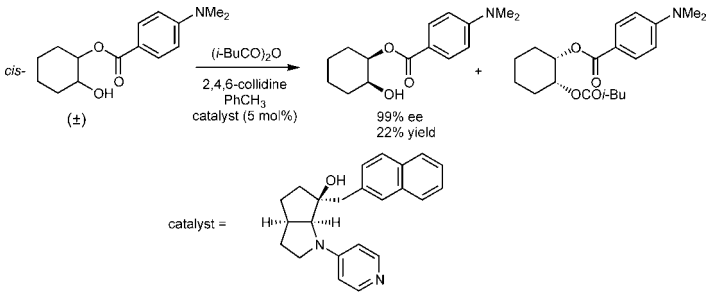
Scheme 5. Fu's kinetic resolution of secondary alcohols

Overview of Fu's Acylative Resolution of Secondary Alcohols

Catalyst availability	The catalyst is very precious, and it is not available commercially. The reported synthesis involves preparation of racemic catalyst and resolution by preparative chiral HPLC. On the other hand, catalyst loadings needed for most substrates are relatively low (1–2 mol %), and the catalyst has been recycled successfully.
Substrate scope	The substrates successfully resolved thus far are limited to benzylic, allylic, and propargylic alcohols.
Availability of racemate	Very high
Alternative methods for accessing enantiopure substrate/product	There are more economical methods to resolve these substrates using enzymes, and in many cases highly effective enantioselective routes to the same products are known (e. g., via ketone reduction).
General experimental considerations	• The stoichiometric reagent, acetic anhydride, is inexpensive. • Reaction is relatively slow, requiring 20–40 h to reach completion. • Reactions can be run up to 0.5 M in substrate. Higher concentrations give lower k_{rel}'s. • The optimal solvent, *tert*-amyl alcohol, is relatively expensive. • Products are isolated chromatographically.

At this stage, it is clear that this process has significant limitations, particularly given that the secondary alcohols that can be resolved successfully are accessible in highly enantioenriched form by a variety of other highly practical methods. On the other hand, it must be noted that the Fu catalyst represents one of the greatest achievements in asymmetric catalyst design, and it serves as a powerful foundation for future research in nucleophilic catalysis.[29]

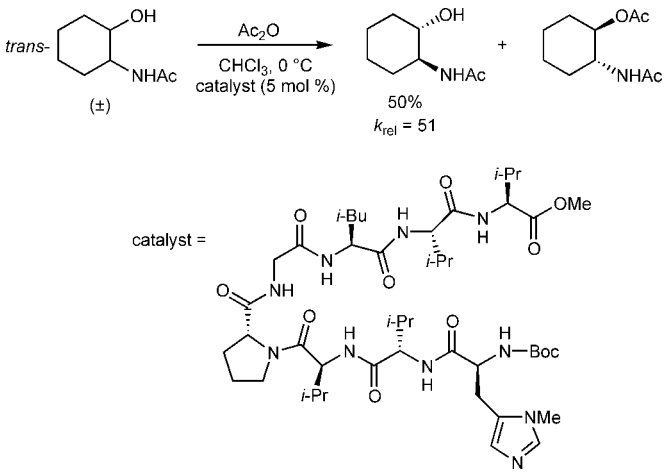
Several other groups have also made significant recent contributions to the development of synthetic acylase-like catalysts.[30] Fuji designed a novel chiral pyrrolidinopyridine catalyst for the kinetic resolution of monoacylated *cis*-diols (Scheme 6).[31] The selectivities obtained were variable (ee's 54 to 99%). More significant from a synthetic standpoint, the *meso cis* diol precursors to the substrates chosen for this study are generally excellent substrates for lipase-catalyzed desymmetrization reactions, wherein theoretical yields of 100% are obtainable.



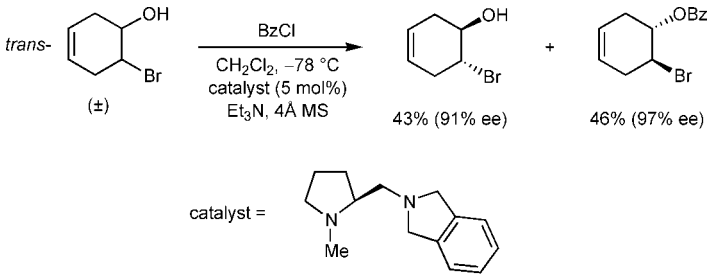
Scheme 6. Fuji's kinetic resolution of secondary alcohols

Miller has examined the use of peptidic catalysts bearing modified histidine residues for the acylative resolution of secondary *N*-acetylamino alcohols (Scheme 7).[32] These interesting enzyme mimics have been examined against a small number of substrates with promising success (k_{rel} = 15–51 with an octapeptide catalyst).[33] From a preparative standpoint, it should be noted that the *trans*-1,2-amino alcohol derivatives accessible by this methodology can be prepared with high enantioselectivity and yields via catalytic ring-opening of *meso* epoxides.[34] However, the greater significance of the Miller work is certainly the observation that small, conformationally-constrained peptides can serve as true mimics of acylases.[35]

A remarkably simple proline-derived catalyst has been developed by Oriyama[36] and applied with impressive success to the resolution of cyclic α-substituted secondary alcohols (Scheme 8). Benzoyl chloride is used as the acylating agent at –78 °C in the presence of the diamine catalyst. A variety of *trans*-α-substituents are tolerated in the cyclic substrates (Ph, CO_2Et, Br) with ee's ranging from 79–95%, but acyclic substrates undergo resolution much less selectively (substrate recovered in 51–78% ee). This system is very promising from a practical standpoint given the simplicity of the catalyst, the low loadings in which it can be used (0.3 mol %), and the ready accessibility of the racemic precursors.



Scheme 7. Miller's kinetic resolution of secondary alcohols



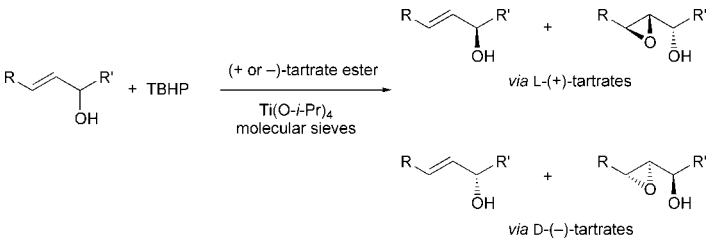
Scheme 8. Oriyama's kinetic resolution of secondary alcohols

3.2 Oxidative Kinetic Resolutions

3.2.1 Sharpless Kinetic Resolution of Secondary Allylic Alcohols

In 1981, Sharpless followed up on his landmark paper of the previous year[37] on asymmetric epoxidation of allylic alcohols with a report on the application of the Ti(O-*i*-Pr)$_4$/diisopropyl tartrate catalyst system to the kinetic resolution of secondary allylic alcohols (Scheme 9).[38] The subsequent recognition that trace amounts of water had a severely deleterious effect on catalyst turnover led to the discovery that addition of molecular sieves to the reaction mixtures allowed the use of as little as 5–10 mol % of catalyst in both asymmetric epoxidations and kinetic resolutions.[39] Although the basic experimental protocol for kinetic resolutions is the same as that used for asymmetric epoxidation of prochiral allylic alcohols, there are some important differences in the details. For example, in contrast to enantioselective epoxidations of primary alcohols, where different tartrate esters lead to essentially identical results, in kinetic resolutions there is a marked dependence on the steric properties of the ligand. Selectivities are improved with larger ester derivatives (dimethyl tartrate < diethyl tartrate < diisopropyl tartrate), and in fact the more bulky dicyclohexyl and dicyclododecyl tartrates afford optimal results under catalytic conditions.[40] The choice of titanium alk-

oxide precursor is also critical, with Ti(O-*i*-Pr)$_4$-derived catalysts displaying higher k_{rel} values than the corresponding catalysts generated from Ti(O-*t*-Bu)$_4$.

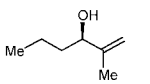
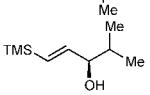
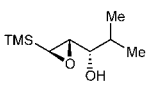
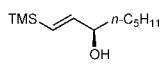
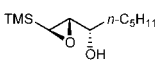
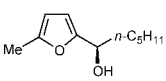
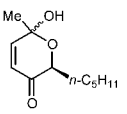
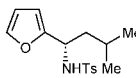
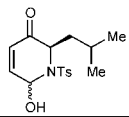


Scheme 9. Sharpless' kinetic resolution (SKR)

The impact of the Sharpless kinetic resolution (SKR) was profound and felt almost immediately.[41] Although enzymatic resolutions were already well-established, very little had been accomplished prior to 1980 with respect to kinetic resolutions with synthetic catalysts. The broad scope of the reaction, combined with the ready accessibility of the catalyst components led to the rapid adoption of the SKR by synthetic chemists, and to date it has certainly been the most often-used kinetic resolution reaction involving synthetic catalysts. A comprehensive listing of the 170+ substrates to which the SKR has been applied is provided as Supplementary Material.

In general, *E*-1,2-disubstituted and 2,2-disubstituted secondary allylic alcohols are excellent substrates in the SKR, with *Z*-1,2-disubstituted substrates leading to much lower k_{rel} values. Sato identified a remarkable effect of silyl substituents,[42] with appropriate substrates (e. g., Table 3, entries 2–3) undergoing resolution with k_{rel} values estimated to be as high as 700. Further studies by Sharpless[43] revealed that, in general, large *E*-*β*-alkenyl substituents lead to substantial improvement in k_{rel} values.

Table 3. SKR examples

entry	recovered substrate	tartrate	yield (%)	ee (%)	product	yield (%)	ee (%)	ref.
1		(+)-DIPT (+)-DCHT (+)-DCDT	47 46 45	94 97 >98	not isolated			[40]
2		(+)-DIPT	40-48	>99		40-48	99	[42e]
3		(+)-DIPT	39-45	99		39-45	99	[42a]
4		(+)-DIPT	40	>95		55		[44b,c]
5		(+)-DIPT	23	>98		73		[46a,d,g]

DIPT = Diisopropyl tartrate; DCHT = Dicyclohexyl tartrate; DCDT = Dicyclododecyl tartrate.

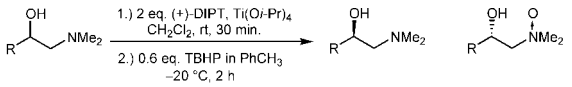
Unlike the Ti-tartrate-catalyzed asymmetric epoxidation of prochiral substrates, which is limited in scope to allylic alcohols, the kinetic resolution reaction has been adapted with varying success to a number of other substrate classes. For example, furyl[44] and pyrryl alcohols[45] undergo kinetic resolution, with the fast reacting enantiomer undergoing epoxidation followed by ring expansion to give enantioenriched pyranones (Table 3, entry 4). The corresponding furyl sulfonamides also react with good selectivity to give optically active piperidone derivatives.[46] The kinetic resolution of tertiary amino alcohols has also been effected with some success using catalysts composed of a titanium:tartrate ratio of 2 : 1 (vs. 2 : 2 for allylic alcohols).[47] A number of interesting amino alcohols has been resolved in good yield by this method, with ee's of the recovered amines frequently in excess of 90% (Table 4). Of course, any kinetic resolution of amines has to be weighed against often highly practical alternative classical resolution schemes using chiral acids.

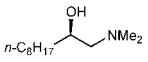
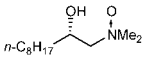
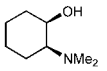
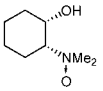
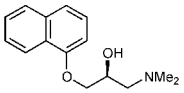
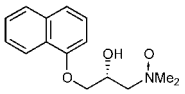
Overview of the Sharpless Kinetic Resolution of Allylic Alcohols

Catalyst availability	The catalyst is prepared *in situ* from very inexpensive, commercially available titanium alkoxides and tartrate esters.
Substrate scope	High selectivities are obtained for a wide range of secondary allylic alcohols. *Z*-Disubstituted secondary allylic alcohols and tertiary allylic alcohols are poor substrates.
Availability of racemate	Racemic allylic alcohols are readily prepared by a variety of methods (e. g., by addition of Grignard reagent to aldehyde).
Alternative methods for accessing enantiopure substrate/product	Catalytic methods for the preparation of optically active secondary allylic alcohols have been developed via reduction of *α*,*β*-unsaturated ketones or by alkylation of *α*,*β*-unsaturated aldehydes. These are still limited in scope, and the SKR remains the principal method for accessing secondary allylic alcohols in optically active form.
	The SKR provides one of the only general methods for the preparation of *erythro* epoxy alcohols in high ee.
General experimental considerations	• Separation of product epoxy alcohol from unreacted substrate can be difficult, and it is usually carried out chromatographically. • Catalyst loadings are high (5–25 mol %) and the catalyst is not recyclable. • The reaction is highly sensitive to several parameters, including temperature, concentration, trace water contamination, and solvent. • Reactions can be very slow; requiring several hours to weeks to attain complete kinetic resolution.

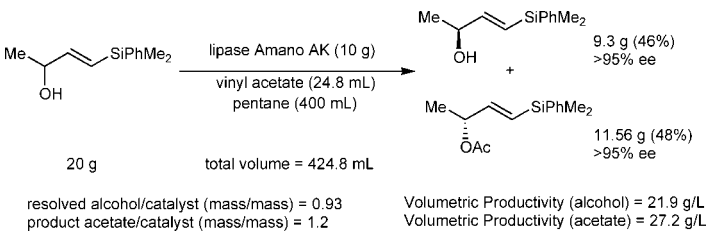
The above points highlight a number of positive elements of the SKR as a laboratory-scale procedure, but also make it clear why the methodology may be difficult to translate to very large scales. In particular, the high catalyst loadings; the sensitivity of the reaction to water, temperature, and catalyst aging; the long reaction times; the stoichiometric use of a potentially-dangerous alkyl hydroperoxide reagent; and often-difficult separation of product from unreacted olefin can present significant obstacles.

Table 4. Kinetic resolution of β-hydroxy amines



entry	recovered amino alcohol	yield (%)	ee (%)	product	yield (%)
1		36	91		54
2		25	95		55
3		40	95		53
4		40	92		56

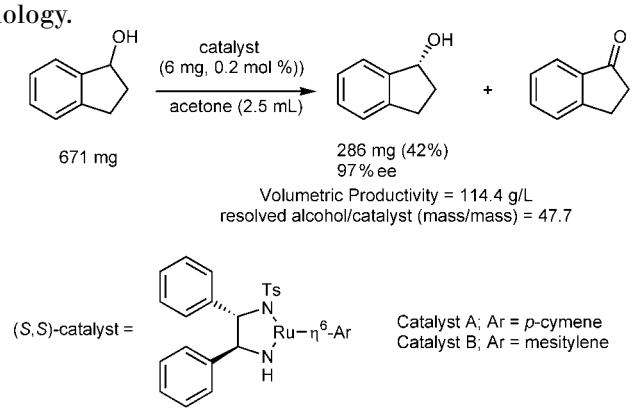
While highly effective catalytic enantioselective methods have been devised recently for preparation of secondary allylic alcohols,[48] the most general alternative route to optically active secondary allylic alcohols currently known employs lipase resolution. Panek has applied the kinetic resolution of silyl-substituted secondary allylic alcohols as a key step in his preparation of chiral allylsilane reagents (Scheme 10).[49] The resolution reaction is run at 0.24 M in substrate using Amano AK lipase in the presence of distilled vinyl acetate at room temperature for 4 hours. The lipase is then filtered off and the crude products are separated chromatographically. In the example shown, the ee's of the product and starting material were both greater than 95% and the yields were nearly quantitative. Such allylic alcohols can be resolved by the SKR and, based on precedent (vide supra), would likely be among the very best substrates for that method. However, this example illustrates how the extraordinary simplicity of the lipase method can present practical advantages from an experimental perspective.



Scheme 10. Panek's kinetic resolution of allylic alcohols with Amano AK lipase

3.2.2 Noyori Kinetic Resolution of Secondary Benzylic Alcohols

Noyori's Ru-catalyzed oxidative kinetic resolution of racemic benzylic and allylic alcohols also merits special consideration from a practical perspective (Scheme 11).[50] Because oxidation of these substrates is favorable thermodynamically relative to oxidation of aliphatic alcohols, it is possible to use acetone as an effectively irreversible hydrogen acceptor in the oxidation reaction. Using the Ru(II) catalyst shown in Scheme 11, the fast-reacting enantiomer was oxidized to the corresponding achiral ketone, leaving the less reactive enantiomer. Table 5 lists some of the substrates that were resolved successfully using this methodology.

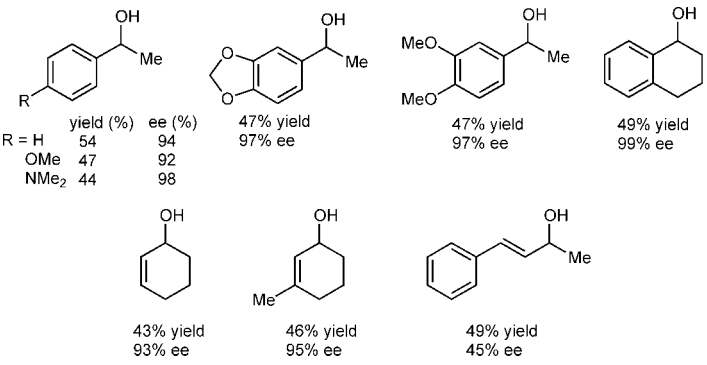


Scheme 11. Noyori's kinetic resolution of benzylic alcohols via transfer hydrogenation

Analysis of Noyori's Oxidation of Benzylic Alcohols

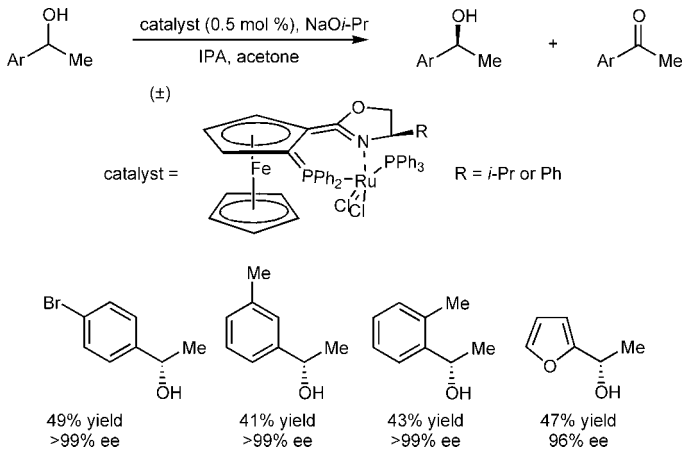
Catalyst availability	The Ru catalyst is prepared in two steps from a commercially-available 1,2-diamine and used at low loadings (0.2–0.5 mol %). The catalyst is not recycled.
Substrate scope	A variety of benzylic and allylic alcohols undergo resolution with very high selectivity.
Availability of racemate	Very high
Alternative methods for accessing enantiopure substrate/product	In almost all cases examined, the alcohol substrates can be obtained enantioselectively by asymmetric reduction of the corresponding ketones.
General experimental considerations	• Very practical experimental protocol, with use of acetone as a stoichiometric reagent. • Yields are nearly quantitative. • Reaction is moderately slow, requiring 5–36 h to reach completion. • Reactions can be run 2.0 M in substrate. • The product and unreacted substrate are separated chromatographically. • The ketone product can be recycled by reduction back to racemic alcohol.

Table 5. Substrates resolved successfully using Noyori's transfer hydrogenation method



This kinetic resolution method is striking in its simplicity and effectiveness. The only limitation to the widespread application of the approach arises from the fact that Noyori has successfully applied the same transfer hydrogenation reaction in the opposite direction to effect the enantioselective reduction of ketones.[51] Naturally, all other factors being equal, enantioselective reaction of a prochiral substrate is preferable over kinetic resolution of a racemate, and this is certainly a case where all other factors are as close to equal as one could imagine possible (same catalyst, similar conditions, etc.). There may still, however, be instances where the kinetic resolution is preferable to the enantioselective reduction, if for instance the racemic alcohol is very inexpensive relative to the corresponding ketone.

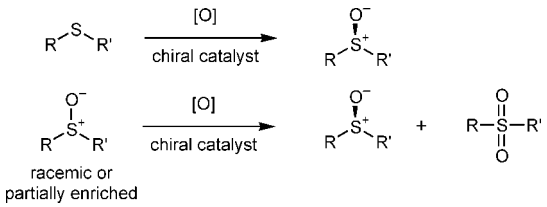
More recently, Uemura and Hidai reported the successful kinetic resolution of benzylic alcohols catalyzed by an (oxazolinylferrocenylphosphine)Ru complex (Scheme 12).[52] The experimental protocol, selectivities, and substrate scope appear comparable to those of the Noyori system.



Scheme 12. Uemura's kinetic resolution of secondary benzylic alcohols

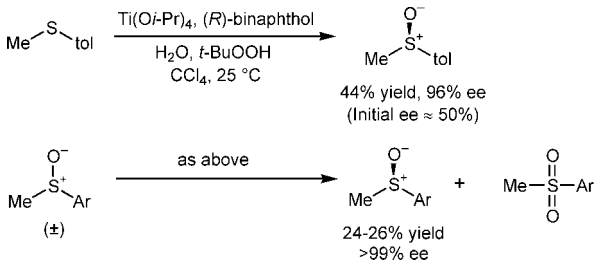
3.2.3 *Oxidative Resolution of Sulfoxides*

In principle, asymmetric catalysis can provide access to enantioenriched sulfoxides either by enantioselective oxidation of sulfides or by oxidative kinetic resolution of sulfoxides to sulfones (Scheme 13). Several valuable methods for the former reaction have been developed, but as yet there are no catalytic systems for sulfide oxidation that provide very high enantioselectivity for a broad range of substrates.[53] Since most low molecular weight sulfoxides are liquids at room temperature and do not readily form salts, it is not a straightforward matter to enhance the enantiomeric purity of an enantioenriched sulfoxide by recrystallization.[54] In that light, kinetic resolution – or, perhaps better, enantioselective sulfide oxidation coupled to kinetic resolution – is an attractive strategy for accessing enantiopure sulfoxides.



Scheme 13. Enantioselective synthesis and kinetic resolution of sulfoxides

In this context, the most promising system developed thus far is the Ti(O*i*Pr)$_4$/BINOL catalyst reported by Uemura (Scheme 14). His group found that alkyl aryl sulfides undergo enantioselective oxidation with aqueous TBHP as a stoichiometric oxidant in the presence of that catalyst.[55] A study of the reaction course revealed that the enantiopurity of the sulfoxide increased with time with concomitant formation of sulfone, consistent with participation of a secondary kinetic resolution process. It was verified that the same catalyst system could be applied to the kinetic resolution of racemic substrates to provide enantiopure sulfoxides in moderate yield.



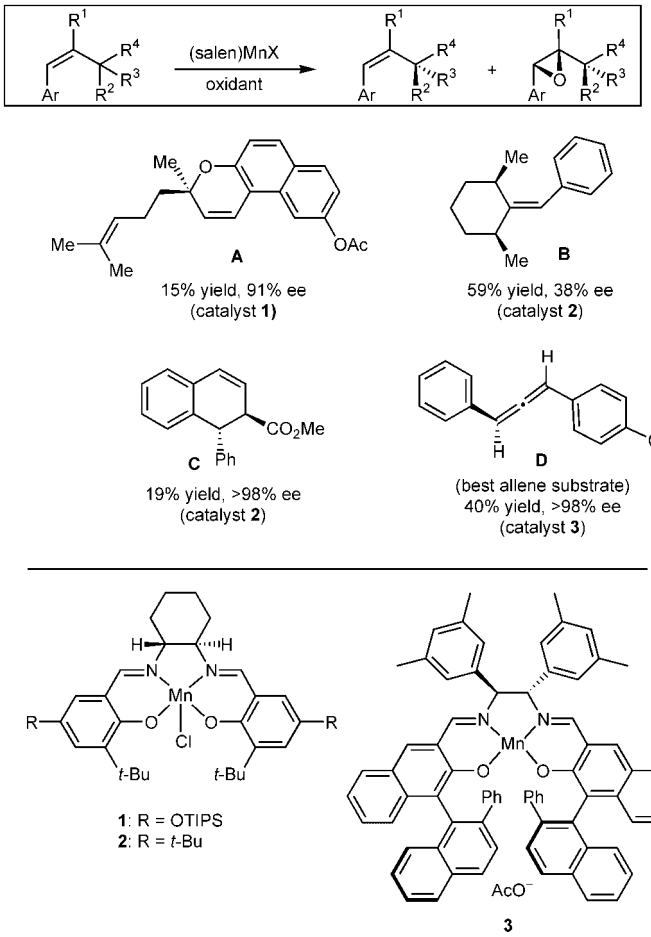
Scheme 14. Uemura's asymmetric synthesis/kinetic resolution of sulfoxides

3.2.4 *Oxidative Resolution of Alkenes and Allenes*

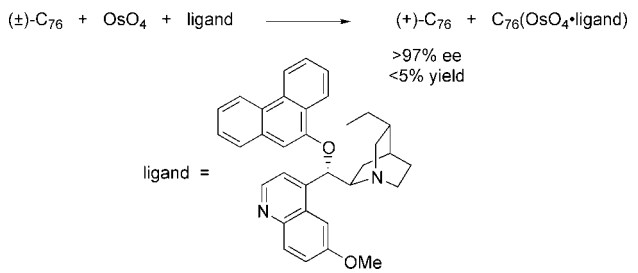
Kinetic resolution of simple alkenes is a particularly attractive target for asymmetric catalysis, given that racemic alkenes are generally readily accessible and that very few effective methods exist for their direct enantioselective synthesis. In this context, the two most widely-studied synthetic catalytic systems for asymmetric oxidation of unfunctionalized olefins – the (salen)Mn epoxidation catalysts and the (cinchona alkaloid)OsO_4 dihydroxylation catalysts – have been adapted to kinetic resolutions of alkenes, albeit with moderate success.[56]

Scheme 15 summarizes the different classes of alkenes that have been investigated as substrates for kinetic resolution with (salen)Mn catalysts. Dialkylchromene derivatives (e. g., **A**) undergo epoxidation with very high levels of catalyst control, but poor substrate control, leading to both enantiomers reacting at similar rates to afford diastereomeric products in high ee (parallel kinetic resolution).[57] Limiting epoxidation to partial conversion allowed recovery of unreacted alkene in enantioenriched form, but in very moderate yield. Benzylidenecyclohexane derivatives (e. g., **B**) underwent kinetic resolution with poor selectivity. Better results were obtained in the kinetic

resolution of dihydronaphthalene derivatives such as **C**, with k_{rel} values as high as 9.1.[58] The most interesting substrate class identified thus far for (salen)Mn catalyzed kinetic resolutions are diarylallene derivatives (e.g., **D**), which were resolved with k_{rel} values as high as 23.[59]



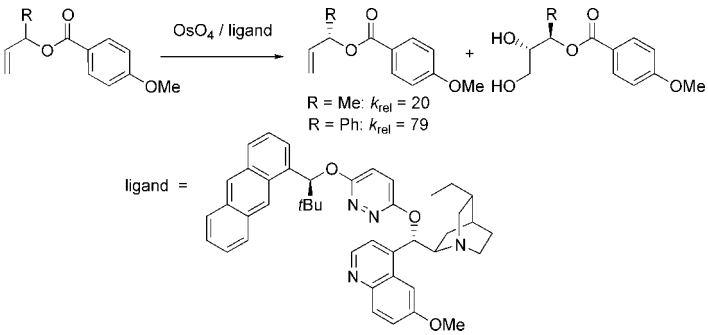
Scheme 15. Kinetic resolutions via (salen)Mn-catalyzed epoxidation



Scheme 16. Kinetic resolution of C_{76}

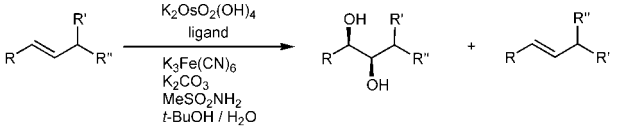
Success in the application of the Sharpless asymmetric dihydroxylation (AD) catalysts to kinetic resolutions has been limited to a small number of examples. Certainly most dramatic among these is the kinetic resolution of C_{76} reported by Hawkins.[60] This chiral allotrope of carbon proved impossible to resolve by classical means, but partial reaction with stoichiometric $OsO_4 \cdot$ dihydroquinidine derivative led to recovered starting material estimated to be >97% ee (Scheme 16). This stands as a particularly notable example of a kinetic resolution with clear practical limitations (precious racemate, stoichiometric use of catalyst, low recovery of unreacted substrate) that is nonetheless very useful because no alternative route to the enantiopure target exists.

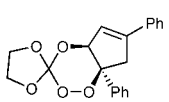
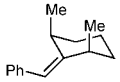
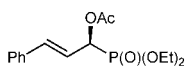
Less exotic substrates that undergo kinetic resolution via Sharpless AD include conformationally-restricted alkylidene cyclohexane derivatives,[61] *cis*-fused cyclopenteno-1,2,4-trioxanes,[62] 1-acyloxy-2(*E*)-alkenylphosphonate derivatives,[63] and allylic alcohol derivatives (Table 6).[64] In the latter case, Corey devised a novel ligand specifically optimized for alkenes bearing electron-rich aromatic substituents, and found that *para*-methoxybenzoate ester derivatives of secondary allylic alcohols were very good substrates for kinetic resolution with the corresponding osmium complexes (Scheme 17). Because of the exotic nature of the ligand and the fact that more straightforward methods exist for kinetic resolution of allylic alcohol derivatives (vide supra), this example is primarily of interest on a mechanistic level.



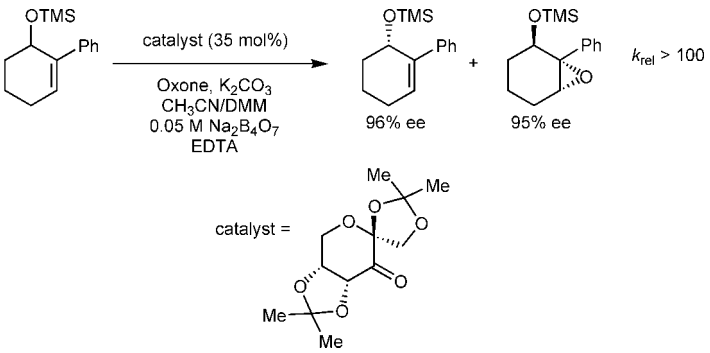
Scheme 17. Kinetic resolution of allylic esters via AD

Table 6. Kinetic resolution of alkenes by asymmetric dihydroxylation



recovered substrate	yield (%)	ee (%)	ligand	ref
	25 -30	>98	$(DHQ)_2PHAL$	62
	47	>98	$(DHQ)_2PHAL$	61
	35	99	$(DHQD)_2PHAL$	63

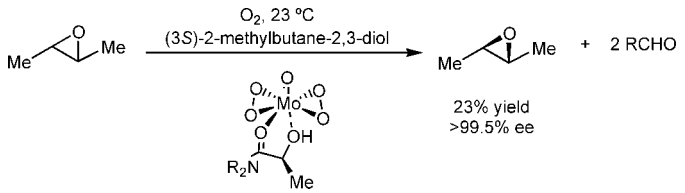
Recently, Shi has applied his newly discovered fructose-derived epoxidation catalysts to the kinetic resolution of certain cyclic olefins.[65] Very high selectivity was observed with a limited set of trisubstituted allylic alcohol derivatives (Scheme 18). Unfortunately, the high catalyst loadings (0.25–0.75 equiv relative to racemic substrate) and narrow substrate scope limit the practical utility of this methodology at this stage.



Scheme 18. Shi's kinetic resolution by epoxidation with a fructose-derived dioxirane

3.2.5 Other Oxidative Kinetic Resolutions

A variety of other types of oxidative transformations has been investigated in the context of kinetic resolution. Notable examples include the resolution of racemic ketones via Baeyer–Villiger reactions,[66] the enzymatic oxidation of allylic alcohols,[67] and the oxidative cleavage of racemic epoxides.[68] In the latter case, a catalytic method utilizing a chiral molybdenum(VI)(oxodiperoxo)hydroxy acid/amide/diol catalyst and O_2 was disclosed that effected the kinetic resolution of certain *trans*-disubstituted epoxides (Scheme 19). This result is particularly interesting given the limited alternative methods that exist currently for accessing these epoxides in enantiopure form.



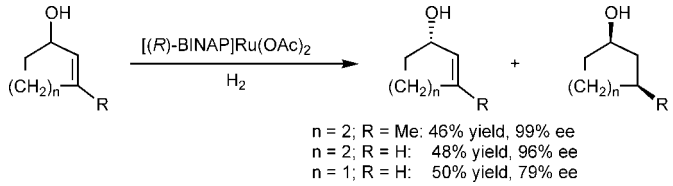
Scheme 19. Schurig's oxidative kinetic resolution of epoxides

3.3 Reductive Kinetic Resolutions

3.3.1 Reductive Resolution of Alkenes

In principle, asymmetric hydrogenation could provide an attractive strategy for the kinetic resolution of alkenes that would be complementary to the oxidative methods outlined in the previous section, particularly given the wide range of known effective asymmetric hydrogenation catalysts. However, the question of how to separate alkene from alkane presents itself as a fundamental technical consideration in any hydrogenative kinetic resolution of a racemic alkene substrate. Because of the similar boiling points and polarity properties of alkenes and their hydrogenated counterparts, chemical derivatization of the double bond is often the only approach for effecting separation.

Nonetheless, several examples of kinetic resolution of functionalized alkenes have been described. Noyori developed a complementary method to the SKR for the kinetic resolution of allylic alcohols using a Ru(II)/binap complex (Scheme 20).[69] Whereas cyclic allylic alcohols such as 2-cyclohexenol are poor substrates for the SKR, the Noyori protocol allowed highly efficient kinetic resolution of this valuable chiral building block.



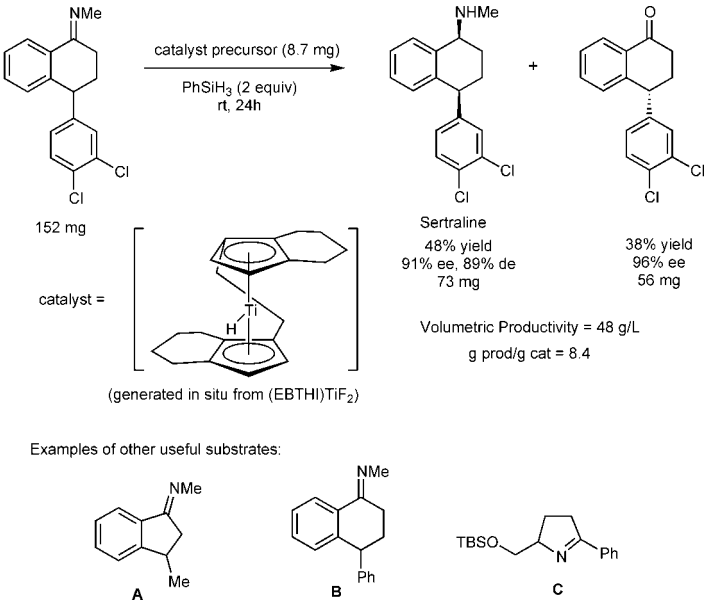
Scheme 20. Noyori's reductive resolution of allylic alcohols

3.3.2 Reductive Resolution of Imines

The recent development of effective catalysts for asymmetric hydrogenation and hydrosilylation of imines[70] has inspired several related efforts in kinetic resolution. Buchwald has examined the resolution of three important classes of substrates: imines derived from 3-substituted indanones and 4-substituted tetralones,[71] and disubstituted 1-pyrrolines[72] (e. g., **A** – **C**, Scheme 21). The pyrroline derivatives were resolved using a binaphthoate derivative of Brintzinger's catalyst as the catalyst precursor, while the exocyclic imines were resolved with the corresponding difluoro derivative. With all three substrate classes, excellent ee's and good yields were achievable. Unreacted exocyclic imines were not recovered as such, but rather as the corresponding chiral ketones produced upon hydrolysis. *N*-Methylimine derivatives of tetralones proved to be particularly good substrates for the kinetic resolution, with k_{rel}'s ranging from 18 to 114. This constituted the basis for an efficient synthesis of the important antidepressant drug sertraline (Scheme 21).

Analysis of Buchwald's Kinetic Resolution of Imines

Catalyst availability	The catalyst is relatively precious and it is not recyclable. The Ti-binaphthoate derivative of Brintzinger's catalyst is prepared in 5 steps, and the difluoride analogue in 6 steps. Catalyst loadings used in the resolutions are 1–5 mol %.
Substrate scope	Excellent selectivities for cyclic and exocyclic imines.
Availability of racemate	Most substrates are prepared by multi-step procedures, but are generally inexpensive relative to the enantiopure counterparts.
Alternative methods for accessing enantiopure substrate/product	Very few effective direct catalytic methods exist for the enantioselective synthesis of imines and amines. However, classical resolution of amines via salt formation with chiral carboxylic acids provides a practical alternative strategy to kinetic resolution.
General experimental considerations	• Reactions can be run up to 0.5 M in substrate. • Separation of amine product from unreacted imine (isolated after hydrolysis to ketone) can be effected by simple extraction.



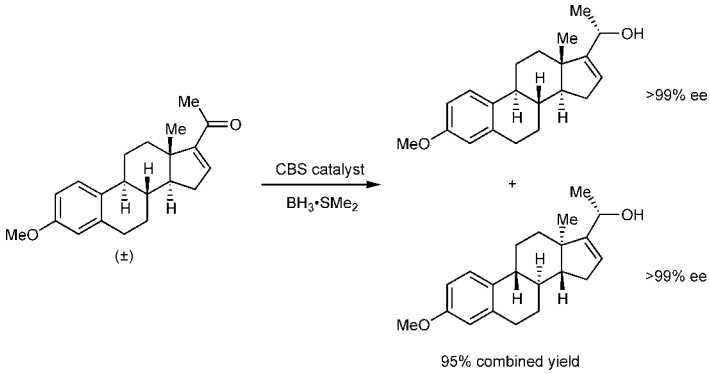
Scheme 21. Buchwald's kinetic resolution of imines

The Buchwald methodology provides access to pyrrolines, indanones, and tetralones in highly enantioenriched form. To the extent that these compounds are otherwise not accessible by direct asymmetric synthesis, resolution strategies can provide the only attractive approaches to these synthetically important compounds. However, the principal limitation of this kinetic resolution is the high cost contribution of the catalyst. In addition, classical resolution strategies can provide a most attractive alternative to kinetic resolution, particularly with respect to the preparation of optically active amines. For example, the commercial synthesis of sertraline employs a classical resolution with inexpensive D-mandelic acid.[73]

3.3.3 Reductive Kinetic Resolution of Ketones

An interesting example of a parallel kinetic resolution involving asymmetric ketone reduction was reported by Kishi in the context of batrachotoxin synthesis.[74,75] As shown in the example in Scheme 22, essentially perfect selectivity was achieved in the reduction of model steroidal ketones using the commercial CBS catalyst (Strem), and the epimeric alcohol products were separated as the corresponding acetates by chromatography. Limiting the reaction to 60% conversion led to kinetic resolution with recovered ketone isolated in 40% yield and 93% ee ($k_{rel} = 27$).

This is a most extreme example of kinetic resolution of a highly precious racemate, where it would clearly be undesirable to discard 50% of the material. In addition, the corresponding enantiopure derivatives are accessible using the Wieland-Miescher diketone, which is readily prepared as either enantiomer via asymmetric catalysis.[76] Nonetheless, the significance of this kinetic resolution is twofold. First, it is a most extraordinary example of selectivity in parallel kinetic resolution. Second, such a late-stage kinetic resolution strategy can hold considerable appeal if both enantiomers of the target compound are sought.

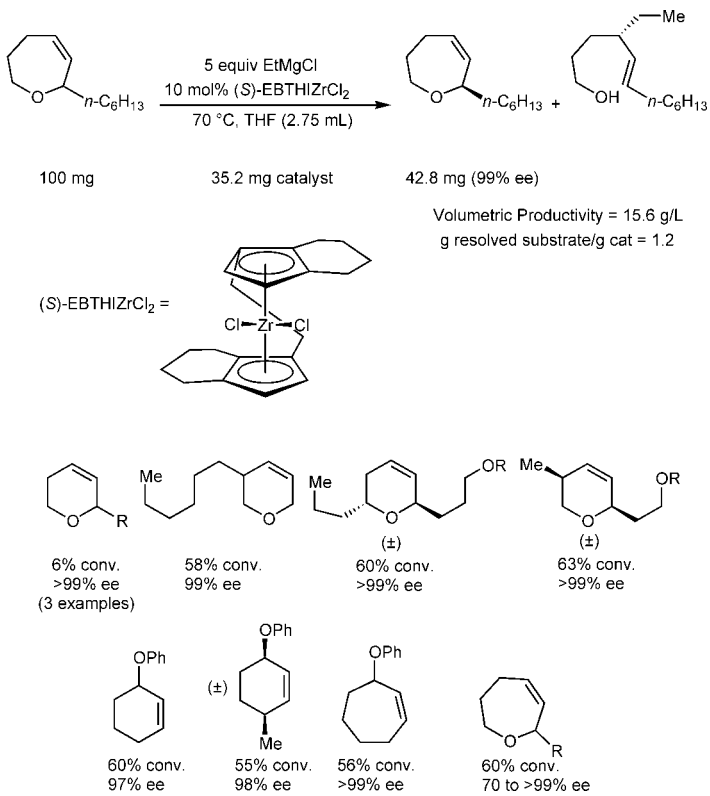


Scheme 22. Kishi's parallel kinetic resolution of a steroidal ketone

3.4 Organometallic Kinetic Resolutions

3.4.1 Resolution of Cyclic Allylic Ethers

In 1994, Hoveyda disclosed the discovery that (EBTHI)$ZrCl_2$ catalyzed the kinetic resolution of pyrans by reaction with excess EtMgCl.[77] Subsequent studies revealed that the process is applicable to larger and smaller ring sizes (Scheme 23).[78] In the case of dihydrofurans, parallel kinetic resolution was observed, with both enantiomers reacting to give different products, both of which could be obtained in good yield and excellent ee.[79]

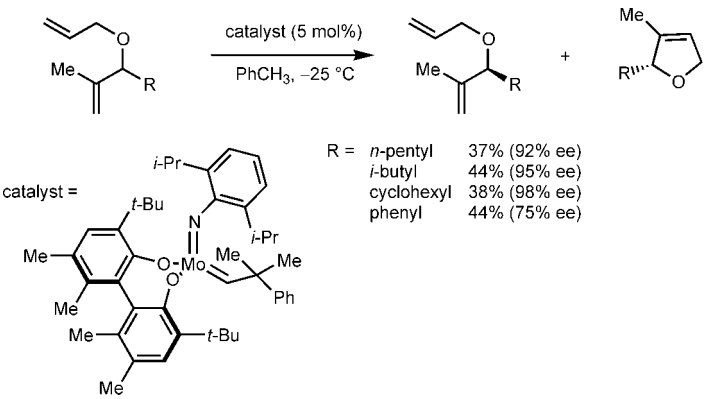


Scheme 23. Hoveyda's kinetic resolution of allylic ethers

Analysis of Hoveyda's Kinetic Resolution of Allylic Alcohols

Catalyst availability	The catalyst is relatively precious and it is not recyclable (see discussion of Buchwald's imine resolution, which employs analogous Ti-based catalysts). Catalyst loadings used in the resolutions are high (10–20 mol % relative to racemate).
Substrate scope	Extremely high selectivities for a wide variety of cyclic ethers. Excellent ee's are obtained at 60% conversion with most substrates.
Availability of racemate	Most substrates accessed in three synthetic steps from racemic allylic alcohols.
Alternative methods for accessing enantiopure substrate/product	Allylic alcohols are good substrates for kinetic resolution by a variety of methods (vide supra), so in principle an earlier stage kinetic resolution could provide more efficient access to the same cyclic ethers.
General experimental considerations	• Reaction can be carried out at elevated temperatures (70 °C) with good results. • Products are isolated chromatographically, with generally large differences in polarity between products and unreacted substrates. • Reactions are run at moderately high concentration (0.4 M). • Large excess of expensive and highly reactive Grignard reagents is employed.

While Hoveyda's kinetic resolution of cyclic ethers is extraordinarily selective and highly interesting from a mechanistic perspective, it does suffer from several key practical limitations. The catalyst is expensive and used at high loadings. This presents not only a cost consideration, but also a technical problem at large scale since the mass of catalyst used is nearly equal to the mass of product isolated. Certainly, the use of excess of EtMgCl at elevated temperatures adds another technical challenge to scale-up efforts. Perhaps the most serious limitation, however, is the fact that the racemic substrates can be prepared in enantiopure form from resolved secondary allylic alcohols.



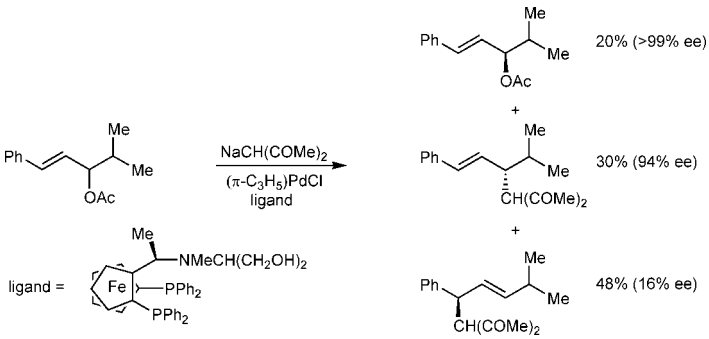
Scheme 24. Hoveyda-Schrock kinetic resolution of allylic ethers via RCM

3.4.2 *Ring Closing Metathesis*

Hoveyda and Schrock reported recently the application of a new chiral molybdenum catalyst for the kinetic resolution of chiral dienes by ring closing metathesis (RCM).[80,81] Although this methodology has found most significant application in the desymmetrization of prochiral dienes, very effective kinetic resolutions were also described with a number of racemic acyclic dienes undergoing resolution with k_{rel} values ranging from 4–58 (Scheme 24). From a purely practical perspective, however, it must be noted that the racemic substrates for the RCM are derived from secondary allylic alcohols, which are generally easily resolved (vide supra). RCM presents a particularly attractive approach on other fronts, however, particularly to the extent that no added reagent is required and the sole stoichiometric by-product is ethylene.

3.4.3 *Palladium-Catalyzed Resolution of Allylic Esters*

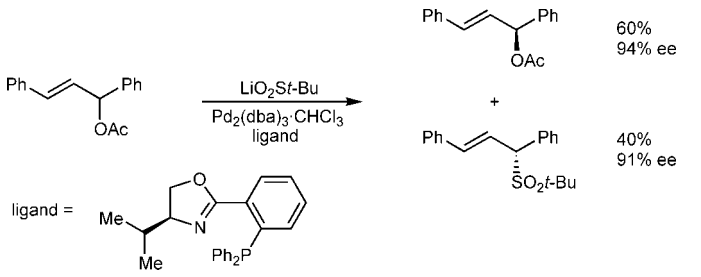
In principle, palladium-catalyzed allylic substitution can provide yet another strategy for the kinetic resolution of allylic alcohol derivatives. In an early result, Hayashi and Ito applied a chiral ferrocenylphosphine-palladium complex to the kinetic resolution of allylic acetates with sodium dimethylmalonate.[82] Excellent ee's were obtained with one substrate at high (ca. 80%) conversions (Scheme 25).



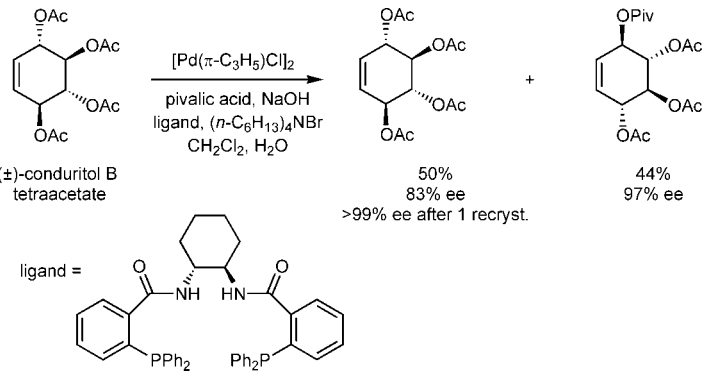
Scheme 25. Hayashi-Ito kinetic resolution of allylic acetate derivatives

More recently, Osborn developed a similar protocol utilizing a duxantphospholane/Pd complex as the catalyst and dimethyl malonate as the nucleophile.[83] The selectivity of the resolution was moderate, with the highest k_{rel} value reported being 8.1. Gais reported higher selectivity in the kinetic resolution of the ubiquitous diphenylallyl acetate derivative in Scheme 26 by partial reaction with lithium *tert*-butylsulfinate in the presence of phosphinooxazoline-based catalysts.[84] In a most interesting example from a synthetic perspective, Trost applied his highly effective asymmetric allylation catalyst to the kinetic resolution of the C_2 symmetric conduritol B tetraacetate (Scheme 27), an intermediate in the synthesis of (+)-cyclophellitol.[85] The racemic substrate was accessed in only 3 steps from benzoquinone. This kinetic resolution obeys several of the practical requirements outlined in the introduction: the racemate is accessible and the enantiopure material is difficult to make otherwise; the catalyst is highly effective and commercially available; and the reaction is quite user-friendly and employs an inexpensive stoichiometric reagent. Perhaps the only drawback is that the substrate and product are chemically similar entities and therefore

almost certainly difficult to separate. Nonetheless, the kinetic resolution of conduritol B is an excellent example of a practical reaction, particularly on the laboratory scale.



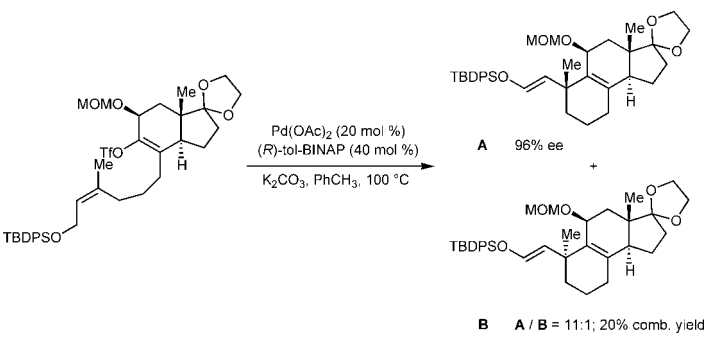
Scheme 26. Gais' kinetic resolution of allylic acetates



Scheme 27. Trost's kinetic resolution of conduritol B tetraacetate

3.4.4 Kinetic Resolution via the Heck Reaction

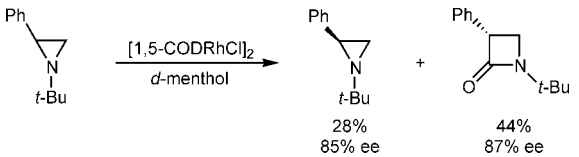
Shibasaki reported a very late stage kinetic resolution in synthetic studies related to wortmanin. The transformation generated a chiral quaternary center yielding 20% of the desired product in 96% ee (Scheme 28).[86] High catalyst loadings were required, and combined with the fact that the racemic substrate is very precious, this transformation has obvious practical limitations. In addition, unlike the Kishi result described in Section 3.3, unreacted substrate could not be recovered in the present case. As a result, this kinetic resolution strategy cannot be applied to the simultaneous synthesis of both enantiomers of a natural product through a common late stage racemic intermediate.



Scheme 28. Kinetic resolution via asymmetric Heck reaction

3.4.5 Kinetic Resolution via Carbonylation of Aziridines

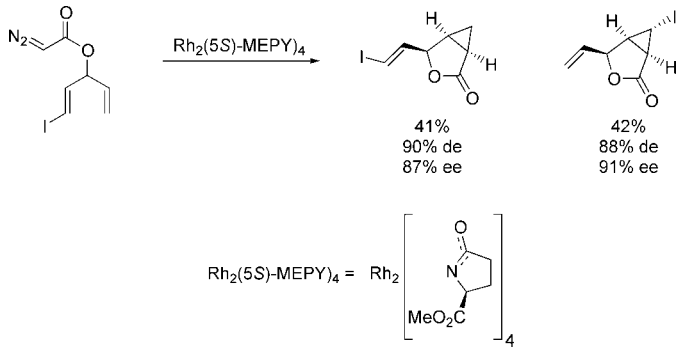
Alper reported an intriguing example of kinetic resolution by means of carbonylation of racemic aziridine derivatives. A highly unusual system based on Rh(I) and menthol as the chiral agent catalyzed the formation of β-lactams from aryl-substituted aziridines (Scheme 29).[87] The CO insertion was found to take place regioselectively into the benzylic C–N bond. The direct synthesis of the racemic aziridines required for this reaction is not straightforward and is typically carried out from the corresponding epoxides, which are in fact accessible in enantiopure form via other kinetic resolution protocols (vide infra). Therefore, to the extent that it is preferable to effect resolutions as early as possible in a synthetic scheme, the carbonylation protocol cannot be considered the most practical approach to the enantioenriched aziridines or the derived β-lactams. However, asymmetric carbonylation is a most interesting strategy for kinetic resolution, and the Alper catalyst is significant both because of the unique and extraordinarily simple nature of the chiral ligand, and because it represents the most effective system for kinetic resolution described to date.



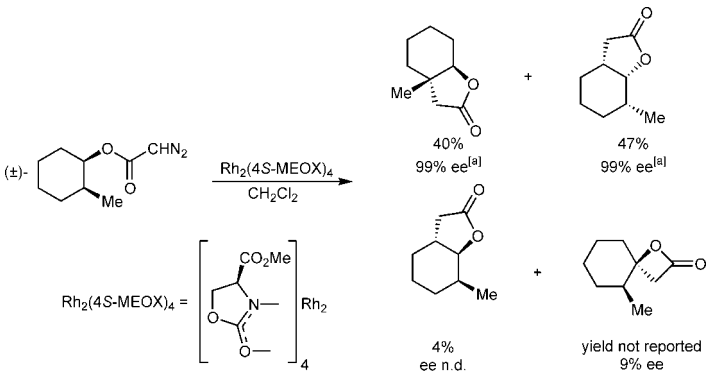
Scheme 29. Kinetic resolution of aziridines via carbonylation

3.4.6 Kinetic Resolution via Catalytic Decomposition of Diazo Compounds

Doyle's chiral dirhodium(II) carboxamidate catalysts have been applied with some success to kinetic resolutions, with interesting results emerging especially in the context of parallel kinetic resolution. Martin examined the intramolecular cyclopropanation of a racemic diazoester derived from a divinylcarbinol (Scheme 30).[88] This substrate bears two chemically inequivalent double bonds, each one having diastereotopic faces. Both enantiomers underwent cyclopropanation in the presence of the chiral Rh_2(5*S*-MEPY)$_4$ catalyst, with one selectively reacting at the unsubstituted alkene and the other at the iodo-substituted alkene. The resulting cyclopropyl-fused γ-lactones were both isolated in high ee and de. Doyle investigated C–H insertion pathways resulting from decomposition of saturated diazoester derivatives in the context of kinetic resolution (Scheme 31).[89] As is the case in enantioselective C–H insertion reactions, a significant effect of ligand on stereoselectivity was observed. Parallel kinetic resolution took place, with one enantiomer of substrate undergoing regioselective insertion into a tertiary C–H bond, and the other into a secondary C–H bond. The resulting isomeric lactones were produced in nearly perfect enantiopurity.



Scheme 30. Martin's parallel kinetic resolution of diazoacetates



[a] Absolute stereochemistries were not assigned.

Scheme 31. Doyle's kinetic resolution of alkyl diazoacetates

3.5 Kinetic Resolution of Epoxides by Nucleophilic Ring-Opening

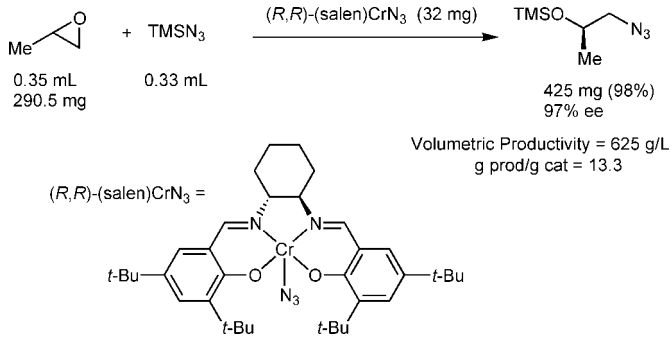
Epoxides are among the most useful chiral building blocks for organic synthesis, and as a result substantial effort in asymmetric catalysis has been directed toward the development of practical routes to these compounds in enantioenriched form. Several important catalytic technologies have been discovered as a result, including the Sharpless epoxidation of allylic alcohols, the (salen)Mn-catalyzed epoxidation of unfunctionalized olefins, and the Shi epoxidation with fructose-derived ketone catalysts.[90] Despite this progress, however, there are still several important classes of epoxides that are not readily accessible in enantioenriched form by asymmetric synthesis. Foremost among these are terminal epoxides, arguably the most valuable class of epoxides from a synthetic standpoint.

In principle, kinetic resolution can be a practically appealing strategy for accessing terminal epoxides in high ee. First, racemic terminal epoxides are either items of commerce and inexpensive, or they can be accessed easily by epoxidation of readily available terminal alkenes. Second, most simple epoxides do not form stable salts or complexes with typical resolving agents. As a result, classical resolution is not a realistic option. Third, terminal epoxides are usually liquids at room temperature, so enantioenrichment of non-racemic epoxides by recrystallization is not possible. This becomes an important consideration if one takes into account that even if a highly enantioselective method for epoxidation of terminal olefins were developed, it is unlikely to provide 100% ee material. In contrast, and as discussed in Part 2, kinetic resolution can provide access to material that is virtually enantiopure as long as the resolution is carried out to sufficiently high conversion.

There has been considerable progress in the development of catalytic methods for the enantioselective desymmetrization of *meso*-epoxides by nucleophilic ring-opening.[91] More recently, this has been extended to the kinetic resolution of terminal epoxides with dramatic success.[92]

3.5.1 Kinetic Resolution by Ring-Opening with $TMSN_3$

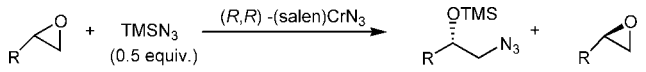
In 1995, our group discovered that chiral (salen)Cr complexes catalyze the enantioselective ring-opening of *meso*-epoxides by $TMSN_3$ with moderate-to-good enantioselectivities, ranging from 86–94% in the better cases.[93] Given this result, it was in fact somewhat surprising to find that a chiral terminal epoxide such as propylene oxide undergoes kinetic resolution with the same catalyst system with extraordinarily high selectivity ($k_{rel} > 200$, Scheme 32).[94] Ring-opening was found to occur with nearly complete regioselectivity for the terminal position. The resulting 1-azido-2-siloxy products are easily converted to the corresponding 1,2-amino alcohols, compounds of proven synthetic utility. The process proved to be remarkably general for a number of terminal epoxides, with k_{rel} values ranging from 44–280 (Table 7). The method was also applicable to the kinetic resolution of a smaller range of 2,2-disubstituted oxiranes.[95]



Scheme 32. Kinetic resolution of propylene oxide by ring opening with $TMSN_3$

The (salen)Cr-catalyzed kinetic resolution of epoxides with $TMSN_3$ has a number of positive practical features that make it one of the most attractive methods for preparing enantioenriched 1,2-amino alcohol derivatives. As noted in Section 2, very high selectivities in kinetic resolutions are required if product (instead of recovered substrate) is to be obtained in high yield and ee, and this is in fact the case in this reaction. However, as a method for preparing enantioenriched epoxides, this procedure has a significant shortcoming. The nucleophile, $TMSN_3$, is rela-

Table 7. (salen)Cr-catalyzed kinetic resolution of terminal epoxides with $TMSN_3$



R	yield (%)	ee (%)
CH_2CH_3	41	97
$(CH_2)_3CH_3$	44	97
CH_2Cl	47	95
CH_2OTBS	48	96
CH_2O(1-naphthyl)	37	93
CH_2Ph	47	93
c-C_6H_{11}	42	97
$(CH_2)_2CH{=}CH_2$	47	98
$CH(OEt)_2$	48	89
CH_2CN	40	92

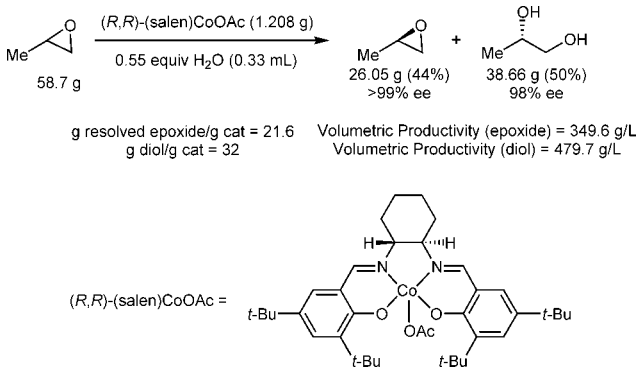
tively expensive and it is clearly not the ideal choice for a reagent that has as its role the destruction of one enantiomer of the racemic epoxide. The kinetic resolution of terminal epoxides with $TMSN_3$ is therefore only of interest with respect to product isolation. On the other hand, no alternative kinetic resolution methods have been identified for 2,2-disubstituted oxiranes, and as a result the kinetic resolution with $TMSN_3$ stands as a useful approach to these epoxides in enantioenriched form, at least on a laboratory scale.[96]

Analysis of the Kinetic Resolution of Epoxides by Ring-Opening with $TMSN_3$

Catalyst availability	The catalyst is prepared in one step from the corresponding salen ligand, which is available commercially and in bulk.
Substrate scope	Extremely broad scope with terminal epoxides. Kinetic resolution of internal epoxides has not been demonstrated.
Availability of racemate	Very high; several racemic terminal epoxides are commodity items.
Alternative methods for accessing enantiopure substrate/product	Enantioenriched 1,2-amino alcohol derivatives can be prepared by several methods, but the ring-opening of terminal epoxides with azide is certainly one of the most attractive strategies. Azide is relatively expensive, and more practical reagents for obtaining resolved terminal epoxides have been identified (vide infra).
General experimental considerations	• Azido alcohol derivatives are obtained in very high yield and ee. • Reactions are carried out under solvent-free conditions, allowing exceptionally high volumetric productivities. • Azide derivatives must be handled with appropriate precautions because of their thermal instability. • Separation of ring-opened product from unreacted epoxide is carried out easily by distillation.

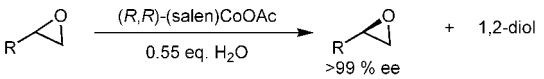
3.5.2 Hydrolytic Kinetic Resolution of Terminal Epoxides (HKR)

In 1997, the practical limitation to the kinetic resolution of terminal epoxides described above was overcome with the discovery that water could be employed as a nucleophile. In the presence of Co(III) analogues of the same salen catalyst used in $TMSN_3$ reactions, water adds cleanly to propylene oxide with nearly perfect selectivity (k_{rel} = ca. 500, Scheme 33).[97] Once again, the reaction proved remarkably general with regard to substrate scope, and virtually every terminal epoxide examined to date has been found to undergo kinetic resolution to afford recovered epoxide in highly enantioenriched form (Table 8). With some more valuable racemic substrates, available asymmetric epoxidation methods can be coupled to the HKR reaction to afford enantiopure epoxides in greater than 50% overall yield. Such a strategy was applied successfully to the preparation of (*R*)-3-chlorostyrene oxide (Scheme 34).[98]



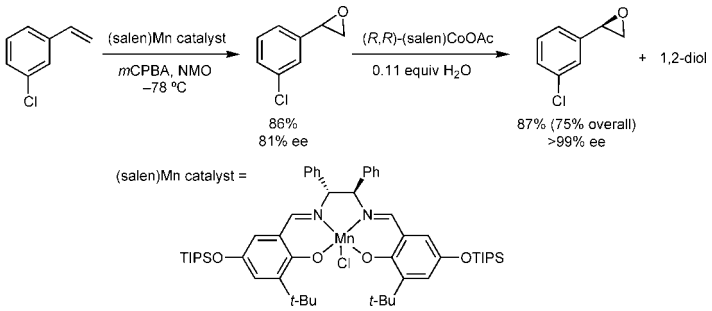
Scheme 33. Hydrolytic kinetic resolution (HKR) of propylene oxide

Table 8. HKR of terminal epoxides



R	yield (%)[a]	R	yield (%)[a]
$(CH_2)_3CH_3$	43	oxiranyl	36
CH_3	46	$CH_2OCO(CH_2)_2CH_3$	46
$(CH_2)_{11}CH_3$	43	CH_2CO_2Et	43
$(CH_2)_2CH{=}CH_2$	43	CO_2Me	43
CH_2Ph	46	COMe	40
c-C_6H_{11}	44	$COCH_2CH_3$	41
t-Bu	41	$CH{=}CH_2$	36
CH_2Cl	43	≡—TBS	41
CH_2F	43	Ph	44
CF_3	43	(4-Cl)C_6H_4	39
CH_2OBn	48	(3-Cl)C_6H_4	40
CH_2OTBS	47	(2-Cl)C_6H_4	38
CH_2OPh	47	(3-MeO)C_6H_4	41
CH_2O(1-naphthyl)	38	(3-NO_2)C_6H_4	37
$(CH_2)OBn$	42		

[a] Yield of epoxide recovered in >99% ee.



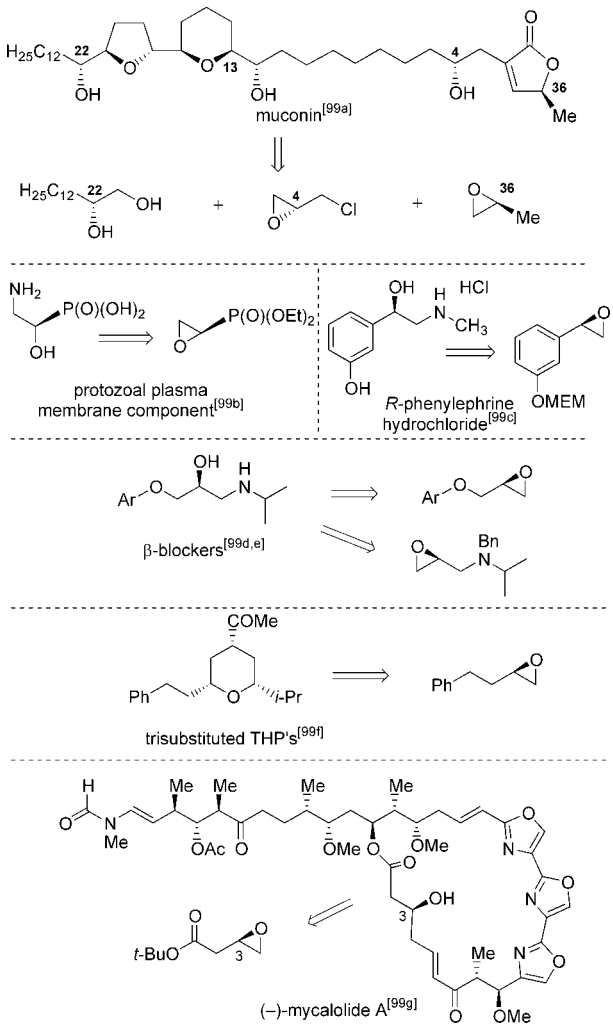
Scheme 34. Asymmetric epoxidation/HKR sequence for the preparation of R-3-chlorostyrene oxide

Analysis of the Kinetic Resolution of Epoxides by Hydrolytic Kinetic Resolution (HKR)

Catalyst availability	Both enantiomers of the Co(II) catalyst precursor are available commercially and in bulk.
Substrate scope	Extremely broad scope with terminal epoxides. Kinetic resolution of internal epoxides has not been demonstrated.
Availability of racemate	Very high; several racemic terminal epoxides are commodity items.
Alternative methods for accessing enantiopure substrate/product	For the vast majority of cases, no direct methods exist for the preparation of enantiopure terminal epoxides. The Sharpless asymmetric dihydroxylation (AD) reaction provides an alternative approach to many 1,2-diol derivatives. However, the HKR provides a superior route in certain cases.
General experimental considerations	• Epoxides can be recovered in >99% ee and good-to-excellent yield. Diol products can also be isolated in high ee. • Reactions are carried out under solvent-free conditions for certain substrates. In other cases, one volume equivalent of solvent provides better results. In general, very high volumetric productivities are attainable. • Water is inexpensive and safe. • Separation of ring-opened diol product from unreacted epoxide is carried out easily by distillation or extraction. • Reactions are run at 0–25 °C. • The catalyst is used at low loadings and can be recycled repeatedly. • The HKR can be run effectively on milligram to multiton scale.

The analysis provided above may well describe an ideal scenario for kinetic resolution from a practical standpoint. Both the resolved epoxide and product diol are obtained in very high ee and are valuable chiral building blocks. The stoichiometric nucleophile, water, is most cost-effective and environmentally friendly. With many substrates, the reaction can be carried out solvent-free and therefore generates no waste at all except for the byproduct diol, itself a useful chiral building block. The catalyst has been shown to be recyclable through several reactions with no diminishment in either reactivity or enantioselectivity. As a result of the large boiling point differences between epoxides and diols, the products can distilled directly from the reaction vessel and isolated in pure form leaving only the catalyst residue. Furthermore, it has been shown that the catalyst can be attached to solid supports with no deleterious effect on activity or selectivity, making its recovery and reuse even simpler.

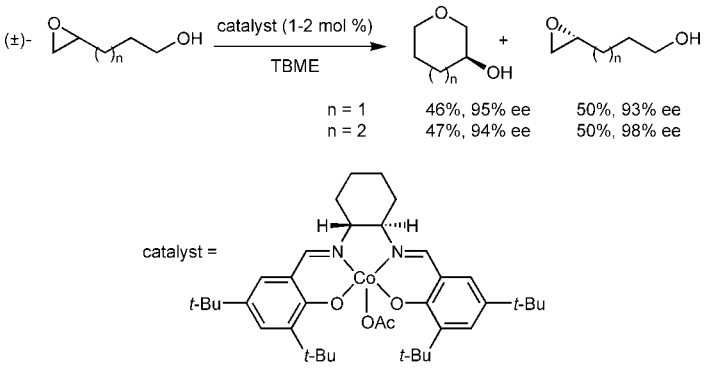
Perhaps the most concrete evidence of the practicality of the HKR is the fact that the process has seen widespread use in both academic and industrial laboratories. For example, Scheme 35 lists a series of chiral intermediates and natural product targets prepared using the HKR of terminal epoxides.[99] In a commercial context, the resolution of propylene oxide, epichlorohydrin, and styrene oxide have been carried out on 100 kg to multi-ton scale, and this has led to a significant reduction in cost and increase in availability of these useful chiral building blocks.[100]



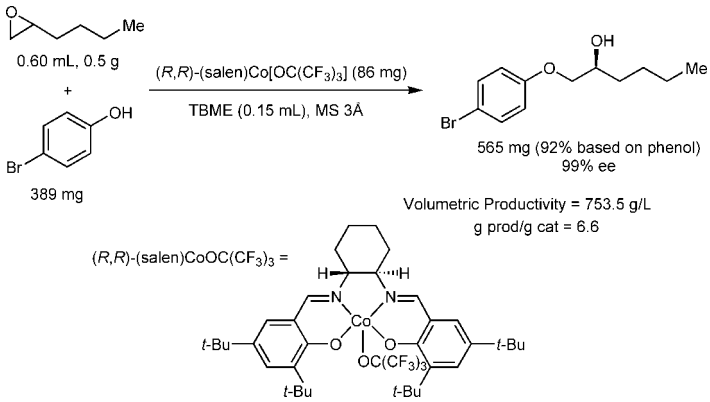
Scheme 35. Some synthetic applications of the HKR

3.5.3 Kinetic Resolution of Epoxy Alcohols via Intramolecular Ring Opening

Racemic 1,2-epoxy-ω-alcohols were found to undergo kinetic resolution catalyzed by chiral (salen)Co complexes in the absence of added reagent. In the case of substrates bearing 5 or 6 carbons, intramolecular addition of the alcohol to the epoxide occurred with high *endo* regioselectivity, in violation of Baldwin's rules, to afford the 6- or 7-membered ring ethers, respectively (Scheme 36).[101] Both recovered epoxide and cyclization product were produced in high ee.



Scheme 36. Intramolecular kinetic resolution of epoxy alcohols

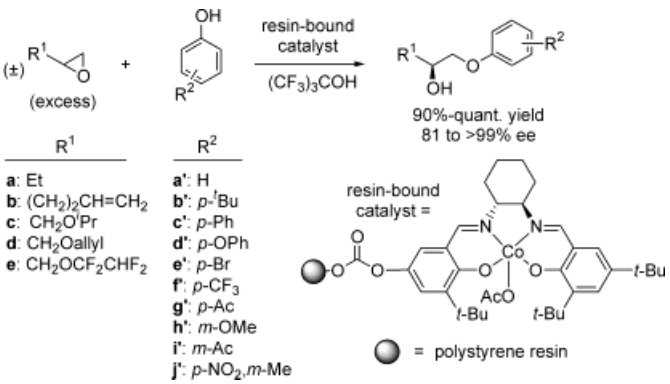


Scheme 37. Phenolic kinetic resolution of 1-hexene oxide

Instances of intramolecular kinetic resolutions such as these are unusual. The transformations in Scheme 36 might appear to hold practical appeal relative to the HKR of the same substrates because no added reagent is needed. However, this is in fact an example of a kinetic resolution that fails on a practical level simply because it is very difficult to separate the unreacted substrate from the product. The two are isomeric hydroxy ethers with very similar physical and chemical properties. In order to effect separation, it proved necessary to carry out careful column chromatography of the benzoate ester derivatives. This serves to highlight one of the most attractive features of the HKR, which affords epoxide and diol that are very easily separated by distillation or extraction.

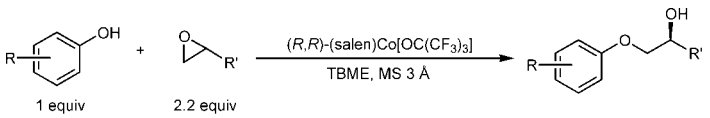
3.5.4 Kinetic Resolution by Ring Opening with Phenols

Phenols were also found to be effective nucleophiles for the (salen)Co-catalyzed kinetic resolution of terminal epoxides (Scheme 37).[102] While water is clearly a more attractive reagent for kinetic resolution if epoxide recovery is desired, the phenolic ring-opening provides direct access to α-aryloxy alcohols, which are valuable synthetic intermediates that are otherwise not easily accessed. The phenolic kinetic resolution displays similar generality with regard to terminal epoxide substrates as does the HKR (Table 9). In addition, the nucleophilic component can be varied, and phenols with a wide range of electronic properties are effective substrates. This is a highly unusual example of an asymmetric catalytic process that is general with respect to each of two different reacting partners, and this feature was showcased through the preparation of parallel libraries of α-aryloxy alcohols using a polystyrene-supported catalyst.[103] Small libraries of 50 members each were prepared and the products analyzed in terms of purity and enantioselectivity (Scheme 38). Product was isolated by removal of catalyst by filtration and of unreacted epoxide by evaporation, and good-to-excellent ee's were observed for all cases examined. This first application of asymmetric catalysis as a diversity-generating step in a library synthesis provides a non-obvious, but nonetheless compelling, illustration of a practical application of kinetic resolution.



Scheme 38. Library synthesis via phenolic kinetic resolution

Table 9. Phenolic kinetic resolution of terminal epoxides



R	R'	yield (%)[a]	ee (%)
H	$(CH_2)_3CH_3$	97	98
H	CH_2Cl	97	99
H	CH_2O(allyl)	93	97
H	c-C_6H_{11}	99	97
H	$COCH_2CH_3$	96	96
H	CO_2Me	98	96
p-Me	$(CH_2)_3CH_3$	97	98
m-Me	$(CH_2)_3CH_3$	95	97
o-Br	$(CH_2)_3CH_3$	98	92
p-OMe	$(CH_2)_3CH_3$	75	99
p-NO_2	$(CH_2)_3CH_3$	93	91
p-$(CH_2)_2$NHBoc	$(CH_2)_3CH_3$	86	99

[a] Based on phenol as the limiting reagent.

4 Conclusions and Outlook

Among the numerous examples of kinetic resolution reactions analyzed in this review, there are certainly no "perfect reactions" from a practical standpoint. Nonetheless, there are now several examples of kinetic resolution processes that have been developed into virtually unbeatable methods for the preparation of useful chiral building blocks on laboratory and/or large scales. Certainly, it is hoped that the notion is dispelled that a reaction that can only produce material in up to 50% yield is inherently impractical. At the same time, we hope that the parameters for practicality outlined here will be taken into account in future work, particularly those of catalyst availability, substrate scope, availability of the racemic substrate and of alternative methods for accessing enantiopure substrate or product, and critical experimental considerations.

With the practical considerations outlined in the Introduction in mind, it is interesting to ask what targets for kinetic resolution processes would be interesting to consider for future development. The list should be comprised of classes of compounds where the racemates are readily available and the enantiopure materials are not. In that light, chiral alkanes and alkenes, aziridines, and phosphines are just a few of the prime possibilities. It remains to be seen if truly practical catalytic methods can be devised for the kinetic resolution of these compounds.

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[6] This is driven home by the recent example of Crixivan®, the HIV-protease inhibitor drug developed by Merck. Although it served as inspiration for a large body of exciting research in asymmetric catalysis, in the end its commercial synthesis relies on the use of two classical resolutions and three diastereoselective reactions. See: P. J. Reider, *Chimia* **1997**, *51*, 306–308.
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