Asymmetric Synthesis of Active Pharmaceutical Ingredients

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1. Introduction: Perspective on the Role of Chirality in Current API Discovery

Recent trends in the pharmaceutical industry demonstrate that the number of new chemical entities (NCEs) launched on the market each year has been steadily declining over the last 10−15 years. Whereas the reasons for this trend are a hotly debated topic and constitute the main theme of countless conferences on drug discovery, it is clear that the current drought is partially caused by a paradigm shift that occurred a decade or two ago, *i.e.* the shift of research focus away from already established and crowded therapeutic areas into new, unproven biological areas. This shift, despite the formidable new technological tools employed by the industry, has been slow to yield fruits.

While the search for the "blockbusters" has resulted in a pipeline drought, those active pharmaceutical ingredients (APIs) which have reached the market do not look appreciably different, from a structural standpoint, from those of 10−20 years ago. Despite the explosive growth in the field of asymmetric synthesis and, in particular, of asymmetric catalysis, a search through the MDL database shows that over the last 12 years approximately 50% of the drugs launched contain no stereochemical elements, whereas the remaining 50% have at least one element of chirality. Drugs with multiple chiral centers are less common and are usually limited to a few well-established classes (such as the viral protease inhibitors). This trend is illustrated in Figure 1.

It seems clear that the new enantioselective synthetic methods have not caused a major revolution in the way drugs are discovered and produced, at least until 2003, the last year for which the MDL database contains a complete record. In terms of dealing with the issue of enantiomers, however, a paradigm shift is quite evident. The FDA's 1992 policy statement on stereoisomers has triggered a move away from the development of racemates to the development of single-enantiomer drugs.

Clearly, the additional cost of producing a single enantiomer is almost always lower than the development work which is needed to elucidate the toxicological and pharmacokinetic profile of the unwanted enantiomer (distomer) as well. This trend is illustrated in Figure 2. As of 2001, racemic mixtures are virtually no longer registered.

This important trend toward single-enantiomer drugs is what has brought asymmetric synthesis to the forefront as a theme in drug discovery and development. Table 1 summarizes the data already discussed for new drugs registered in the last 12 years. There are now about 10 new NCEs per year which need to be produced as single enantiomers and, if the current attrition rate in the industry can be extrapolated from the average drug to all single-enantiomer drugs, then there are currently 150−200 single-enantiomer drugs progressing into development each year in the pharmaceutical industry. Given an average development time of 7 years and standard attrition rates, one can estimate that there are currently 500−1000 single-enantiomer APIs being developed within the industry,[1] *i.e.* in the global pipeline somewhere between preclinical development and registration. These numbers are large enough to warrant reviewing the field, with special attention to asymmetric synthetic methodologies

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that have been used for large-scale production of pharmaceuticals.

2. Approaches to Chiral Synthetic Targets and Scope of the Review

When we look strictly at marketed single-enantiomer drugs, it is obviously difficult to establish how these APIs are produced. In some cases, only one process is described in detail in the literature, and we have therefore assumed that this is at least a viable route. When two processes are described, we have counted both as viable. In some cases,

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there is no information whatsoever on the process, but examination of the patent literature can give a rather obvious hint as to the type of approach used to prepare the API. The

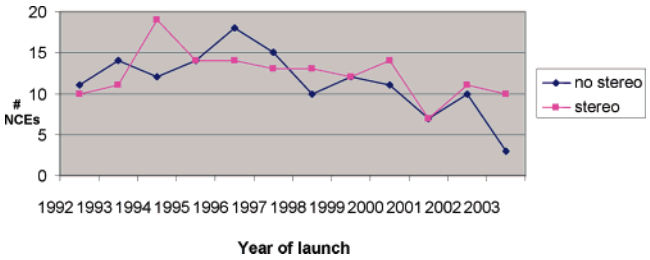


Figure 1. Marketed drugs with and without stereochemistry.

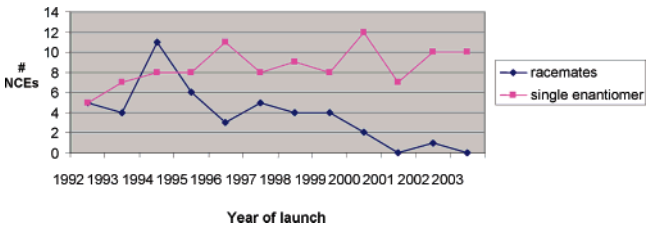


Figure 2. Single enantiomers vs racemates.

data we have assembled in Table 2, although rather uncertain and built on incomplete information, leave little doubt as to the main conclusions to be drawn: much of the chirality contained in marketed drugs is derived from the chiral pool, *i.e.* chirality already present in nature. Although we have counted each "enantioselective" process even when alternative (and probably better) ones are available, it is evident that use of asymmetric synthesis has been the exception rather than the rule. In any given year, an average of only two launched NCEs has been prepared by some kind of a practical asymmetric approach.

The success of the chiral pool strategy relies not so much on its intrinsic power, which is limited, but rather on the commercial availability of such building blocks to the discovery chemist. Since fine chemical producers have focused mostly on nature as source of synthons for the pharmaceutical industry, discovery chemists often use just what is available. The process chemists, in turn, pressed by more and more challenging time lines, have usually little incentive to totally redesign a discovery synthesis, especially if it uses building blocks that are readily available on large scale at reasonable cost. Further problems hindering the use of modern asymmetric synthesis, and especially asymmetric catalysis, have been discussed elsewhere[2] and are only briefly echoed in this review. Indeed, although this review will illustrate the availability of asymmetric approaches to marketed and developmental drugs, few of these approaches, although apparently viable, have actually found their way into the production plants of the pharmaceutical or fine chemical (in the case of intermediates) industries.[3]

Time frames are very tight in the pharmaceutical industry, and there is a tendency to identify, very early in the development process, one scalable route. Major deviations from this route are usually avoided, because they introduce uncertainty and potential delays. Rather, fine-tuning of this route often takes place. Newer methods, being less established, are perceived as requiring more time to be fully developed and turned into robust chemistry (*i.e.* not prone to failure on scale-up). Classical resolution is a very powerful and simple method for obtaining optically pure materials, and as Table 2 shows, it is still used rather often, *i.e.* more or less as often as enantioselective syntheses.[4]

The tendency to patent new chiral ligands and catalysts has also put a damper on their industrial use.[2] It often takes time to define the IP (intellectual property) situation around a synthetic method or reagent and clarify the licensing model preferred by the IP holder. Pharmaceutical companies, to minimize risk, often find it more convenient to avoid the technology altogether or simply bypass it by using similar technology that is patent free, be it homegrown or already published. This turns out to be surprisingly easy, in the majority of the cases. Later on, however, when the drug is on the market, new asymmetric technologies can actually gauge their practical potential by bidding on the supply of the key chiral intermediates, which are now established. Here the criteria are quite simple: price and availability. Held to these tough benchmarks, very few chiral technologies have shown practicality.[5] Our aim is to highlight this state of affairs with examples from the recent literature.

It is quite difficult to search the literature for asymmetric processes as they relate to drug synthesis. First of all, as the Table of Contents illustrates, we have restricted our scope to truly asymmetric technologies. Classical approaches using diastereoselective transformations of synthons derived from the chiral pool are not covered, and also resolution processes are not discussed, be they by salt formation or enzymatic.[6] Only asymmetric synthesis, both stoichiometric and catalytic, is discussed here. We have searched through the last 10 years of the major journals, with the main focus being publications from the pharmaceutical industry, especially process groups. Chemistry from academic labs is discussed only in some cases, especially when its practicality was judged as reasonable and the techniques potentially interesting to be explored further. For marketed products, the MDL database was used for the last 12 years (1992−2003), and each marketed drug which met our requirements (*i.e.,* chiral, nonracemic) was the subject of a separate individual literature search. In addition, we browsed through a variety of reviews and monographs on the topic. Only chemistry where the API target was clearly identified is reviewed here. The patent literature is not covered, as useful preparative information is not normally found there.

In each example, we will attempt to judge the efficiency of the method, discuss the scale and equipment on which it was run (if possible), and also comment on the practicality (cost and safety) of using the particular chiral reagent or catalyst employed. Thus, our approach is designed to inform the reader of what technology has been practiced within the pharmaceutical industry and perhaps enhance awareness of useful but little-explored methods.

3. Synthesis of Chiral APIs Using Optically Pure Removable Auxiliaries

Chiral auxiliary-controlled asymmetric reactions have been extensively studied for the past few decades and have reached a high level of sophistication.[7] In these processes, an optically pure chiral residue is covalently attached to a substrate. In the subsequent transformation, the absolute configuration of the newly created stereocenter(s) is dictated by the stereochemistry of the chiral auxiliary. After the asymmetric induction step, the chiral auxiliary is cleaved from the substrate. The cleavage of the chiral auxiliary from the reaction product is just as important as the asymmetric reaction itself and, therefore, should always be considered during the synthetic design. Conditions for removing the chiral auxiliary must be mild and simple and not cause any racemization or epimerization of the newly formed stereocenter(s) and/or the stereocenter(s) on the chiral auxiliary.

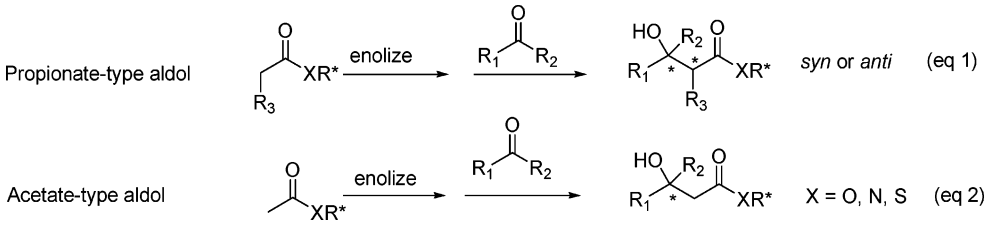
Table 1. Marketed Drugs by Year and by Type

type	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
nonchiral molecule	11	14	12	14	18	15	10	12	11	7	10	3
chiral, racemic	5	4	11	6	3	5	4	4	2		1	
chiral, single enantiomer	5	7	8	8	11	8	9	8	12	7	10	10
natural products and their semisynthetic derivatives	11	8	6	7	4	1	6	8	3	3	6	1
proteins, polymers, antibodies, polysaccharides	11	5	8	6	11	9	14	10	9	16	7	11
inorganic									2	1		
total	**43**	**38**	**45**	**41**	**47**	**38**	**43**	**42**	**39**	**34**	**34**	**25**

Table 2. Methods To Introduce Chirality

type	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
use of chiral pool	3	4	6	4	6	4	4	5	7	6	4	4
resolution approach	1	2		1	3	1		1	2	1	4	2
enantioselective synthesis	1	1	1	3	2	3	5	1	2		2	4
not available			1					1	1			
total	**5**	**7**	**8**	**8**	**11**	**8**	**9**	**8**	**12**	**7**	**10**	**10**

Scheme 1



Chiral auxiliary-based reactions are usually well understood in terms of reaction mechanisms and often have a broad substrate scope. An optimum chiral auxiliary often exerts powerful control over the stereochemical course of the reaction in a predictable manner. Compared to catalytic processes, diastereoselective methods are generally more robust on scale and not as sensitive to minor perturbations such as impurities present in starting materials, solvents, or reagents. Since the potential isomeric byproducts are diastereomer(s) of the desired product, the purification and isolation of the major isomer from the product mixture is usually more straightforward. Therefore, the use of auxiliary-based methods often results in a relatively short development time, and it is particularly useful for speedy delivery of APIs for preclinical and early clinical studies.

Over the years, a large array of chiral auxiliaries have been developed, including several so-called "privileged" chiral controllers (*e.g.* Evans's oxazolidinones, *cis*-1-amino-2-indanol, pseudoephedrine, α-phenethylamine, etc.). The popular use of these readily available and inexpensive chiral auxiliaries has had a great impact on the asymmetric synthesis of complex natural products as well as novel active pharmaceutical ingredients. A variety of chiral auxiliary-based transformations, including aldol, alkylation, conjugate addition, cycloaddition, and nucleophilic addition reactions, have found industrial applications in the context of API synthesis.

It should be recognized that the main disadvantage of the auxiliary-based approach is that it requires extra steps for attaching and removing the chiral auxiliary. Another issue that needs to be addressed is how to separate the cleaved stoichiometric amount of auxiliary from the product during workup without having to resort to chromatography on process scale. As can be seen in the following discussions, many times this task can be achieved by taking advantage of the differences in physical properties of the specific product and the chiral auxiliary (*e.g.* pK_a or solubility differences). The recovery and reuse of the chiral auxiliary is highly desirable, not only because it decreases the raw material costs but also because it renders the process "greener" by reducing the amount of waste for disposal.

3.1. Aldol Reactions with Chiral Enolates

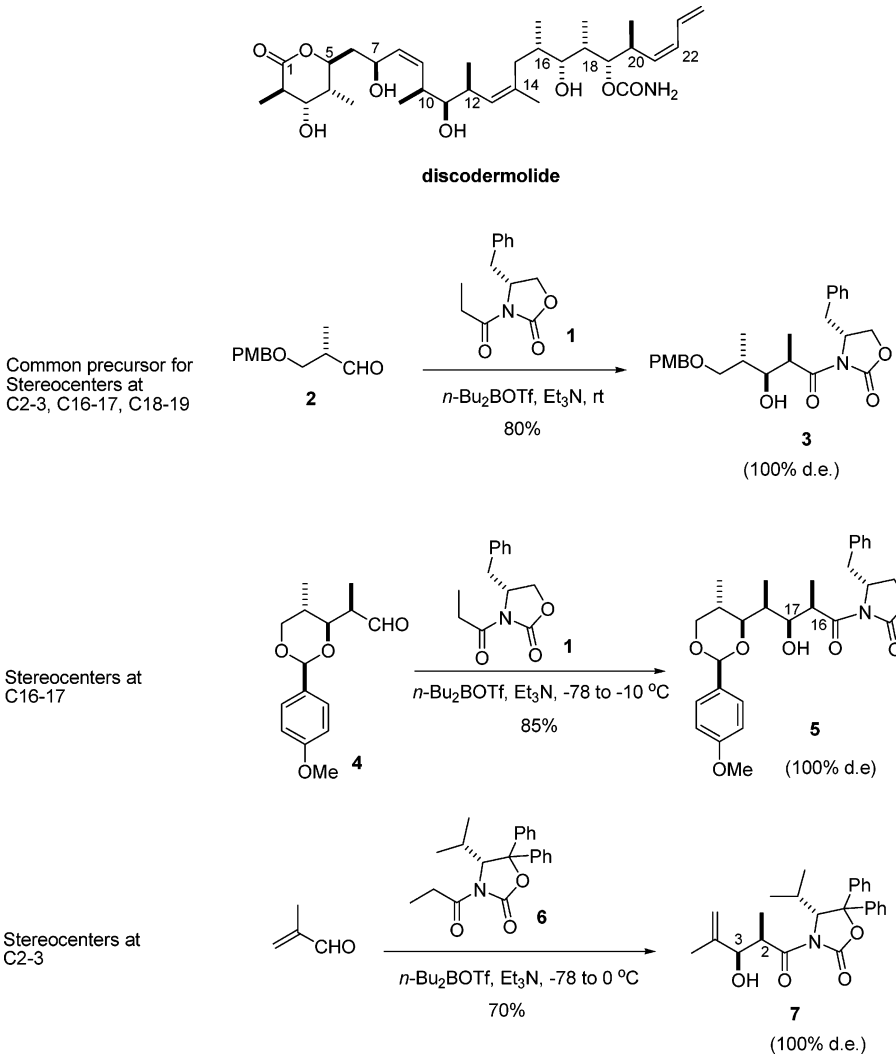
Auxiliary-controlled aldol reactions are frequently used in API synthesis. In an aldol reaction, one C−C bond and up to two stereogenic centers can be formed in a single chemical step. Aldol reactions can be categorized into two major families based on the structure of the enolate component (Scheme 1).[8]

The first type involves the use of enolates derived from acetates bearing an α-substituent (R_3, eq 1). Most often, this α-substitution is simply a methyl group, and this class of aldol additions is termed "propionate-type" aldol reactions. Aldol reactions using simple acetate enolates lacking an α-substitutent are naturally called "acetate-type" aldols (eq 2). The reason for this classification is due to the fact that propionate-type enolates and simple acetate enolates behave quite differently in chiral auxiliary-controlled aldol reactions. While many chiral auxiliaries have been shown to effectively control the stereochemical course of propionate-type aldol reactions, the stereocontrol of an acetate-type aldol reaction turns out to be far more challenging. As a consequence, asymmetric acetate aldol reactions have been utilized much less frequently in the total syntheses of natural products as well as novel biologically active compounds.

3.1.1. Propionate-Type Aldol Reactions

As stated above, a host of chiral auxiliaries are available to effect asymmetric propionate-type aldol reactions. In particular, Evans chiral oxazolidinone-mediated, *syn*-propionate aldol reactions[9] have proven to be reliable and practical,

Scheme 2



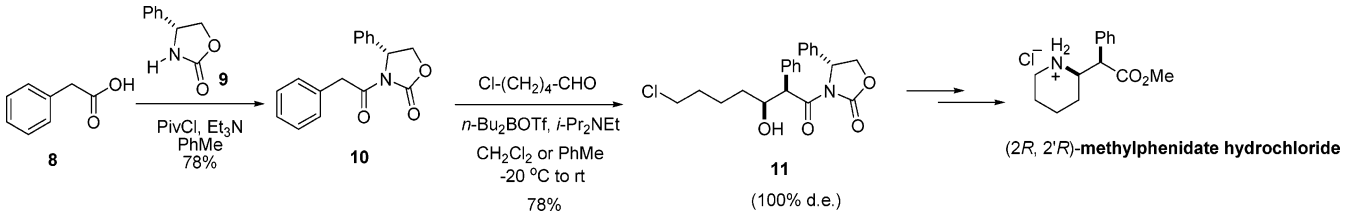
and have received widespread application in API synthesis on multi-kilogram scales. Some recent examples are summarized in this section.

Evans aldol reactions can be carried out with little or no modification from the originally reported standard conditions (*n*-Bu_2BOTf, Et_3N or *i*-Pr_2NEt, CH_2Cl_2 or toluene, −78 °C to room temperature) to give, in almost all cases, extremely high levels of diastereoselectivity (>99% d.e.). The workup requires the oxidation of the product boronate with 30% H_2O_2, which is a relatively safe reagent to store and handle, although precautions should always be taken when dealing with strong oxidants.[10]

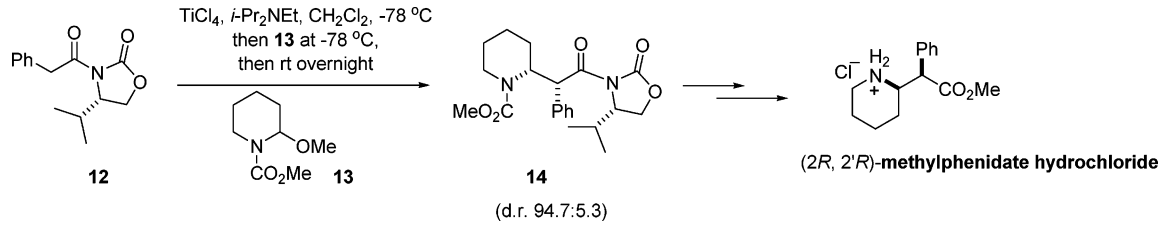
One impressive application of Evans *syn*-propionate aldol reactions is Novartis' large-scale synthesis of discodermolide, an anticancer natural product (Scheme 2).[11] After evaluating all reported syntheses of discodermolide and its fragments,[12] the Novartis team decided to pursue a hybrid synthetic scheme which integrated the best features of total syntheses developed by the Smith[13] and Paterson[14] groups. Two benzyl oxazolidinone-based aldol reactions were utilized to install 8 out of the 13 stereocenters embedded in discodermolide at C2−3, C11−12, C16−17, and C18−19. (*R*)-3-Propionyl-4-benzyloxazolidinone **1** was treated with dibutylboron triflate in the presence of triethylamine at 0 °C to form the *Z*-(O)-boron enolate. Aldol condensation with aldehyde **2** at −78 °C afforded the adduct **3** with complete diastereoselectivity. This procedure gave >75% yield on a 20−50 g scale. However, a lower yield (46−55%) was seen on a 20−25 kg scale. The reason for this variability is still unclear. It was noticed that the use of high-quality dibutylboron triflate seemed to be critical for obtaining higher yields. The reaction can also be run at room temperature without a significant decline in stereoselectivity. In contrast, the aldol reaction with a more complex aldehyde (**4**) has to be maintained below 0 °C in order to avoid byproduct formation (caused by *n*-Bu_2BOTf). Products **3** and **5** were isolated and purified by crystallization. It is worth noting that 3-propionyl-5,5-diphenyl-4-isopropyl oxazolidinone (**6**), developed in the Seebach laboratories,[15] was also applied to discodermolide synthesis. The main benefit of using this template is that it often confers high crystallinity to synthetic intermediates, which would facilitate isolation and purification.

The cleavage of oxazolidinone auxiliaries is typically achieved by hydrolysis, hydride reduction, or transamidation to the corresponding Weinreb amide. During the discodermolide work, the Novartis team noticed that trialkyl aluminum-promoted transamidation of aldol product **3** presented some thermal hazards, as suggested by calorimetry studies. Alternatively, aldol adduct **3** was converted into the corresponding Weinreb amide via a two-step sequence. Compound **3** was first saponified to give the carboxylic acid which was transformed into the Weinreb amide via traditional amide

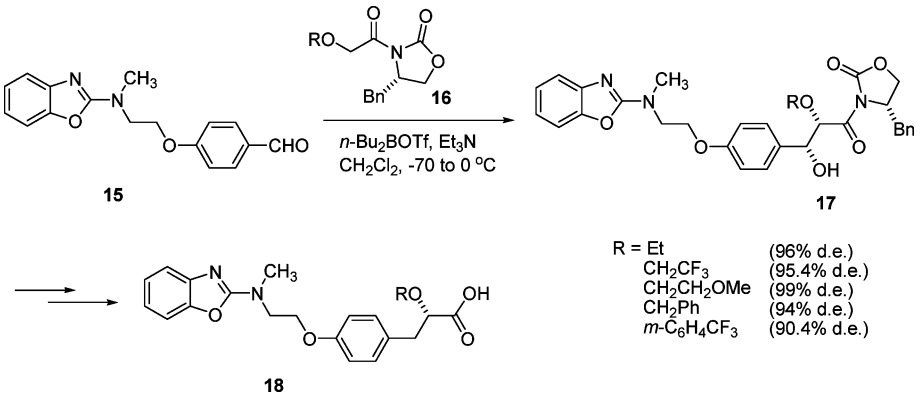
Scheme 3



Scheme 4



Scheme 5



coupling. The detached chiral auxiliary was separated from the carboxylic acid product through acid/base extraction. These aldol reactions have been executed on multi-kilogram scale.

(±)-*threo*-Methylphenidate hydrochloride (ritalin hydrochloride, Scheme 3) is widely used for treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children. (2*R*,2′*R*)-(+)-*threo*-Methylphenidate hydrochloride is 5−38 times more active than its enantiomer. Prashad *et al*. at Novartis have employed an aldol reaction to establish the two chiral centers in this molecule.[16] Aldol condensation of **10** with 5-chloropentanal was performed under standard conditions to provide the desired adduct **11** as a single isomer. It should be mentioned that the reaction was carried out at −20 °C, which is easily achievable at regular manufacturing plants. The use of (*R*)-4-benzyl-2-oxazolidinone gave the same diastereoselectivity.

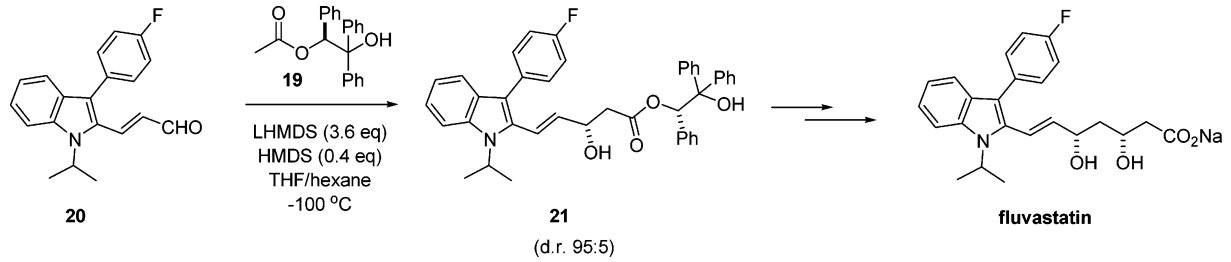
It is worth noting that the oxazolidinone auxiliary **9** was coupled with the acid **8** by using a method previously developed by the same group.[17] The acid was first activated with PivCl by forming the mixed anhydride. Chemoselective attack at the less hindered carbonyl group by **9** led to the desired product **10**. This protocol avoids the need for isolating the unstable, corrosive acyl chloride, and seems to offer advantages in terms of practicality.

In another approach to methylphenidate, a Ti-mediated oxazolidinone aldol reaction was applied to an in situ-generated imine, thereby introducing the 2′-amino group directly (Scheme 4).[18] The titanium enolate of **12** was formed by treatment with $TiCl_4$ and *i*-Pr_2NEt in CH_2Cl_2 at −78 °C. Then the *N*,*O*-acetal **13** was added to the reaction mixture at the same temperature. The reaction was highly diastereoselective, favoring the desired *threo* isomer (*threo*/*erythro* ratio = 94.7:5.3). The enantiomeric excess for the (2*R*,2′*R*)-*threo* isomer (**14**, ritalin precursor) was 99.6% when the 4-isopropyl oxazolidinone was used as the stereochemical controller.

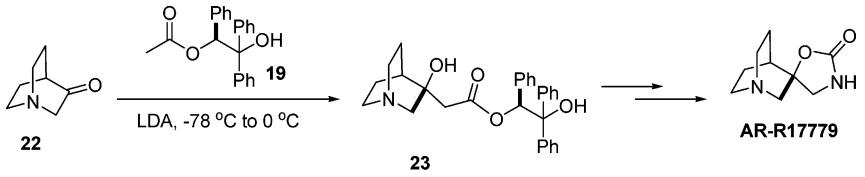
Removal of the chiral auxiliary was achieved by hydrolysis using lithium peroxide to produce the corresponding acid. The chiral auxiliary was readily separated from the product by acid/base extraction. This interesting synthetic strategy was also demonstrated to be useful for making a number of ritalin analogues.

Lactate-derived compound **16** was applied to the synthesis of a class of antihyperglycemic agents of the general formula **18** (Scheme 5).[19] Aldol condensation between the aldehyde **15** and the boron enolate of **16** furnished compound **17** with excellent stereoselectivities for a range of different R substitutions (*syn*/*anti* selectivity = 90−99% d.e.; >99.5% e.e. for individual *syn* or *anti* isomers). The benzylic alcohol was then removed by reductive deoxygenation (Et_3SiH, TFA) to complete the synthesis of the chiral α-alkoxy acid moiety in the API. It was noted in the paper that the moderate yield (65%) of the aldol reaction is attributed to the variable quality of commercial *n*-Bu_2BOTf solutions, which seems to be a generally observed issue associated with this type of boron enolate aldol reaction (cf. discodermolide work). The use of an excess of boron triflate reagent (1.6 equiv) did improve the yield of this reaction to 78%, but with unacceptable *syn*/*anti* selectivity (80% d.e.). It is not mentioned in the paper

Scheme 6



Scheme 7



whether the direct alkylation of the same enolate with, for example, a benzyl halide derived from **15** was ever attempted.

3.1.2. Acetate-Type Aldol Reactions

As mentioned earlier, in contrast to the impressive progress of asymmetric *syn*-propionate-type aldol reactions, the development of auxiliary-controlled acetate-type aldol reactions has met with limited success. Braun has discovered that the lithium enolate derived from the optically pure 2-acetoxy-1,1,2-triphenylethanol (**19**, Scheme 6) can react with aldehydes in a stereoselective fashion, providing acetate aldols with synthetically useful diastereoselectivities.[20] Two applications of this method to API synthesis were found in the recent literature.

During the course of the development of a practical synthesis of the antihyperlipoproteinemic agent fluvastatin (Scheme 6), Novartis chemists used an acetate aldol reaction between aldehyde **20** and Braun's reagent **19**.[21]

When the reaction was carried out using 3.6 equiv of LHMDS and 0.4 equiv of HMDS in THF/hexane at −100 °C, a stereoselectivity of 90% d.e. was achieved. It was found that running the reaction at −78 °C resulted in only a slight drop in stereoselectivity to 89% e.e. (after cleaving the auxiliary). When the reaction temperature was raised to −20 °C, much lower stereoselectivity was observed (78% e.e.). This process was reported to have been executed on pilot plant scale.

AR-R17779 is a selective α7 nicotinic receptor discovered at AstraZeneca (Scheme 7). Originally, the active enantiomer was prepared via a low-yielding classical resolution. In their asymmetric approach to this target, Macor *et al*. have applied Braun's asymmetric acetate aldol reaction to a ketone substrate **22**.[22]

The aldol reaction provided a very modest diastereoselectivity (d.r. = ∼3:2). Fortunately, the solubilities of the two diastereomers in chloroform were drastically different, therefore enabling the easy isolation of the desired diastereomer **23** from the product mixture by precipitation (48%, two-crop yield). Compound **23** was converted into the target in two more steps.

3.2. Alkylation Reactions

Alkylation of metal enolates derived from carboxylic acid derivatives is one of the most important and useful C−C bond-forming reactions. The stereocontrol of this process can be accomplished by using a chiral auxiliary such as Evans's oxazolidinones,[23] Myers's pseudoephedrine amides,[24] or Merck's *cis*-1-amino-2-indanol derivatives (*vide infra*). Due to the reliability of these reactions as well as the ready availability and low cost of the chiral auxiliaries, these asymmetric alkylation methodologies have proven to be particularly applicable to large-scale API synthesis.

PNP405 is a purine nucleoside phosphorylase (PNP) inhibitor which was studied as a potential therapy for transplant rejection, rheumatoid arthritis, and autoimmune and T-cell-mediated inflammatory diseases (Scheme 8). The chiral center in PNP405 was introduced via the (*R*)-4-phenyl-2-oxazolidinone-mediated asymmetric alkylation reaction with bromoacetonitrile.[25] The coupling of the chiral auxiliary and acid **24** was achieved by using the mixed anhydride method.[16]

Initially, the alkylation of the sodium enolate of **25** gave variable stereoselectivities due to partial epimerization during the workup. Subsequent refinement of the reaction conditions showed that the use of a substoichiometric amount of LHMDS (0.97 equiv) and an inverse quench of the reaction mixture into aqueous HCl solution were critical for obtaining reproducible results (d.r. = 7:1). Raising the reaction temperature from −78 to −20 °C resulted in only 6% yield loss but obviated the requirement for cryogenic equipment. The desired diastereomer was isolated in 80% yield and with >99% d.e. after a recrystallization from *tert*-butyl methyl ether.

The cleavage of the chiral auxiliary using traditional reducing agents such as $LiBH_4$ led to various degrees of racemization of the newly formed stereogenic center, particularly on pilot plant scale. To overcome this problem, the authors developed a new racemization-free method by using $NaBH_4$ in THF/water. The cleaved chiral auxiliary was readily separated from the oily product by crystallization and filtration. This procedure was reported on a few hundred gram scale.

Some other oxazolidinones were also screened for the alkylation step (Table 3). It was found that the use of (*R*)-4-isopropyl-2-oxazolidinone (**29**) as the auxiliary provided a higher diastereoselectivity (13.4:1). However, the isolation of the product derived from this auxiliary required chromatography, which is not practical on scale. Therefore, (*R*)-4-phenyl-2-oxazolidinone (**9**) was selected for the large-scale preparation, because it afforded crystalline intermediates

Scheme 8

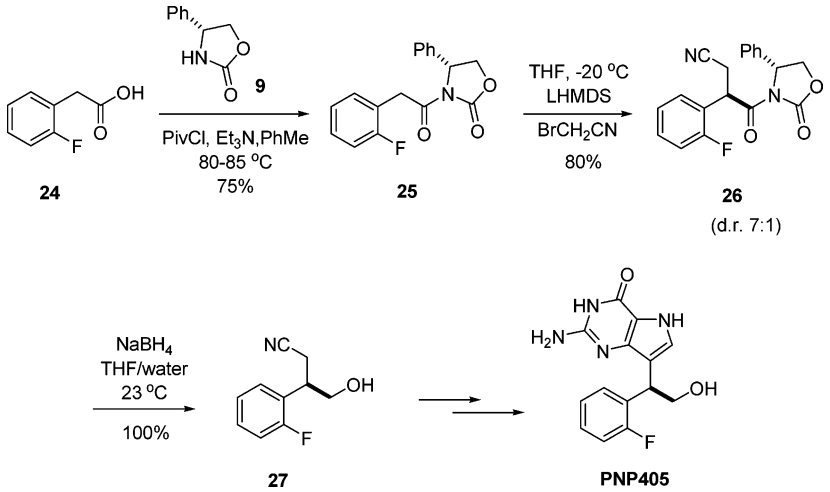
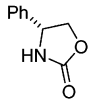
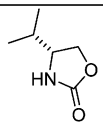
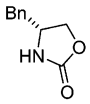
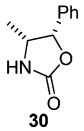


Table 3. Survey of Different Oxazolidinones for Alkylation

auxiliary	d.r. (yield)	auxiliary	d.r. (yield)
 **9**	7:1 (80%)	 **29**	13.4:1 (81%)
 **28**	5.3:1 (56%)	 **30**	3.7:1 (52%)

although it offered a lower diastereoselectivity (7:1). This example underscores the importance of crystallinity in the isolation/purification of intermediates during large-scale API synthesis.

A chiral oxazolidinone-based alkylation was employed in the synthesis of endothelin receptor antagonist ABT-627 (Scheme 9).[26] Compound **32** was enolized with NaHMDS, and the resulting sodium enolate was treated with *tert*-butyl bromoacetate at low temperature to furnish compound **33** as the predominant stereoisomer. After the auxiliary was cleaved by LiOOH, the carboxylic acid **34** was obtained in 76% overall yield and with 93% e.e.

A very similar alkylation reaction was found in the synthesis of Hoffmann-La Roche's MMP inhibitor trocade (Scheme 10).[27]

Alkylation of the lithium enolate of **35** with *tert*-butyl bromoacetate afforded compound **36** in excellent stereoselectivity (99.6% e.e. after cleaving the auxiliary). This step was reported to have been practiced on metric ton scale.

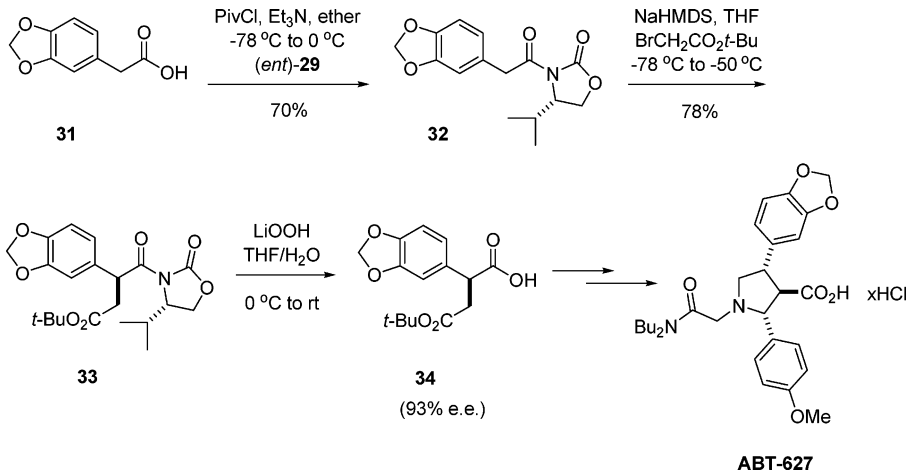
Indinavir is an orally active HIV protease inhibitor and is one of the major drugs for treatment of AIDS. The asymmetric synthesis of this important compound involves a *cis*-1-amino-2-indanol-based alkylation strategy, as depicted in Scheme 11.[28]

The lithium enolate of compound **37** was allylated with allyl bromide with a high level of stereochemical control (97:3 d.r. at −35 °C or 96:4 at −15 °C) to afford product **38** in >95% yield. Alternatively, the chiral epoxide **39** can be used as an alkylating agent at −45 to −25 °C to give **40**, after recrystallization, with 99% d.e. in 72% isolated yield. Both **38** and **40** can be elaborated into indinavir.

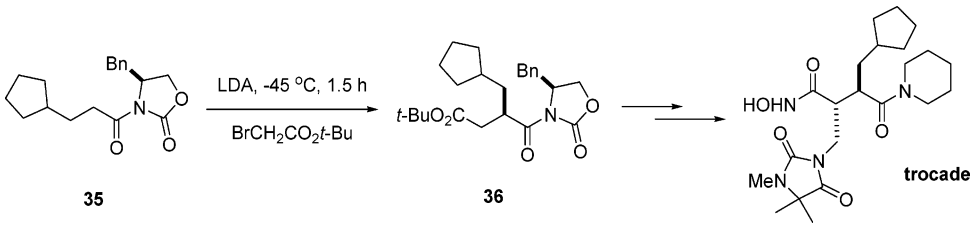
The *cis*-1-amino-2-indanol-mediated asymmetric alkylation reaction was further exemplified in Merck's synthesis of an endothelin receptor antagonist (**45**, Scheme 12).[29] This compound was being developed for congestive heart failure and hypertension.

Alkylation of the chiral amide **41** with benzyl chloride **42** at −30 °C afforded product **43** in excellent stereoselectivity (d.r. = 98:2), demonstrating the impressive stereodirecting power of *cis*-1-amino-2-indanol-based templates. Acid hydrolysis (6 N HCl, reflux, 2 h) of the amide provided the free carboxylic acid **44** without racemizing the newly

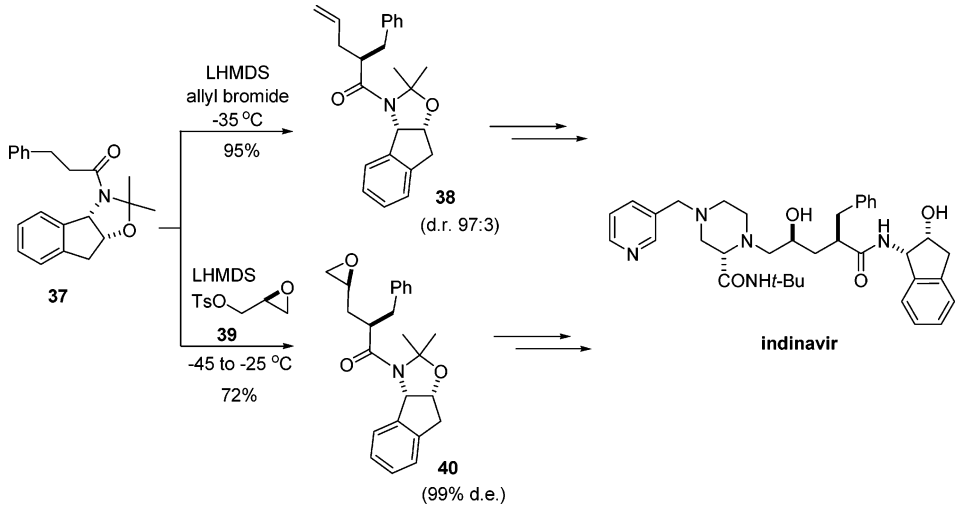
Scheme 9



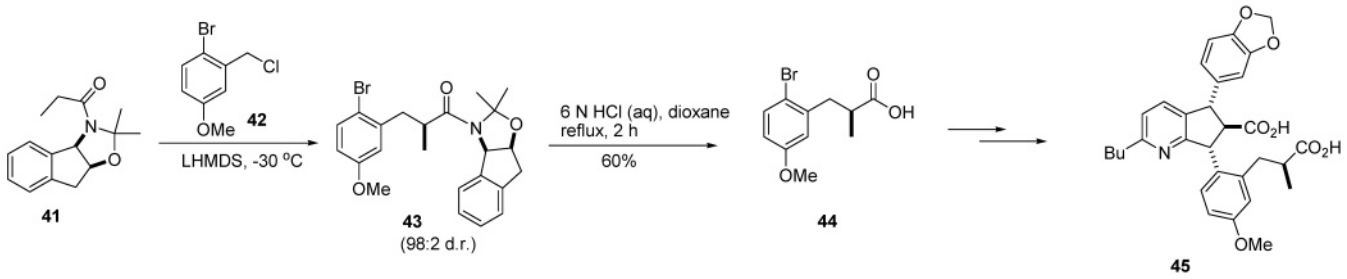
Scheme 10



Scheme 11



Scheme 12



installed stereocenter. This sequence has been demonstrated on multi-kilogram scale.

The above examples clearly show that, for acid-stable substrates, the *cis*-1-amino-2-indanol-derived chiral amides are good alternatives to the traditional Evans oxazolidinones for enolate alkylation reactions. Both enantiomers of *cis*-1-amino-2-indanol are commercially available in bulk, are inexpensive, and have been extensively used for other types of reactions.[30]

Myers described the use of readily available (in both enantiomeric forms) and inexpensive pseudoephedrine as a highly practical chiral auxiliary for asymmetric alkylation reactions.[24] Due to the higher reactivity of an amide enolate compared to Evans imide enolate, Myers' method is not limited to reactive halides (*e.g.* allyl halides). These enolates can be alkylated diastereoselectively with a wider range of alkyl halides, including less reactive electrophiles such as β-branched alkyl iodides. This methodology was nicely showcased (twice) in the Novartis synthesis of CGP60536B, an orally active renin inhibitor (Scheme 13).[31]

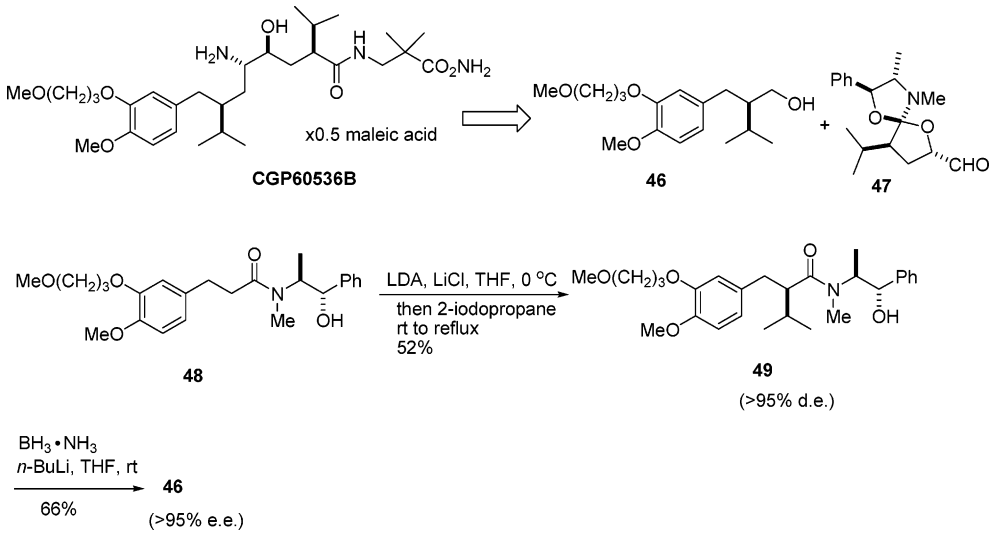
For the synthesis of the left-hand side piece **46**, (+)-pseudoephedrine-derived amide **48** was enolized and reacted with 2-iodopropane in THF at refluxing temperature to yield **49** as a single isomer. This result deserves some emphasis because it is one of the rare examples in which secondary halides can be employed in an enolate alkylation reaction. Reduction of the amide to the corresponding primary alcohol was achieved by treatment with lithium amidotrihydroborate.

Similarly, synthesis of the right-hand side segment **47** started with the highly diastereoselective allylation of (+)-pseudoephedrine isovaleramide (**50**, Scheme 14). Allylated product **51** was isolated with high optical purity via crystallization of the crude product mixture. Compound **51** was then subjected to a novel NBS-induced bromolactonization to give amide acetal **52** as a 6:1 mixture.[32] Subsequent crystallization yielded the diastereomerically pure **52**, which was manipulated into fragment **47**.

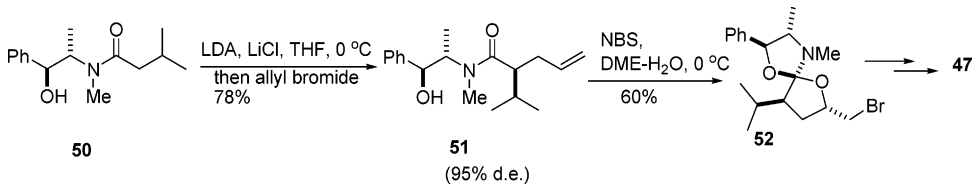
Ontazolast (BIRM270, Scheme 15) is a novel LTB_4 inhibitor discovered by Boehringer Ingelheim.[33] To support further development activities, a scalable asymmetric route was established by using a highly diastereoselective alkylation of a chiral Schiff base.[34]

In preliminary studies, alkylation of the Schiff base prepared from amine **53** and camphor provided only modest selectivity (35% e.e. after cleaving the auxiliary). Next, attention was turned to (*R*)-(+)-2-hydroxy-3-pinanone (**54**).[34e] Thus, imine **55** was prepared according to a known method and treated with 2.1 equiv of *n*-BuLi to generate the requisite

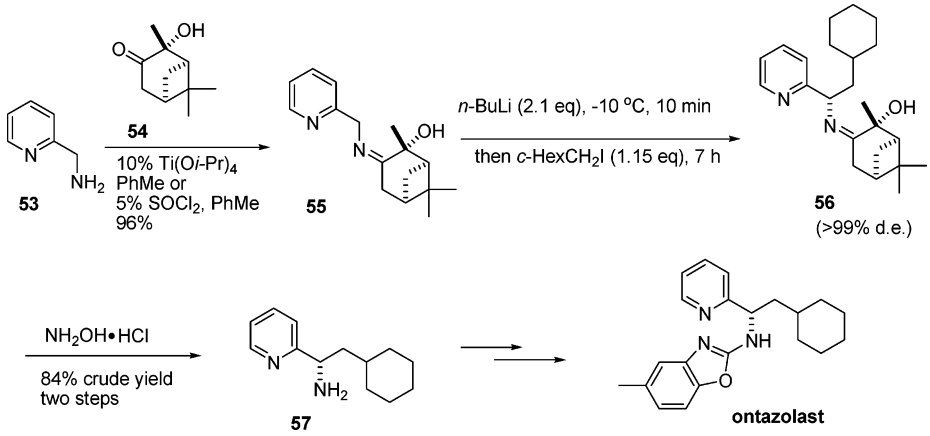
Scheme 13



Scheme 14



Scheme 15



dianion. Reaction of the dianion with 1.15 equiv of cyclohexylmethyl iodide at −10 to 0 °C smoothly furnished the desired alkylated product with >99% d.e. The choice of leaving group on the alkylating agent had a major impact on the outcome of the alkylation reaction. For the alkyl bromide, 2 equiv of the electrophile was required in order to achieve a complete conversion. Reaction of the dianion with cyclohexylmethyl mesylate, however, could not be pushed to completion even with an excess of the alkylating agent.

Attempted acidic hydrolysis of imine **56** was unsuccessful due to partial racemization. On the other hand, treatment of alkylated imine with hydroxylamine hydrochloride in ethanol/water smoothly removed the auxiliary, leading to the (*S*)-pyridylamine **57** without racemization. The cleaved auxiliary (as its corresponding oxime) can be easily separated from the product through acid/base extraction. This process has been successfully demonstrated on pilot plant scale.

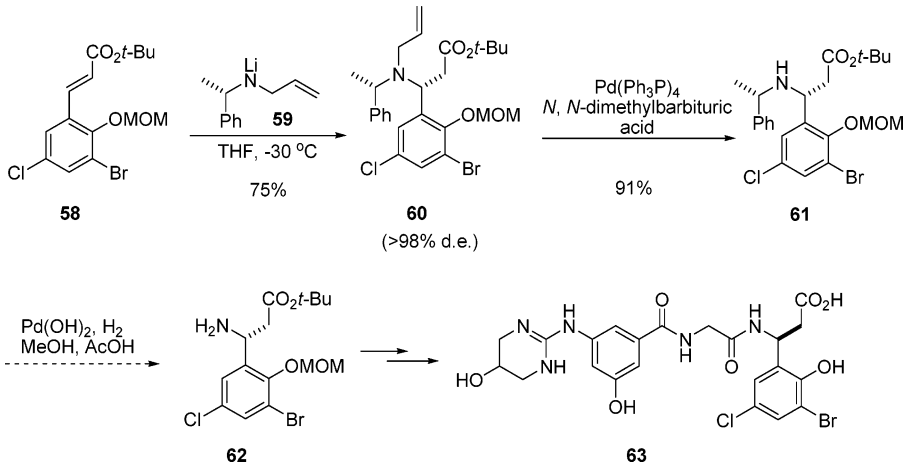
3.3. Conjugate Addition Reactions

Conjugate addition of a nucleophile to an activated olefin is arguably one of the most important fundamental transformations in organic chemistry. A range of carbon- or heteroatom-based nucleophiles have been shown to participate in this reaction manifold.

3.3.1. Conjugate Addition Reactions with Nitrogen-Based Nucleophiles

The conjugate addition of chiral lithium amides to activated olefins has been widely utilized for the asymmetric synthesis of β-amino acids.[35] The 1,4-addition of chiral lithium amides to β-substituted acrylates usually proceeds with good to excellent diastereoselectivities at −78 °C (80−95% d.e.). *tert*-Butyl esters are employed more often than other, less bulky esters because the *tert*-butyl group can help minimize competing 1,2-addition to the carbonyl. Due to its demonstrated generality, high selectivity, and ease of opera-

Scheme 16



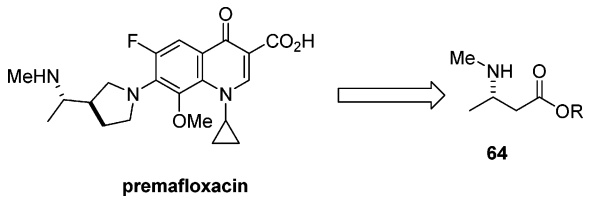
tion, this reaction has found widespread applications in organic synthesis including large-scale API synthesis.

In one approach to Pfizer's $\alpha_v\beta_3$ integrin antagonist **63** (Scheme 16), conjugate addition of the optically pure lithium amide **59** to enoate **58** at −30 °C was carried out to produce adduct **60** in 75% yield and with >98% d.e.[36] The use of a methoxymethyl protecting group and the *tert*-butyl ester proved to be critical for the success of this reaction by avoiding the unwanted 1,2-nucleophilic addition.

The allyl group can be cleaved by using $Pd(PPh_3)_4$ and *N*,*N*-dimethylbarbituric acid. However, major difficulties were encountered in the debenzylation step. $Pd(OH)_2$ effectively catalyzed the hydrogenolysis of the benzyl group, but concurrent dehalogenation always took place. Although the highly stereoselective Michael addition is very interesting, this route was not pursued for further development.

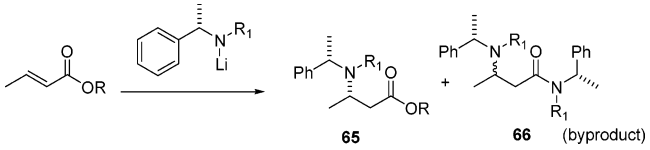
Premafloxacin, an antibiotic with potential veterinary applications, could be derived from a chiral *β*-aminobutanoate of type **64** (Scheme 17).[37] This intermediate has been

Scheme 17



previously prepared by Davies[35] using a highly diastereoselective Michael addition of a chiral lithium amide derived from (*S*)-(*N*-benzyl)[*N*-(1-phenyl)ethyl]amine to *t*-Bu crotonate (entry 1, Table 4). In adapting this method to the synthesis of premafloxacin, Fleck *et al*. at Pfizer have made a number of modifications. To eliminate the need to change the benzyl group on the nitrogen in compound **65** to the required methyl group later in the synthesis, the addition of lithium amides derived from the sterically less demanding (*S*)-(*N*-methyl)[*N*-(1-phenyl)ethyl]amine (R_1 = Me) to a series of crotonate esters was examined. Since the *t*-Bu ester

Table 4.



R	R_1	*T* (°C)	d.r.	% yield of **65**	% yield of **66**
t-Bu	Bn	−78	single isomer	95	0
Et	Bn	−78	34:1	68	minor
Me	Me	−70	18:1	73	23
Et	Me	−70	17:1	84	11
i-Bu	Me	−70 (0.6 M)	18:1	88	7
i-Bu	Me	−70 (0.6 M)	17:1	83	12
i-Bu	Me	−40	11:1	78	15
neo-Pen	Me	−70	4:1	49	39

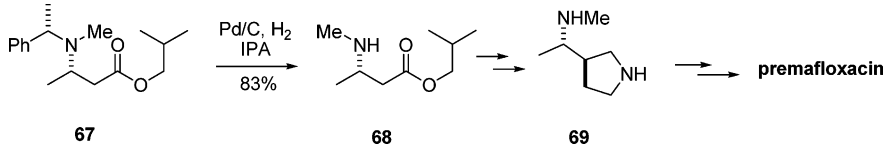
was not suitable for downstream chemistry, less bulky esters, such as Et, Me, *i*-Bu, and neopentyl esters were investigated for this reaction.

As can be seen from Table 4, except for the reaction with neopentyl crotonate, this smaller amine has exhibited a very high degree of diastereoselectivity in the asymmetric Michael addition reaction. It should be noted that, with less bulky esters, a significant amount of the unwanted 1,2-addition byproduct was observed. In the end, isobutyl crotonate was selected as the Michael acceptor for further development due to its low cost and overall favorable reaction/isolation profiles.

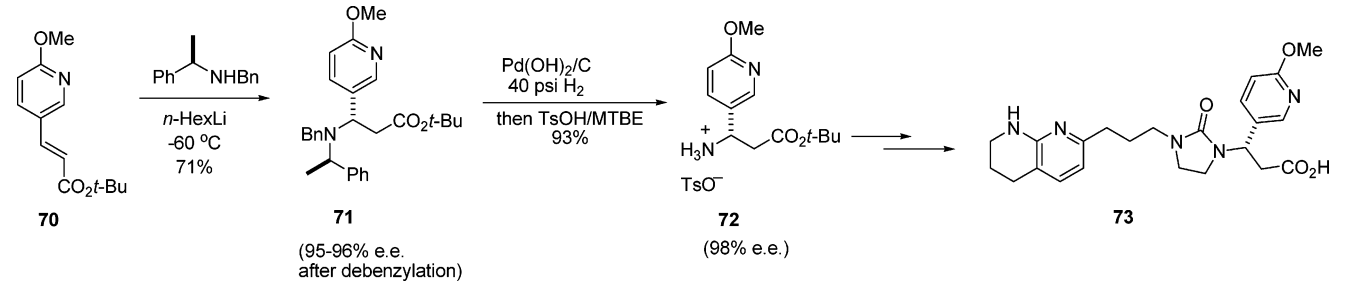
The *N*-benzyl group in compound **67** was removed by Pd/C-catalyzed hydrogenolysis to give the free *β*-amino ester **68**, which can be further elaborated into premafloxacin (Scheme 18).

Compound **73** was studied by Merck as an $\alpha_v\beta_3$ integrin antagonist (Scheme 19).[38] For the synthesis of this target, Davies's method[35] was directly applied. Conjugate addition of the lithiated (*R*)-(+)-*N*-benzyl-α-methylbenzylamine was conducted at −60 °C. This low reaction temperature was required in order to attain the best diastereoselectivity. The free amine was liberated by $Pd(OH)_2$-catalyzed hydrogenoly-

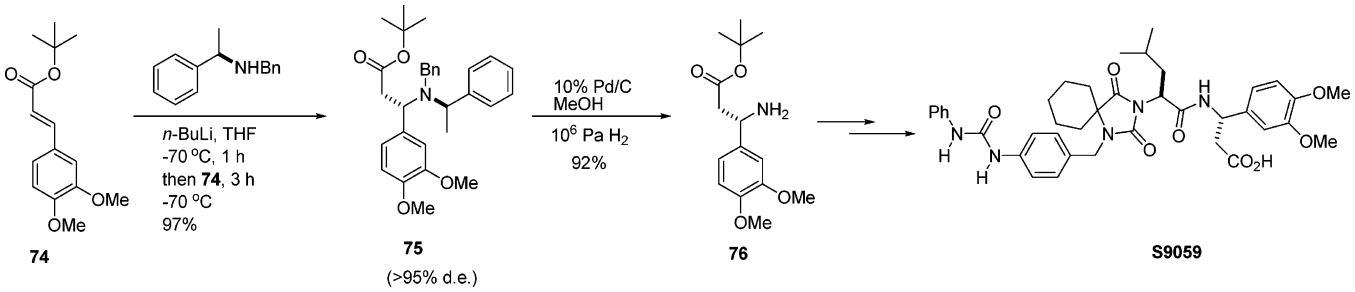
Scheme 18



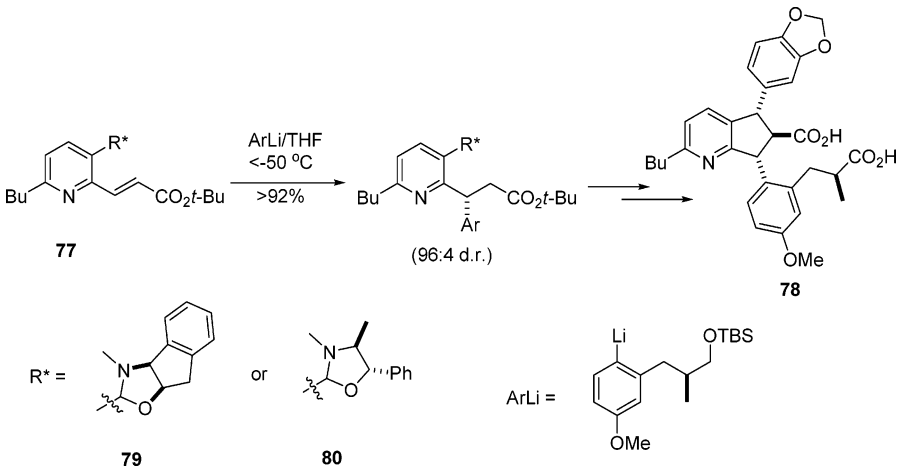
Scheme 19



Scheme 20



Scheme 21



sis and was isolated in 97% yield and with 95−96% e.e. Subsequent formation of the tosylate salt **72** and recrystallization upgraded the optical purity to >98% e.e. This method was implemented on multi-kilogram scale.

Another example of this remarkable reaction was documented in connection with the synthesis of VLA-4 antagonist S9059 (Scheme 20).[39] Again, addition of the lithium amide derived from (*R*)-(+)-*N*-benzyl-α-methylbenzylamine to *t*-Bu ester **74** proceeded with >95% d.e. to furnish the desired adduct **75** in 97% yield. Complete deprotection of the nitrogen was accomplished by means of Pd/C-catalyzed hydrogenolysis to deliver the free *β*-amino ester fragment **76** required for the S9059 synthesis.

As clearly illustrated by the above examples, the stereocontrolled addition of chiral amide anions to properly selected α,*β*-unsaturated esters represents a practical and reliable methodology for the synthesis of chiral *β*-amino acid derivatives.

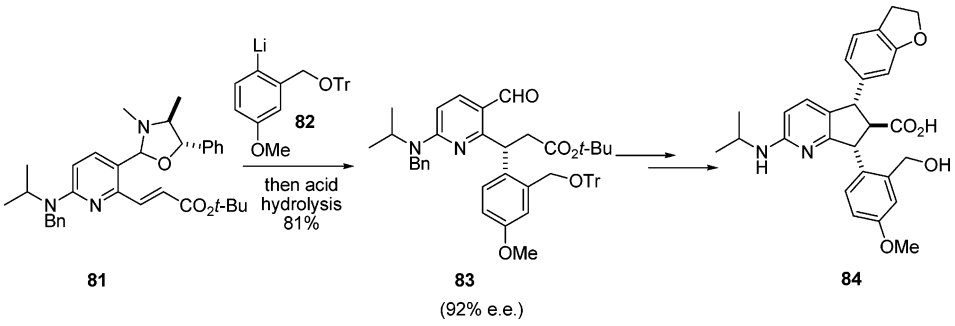
3.3.2. Conjugate Addition Reactions with Carbon-Based Nucleophiles

A very useful method to achieve asymmetric 1,4-addition of a carbon-based nucleophile to an activated olefin was reported by Alexakis[40] and has been successfully adapted for large-scale applications, as showcased by the synthesis of a family of endothelin receptor antagonists shown in Scheme 21. To introduce the bottom aryl group in compound **78**,[29] asymmetric Michael addition to enoate **79** was envisioned. A chiral amino alcohol [(+)-pseudoephedrine or (1*S*,2*R*)-*N*-methyl-1-amino-2-indanol] was attached to the substrate by forming a cyclic hemiaminal. Conjugate addition of the bottom aryllithium to **79** took place diastereoselectively (96:4 d.r.) at −60 °C. Optimal yield was observed when the aryllithium was introduced into a solution of ester **79** at a temperature < −50 °C.

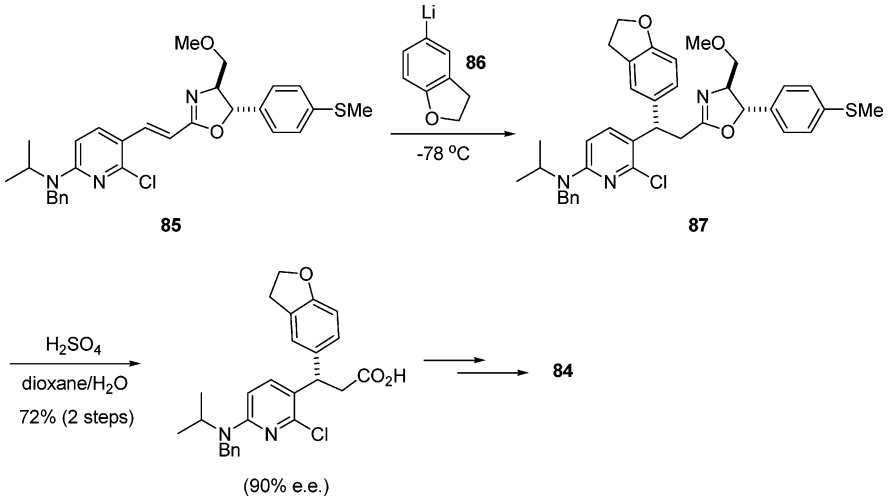
Compared to the original conditions reported by Alexakis,[40] this modified method offered some advantages in terms of practicality, such as the use of readily available amino alcohols instead of the more expensive chiral diamines as the auxiliaries. In addition, the present method uses only 1 equiv of aryllithium as opposed to the case of the organocuprate species, which need to be prepared from 2 equiv of the corresponding organolithium precursors.

In the synthesis of a close analogue **84** (Scheme 22), it was found that the stereoselectivity of the reaction between ester **81** and aryllithium **82** was strongly influenced by the

Scheme 22



Scheme 23



choice of auxiliary and protecting groups on the aryllithium moiety as well as on the pyridyl amino group.[41]

As shown in Scheme 22, the best combination was to use *N*-benzyl protection for the amino group in compound **81**, trityl protection for the alcohol of the bottom aryl piece, and (+)-pseudoephedrine as the chiral auxiliary. The key conjugate addition reaction was conducted by adding the Michael acceptor **81** into the aryllithium solution at < -50 °C. After the auxiliary was cleaved with citric acid, the desired product **83** was isolated in 81% yield and with 92% e.e. Several other auxiliaries [*e.g.* (*S*)-*N*-methylphenylglycinol and (1*S*,2*R*)-*N*-methyl-1-amino-2-indanol] as well as some alternative protecting group combinations were investigated, and they gave less satisfactory results.

It is of interest to note that this class of compounds can also be constructed in a top-to-bottom fashion.[42] In this case, the chiral auxiliary (1*S*,2*S*)-(+)-thiomicamine was installed as an oxazoline functionality such as in compound **85** (Scheme 23). Michael addition of the top aryllithium **86** occurred diastereoselectively. The crude product mixture was hydrolyzed using H_2SO_4 to provide the carboxylic acid with 90% e.e. in 72% overall yield.

A third route to this class of structures involved a novel intramolecular Nazarov cyclization (formal 1,4-addition of an aryl group to an activated olefin) reported by Pridgen *et al*. from SmithKline Beecham (Table 5).[43] Precursor **88** was prepared in a number of routine steps from 3-propyloxyacetophenone. The cyclization can be initiated using Lewis acids such as $SnCl_4$ or $TiCl_4$, or simply methanesulfonic acid. By using 4-phenyl or 4-isopropyl oxazolidinone or 8-phenylmenthol as chiral auxiliary, the desired product **89** was obtained with diastereomeric ratios ranging from 70:30 up to 92:4. The stereochemistry of the unwanted diastereomeric byproduct was determined to be as in epimer **90**.

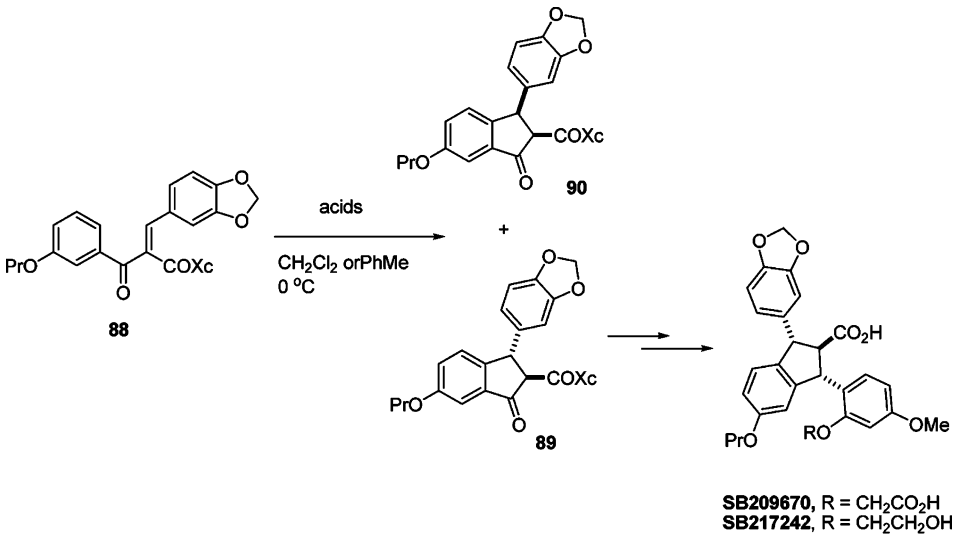
Sampatrilat is an inhibitor of the zinc metalloprotease neutral endopeptidase 24.11 and was evaluated in clinics during the 1990s (Scheme 24). Dunn *et al*. have recently described the development of a scalable route to sampatrilat.[44] It involves the optimization of a conjugate addition reaction of a carbon dianion to a chiral α,β-unsaturated ester.

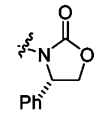
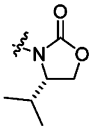
In the original medicinal chemistry synthesis, the addition of the dianion of cyclopentane carboxylic acid to compound **91** gave variable results and also required cryogenic conditions (-78 °C). During the course of process optimizations, it was found out that excellent selectivity (d.r. = 97:3, 88% yield) can be achieved even at 0 °C. The debenzylation was accomplished by standard Pd/C-catalyzed hydrogenolysis. This reaction was readily scaled up to multi-kilogram scale.

An alternative approach to sampatrilat was also explored, in which an asymmetric Michael addition of the lithiated [*N*-(1-phenyl)ethyl](*N*-methyl)amine to the acrylate **93** was attempted (Scheme 25). Unfortunately, only modest and variable diastereoselectivity (d.r. = 3:1 to 1.4:1) was observed. Due to the additional problems of incomplete conversion and a difficult benzyl deprotection, this approach was abandoned.

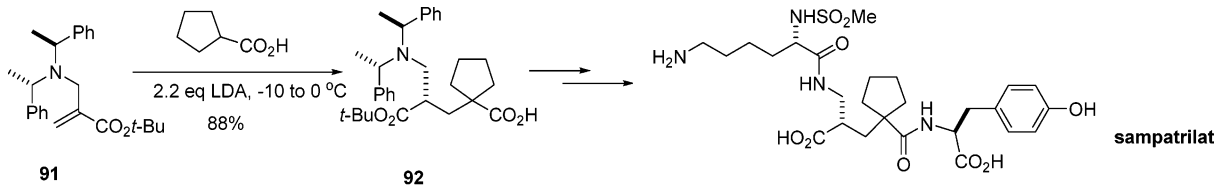
It has been shown in the literature that oxazolidinone-based enolates undergo Michael additions to α,β-unsaturated esters, nitriles, and ketones.[45] One recent application of such a reaction to API synthesis was represented in the synthesis of a dual NK1/NK2 antagonist SCH206272 (Scheme 26).[46] The titanium enolate of compound **95** was generated by treatment with Ti(O*i*-Pr)Cl_3 and *i*-Pr_2NEt at 0 °C. Reaction of this enolate with acrylonitrile proceeded in a 1,4-fashion

Table 5

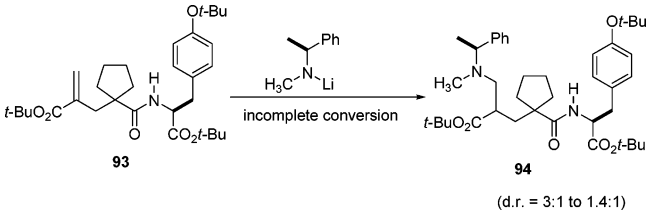


Xc	acid	yield	d.r. (**89/90**)
	$SnCl_4$	85%	88:12
	CH_3SO_3H	88%	85:15
	$TiCl_4$	60%	70:30
	$SnCl_4$	74%	71:16+ 14% other isomers
8-phenylmenthol	$SnCl_4$	90%	92:4 + 4% other isomers

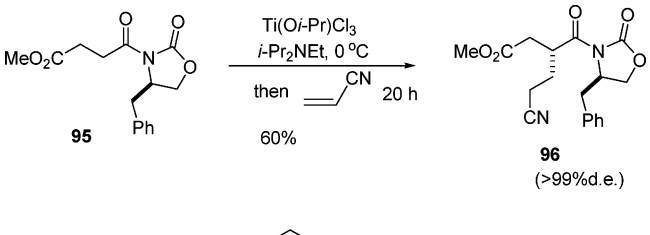
Scheme 24



Scheme 25

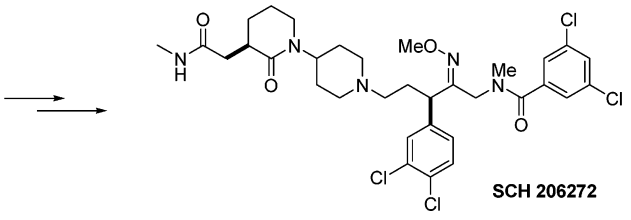


Scheme 26



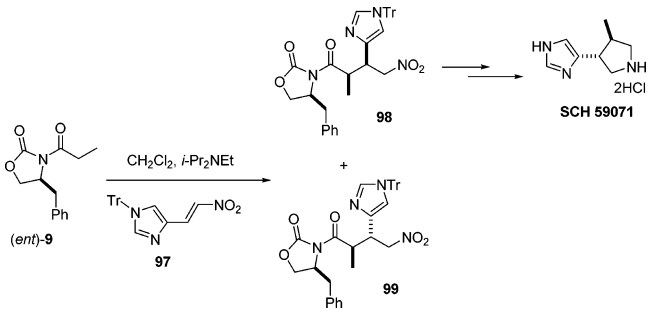
to give adduct **96** with >99.5:0.5 d.r. in 60% yield. This step was carried out on one hundred gram scale.

A similar Michael reaction of an oxazolidinone enolate with a nitroolefin (**97**) was utilized in the synthesis of SCH59071 (Table 6).[47] Initially, under the standard conditions employed by Evans [$Ti(Oi\text{-}Pr)Cl_3$, i-Pr_2NEt, CH_2Cl_2, 0 °C to room temperature], with 2 equiv of the enolate, the desired product was formed with a synthetically useful diastereoselectivity (6:1). The selectivity can be enhanced to 9:1 if the reaction is kept at a slightly lower temperature (0−15 °C). To improve upon this preliminary result, several



reaction parameters, such as the transition metal, ligand stoichiometry, reaction temperature, and solvents, were studied (Table 6). It was found that the use of other solvents

Table 6.



entry	$TiCl_4/Ti(Oi\text{-}Pr)_4$	*T*	d.r. (**98**/**99**)	yield (%)
1	3:1	0−15 °C	9:1	75
2	4:0	0 °C to rt	3:2	80
3	1:1	0 °C to rt	12:1	76
4	1:3	0 °C to rt		10
5	1:1	0−4 °C	16:1	77

(DMF, DME, PhCl, $CHCl_3$) or triethylamine had a negative impact on the product yields. On the other hand, it was discovered that the chloride and isopropoxide ratio on titanium played a key role in this reaction. The diastereoselectivity increases with increasing number of isopropoxide ligands on Ti. The optimum conditions determined by this study involved the use of $TiCl_2(Oi\text{-}Pr)_2$ instead of the original $Ti(Oi\text{-}Pr)Cl_3$ at 4 °C in CH_2C1_2, with *i*-Pr_2NEt as the base. These conditions gave **98** and **99** in a 16:1 ratio and 77% yield. Recrystallization of the crude product mixture from IPA/hexane enriched the diastereomeric purity to 22:1.

PNU-140690 (tipranavir) is a nonpeptide HIV protease inhibitor discovered at Pharmacia & Upjohn (Scheme 27). In a published synthesis by Gammill *et al.*, an auxiliary-controlled conjugate addition was employed to install the ethyl benzylic stereocenter.[48] Reaction between the aryl cuprate derived from Grignard reagent **101** and the chiral α,β-unsaturated imide (**100**) at −40 to 0 °C provided the desired adduct as a single diastereomer. The trimethylsilyl protecting groups were switched to dibenzyl protection under mild conditions, to produce crystalline intermediate **102** in 78% overall yield.

The same strategy was utilized for the synthesis of (+)-tolterodine,[49] a muscarinic receptor antagonist for potential treatment of urge incontinence and other symptoms of unstable bladder (Scheme 28). The synthesis starts with a copper-mediated conjugate addition of an aryl Grignard to cinnamoyl oxazolidinone **103**. The reaction occurred with excellent diastereoselectivity in high yield to afford **104**. Removal of the chiral auxiliary using LiOOH followed by a series of standard manipulations gave enantiomerically pure tolterodine.

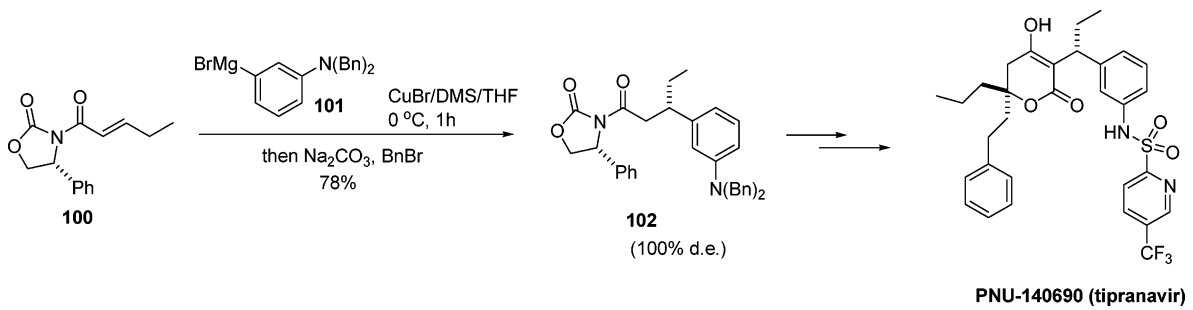
DPC-961 (Scheme 29) is an HIV non-nucleoside reverse transcriptase inhibitor (NNRTI). A recently reported practical synthesis of DPC-961 featured a novel diastereoselective 1,4-addition reaction.[50] The synthesis started with the preparation of the hemiaminal **106** by reacting hydrate **105** with (*R*)-(+)-α-methylbenzyl isocyanate. Hemiaminal **106** was formed as a 93:7 mixture of diastereomers. Subsequent treatment of compound **106** with thionyl chloride and Et_3N in toluene at 0 °C produced intermediate **107**, which was trapped at −60 °C by cyclopropylethynylmagnesium chloride to yield compound **108**. The stereoselectivity of the conjugate addition step was 92%. After crystallization from methanol, product **108** was isolated in 85% yield as the single diastereomer. Deprotection of the benzyl group was effected by treatment with either wet TFA at 18 °C or formic acid at 60 °C.

This sequence has been scaled up to prepare multi-kilograms of the API. The authors have also reported that a variety of nucleophiles can add to **107** with good to excellent diastereoselectivities, thereby demonstrating the generality of this approach for the synthesis of related analogues.

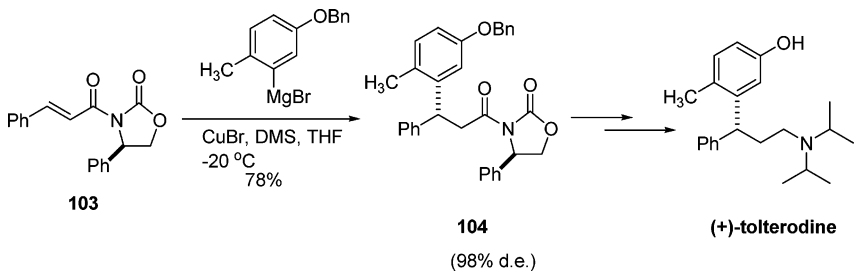
3.4. Nucleophilic Addition to C=X Double Bonds Bearing a Chiral Auxiliary

A variety of reagents undergo nucleophilic additions to C=X double bonds. Stereofacial differentiation of a carbonyl

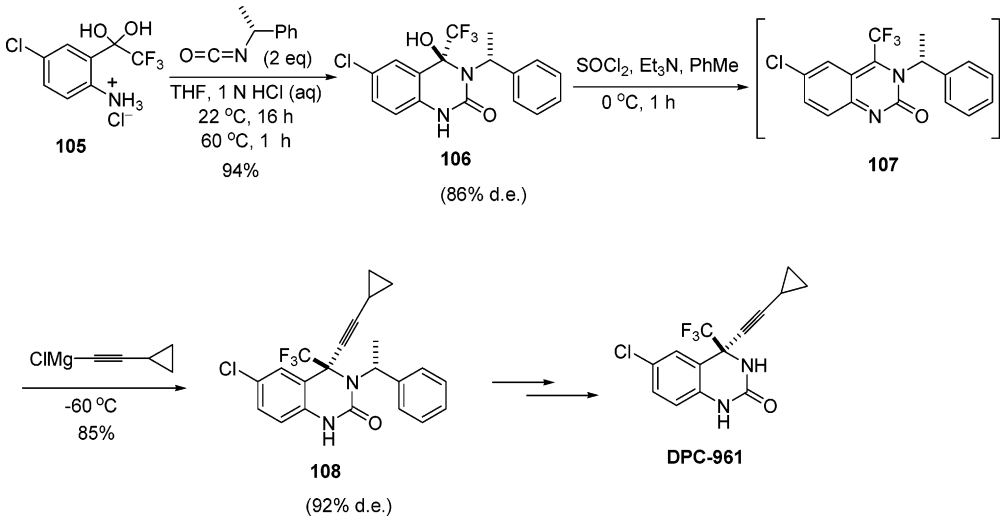
Scheme 27



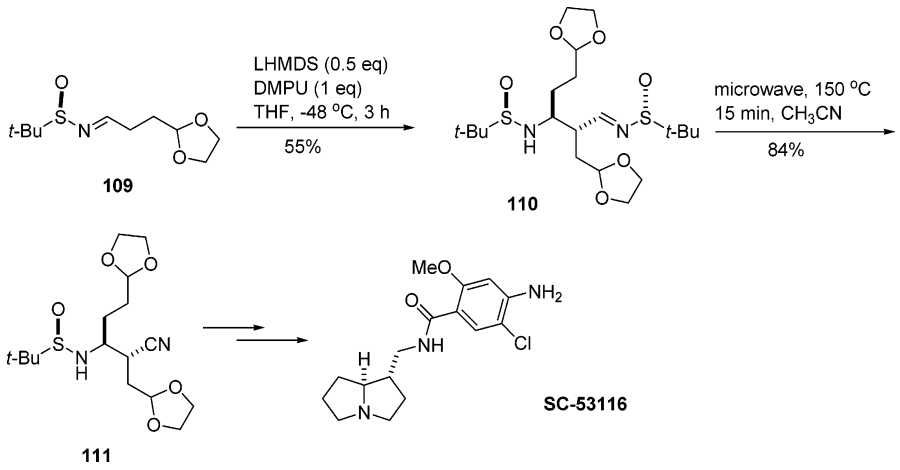
Scheme 28



Scheme 29



Scheme 30



group or an imine functionality during a nucleophilic addition reaction can be achieved by attaching a chiral auxiliary within the electrophile. Several examples of this type of reaction are discussed in this section as they are applied to API synthesis.

3.4.1. Addition to Sulfinyl Imines

In recent years, the scope of chiral sulfonamide- or chiral sulfoxide-mediated chemistry has grown substantially, thanks to the discovery of some efficient methods[51] that have allowed easy access to many structurally diverse sulfinamides and sulfoxides. These new developments have already found practical applications in the synthesis of a number of chiral biologically important targets, as shown below.

In Ellman's synthesis of SC-53116[52] (a serotonin 5-HT_4 agonist, Scheme 30), sulfinyl imine **109** underwent a novel dimerization reaction in the presence of 0.5 equiv of LHMDS and 1.0 equiv of DMPU in THF to deliver the desired compound **110** as the major isomer in 55% isolated yield and good diastereoselectivity (d.r. = 91:5:4:0 for four possible diastereomers). Subsequent microwave-assisted conversion of compound **110** into nitrile **111** proceeded with 84% yield. Compound **111** was then elaborated into SC-53116 in three steps.

Chiral sulfinamide chemistry was recently applied to the asymmetric synthesis[53] of chiral amine **114**, a key synthetic intermediate for sibutramine (Scheme 31). The racemic form of sibutramine is being used for the treatment of obesity.

The key step in this synthesis is the diastereoselective addition of an isobutyl group to the chiral imine of type **112**. After evaluating a variety of sulfinamides, it was found that both *tert*-butylsulfinamide and (triethyl)methylsulfinamide (TESA) provided high selectivities (99% e.e. after cleavage of auxiliary). (*R*)-**114** was then isolated as its D-tartaric acid salt (**115**) in 83% yield with >99% chiral purity. The advantage of using the (*R*)-(triethyl)methylsulfinyl imine is that, unlike the case of its *tert*-butyl analogue, no unpleasant odor is generated during the acidic deprotection.

(*S*)-Cetirizine bishydrochloride is a nonsedating histamine H1-receptor antagonist used for the treatment of allergies (Table 7). Senanayake and co-workers have reported an efficient asymmetric route to the key intermediate (*S*)-4-chlorophenylphenylmethylamine.[54] In their initial studies, the addition of PhMgBr to *N*-*tert*-butylsulfinyl-*p*-chlorobenzaldimine **116** in toluene gave, after deprotection, the desired product **117** with moderate selectivity (75% e.e.). In an effort to increase the stereoselectivity, a variety of sulfinamides were evaluated for this reaction (Table 7). A structure−selectivity relationship can be clearly seen in the aromatic sulfonamide series with tolyl, mesityl, or trisopropylphenyl as substituents. The best stereoselectivity was obtained with the use of triisopropylphenyl sulfonamide (91% e.e. at 0 °C and 94% e.e. at −20 °C).

Scheme 31

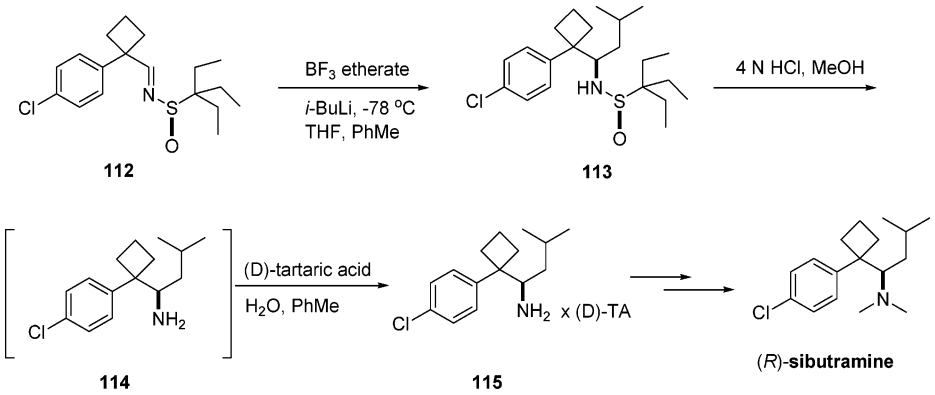
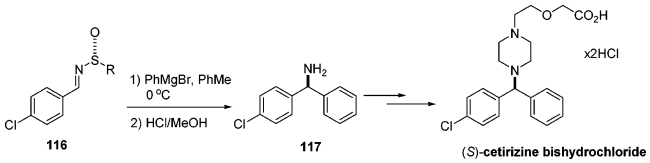


Table 7.



R	*T* (°C)	% yield of **117**	e.e. (%)
t-Bu	0	81	75
Ad	0	85	68
(ethyldimethyl)methyl	0	79	76
(triethyl)methyl	0	88	79
p-tolyl	0	77	10
mesityl	0	83	50
2,4,6-triisopropylphenyl	0	84	91
2,4,6-triisopropylphenyl	**−20 to 0**	**80**	**94**

3.4.2. Addition to Other Electrophiles

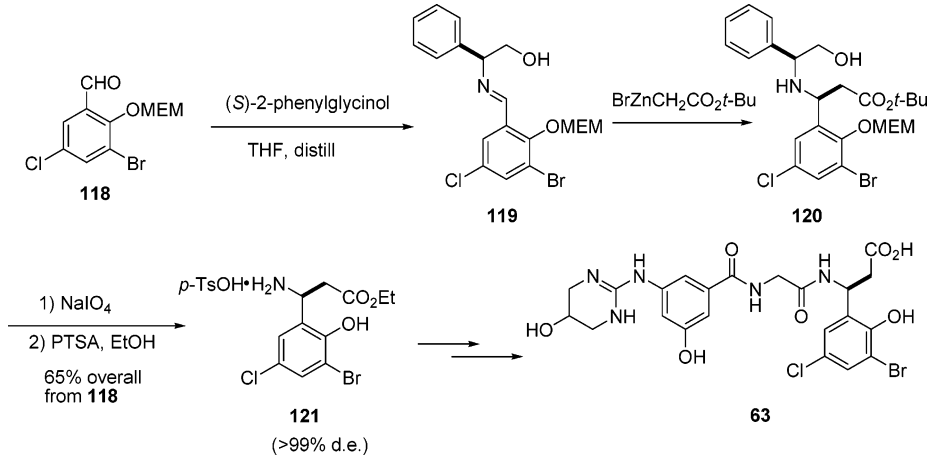
During the process research and development for an $\alpha_v\beta_3$ integrin antagonist (**63**, Scheme 32), a Pfizer team investigated four synthetic approaches[35] to the β-amino acid moiety: (a) asymmetric conjugate addition (see Scheme 16 in Section 3.3); (b) transition-metal-catalyzed enantioselective hydrogenation reaction; (c) classical resolution; (d) novel imino-Reformatsky reaction. Among all the four options, the diastereoselective imino-Reformatsky approach proved to be the most successful, as shown in Scheme 32.

Condensation of aldehyde **118** with (*S*)-2-phenylglycinol gave the imine **119**, which was used directly in the next step without isolation. The Reformatsky reagent derived from *tert*-butyl α-bromoacetate was allowed to react with the imine to give the desired adduct **120**. The cleavage of the chiral auxiliary was accomplished by $NaIO_4$ oxidation in the presence of methylamine as the sequestering agent for the liberated formaldehyde. Since this imino-Reformatsky reaction was found to be a relatively high-energy transformation, extensive efforts were devoted to process development of this step to ensure safe operations. To this end, a detailed calorimetry study was conducted that led to the establishment of well-defined experimental parameters as reported in the paper. This novel imino-Reformatsky reaction has been practiced on a few hundred kilogram scale.

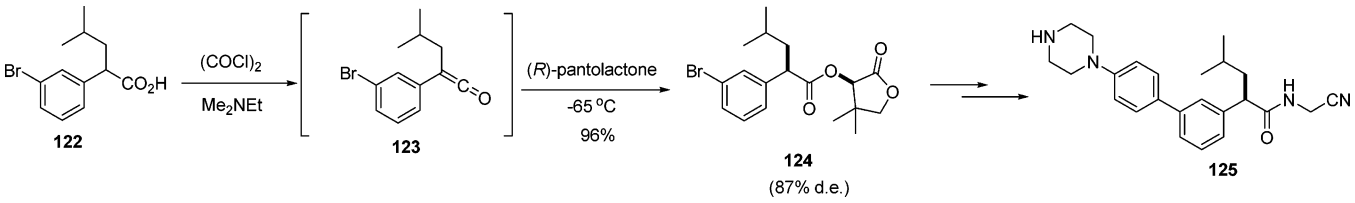
A scalable synthesis of a Cathepsin K inhibitor (**125**) is described by Chen *et al*. at Merck (Scheme 33).[55] The key transformation involved the addition of a chiral alcohol to a ketene intermediate followed by a diastereoselective protonation reaction. The general methodology was previously described by the same laboratories.[56] Ketene **123** was generated from carboxylic acid **122** via the acyl chloride intermediate as shown in the scheme. Addition of (*R*)-(−)-pantolactone to the ketene at < −65 °C afforded the (*R*,*R*)-ester **124** in 96% yield and with 87% d.e.

The removal of pantolactone by hydrolysis without racemizing the newly formed stereocenter was not a trivial task. Acidic hydrolysis using AcOH/HCl was slow at 85 °C. When the acid hydrolysis was carried out at higher temperatures, ∼10% loss in enantiomeric excess was observed. Similarly, alkaline conditions (LiOH in MeOH or THF/water) resulted in a considerable amount of racemization (25%). It was then discovered that treatment of compound **124** with $LiOH/H_2O_2$ at 0 °C gave a complete hydrolysis with minimal racemization (∼4% loss in % e.e.). The optical purity was enriched from 83% e.e. to 98.5% e.e. by crystallization of the

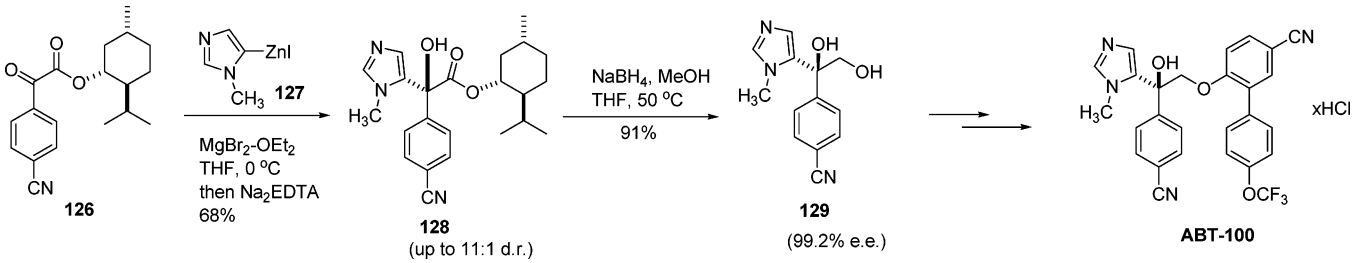
Scheme 32



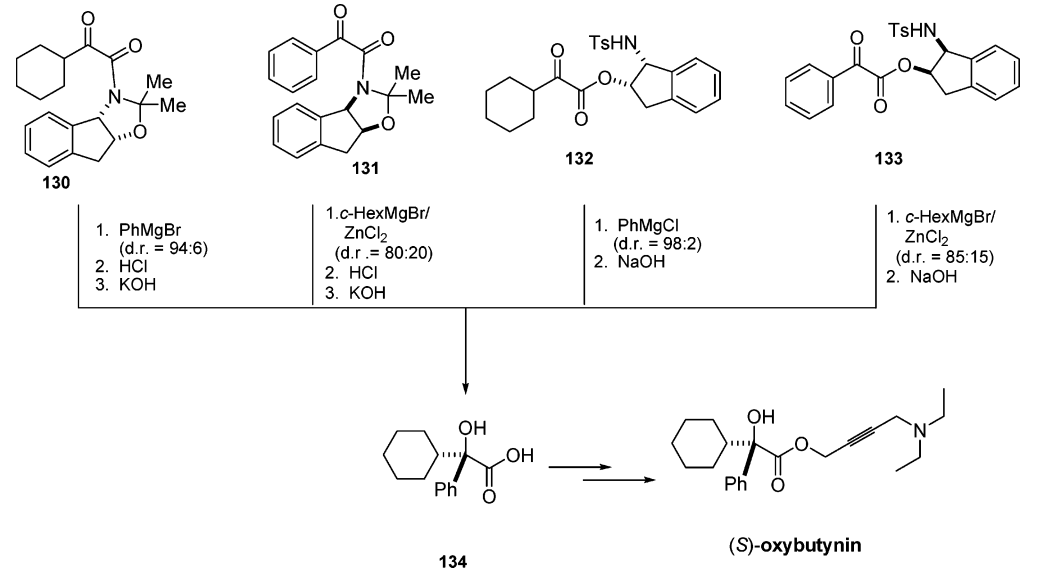
Scheme 33



Scheme 34



Scheme 35



carboxylic acid as its (*R*)-(+)-α-methylbenzylammonium salt. This reaction sequence was implemented on pilot plant scale.

Chelation-controlled stereoselective additions by organometallic reagents (*e.g.* Grignards) to α-keto esters bearing a chiral auxiliary have been extensively exploited for the synthesis of optically active tertiary α-hydroxyacid derivatives.[57] This strategy was recently employed in the synthesis of a novel farnesyl transferase inhibitor, ABT-100 (Scheme 34).[58] The readily synthesized keto ester **126** was treated with zinc reagent **127** at 0 °C in THF in the presence of $MgBr_2-OEt_2$ to furnish the coupled products with up to 11:1 d.r. The optical purity of **128** was enriched to >99:1 d.r. upon crystallization as its 2:1 zinc chloride complex from toluene. Reduction of the α-hydroxy ester gave the desired diol **129** in high yield. This process has been practiced on kilogram scale.

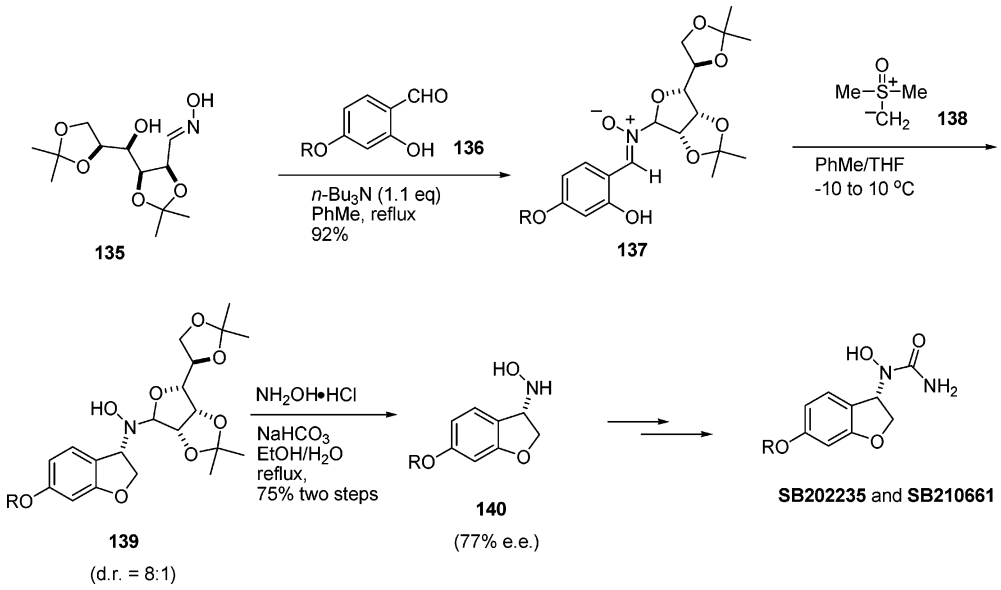
The rigid *cis*-1-amino-2-indanol system was used by a Sepracor team[59] as a chiral auxiliary for the synthesis of the chiral tertiary α-hydroxy acid functionality found in (*S*)-oxybutynin, a muscarinic receptor antagonist (Scheme 35).

Four different routes to the key intermediate **134** were investigated as shown in Scheme 35. These sequences involved the diastereoselective addition of either phenyl or cyclohexyl Grignard to the appropriate keto ester or keto amide followed by removal of the *cis*-1-amino-2-indanol auxiliary. The most successful approach is the addition of phenylmagnesium chloride to ester **132**, in which excellent diastereoselectivity (d.r. = 98:2) was obtained.

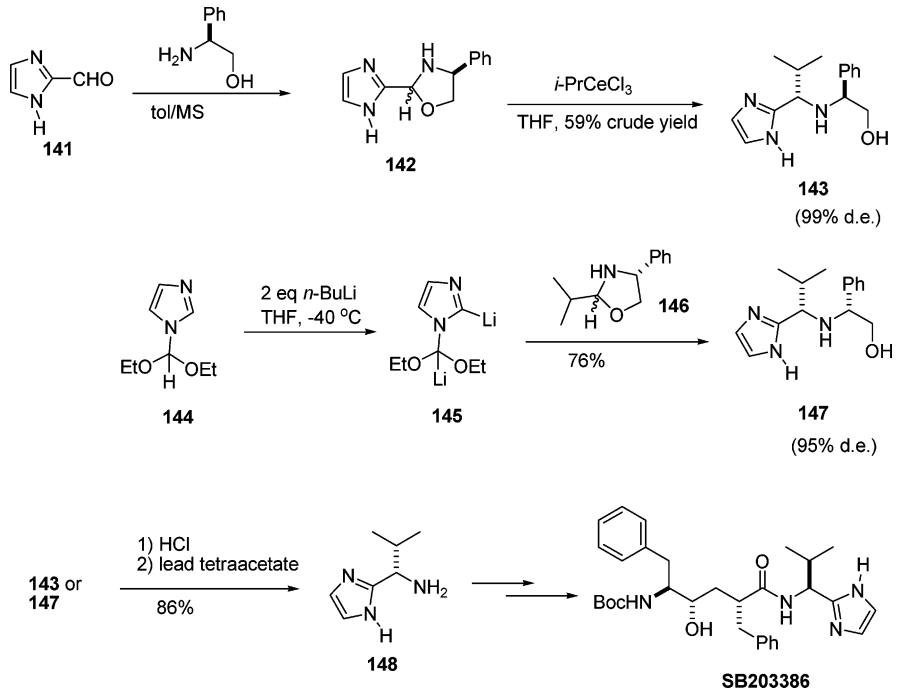
Compounds SB202235 and SB210661 were developed by SmithKline Beecham as 5-LO enzyme inhibitors (Scheme 36). They both contain a novel hydroxyurea moiety. An enantioselective synthesis of these compounds was achieved based on a novel tandem nucleophilic addition−intramolecular cyclization sequence.[60]

Aldehyde **136** was first allowed to condense with the commercially available mannose bis-acetonide **135** to give nitrone intermediate **137** in 80% yield. When the sulfur ylide **138** was added to this chiral nitrone at −10 °C in THF, cyclic product **139** was obtained directly with a d.r. of 8:1. After removal of the auxiliary with $NH_2OH-HCl$ in refluxing ethanol, hydroxy amine **140** was isolated with 77% e.e. in 75% overall yield from compound **137**. The optical purity was upgraded later in the synthesis to 99% e.e. by recrystallization.

Scheme 36



Scheme 37

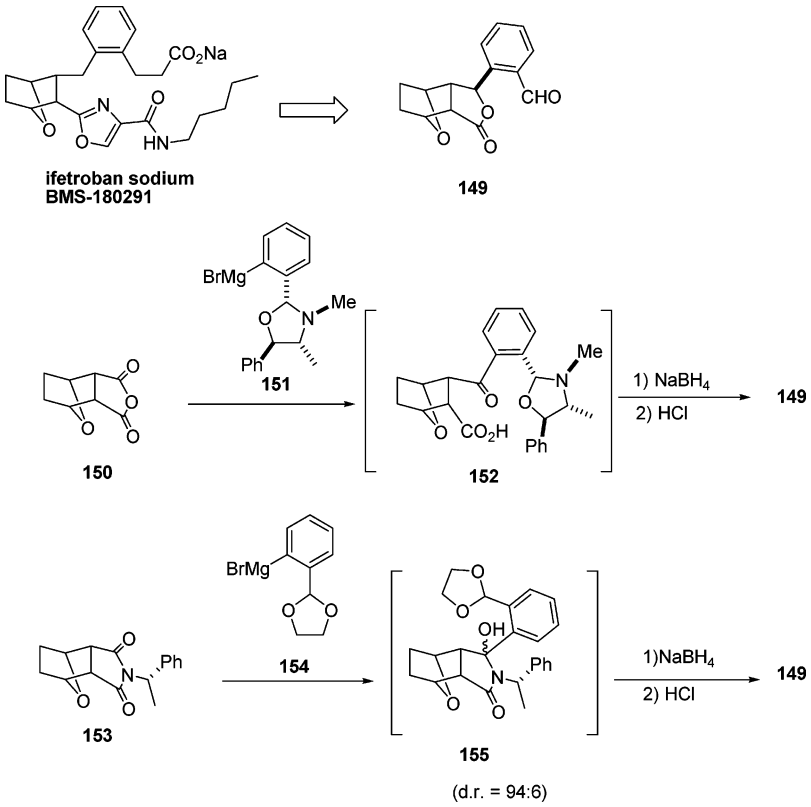


SB203386 is an orally bioavailable HIV-1 protease inhibitor (Scheme 37). Pridgen and colleagues have reported an interesting synthesis[61] of the key intermediate 2-(1′-amino-2′-methylpropyl) imidazole (**148**) by using a diastereoselective nucleophilic addition methodology which was previously developed by the same group.[62] It involves the addition of an organometallic reagent, such as a Grignard, to chiral oxazolidines.

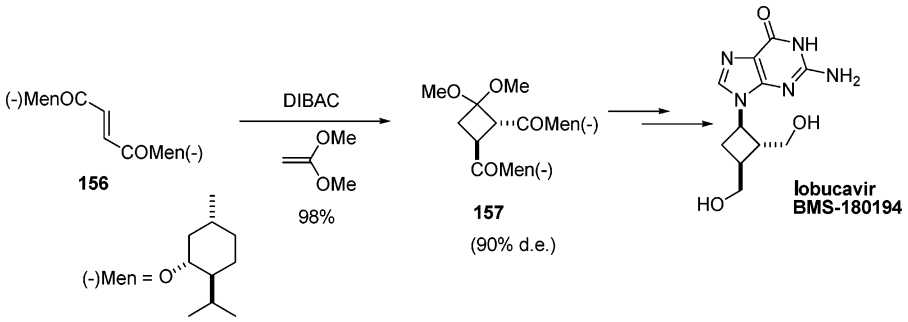
Aldehyde **141** condensed with the optically pure (*S*)-phenylglycinol to give oxazolidine **142** as a mixture of diastereomers. Upon addition of *i*-PrCeCl$_3$, oxazolidine **142** ring-opened to give a putative imine intermediate, which underwent nucleophilic addition reaction to furnish the product **143** with >99% d.e. Alternatively, the lithiated imidazole **145** can be used as the nucleophile to add to the 2-isopropyloxazolidine **146** derived from (*R*)-phenylglycinol to establish the same configuration at the isopropylamine carbon. The chiral auxiliary was cleaved by treatment with lead tetraacetate (LTA) to afford the free amine. However, the use of LTA would obviously present a major issue for the large-scale application unless alternative reagents could be found. It was mentioned in the paper that compound **148** can also be prepared using a chiral-pool approach in three steps from L-valine.[63]

Ifetroban sodium (BMS-180291) is a long-acting, orally bioavailable, highly selective thromboxane A2 receptor antagonist with potent antithrombotic and anti-ischemic activities (Scheme 38). During the course of the chemical development of this compound, chiral aldehyde **149** was identified as a key intermediate. In a previous asymmetric route to aldehyde **149**,[64] *meso*-anhydride **150** was desymmetrized with a chiral Grignard reagent (**151**) to provide the

Scheme 38



Scheme 39



chiral aldehyde segment after *in situ* borohydride reduction. This reaction sequence proceeded with a very high stereoselectivity (99% e.e.).

More recently, Mueller *et al*.[65] disclosed a complementary approach in which desymmetrization was accomplished by reacting a *chiral* imide with an *achiral* Grignard reagent. Thus, reaction of (*S*)-methylbenzylamine-derived imide **153** and Grignard reagent **154** gave, after borohydride reduction and deprotection, the same aldehyde **149** with a 94:6 diastereoselectivity. The optical purity was upgraded to >99:1 by direct crystallization of the crude reaction mixture (89% yield).

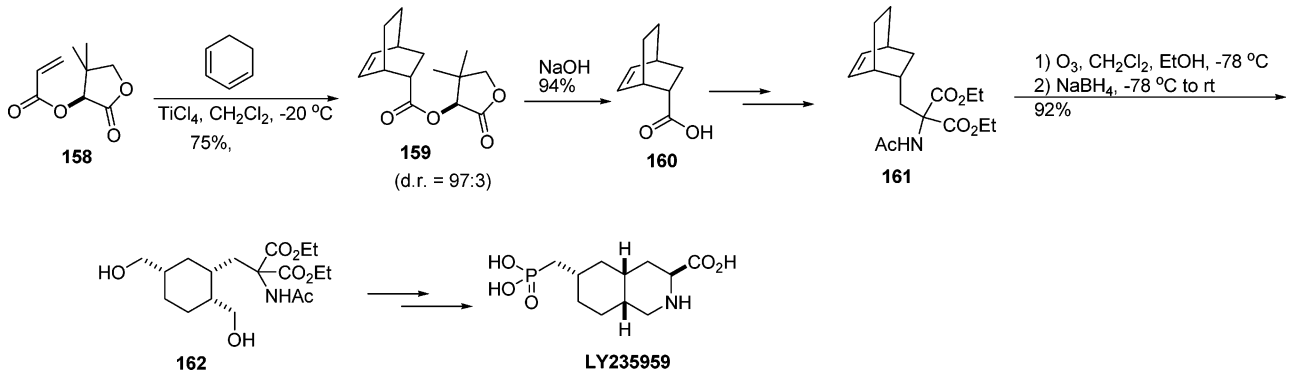
3.5. Cycloaddition Reactions

Asymmetric cycloaddition reactions are powerful methods for the quick construction of cyclic frameworks in APIs including four-, five-, and six-membered rings.

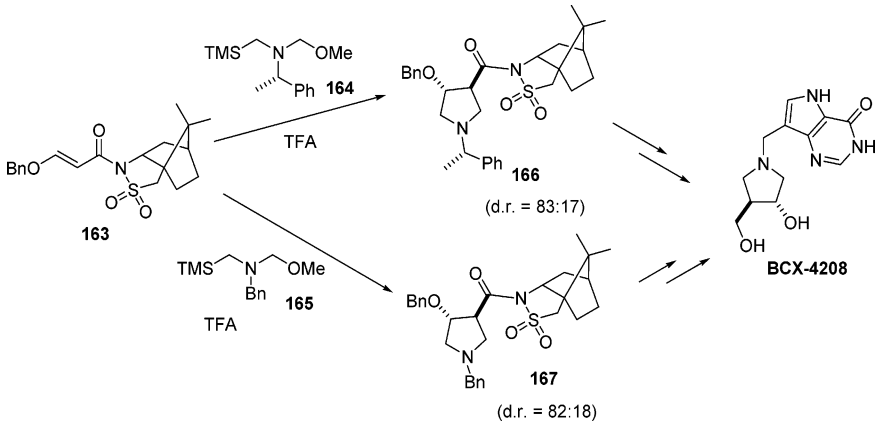
In a recently reported synthesis of lobucavir, a potent antiviral agent, chemists at BMS described the application of an asymmetric [2+2] cycloaddition reaction for the synthesis of the unique cyclobutane moiety bearing three contiguous stereocenters (Scheme 39).[66] This reaction was previously reported by Ahmad *et al*.[67] Ketene dimethyl acetal and dimenthyl fumarate were allowed to react in the presence of diisobutylaluminum chloride (DIBAC) (toluene, −70 °C) to produce the cycloadduct **157** with 90% d.e. (98% solution yield, 83% first crop isolated yield). Detailed studies on various reaction parameters showed that 2 equiv of the Lewis acid was necessary for the success of this reaction. Cryogenic conditions (below −70 °C) were essential for minimizing polymerization of the ketene dimethyl acetal. Among a number of Lewis acids examined for this cycloaddition reaction, only DIBAC and Et_2AlCl formed the cycloadduct with satisfactory diastereoselectivities. Other catalysts, such as BF_3, $TiCl_4$, $SnCl_4$, or $AlCl_3$, caused significant decomposition of the ketene dimethyl acetal. The chiral auxiliary (−)-menthol was easily cleaved by lithium aluminum hydride (LAH) reduction. This approach is very practical considering the good selectivity, the simplicity of the reaction conditions and the low cost of menthol. This step has already been successfully reproduced on pilot plant scale.

Another example of the chiral auxiliary-controlled cycloaddition reaction was reported by Hansen *et al*. from Lilly[68] for the synthesis of LY235959, a potential API to

Scheme 40



Scheme 41



treat Alzheimer's disease (Scheme 40). The key step in the synthesis involves the use of a highly stereoselective Diels−Alder reaction described by Helmchen and co-workers.[69]

The $TiCl_4$-catalyzed Diels−Alder cycloaddition of chiral acrylate with cyclohexadiene in CH_2Cl_2 at −20 °C provided the cycloadduct **159** in 75% yield and with 94% d.e. The chiral auxiliary was cleaved by saponification and readily recovered. The tricyclic ring system was then cleaved by ozonolysis to furnish the optically pure trisubstituted cyclohexane system in LY235959.

Substituted pyrrolidines are common structural motifs frequently found in novel biologically active molecules. Stereoselective construction of these structures can be achieved via a [2+3] cycloaddition reaction between a 1,3-dipole such as azomethine ylide and an olefin bearing a chiral auxiliary. As for all concerted cycloadditions, the [2+3] cyclization is stereospecific with respect to the geometry of the olefin. The *Z* olefin gives *cis*- whereas the *E* olefin gives *trans*-substituted product. This reaction has been exploited by research groups at a number of pharmaceutical companies for API synthesis.

In developing a practical synthesis of the chiral pyrrolidine portion of a PNP inhibitor, BCX-4208, Chand *et al*. from BioCryst Pharmaceuticals applied an asymmetric [2+3] cycloaddition reaction (Scheme 41).[70] Compound **166** has been made previously by Karlsson and Hogberg[71] using a chiral ylide **164** and a chiral dipolarophile **163** via a double asymmetric reaction. However, compound **164** and the corresponding products are oils or semisolids, and silica gel chromatography was required for purification. Since it is known that the [2+3] cycloaddition of a *chiral* azomethine ylide with an *achiral* dipolarophile proceeds with essentially no stereoselectivity, it was decided to utilize the achiral but crystalline **165** for subsequent studies, hoping that the chirality on the dipolarophile would be adequate for achieving the desired stereocontrol.

Thus, the cycloaddition of (*E*)-3-benzyloxypropenoyl-(2′*S*)-bornane-10,2-sultam (**163**) with achiral **165** was examined in dichloromethane in the presence of a catalytic amount of TFA at room temperature. The diastereoselectivity was found to be 82:18, comparable to that obtained using the chiral ylid (83:17). The desired isomer **167** was isolated with 90% recovery via two consecutive recrystallizations. The chiral sultam residue was cleaved by LAH reduction. This reaction was readily implemented on kilogram scale.

Similarly, the TFA-catalyzed [2+3] dipolar cycloaddition of a *cis*-olefin **168** with the compound **165** gave adduct **169** with a 4:1 d.r. (Scheme 42).[72] The major isomer was elaborated into the desired building block **171** via the quaternary ammonium chloride **170**.

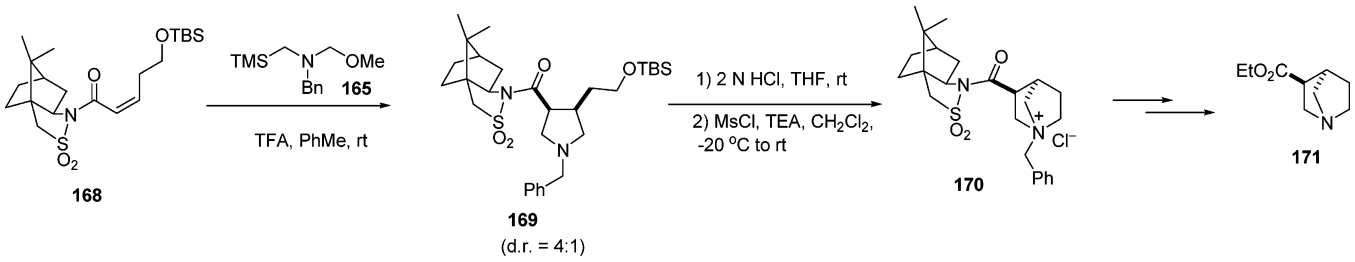
3.6. Reduction and Miscellaneous Reactions

Asymmetric hydrogenations of olefins or ketones are most commonly achieved through transition-metal-catalyzed enantioselective reactions. However, chiral auxiliary-controlled hydrogenations have also occasionally been utilized to prepare certain APIs.

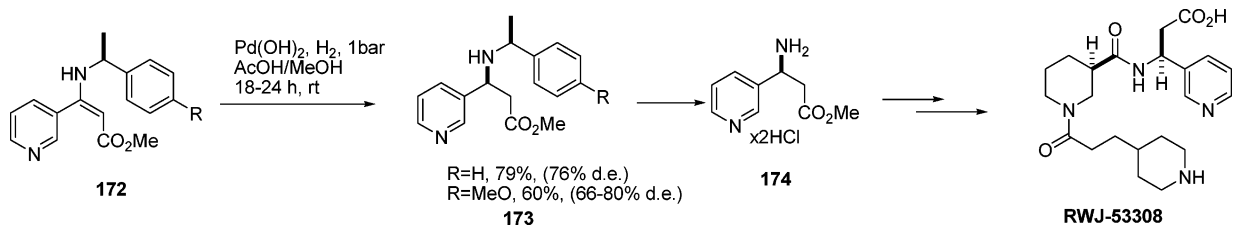
RWJ-53308 is an orally active antagonist of the platelet fibrinogen receptor (GP IIb/IIIa antagonist, Scheme 43). The chiral β-amino acid moiety **174** was constructed through an asymmetric hydrogenation reaction.[73] It is interesting to note that a very similar building block (**72**, Section 3.3) was prepared via a conjugate addition reaction using a chiral lithium amide.

Enamine **172**, prepared from methyl nicotinoyl acetate and (*S*)-phenethylamine, was subjected to $Pd(OH)_2$-catalyzed

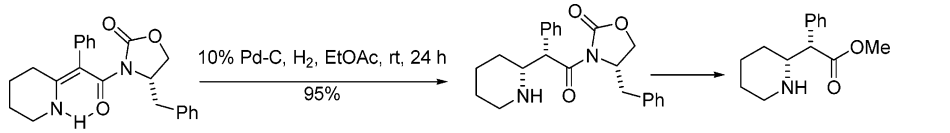
Scheme 42



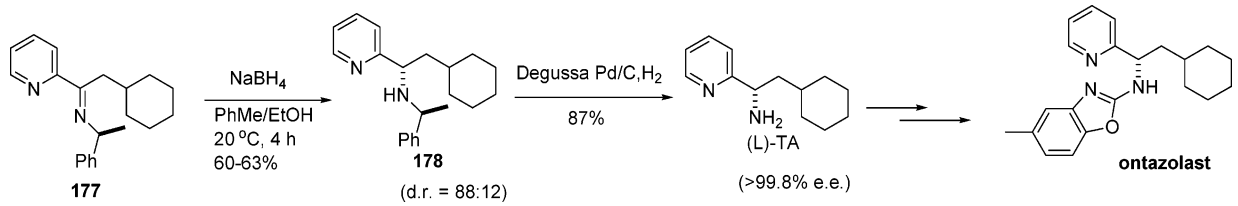
Scheme 43



Scheme 44



Scheme 45



hydrogenation to provide the chiral amine **173** in 76% d.e. However, the debenzylation of the product to give the free amine proved to be challenging. To circumvent this problem, *p*-methoxyphenyl ethylamine was evaluated as the auxiliary for asymmetric hydrogenation, and 66−80% diastereoselectivities were achieved. The desired isomer was isolated in >99% d.e. and 60% yield by recrystallization. The *p*-methoxyphenyl group was then readily removed by treatment with formic acid and Et_3SiH (as a cation scavenger). The observed variability in the d.r. (66−80%) seems to indicate that more development work is required to turn this step into a robust process. It was also noted in the paper that hydride reduction [$NaBH_4$ or $NaBH(OAc)_3$] of the enamine **172** was attempted and gave disappointing diastereoselectivities (4−46% d.e.).

A chiral auxiliary-controlled hydrogenation was employed by Prashad and co-workers[74] in their enantioselective synthesis of (2*S*,2′*R*)-*erythro*-methylphenidate (Scheme 44). The requisite enamine **175** was prepared in a few steps as a single geometric isomer. ^1H NMR analysis suggests that the NH proton forms an intramolecular H-bonding with the carbonyl group as indicated in Scheme 44.

This rigid conformation is expected to confer high facial selectivity. Hydrogenation of **175** in ethyl acetate gave **176** in 95% yield with a 97:3 diastereoselectivity. The catalyst loading (2−20%) had little influence on the diastereoselectivity of the reaction. However, it was mentioned in the paper that enamine **175** had to be rigorously purified by silica gel chromatography before hydrogenation in order to achieve the optimal reaction outcome.

In an earlier approach to ontazolast, a chiral auxiliary-controlled imine reduction was used to install the stereogenic center in the molecule (Scheme 45).[75]

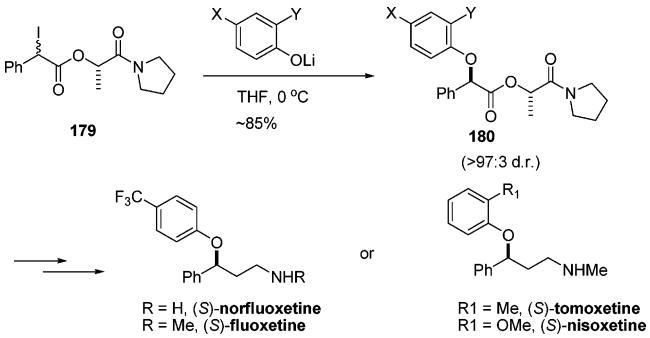
A variety of reducing agents were examined for the reduction of the chiral imine **177**. Reduction with $NaBH_4$ at room temperature for 4 h gave an 88:12 d.r. (60−63% yield).

Significantly better stereoselectivities (∼95:5 d.r.) were observed with sterically more demanding reducing agents such as L-Selectride and $Na[BH(OAc)_3]$. However, the reactions were much slower. Consequently, $NaBH_4$ was selected for further scale-up.

Difficulties were encountered for the debenzylation of **178**, since competing reduction of pyridine ring and partial racemization of the new benzylic chiral center took place during catalytic hydrogenolysis. After testing a variety of catalysts, it was found that a Pd/C catalyst from Degussa provided the best result. The desired amine could be obtained in 87% yield and with >99.8% e.e. as its L-tartrate salt. This route was used to prepare >100 kg batches of the chiral amine fragment of ontazolast.[75]

Devine *et al*. from Merck[76] reported a novel approach to fluoxetine and related analogues (Table 8). The key step involves a novel dynamic diastereoselective alkylation of the lithium salt of phenols with an α-iodoester such as **179**.[77]

Table 8.



X	Y	time (h)	% yield	d.r.
H	CH_3	0.1	85	98:2
H	OCH_3	2	87	97:3
CF_3	H	2	83	99:1

For example, the lithium salt of *p*-CF_3-phenol coupled with **179** at 0 °C to give product **180** with 99:1 d.r. The chiral auxiliary was cleaved by LAH reduction to give the corresponding alcohol. Subsequent elaboration gave fluoxetine and other analogues.

4. Enantioselective Processes Promoted by Stoichiometric Chiral External Ligands

Among non-auxiliary-based processes, catalytic procedures for introducing stereochemistry are generally preferred over methods requiring stoichiometric (or greater) quantities of a chiral reagent or ligand. From a development perspective, the need to separate equimolar quantities of reagent/ligand from products and the greater cost of stoichiometric vs catalytic loadings are key concerns. Many processes have nonetheless been developed which utilize stoichiometric amounts of chiral ligands or reagents. In some cases, efficient separation of the product from the ligand/reagent (or derived byproducts) can be accomplished by crystallization or acid/base extraction. The recovered ligand/reagent often may be recycled, and processes in which the recovery is high can become economically competitive with catalytic alternatives. Most of the reactions described herein employ cheap and abundant chiral pool-derived ligands/reagents (α-pinene, proline, cinchona alkaloids, ephedrine, tartaric acid), and this feature also helps to offset the cost of using stoichiometric quantities, particularly if alternative catalytic processes utilize more exotic (and expensive) reagents.

Brown's B-chlorodiisopinocampheylborane (DIP-Cl) has become a choice method among stoichiometric reagents for the asymmetric reduction of ketones since its introduction 20 years ago.[78] The reliably high enantioselectivities (particularly for aryl alkyl ketones), mild reaction conditions, commercial availability of the reagent, and abundance of either enantiomer of α-pinene add to the appeal of the process.[79] Significantly, the Merck Process Research group found that DIP-Cl prepared from cheap technical grades of α-pinene (70−92% e.e.) can be used to reduce ketones with high enantioselectivities due to nonlinear effects in the formation of DIP-Cl.[80] Sidler and co-workers at Merck reported the synthesis of the LTD_4 antagonist L-708,738 using (−)-DIP-Cl reduction of ketone **181** for introduction of the lone stereocenter as illustrated in Scheme 46.[81] The reagent was prepared prior to use from $BH_2Cl{\cdot}SMe_2$ and (+)-α-pinene. No mention was made regarding the optical purity of the (+)-α-pinene used. While the reduction was slow at −20 °C (50% conversion/6 h), increasing the temperature to 0 °C gave complete reaction in 4−6 h. The alcohol **182** was formed in 92.4% e.e., but isolation by crystallization (hexanes/H_2O) allowed an upgrade to >99% e.e. (89% yield). A subsequent stereospecific lithium thiolate displacement of the derived mesylate provided the sulfur-subsituted stereocenter found in L-708,738. The reduction was reported on a 350 g scale.

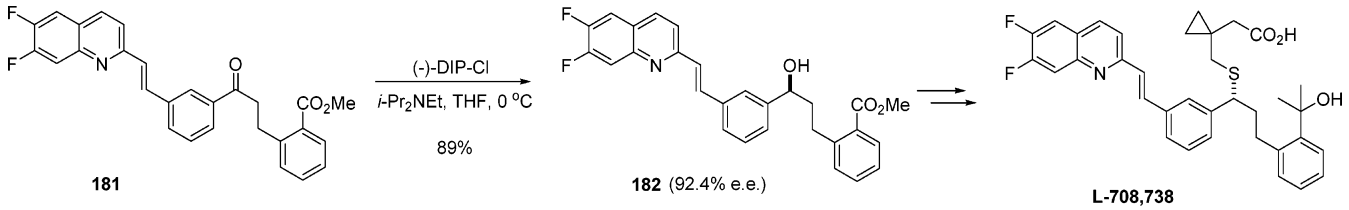
Conrow and co-workers at Alcon Laboratories described the synthesis of the topical carbonic anhydrase inhibitor AL-4862 (Scheme 47).[82] Kilogram-scale reduction of α-bromoketone **183** using commercial (+)-DIP-Cl (2 equiv) produced an intermediate bromohydrin, which was not isolated but treated in the same pot with aqueous NaOH to effect cyclization to the thienothiazine **184**, isolated in 77% yield and >98% e.e. The acidic sulfonamide N−H group allowed efficient partitioning of the product into the aqueous NaOH solution and provided an extractive method for separation of reagent-derived byproducts. In syntheses of N-alkylated analogues of **184** where this extractive purification was not possible, standard methods for separation of diisopinocampheylboron-derived byproducts (complex formation with diethanolamine or deborination with acetaldehyde) were ineffective, and in these cases chromatographic purification proved necessary.[83] Although MTBE gave superior results for the reduction compared to THF, the authors noted that upon prolonged storage (>1 month) several bottled solutions of (+)-DIP-Cl in MTBE burst from pressure buildup.

Wu and co-workers at Pfizer described the development of an asymmetric synthesis of trecetilide hemi-fumarate (Scheme 48), a treatment for atrial arrythmia.[84] A first-generation route utilized enzymatic resolution for introduction of the sole chiral center, but chromatography was necessary for purification. In addition, poor crystallinity of intermediates made purifications difficult, and the drug substance produced by this route did not pass developmental purity requirements. Asymmetric reduction of ketone **185** was investigated during development of an alternative route. After screening several different reagents, (−)-DIP-Cl was found to be superior. Treatment of **185** with 2 equiv of commercial (−)-DIP-Cl in THF at 0 °C for 3−4 days gave alcohol **186** in 85% yield and 98.4% e.e. The reaction time for complete conversion could be reduced to 1 day if the temperature was raised to 23 °C, although the optical yield dropped to 93% e.e. After quenching with acetone and switching solvent to MeOH, washing with heptane conveniently allowed complete removal of the α-pinene-derived byproducts. The reaction was reported on a 20 g scale. The authors note that the long cycle time and low volume efficiency ($V_{max} \sim 40$ L/kg) of this process would have required improvement for further scale-up, but the project was terminated before these issues could be addressed.

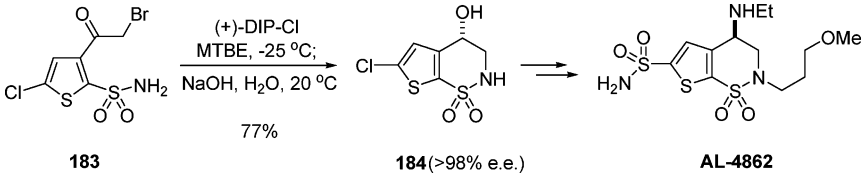
Brown reported the application of his DIP-Cl reduction to the syntheses of both enantiomers of the structurally related antidepressant drugs tomoxetine, fluoxetine, and nisoxetine as depicted in Scheme 49.[85] Reduction of 3-chloropropiophenone **187** with (−)-DIP-Cl (THF, −25 °C) gave alcohol **188** in 97% e.e. Recrystallization from hexane upgraded the optical purity to 100% e.e.

This common intermediate was converted to (−)-tomoxetine·HCl, (−)-fluoxetine·HCl, and (+)-nisoxetine·HCl by Mitsunobu reaction with the appropriate phenol, condensation with methylamine, and salt formation. The opposite enan-

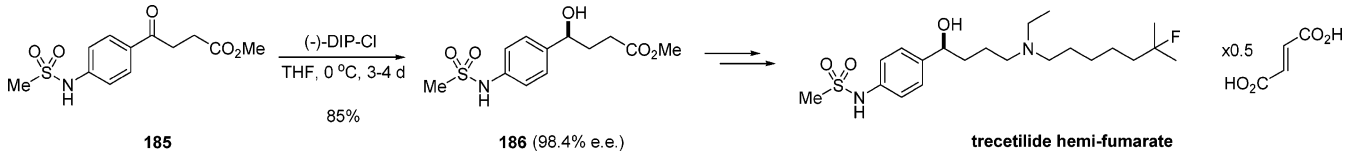
Scheme 46



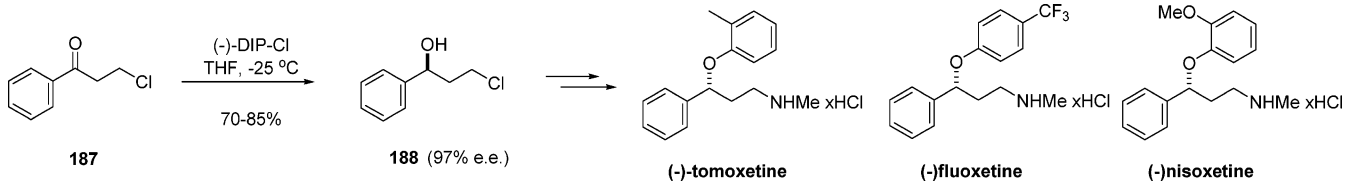
Scheme 47



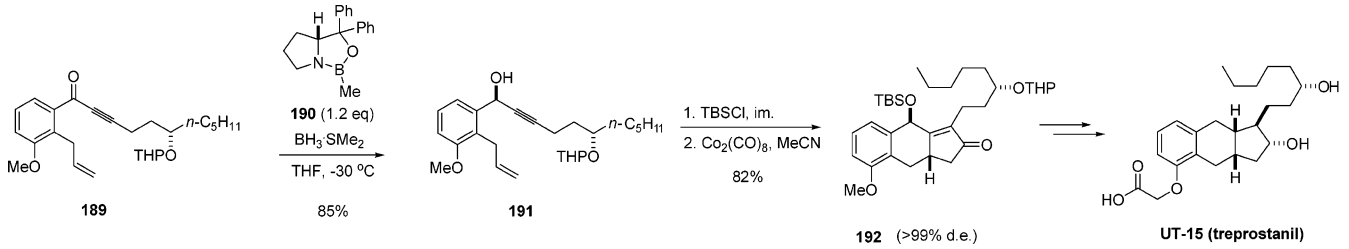
Scheme 48



Scheme 49



Scheme 50



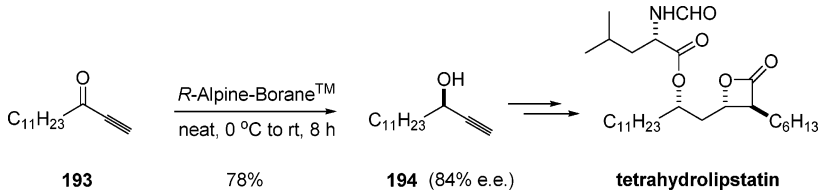
tiomers of each drug were also prepared using (+)-DIP-Cl for the reduction of **187**.

The CBS (Corey−Bakshi−Shibata) reduction represents another reliable and industrially popular choice for enantioselective reduction of ketones.[86] The reagent consists of an amino alcohol-derived oxazaborolidine catalyst in combination with a stoichiometric reductant (typically $BH_3 \cdot SMe_2$ or $BH_3 \cdot THF$). While the oxazaborolidine is typically used only in catalytic amounts (5−20%), some substrates require stoichiometric quantities for maximum optical yield. Moriarty *et al*. described the synthesis of the benzindene prostacyclin UT-15, also known as treprostanil, using a stoichiometric CBS reduction of alkynyl aryl ketone **189** as a key asymmetry-inducing event (Scheme 50).[87]

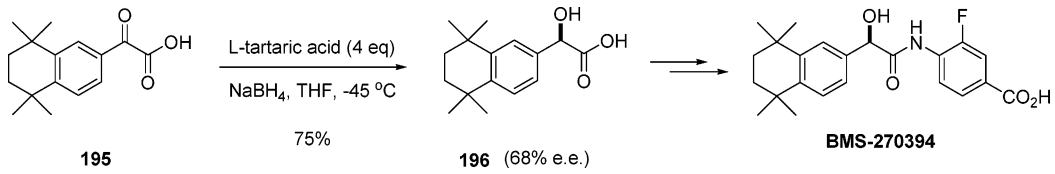
Thus, treatment of **189** with 1.2 equiv of commercially available (*R*)-*B*-methyl oxazaborolidine **190** and 2 equiv of $BH_3 \cdot SMe_2$ in THF at −30 °C gave alcohol **191** in 85% yield with complete diastereoselectivity at the newly formed stereocenter. No comment was made on whether the remote stereocenter had any influence on the selectivity of the reduction. After silylation of the alcohol, an intramolecular Pauson−Khand cyclization efficiently relayed the benzylic stereochemistry, providing cyclopentenone **192** with >99% d.e. Although the process was demonstrated on a nearly 5 kg scale, chromatography was nonetheless employed for purification of the product (an oil).

The stoichiometric chiral reductant Alpine-Borane (B-isopinocampheyl-9-borabicyclo[3.3.1]nonane), also known as the Midland reagent, is a commercially available alternative to DIP-Cl for the reduction of ketones.[88] The reagent is effective for reduction of electronically activated, sterically uncrowded ketones (alkynyl or α-halo), although more hindered ketones can be reduced at reasonable rates by running the reaction neat[89] or under high-pressure conditions.[90] Kocieński and Pons published an approach to the marketed antiobesity drug tetrahydrolipstatin using *R*-Alpine-Borane as illustrated in Scheme 51.[91] Treatment of alkynyl ketone **193** with 1.4 equiv of *R*-Alpine-Borane (neat) at 0 °C to room temperature for 8 h gave propargyl alcohol **194** in 84% e.e. (78% yield). Ten additional steps led to tetrahydrolipstatin.

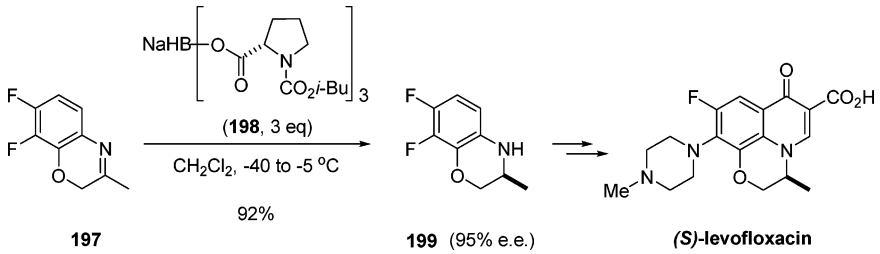
Scheme 51



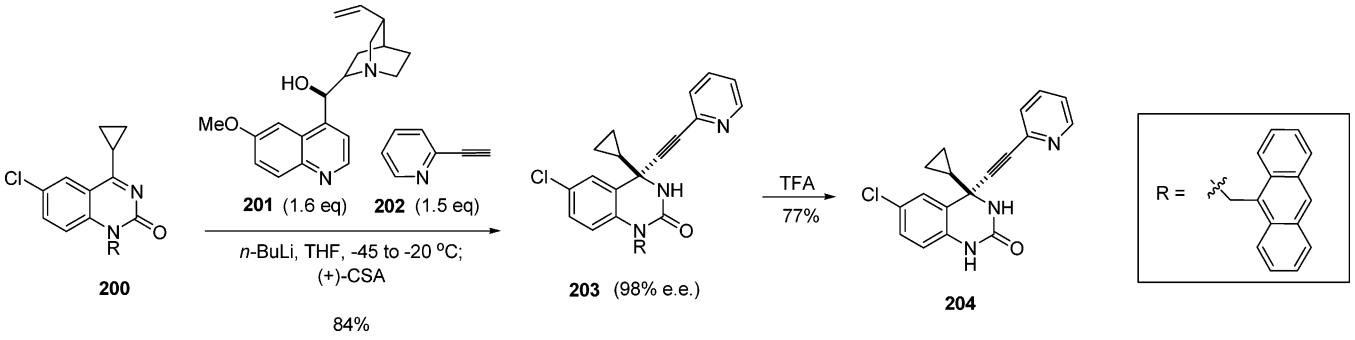
Scheme 52



Scheme 53



Scheme 54



Chidambaram and co-workers at BMS described the synthesis of the retinoic acid receptor (RARγ) agonist BMS-270394 (Scheme 52).[92] The chiral secondary alcohol was derived from α-ketoacid **195** by $NaBH_4$ reduction in the presence of 4 equiv of L-tartaric acid in THF at -45 °C for 48 h. This reagent combination furnished a 75% yield of **196** in 68% e.e.

Crystallization with (1*R*,2*R*)-(−)-*N*,*N*′-dimethylcyclohexane-1,2-diamine and subsequent salt liberation allowed an upgrade to >99% e.e. The authors noted that the original synthesis utilized *R*-Alpine-Borane for reduction of the allyl ester of **195** (93−94% e.e., >99% e.e. after two recrystallizations). The relative expense of *R*-Alpine-Borane as well as its pyrophoric properties provided the impetus for seeking alternative procedures. The reduction was reported on a 50 g scale.

Atarashi and co-workers at Daiichi Pharmaceutical Co. developed a chiral reduction for the synthesis of the active *S*-enantiomer of the antibacterial agent levofloxacin (also known as DR-3355) as illustrated in Scheme 53.[93]

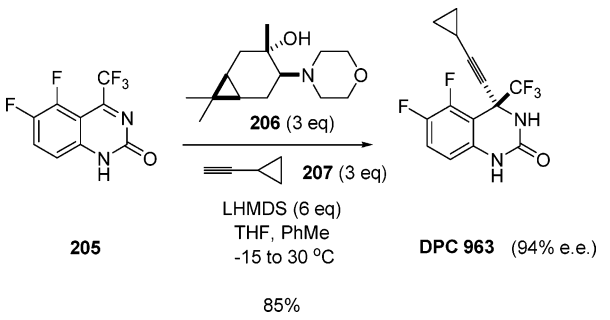
A variety of sodium triacyloxyborohydrides were prepared by reaction of *N*-protected amino acids with $NaBH_4$ (3:1 ratio) and screened in the reduction of cyclic imine **197**. The reagent **198** derived from *N*-isobutyloxycarbonyl-L-proline gave the best results, providing the product **199** in 95% e.e. (92% yield). The reaction was reported on gram scale. The reagent was prepared and isolated prior to use in the reduction and was employed in a 3-fold excess relative to the imine **197**.

Huffman and co-workers (Merck) described the synthesis of the reverse transcriptase inhibitor **204** by an enantioselective acetylide addition to a cyclic *N*-acyl ketimine (Scheme 54).[94]

A variety of amino alcohols were screened as chiral ligands for the addition of lithiated 2-ethynylpyridine **202** to *N*-acyl ketimine **200**. Dihydroquinine and quinine **201** were found to give the best optical yields, and due to its lower cost and ready availability, the latter was chosen for optimization. The *N*-protecting group R in **200** was found to have a major effect on the enantioselectivity, with the large 9-anthrylmethyl moiety providing the highest e.e. Optimized reaction conditions involved treatment of a THF solution of **201** and **202** with *n*-BuLi at -45 °C, aging 1 h at -45 to -40 °C, addition of **200**, warming to -20 °C, and quenching with 1 N HCl. The product **203** was formed in 97% e.e. and was upgraded to 98% e.e. on isolation as the (+)-CSA salt (84% overall yield). The reaction was reported on kilolab scale.

A related strategy was employed by Nugent and co-workers (Merck) for the synthesis of the non-nucleotide reverse transcriptase inhibitor DPC 963 as illustrated in Scheme 55.[95] In this case the (+)-3-carene-derived amino

Scheme 55

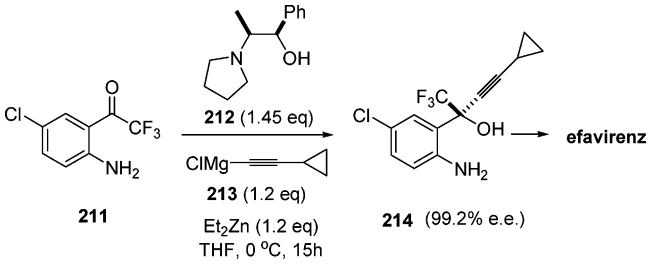


alcohol **206** was found to be uniquely effective for the asymmetric addition of lithium cyclopropyl acetylide **207** to ketimine **205**. Typical reaction conditions involved treatment of a toluene solution of **206** and **207** with LHMDS in THF at −5 °C to reflux for 15 min, addition of the ketimine **205** at −15 °C, stirring at 0 °C for 16 h, and warming to 30 °C for 3 h. The product was formed in 94% e.e., and isolation by recrystallization from heptane increased the optical purity to 99.6% e.e. (85% yield). The reaction was reported on gram scale.

A series of papers from Merck and DuPont chronicle the chemical development of an asymmetric approach to the marketed HIV-1 reverse transcriptase inhibitor efavirenz (Sustiva), also known as L-743,726 and DMP 266.[96] In a full account, Pierce and co-workers (DuPont) and Chen and Tillyer and co-workers (Merck) described the enantioselective addition of lithium cyclopropyl acetylide **207** to *ortho*-(trifluoroacetyl)aniline **208** mediated by lithium (1*R*,2*S*)-*N*-pyrrolidinyl norephedrate **209** (Scheme 56).[96b] Optimal experimental conditions involved aging a THF solution of **207** and **209** (2.0 equiv each) at 0 °C for 30 min and adding ketoaniline **208** at −55 °C. The product alcohol **210** was formed in 96−98% e.e. in the solution, and crystallization provided an upgrade to >99.5% e.e. (91−93% isolated yield). The use of cinchona alkaloids as chiral additives gave **210** of 50−60% e.e., and among a variety of ephedrine-derived ligands screened, it was found that the substituents on nitrogen had a dramatic effect on enantioselectivity, with the pyrrolidinyl group giving the best optical yield. Aging of the Li-acetylide/aminoalkoxide mixture at 0 °C prior to low temperature (−55 °C) addition of the ketone was crucial for high enantioselectivity: conducting the entire reaction at −50 °C gave **210** of only 82% e.e. These results were rationalized in terms of an aggregate equilibration which is driven at temperatures above −40 °C to a single, C_2-symmetrical cubic tetramer composed of two molecules of Li-acetylide **207** and two molecules of Li-norephedrate **209**.[96c,e] The structure of this aggregate and its role in the stereochemistry-defining step were elucidated by extensive ^{6}Li NMR studies. These NMR studies also revealed the formation of an unreactive 2:1:1 tetramer which rationalized the requirement for 2 equiv of **207** and **209** for complete reaction with high e.e. These studies as well as React-IR experiments showed that the NH group of the starting material is not deprotonated by 1 equiv of acetylide. Asymmetric amplification observed on using ligand **209** of varying levels of enantiopurity also supported the cubic tetramer structure for the aggregate. The alcohol **210** was converted in three steps to efavirenz. The synthesis proceeds in 62% overall yield in seven steps from 4-chloroaniline. Although the ligand **209** is required in 2-fold excess for the acetylide addition reaction, it is efficiently recovered (98% yield, >99% purity) on basification of the aqueous layer and can be recycled. The process is reported on multi-kilogram scale.

While the above synthesis of efavirenz is remarkably efficient, it nonetheless requires low temperatures, excess quantities of chiral ligand and acetylene, and the protection/deprotection of the aniline nitrogen. An improved synthesis which addresses all three of these issues was reported by Tan and colleagues at Merck.[96d] They employed a chiral zinc alkoxide, derived from 1 equiv of (1*R*,2*S*)-*N*-pyrrolidinyl norephedrine **212**, 1 equiv of achiral alcohol (such as methanol), and 1 equiv of R_2Zn (R = Me or Et) in combination with chloromagnesium cyclopropyl acetylide **213** as an alkynylating agent (Scheme 57). It was reasoned

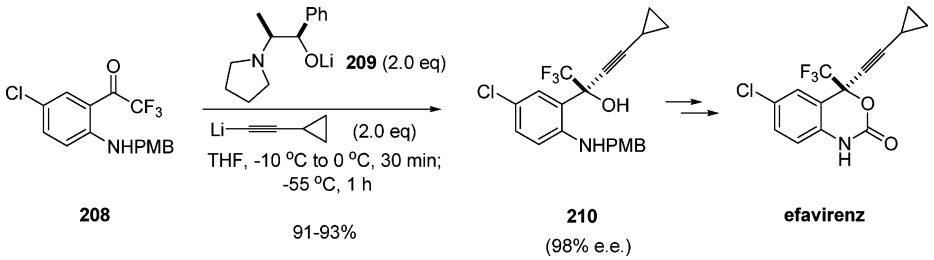
Scheme 57



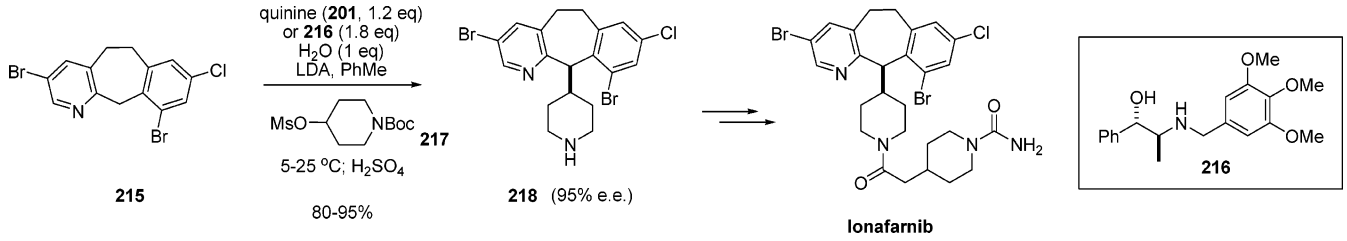
that the use of a zinc alkoxide would reduce the basicity of the acetylide and permit the free aniline to be used. This proved to be the case, and under the optimized conditions aniline **211** reacted to give **214** in 95% yield and 99.2% ee.

It was found that the reaction required only 1.2−1.5 equiv of chiral ligand **212** and 1.2 equiv of chloromagnesium cyclopropyl acetylide **213**. In addition, the entire reaction could be run at 0 °C, a significant improvement from the −55 °C requirement of the previous synthesis. This process represents the most efficient route to efavirenz reported to date, and has been described on multi-kilogram scale.

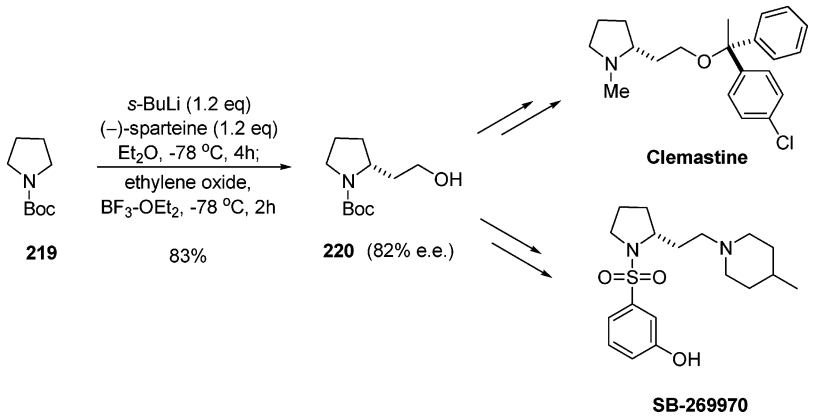
Scheme 56



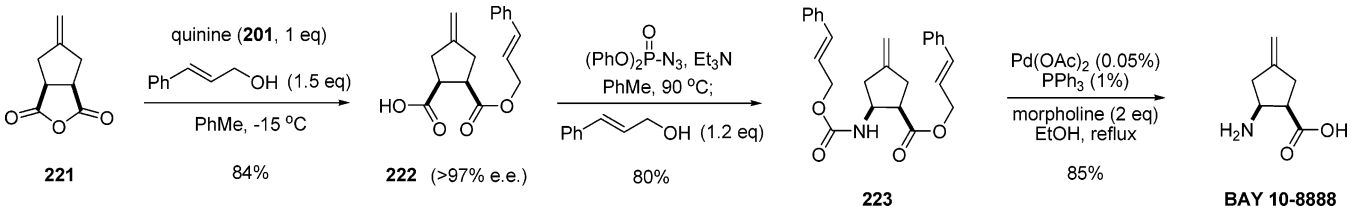
Scheme 58



Scheme 59



Scheme 60



Wu and co-workers at Schering-Plough described the synthesis of the potent farnesyl protein transferase inhibitor lonafarnib via an asymmetric alkylation reaction of doubly annulated cycloheptane **215** with the piperidinyl mesylate **217** (Scheme 58).[97] After extensive screening of chiral amine ligands, it was found that quinine **201** and hydroquinine gave **218** in up to 85% e.e. following removal of the Boc group. In addition, the norephedrine-derived ligand **216** provided the product in 88% e.e.

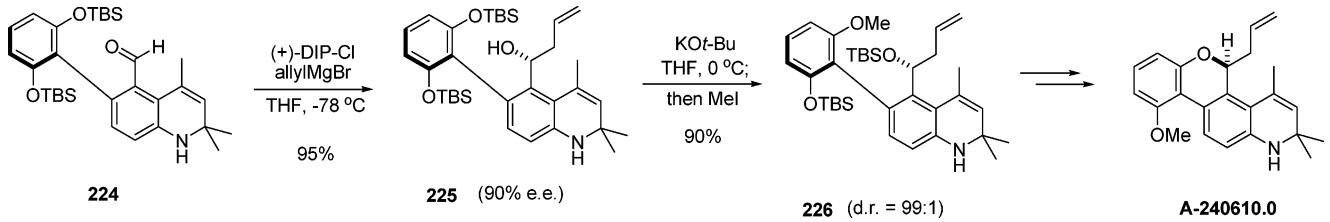
The presence of water in the reaction mixture had a dramatic effect on enantioselectivity. Thus, the optical yield increased to 95% e.e. when 1 equiv of water was included for reactions using either **210** or **216**. Toluene was found to be the optimal solvent, as reactions in THF gave substantial amounts of elimination of the mesylate electrophile. The alkylation was scaled up to a 33 kg batch size, and >200 kg of lonafarnib was delivered in 80% isolated yield and >99% e.e. The availability, low cost, and recyclability of quinine, the mild reaction conditions (5−25 °C), and the good chemical and optical yield of the reaction make this an attractive process.

The chiral hydroxyethylpyrrolidine **220** is a key intermediate in the synthesis of the antihistamine clemastine and the $5HT_7$ receptor antagonist SB-269970. Deng and Mani at Johnson & Johnson reported an asymmetric synthesis of **220** via enantioselective deprotonation of pyrrolidine **219** with *s*-BuLi/(−)-sparteine as shown in Scheme 59.[98] Alkylation of the anion with ethylene oxide in the presence of BF_3·OEt_2 furnished the alcohol **220** in 83% yield and 82% e.e. BF_3·OEt_2 was essential for the alkylation; in its absence no reaction occurred.

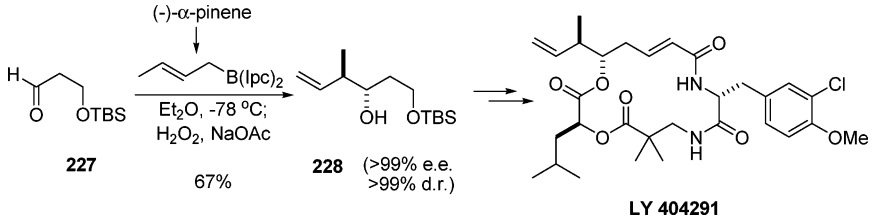
Mittendorf and co-workers at Bayer AG reported the asymmetric synthesis of the antifungal *β*-amino acid BAY 10-8888 by desymmetrization of *meso* anhydride **221** as depicted in Scheme 60.[99] Treatment of **221** with 1 equiv of quinine **201** and 1.5 equiv of cinnamyl alcohol in toluene at −15 °C gave the hemiester **222** in 85% e.e. Approximately 10% of racemic product crystallized from toluene, leaving **222** of >97% e.e. in the remaining solution (84% isolated yield). The use of substoichiometric quantities of quinine gave greatly reduced enantioselectivities. Cinnamyl alcohol was employed for the alcoholysis, as it gave optimal results not only in terms of yield and enantioselectivity but also due to the crystallinity rendered in subsequent intermediates and the ester cleavage conditions it allowed. Curtius rearrangement of **222** using diphenylphosphoryl azide and trapping the resultant isocyanate with cinnamyl alcohol gave carbamate **223** in 80% yield and >99.5% e.e. Deprotection of the cinnamyl ester and carbamate groups was effected with catalytic $Pd(OAc)_2/PPh_3$ and morpholine in ethanol to give BAY 10-8888 in 85% yield and >99.5% e.e. The process was reported on multi-kilogram scale.

Ku and co-workers at Abbott Laboratories reported the synthesis of the anti-inflammatory agent A-240610.0 using Brown's allylboration methodology[100] (Scheme 61).[101] Thus, aldehyde **224** was treated with the allylborane derived from (+)-*B*-chlorodiisopinocampheylborane [(+)-DIP-Cl] and allylmagnesium bromide to provide homoallylic alcohol **225**

Scheme 61



Scheme 62



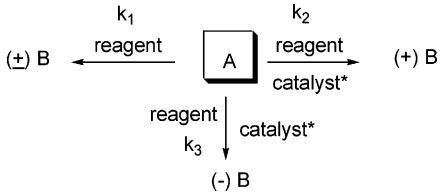
in 95% yield and 90% e.e. Treatment of **225** with potassium *tert*-butoxide effected a diastereoselective intramolecular silyl migration, and the resultant intermediate phenoxide was alkylated with methyl iodide to give the atropisomeric compound **226** in 90% yield with 99:1 diastereoselection. Removal of the TBS groups with TBAF and intramolecular Mitsunobu displacement gave the final API. The authors demonstrated that only one atropisomer is effectively cyclized in the Mitsunobu reaction; the other undergoes elimination and other side reactions. The reaction was reported on gram scale.

Dhokte, Martinelli, and co-workers at Eli Lilly disclosed their approach for the total synthesis of the cryptophycin family of depsipeptide natural products.[102] These compounds and several synthetic analogues have potent antitumor activity. A key stereochemical diad was prepared using Brown's crotylboration methodology[103] as illustrated in Scheme 62. Treatment of silyloxy aldehyde **227** with *E*-crotyl diisopinocampheylborane derived from (−)-α-pinene gave *anti* adduct **228** after oxidative workup in 67% yield in ≥99% e.e. and d.e. This fragment was elaborated into the analogue LY 404291 as well as an epoxy analogue LY 404292 and cryptophycins 51 and 52.

5. Asymmetric Catalysis: General Principles and Scope

The principles of asymmetric catalysis have been clearly articulated in a number of monographs.[104] In general, a prochiral substrate **A** is treated with a nonchiral reagent in the presence of (ideally) small amounts of a chiral catalyst (Scheme 63). There are two major competing pathways with

Scheme 63



respect to formation of the desired product [*e.g.* (+)-**B**]: the direct reaction of the nonchiral reagent with the substrate, leading to a racemate, and the less-than-perfect recognition of substrate **A** by the reagent/catalyst complex, leading to variable amounts of (−)-**B**, which erodes the enantiomeric purity. Therefore, one must ensure that, in Scheme 63, $k_2 \gg k_3$ and k_2[catal] $\gg k_1$.

In view of this, it is clear that the challenges associated with developing effective chiral catalysts are exceedingly complex. The reaction must be designed in such a way that, under the chosen reaction conditions, the catalyst/reagent complex will be much more reactive vs substrate **A** than the reagent itself. In addition, the catalyst must cycle efficiently; that is, none of the catalytic intermediates on the pathway to product must be exceedingly stable, or the reaction will appear "stuck". The most common medicine against a slowly cycling catalyst is an increase in the catalyst load, which, of course, reduces the efficiency of the process and often discourages industrial applications. A better catalyst design is, of course, much preferred but not always easy. Finally, the catalyst must operate with exquisite selectivity and lead preferentially or exclusively to only one enantiomer of the product.

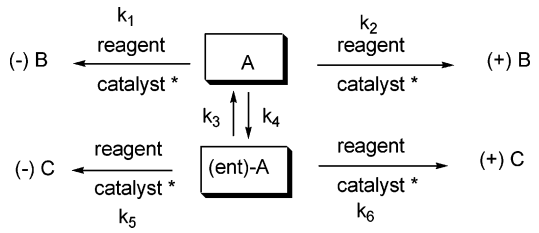
From this premise, one would be tempted to speculate that efficient enantioselective catalysts should be extremely rare. Luckily, however, in the last 10 years, enantioselective catalysis has progressed dramatically, and currently the classes of reactions that have yielded to truly practical asymmetric catalysis are in the dozens.[105] For industrial applications, asymmetric catalysis must compete with older and established processes. One of the challenges is that, whereas enantioselective catalysts are often developed for generality and scope, the process chemist only needs the application for a single substrate. Therefore, even established methods of high generality usually require extensive optimization in terms of solvent, concentrations, additives, temperature, etc. New esoteric ligands may also be unavailable on a large scale. When a new catalyst is deemed acceptable in early lab trials, the problem of procuring the same catalyst on a kilo scale and of reproducible quality is often a major issue, which may delay the project. The catalyst load is also of paramount concern to the process chemist, because of cost and also because of the need to remove the catalyst from the API itself. Many academic processes do not operate at high enough TON (turnover number) to be of practical utility. Developing solutions to all these problems is extremely time-consuming; given the often pressing timelines experienced in the pharmaceutical industry, it is not surprising when process chemists choose to avoid

enantioselective catalysts. One of the consequences of this complex situation seems to be that only a handful of catalytic tools have become truly accepted and practiced in the synthesis of APIs, *i.e.* those tools that have shown wide scope, are relatively well understood, and therefore have passed the relatively high activation barrier toward widespread utilization. Reductive and oxidative processes are used widely, as we will explore in the following sections. In contrast, C−C bond-forming reactions, although well established, are used rarely in industry, and many of the examples given are from academic labs. Although they are often only synthetically elegant curiosities, we have chosen to present some of them because, although their practicality remains to be proven, they may stimulate process chemists to follow in the footsteps of their academic colleagues and experiment with the new methodologies in terms of practicality, robustness, and cost. Indeed, while the processes in which these key steps are embedded may be lacking in overall practicality, the catalytic steps *per se* are often very elegant, selective, and efficient.

5.1. Dynamic Kinetic Resolution Processes

As already stated, resolution processes, *i.e.* those processes that rely on any form of separation of two enantiomers, be it by chromatography, diastereomeric salt formation, or enzymatic transformation, are not covered in this review. In certain cases, however, processes can be set up in such a way that the enantiomers of the starting material racemize more rapidly than the rate of the catalytic transformation. In such cases, full conversion of the starting material is achieved. These processes are usually elegant, but they are difficult to engineer. Scheme 64 illustrates the general

Scheme 64



situation.

The problem is even more complex than in simple enantioselective catalysis. Thus, **A** and its enantiomer (*ent*)-**A**, when treated with a reagent under the influence of a chiral catalyst, may lead, in general, to four diastereomers (labeled as **B** and **C**, each existing as two enantiomers). It is therefore necessary to set up a kinetic scheme where **A** and (*ent*)-**A** interconvert much more rapidly than any of the catalytic steps (k_3, $k_4 \gg k_1$, k_2, k_5, k_6). In addition, the kinetic rate constant for the desired step, *e.g.* k_2, must be much faster than the other three. Thus, the chemist must evaluate and balance, at least qualitatively, a complex set of rate constants. When successful, these processes are extremely elegant and often very efficient, as they selectively establish two chiral centers in one step. After these operations, both enantioselectivity and diastereoselectivity must be measured. Only those dynamic kinetic resolution schemes that start with racemates and do not employ chiral auxiliaries will be discussed.[106]

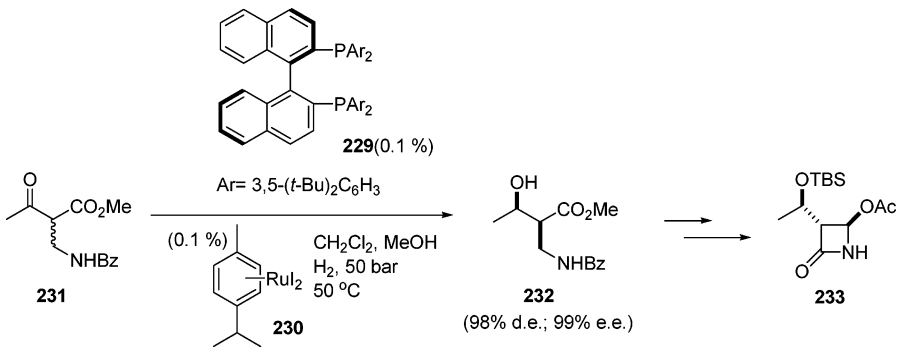
Among the several dynamic kinetic resolution schemes that have been demonstrated, very few examples have been applied to API synthesis. The enantioselective hydrogenation of ketones using a chiral Ru catalyst is a very powerful technique in organic synthesis (*vide infra*).[107] Because the reaction needs strongly basic conditions, the reduction of a ketone bearing an enolizable chiral center α to the carbonyl could be an excellent substrate for a dynamic kinetic resolution.

Indeed, Takaya (Kyoto), in collaboration with chemists at Takasago, has applied the Ru-catalyzed dynamic kinetic resolution of 1,3-dicarbonyls on a metric ton scale. This led to the preparation of important API intermediates. For example (Scheme 65), modified BINAP ligand **229**, in conjunction with a suitable Ru source (**230**), is able to reduce substrate **231** in extremely high diastereo- and enantioselectivity under synthetically useful conditions (TON up to 1000). The final product of this sequence, β-lactam **232**, is a key chiral intermediate in the synthesis of the therapeutically important class of carbapenem antibiotics.[108] Recently, modified SEGPHOS ligands which are claimed to be optimal (98.4% d.e. and 99.4% e.e) in the same transformation were reported by Saito (Takasago).[109] However, full experimental details and process conditions (for example, yields and relative catalyst load) for these processes have not been described, and it is therefore difficult to confirm their practical utility and relative performance.

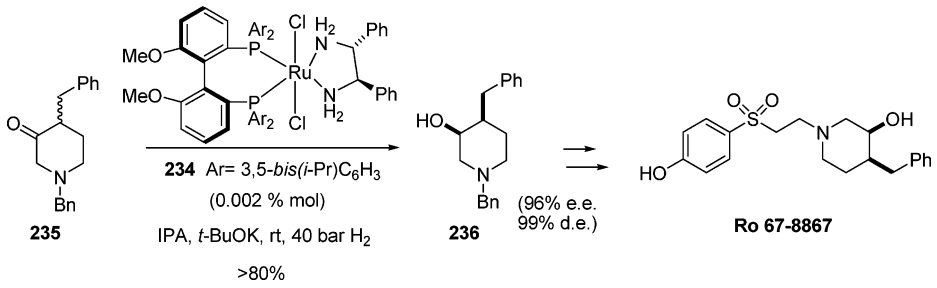
Scalone and Waldmeier (Roche) have put the same principle into practice and developed an extremely efficient process for the synthesis of NMDA receptor antagonist Ro 67-8867 (Scheme 66). Using a very small load of catalyst **234** (TON up to 200 000!), the authors were able to reduce racemate **235** to alcohol **236** in very high enantiomeric and diastereomeric excesses. [110]

Extensive catalyst screening took place, and the enantioselectivity was carefully fine-tuned with respect to the substituents on the diarylphosphino moiety of the catalyst and, to a lesser extent, the substituents on the diamine. Many bases were also screened before settling on potassium *tert*-butoxide. Finally, small amounts of water were found to exert

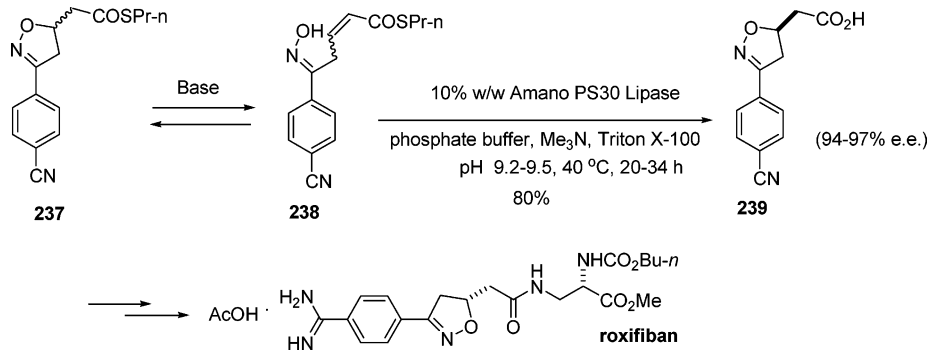
Scheme 65



Scheme 66



Scheme 67



an extremely deleterious effect on the enantioselectivity. Successful scale-up of this elegant process to ~9 kg was carried out in a kilolab. Other applications describe model studies toward dopamine D1 antagonist Sch 39166[111] and small-scale academic approaches to the chiral segment of channel blocker diltiazem[112] and the side chain of the potent anticancer agent taxotere.[113]

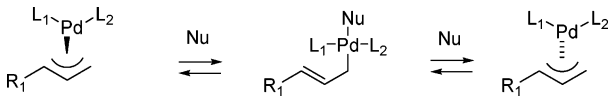
Many unnatural amino acids, some of which can be used for API synthesis, are routinely made by dynamic resolution processes. Thus, kinetic resolution of hydantoins has been achieved using amidohydrolases,[114] and resolution of *N*-acylamino acids in the presence of racemases.[115] This specialized field is outside the scope of this review. In some cases, other types of API intermediates can be obtained by enzymatic resolution, while a vicinal chiral center is being rapidly epimerized, *i.e.* under dynamic conditions. An elegant example in this class is represented by an enantioselective approach to roxifiban, a selective antagonist of the glycoprotein IIb/IIIa receptor (Scheme 67).[116]

Pesti and co-workers (BMS) devised a clever retro-Michael racemization process which turned out to be faster than the resolution step, turning the enzymatic resolution into a dynamic process, which completely converted (>99%) **237** through **238** to optically active acid **239** in high e.e.

The process was scaled to 45 kg batches and operated at a respectable concentration of ~0.2 M. The reaction times are rather long, and the authors report variability depending on scale, as well as foaming problems. In addition, evolution of malodorous propanethiol was obviously a drawback for the process.

Allyl-Pd intermediates offer unique opportunities for dynamic resolution processes. The deracemization process relies on a facile $\eta^3-\eta^1$ equilibration in allyl-Pd intermediates; if this is faster than nucleophilic attack onto the allylic carbon atoms, this can result, in special cases such as the one in Scheme 68, in the overall mobility of the Pd between the two diastereotopic faces of the allyl moiety. This, in turn, may lead to the enantioconvergent reaction of a racemic allylic electrophile to yield a single product upon nucleophilic

Scheme 68



addition. Such a desirable result will occur only if the regiochemistry can be controlled and an effective chiral environment at Pd can be provided. Such elegant processes have been successfully designed, but applications to API synthesis are rare.[117]

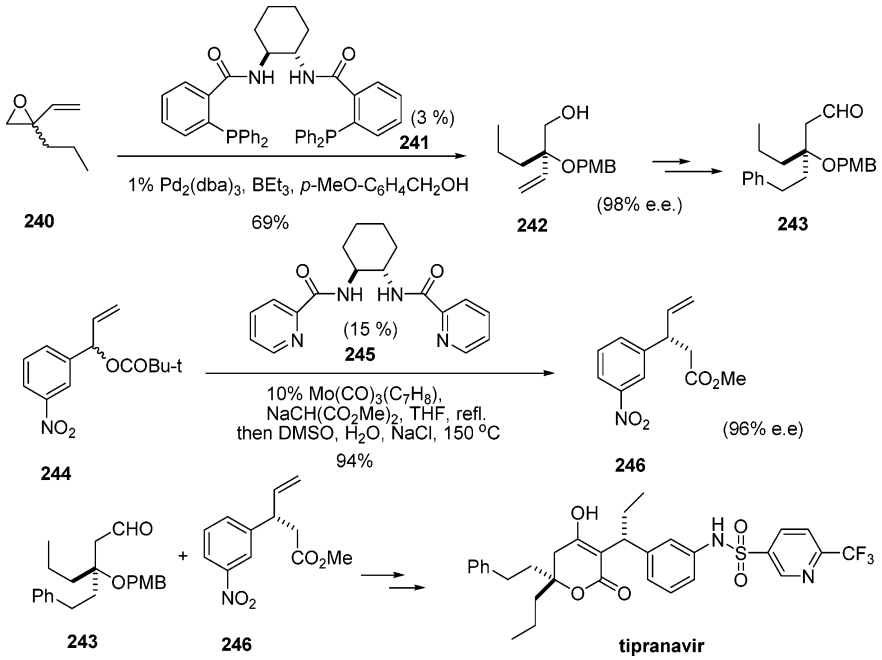
Trost *et al.* have exploited this concept in an elegant academic synthesis of the marketed HIV protease inhibitor tipranavir. Thus, racemic epoxide **240** was reacted with *p*-MeO-benzyl alcohol under the action of Pd(0), a boron cocatalyst, and chiral ligand **241**. Under these conditions, both enantiomers of the starting material were converted to **242** in fair yield, complete regioselectivity, and excellent enantioselectivity (Scheme 69).

This product was subsequently transformed, through a lengthy sequence, into synthon **243**, which constitutes part of the pyrone moiety of tipranavir. The right-hand side of the unit was also synthesized by a dynamic resolution process, this time a Mo-catalyzed asymmetric allylic alkylation,[118] also shown in Scheme 69. Thus, malonate alkylation of racemic **244** under the catalysis of Mo(0) and ligand **245** yielded, after decarboxylation, γ,δ-unsaturated ester **246** in excellent regio- and enantioselectivity. Combination of **243** and **246**, followed by further manipulations, led to tipranavir.[119] Clearly, as shown by their versatility, dynamic kinetic processes using π-allyl Pd intermediates have tremendous potential in organic synthesis, and practical applications to API synthesis are expected in the future.

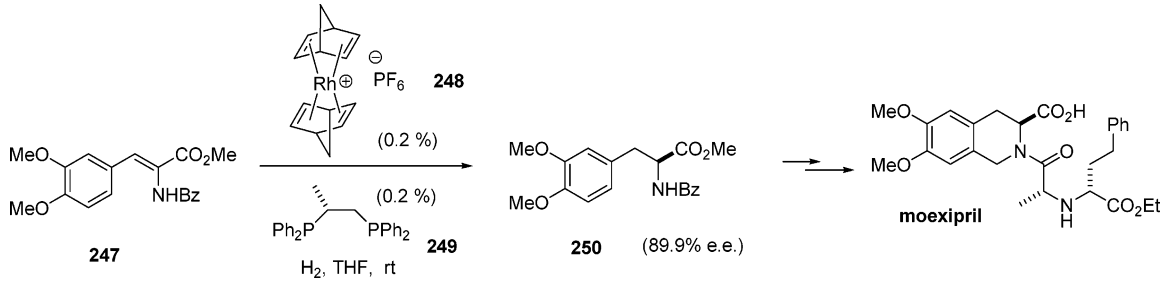
5.2. Asymmetric Hydrogenation of Alkenes

The Rh-catalyzed enantioselective hydrogenation of functionalized olefins, *e.g.* enoates, enamides, and α,β-dehydroamino acids, has been known for over 30 years. After the initial disclosures by Horner and Knowles,[120] and the

Scheme 69



Scheme 70



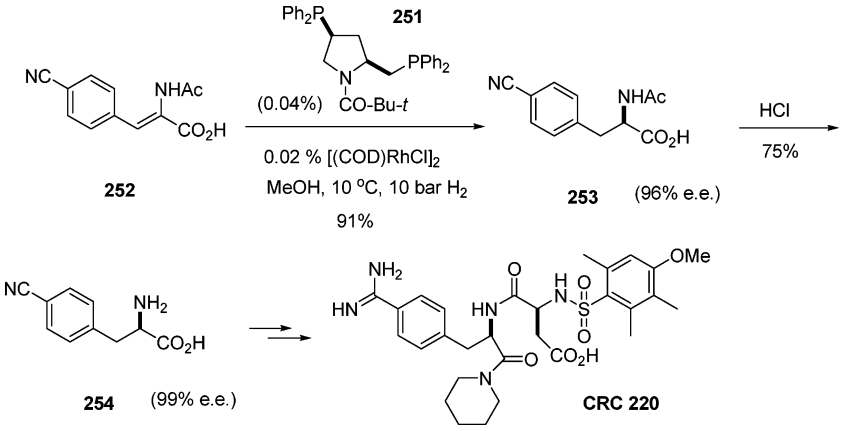
first application to the chiral syntheses of L-DOPA, Kagan steered the chirality of the system away from phosphorus to the carbon atoms contained in the chain of a bidentate ligand, such as DIOP.[121] Kagan's design has been thoroughly optimized and perfected over the last 20 years, and nowadays a rich and varied menu of chiral ligands is available for large-scale asymmetric hydrogenation of functionalized olefins.[122] It must be noted that enantioselective hydrogenation of nonfunctionalized alkenes, although precedented, remains a challenging field,[123] and it has not yet been applied to API synthesis. On the other hand, the enantioselective catalytic hydrogenation of functionalized alkenes has been quite successful industrially,[124] given the ubiquitous availability of large-scale hydrogenators, the high enantioselectivity often obtained, the vast array of useful catalysts available, and the generally good substrate/catalyst ratio employed (high turnover number, or TON). The latter is an important factor, due to the high cost of rhodium metal and the need to reduce the metal contamination in the API to a very small level (usually less than 10 ppm). An extremely attractive feature of hydrogenations is that the reactions usually do not need workup. In almost every single case, the material can be precipitated by adding an antisolvent or, after a solvent switch, it can simply be used for the next step in the synthesis.

An early application of the technique was described by O'Reilly *et al.* at Occidental.[125] Dehydroamino ester **247** was hydrogenated at ambient temperature and pressure under a variety of conditions. Design of Experiment (DOE) was used to arrive at optimum conditions with respect to solvent and substituents on the substrate. Unfortunately, only two chiral ligands were screened in conjunction with $[Nbd]_2RhPF_6$ (**248**), and (*R*)-Prophos (**249**) proved superior to (*R*)-BINAP. The enantioselectivity obtained was modest but could be boosted to 95.9−97.7% after one recrystallization (87.7% yield). The reaction was reportedly run only on a 500 mL scale, and given the rather low TON (500) and the modest enantioselectivity, it is very doubtful that it could compete with resolution processes (Scheme 70). Amido ester **250** is a key component of the marketed ACE inhibitor moexipril.[126] Its current "best" manufacturing process has not been disclosed.

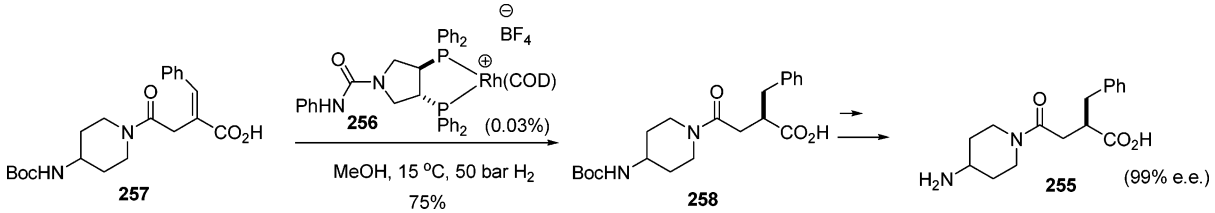
(*S,S*)-BPPM (**251**), a ligand disclosed by Achiwa in 1976, has received several applications. Its attractiveness lies both in its generally high performance (high e.e., high TON) and the fact that it is patent-free, an important feature for pharmaceutical applications. For example, Jendralla *et al.* at Höchst have applied a Rh catalyst derived from this ligand to the enantioselective hydrogenation of dehydroamido acid **252**, an intermediate en route to the potent thrombin inhibitor CRC 220. The synthesis was performed at the kilolab scale (Scheme 71). Note that the stereochemistry of **252** was presumed to be *Z*, as shown, and that the *E* isomer was not detected in the recrystallized substrate.

The reaction was run in methanol at subambient temperatures for best enantioselectivity (96% e.e.), and with a rather favorable substrate/catalyst ratio (1300). After completion and extraction, the crude **253** was hydrolyzed to **254**, and at

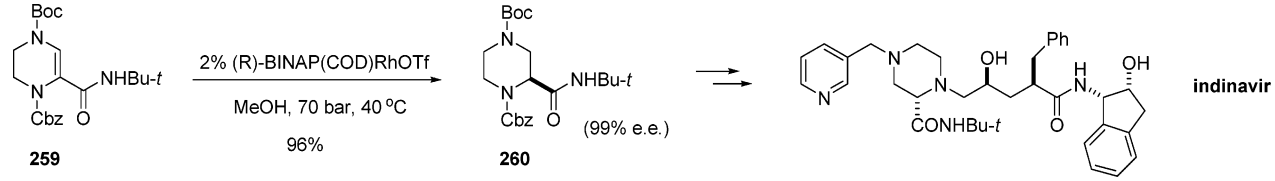
Scheme 71



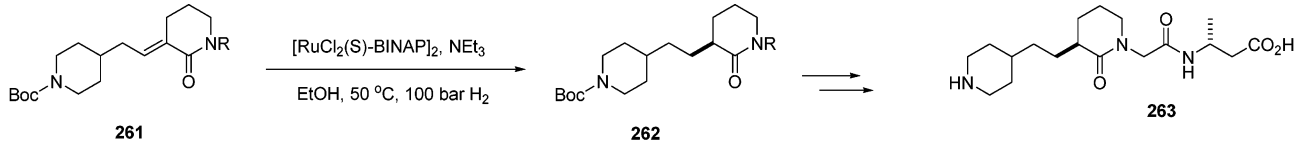
Scheme 72



Scheme 73



Scheme 74



this stage, through crystallization, the e.e. was upgraded (99%). Standard peptide chemistry was used to elaborate this intermediate to CRC 220.[127]

Another application of **251** was described, also by Jendralla *et al*., in connection with the enantioselective synthesis of renin inhibitor **255**. However, due to the length of the synthetic route to **251**, the authors prefer the use of catalyst **256**, obtained from tartaric acid. The e.e. of the crude product was not disclosed, but recrystallization and deprotection gave the API in >99% e.e. and in acceptable yield. Although the process has been scaled in a kilolab and appears efficient under all aspects, some operational features of the process (use of magnesium sulfate and diethyl and diisopropyl ethers) would have to be phased out before transfer to a pilot plant (Scheme 72).

Another report by Rossen *et al*. (Merck) describes the enantioselective preparation of the piperazine subunit of the marketed anti-HIV drug indinavir. This is illustrated in Scheme 73. The Merck group screened many traditional ligands under a variety of conditions, and surprisingly, the old (*R*)-BINAP proved the best, affording an excellent e.e., albeit with a low TON.

A follow-up paper described a slight variant which used even more catalyst (7 mol %).[128] The experimental procedure given is on a milligram scale, and the actual preparative details (which include evaporation to dryness), in addition to the impractically high catalyst load (low TON), suggest that a lot of development would have to be carried out to translate this procedure into scalable chemistry. In addition, Pye *et al*. (Merck) report designing a new ligand ([2.2]-PHANEPHOS) for this hydrogenation, presumably for proprietary reasons. The ligand performs fairly well in conjunction with a Rh(I) source, delivering the target in 86% e.e.[129]

In another early application, in which scale and TON were not discussed, Chung *et al*. at Merck disclosed the Ru-catalyzed enantioselective hydrogenation of unsaturated amide **261** (usually 90:10 *E*/*Z*) to **262** with varying enantioselectivity. Further standard manipulation yielded **263**, an antithrombotic agent. It was found that the enantioselectivity depended strongly on the substituent on the lactam nitrogen (Scheme 74, Table 9).[130] With acetamide side chains, the best e.e. was obtained (entries 4 and 5). When chiral side chains were introduced, the selectivity increased, although strictly speaking, this is no longer enantioselective but diastereoselective catalysis. A recent improvement within this field was reported, using similar but simpler substrates, by Yue and Nugent at BMS.[131] Their catalyst of choice was

Table 9. Effect of Substituents on the e.e. for the Hydrogenation of 261

entry	R	e.e. (%)
1	H	57
2	CH_2CO_2H	52
3	CH_2CO_2Et	76
4	CH_2CONMe_2	81
5	(*R*)-$CH_2CONHCH(Me)CH_2CO_2t$-Bu	92

$[(COD)_2Ir](BDPP)BF_4$, and the e.e.'s exceeded 90%.

A rather common theme in API development is the switch from a racemic mixture to a single enantiomer. In the case of warfarin (Scheme 75), the racemate is the most commonly prescribed oral anticoagulant in the U.S., and both enantiomers are potent inhibitors of vitamin K epoxide reductase. Yet, the *S* enantiomer has undesirable metabolic properties and an enantioselective approach to the *R* enantiomer would be useful. Li and colleagues at DuPont Merck found that racemic warfarin can be readily oxidized using air and a Cu catalyst, to yield dehydrowarfarin as a single double bond isomer in excellent yield. Although enantioselective hydrogenation of enones is not as well precedented as that of enoates, it was possible to hydrogenate **264** to (*R*)-warfarin in 88% e.e., which could be upgraded to 98% after recrystallization of the Na salt. [132]

The scale of the transformation is not discussed. Clearly, to make this procedure practical, much more development work would have to be carried out.

Scalone *et al*. (Roche) applied the Rh-catalyzed hydrogenation, using ferrocenyl ligands such as **265**, to the production of a key intermediate en route to the antihypertensive drug mibefradil. The key step is shown in Scheme 76.

Although the method gave excellent enantioselectivity, the decision was made to opt for a cheaper and simpler alternative, even if less enantioselective. In fact, recrystallization of the Na salt of **267** was effective at increasing the e.e. This highlights the important fact that sometimes a slightly better enantioselectivity is offset by the fact that the ligand is not accessible on large scale and/or is covered by patents. Eventually, the reaction that was developed used a Ru(II) catalyst and utilized a more inexpensive ligand (MeOBIBHEP, **268**). In this case (Scheme 77), it was found that a semistoichiometric amount (0.3−0.6 equiv) of triethylamine improved the enantioselectivity, and the process was carried out at the kilolab scale.[133]

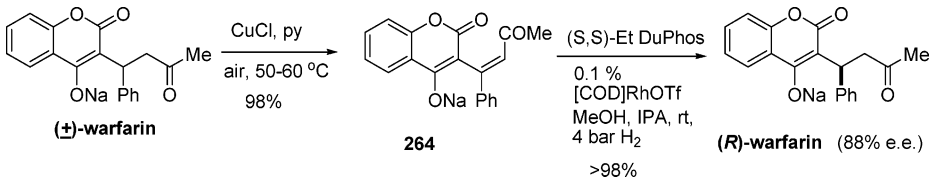
With minimal changes in the conditions, the process was scaled up in an isothermal continuous stirred tank reactor (CSTR), where both rates and enantioselectivity could be improved by simply increasing the pressure to 270 bar. In this way, two 1.5 L autoclaves yielded a productivity of 38.8 kg/week.[134]

To develop the endopeptidase C inhibitor candoxatril, Challenger *et al*. at Pfizer devised a highly enantioselective catalytic hydrogenation of intermediate enoate **269**. The reaction was executed only on a gram scale, but it appears practical, given the use of a rather inexpensive catalyst, and achieves reasonable TONs (Scheme 78).[135] On the other hand, a double bond isomerization in **269** limits the overall yield to 75%.

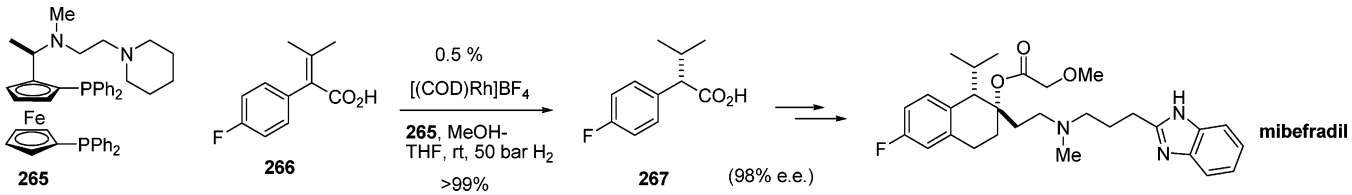
A marked improvement over this procedure was described by Burk *et al*. at Chirotech, who carried out the hydrogenation on the Na salt of **269** using the Rh(I) (*R,R*) Me-DuPHOS catalyst. The substrate/catalyst ratio was 3500:1 and the reaction operated in MeOH at ambient temperature under only 5 bar of hydrogen pressure. There was none of the undesired olefin isomerization. The e.e. (>99%) and isolated yield (97%), coupled with the ready availability of this catalyst on multi-kilogram scale, made this process extremely attractive for commercialization. In fact, the protocol was scaled to 12.2 kg batches in 200 L equipment and performed flawlessly.[136]

It is interesting to note that a chemically *inferior process* was selected for the ton scale production of the Phase III lots of candoxatril.[2] In fact, Bulliard *et al*. at PPG-SIPSY describe the optimized ton scale hydrogenation of **271** to **272** (Scheme 79).[137] The proportion of isomerization product **273** was kept at about 8% by selecting the best solvent combination (THF/water), and the process to the precatalyst

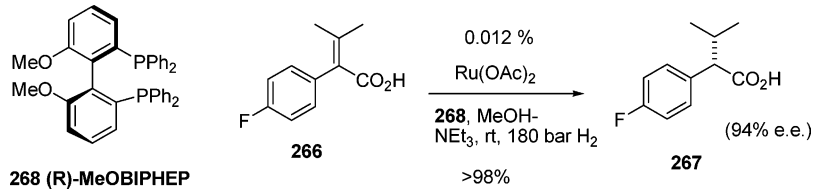
Scheme 75



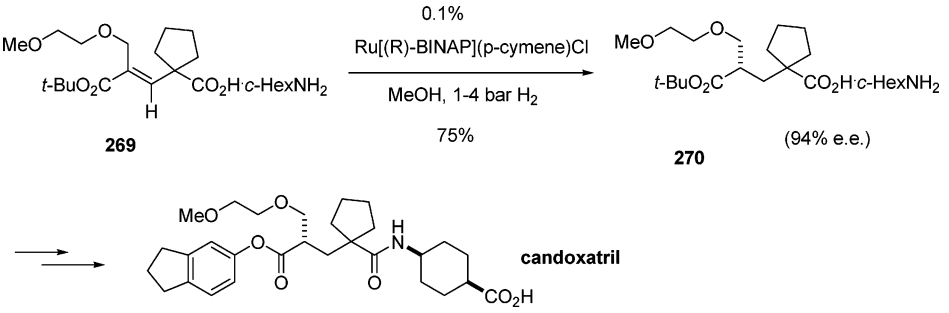
Scheme 76



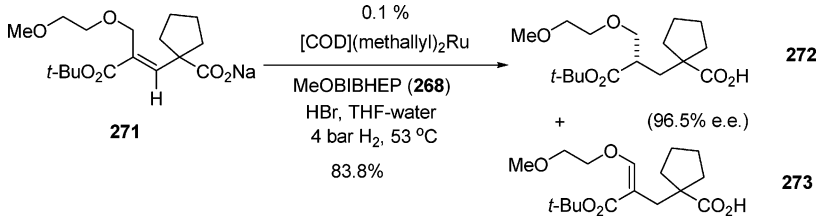
Scheme 77



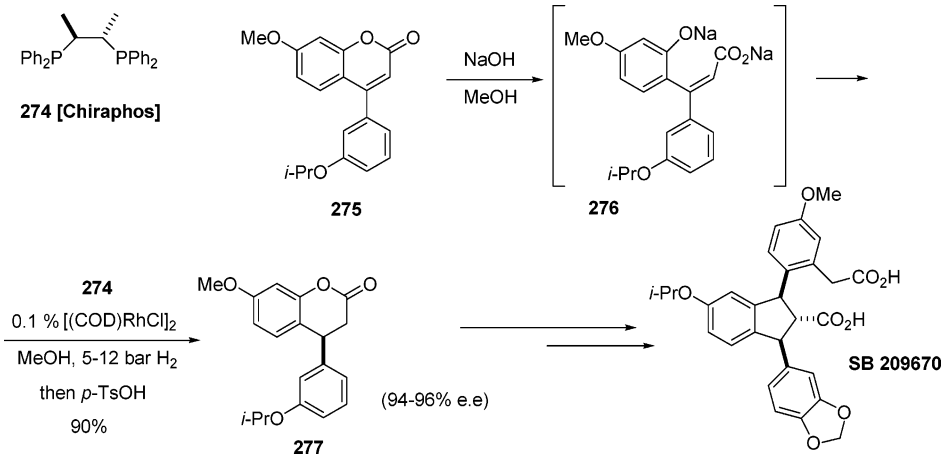
Scheme 78



Scheme 79



Scheme 80



was scaled up for the first time to produce multi-kilogram amounts. With a cheaper ligand, which was also unencumbered by royalty issues, this "inferior process" was apparently financially superior to the one described by Burk, which gave no isomerization and essentially a quantitative yield of enantiopure (>99% e.e.) product.

Note that in the PPG process the e.e., although quite good already in the crude product (96.5%), necessitated an upgrade (99.6% after recrystallization of the cyclohexylamine salt from isopropyl acetate), which reduced the overall yield to ~70% (on 591 kg scale, three batches run in a 4000 L stainless steel hydrogenator). This example illustrates the fact that, in choosing a production-scale process, freedom-to-operate issues can override pure chemical issues in the overall financial equation.

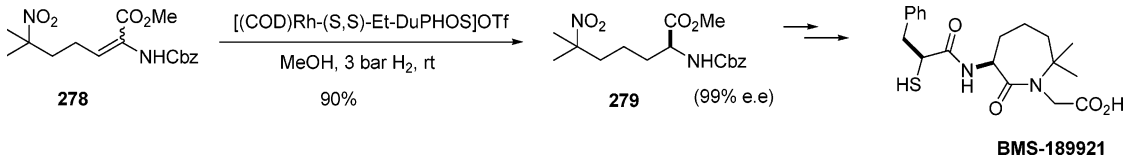
Enantioselective hydrogenation of coumarins is difficult because of the rigidity of the system and the inability of the carbonyl oxygen to properly coordinate the metal in the reactive complex. McGuire *et al*. from SKB found an ingenious way around this problem and were able to apply a Rh−Chiraphos (**274**) catalyst to the preparation of a series of endothelin antagonists such as SB 209670 (Scheme 80).

Thus, *in situ* hydrolysis of coumarin **275** yielded an enoate (**276**), which underwent effective catalytic hydrogenation in the presence of a number of classical ligands. In this case, Chiraphos was superior to the more established BINAP and DuPHOS ligands, which did not even reach 80%. After the hydrogenation, acid treatment regenerated the lactone (**277**). Further transformations led to inhibitor SB 209670. The synthesis was only scaled to ~500 g, but it appears practical and high-yielding.[138]

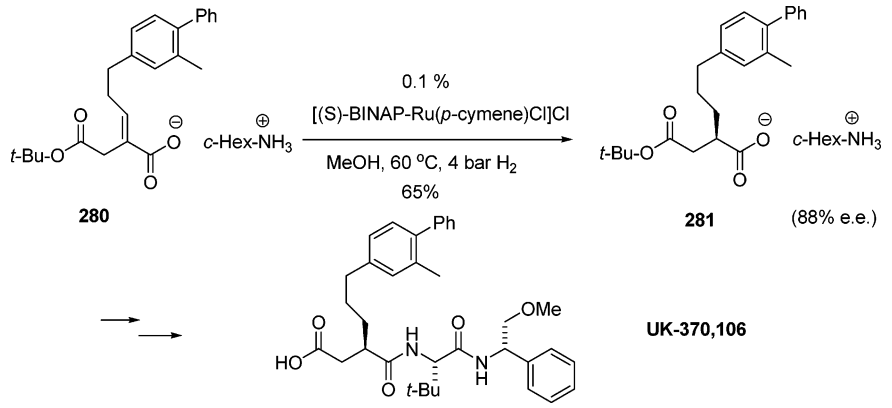
Singh *et al*. at BMS evaluated the scale-up of an enantioselective hydrogenation in relation to the synthesis of BMS-189921, a potent vasopeptidase inhibitor. The key step is shown in Scheme 81.

Although enantioselective hydrogenation of the *E*/*Z* mixture **278** gave, as expected, excellent e.e. (99%) of **279**, the process was not scaled up: instead, it was abandoned for an alternative scheme involving classical dynamic resolution. It was found that the DuPHOS−Rh catalyst was sensitive to small amounts of impurities present in the substrate, and TONs could not be reproduced on scale-up.[139] This highlights an important drawback of catalytic processes: much work is needed to make them robust, and it can be difficult to reproduce the impurity profile of the intermediates undergoing the catalytic step without resorting to chromatography. Often, impurities down to 0.1% w/w or less have to be controlled when an efficient catalytic process (*i.e.* TONs > 1000) is desired. This is often achieved by having a highly crystalline intermediate as substrate in the catalytic step.

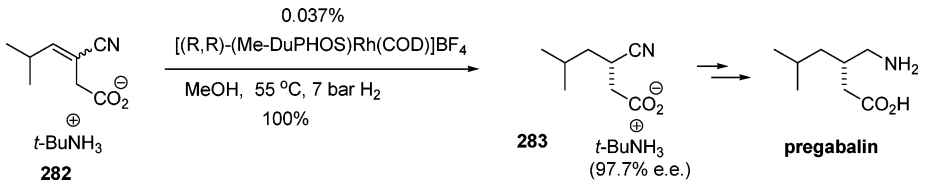
Scheme 81



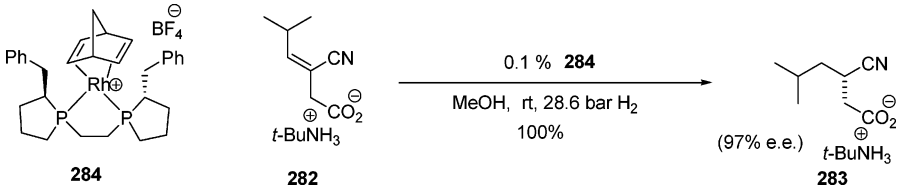
Scheme 82



Scheme 83



Scheme 84



Thomson *et al*. (Pfizer) recently disclosed another application of the enantioselective Rh-catalyzed hydrogenation to the synthesis of the chiral succinate moiety of metalloprotease inhibitor UK-370,106. The key reaction is illustrated in Scheme 82. Of the many catalysts screened, Ru−BINAP gave inferior results with respect to Rh[(*S*,*S*)-Et-DuPHOS] and other newer catalysts in terms of enantioselectivity, but once again the more inexpensive ligand was used, because a single crystallization upgraded the e.e. of the product to the desired level (≥98%).[140]

The asymmetric synthesis of pregabalin, a marketed anticonvulsant, is illustrated in Scheme 83. It involves the Rh-catalyzed hydrogenation of an α,β-unsaturated nitrile (3.5:1 *E*/*Z* mixture, **282**), a synthetic transformation with little precedent. Burk and colleagues (Chirotech/Dowpharma) were able once again to apply their DuPHOS−Rh catalyst manifold to obtain excellent yield and selectivity of key intermediate **283**.[141]

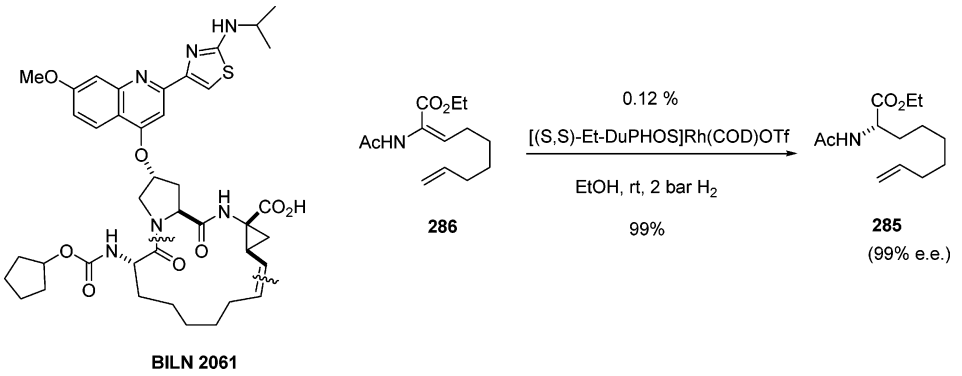
Of the salts screened, the *tert*-butylammonium salt yielded the best results, although the Na salt also worked well, and the selection was made on the basis of easier operability. One must note that the ethyl ester from which **282** was obtained (by hydrolysis) underwent sluggish hydrogenation and yielded low e.e. under conditions similar to those in Scheme 83. The procedure is described on a 125 g scale and is straighforward to execute. A multi-kilogram campaign is also mentioned.

A modification of this procedure was reported by Hoge at Pfizer (Scheme 84). Hoge devised a new enantioselective catalyst (**284**), featuring a variant on the bis-phospholanoethane theme. The catalyst is of general utility, but in this particular case, high enantioselectivity is only obtained at higher hydrogen pressures. In addition, the higher the catalyst load, the higher the e.e. Thus, at 2 bar pressure, 1 mol % catalyst leads to 92% e.e., but 0.1 mol % only leads to 47% e.e. However, use of 28−29 bar of pressure (0.1 mol % catalyst) raises the e.e. to 97%, and no further improvements were realized at higher pressures.

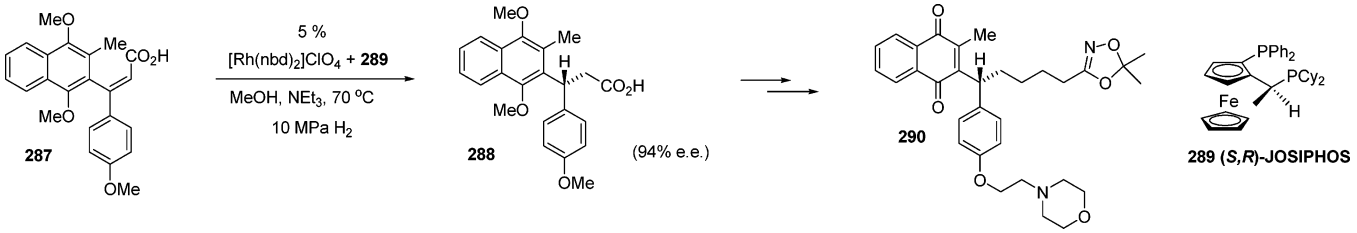
This behavior illustrates the difficulties in optimizing catalytic reactions in general and points to mechanistic subtleties that remain unclear. The author hypothesizes that "increase in pressure (400 psi or greater) are capable of preventing the catalytically active species leading to low enantiomeric excess from forming, or, if they have formed during the course of the reaction, the increases in pressure prevent them from catalytically converting substrate to product".[142]

As recently described by Faucher *et al*. at Boehringer-Ingelheim, one of the building blocks for a new prototype of HCV protease inhibitor, BILN 2061, is ethyl (*S*)-

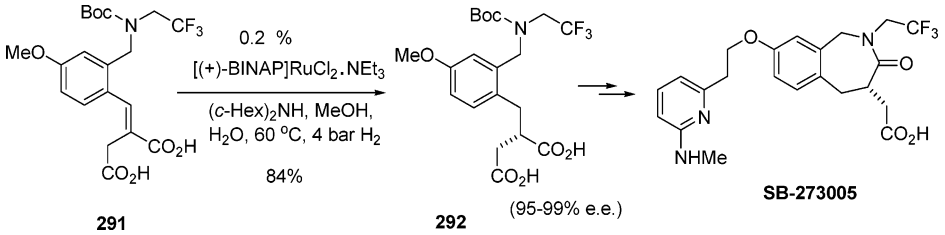
Scheme 85



Scheme 86



Scheme 87



acetamido-8-nonenoate (**285**). This was obtained (Scheme 85) by chemo- and enantioselective hydrogenation of the corresponding dehydroamino acid ester **286** with the (*S*,*S*)-Et-DuPHOS−Rh ligand in essentially complete enantioselectivity.

This enantiomerically pure amino acid was then attached to a P1−P2 construct and the ring closed by a RCM reaction.[143] The chemistry was employed in the discovery route, and further scale-up has not yet been described.

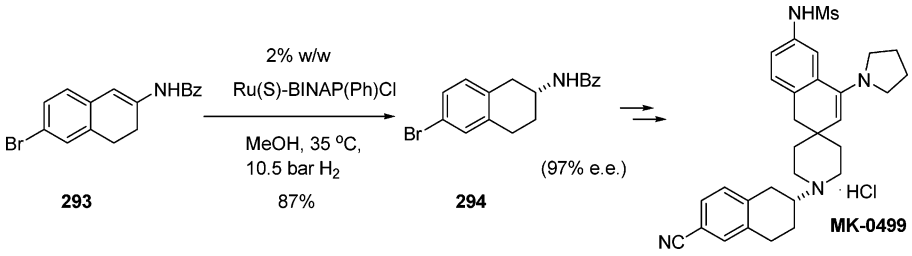
Another example of the enantioselective hydrogenation applied to a challenging and sterically hindered substrate was described recently by Nagata and co-workers at Takeda. Thus, enoate **287** was hydrogenated to **288** under a variety of conditions, all of them in the presence of a base, to form *in situ* the corresponding salt, a better substrate for this type of asymmetric transformation. Of the 10 well-established ligands screened, only (*S*,*R*)-JOSIPHOS (**289**) gave acceptable enentioselectivity (>90% e.e), as shown in Scheme 86. The e.e. was upgraded through the brucine salt. This procedure has not been scaled; although preliminary (the high catalyst load and the following resolution are impractical), it represents a promising approach to a class of anti-neurodegenerative drugs exemplified by compound **290**. [144]

Another example of an enantioselective hydrogenation on an itaconate derivative was recently described by Wallace *et al*. at GSK. Thus, six catalysts were screened in the enantioselective hydrogenation of **291** (Scheme 87), and two catalysts gave acceptable results: the classical Ru−BINAP system and the ubiquitous (*S*,*S*)-Et-DuPHOS−Rh catalyst. Although the latter gave better e.e., the former was selected for optimization due to lower cost and the ability to prepare the catalyst in house.

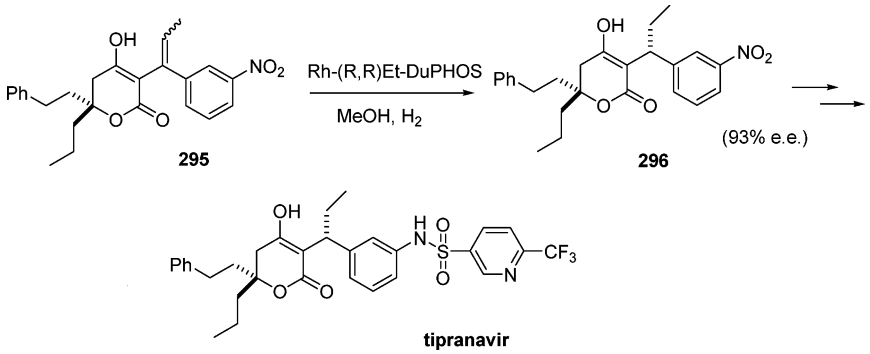
In fact, the initial 84.2% e.e. obtained with the Ru catalyst was improved by optimizing for solvent and base (dicyclohexylamine), which provided a crystalline compound (DCA salt of **292**) in >99% e.e. after crystallization. The e.e. of the crude product was also rather good (94%). The procedure ran smoothly on >100 kg batches. Although the reaction time was inconveniently long (30 h), the purification by direct isolation was rather simple, and partial solvent replacement with MeCN gave crystalline material without any workup. Further standard chemistry led to the manufacturing of vitronectin receptor antagonist SB-273005. Rather uncharacteristically, the paper discloses the cost of the API ($2,100/kg), which gives the reader some reference point about the types/costs of chiral technologies one can afford to use in the synthesis of an average chiral API.[145]

So far, all substrates described were alkenes conjugated with carbonyl or nitrile groups. There are few examples in API synthesis where the substrate is of a different structural type. Prochiral enamides can also be hydrogenated in high e.e. using BINAP−Ru catalysts, and an example is shown in Scheme 88. Enamide **293** was hydrogenated to **294** in 97% e.e., which was upgraded to 99% by one recrystallization. The product crystallized simply on concentration of the MeOH solution. Although the reaction is described only on 20 g scale, it could probably be scaled up without major procedural changes. Tschaen *et al*. (Merck) used this approach to prepare the potent K channel blocker MK-0499.[146]

Scheme 88



Scheme 89



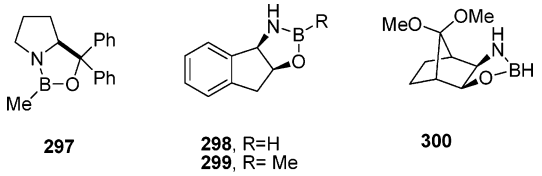
Another example where the DuPHOS class of Rh hydrogenation catalysts has been used is provided by the marketed HIV protease inhibitor tipranavir. The hydrogenation of **295** (*E*/*Z* mixture), in which the alkene is not conjugated with a carbonyl, *i.e.* the substrate is a β,γ-enoate, and where the pre-existing chiral center has no effect on the induction of stereochemistry at the newly formed chiral center, is a uniquely challenging case, which is described only in the patent literature. Although the detailed conditions are not given, we describe briefly the process, because it is rather unique and it proceeds with good enantioselectivity (Scheme 89).[147] Another hydrogenation followed by acylation yields tipranavir.

5.3. Asymmetric Reduction of Carbonyl Groups and Imines

Hydroboration of the carbonyl group, which after B−O bond hydrolysis results in an overall reduction, can be rendered enantioselective under the catalysis of 1,3,2-oxazaborolidines. This reaction, originally described by Corey, Bakshi, and Shibata, is commonly referred to as the CBS reduction.[86] It has been applied often to API synthesis, even on very large scale. The stoichiometric reducing agent is usually the THF or DMS complex of BH_3. One must appreciate that these reagents are associated with serious storage and handling hazards.[148] Borane−amine complexes are generally safer and have been used in a few cases, if their reactivity is sufficient for the reaction under consideration. Both from a safety and from an efficiency standpoint (the TON of these systems is low), the CBS reduction is not as convenient to run as methods based on molecular hydrogen or transfer hydrogenation (*vide infra*). However, their versatility and often high enantioselectivity has made them the object of intense application in the API arena.

A note must be made regarding the protocol to be followed for these reductions: because the mechanism of these reactions is rather complex, experimental parameters such as solvent, concentration, catalyst, and also mode of addition must be carefully optimized, as demonstrated in the examples we are about to describe.[149] Among the many oxazaborolidine catalysts used in synthesis, those in Scheme 90 will be discussed in conjunction with processes to prepare APIs.

Scheme 90



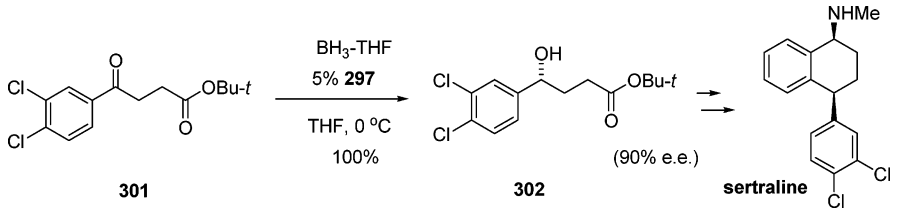
An early application of the CBS reaction was described by Quallich *et al*. (Pfizer). Reduction of ketone **301** using catalyst **297** occurred with an acceptable e.e. at a reasonable substrate/catalyst ratio. A lengthy series of transformations then led to sertraline, a serotonin uptake inhibitor. The reaction is described only on a 3 g scale, and the route appears to have limited practical potential (Scheme 91).[150]

Another early application of this technology was described by Jones *et al*. (Merck). CBS reduction of prochiral ketone **303** (Scheme 92) was studied in much detail, and it was discovered that early preparations of **297** were not pure enough. The presence of other catalytic boron-containing species caused erratic e.e. values. In addition, small amounts of water caused large drops in enantioselectivity. After a tremendous amount of optimization work, the e.e. reached 95%. Scale-up to a pilot plant is not described, and only a 100 g procedure is given. This reduction resulted in a practical approach to carbonic anhydrase inhibitor MK-0417.[151]

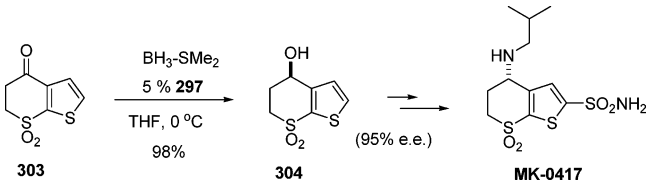
Gao and co-workers (Sepracor) described an enantioselective synthesis of the well-known bronchodilator (*S*)-albuterol. Thus, ester ketoamide **305** was exhaustively reduced to (*S*)-albuterol (Scheme 93), using 10−20% of catalyst **297** and an excess of borane−DMS complex.

Separate but simultaneous addition of substrate and reagent to a toluene solution of the catalyst was found important in order to achieve the best e.e. (93−95%). This reaction has been described only on a 50 mL scale, and its practicality cannot be properly judged.[152]

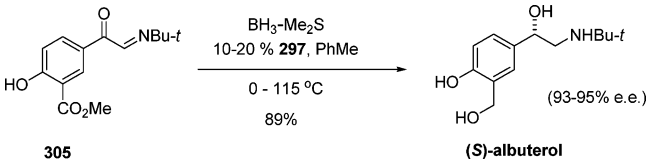
Scheme 91



Scheme 92



Scheme 93



Larsen and co-workers (Merck) described a very similar application to a new class of LTD_4 receptor antagonists. The conditions used were standard (Scheme 94), but the workup was rather volume inefficient and complex, due to the use of THF as reaction solvent.

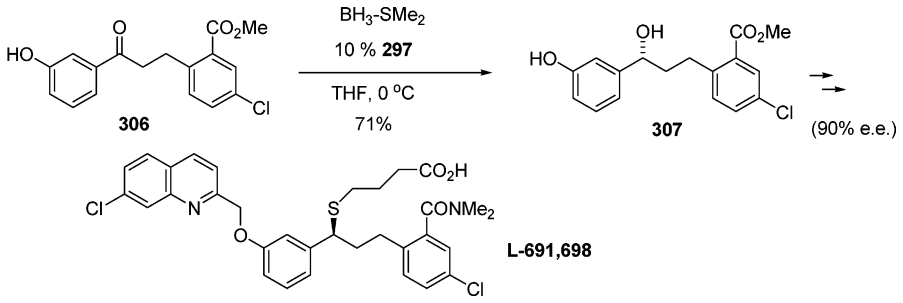
The reaction was described only on a 20 g scale, and it is likely that substantial redevelopment would be needed for scale-up in a pilot plant. The modest e.e. could be increased after crystallizing out a solid conglomerate containing a 2:1 *S*/*R* enantiomeric mixture. Further crystallization of the mother liquors gave **307** in >98% e.e., and subsequent transformations yielded L-691,698.[153]

Scheme 95 describes an application of catalyst **297** to the reduction of aryl chloroketone **308** en route to the preparation of the antiarrhythmic agent (*D*)-sotalol. The synthesis, designed by Vemishetti *et al*. (BMS), does not appear to have been scaled up, and given that the whole process includes a chromatography, it is unlikely that the process has practical applicability. Further development would certainly be needed before transfer to a manufacturing plant.[154]

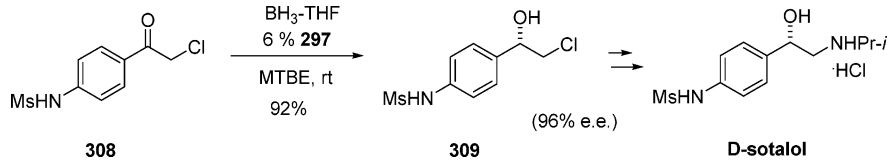
The more novel catalysts **298** and **299** are featured in an enantioselective approach to the bronchodilator (*R,R*)-formoterol, as described by Hett and co-workers (Sepracor). Although both catalysts worked well, **298** was more practical because its operating temperature is room temperature. The e.e. was quite good, and further transformations led to an enantiomeric upgrade. The process is described on a 100 g scale only (Scheme 96).[155]

For the large-scale process, the Sepracor group selected diethylaniline−borane as a safer reducing agent. Its enantioselectivity was only slightly lower (90% e.e.), and it was safely handled as a neat liquid, therefore overcoming the chronic problem of the instability of the borane THF solutions. A multi-kilogram reduction of **310** to **311** (in 50 L vessels) is described, and the paper is important also because of its practical considerations regarding the use of the various borane reagents.[156]

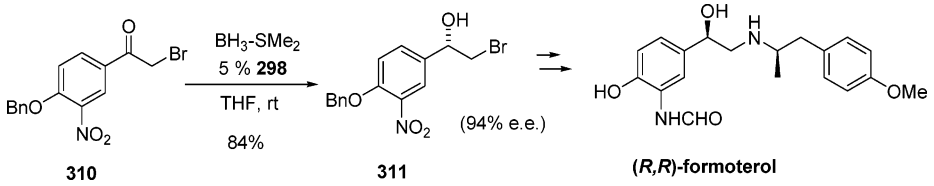
Scheme 94



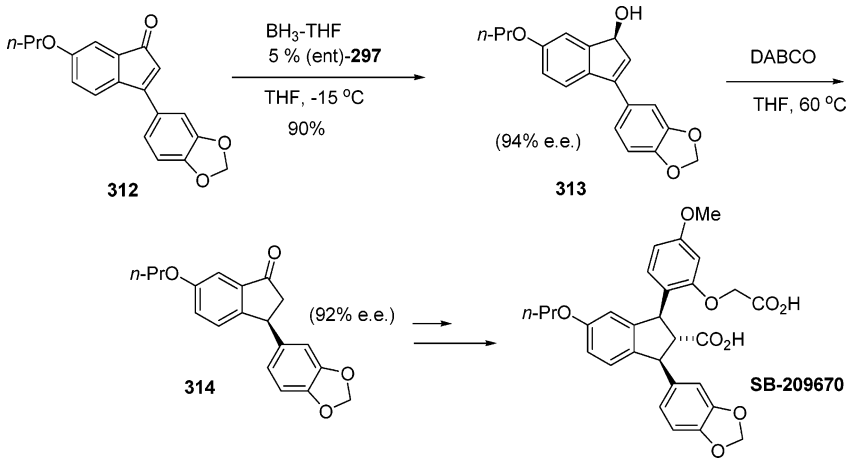
Scheme 95



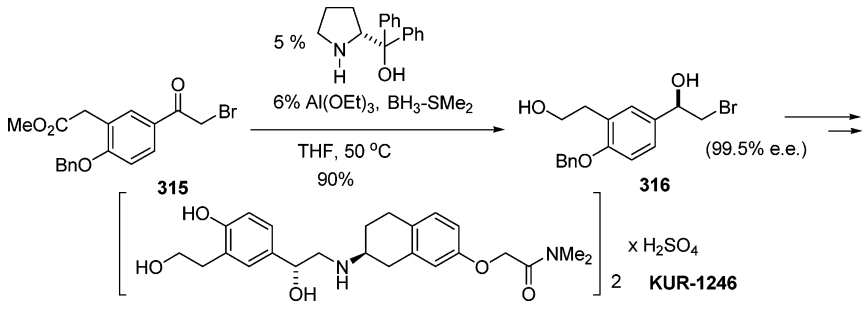
Scheme 96



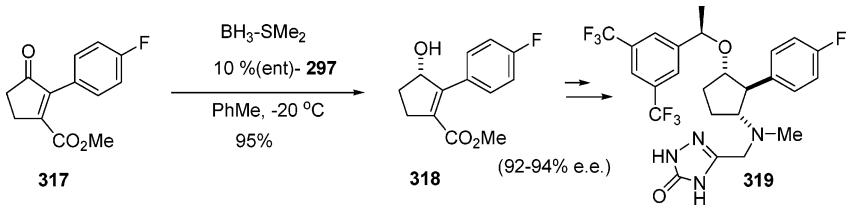
Scheme 97



Scheme 98



Scheme 99



A very interesting application of the CBS reduction to enone **312** followed by a 1,3-hydride shift results in a formal enantioselective conjugate reduction of the enone. Thus, Clark and co-workers (SmithKline Beecham) describe the highly enantioselective reduction of **312** to **313**, followed by DABCO-promoted hydride shift to yield enantiopure **314**. The base-promoted shift was almost totally stereospecific. Further manipulations led to endothelin receptor antagonist SB-209670 and analogues (Scheme 97) in high e.e. (>99.9%), after upgrade by crystallization of a later intermediate. It is not clear whether this synthesis would be suitable as a basis for a manufacturing process, because no information regarding scale was given.[157]

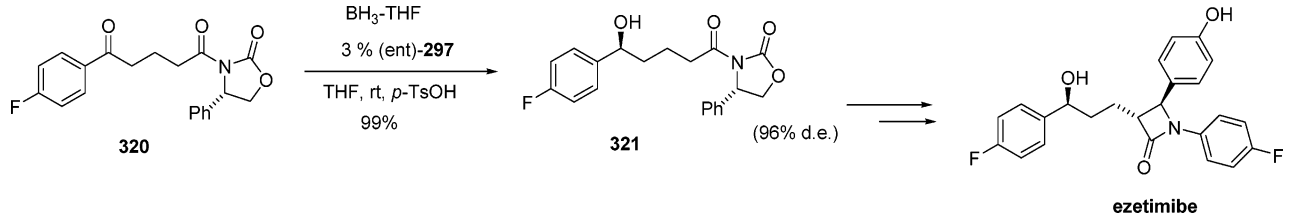
A very highly selective example of the CBS reduction applied to β-adrenoceptor agonist KUR-1246 was described by Yanagi *et al*. (Kissei), as shown in Scheme 98. Thus, bromoketone **315** was reduced in almost complete enantioselectivity to **316**, a precursor to the API. In this case, (*R*)-α,α-diphenyl-2-pyrrolidinemethanol was used as the catalyst, generating, with $Al(OEt)_3$, the active species *in situ*; lower catalyst loads gave decreased enantioselectivity.

The synthesis of KUR-1246 was described on a 1 g scale only. The use of excess borane−DMS allows for the simultaneous reduction of the carbonyl and carboxylate groups.[158] More recently, Kuethe *et al*. (Merck) described the enantioselective reduction of a similar enone, en route to a stereochemically complex neurokinin-1 antagonist (Scheme 99). Under standard conditions, enone **317** was hydroborated in good enantioselectivity, and further transformation led to the target compound (**319**). The authors comment that the borane/dimethylamine complex was unreactive with **317**, and borane/THF gave inferior results in terms of e.e. Unfortunately, the study is described only on a laboratory scale.[159]

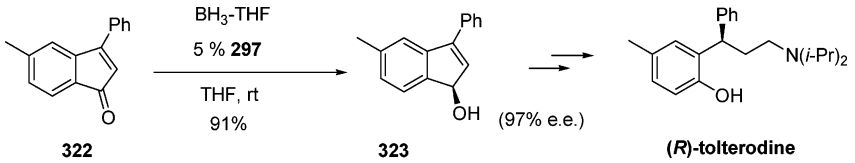
Recently, Fu *et al*. (Schering-Plough) reported a reagent-driven diastereoselective reduction of ketoamide **320** en route to the cholesterol absorption inhibitor ezetimibe. In this case, the pre-existing chiral center has no effect on the carbonyl being reduced, and the reaction can basically be considered enantioselective. Reduction of the imide was also a side reaction, at least under the initial conditions, but this was subsequently minimized by thorough optimization.

Whereas the reaction could be optimized to a satisfactory extent and presumably also scaled, the enantioselectivity was highly dependent on small experimental fluctuations, such as traces of moisture and of impurities contained in some lots of borane−THF. After much experimentation, the authors were able to obtain **321** in excellent yield and e.e. However, this example once again illustrates the optimization of reaction variables that is often necessary in order to be

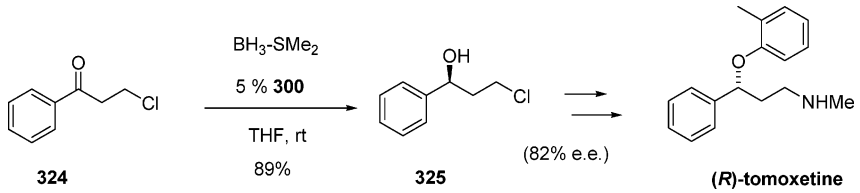
Scheme 100



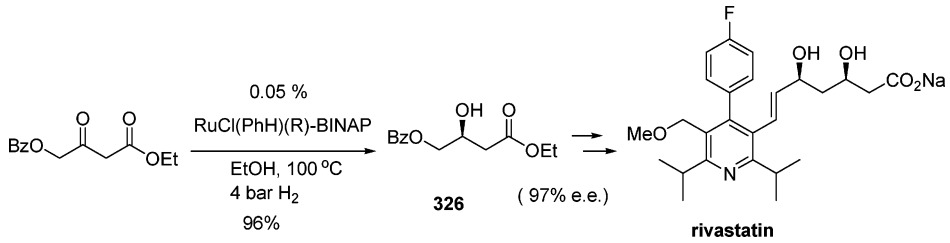
Scheme 101



Scheme 102



Scheme 103



able to scale CBS reductions with good reproducibility (Scheme 100).[160]

A catalytic asymmetric synthesis of the muscarinic receptor antagonist (*R*)-tolterodine was recently reported by Andersson *et al*. (Uppsala University), albeit on a milligram scale (Scheme 101).[161] The key step was a CBS reduction of enone **322**. Simple transformations smoothly led to the API in about 99% e.e.

An academic enantioselective synthesis of the antidepressant (*R*)-tomoxetine by Pilli and co-workers (UNICAMP) illustrates the use of novel oxazaborolidine catalyst **300**, which, however, performs only fairly (82% e.e.). One extra recrystallization affords the alcohol **325** in excellent enantiopurity (>99%), as shown in Scheme 102.[162]

In contrast to the complications associated with the CBS hydroboration (reduction) of carbonyls, hydrogenation offers a simpler solution to the problem of carbonyl enantioselective reduction. Whereas early examples required rather vigorous conditions (high pressure and temperature), more modern catalysts, *e.g.* those described by Noyori, afford products in high e.e. under conditions which are not problematic in most modern pharmaceutical or fine chemical plants, and in addition, TONs are orders of magnitude better than those in the CBS reaction.

The advent of phase-transfer hydrogenation catalyzed by Ru complexes has further simplified operations and has also broadened the range of useful substrates.[163] Yet, enantioselective hydrogenation techniques for ketones are still employed less frequently than their hydroboration counterparts for the synthesis of APIs.

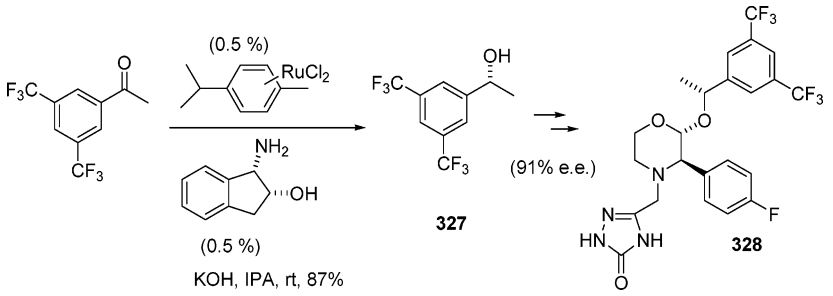
Early examples involve the classical application of BINAP−Ru catalysts to the reduction of β-keto esters. An example of this effective technique, by Beck *et al*. (Höchst), is shown in Scheme 103. Thus, **326** could be obtained in high yield and enantioselectivity on a >10 kg scale. This building block can be used to synthesize many members of the blockbuster class of cholesterol-lowering agents, exemplified by rivastatin. The TON reached a practical level (2000), and the product was easily isolated.[164]

It is instructive to compare the CBS reduction vs the H-transfer hydrogenation in the context of the pilot plant synthesis of **327**, a key intermediate in the synthesis of neurokinin receptor antagonist **328**. As described by Brands and co-workers (Merck), the process group evaluated both a classical CBS reduction and a Noyori-style Meerwein−Ponndorf reaction. Although the two approaches yielded similar e.e. (93% vs 91%), eventually the H-transfer reduction was chosen, presumably due to its operational simplicity (Scheme 104).[165]

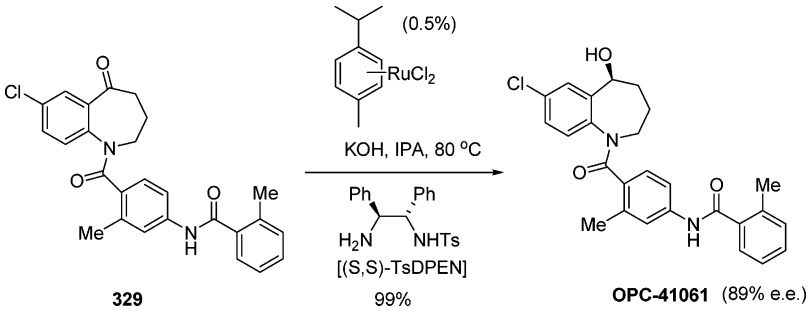
The scale-up of the process to prepare **327** is described in a separate paper by Hansen and co-workers. Interestingly, although a series of patented monotosyl diamines proved to be the best ligands in term of enantioselectivity, the Merck group settled on *cis*-1-amino-2-indanol, because it was patent-free and amply available in house from other programs. This illustrates another example of the tendency to avoid patented reagents, even when this means a slight drop in catalytic performance.

The synthesis was smoothly scaled to 40 kg batches, and the execution appears quite simple, with the exception of

Scheme 104



Scheme 105



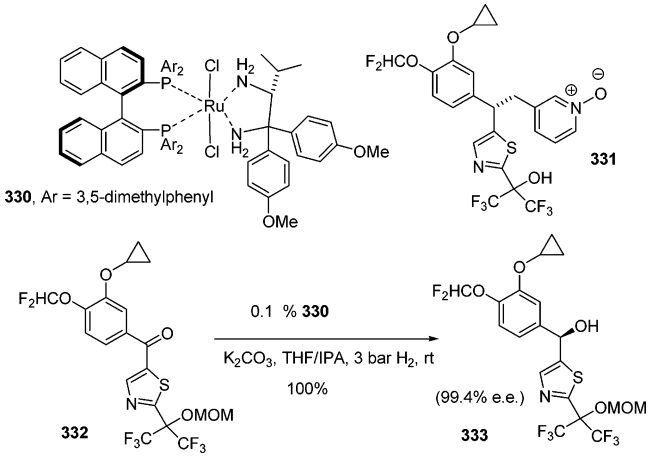
the problems encountered in the isolation of noncrystalline alcohol **327**. This was eventually purified through a very clever technique, *i.e.* by creating a highly crystalline DABCO inclusion complex of fixed composition.[166]

A very challenging example appears to be constituted by the enantioselective reduction of the ketone **329** to yield the vasopressin receptor antagonist OPC-41061 (Scheme 105). Thus, Yamashita *et al*. (Otsuka) screened a number of well-established synthetic methods. For example, the well-established reagent (−)-diisopinocampheylchloroborane yields the API in only 71% e.e. Use of (ent)-**297** under typical CBS reduction conditions likewise leads to only 73% e.e.

Finally, use of hydrogen-transfer conditions using Ru(II) and Noyori's Ts-DPEN ligand yielded the API in higher e.e. (89%). Unfortunately, because this was the last step of the synthesis and the enantiomeric purity was not sufficient, enhancement of the e.e. had to be carried out through the benzoate derivative of OPC-41061, which was recrystallized and cleaved back to the API. It is not clear why the Otsuka group placed the enantioselective reduction at the end of the synthesis, therefore forfeiting the possibility of enriching the e.e. through further synthetic manipulations. The synthesis is described only on a gram scale.[167]

A recent, also very challenging example, illustrating the power of the new generation of Ru catalysts, is shown in Scheme 106. Thus, Chen *et al*. (Merck) employed Noyori catalyst **330** in the key step of the enantioselective approach to PDE-IV inhibitor **331**. The reduction of **332** proceeded under most attractive conditions (low hydrogen pressure, room temperature) and with a TON > 1000 to afford a quantitative yield of **333** in almost complete enantioselectivity.[168] The conditions were carefully optimized for throughput, and the process is described by the authors as viable, although scale-up was not discussed. In a later publication, Chen and O'Shea and co-workers discuss separately the challenges of reducing diaryl ketones such as **332** in high enantioselectivity.[169] Whereas standard CBS reduction failed to lead to optimal e.e. (80% e.e. was the best result, and crystallization failed to upgrade it), and BINAL-H reduction is effective but not catalytic, the protocol described in

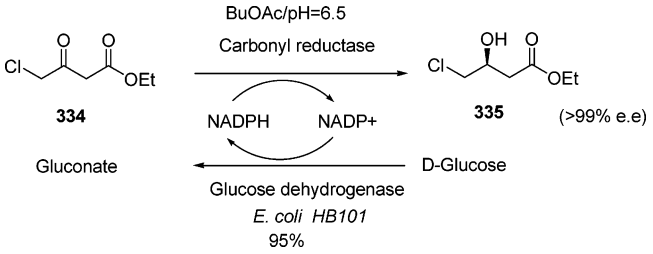
Scheme 106



Scheme 106 turned out to be eminently practical, and a thorough study on the scope of the reduction of aryl heteroaryl ketones was carried out as well.

In comparison with the powerful, high-TON Ru catalysts and the extremely low cost of IPA as a hydride source, biocatalytic methods[170] have a major disadvantage: although in principle highly stereoselective, they traditionally need a long development time to become practically useful (*i.e.* high enough throughput).[171] It is not surprising, therefore, that process chemists do not often turn to bioreductions when the task of enantioselectively reducing a ketone presents itself.[172] Bioreductions are achieved with carbonyl reductases employing expensive cofactors such as NADH and NADPH. The problem of cofactor regeneration has been solved by coupling a second enzymatic step with the reduction or by the use of recombinant whole-cell biocatalysis. The detailed description of this field is outside the scope of this review.[173] Although difficult to implement quickly, reductases have been used in conjunction with established markets. Once a large market for a building block is established, synthetic biotechnologists have time to optimize their methods; some whole cell processes which have been engineered have proven to be competitive, in price and volume, with purely

Scheme 107



chemical processes. One specific example is in the chemoenzymatic synthesis of statin building blocks. Given that cholesterol-lowering drugs represent today a $20 billion market worldwide, and that the chiral side chain represents a constant motif in their structure, it is not surprising that a fierce competition has sparked major advances in this area.[174]

As shown in Scheme 107, using a strain of *E. coli* overexpressing alcohol dehydrogenase and glucose dehydrogenase (for cofactor regeneration), Yasohara *et al.* (Kaneka) reduced **334** to **335** (S enantiomer) in almost quantitative yield and complete enantioselectivity in biphasic organic/aqueous mixtures. The product concentration in the organics reached a respectable 63 g/L.[175]

Another popular approach to biocatalytic carbonyl reductions is bacterial screening.[176] For example, Patel *et al.* (BMS) reported the microbial reduction of ketoester **336** en route to retinoid analogue BMS 270394, which is an experimental dermatological and anticancer agent. Although a strain of *A. pullulans* could be identified which reduced the target carbonyl in excellent enantioselectity, the long reaction times (>100 h) and the low throughput (5 g/L per batch) contribute to limit the practicality of the biocatalytic method (Scheme 108).[177]

Similar processes toward tomoxetine, fluoxetine, and salmeterol have been described.[178] Of course, the separation of the product from the huge mass of the cofactor-regenerating product and/or the biological debris, such as those in yeast reductions,[179] introduces problems that are typically absent from classical metal-catalyzed hydrogenations.

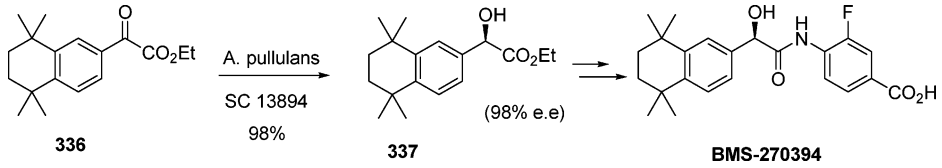
In contrast to the many successful examples of enantioselective carbonyl reductions in API synthesis, enantioselective imine reductions are rare. In an early example, Kanai and co-workers (Daiichi) reported a chiral synthesis of the antibiotic (*S*)-levofloxacin using the Ir-catalyzed enantioselective reduction of imine **338** (Scheme 109). The best ligand was (*S*,*S*)-BPPM (**251**), and addition of salts such as BiI_3 was empirically found beneficial to the enantioselectivity.

The catalyst load appears relatively high, and it is not clear whether the process has been scaled up.[180] In addition, the use of benzene and chromatography would have to be phased out for the process to be economically competitive and environmentally acceptable in a typical plant environment.

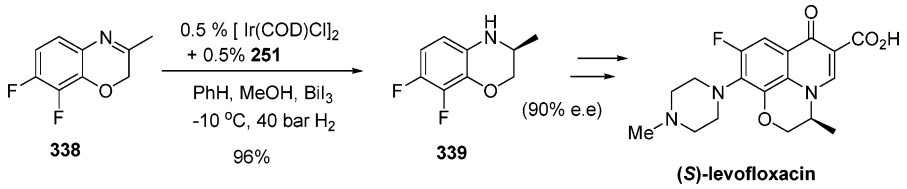
The enantioselective reduction of imine **340** using the Noyori catalyst **341** led to the synthesis of the neuromuscular blocker GW 0430 (Scheme 110). Samano and co-workers (Glaxo Wellcome) report no details of this successful H-transfer reduction, which proceeds with rather modest enantioinduction. However, upgrade to 99% e.e. can be achieved by recrystallization of the formate salt of **342**.[181]

Ramsden *et al.* (Dowpharma) recently described an enantioselective approach to the AMPA receptor modulator S-18986 (Scheme 111). Sulfonylimine **343** was hydrogenated

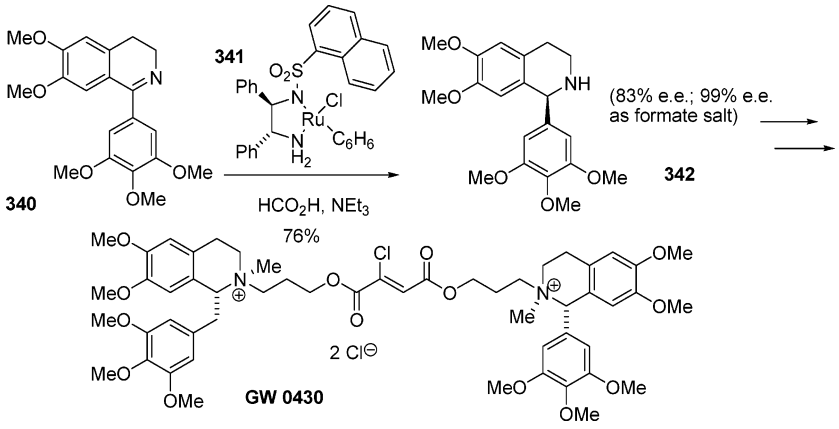
Scheme 108



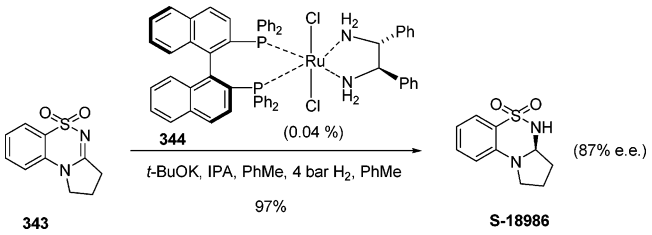
Scheme 109



Scheme 110



Scheme 111



using a rather small amount of Noyori catalyst **344** (TON = 2500) under mild conditions, to obtain S-18986 in modest e.e. However, a single crystallization from MeCN upgraded the e.e. to >99%.

The reaction was thoroughly optimized using Design of Experiment (DOE). Although the scale of the reaction was only 100 g, the authors conclude that the process could be practical for the production of the API.[182] In this case, the residual level of toxic acetonitrile in the API would have to be controlled.

5.4 Asymmetric C–C Bond Formation

Surprisingly, only scattered examples exist in the literature where enantioselective C−C bond formation has been used in practical API synthesis, despite the relative abundance and maturity of the field.[183] It is difficult to explain this situation: on one hand, it is likely that, of the many enantioselective techniques that have surfaced in the past decade, only a handful will prove efficient and practical enough when evaluated with the impartial approach of cost analysis. In addition, it is possible that new chemistry takes a certain amount of time to be widely accepted and exploited in practical organic synthesis (*i.e.* process chemistry). One reaction which has received a large amount of attention within the academic community is the addition of organozinc reagents to aldehydes catalyzed by chiral Lewis acids.[184] A host of chiral catalysts have been applied to this problem, but their application to API synthesis has been limited.

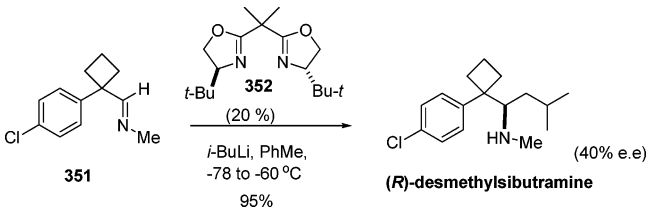
Cvetovich *et al*. at Merck have described the use of ligand **345** in the Ti-catalyzed addition of dipropylzinc to aldehyde **346** en route to the elastase inhibitor L-694,458 (Scheme 112). The method employs a large amount of chiral ligand (∼5% w/w) and seems to be of modest efficiency. A scale-up using >600 g of **346** is described: the procedure involves separate reactors for the precomplexation of **345** and titanium isopropoxide, and for the addition into the organozinc solution. The reaction is followed by an acidic quench, and the product **347** is not isolated but is handled in solution.

The yield represents therefore an HPLC assay. An alternative approach using the CBS reduction of the corresponding ketone is also successful.[185]

Addition reactions of organozinc compounds to aldimines are also well developed.[186] In a recent example, Charette *et al*. (University of Montréal) introduced a new class of ligands, exemplified by BozPHOS (**348**), which achieve high enantioselectivity in the addition of organozinc reagents to *N*-phosphinoylimines.[187] An application to the preparation of the acetylcholinesterase inhibitor rivastigmine is shown in Scheme 113.

In their enantioselective approach to the antiobesity drug desmethylsibutramine, Krishnamurthy and co-workers (Sepracor) screened a variety of ligands as catalysts for the addition of isobutyllithium to aldimine **351**. Bis-oxazoline **352** was the best one in terms of enantioselectivity. Although the TON and enantioselectivity for this transformation are modest, the optical purity could be upgraded by a single recrystallization with mandelic acid to the required >99% e.e. (Scheme 114).[188]

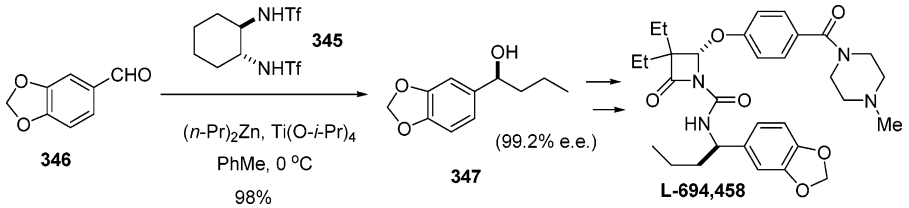
Scheme 114



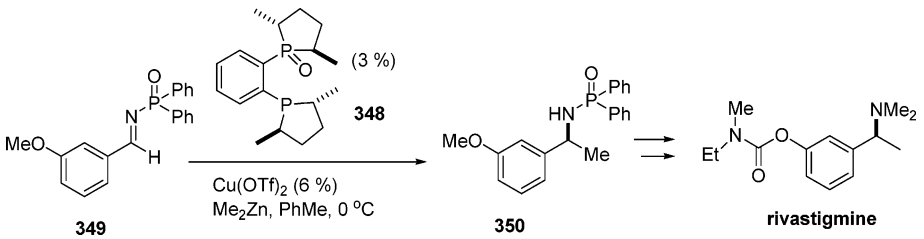
Fu and co-workers (MIT) have developed an enantioselective acylation of silyl ketene acetals to create quaternary stereocenters in fair to good e.e., using complex chiral bases as catalysts (*e.g.* **353**). Recently, the methodology was showcased in an asymmetric synthesis of the coronary vasodilator (*S*)-verapamil (Scheme 115). The key step involves the enantioselective acylation of ketenimine **356**, which proceeds in fair TON and e.e. This represents the first catalytic enantioselective approach to the drug.[189]

Barnes and co-workers at Abbott have described an elegant enantioselective conjugate addition of a stabilized enolate

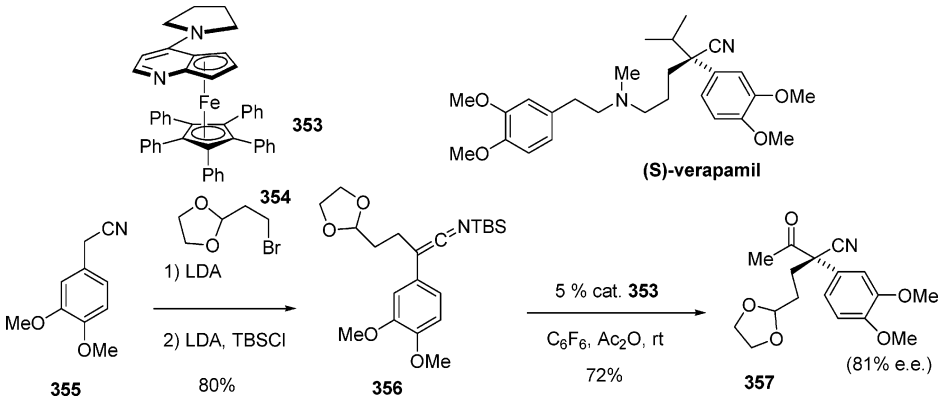
Scheme 112



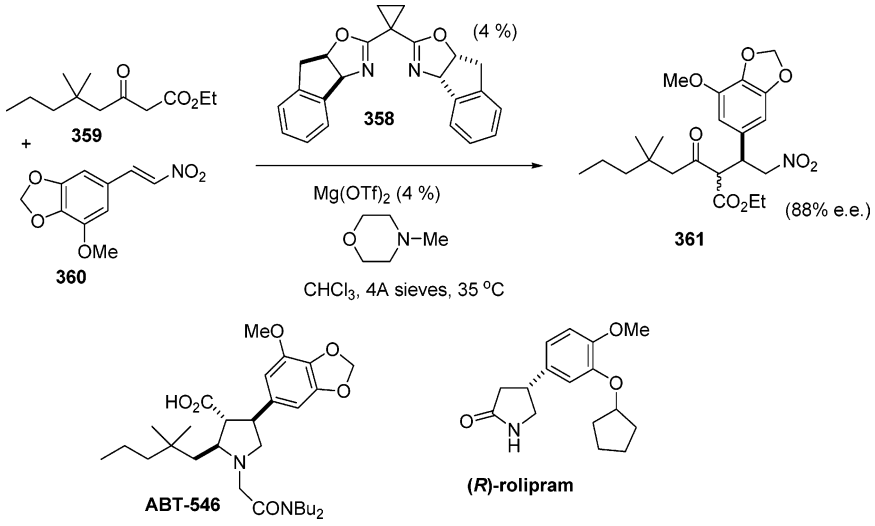
Scheme 113



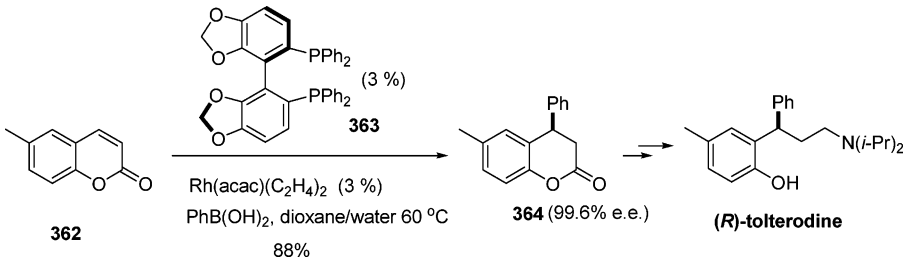
Scheme 115



Scheme 116



Scheme 117



to a nitroalkene, using a chiral catalyst composed of ligand **358** and magnesium triflate.

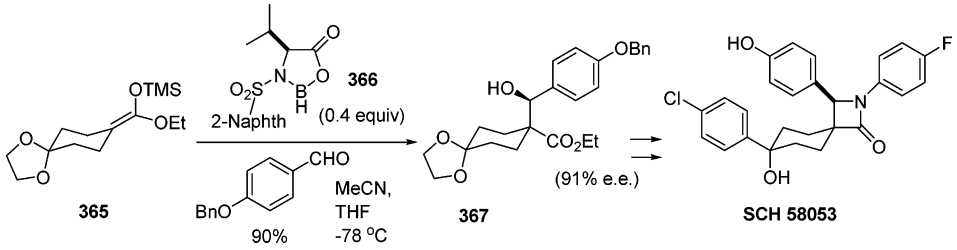
The reaction was carefully optimized with respect to base, solvent, and even solvent grade. The reaction of **359** with **360** (Scheme 116) was negatively affected by the low levels of EtOH added to chloroform as stabilizer, and a hydrocarbon stabilizer was much preferred. In addition, water had a major effect on rate and enantioselectivity. Whereas the magnesium triflate had to be hydrated in order to form the active catalytic species, the reaction medium had to be scrupulously anhydrous, hence the use of molecular sieves. The complex role of water is, in general, not clearly understood, but very important, illustrating a constant key variable in process chemistry. Further manipulations of **361** led to the endothelin inhibitor ABT-546. One must remark that the ester-bearing carbon undergoes ready epimerization, and therefore the selectivity (88%) represents the chiral purity at the neighboring carbon. An analogous synthesis leads, in even higher enantioselectivity, to the PDE-IV inhibitor (*R*)-rolipram.[190]

Hayashi and co-workers (Kyoto University) have developed an extremely efficient enantioselective protocol for the Rh-catalyzed addition of boronic acids to unsaturated systems. In a recent paper, they showcased their methodology by applying it to the enantioselective synthesis of (*R*)-tolterodine (Scheme 117). Thus, coumarin **362** is treated with phenylboronic acid in the presence of Segphos (**363**) and a Rh(I) precatalyst, to yield **364** in extremely high e.e.

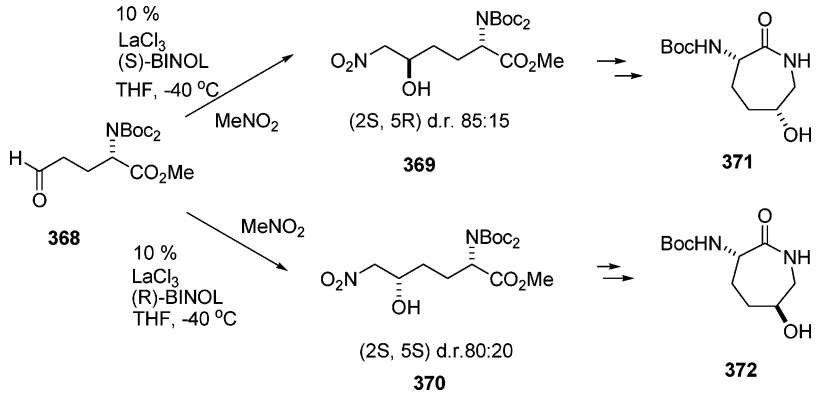
Some limitations to the practical exploitation of this reaction are represented by the low TON of the Rh catalyst and the huge (10-fold) excess of boronic acid needed for the transformation, which makes the reaction poor in terms of reaction mass efficiency. A common side reaction in these processes is, in fact, protodeboronation, leading in this case to benzene, thereby necessitating such a large excess.[191]

The enantioselective addition of silyl ketene acetals to aldehydes under the catalysis of oxazaborolidinones is a well-established technique.[192] Recently, Wu and colleagues at Schering-Plough applied this reaction to the synthesis of

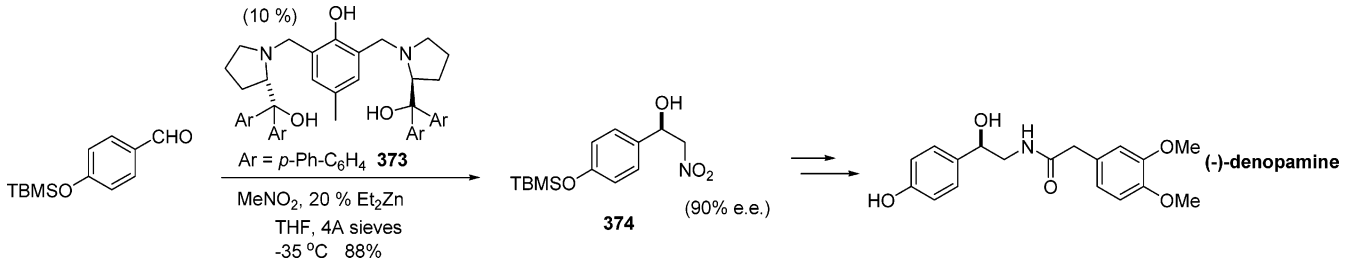
Scheme 118



Scheme 119



Scheme 120



cholesterol absorption inhibitors (Scheme 118). The reaction was described only on gram scale, and the huge catalyst load employed (40 mol %) makes the reaction quasistoichiometric. However, the protocol described allows for the ready recovery of the catalyst in >95% yield at each cycle as the sulfonylamino acid, which must be resubmitted to borane−THF to regenerate the catalyst. Thus, **365** reacts with a number of aryl aldehydes in ∼90% e.e. In this case, **367** was further transformed into SCH 58053.[193]

Although the enantioselective Henry reaction has been well developed,[194] applications to API synthesis are rare. In one recent example, Prasad *et al*. (Novartis) used a catalyst-driven diastereoselective Henry reaction in the synthesis of building blocks of the antitumor agent bengamide (Scheme 119). That the pre-existing chiral center in **368** has little effect on the stereochemical course of the reaction is shown by the fact that enantiomeric catalysts lead to stereocomplementary products **369** and **370** (*i.e.* no match/mismatch effect). Further transformation yields the targets **371** and **372**. The high catalyst load and the rather modest diastereoselectivity negatively affect the practicality of this protocol.[195]

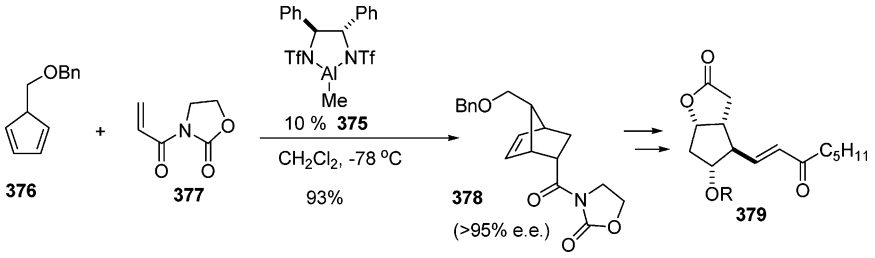
An enantioselective Henry reaction has been used by Trost *et al*. (Stanford University) in their enantioselective synthesis of the β-adrenoceptor agonist (−)-denopamine (Scheme 120). Trost has devised a novel diamine ligand (**373**) which is precomplexed with the catalytic metal center, in this case Zn(II).[196] The reaction operates with a modest TON, but the yield and enantioselectivity are fairly good, and the procedure may have practical potential.

The enantioselective Diels−Alder reaction is a powerful tool that allows the chemist to set the stereochemistry of multiple chiral centers in a single operation.[197] Although the reaction is relatively well developed, applications to API synthesis have not been forthcoming. In an early showcasing of the power of this reaction, Corey *et al*. (Harvard University) have shown that catalytic amounts of Lewis acid **375** promote the enantioselective cycloaddition of benzyloxycyclopentadiene (**376**) with dienophile **377**, to yield, after further transformations, **379**, a key intermediate in the synthesis of prostaglandins (Scheme 121).[198]

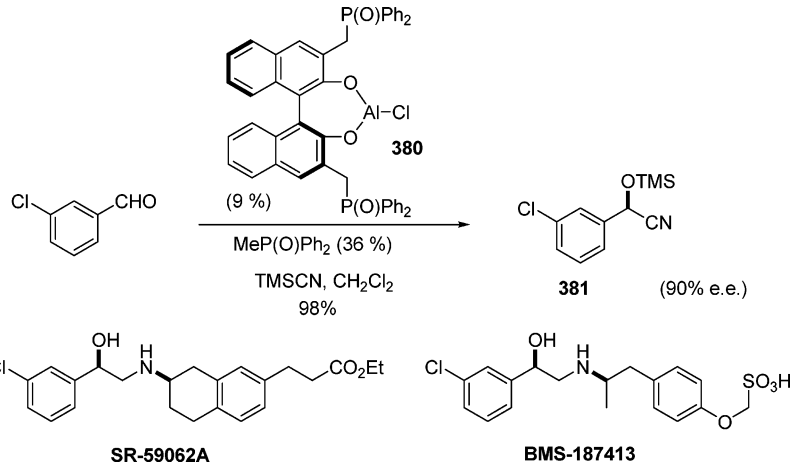
Corey and co-workers, in a separate study, have also shown that boron-based catalysts achieve a similar transformation in analogous enantioselectivity and efficiency.[199] Although these are academic syntheses, they are extremely powerful, and it is expected that they will be adapted and further developed for API synthesis.

Nogami *et al*. (Mitsubishi) have applied Shibasaki's enantioselective cyanohydrin formation promoted by Lewis acid−Lewis base bifunctional catalyst **380** to the synthesis of APIs featuring the amino alcohol motif (Scheme 122). In a typical example, *m*-chlorobenzaldehyde led to protected cyanohydrin **381** in good yield and e.e. This compound is an intermediate to a variety of β_3-adrenergic receptor agonists, such as SR-59062A and BMS-187413.[200]

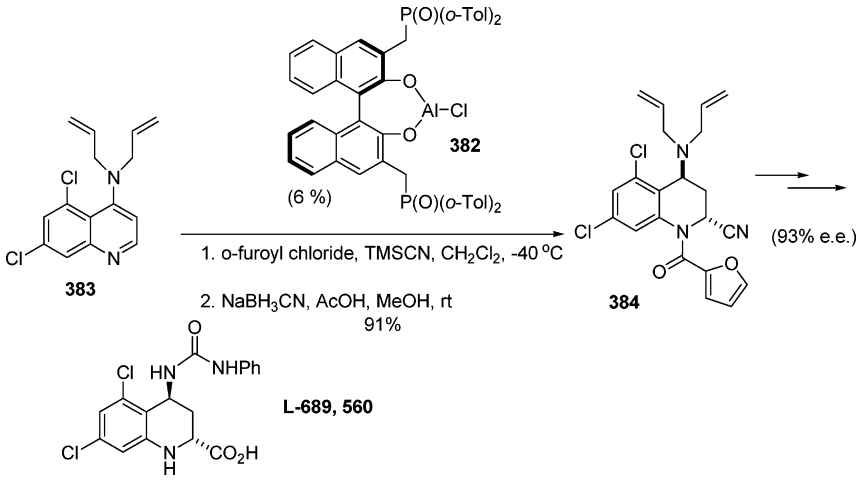
Scheme 121



Scheme 122



Scheme 123



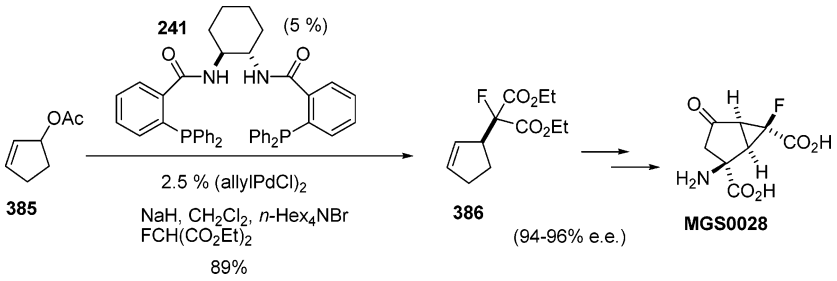
An application of analogous catalyst **382** to the enantioselective synthesis of Reissert compounds en route to the potent NMDA receptor antagonist L-689,560 was reported by Shibasaki (Scheme 123). Thus, quinoline **383** is cyanated in high enantioselectivity and the resulting enamine is directly reduced in good diastereoselectivity to **384**, thereby effectively setting the stereochemistry of both chiral centers.[201] As shown by the two preceding effects, Shibasaki's technology has potential for the synthesis of APIs containing the α-amino acid and α-hydroxy acid motifs.

The transition-metal-catalyzed asymmetric allylic alkylation (AAA)[202] has found application in API synthesis. Recently, Zhang *et al*. (Merck) have applied the technique to the synthesis of MGS0028, an mGluR 2 receptor agonist. The initial reaction sets the crucial absolute configuration, using **241** as the Pd ligand. Given the symmetry inherent in **385**, the initial ionization yields a symmetrical substrate, and the ligand provides the only asymmetry in the system.

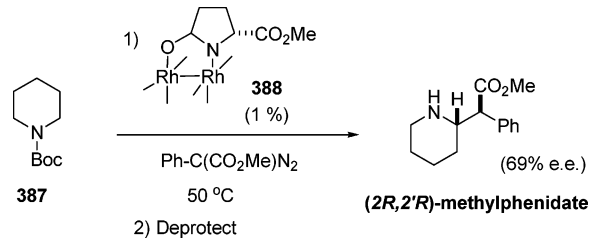
The enantioselectivity of the system was enhanced by using a bulky tetraalkylammonium halide. The catalyst load also has a marked influence on the reaction course. At 2 mol % catalyst load, the reaction was less enantioselective. The process is described on a small scale, and it is not clear whether it would be a contender for the manufacturing route (Scheme 124).[203] Similar applications have been described.[204]

(2*R*,2′*R*)-Methylphenidate is the active enantiomer of Ritalin, the most widely prescribed treatment for attention deficit hyperactivity disorder (ADHD), and as such, it has attracted a lot of attention in relation to its asymmetric synthesis.[205] Recently, Winkler (University of Pennsylvania) and Davies (SUNY Buffalo) have reported, almost simultaneously, a very elegant strategy based on Rh-catalyzed C−H insertion. Using Doyle's Rh_2(5*R*-MEPY)$_4$ catalyst (**388**), Winkler *et al*. showed that insertion of methyl phenyldiazoacetate in the α-CH bond of Boc-piperidine (**387**) afforded mainly the desired enantiomer among four possible

Scheme 124



Scheme 125



diastereoisomers (Scheme 125). The catalyst load was only 1 mol %, and the diastereomeric purity was impressive (97:3). Two crystallizations afforded enantiopure material (>95% e.e.).[206] Although the selectivity of the process is not perfect, the synthesis involves only two steps and is exceedingly efficient when compared with the existing asymmetric approaches.

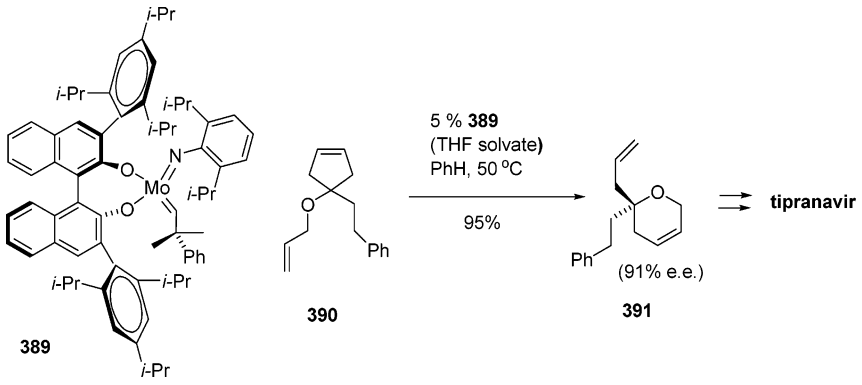
The approach reported by Davies is quite similar, except that it employs the catalyst Rh(*S*-biDOSP)$_2$, which is much less diastereoselective (*threo*:*erythro* = 2.5:1), although more enantioselective (86% e.e.).[207] Thus, enantioselective Rh-catalyzed C−H insertion may be a promising avenue to API synthesis when the proper selectivity can be engineered into the system and the cost of the catalyst can be kept low by increasing the TON.

Metathesis reactions are currently quite popular in organic synthesis, but their applications to asymmetric processes are rare. In one such application, Hoveyda *et al*. (Boston College) have devised an enantioselective tandem ring opening−ring closing metathesis strategy using Mo catalyst **389** and have used it to prepare, in high optical purity, dihydropyran **391**, a precursor of the already discussed anti-HIV drug tipranavir (Scheme 126).[208] The mechanism for the enantioselectivity has not been clarified, but it is suggested that the ROM step is the stereodifferentiating one. Although the complete route is rather long and is unlikely to be competitive with the manufacturing process, this example highlights the potential of metathesis processes for the creative asymmetric synthesis of APIs.

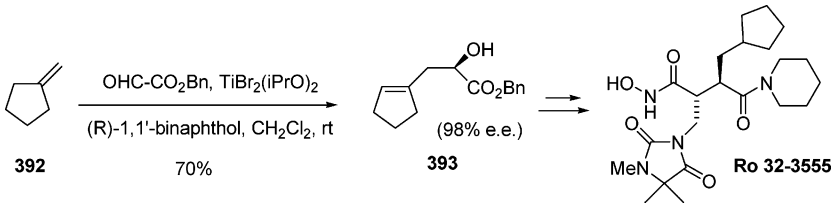
Scheme 127 shows an example of an enantioselective ene reaction. Hilpert (Roche) used a Ti−BINOL ligand to catalyze the addition of benzyl glyoxylate to methylenecyclopentane in excellent enantioselectivity. The hydroxy ester **393** was then elaborated to matrix metalloproteinase inhibitor Ro 32-3555. The reaction is reported only on a gram scale.[27]

The use of enzymes for enantioselective C−C bond formation is, of course, ubiquitous in nature, but it has been used only rarely in API synthesis, probably for the reasons explored above in conjunction with bioreductions. Nevertheless, some impressive results have been obtained in select areas. For the production of the antibacterial carbacephem loracarbef, a Lilly team headed by Zhang explored the use of a serine hydroxymethyltransferase (SHMT) derived from recombinant *E. coli* for the formation of the key C−C bond. The reaction of glycine with 4-pentenal turned out to be diastereo- and enantioselective, to yield key intermediate **394** (Scheme 128). The enzyme load was rather high (15% w/w), and the isolation required elution from an SP207 resin

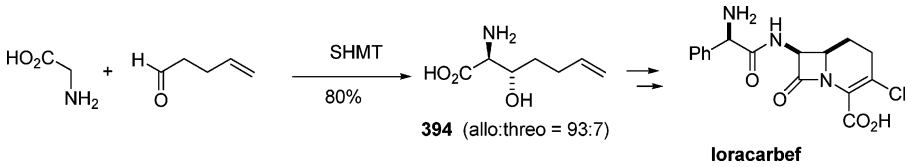
Scheme 126



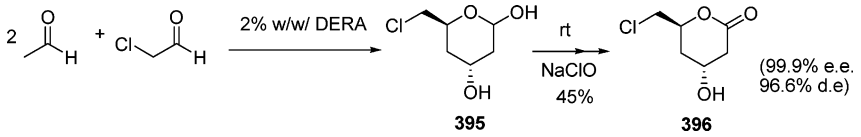
Scheme 127



Scheme 128



Scheme 129

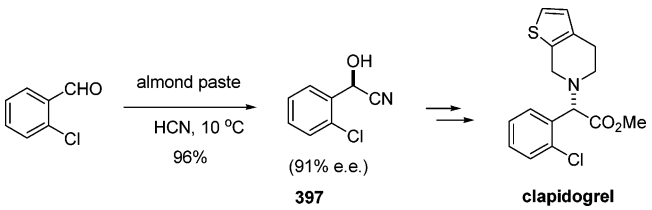


column. The experimental description of a medium-scale aldol reaction is given (>120 g product).[209]

The use of aldolases is well established in bio-organic synthesis, yet applications to API synthesis have been few. Among the most elegant approaches recently published, Greenberg and Burk at Diversa have reported a very efficient synthesis of the statin side chain using a new aldolase (deoxyribose-5-phosphate aldolase, DERA) created from an environmental DNA library. The process is extremely simple, as it condenses 1 equiv of chloroacetaldehyde with 2 equiv of acetaldehyde in excellent selectivity, good volume efficiency (>30 g/L per h), and low catalyst load (Scheme 129). The e.e. is virtually complete (99.9%) in favor of the desired 3*R*,5*S* isomer **395**, with only 1.7% diastereomeric contamination. Oxidation gave lactone **396**. A pilot-scale process is not described, but a 100 g synthesis is reported. The process is considered a practical and economical route to a variety of statins.[210]

Another class of enzymes that has found wide application are the oxynitrilases. Found commonly in almonds, they can be used as crude preparations in the enantioselective cyanohydrin formation. For example, Sheldon *et al*. (Delft University) optimized the biocatalytic synthesis of **397**, a key intermediate in the manufacturing route of the antithrombotic agent clapidogrel. As shown in Scheme 130, the

Scheme 130



cyanohydrin of *o*-chlorobenzaldehyde was obtained in excellent yield and good e.e. After hydrolysis of **397** to the corresponding acid, the e.e. could be upgraded to >99% by one simple crystallization. The process was optimized to yield the fair throughput of 14 g/L per h, and the biocatalyst used was 1 g per 1.3 g of product. The scale described is 1 L, which leads to the production of ~25 g of (*R*)-chloromandelic acid per batch.[211]

5.5. Asymmetric Oxidative Processes

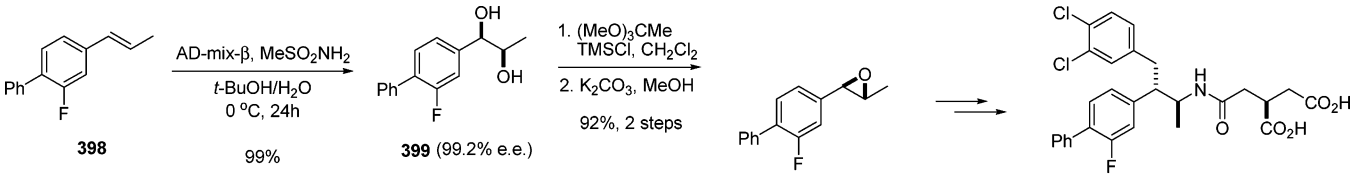
Although the adjustment of oxidation states is ideally avoided in process development, primarily due to the safety issues associated with many oxidizing and reducing reagents, several asymmetric oxidation reactions are commonly employed in large-scale API synthesis. Sharpless's report of the asymmetric titanium tartrate-catalyzed epoxidation of allylic alcohols in 1980 initiated an explosion in the development of asymmetric catalysis, and over the next decade, several additional asymmetric oxidative processes were discovered.[212] The application of Sharpless's titanium tartrate reagent to the oxidation of sulfides, reported independently in two variations by Kagan[213] and Modena[214] in 1984, allowed access to chiral sulfoxides with high enantioselectivities. Sharpless's extensive work on the osmium-mediated dihydroxylation of olefins culminated in the development of the catalytic asymmetric procedure in 1988,[215] and subsequent refinements of ligand structure have permitted the attainment of uniformly high enantioselectivities in the dihydroxylation of a broad structural range of olefins.[216] Jacobsen's manganese-salen-catalyzed epoxidation (1990) allowed for the enantioselective epoxidation of unfunctionalized olefins.[217] In particular, the high enantioselectivities obtained for Jacobsen epoxidation of *cis* olefins nicely complement the Sharpless epoxidation and dihydroxylation protocols, which give reduced enantioselectivities for these substrates. The Sharpless, Jacobsen, and Kagan procedures account for the majority of asymmetric oxidative reactions used in API synthesis, although more recent organocatalytic procedures (chiral dioxiranes) are attractive due to the lack of toxic transition metals and may have the potential to become practical processes. On pilot plant scale, the safety issues associated with using peroxides and other stoichiometric oxidants must be addressed. The removal of residual catalyst-derived metals from the final API can also present challenges, although many treatments are now available (charcoals, resins) for this task, and in many cases simple recrystallization is sufficient. A buffer of additional steps between the metal-catalyzed reaction and the final API is desirable in this regard, as each subsequent transformation usually helps to reduce the residual metal content.

5.5.1. Sharpless Asymmetric Dihydroxylation of Alkenes

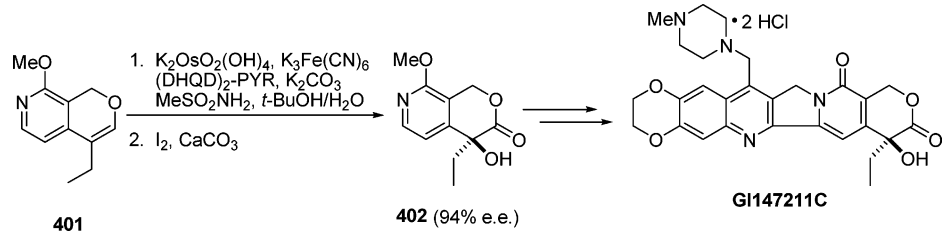
Sharpless's asymmetric dihydroxylation reaction (SAD) is a powerful, general method for the introduction of chiral 1,2-diol functionality onto unfunctionalized alkenes.[213,214] The current library of cinchona alkaloid-derived ligands allows olefins of almost all substitution patterns to be dihydroxylated with high enantioselectivity. From a development perspective, the use of a highly toxic osmium catalyst, albeit in low (<1 mol %) loadings, can present problems if removal from the product and/or subsequent intermediates is not efficient.

An SAD-based synthesis of the potent inhibitor of squalene synthase J-104,118 was reported by Iwasawa and co-workers at Banyu Pharmaceutical Co. (Scheme 131).[218] Dihydroxylation of *E*-olefin **398** using AD-mix-β with $MeSO_2NH_2$ gave

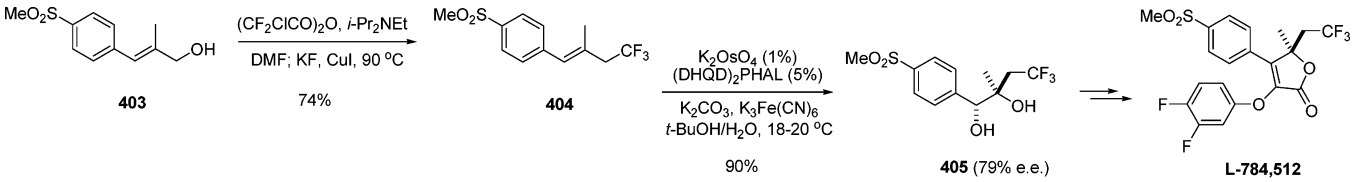
Scheme 131



Scheme 132



Scheme 133



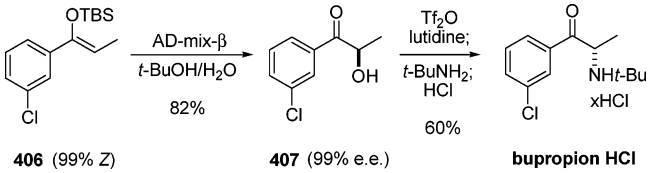
diol **399** in 99% yield and 99.2% e.e. Conversion to epoxide **400** was effected under the Sharpless−Kolb conditions[219] (92%) and gave material of undiminished optical purity. This route proved to be much more efficient than an alternative resolution-based approach to J-104,118. The procedure is described on multigram scale.

Fang *et al*. (Glaxo-Wellcome) described a catalytic asymmetric synthesis of the water-soluble topoisomerase I inhibitor GI147211C in which the tertiary stereocenter was introduced by SAD of vinyl ether **401** employing the pyrimidine-linked ligand $(DHQD)_2$-PYR (Scheme 132).[220] The resultant hydroxy acetal was oxidized *in situ* to give hydroxy lactone **402** in 94% e.e. The yield was not reported for this sequence. Crystallization of a subsequent intermediate upgraded the e.e. to >99%. Interestingly, dihydroxylation of **401** using the phthalazine-linked ligand $(DHQD)_2$-PHAL gave the product in only 26% e.e. This chromatography-free synthesis of GI147211C was reported on >100 g scale.

Another application of SAD for chiral tertiary alcohol formation was described by Tan and colleagues at Merck in their synthesis of the COX-2 inhibitor L-784,512 (Scheme 133).[221] The requisite *E* olefin **404** was prepared from allylic alcohol **403** by a one-pot trifluoromethylation reaction. Dihydroxylation of **404** under standard Sharpless conditions was investigated using several different ligands. The phthalazine-linked ligands $(DHQD)_2$PHAL and $(DHQD)_2$-DP-PHAL gave the best results (79% e.e. and 70% e.e., respectively). No increase in the enantioselectivity was observed on decreasing the reaction temperature to 0 °C. Importantly, the modest optical purity of crude **405** could be increased to >98% e.e. after a single recrystallization from *i*-PrOAc/hexane. Swern oxidation and a one-pot acylation/Dieckmann condensation led to L-784,512. The synthesis was described on gram scale.

The antidepressant Wellbutrin and the smoking cessation drug Zyban (both Glaxo-Wellcome) both contain racemic bupropion as the active ingredient. Fang and Senanayake and co-workers (Sepracor) reported an asymmetric synthesis of (*S*)-bupropion hydrochloride via SAD of *Z*-silyl enol ether **406** to give the α-hydroxyketone **407** in 99% e.e. (Scheme 134).[222] Triflation of the alcohol and stereospecific displacement with *tert*-butylamine followed by salt formation gave (*S*)-bupropion hydrochloride in 60% yield. The procedure was reported on <1 g scale.

Scheme 134

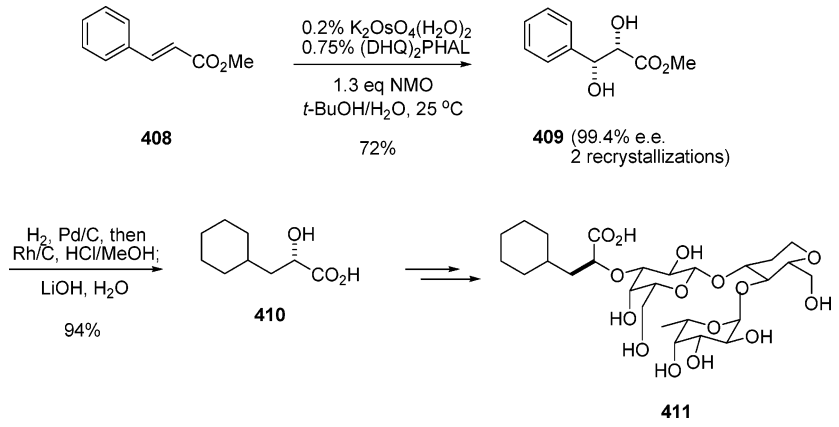


The selective E-selectin inhibitor **411** (Novartis) contains a cyclohexyl lactic acid moiety as a substitute for the *N*-acetylneuraminic acid residue found in sialyl Lewis^x. Storz and co-workers described the development and evaluation of several different approaches to cyclohexyl lactic acid **410**, including SAD, resolution, biocatalytic reduction, and chiral pool-based routes.[223] Sharpless dihydroxylation of methyl cinnamate **408** gave the diol **409** in 99.4% e.e. and 72% yield after two recrystallizations (Scheme 135).

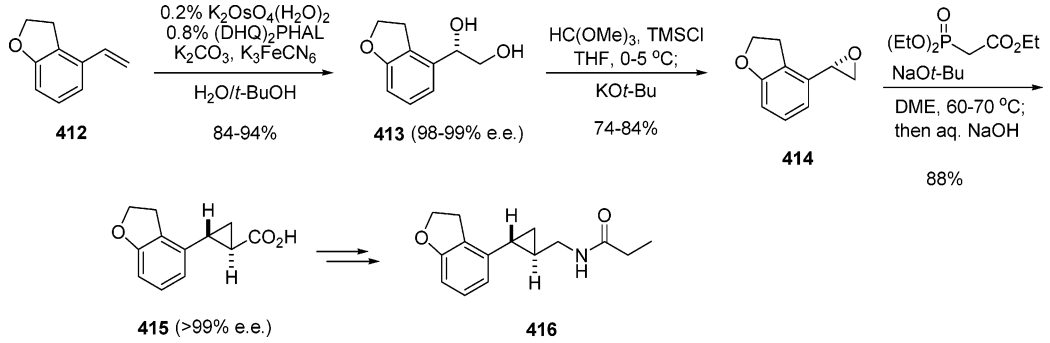
A one-pot benzylic hydrogenolysis/phenyl ring hydrogenation and subsequent hydrolysis of the methyl ester provided **410** in 94% yield. The initial level of osmium (100−200 ppm in **409**) dropped to 4 ppm on conversion to **410**. After evaluation of several routes to **410** with respect to raw material costs, number of steps, overall yield (chemical and optical), and operational simplicity, it was found that the cinnamate dihydroxylation approach was the most attractive. The procedure is reported on ∼45 g scale.

The dihydrobenzofuran epoxide **414** was identified as a key chiral intermediate in the synthesis of the melatonin agonist **416** (Scheme 136). Prasad and colleagues at BMS

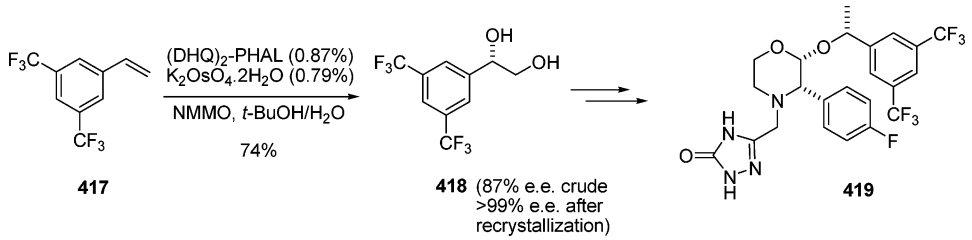
Scheme 135



Scheme 136



Scheme 137



reported the Sharpless dihydroxylation of **412** for the preparation of diol **413** in 84−94% yield and 98−99% e.e.[224] A modified Sharpless−Kolb procedure was developed allowing for one-pot conversion of the diol to epoxide **414**. This two-step process was demonstrated on multi-kilogram scale.

Compared to an alternative Jacobsen epoxidation approach for **414** (*vide infra*), the SAD procedure was chosen for further scale-up due to the higher overall yield in the synthesis of **416** (43% versus 22%). Several techniques were investigated for the removal of residual osmium metal, and ultimately the most effective procedure involved a simple wash with aqueous sodium sulfite during workup. This reduced the levels of osmium to 6 ppm or less in the isolated diol, below the 10 ppm upper limit. A diastereoselective cyclopropanation reaction of **414** provided the *trans*-cyclopropane **415** with complete transmission of chirality.[225]

Another example of Sharpless dihydroxylation of a styrene comes from Merck's synthesis of the substance-P inhibitor **419**, illustrated in Scheme 137.[226] Pye, Rossen, and coworkers reported the SAD of **417**, which gave diol **418** in 87% e.e. Recrystallization of the crude product (hexanes/EtOAc) upgraded the optical purity to >99% e.e. (74% yield). All three chiral centers in the final drug substance derive from the stereochemistry set in the dihydroxylation reaction.

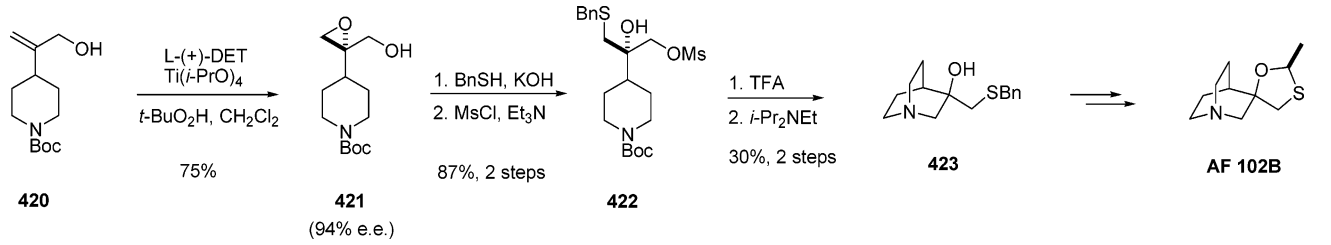
5.5.2. Asymmetric Epoxidation of Alkenes

Sharpless' titanium tartrate-catalyzed asymmetric epoxidation (SAE) is a method of choice for the epoxidation of allylic alcohols.[209] Consistently high enantioselectivities are observed for nearly all substitution patterns of the substrate, and a multitude of subsequent transformations are amenable to the epoxy alcohol products. Although the use of concentrated solutions of *tert*-butyl hydroperoxide poses potential safety concerns, the reaction has nevertheless been extensively utilized industrially.[227]

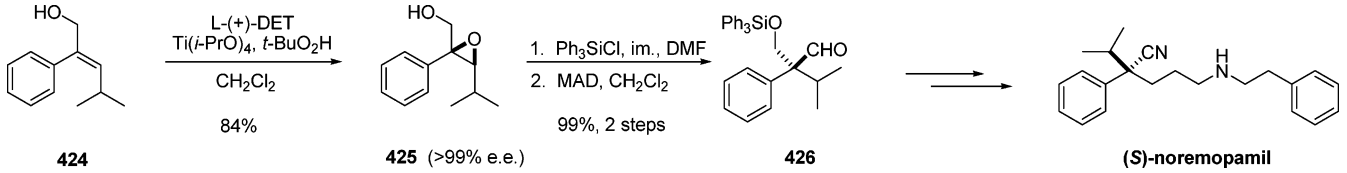
Bös and Canesso at Hoffmann-La Roche reported an asymmetric synthesis of the marketed muscarinic M1-type agonist AF 102B in which the stereochemistry derives from SAE (Scheme 138).[228] Treatment of olefin **420** with Ti(*i*-PrO)$_4$/L-(+)-DET/*t*-BuO$_2$H at −20 °C furnished epoxide **421** in 75% yield and 94% e.e. Opening of the epoxide with benzylmercaptan followed by mesylation of the primary alcohol gave the sulfonate **422**.

Deprotection of the Boc-group with TFA and subsequent treatment with *i*-Pr$_2$NEt gave the quinuclidine **423**, which could be elaborated by known procedures into AF 102B.

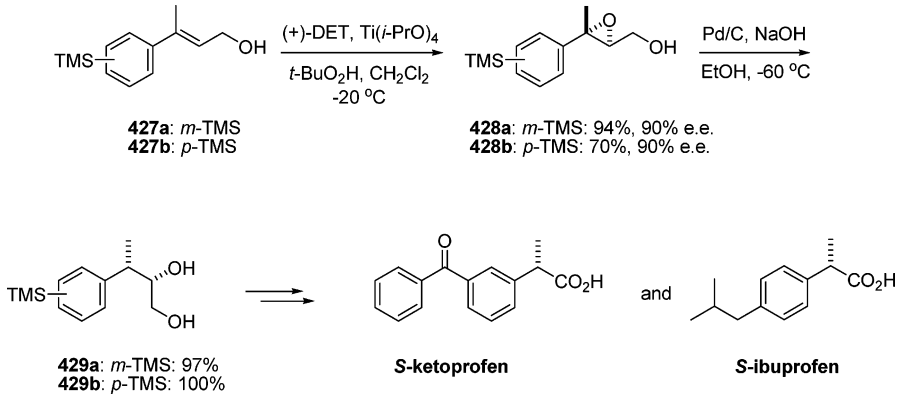
Scheme 138



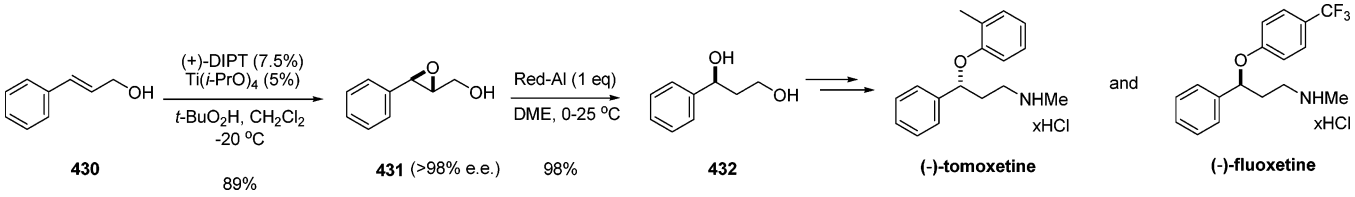
Scheme 139



Scheme 140



Scheme 141



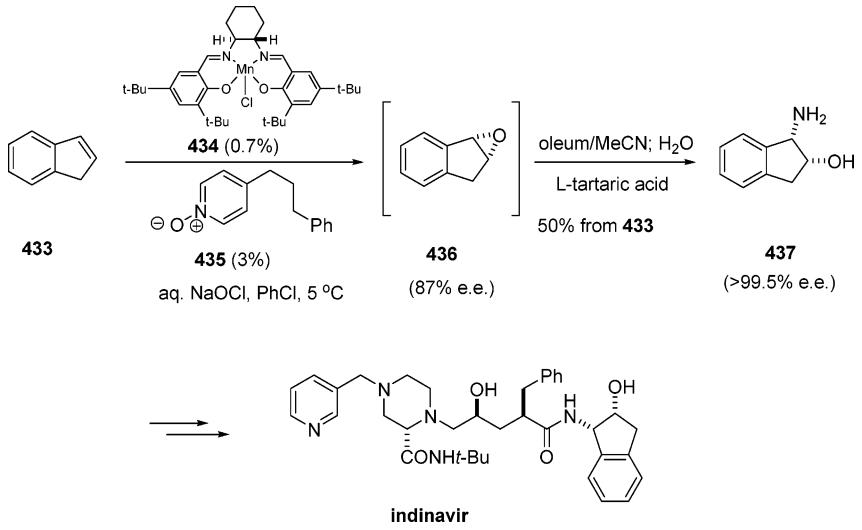
The synthesis was reported on gram scale. No mention is made of any upgrade in optical purity during the remainder of the synthesis.

Kimura and co-workers at Eisai developed an enantioselective synthesis of the L-type calcium channel blocker (*S*)-noremopamil using SAE to introduce chirality, which is cleverly transformed into the challenging all-carbon quaternary stereocenter (Scheme 139).[229] Epoxidation of allylic alcohol **424** gave the crystalline epoxy alcohol **425** in 84% yield and >99% e.e. After protection of the alcohol as its triphenylsilyl ether, a stereospecific rearrangement using Yamamoto's MAD [methyl aluminum bis(4-methyl-2,6-di-*tert*-butylphenoxide)] reagent provided the α-tertiary-*β*-silyloxy aldehyde **426** in 99% yield for two steps. This aldehyde was elaborated into (*S*)-noremopamil as well as a library of related phenylalkylamines. The epoxidation reaction was reported on 20 g scale.

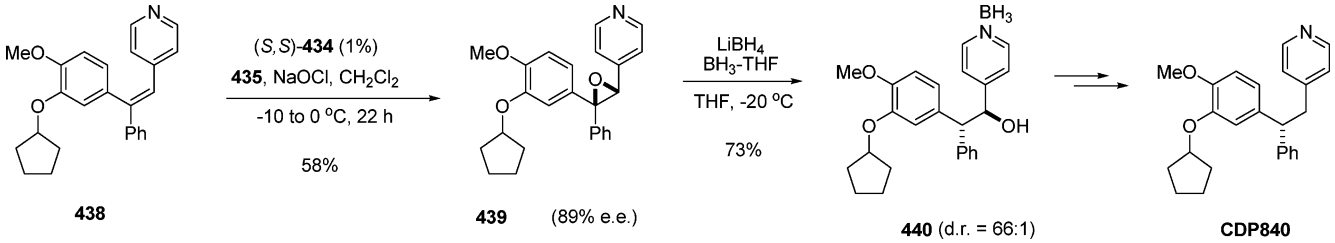
Hamon and co-workers (University of Adelaide, Australia) described the syntheses of the marketed anti-inflammatory drugs ketoprofen and ibuprofen, illustrated in Scheme 140.[230] The strategy involved SAE of trisubstituted allylic alcohols **427a**−**b** (90% e.e. in both cases) followed by catalytic hydrogenolysis of the epoxides **428a**−**b** with inversion of the benzylic stereocenters to give the diols **429a**−**b**. The hydrogenolysis required low temperature (−60 °C) for complete inversion. The optical purity of *meta*-isomer **428a**, an oil, could be upgraded to >98% e.e. by crystallization of the derived 3,5-dinitrobenzoate, while *para*-isomer **428b** was a solid and could be crystallized directly to >98% e.e. Both of these syntheses were described on gram scale.

Sharpless has described the application of his epoxidation to the preparation of both enantiomers of the marketed antidepressants tomoxetine and fluoxetine (Scheme 141).[231] Epoxidation of cinnamyl alcohol **430** with (+)-DIPT/Ti(*i*-PrO)$_4$ and *t*-BuO$_2$H in CH$_2$Cl$_2$ at −20 °C for 3 h gave epoxy alcohol **431** in >98% e.e. (89% yield). Regioselective reduction of **431** with Red-Al (1.0 equiv) in DME at 0−25 °C provided 1,3-diol **432** in 98% yield. This diol was elaborated in three additional steps to either (−)-tomoxetine or (−)-fluoxetine in 39% or 40% overall yield, respectively, for the five steps from cinnamyl alcohol. The (+)-isomers of each drug were prepared in an analogous manner by using (−)-DIPT in the epoxidation.

Scheme 142



Scheme 143



The advent of Jacobsen's Mn-salen-catalyzed epoxidation allowed access to chiral epoxides not available by SAE, since no functionalization of the substrate is required.[215] In particular, the high stereoselectivity attained in Jacobsen's epoxidation of *cis* olefins is complementary to both SAE and SAD methodologies, which generally give reduced enantioselectivities for *cis*-disubstituted substrates.

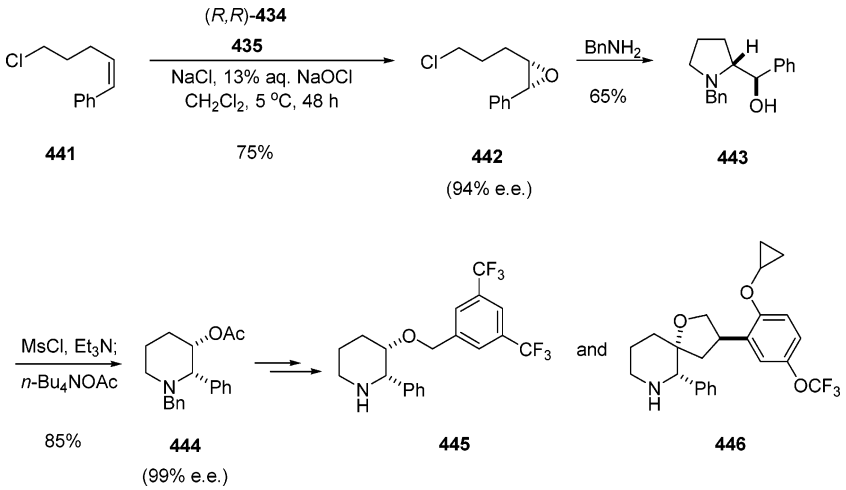
Merck's synthesis of the marketed HIV protease inhibitor Crixivan (indinavir) required an efficient synthesis of (1*S*,2*R*)-*cis*-amino indanol **437** (Scheme 142). The fragment **437** not only contains two of the five chiral centers in indinavir but also controls the formation of two additional stereocenters. Senanayake and co-workers described a concise synthesis of **437** from indene **433**.[232] Jacobsen epoxidation of indene using (*S*,*S*)-Mn(salen)Cl complex **434** (0.7%) and 4-(3-phenylpropyl)pyridine *N*-oxide **435** (3%) provided (1*S*,2*R*)-indene oxide **436** in 87% e.e. The *N*-oxide **435** served to stabilize the catalyst and also accelerate the epoxidation, and it allowed the catalyst load to be reduced from 1.5 mol % to as low as 0.4 mol %. Notably, CH_2Cl_2 was replaced with chlorobenzene, thus circumventing the volatility issues associated with CH_2Cl_2 and also allowing for direct conversion to **437** without isolation of indene oxide. A stereospecific Ritter-type reaction of **436** with MeCN/oleum and subsequent hydrolysis gave **437**, isolated in 78% yield and 87% e.e. Crystallization with L-tartaric acid provided enantiopure **437** (>99.5% e.e.) in an overall yield of 50% from indene. The process has been reported on 600 kg scale, which testifies to the efficiency and practicality of the chemistry.[233]

Lynch *et al*. at Merck reported the synthesis of the selective phosphodiesterase IV inhibitor CDP840 (Scheme 143).[234] Jacobsen epoxidation of trisubstituted olefin **438** using the (*S*,*S*)-salen-Mn complex **434** (1%) and *N*-oxide **435** provided the epoxide **439** in 58% yield and 89% e.e. Reductive opening of the epoxide with $LiBH_4/BH_3$·THF gave alcohol **440** in high diastereoselectivity (66:1). The reduction occurred with retention of configuration at the tertiary benzylic stereocenter, and a mechanism involving initial carbonium ion formation was proposed to rationalize this result. Decomplexation of the pyridyl borane and reduction of the benzylic alcohol furnished the target compound CDP840. The epoxidation was described on a gram scale.

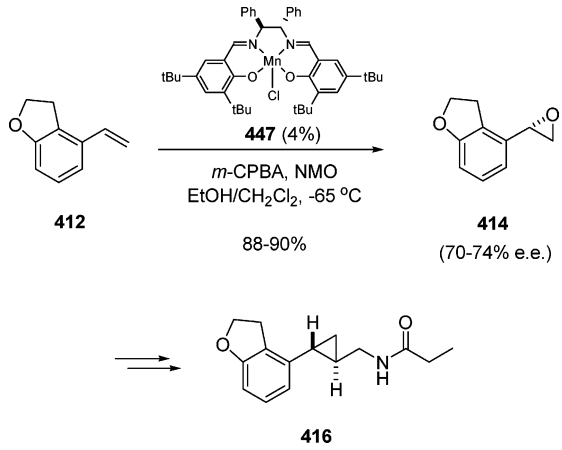
Lee and co-workers at Merck reported the synthesis of (2*S*,3*S*)-3-acetoxy-*N*-benzyl-2-phenylpiperidine **444**, a key intermediate in the syntheses of the neuropeptide substance-P receptor antagonists **445** and **446,** utilizing the Jacobsen epoxidation (Scheme 144).[235] Epoxidation of *cis*-styrene **441** with (*R*,*R*)-**434** in the presence of 4-(3-phenylpropyl)-pyridine-*N*-oxide **435** provided the epoxide **442** in 94% e.e. and 75% yield. Treatment with benzylamine in refluxing acetonitrile furnished the pyrrolidine **443** in 65% yield. The formation of **443** was presumed to arise from 5-*exo*-*tet* cyclization of an intermediate aminoepoxide. Ring expansion was effected by mesylation of **443** to generate an intermediate isolable aziridinium ion which was opened stereoselectively with *n*-Bu_4NOAc to give the 2,3-*cis*-disubstituted piperidine **444** in 85% yield and 99% e.e. The procedure is described on <10 g scale.

Prasad and colleagues (BMS) reported an alternative preparation of epoxide **414** via Jacobsen epoxidation as illustrated in Scheme 145.[224] The epoxide **414** was obtained directly from olefin **412** in 88−90% yield and 70−74% e.e. using 4 mol % of catalyst **447** and *m*-CPBA as the stoichiometric oxidant. Application of alternative oxidants (NaOCl or magnesium monoperphthalate) resulted in significantly lower yields and enantioselectivities. Resolution of a later carboxylic acid intermediate was necessary to

Scheme 144



Scheme 145



upgrade the enantiomeric excess to >99%. Extensive safety evaluation of the use of *m*-CPBA was conducted, as the reagent is shock sensitive and potentially explosive in the solid state. Ultimately, a procedure involving the addition of a ~4 M solution of *m*-CPBA in EtOH to the reaction mixture was employed. The solubility of the reagent in this solvent was excellent, and thus crystallization of *m*-CPBA during addition, as was observed when CH_2Cl_2 solutions were used, was not encountered. The authors noted an experiment on 700 g scale using a CH_2Cl_2 solution of *m*-CPBA in which chunks of the crystallized reagent fell into the reaction mixture, causing off-gassing which resulted in the ejection of a glass stopper from the 22 L reaction flask. The procedure was reported on up to 1 kg scale. Although more direct than the previously described SAD/Sharpless−Kolb epoxide formation route, the lower optical yield of this process ultimately rendered it less practical, and the SAD-based route was used for further scale-up.

The use of transition-metal-free, organocatalytic asymmetric oxidation procedures is particularly attractive for industrial application, as the need to control metal impurities in the final API is eliminated. Roberts and co-workers (Chiroscience Ltd. and Liverpool University) reported an improved procedure for the Juliá−Colonna epoxidation of enones and its application to the total synthesis of the blood pressure reducing agent diltiazem (Scheme 146).[236] The reaction utilizes immobilized poly-L-leucine as catalyst, urea-hydrogen peroxide as the oxidant, and DBU as the base, allowing the reaction to be conducted in nonaqueous medium. Relative to the originally reported conditions, this procedure gives much shorter reaction times and improved yields. Epoxidation of enone **448** gave the epoxide **449** in >96% e.e. Subsequent Baeyer−Villiger oxidation provided the epoxy ester **450**, which on refluxing with *o*-aminothiophenol in toluene gave α-hydroxester **451** in 90% yield. Interestingly, the opening of epoxide **450** occurred with complete *retention* of configuration. Three additional steps provided diltiazem. The procedure was reported on 4 g scale.

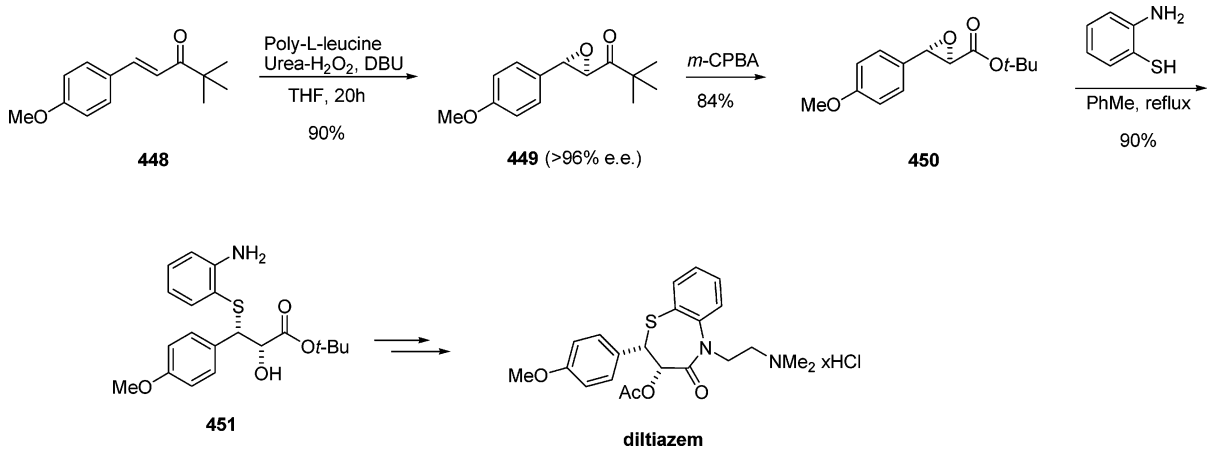
Another metal-free approach to a chiral epoxide intermediate for diltiazem was reported by Seki *et al*. at Tanabe Seiyaku Co. (Scheme 147).[237] Cinnamate ester **452** was epoxidized with the dioxirane derived from 5% ketone **453** and 1 equiv of oxone, furnishing epoxy ester **454** in 77% e.e. (89% yield). The crude mixture of epoxy ester and catalyst was run through an apparatus containing a lipase column and two differentially cooled vessels allowing for continuous dissolution and crystallization. The lipase selectively transesterified the minor enantiomer of **454** to an oily *n*-butyl ester, allowing the isolation of the desired enantiomer of **454** in >99% e.e. (74% yield). The catalyst **453** was also separated (91% recovery) in the apparatus.

The process was reported on 155 g scale. The authors noted the efficiency of the lipase-catalyzed transesterification (1.2 g of Celite-immobilized lipase SM/1 mol epoxy ester) as well as the simplicity of the equipment used for separation of **453** and **454**. The use of asymmetric dioxirane oxidations may prove industrially viable with improvements in catalyst availability and efficiency.

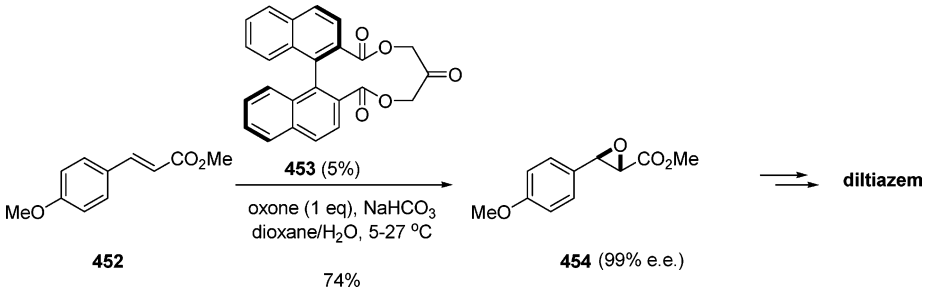
5.5.3. Asymmetric Oxidation of Sulfides

Pharmaceuticals possessing a chiral sulfoxide moiety are becoming increasingly common, and as a result, Kagan and Modena independently reported the application of the Sharpless epoxidation reagent, with some modifications, to the asymmetric oxidation of prochiral sulfides.[213,214] Kagan's procedure utilizes *tert*-butyl hydroperoxide with stoichiometric quantities of Ti(*i*-PrO)$_4$/tartrate ester (1:2) as well as one crucial equivalent of water.[213] The Modena procedure uses additional quantities of tartrate ester (3−4 equiv) in lieu of added water.[214] Both procedures provide sulfoxides with high enantioselectivities, particularly in the oxidation of aryl alkyl sulfides. Kagan's procedure is generally favored industrially due to the lesser quantity of tartrate ester it necessitates.

Scheme 146

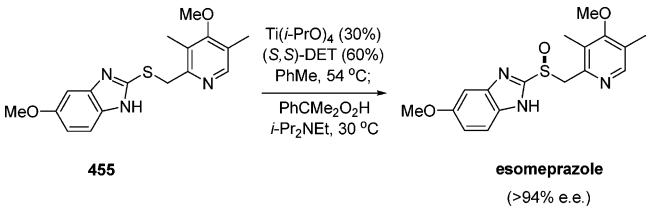


Scheme 147



von Unge and co-workers at AstraZeneca reported the application of an asymmetric sulfoxidation to the synthesis of the marketed proton pump inhibitor esomeprazole (Scheme 148).[238] Initial experiments oxidizing sulfide **455** using

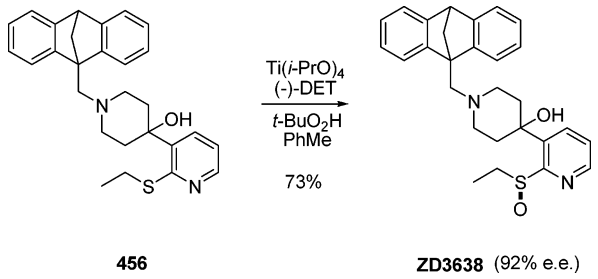
Scheme 148



Kagan's original method gave nearly racemic esomeprazole. This result was attributed to the lack of significant size difference of the sulfide's two substituents. Further studies of reaction conditions led to the discovery of three modifications of Kagan's procedure which allowed esomeprazole to be produced in high e.e. It was found that the titanium complex consisting of Ti(*i*-PrO)$_4$, (*S*,*S*)-DET, and H_2O must be prepared in the presence of sulfide **455**. In addition, this complex preparation must be performed at elevated temperature and/or for an extended period of time. Finally, it was found that the inclusion of *N*,*N*-diisopropylethylamine significantly increased the enantioselectivity. It was noted that each of the above modifications independently increases the e.e. of the reaction, but the application of all three allows high enantioselectivity to be obtained. The catalyst loading could be reduced to 4 mol % without significant reduction of e.e. (91%), although higher loadings gave more reproducible results. It is speculated that the benzimidazole N−H group may be important for the observed enantioselectivity, as substrates lacking this moiety gave inferior results. Among the bases examined, *i*-Pr_2NEt was uniquely effective. Bases of similar pK_a, such as Et_3N or *N*-methyl morpholine, gave lower enantioselectivity, while stronger bases such as DBU and 1,1,3,3-tetramethylguanidine gave dramatically lower e.e. and actually caused the opposite enantiomer to be formed predominantly. Variation in the solvent or the reaction temperature had little effect on the enantioselectivity of the reaction. Crude esomeprazole of >94% e.e. could be crystallized from MIBK/MeCN as the sodium salt in >99.5% e.e. This process was reported on multi-kilogram scale.

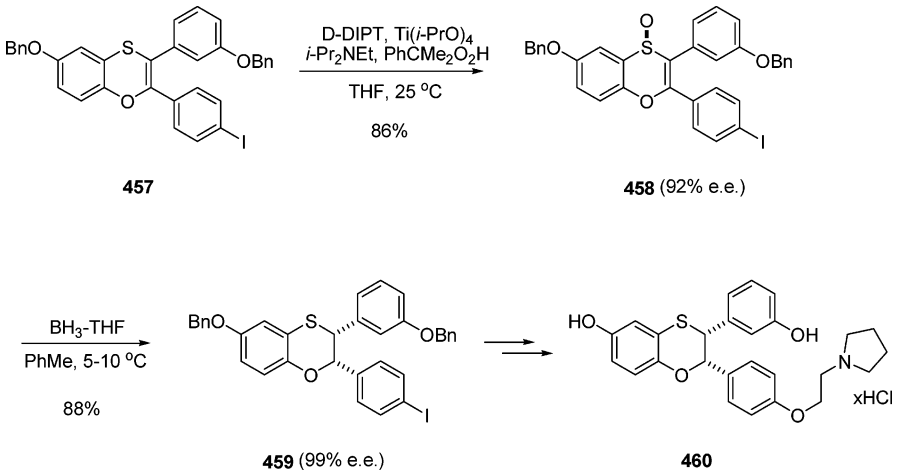
The atypical antipsychotic agent ZD3638 (AstraZeneca) was in development from 1993 to 1997 for the treatment of schizophrenia.[239] The drug was required in >99% e.e., since the minor enantiomer was shown to have an undesirable CNS profile. Patel and co-workers reported the development of an asymmetric sulfoxidation of thioether **456** for the synthesis of ZD3638 (Scheme 149). Initial application of standard

Scheme 149

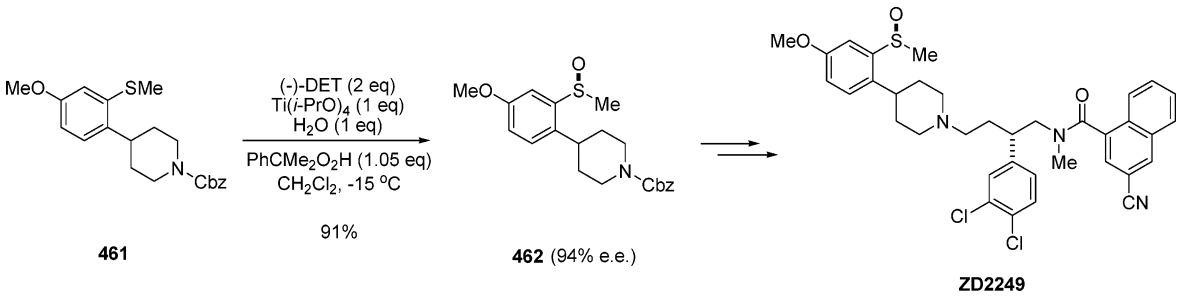


Sharpless conditions for epoxidation of allylic alcohols provided material of 60% e.e. Optimization of these conditions with respect to the order of addition of reagents improved the optical yield to 80% e.e. Factorial experimental design was then used to examine 13 variables involved in catalyst formation.

Scheme 150



Scheme 151



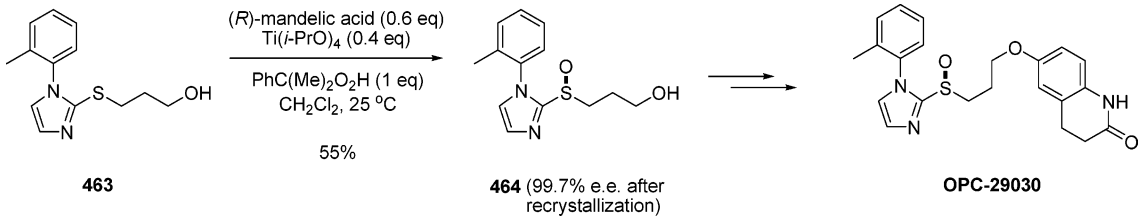
These experiments showed increased e.e. at lower charge ranges of (−)-diethyl tartrate and titanium isopropoxide. Optimized conditions achieved 92% e.e. in the crude reaction mixture, with an upgrade to >99.5% e.e. after crystallization (73% isolated yield).

Song and co-workers at Merck described the asymmetric synthesis of the selective estrogen receptor modulator **460** (Scheme 150).[240] Asymmetry was initially incorporated into the molecule by a modified Kagan oxidation of vinyl sulfide **457**. Preliminary ligand screening under Kagan's original reaction conditions showed D-diisopropyl tartrate gave the best enantioselectivity (38% e.e.). Further optimization studies with this ligand showed a significant increase in e.e. upon addition of diisopropylethylamine. Variation of solvent and temperature, however, had little effect on the enantioselectivity. The order of addition of reagents proved critical to the reproducibility of the e.e. Optimized conditions consisted of adding Ti(*i*-PrO)$_4$ to a mixture of D-diisopropyl tartrate, *i*-Pr$_2$NEt, water, and THF at room temperature, aging the catalyst mixture overnight, adding the vinyl sulfide **457** at 25 °C, and finally adding cumene hydroperoxide.[241] The product sulfoxide **458**, formed in 92% e.e., was crystallized directly from the reaction mixture in 99% e.e. and 86% isolated yield. The authors note that this efficient, direct isolation of the product avoids the difficulties associated with removal of titanium oxide encountered with an aqueous workup. A subsequent stereospecific sulfoxide-directed reduction of the vinyl sulfoxide **458** with borane·THF gave the saturated sulfide **459** in 88% yield and 99% e.e. Labeling experiments using BD_3, and quenching with AcOH showed nearly complete deuterium incorporation at both positions. In addition, experiments using BH_3 and quenching with CD_3CO_2D gave no deuterium incorporation into the product, indicating that both hydrogens are derived from the borane and neither is introduced during the quench. The authors present a possible mechanism for the reduction involving intramolecular hydride addition to the β-carbon of the BH_3-complexed sulfoxide followed by intramolecular delivery of the second hydrogen to the α-carbon with simultaneous S−O bond cleavage. The proposed mechanism was supported by kinetic studies which were consistent with a second-order reaction that was first order in both BH_3 and sulfoxide **458**. The process was performed on multi-kilogram scale.

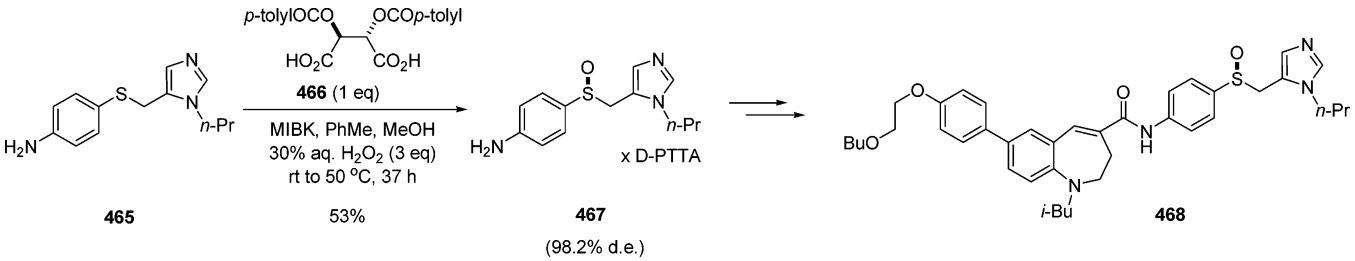
Moseley and colleagues at AstraZeneca disclosed the synthesis of the neurokinin antagonist ZD2249 (Scheme 151).[242] An asymmetric sulfoxidation of sulfide **461** using Kagan's conditions was employed, providing sulfoxide **462** in 94% e.e. The reaction temperature of −15 °C was a compromise between reaction rate and enantioselectivity; at lower temperature, % e.e. increased but the reaction required several days for completion. The charge of cumene hydroperoxide was also critical; higher loadings resulted in faster reaction but produced unacceptably high levels of sulfone overoxidation byproduct. The use of a nearly stoichiometric quantity (1.05 equiv) of the oxidant minimized this impurity (∼1.3%). The sulfoxidation was reported on 0.95 kg scale.

Matsugi *et al*. at Otsuka Pharmaceutical Co. described an efficient asymmetric sulfoxidation in their synthesis of the platelet adhesion inhibitor OPC-29030 as illustrated in Scheme 152.[243] Application of Kagan's procedure to sulfide **463** gave the sulfoxide **464** in only 54% e.e., and although the optical purity could be raised to >99.5% e.e. (42% overall yield) after one recrystallization from MeOH, a more efficient approach was sought. After screening numerous alternative ligands for titanium, (*R*)-mandelic acid was found to give the best results, providing **464** in 76% e.e. Recrystallization from EtOAc upgraded the e.e. to 99.7% (55% overall yield). The reaction could be run at ambient temperature, it was relatively insensitive to residual moisture, and the mandelic

Scheme 152



Scheme 153



acid could be recovered by aqueous base extraction. The process was reported on up to 26.7 kg scale.

Ikemoto and co-workers at Takeda Pharmaceutical Company reported a metal-free asymmetric sulfoxidation reaction for the synthesis of the orally active CCR5 antagonist **468**.[244] Initially, a resolution using di-*p*-toluoyl-D-tartaric acid (D-PTTA, **466**) was employed to give the chiral sulfoxide **467** in 37% yield and >99% e.e. after salt liberation. Subsequently, an approach based on diastereoselective oxidation of the salt formed from sulfide **465** and D-PTTA was investigated (Scheme 153). Optimal conditions, reported for a 3.9 g scale, involved salt formation in toluene/methyl isobutyl ketone and treatment with aqueous H_2O_2 (3 equiv) at room temperature to 50 °C for 37 h. The salt **467** was crystallized from the reaction mixture in 98.2% d.e. (53% yield). Allowing the oxidation to proceed for 3 weeks at room temperature increased the yield of **467** to 72% (98.1% d.e.). The extended reaction times and high volume requirements of this process ($V_{max} \sim 65$ L/kg) may render the original resolution-based approach more suitable for further scale-up, despite the lower yield.

6. Conclusion and Outlook

From the preceding discussions, it is clear that a wide range of stereoselective synthetic methods have found applications in the large-scale asymmetric synthesis of APIs. Chiral auxiliary-based approaches are still a frequently employed strategy for rapid access to optically pure APIs, particularly for preclinical and early clinical supplies. The obvious advantages of this approach include the ready availability of some very powerful chiral auxiliaries as well as the proven generality with respect to substrates.

During the past decade, the field of asymmetric catalysis has been growing at a phenomenal rate. As a result, asymmetric catalysis is being more widely practiced on scale for the synthesis of single enantiomer APIs in the pharmaceutical industry. It is evident that industrial process chemists have already come to appreciate the value of these catalytic methods for the development of cost-effective, scalable, and environmentally sound processes, and have started to integrate these technologies into many API syntheses as highlighted in this review. It is also encouraging to note that, in addition to a few well-established asymmetric catalytic protocols such as asymmetric hydrogenation and asymmetric epoxidation, many other types of catalytic transformations, particularly asymmetric C−C bond-forming and dynamic kinetic resolution approaches, are slowly beginning to be incorporated into the large-scale synthesis of APIs.

Although the industry still has to tackle a number of practical issues related to asymmetric catalysis such as IP situation, economics, and the limited commercial availability of some novel catalysts/ligands, we believe that asymmetric catalysis, which is intrinsically more efficient than many stoichiometric protocols, will become much more widely employed in API synthesis in the future.

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