Introduction

Asymmetric synthesis of bioactive molecules is in the forefront of synthetic organic chemistry due to its varied applications in drug and pharmaceutical industries and biotechnologies. 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.

In the last two decades, many powerful asymmetric reactions have emerged as a result of the growing need to develop efficient and practical syntheses of biologically active compounds. Catalytic asymmetric reactions provide an especially practical entry into the chiral world due to their economical use of asymmetric inducing agents. Especially useful is the carbon-heteroatom bond forming reaction, since the resulting functionality can be readily manipulated to produce many important classes of compounds. It is not surprising, therefore, that the oxidative addition of heteroatoms to olefins has been a fruitful area in last three decades. A number of transition metal-mediated methods for the epoxidation, oxidative cyclization, halohydrin formation, dihydroxylation and aminohydroxylation have emerged. A common feature of most of these processes is the phenomenon of ligand acceleration, wherein a metal catalyzed process turns over faster in the presence of a coordinating ligand.

Epoxides are versatile and important intermediates in organic chemistry. The strain of three membered heterocyclic ring makes them accessible to a large variety of reagents. Metal catalyzed epoxidation process was discovered by K. Barry Sharpless & Katsuki in 1980 and allows the transformation of a prochiral substrate into an optically active (or optically pure) product using a chiral catalyst. The asymmetric induction is achieved by adding an enantiomerically enriched tartrate derivative. This epoxidation is arguably one of the most important reactions discovered in the last 30 years. This has been recognized by the award of the 2001 Nobel Prize to Professor Barry Sharpless.

In this epoxidation reaction, double bond of allylic alcohols is converted into epoxides using a transition metal catalyst (Ti(O\(^{i}Pr\))\(_4\), titanium tetra-isopropoxide) and a chiral additive (dialkyltartrate, i.e., DET or DIPT used). The oxidant for the epoxidation is tert-butylhydroperoxide. Notably, this reaction exhibits high levels of enantioselectivity (usually >90% ee) and proceeds under mild condition with good
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chemical yield. It is proposed that, coordination of the chiral ligand DET and the oxidant source TBHP to the metal center forms the catalytically active species.

Asymmetric epoxidation with the titanium (VI) tartrate Catalyst

The combination of Ti(OPr̃)₄, a dialkyl tartrate, and tert-butyl hydroperoxide epoxidizes most allylic alcohols in good chemical yield and with predictably high enantiofacial selectivity according to the empirical rule illustrated in Scheme 1. When an allylic alcohol (R⁴, R⁵ = H) 1 is drawn in a plane with the hydroxymethyl group positioned at the lower right, the delivery of oxygen occurs from the bottom side of the olefin to give the (2S)-epoxide 5 if an (R,R)-dialkyl tartrate 3 is used as the chiral auxiliary. When an (S,S)-dialkyl 2 tartrate is employed, oxygen is delivered from the top side. The enantiofacial selectivity of the reaction is > 90% ee for substrate without a Z-olefinic substituent (R³ = H). The degree of facial selectivity for a Z-allylic alcohol depends on the nature of the Z substituent R³. The enantioselectivity for substrate with unbranched R³ substituents ranges from 80 to 94% ee, but that for substrates with branched substituent is lower.⁹

Scheme 1

![Scheme 1](image)

Scheme 2: Representative examples of epoxidation of allylic alcohols

Mechanism

The reaction sequence proposed for the metal-catalyzed epoxidation of allylic alcohols is shown in scheme 3.¹³ Metal alkoxides generally undergo rapid ligand
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exchange with alcohols. When a metal alkoxide, an allylic alcohol, and an alkyl hydroperoxide are mixed, ligand exchange occurs to afford a mixture of complexes $\text{M(OR)}_{n-x-y}-(\text{OCH}_2\text{CH}═\text{CH}_2)_{x}(\text{OOR})_{y}$. Among them, only species such as ‘a’, bearing both allylic alkoxide and alkyl hydroperoxide groups, are responsible for the epoxidation. The incorporated alkyl hydroperoxide is thought to be further activated by coordination of the second oxygen atom (O-2) to the metal center. The ensuing transfer of O-1 to the double bond of the allylic alcohol occurs in an intramolecular fashion is supported by comparison of the epoxidation rate of allylic alcohol with that of allyl methyl ether $^{14}$ However controversy still surrounds the oxygen transfer process (b-e). One suggestion is that the double bond first coordinates to the metal center and then inserts into the $\mu_2$-alkyl hydroperoxide ligand to give an epoxide via the peroxometallocycle intermediate. $^{15}$ An alternative proposal is that the double bond attacks the distal oxygen along the axis of the O-O bond that is broken. $^{9,13d,15}$ Frontier molecular orbital treatment of peroxometal complexes also suggests that d-transition metal complexes of ROO- exhibit electrophilic behaviour. $^{16}$

Scheme 3

Finally, exchange of tert-butoxide and the epoxy alkoxide so formed with allylic alcohol and alkyl hydroperoxide completes the reaction cycle. The titanium tartrate mediated asymmetric epoxidation of allylic alcohols also follows the same basic reaction pathway of Scheme 3. Therefore the remaining mechanistic question is how oxygen is transferred enantioselectively to substrates. To answer this question, structures of titanium-dialkyl tartrate complexes, $^{15,17}$ as well as those prepared from Ti(O$^\text{OPr}$)$_4$ and ($R$,$R$)-$N$,$N'$-dibenzyltartramide and from Ti(OEt)$_4$, ($R$,$R$)-diethyl tartrate, and Ph(CO)-N(OH)Ph were determined. $^{18}$ Based on the X-ray analysis of these complexes, the structure of the asymmetric epoxidation catalyst 12 (Fig. 1) has been proposed.
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When structure shown in Fig. 1 is viewed down the distal peroxide oxygen-titanium bond axis (O1-Ti), the symmetry of the tartrate “windmill arms” becomes apparent. Within this model, conformer 13 (Fig 2), in which the allylic alcohol and the TBHP-ligand align meridionally and the TiO-C-C=C dihedral angle is as small as 30°, has been suggested as a transition state.9

This conformer experiences severe steric interactions only when R5 ≠ H. This explains the high efficiency of kinetic resolution of racemic secondary allylic alcohols where one enantiomer (R4 = alkyl, R5 = H) reacts much faster than the other isomer (R4 = H, R5 = alkyl). The poor reactivity of tertiary allylic alcohols (R4 and R5 = alkyl) is rationalized analogously.18 We also see that the Z olefinic substituent (R3) is close to the hydroxymethyl group bound to titanium because of the small O-C-C=C dihedral angle. These interactions destabilize conformer 14 (Fig. 3) and lower the reactivity of this complex. The C-2 substituent (R2) (Fig. 2) is also in the vicinity of the titanium complex, and only the E olefinic substituent (R1) projects toward an open quadrant. This model explains following three observations.

Figure 1

Figure 2

Figure 3
1. Bulky Z olefinic substituents retard epoxidation reactions, and substrate with branched Z substituents exhibit poor reactivity and decreased enantioselectivity. This may be rationalized by the conformational requirements for minimization of allylic strain due to the small C=C-COTi dihedral angle. That is, the conformation in which H is in the plane of the olefin is energetically more accessible than the other two conformations (R and R’ in-plane conformations). Thus the disposition of an alkyl group (R1) to the bottom side raises the energy of the transition state depicted in Fig. 3 [using (R,R) tartrate], causing retardation of the reaction and decreased enantioselectivity. When R \neq R^1, each enantiomer of a racemic substrate has different reactivity and treatment of such a racemic mixture with Ti(OiPr)4-tartrate affects kinetic resolution.

2. The C-2 substituent is near the Ti-tartrate moiety; its chirality also affects substrate reactivity. Thus enantiomers of a racemic substrate bearing a chiral C-2 substituent have different reactivities, and in some cases a good level of kinetic resolution is observed.

3. Except for a few examples, the E substituent, which is located in an open quadrant, has little effect on the stereoselectivity of the reaction. Therefore, the epoxidation of chiral E-allylic alcohols should proceed with same high level of enantioselectivity seen with achiral E-allylic alcohols. Since the principal difficulties (isolation of unstable and/or water soluble epoxy alcohols) with the stoichiometric reaction are mainly attributed to the mild Lewis acidity of titanium alkoxide and the aqueous workup required for hydrolysis of the stoichiometric catalyst, Sharpless discovered that addition of molecular sieves to the reaction mixture allows epoxidation to proceed to completion in the presence of only 5-10 mol% of the Ti(OPr'i)4 and 6 mol% tartrate has been recommended as the most widely applicable system for asymmetric epoxidation. Below the 5 mol% level, the enantioselectivity of the reaction decreases remarkably. The amount of tartrate ester must be carefully controlled, because a large excess of tartrate (>100 % excess) decreases the reaction rate while with too little tartrate (<10 % excess) the enantioselectivity may suffer.
Introduction

Enormous advances have been made over the past several years in asymmetric synthesis, with particular emphasis having been placed on the development of enantioselective catalytic reactions. Different factors influence the practicality of an asymmetric reaction. A list of the features 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. 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 enantio-enriched 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.\textsuperscript{23}

Resolutions fall broadly into three classes. Classical resolutions involve the use of a stoichiometric amount of a chiral resolving agent.\textsuperscript{24} 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.\textsuperscript{25} 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 enantio-enriched starting material and product, and the desired component is then isolated.\textsuperscript{26}

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. 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. 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 following conditions must be met in order for kinetic resolution to be practical:

- 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 enantio-enriched form.

The importance of epoxides in organic synthesis arises partly from the occurrence of the strained three-membered ring unit in a number of interesting natural products but more so because the ring opening of epoxides allows straightforward elaboration to useful new functionality, often with generation of new carbon-carbon bonds. Indeed, reactions of epoxides with nucleophiles, Lewis acids, radicals, reducing agents, oxidizing agents, acids, and bases have all been well documented and utilized in synthesis. Further, the stereospecific manner in which epoxides generally react renders these compounds attractive chiral building blocks for asymmetric synthesis.

Since those epoxides that are produced naturally are typically complex compounds available only in limited amounts, Nature’s chiral pool has not proven to be a useful direct source of optically active epoxides for use in organic synthesis. Instead, enantio-enriched epoxides have been accessed indirectly from the chiral pool via multistep procedures. These, however, tend to be inherently inefficient, and the range of epoxides available by this approach is also quite limited. As a consequence, the preparation of enantio-enriched epoxides has long stood as a most significant target for asymmetric synthesis. In particular, the identification of catalytic asymmetric olefin oxidation methods has been an area of active research for several
decades, and the advances made in this field have increased greatly the number of enantiomerically enriched epoxides available for use in organic synthesis. Among available methods for the preparation of enantio-enriched epoxides, the Sharpless epoxidation reaction has arguably had the most profound impact of any asymmetric catalytic reaction discovered thus far, providing general access to highly enantio-enriched epoxyalcohols. More recently, the epoxidation of unfunctionalized conjugated olefins by chiral (salen)Mn complexes has enabled the practical synthesis of certain classes of enantiomerically enriched epoxides. A highly complementary strategy for epoxidation of simple olefins involving chiral dioxirane intermediates has expanded the range of chiral epoxides now accessible in enantio-enriched form to a significant extent. Indirect routes to enantiopure epoxides involving asymmetric catalytic dihydroxylation or reduction reactions have also proven highly valuable in specific contexts. Despite these considerable advances in asymmetric catalytic synthesis of epoxides, no general methods have been identified for the direct preparation of highly enantio-enriched 1-oxiranes, arguably the most valuable class of epoxides for organic synthesis. The utility of terminal epoxides as chiral building blocks is perhaps best illustrated by the fact that the few examples for which effective catalytic approaches exist have found extensive use in asymmetric synthesis. In particular, glycidol and a number of its derivatives are available in enantiomerically enriched form using the Sharpless epoxidation technology or by enzymatic kinetic resolution methods, and these compounds have become widely used starting materials for target-oriented synthesis. Epichlorohydrin has been rendered commercially available in bulk by microbial resolution of ((±)-2,3-dichloro-1-propanol, and it, too, has found widespread application. Recently Jacobsen had discovered the (salen)Co complex catalyzed efficient hydrolytic kinetic resolution (HKR) of a variety of terminal epoxides (Scheme 4). This new method appeared to hold considerable promise with regard to meeting all of the criteria outlined above for kinetic resolution to be practical. Racemic 1,2-epoxides are generally available directly from commercial suppliers at low cost or are obtainable in one step from inexpensive olefins or aldehydes. In fact, certain racemic epoxides, such as propylene oxide, epichlorohydrin, styrene oxide, and butadiene monoepoxide, are commodity chemicals and are no more expensive than common organic solvents. Second, the ligands for catalyst had previously been commercialized and manufactured on a ton scale in the context of (salen)Mn
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epoxidation catalysts. The cobalt analogues $(R,R)$-15 and $(S,S)$-15 proved equally accessible, and these are also now available in bulk. Third, water is perhaps the ideal reagent for effecting the resolution reaction: it is inexpensive and safe, and the rate of the ring-opening reaction can be controlled simply by modulating the rate of addition of water to the epoxide-catalyst mixture. Fourth, for those examples that were described in the preliminary report, highly enantio-enriched epoxides were recovered from the HKR. Finally, the HKR provided useful enantio-enriched 1,2-diols, including many that are otherwise not readily accessible using existing asymmetric dihydroxylation methods.

**Figure 4: Jacobsen catalyst**

The HKR has seen rapid adoption as the method of choice for the preparation of a variety of terminal epoxides in enantio-enriched form, and a number of applications in target oriented synthesis have been reported already. In addition, the commercial manufacture of enantio-enriched propylene oxide, epichlorohydrin, and styrene oxide using HKR methodology has been implemented, thereby reducing the cost of these useful chiral building blocks. Jacobsen has discovered that the HKR is an extraordinarily general reaction, allowing efficient kinetic resolution of virtually any type of terminal epoxide.

**Preparation of Catalyst and General Experimental Considerations**

Both enantiomers of the (salen)CoII complex 15 are available commercially on research or commercial scale, or they can be prepared from the commercially

![Diagram](image-url)
available ligands using \( \text{Co(OAc)}_2 \). The \( \text{Co}^{II} \) complex 15 is catalytically inactive, however, and it must be subjected to one-electron oxidation to produce a (salen)\( \text{Co}^{III} \)-X complex (X= anionic ligand) prior to the HKR. This may be done conveniently by aerobic oxidation in the presence of a mild Brønsted acid. Water alone was found not to mediate the oxidation reaction, but a screen of additives revealed that acetic acid was effective and that the corresponding \( \text{Co}^{III} \) precatalyst 15.OAc is convenient for use in HKR reactions both in terms of its preparation and reactivity. Two useful methods for the generation of complex 15.OAc have been developed. Method A involves isolation of 15.OAc as a crude solid prior to the HKR. The \( \text{Co}^{II} \) complex 15 is dissolved in toluene to generate a ca. 1 M solution, and acetic acid (2 equiv) is added. The resulting solution is stirred open to air at room temperature for 30 min, during which time the color of the mixture changes from orange to dark brown. All volatile materials are removed in vacuo, affording 15.OAc as a brown solid residue that can be used without further purification. Method B involves in situ generation of 15.OAc under HKR conditions by suspension of the \( \text{Co}^{II} \) complex 15 in epoxide or epoxide/solvent and addition of HOAc under an aerobic atmosphere. Catalyst obtained by both methods was examined for each of the epoxides described in this study. For certain substrates such as 1-hexene oxide, catalyst prepared by either method leads to essentially identical results. In these situations, in situ catalyst generation (method B) is preferable since the procedure avoids an extra solvent removal step. On the other hand, catalyst prepared by method A was found to be more effective with less reactive substrates (vide infra) and was applicable to all substrates examined. Therefore, if HKR did not afford epoxide in >99% ee with catalyst prepared by method B after optimization of solvent and catalyst loading, then catalyst prepared by method A was employed.

![Scheme 5](image_url)
Aside from the method of generation of 15.OAc, the only reaction parameters in the HKR that required optimization for individual substrates were catalyst loading and choice of solvent. With few exceptions, epoxide of >99% ee could be obtained using 0.55 equiv of water relative to racemate. Relatively small epoxides with some degree of water solubility could be resolved effectively without added solvent. However, the HKR of more lipophilic substrates did benefit from inclusion of a water miscible organic solvent such as tetrahydrofuran (THF), 2-propanol, or 1,2-hexanediol. In general, one volume of solvent relative to racemic epoxides was sufficient to allow efficient HKR. Catalyst loadings of 0.5 mol % or lower relative to racemic epoxide were effective for many substrates, but epoxides bearing sterically hindered or unsaturated substituents often required more catalyst (up to 2 mol %) to attain complete resolution. Reactions were initiated at 0 °C and then allowed to warm to room temperature with continued stirring for 12-18 h.

\[ \text{[(R,R)-N,N'-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminato(2-\text{\textsuperscript{2}})]cobalt(II) ((R,R)-15).} \]

A solution of cobalt(II) acetate tetrahydrate (5.98 g, 24.0 mmol) in MeOH (80 mL) was added to a solution of ligand \[ \text{[(R,R)-N,N'-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediamine]} \] (10.9 g, 20.0 mmol) in \( \text{CH}_2\text{Cl}_2 \) (80 mL) via cannula under an atmosphere of \( \text{N}_2 \) with careful exclusion of air. A brick-red solid began to precipitate before addition was complete. The sides of the reaction flask were rinsed with MeOH (20 mL), and the mixture was allowed to stir for 15 min at room temperature and then 30 min at 0 °C. Precipitated solids were isolated by vacuum filtration and rinsed with cold (0 °C) MeOH (2 x 75 mL). The red solid was collected and dried in vacuo to yield \[ \text{[(R,R)-N,N'-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminato(2-\text{\textsuperscript{2}})]cobalt(II) ((R,R)-15)} \] (11.6 g, 19.2 mmol, 96%).

**Representative Procedures for the HKR of Terminal Epoxides**

(a) **Method A.** (S)-Propylene Oxide. A 100 mL flask equipped with a stir bar was charged with (S,S)-15 (242 mg, 400 \( \mu \text{mol} \), 0.002 equiv). The catalyst was dissolved in 5 mL of PhMe and treated with AcOH (240 \( \mu \text{L} \), 4.2 mmol). The solution was allowed to stir at room temperature open to air for 30 min over which time the color changed from orange-red to a dark brown. The solution was concentrated in vacuo to leave a crude brown solid. The resulting catalyst residue was dissolved in propylene oxide (14.0 mL, 11.6 g, 200 mmol) at room temperature, the reaction flask was cooled to 0
°C, and H₂O (1.98 mL, 110 mmol, 0.55 equiv) was added dropwise over 5 min. The reaction was allowed to warm to room temperature and stir for 14 h at which time (S)-propylene oxide (5.35 g, 92.1 mmol, 46%) was isolated by distillation from the reaction mixture at atmospheric pressure and 36 °C. Propylene diol was removed by vacuum distillation (65 °C, 0.25 Torr). The catalyst was recovered by suspension in MeOH and collection by vacuum filtration. The ee of the propylene oxide was determined to be 99.7% by chiral GC analysis of the 1-azido-2-trimethylsiloxypropane derivative obtained by opening the epoxide with TMSN₃ (Cyclodex-B, 55 °C, isothermal, \( t_R \) (minor) ) 12.29 min, \( t_R \) (major) ) 12.57 min).

(b) Method B. \((R)-1,2\)-Epoxy-5-hexene. A 100 mL flask equipped with a stir bar was charged with \((R,R)-15\) (302 mg, 500 μmol, 0.005 equiv). The catalyst was treated with (±)-1,2-epoxy-5-hexene (11.3 mL, 9.81 g, 100 mmol), AcOH (120 μL, 2.1 mmol, 0.02 equiv), and 1 mL of THF. The reaction flask was cooled to 0 °C, and H₂O (1.0 mL, 55 mmol, 0.55 equiv) was added in one portion. The reaction was allowed to warm to room temperature and stir 16 h at which time the volatile materials were isolated by vacuum transfer at 0.25 Torr into a cooled (-78 °C) receiving flask. The recovered epoxide was filtered through a silica plug to remove residual water, and the THF was removed by rotary evaporation to yield \((R)-1,2\)-epoxy-5-hexene (4.23 g, 43.1 mmol). The diol was distilled under reduced pressure (56 °C, 0.25 Torr). The catalyst was recovered by suspension in MeOH and vacuum filtration. The ee of the recovered epoxide was determined to be 99.5% by chiral GC analysis of the 1-azido-2-trimethylsiloxy-5-hexene derivative obtained by opening the epoxide with TMSN₃ (Cyclodex-B, 70 °C, isothermal, \( t_R \) (minor), 38.00 min, \( t_R \) (major), 39.06 min).

**Catalyst Recycling**

The possibility of recycling a catalyst has obvious practical appeal, particularly in cases where the catalyst is precious due to cost or limited availability. Catalyst 15 is prepared in bulk from low-cost components, and as a result it is quite inexpensive relative to most chiral catalysts. On the other hand, the HKR employs reactants (racemic epoxide, water, minimal if any solvent) that impact the cost of the overall process to an almost negligible extent in many cases, and as a result the catalyst is a significant contributor to the material costs. Accordingly, efforts were directed toward identifying practical methods for effecting catalyst recovery and recycling. The HKR reaction of propylene oxide presents an especially straightforward scenario with
respect to catalyst recovery because both the epoxide and the diol are relatively volatile and can be removed by distillation. The solid residue remaining in the reaction vessel after product separation was found to have the characteristic red-brick color of the reduced (salen)CoII complex 15. Reoxidation to 15.OAc with air and AcOH led to catalyst with undiminished levels of reactivity and selectivity. Thus the HKR provides a straightforward method for the preparation of a wide assortment of terminal epoxides in highly enantio-enriched form. Given that in many cases there exist no practical alternatives for accessing the valuable chiral building blocks, it is hoped that the HKR will have a beneficial and enabling effect on the field of organic synthesis.
Proline catalyzed asymmetric organic transformations

Introduction to organocatalysis

The broad utility of synthetic chiral molecules as single-enantiomer pharmaceuticals, in electronic and optical devices, as components in polymers with novel properties, and as probes of biological function, has made asymmetric catalysis a prominent area of investigation. Organocatalysis, or the use of small organic molecules to catalyse organic transformations, is a relatively new and popular field within the domain of chiral molecule (or enantioselective) synthesis. Although chemical transformations that use organic catalysts, or organocatalysts, have been documented sporadically over the past century, it was not until the late 1990s that the field of organocatalysis was ‘born’. It is now widely accepted that organocatalysis is one of the main branches of enantioselective synthesis (the other, previously accepted, branches being enzymatic catalysis and organometallic catalysis), and those who are involved in the synthesis of chiral molecules consider organocatalysis to be a fundamental tool in their catalysis toolbox.

This rediscovery has initiated an explosive growth of research activities in organocatalysis both in industry and in academia. The 1970s brought a milestone in the area of asymmetric organocatalysis, when two industrial groups led by Hajos and Wiechert published the first and highly enantioselective catalytic aldol reactions using simple amino acid proline as the catalyst. Organocatalysis is the catalysis of chemical transformations using a purely organic molecule, which is composed of mainly carbon, hydrogen, nitrogen, sulfur, and phosphorus, and does not contain any metals. The advent of organocatalysis brought the prospect of a complementary mode of catalysis, with the potential for savings in cost, time and energy, an easier experimental procedure, and reductions in chemical waste, which confers a huge direct benefit in the production of pharmaceutical intermediates when compared with transition metal catalysts. Organic molecules not only have ease of manipulation and a “green” advantage but also can be very efficient catalysts. Several aspects of organocatalysis will undoubtedly attract researchers’ attention. Tremendous efforts will continue to be directed towards the discovery and design of catalysts with better efficiency, new reactivities and greater turnover numbers. And in near future asymmetric organocatalysis may begin to catch up with the spectacular advancements of enantioselective transition metal catalysis.
Recently, List\textsuperscript{46} introduced a system of classification based on the mechanism of catalysis (Figure 5). The four categories are Lewis base, Lewis acid, Brönsted base and Brönsted acid catalysis. Accordingly, Lewis base catalysts (B:) initiate the catalytic cycle via nucleophilic addition to the substrate (S). The resulting complex undergoes a reaction and then releases the product (P) and the catalyst for further turnover. Lewis acid catalysts (A) activate nucleophilic substrates (S:) in a similar manner. Brönsted base and acid catalytic cycles are initiated via a (partial) deprotonation or protonation, respectively.

**Figure 5:** Organocatalytic cycles

**Proline a “Universal catalyst”**

Proline has been defined as a “universal catalyst” because of its high utility in variety of asymmetric organic transformations. Proline is the only natural amino acid with a secondary amine functionality, which raises the pKa value and better nucleophilicity as compared to other amino acids. It can act as a nucleophile to carbonyl groups (iminium intermediate) or Michael acceptors (enamines). It can be regarded as a bifunctional catalyst as the secondary amine acts as Lewis base and the acid group
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acts as Brönsted acid (Figure 6). The high stereoselectivity in the proline-catalyzed reactions is possibly due to its formation of organized transition states with many hydrogen bonding frameworks. Proline is not the only molecule to promote catalysis, but it still seems to be one of the best in the diversity of transformations.

![Figure 6: Modes of proline catalysis](image)

It is known to catalyze aldol, Diels-Alder, Michael addition and α-functionalization among many other organic transformations. Particularly proline-catalyzed α-aminoxylation and α-amination of carbonyl compounds have emerged as powerful methods because chiral building materials can be synthesized in effective manner starting from easily available materials.

**Proline-catalyzed α-aminoxylation**

Optically active α-hydroxyaldehydes and ketones are important intermediates in organic synthesis as they are direct precursors to 1, 2-diols. Because of this utility many methods have been developed for their preparation. The more prominent, well-established methods of enantioselective α-oxygenations include the use of Davis oxaziridine, Sharpless dihydroxylation of enol ethers, manganese–salen epoxidation of enol ethers, and Shi epoxidation of enol ethers. It is only rather recently that direct catalytic, asymmetric variants have been reported. Most of these methods, however, require multiple manipulations and there is no direct method, nor catalytic asymmetric method for their synthesis from the corresponding aldehyde. Recently, proline has been found to be an excellent asymmetric catalyst for α-aminoxylation of carbonyl compounds. When an aldehyde without substitution at α-position was reacted with nitrosobenzene in presence of L-proline in DMSO at ambient temperature, aminoxylation of the aldehyde takes place at the α-position. Aldehyde can be reduced in situ with sodium borohydride and the aminoxy moiety
undergoes hydrogenolysis with Pd/C, H₂ or CuSO₄ to give the corresponding diols 21 in very high enantioselectivities (Scheme 6).

**Scheme 6**: Reagents and conditions: (a) (i) S-proline (20 mol%), DMSO, 25 °C; (ii) NaBH₄, MeOH; (b) Pd/C, H₂ or 30 mol% CuSO₄. R= Ph, i-Pr, n-Bu, CH₂Ph etc. > 99% ee

The mechanism of the α-aminoxylation reaction is shown in figure 7. The observed enantioselectivity of the catalytic α-aminoxylation of aldehydes can be rationalized by invoking an enamine mechanism operating through a chair transition state where the Si face of an α-enamine formed from the aldehyde and L-proline approaches the less hindered oxygen atom of nitrosobenzene to provide a chiral α-aminoxyaldehyde with R configuration. Since proline is commercially available in both enantiopure forms, a one pot sequential catalytic α-aminoxylation of aldehydes followed by in situ reduction with NaBH₄ affords R- or S- configured 1, 2-diol units (the secondary alcohol “protected” by an O-amino group) with excellent enantioselectivities and in good yields.

**Figure 7**: Proposed mechanism of the α-aminoxylation reaction

**Proline-catalyzed α-amination**

The importance of optically active α-amino acids, α-amino aldehydes, and α-amino alcohols, formed by asymmetric catalysis, has stimulated an enormous development in synthetic strategies, and two different catalytic, enantioselective approaches are attractive: the C-C and the C-N bond-forming reactions.
Scheme 7: Reagents and conditions: (a) L-proline (10 mol%), CH$_3$CN, 0 °C, 3 h; NaBH$_4$, EtOH; (b) L-proline (10 mol%), CH$_2$Cl$_2$, 25 °C; NaBH$_4$, MeOH; 0.5 N NaOH; (c) L-proline (10 mol%), CH$_2$Cl$_2$, 25 °C; H$_2$O.

Asymmetric $\alpha$-amination$^{53}$ of aldehydes using proline-catalyzed reactions represent a direct approach synthesizing chiral building blocks such as $\alpha$-amino acids, $\alpha$-amino aldehydes, and $\alpha$-amino alcohols. The use of organocatalysis, in particular proline, represents a drastic change in approach to asymmetric $\alpha$-amination. Recently, both List$^{53a}$ and Jørgensen$^{53b}$ disclosed the asymmetric $\alpha$-amination of aldehydes (Scheme 7) using catalytic quantities of proline. While both transition structures lead to identical products directed by the hydrogen bond from the carboxylic acid of proline, they presumably possess unique energies, so one transition state should be favored. However, the operative transition state has yet to be established.

Proline-catalyzed sequential transformations

Proline-catalyzed sequential transformations,$^{56}$ is a emerging research field in organic synthesis as synthesis of complex organic molecules could be accessible in one-pot procedure. Recently a variety of such transformations has been developed by different research groups, some of them are described below.

Sequential amination-aldol$^{56a}$

Barbas III et al. have developed a one-pot protocol for the synthesis of functionalized $\beta$-amino alcohols 27 from aldehydes, ketones and azodicarboxylates (Scheme 8).
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Scheme 8: Reagents and conditions: (a) L-proline (20 mol%), CH₃CN, rt, 72 h, 80%.

Sequential aminooxylolysis-olefination⁵⁶⁶
Zhong et al. have reported sequential asymmetric α-aminooxylolysis/Wadsworth-Emmons-Horner olefination of aldehydes for the synthesis of optically active O-amino-substituted allylic alcohols 28 in good enantioselectivities using cesium carbonate as base (Scheme 9).

\[
\text{RCHO} \xrightarrow{a} \text{RCH(OH)C=O} \quad 28 \\
\text{95-99% ee}
\]

Scheme 9: Reactions and conditions: (a) L-proline (20 mol%), nitrosobenzene (1.0 equiv.), DMSO, rt, 10-20 min then diethyl(2-oxopropyl)phosphonate, cesium carbonate (1.5 equiv.).

Sequential aldol-olefination⁵⁶ᶜ
Cordova et al. have reported one-pot organocatalytic asymmetric tandem cross-aldol/Horner-Wittig-Emmons olefination for the synthesis of polyketide and carbohydrate derivatives (Scheme 10).

\[
\text{CHO} \xrightarrow{a} \text{HOCH=CHC=O} \xrightarrow{b} \text{HOCH=CHC=OEt} \\
\text{2.3:1} \\
\text{93% ee}
\]

Scheme 10: Reagents and conditions: (a) L-proline (10 mol%), DMF; (b) Diethyl(2-oxopropyl)phosphonate, cesium carbonate (1.5 equiv.).

Apart from this transformation, Cordova et al. have also reported tandem Mannich olefination reaction.⁵⁶ᵈ

Sequential α-amination-olefination⁵⁶ᶜ
Sudalai et al. have reported sequential asymmetric α-amination/Wadsworth-Emmons-Horner olefination of aldehydes for the synthesis of optically active allylic amine in good enantioselectivities and yields (Scheme 11).
An organocatalytic approach to syn- and anti-1,3-polyols\(^{56f}\)

Recently, Zhong et al. have reported an \(\alpha\)-aminoxylation directed tandem reaction catalyzed by proline which involves a sequential \(\alpha\)-aminoxylation, HWE-olefination reaction at ambient temperature furnishing \(O\)-amino-substituted allylic alcohol from readily available achiral aldehydes. We envisioned that this reaction could give us stereocontrolled synthetic access to 1,3-polyol motifs. We have developed proline catalyzed new enantioselective approach to synthesize both syn/anti-1,3-polyols by tandem \(\alpha\)-aminoxylation and HWE olefination of aldehyde.\(^{56f}\) Our iterative strategy for the synthesis of polyols is outlined in Scheme 12.

Scheme 11: Reagents and conditions: (a) L-proline (20 mol\%), DBAD (1.0 equiv.), CH\(_3\)CN, rt, 10-20 min then diethyl(2-oxopropyl)phosphonate, cesium carbonate (1.5 equiv.).

Scheme 12. Reagents and Conditions: (a) (i) DIBAL-H, -78 °C; (ii) Nitroso benzene, D/L Proline, DMSO, HWE salt, DBU, LiCl, CH\(_3\)CN; (iii) H\(_2\)/Pd-C, EtOAc; (b) TBSOTf, 2,6-lutidine, CH\(_2\)Cl\(_2\).
Chapter 1

Ring closing metathesis (RCM)

Introduction

The ring closing metathesis has emerged as a powerful tool for organic synthesis and extensively employed in the construction of medium and large ring structures with multiple functionalities. The efficiency of this method is demonstrated by the syntheses of a large number of natural products including ten-membered lactones.

A typical example that illustrates the efficiency as well as the limitation of RCM in this area is a synthesis of jasmine ketolactone.\(^\text{57}\) RCM reaction on diene with high dilution by using Grubbs first-generation catalyst affords the targeted ten-membered lactones as a mixture of \textit{cis} and \textit{trans} isomers (2.5:1) in remarkable yield.

Over the past ten years, the area of olefin metathesis that has expanded most dramatically is the catalytic ring-closing metathesis (RCM).\(^\text{58}\) RCM has developed into a versatile synthetic tool for carbon-carbon double bond construction. In particular, medium (5-8) to large (10-13 and higher) carbon or heterocyclic rings can be very effectively constructed, and thus RCM became a reliable tool for synthesis of the natural products and spurred the synthesis of even more varied structural variants.

The word metathesis is derived from Greek word meta (change) and thesis (position). Metathesis is the exchange of parts of two substances or interchange of covalent bonds between two molecules. In the generic reaction, \(AB + CD \rightarrow AC + BD\), \(B\) has changed position with \(C\). An example is olefin metathesis. It refers to the redistribution of alkylidene moieties between two alkenes in the presence of a catalytic amount of a metal carbene. A compound with a \(C=C\) double bond, in which the strongest bond in an alkene is broken and remade. The 2005 Nobel Prize in Chemistry was awarded to Yves Chauvin, Robert H. Grubbs and Richard R. Schrock for development of the metathesis method in organic chemistry. History of transition metal-catalyzed olefin metathesis was discovered in the 1950’s by industrial chemists at DuPont, Standard oil, and Phillips petroleum (H. S. Eleuterio, E. F. Peters, B. L.
Evering, R. L. Banks, and G. C. Bailey) who reported that propene reacted to form ethylene and 2-butenes when passed over molybdenum on alumina catalyst at high temperature. Olefin metathesis catalyzed by carbene complex has been known in polymer chemistry for 40 years. However, the reaction has been limited to simple, unfunctionalized olefin. After development of new catalyst by Schrock and Grubbs, chemists realized the potential utility of this methodology in organic synthesis.

Olefin metathesis has been utilized in three closely related types of reactions.

a) **Ring opening metathesis polymerization (ROMP):**

In which a cyclic olefin is the substrate and a polymer is the product. ROMP is the thermodynamically favored for strained ring system, such as 3-, 4-, 8-and large-membered compound (Figure-8).

![Figure 8](image)

b) **Ring-closing metathesis (RCM):**

Acyclic diene is converted into cyclic olefin, in which a loss of ethylene takes place (Figure-9).

![Figure 9](image)

c) **Cross metathesis**

Two different olefins react to form a new product olefin and a by-product as a volatile olefin (usually ethylene).

![Figure 10](image)

Another variant of the reaction is the metathesis of an alkene and an alkyne, popularly known as enyne metathesis (EM).
Although a number of catalyst have been developed for metathesis and related reactions, the Schrock’s catalyst, Hoveyda-Grubbs catalyst, Grubbs 1st and 2nd generation catalyst, the distinct catalysts shown in figure 8 and 9 have been used widely for olefin metathesis reaction.

Titanium and tungsten-based catalyst have been also developed but are less used. Schrock’s alkoxy imidomolybdenum complex is highly reactive toward a broad range of substrate; however, this Mo-based has moderate to poor functional group tolerance, high sensitivity to air, moisture or even to trace impurities present in solvents and exhibits thermal instability.

![Figure 11: Tantalum and molybdenum metathesis catalyst](image)

In particular, the ruthenium-based catalyst (Grubbs 1st and 2nd generation) have been used extensively in organic and polymeric chemistry due to its high reactivity with olefin substrate in presence of most common functional groups. Homogeneous Ruthenium catalysts are (generally) stable, more selective and highly active at mild condition. It has superior activity over other cyclization methods like macrocyclization, Diels-alder etc., and adaptable for both solution and solid phase reactions.

![Figure 12: Ruthenium based metathesis catalyst](image)
The construction of a 10-membered ring is by using RCM was first reported by Frustner and Muller in 1997 for the synthesis of Jasmine ketolactone (37 & 38). Frustner also synthesized herbarium I and herbarium II by RCM strategy.

**RCM Mechanism:**

The mechanism of the RCM reaction has been extensively studied both experimentally and theoretically. It is now well accepted that, during the reaction the catalytically active metalacarbene complex such as $[M] = CH_2$ (B) is formed from the diene precursor (A) (figure-13) and the overall reaction mechanism involves, effectively, a series of alternating [2+2] cycloadditions. Metallacyclobutane intermediate such as (C) is formed, which opens in retro [2+2] fashion to form the carbene (D) as intermediate. The latter then undergoes re-cyclization to form the new metallacyclobutane (E), which analogously open to the product cycloalkene (F) and catalyst is regenerated. The mechanism is depicted schematically in figure-13. The equilibrium is continuously shifted towards the cycloalkene, due to the release of a volatile olefin (usually ethylene).

**Figure 13:** RCM mechanism
References


23. This is driven home by the recent example of CrixivanÒ, 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.


27. For reviews and lead references, see: (a) Winstein, S.; Henderson, R. B. In *Heterocyclic Compounds*, Vol. 1; Elderfield, R. C., Ed.; Wiley: New York, 1950; Chapter 1; (b) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* 1959, 59, 737; (c) Barto’k, M.; La’ng, K. L. Small Ring Heterocycles. In *The Chemistry of*
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41. For information, see: http://www.rhodiachirex.com.

42. While it may be assumed that an “ideal” resolution would involve no added reagents i.e., an enantiomer undergoing selective isomerization or polymerizations the rate of such transformation may be difficult to control because of the exothermicity ($\Delta H > 30$ kcal/mol) associated with epoxide ring opening. This is a special concern with reactions carried out on a large scale. The fact that the rate of nucleophile addition can be adjusted to control reaction rate therefore has significant practical advantages.


51. For a review of proline-catalyzed asymmetric reactions see: List, B. Tetrahedron 2002, 58, 5573.


