Organolithium Reagents in Pharmaceutical Asymmetric Processes

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Received December 29, 2005

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1. Introduction

Industrial chemists have developed many efficient, asymmetric processes for synthesizing new drug candidates with increasing structural complexity and multiple chiral centers. Many of these processes involved organolithium species in their asymmetric steps. A review of such processes reported in the past two decades will, hopefully, facilitate future development work.

Organolithium species can generally be used as nucleophiles in asymmetric carbon−carbon and carbon-heteroatom bond formations via alkylations, additions to carbon−heteroatom double bonds, aldol condensations, opening of epoxides, or conjugate additions, as shown in Scheme 1. Organolithium species can be generated from three major pathways: (1) enolization; (2) halogen−lithium exchange; and (3) direct deprotonation with organic lithium reagents. In addition, in-situ generated lithium "ate" complexes were also used in asymmetric syntheses. The most commonly used lithium reagents such as lithium diisopropyl amide (LDA), butyllithium, hexyllithium, phenylithium, and lithium hexamethyldisilazide (LiHMDS) or lithium bis(trimethylsilyl)-amide are commercially available in bulk quantities and are easy to handle in the plant. When appropriate, reactions with organolithium reagents will be compared with other organic reagents, such as organosodium, organopotassium, organomagnesium, organotitanium, and organozinc reagents. Additives, such as LiCl, LiBr, CuX, and water, are often introduced to organolithium reactions to enhance either the reactivity or the enantioselectivity.

While this review focuses on the industrial applications of organolithium reagents to asymmetric processes in the past two decades, there are some excellent reviews of general applications of organolithium reagents. Chiral lithium amides and enantioselective protonation have also been reviewed previously.[1−4] However, most of those reviews do not focus on industrial applications.

2. Organolithium Reagents in Enantioselective Alkylations

Enantioselective alkylation using organolithium reagents as nucleophiles is a simple but very powerful method for asymmetric carbon−carbon bond formation. Most of the reported enantioselective alkylations can be divided into two types of inductions: those using a covalently bonded chiral auxiliary and those using a chiral additive or a catalyst. Chiral auxiliary-based chemistry has been reviewed previously.[4] Chiral auxiliaries are removed in most of the reactions at the end of induction whereas, in some syntheses, an auxiliary is incorporated into the final molecule, the so-called chiral pool-based approach. Chiral additive-induced alkylations are more efficient, as they avoid the attachment and removal of the auxiliary steps. Both primary and secondary electrophiles (RX) can be used for enantioselective alkylations. The major challenge for using a secondary electrophile is how to minimize the elimination. Novel approaches such as 1,3-asymmetric induction, the use of sterically rigid templates, and intramolecular *trans*-alkylations have also been developed.

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10.1021/cr040694k CCC: $59.00
Published on Web 06/15/2006

George Wu received his Bachelor's Degree in 1982 from Xiamen University, China, and his Ph.D. degree in 1988 from the University of Delaware under the direction of Professor Richard F. Heck. From 1988 to 1989, Dr. Wu carried out his postdoctoral research with Professor Negishi at Purdue University. He then joined Process Research and Development at Schering-Plough Research Institute. Dr. Wu's research activities focus on the discovery and development of novel and practical asymmetric processes for synthesizing drug candidates. He has more than 50 publications and patents.

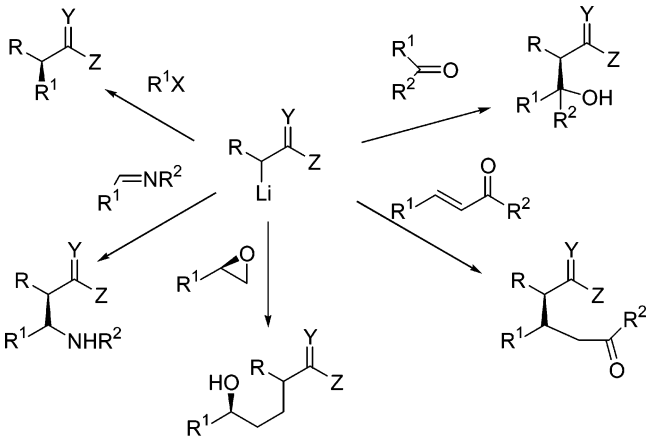
Mingsheng Huang received his B.S. and M.S. degrees from Xiamen University, China. He obtained his Ph.D. degree in chemistry from the University of South Carolina in 1997. He did postdoctoral research at the University of Michigan and the University of Maryland. From 2001 to 2003, he was a postdoctoral fellow at Chemical Process Research and Development, Schering-Plough Research Institute. He joined Vioquest Pharmaceuticals in 2003. He is a coauthor of over 38 publications.

2.1. Chiral Auxiliary-Mediated Asymmetric Alkylations

Chiral auxiliary-induced alkylations of lithium enolates have been widely used in enantioselective formations of C−C bonds. Alkylations with organolithium species often afford chelation-controlled products. Lithium can be replaced with potassium or sodium as the countercation when the chelation product is not preferred.

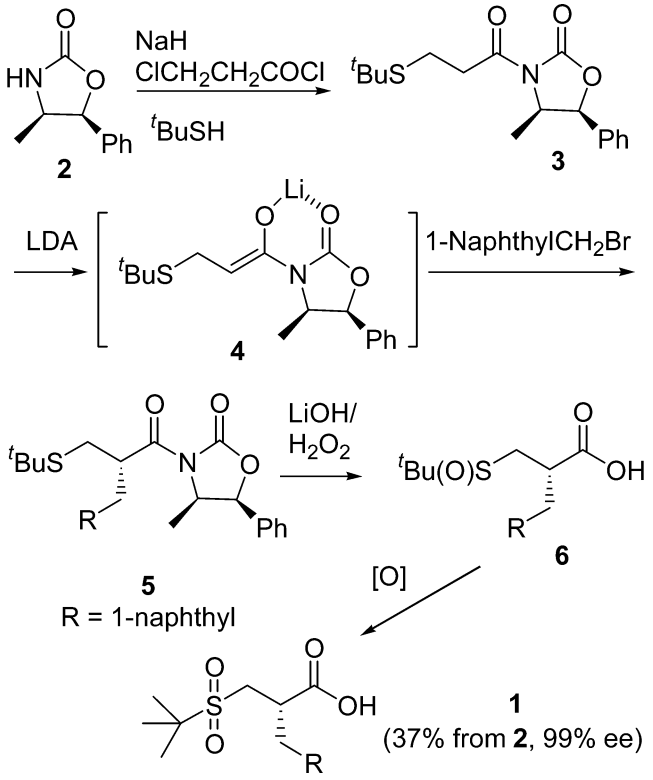
Oxazolidinones are one of the most frequently used chiral auxiliaries for diastereoselective alkylations. For example, Holla et al. of Hoechst used an oxazolidinone **2** as an auxiliary for the diastereoselective alkylation in a concise synthesis of a very potent *N*-terminal component of aspartyl protease inhibitor (**1**).[5] The enantioselectivity was achieved by a stereoselective alkylation of a lithium enolate of thioether oxazolidinone carboximide **3**. First, attachment of the chloropropionyl chloride to auxiliary **2** followed by displacement of the terminal chloride with *t*-BuSH produced amide **3**. A stereoselective enolization of amide **3** with LDA

Scheme 1



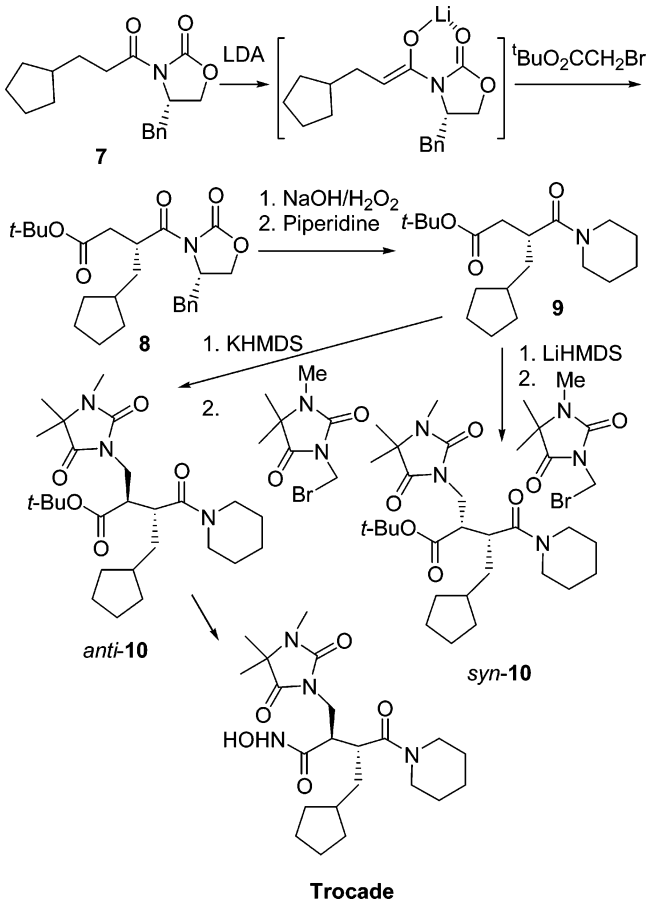
followed by treatment with 1-(bromomethyl)naphthalene gave (*R*)-alkylated product **5**. Presumably, the alkylation proceeded via a chelation-controlled pathway (**4**) with the methyl group on the oxazolidinone ring blocking the front face and the bromomethylnaphthalene approaching from the back side. The alkylated product **5** was converted into the desired drug intermediate **1** via hydrolysis of the auxiliary with a concurrent oxidation of the sulfinyl group. The synthesis was carried out on a 100 g scale and produced **6** in 37% overall yield and 99% ee (Scheme 2).

Scheme 2



In the synthesis of Trocade, a matrix metalloproteinase inhibitor, Hilpert of Hoffmann-La Roche used the oxazolidinone auxiliary to effectively construct two consecutive chiral centers.[6] First, enolization of the cyclopentylpropionic amide **7** with LDA followed by alkylation of the lithium enolate with *tert*-butyl bromoacetate gave the chelation controlled product **8** in 99.6% de (Scheme 3). The alkylation

Scheme 3



product **8** was converted into the corresponding piperidine amide **9** via a two-step sequence. Next, a chemoselective enolization of the ester carbonyl in **9** with a base followed by alkylation with bromomethylhydantoin gave either *syn*- or *anti*-succinate **10**, depending on the base used.

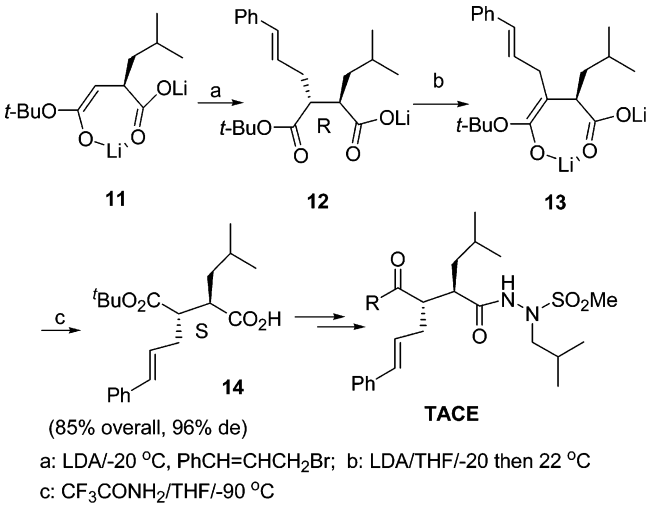
Hilpert also studied the effects of both countercation and temperature on the *anti*/*syn* selectivity. A lithium base such as LDA produced preferentially *syn*-**10** (*anti*/*syn* = 15:85), whereas a potassium base such as KHMDS afforded predominantly *anti*-**10** (*anti*/*syn* ratio up to 99:1). In the second alkylation, it was assumed that the chelation of the lithium enolate with the adjacent carbonyl group induces the alkylation from the sterically less hindered face, leading to the *syn*-**10** isomer. In contrast, the potassium enolate was assumed to favor the nonchelated, thermodynamically more stable conformation, consequently affording the desired *anti*-**10** product. There was a temperature effect on the *anti*/*syn* selectivity. The higher the temperature, the better the selectivity, as summarized in Table 1. The *anti*-**10** intermediate was converted into Trocade in good yield.

Table 1. Cation and Temperature Effects

entry	base	temp (°C)	*anti*-/*syn*-**10**
1	LDA	−78	15:85
2	$NaN(SiMe_3)_2$	−78	50:50
3	$KN(SiMe_3)_2$	−78	80:20
4	$KN(SiMe_3)_2$	−60	92:8
5	$KN(SiMe_3)_2$	−40	99:1

In the synthesis of another Trocade analogue, Hilpert demonstrated that alkylation of a dianion lithium enolate of succinic acid **11** with cinnamyl bromide gave a 93:7 mixture

Scheme 4

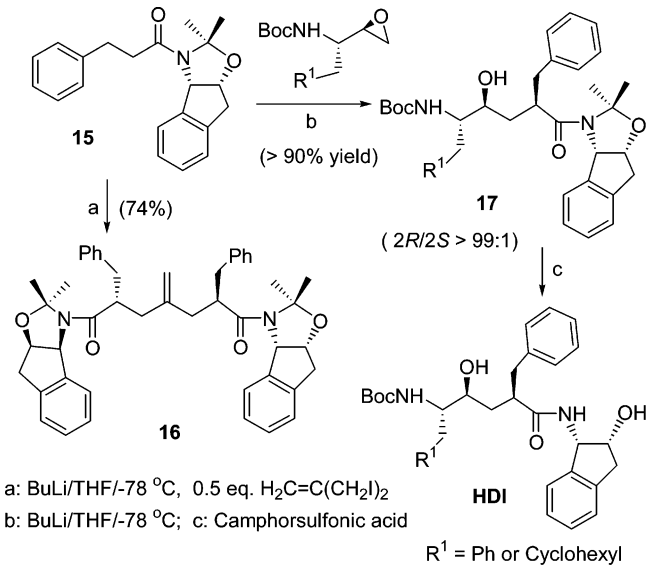


in favor of the *syn*-isomer **12**.[6] As shown in Scheme 4, the *syn*-isomer **12** was converted into its corresponding *anti*-isomer via a second LDA enolization and reprotonation. The alkylation took place from the back side of the enolate, as the front face was blocked by the isobutyl group in the seven-membered ring Li complex. The newly formed chiral center was inverted from *R* to *S* configuration via a second deprotonation to form another Li complex **13** and reprotonation from the back face again to afford *anti*-**14**. The *anti*-**14** was subsequently transformed to the desired TACE.

Both of the above processes have been scaled up in the plant and have produced the desired Trocade and TACE in multiton and multi-kilogram quantities.[6]

Merck chemists developed a new class of chiral auxiliaries, the *cis*- and *trans*-aminoindanols, for the syntheses of various drug candidates. Initially, *cis*-aminoindanol was explored as an auxiliary because it was part of a target protease inhibitor.[7] Since then, it has become an important auxiliary in its own right. Askin et al. reported the first example of using *cis*-aminoindanol as an auxiliary for the synthesis of hydroxyethylene dipeptide isostere (HDI) inhibitors of HIV-1 protease.[7] As shown in Scheme 5, enolization of the 3-phenylpropionic amide of aminoindanol **15** with *n*-BuLi followed by simultaneous alkylations of 2 equiv of enolized

Scheme 5

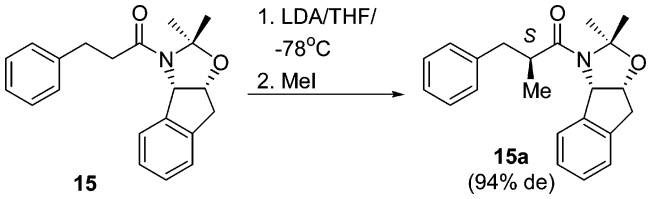


15 with $H_2C{=}C(CH_2I)_2$ gave a C_2 symmetry dimer **16**. The lithium enolate could also be trapped with an epoxide to give hydroxylamide **17** in 90% yield and >98% ee. The *cis*-aminoindanol in compound **17** was hydrolyzed using camphorsulfonic acid to give the desired HDI inhibitor.

The outcome of the *R*-stereochemistry at the C-2 positions of products **16** and **17** indicated that both the alkyliodide and the epoxide electrophiles approached from the opposite site to the aminoindanol group of the lithium enolate. The facial selectivity observed here is different from those of reactions observed with prolinol amide enolates.[7e] Grignard reagents such as isopropylmagnesium chloride gave lower yields (~60%) of the desired product in the epoxide-opening reaction.

Treatment of **15** with LDA followed by reacting with MeI produced alkylated product in 94% de (Scheme 6).

Scheme 6



The high diastereoselectivity obtained with the *cis*-aminoindanol auxiliary can be explained by electrophile attack from the upper level of the enolate being favorable because of the steric interaction between the pseudoaxial methyl and the incoming electrophiles at the lower level of the enolate as shown in Figure 1.

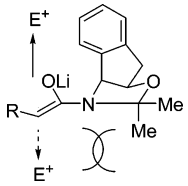
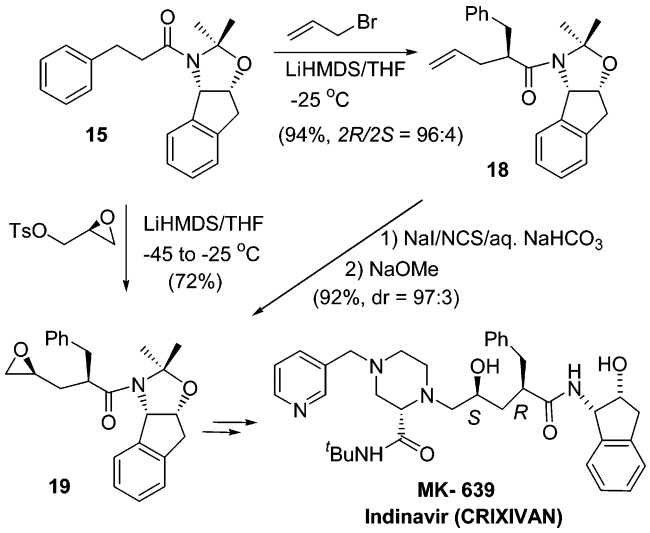


Figure 1.

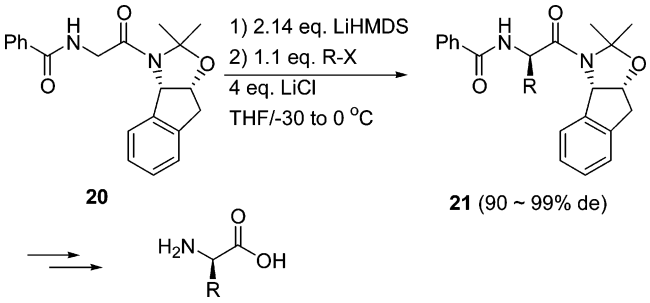
Merck chemists have also successfully applied a rigid tricyclic aminoindanol acetonide to the asymmetric syntheses of Crixivan, one of the leading orally active HIV protease inhibitors.[7] Two alternative approaches were developed starting from indanol amide **15**, as outlined in Scheme 7. In the first approach, *cis*-aminoindanol amide was enolized with LiHMDS followed by addition of allyl bromide to give intermediate **18** in 92% de. The terminal double bond was converted into the corresponding epoxide **19** in 94% yield and 92% de. In the second approach, indanol amide **15** was enolized with LiHMDS and alkylated with a chiral epoxy tosylate to give compound **19** in 72% yield. The predominant pathway was the Li-enolate opening of the epoxide followed by ring closure on to the tosylate to give the desired diastereomers. A minor amount of the epimeric **19** was obtained from a direct enolate attack on the tosylate. Compound **19** was subsequently converted into Crixivan. The above syntheses are very efficient because the *cis*-aminoindanol served both as an auxiliary and as a part of the final molecule.

Under certain reaction conditions, addition of some additives such as LiX, CuX, or water to organolithium reactions can enhance either the reactivity or the enantioselectivity. In general, organolithium species exist as aggregates in solution and addition or in situ generation of another lithium species can either break or change the aggregation state.[8] For example, addition of LiCl to alkylation of *cis*-aminoindanol-modified glycine enolate **20** with a number of alkyl halides gave the corresponding alkylated product **21** in excellent diastereoselectivity (90−99%).[8] In the absence of LiCl, both the diastereoselectivity and the yield suffered. Merck chemists also developed an effective method to remove the auxiliary without epimerization of the newly formed chiral center, providing a practical synthesis of α-amino acids as shown in Scheme 8.

Scheme 7



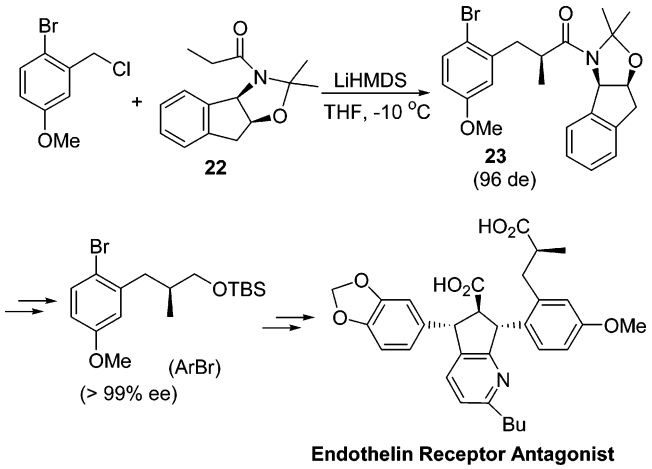
Scheme 8



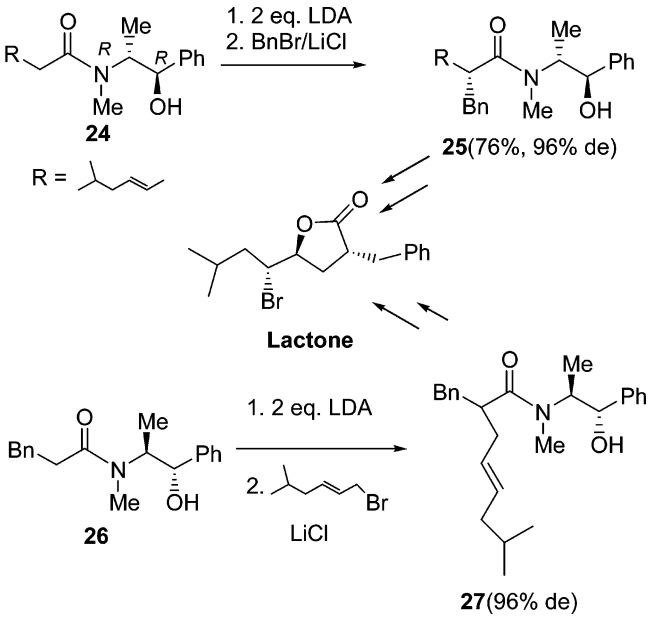
In another successful application of (1*R*,2*S*)-*cis*-aminoindanol as an auxiliary, Song et al. of Merck developed an efficient synthesis of the side chain of an endothelin receptor antagonist.[9] As shown in Scheme 9, enolization of a propionamide **22** with LiHMDS followed by alkylation with benzyl chloride gave 2-methyl-3-(2-bromo-5-methoxy)phenylpropionamide **23** in 96% de. Intermediate **23** was converted into the desired endothelin receptor antagonist in several steps, and the de was further enhanced in the down stream chemistry.

Pseudoephedrine is another useful chiral auxiliary for alkylations initially developed by Myers.[10] Unlike the rigid oxazolidinones or Merck's aminoindanols, the pseudoephedrine auxiliary has a linear structure. In the synthesis of a nonpeptidic enzyme inhibitor, for example, Dragovich of Agouron Pharmaceuticals obtained excellent diastereoselectivity in the alkylation step using pseudoephedrine as a chiral auxiliary.[11] Two equivalents of LDA are required both to deprotonate the alcohol and to enolize the amide carbonyl in 7-methyloct-4-enoic amide **24** (Scheme 10). Alkylation

Scheme 9



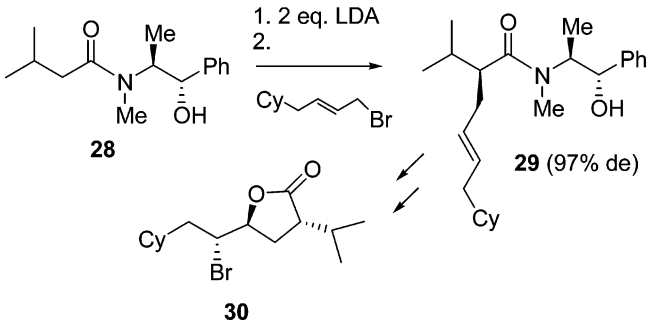
Scheme 10



of the lithium dianion derivative with benzyl bromide gave product **25** in 76% yield and 98% de. Alternatively, the same product (**25**) could be obtained in 96% de using (1*S*,2*S*)-pseudoephedrine as a chiral auxiliary when 3-phenylpropionyl amide **26** was used as a starting amide and an allyl bromide derivative was employed as an electrophile. It is worth noting that LiCl is necessary for this type of auxiliary-promoted alkylation.

The Myers (*S*,*S*)-pseudoephedrine auxiliary was also used in the synthesis of a similar alkylation product **29** in 97% de, as shown in Scheme 11.[11]

Scheme 11



Myers proposed a reactive conformer to explain the high diastereoselectivities in the alkylation of pseudoephedrine amide enolates.[10] As shown in Figure 2, the electrophile

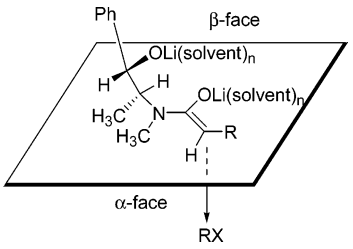
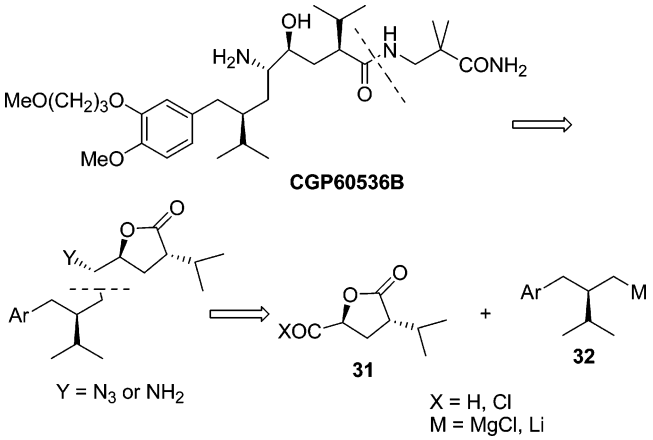


Figure 2.

approached preferentially from the α-face of the conformer because the solvated lithium species blocks the *β*-face of the (*Z*)-enolate.

Sandham et al. of Novartis have applied the chiral alkylation of pseudoephedrine amides to the synthesis of a novel orally active renin inhibitor, CGP60536B (Scheme 12).[12] The two key chiral moieties **31** and **32** in CGP60536B

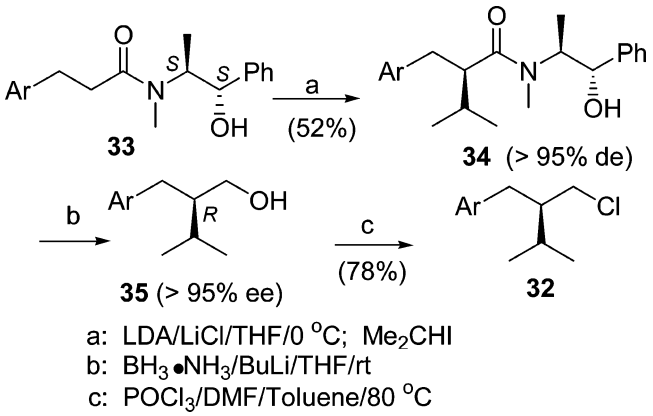
Scheme 12



were both obtained from alkylations using the pseudoephedrine auxiliary.

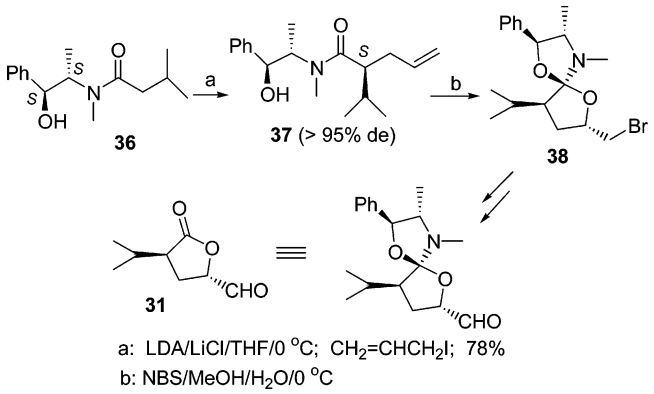
As shown in Schemes 12 and 13, (+)-pseudoephedrine was used to prepare two chiral moieties **31** and **32** in high ee's. First, enolization of (*S*,*S*)-pseudoephedrine amide **33** with LDA along with LiCl followed by addition of isopropyl iodide gave alkylation product **34** in >95% de and 52% yield (Scheme 13). Conversion of **34** to the corresponding alcohol **35** followed by chlorination gave chiral moiety **32** in 78% yield.

Scheme 13



Similarly, the spiro chiral moiety **31** was prepared in several steps starting from alkylation of (*S*,*S*)-pseudoephedrine amide **36** in >95% de (Scheme 14). Interestingly, the

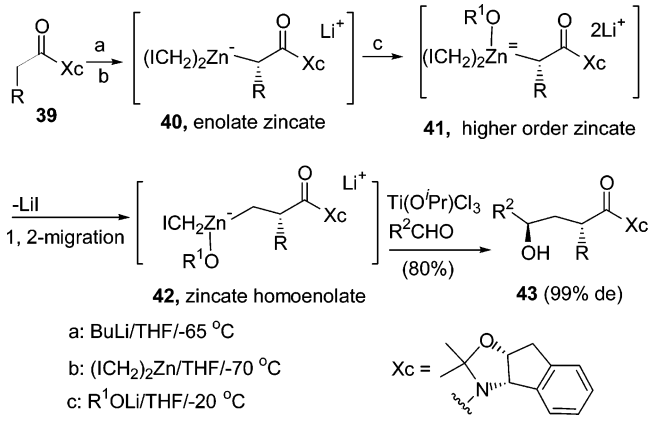
Scheme 14



formation of the amide spiroacetal **38** was used as a novel lactone-protecting group for a stereoselective Grignard addition reaction. The process was reported to be amenable to large-scale operation, demonstrating the feasibility of pseudoephedrine as an inexpensive and recoverable chiral auxiliary.

In an elaborated, tandem asymmetric transformation process, Armstrong et al. of Merck used various chiral auxiliaries to prepare a zincate homoenolate, a key intermediate in the preparation of HIV protease inhibitors and renin inhibitors.[13] In a series of sequential transformations, an amide derivative was converted into a γ-hydroxyl amide **43** with two new chiral centers. First, enolization of aminoindanol amide **39** with BuLi followed by a treatment with bis(iodomethyl)zinc afforded a chiral enolate of lithium zincate **40**. Second, treatment of the resulting zincate **40** with an alkoxyllithium reagent followed by a 1,2-migration resulted in a chiral zincate homoenolated product, **42**. Finally, the homologated zincate **42** could add to an aldehyde, producing γ-hydroxy amide **43** in 80% overall yield and 99% de (Scheme 15). Alternatively, zincate **42** could undergo

Scheme 15

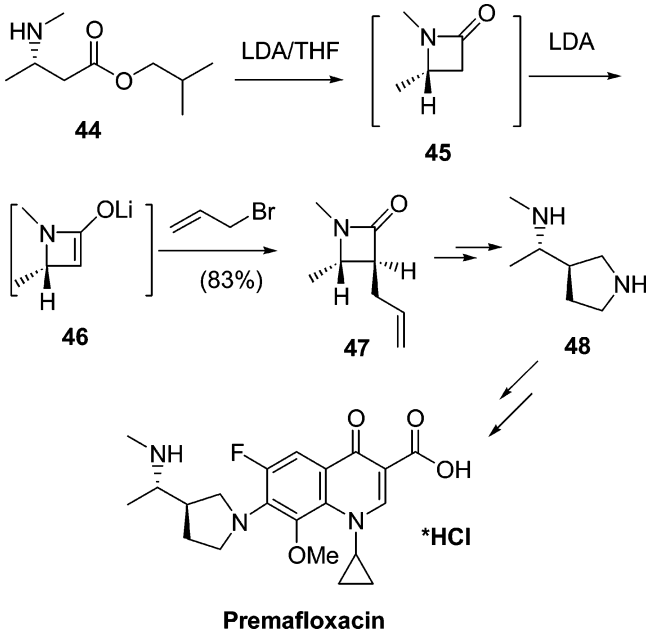


further transmetalation reactions, in a one-pot process. A number of chiral auxiliaries such as *cis*-aminoindanol derivatives, oxazolidinones, Meyer's auxiliaries, camphor derivatives, diamines, amino alcohols, and their derivatives worked well for this process. This novel sequence of transmetalations can be potentially useful in other industrial processes.

2.2. Chiral Pool-Based Alkylations

Recently, McWhorter of Pfizer reported a chelation-controlled stereoselective alkylation of a β-lactam intermediate for the synthesis of Premafloxacin, a potent antibiotic.[14] Treatment of isobutyl (*S*)-3-(*N*-methyl)aminobutyrate **44** with 1 equiv of LDA produced a monosubstituted β-lactam intermediate **45**. Enolization of the monosubstituted β-lactam **45** with a second equivalent of LDA followed by alkylation with allyl bromide generated a *trans* disubstituted β-lactam **47** in 100% de and 83% overall yield (Scheme 16). In this

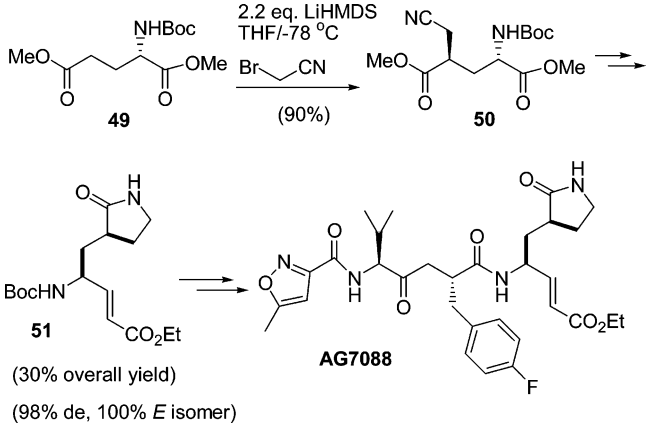
Scheme 16



case, the β-lactam ring served as a chiral template to induce the chiral alkylation *trans* to the existing methyl group. The disubstituted β-lactam **47** was converted into optically pure monosubstituted pyrrolidine **48**, a key intermediate in the formation of Premefloxacin.

Tian et al. of Pfizer have applied a 1,3-asymmetric induction to the synthesis of AG7088 (Scheme 17) by

Scheme 17

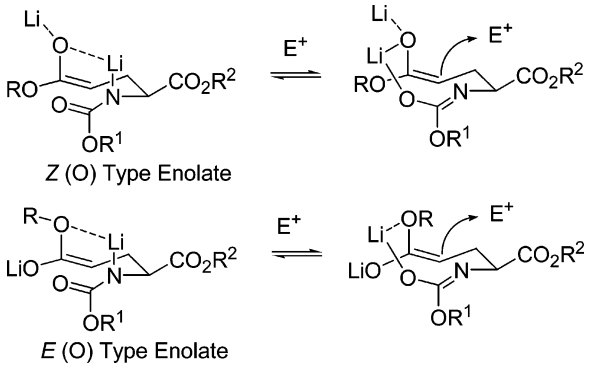


extending Hanessian's method.[15,16] Thus, treatment of *N*-Boc-L-(+)-glutamate **49** with 2 equiv of LiHMDS generated a dianion. Alkylation of the lithium dianion with bromoacetonitrile proceeds with remarkable stereoselectivity in the absence of additives to give almost exclusively the corre-

sponding *anti*-isomers **50** in 90% yield. This asymmetric dianionic cyanomethylation has been applied to an efficient synthesis of the chiral γ-lactam derivative **51**, a key intermediate in the synthesis of the rhinovirus protease inhibitor AG7088. This process was scaled up in the plant and produced AG7088 in multi-kilogram quantities.

Hanessian proposed a transition state to account for the observed 1,3-*trans*-induction as shown in Scheme 18.[16] There

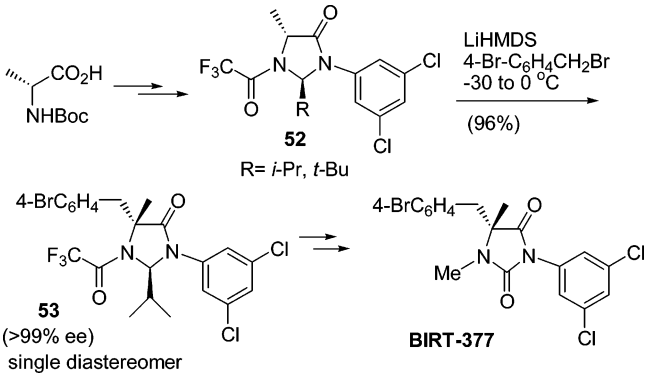
Scheme 18



are two possible chair forms of *Z*(O) or *E*(O) enolate geometries. In both enolates, however, the incoming electrophile approaches from the preferred equatorial position to generate the desired 1,3-*trans*-product.

Yee et al. of Boehringer Ingelheim have applied Seebach's principle of self-regeneration of stereocenters (SROSC)[17] to an enantioselective synthesis of the *N*-arylhydantoin LFA-1 antagonist BIRT-377.[18] The SROSC first relays the amino chiral center in an amino acid to the 2-position of an oxazolidinone or an imidazolidinone. Then, the relayed chiral center is used to induce the stereoselectivity at the α-position of the carbonyl. For example, *N*-Boc-D-alanine was converted into an imidazolidinone derivative **52** in high de. The newly formed *tert*-butyl or isopropyl substituent chiral center in imidazolidinone **52** induced the alkylation of the α-carbonyl position to give **53** in >99% ee and 96% yield (Scheme 19).

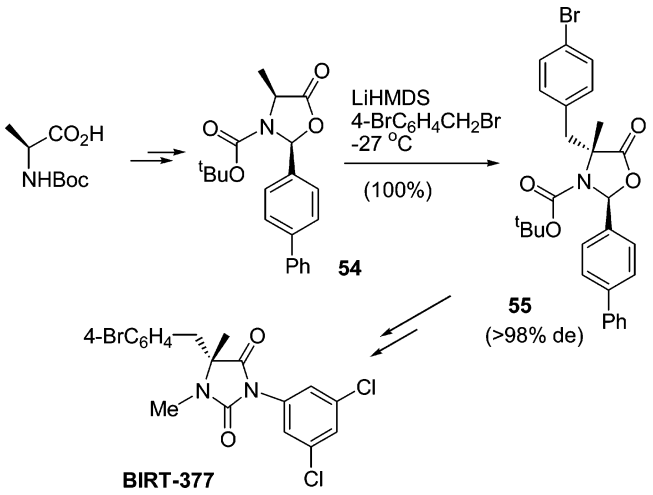
Scheme 19



Both the *tert*-butyl and the isopropyl templates worked equally well for the asymmetric induction in terms of yield and diastereoselectivity. This represented the first application of the 2-isopropylimidazolidinone template to the asymmetric synthesis of α-disubstituted amino acid derivatives.

Analogously, Napolitano and Farina used a *cis*-oxazolidinone derivative for the SROSC in the synthesis of BIRT-377.[19] The amino chiral center in *N*-Boc-L-alanine was completely relayed to the 2-position of 2-aryloxazolidinone **54**. Enolization of the carbonyl in **54** with LiHMDS followed by addition of 4-$BrC_6H_4CH_2Br$ at −27 °C gave the alkylation product **55** in excellent yield and >98% de. Intermediate **55** was converted into **BIRT-377** in 40% overall yield and >99.9% ee (Scheme 20).

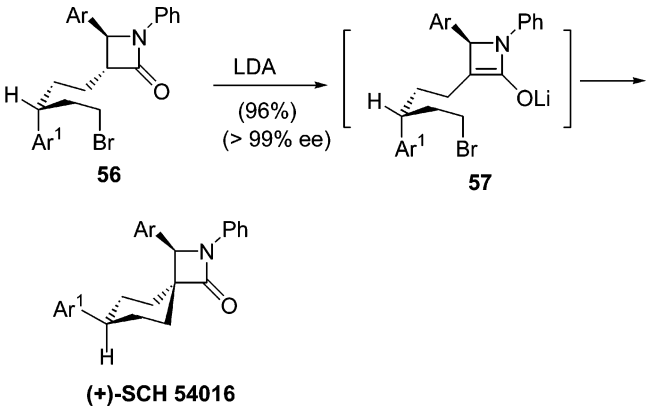
Scheme 20



2.3. Intramolecular Alkylation

Chemists at Schering-Plough have been interested in a series of azetidinone structures for use as novel cholesterol absorption inhibitors. In one of the syntheses, Chen et al. have applied an intramolecular *trans*-alkylation of a 2-azetidinone to the synthesis of a spirocyclic cholesterol absorption inhibitor (Scheme 21).[20] Enolization of **56** with LDA

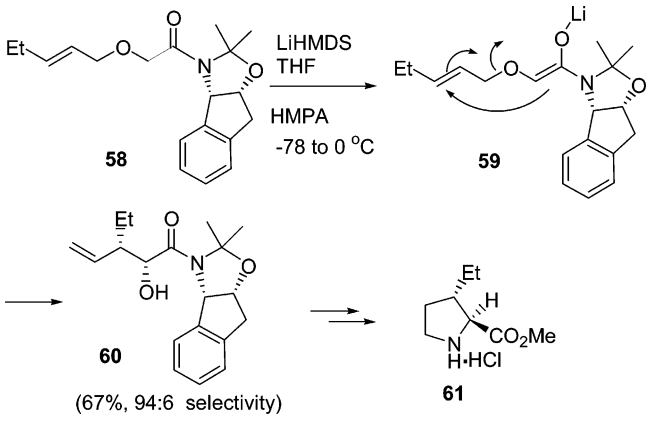
Scheme 21



followed by an intramolecular alkylation gave the spiro β-lactam. The Ar substituent on the β-lactam ring controls the facial selectivity, producing exclusively the desired diastereomer (+)-SCH 54016 in 96% yield and 99% de (Scheme 21).

Kress et al. of Merck reported another intramolecular alkylation for enantio- and diastereoselective synthesis of a substituted proline using (1*S*,2*R*)-1-aminoindanol as a chiral auxiliary. Enolization of 2-pentenoxyamide with LHMDS gave the α-allyloxyamide lithium enolate **59**.[21] An in situ [2,3]-Wittig rearrangement produced homoallyl-3-ethyl-2-hydroxyamide in 67% yield and 94:6 diastereoselectivity. It was found that LiHMDS is a much better base than NaHMDS, KHMDS, or *n*-BuLi. Addition of HMPA or DMPU was required for the reaction. After removal of the auxiliary, the resulting optically active α-hydroxy acid was converted into 3-ethylproline derivative **61** (Scheme 22).

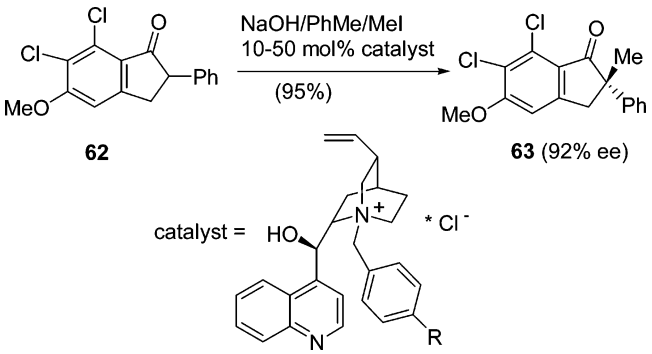
Scheme 22



2.4. Chiral Additive-Mediated Alkylation

One of the major challenges for industrial chemists is to develop efficient, practical, and low-cost asymmetric processes for the synthesis of drug candidates. In general, chiral additive-mediated alkylations are much more efficient than auxiliary-based reactions because the former type does not require the attachment and removal of the auxiliaries, thus increasing the throughput. However, the challenge is how to obtain high enantioselectivity with an external chiral additive. In 1984, Dolling et al. of Merck reported the first example of a catalytic asymmetric alkylation for the synthesis of (+)-Indacrinone (Scheme 23).[22] Methylation of 6,7-

Scheme 23



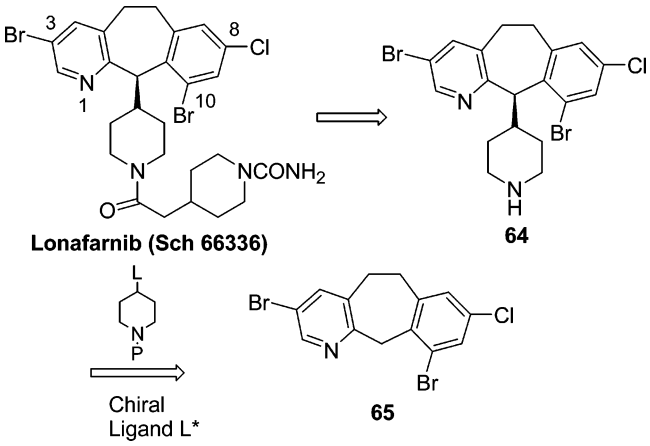
dichloro-5-methoxy-2-phenyl-1-indanol **62** in toluene with aqueous sodium hydroxide in the presence of *N*-benzylcinchoninium chloride as a phase transfer catalyst produced the desired alkylation product **63** in 95% yield and 92% ee.

Other chiral amine-promoted alkylations have been extensively studied in academic research;[23] their application, however, to drug syntheses is rare.

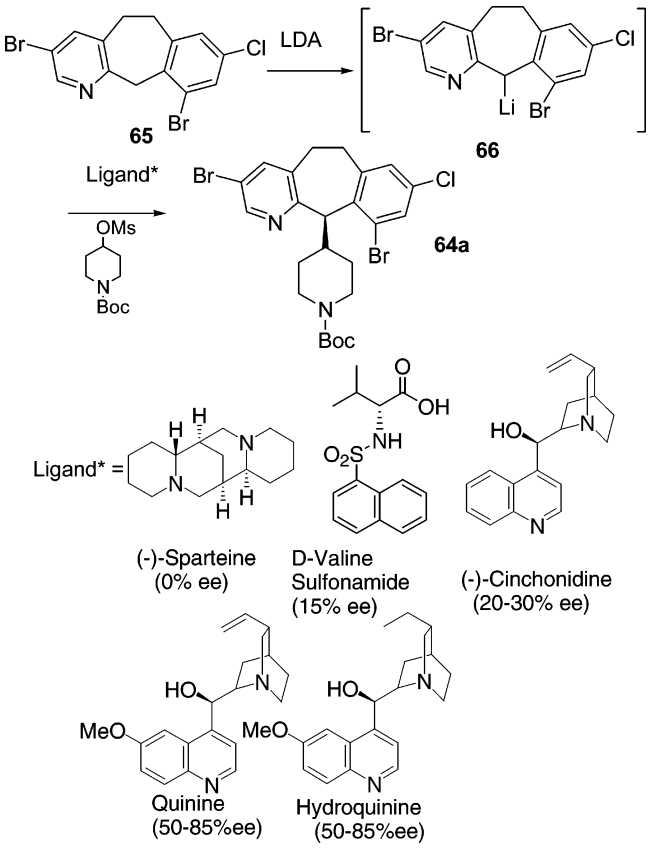
Chemists at Schering-Plough discovered a novel enantioselective alkylation of doubly benzylic substrates with secondary electrophiles and applied it to the synthesis of Lonafarnib, an anticancer agent.[24] As shown in Scheme 24, the desired chiral center in Lonafarnib was established via an alkylation of the doubly benzylic carbon in **65** with a secondary electrophile of the piperidine derivative.

First, lithiation of the doubly benzylic position in **65** with LDA and displacement of *N*-Boc-piperidine mesylate in the presence of a chiral ligand gave alkylated product **64a**. As shown in Scheme 25, (−)-sparteine gave no stereocontrol while D-valine sulfonamide afforded 15% ee. However, quinine and hydroquinine gave up to 85% ee. The common

Scheme 24



Scheme 25



feature of the cinchonidine family is the hydroxy group. In addition, the extra methoxy group on the quinoline moiety exerts a great influence on the enantioselectivity. The presence of the hydroxyl group required 2 equiv of LDA for the dianion formation.

To account for the high enantioselectivity with the cinchonidine additives, a three-point interaction model was proposed for the asymmetric induction (Figure 3). First, both the alkoxyl and the bridge-head nitrogen act as a bidente to chelate the lithium anion at the benzylic position. The π-stacking between the quinoline moiety and the pyridine ring in the substrate provides the third point of interaction. The methoxy group on the quinoline donates the electrons to the aromatic ring and enhances the π-stacking effect. The three-point interaction locked the doubly benzylic anion into a pro-*R* configuration, resulting in the desired alkylation product.

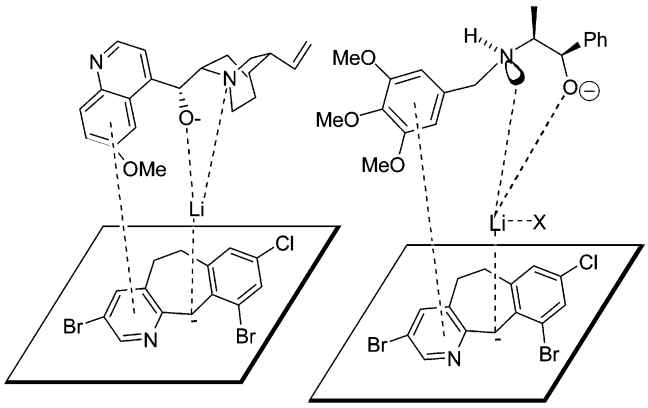


Figure 3.

To further improve the enantioselectivity, chemists at Schering-Plough designed and prepared a norephedrine-derived ligand based on the hypothesis in Figure 3. While tertiary amine **67** gave low induction (13−28% ee), its secondary amine counterpart **68** afforded up to 88% ee (Figure 4). Once again, the presence of the methoxy group(s) on the benzene ring greatly enhances the enantioselectivity.

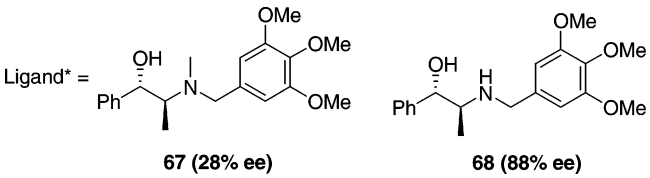


Figure 4.

Furthermore, chemists at Schering-Plough discovered a pronounced water effect on the enantioselectivity. Initially, the enantioselectivity was inconsistent and not reproducible. Later, the reaction mixture was spiked with different amounts of water prior to the addition of LDA. As shown in Table 2,

Table 2. Water Effect

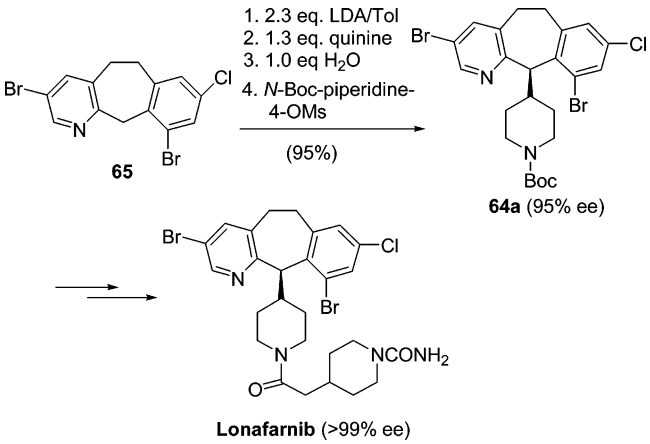
entry	water spiked (equiv)	yield (%)	ee (%)
1	0.0	50−60	55−60
2	0.5	n/a	72
3	0.7	92	85
4	1.0	95	95

the higher the water content, the better the enantioselectivity and the higher the yield. The alkylation with 1 equiv of added water produced the doubly benzylic chiral center in 95% yield and 95% ee using either the quinine or the norphedrine-base ligands. Presumably, water reacted with LDA to form LiOH. The in situ generated LiOH breaks the lithium aggregate and therefore enhances the reactivity. Addition of solid LiOH, however, did not have any impact on the enantioselectivity.

This novel chiral alkylation was scaled up in the plant to a 33 kg batch size and produced multi-hundred kilograms of Lonafarnib (Scheme 26). The enantiomeric excess was further enhanced from 95% to >99% in the down stream processes.

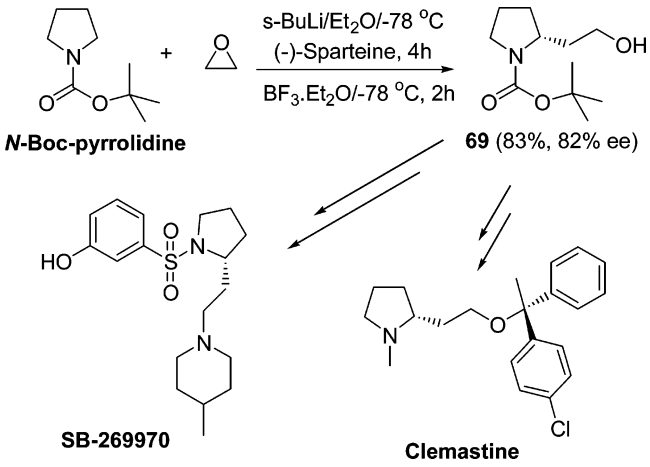
Recently, Mani et al. of Johnson & Johnson developed a practical (−)-sparteine-induced asymmetric lithiation of *N*-Boc-pyrrolidine for the synthesis of (*R*)-*N*-Boc-2-(2-hydroxyethyl)pyrrolidine **69**, a key intermediate in the syntheses of SB-269970 and Clemastine.[25] Lithiation of

Scheme 26



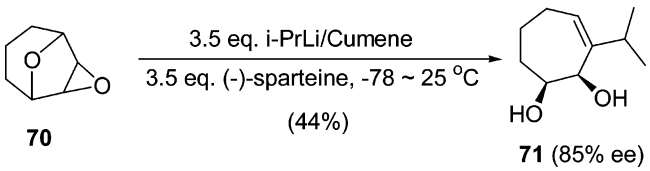
N-Boc-pyrrolidine with *s*-BuLi in the presence of (−)-sparteine followed by trapping the anion with ethylene oxide gave the homologated alcohol **69** in 83% yield and 82% ee. BF_3·OEt_2 was required for the epoxide opening, presumably coordinating with the epoxide and activating it for the attack (Scheme 27).

Scheme 27



Hodgson et al. of Isis Innovation Limited, U.K., reported a process for the preparation of optically active unsaturated alkene diols in a regio-, stereo-, and enantiocontrolled fashion via an alkylative double ring opening of oxa-bicycles with organolithium in the presence of chiral ligands such as (−)-sparteine.[26] For example, exo-6,7-epoxy-8-oxabicyclo[3.2.1]-octane **70** was reacted with isopropyllithium in the presence of (−)-sparteine in cumene to give (1*S*,2*R*)-(−)-3-isopropyl-cyclohept-3-ene-1,2-diol **71** in 44% yield and 85% ee (Scheme 28).

Scheme 28



3. Chiral Nucleophilic Addition of Organolithium Reagents

Addition of organometallic, particularly organolithium, reagents to electrophiles such as imines, ketones, and

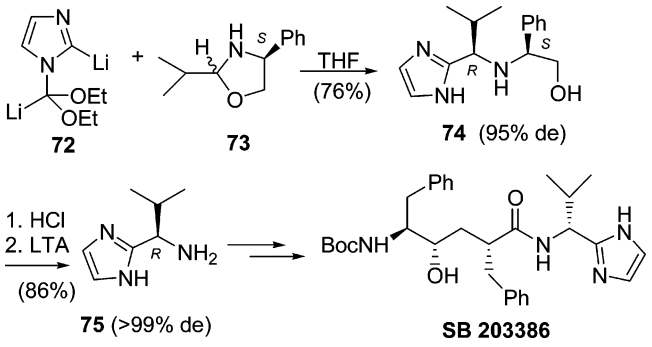
epoxides is a powerful method to form chiral centers. Most of the examples discussed in this section focus on the addition of organolithium reagents to imines for the formation of chiral centers as a key step in drug syntheses.

3.1. Addition to a C=N Bond

While addition of organolithium reagents to imines has been reviewed previously,[27−29] this review focuses on industrial applications. Similar to the case of the alkylation reactions, the chiral centers can be induced by a chiral auxiliary, a chiral additive, a chiral catalyst, or a chiral template that is part of the molecule.

In the synthesis of a key intermediate for a potent protease inhibitor (SB-203386**)**, Pridgen et al. of SmithKline Beecham have developed a nucleophilic addition of a lithium reagent to chiral 1,3-oxazolidines, presumably serving as a masked imine (Scheme 29).[30,31] Thus, addition of the lithium dianion

Scheme 29



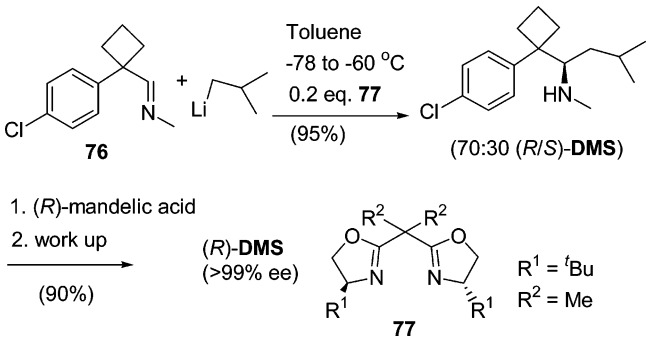
of ortho ester-protected imidazole **72** to 2-isopropyloxazolidine **73** produced (*R*,*S*)-amino alcohol **74** in 76% yield and 95% de. The chiral induction came from the original (*S*)-phenylglycinol, and the nitrogen atom became part of the molecule (**74**) after an oxidative removal of the auxiliary.[31] The corresponding (*S*,*R*)-enantiomer was prepared in 84% yield using the (*R*)-2-phenylglycinol as the auxiliary. Compound **75** was converted into a protease inhibitor (SB-203386) in several steps.

Senanayake et al. of Sepracor have developed an aldimine-catalyzed chiral addition of *i*-BuLi to an imine substrate for an asymmetric synthesis of (*R*)-desmethylsibutramine (DMS), a metabolite of an antiobesity compound.[32] Thus, addition of *i*-BuLi to aldimine **76** in the presence of 0.2 equiv of bisoxazoline **77** gave (*R*)-desmethylsibutramine in 40% ee and 95% conversion. The enantioselectivity was only moderate and was independent of the amount of the chiral ligand used. Use of other C_2 symmetric chiral catalysts such as bisoxazolines or (−)-sparteine gave poorer results. A partial resolution with (*R*)-mandelic acid further enhanced the ee from 40% to >99% with >90% recovery (Scheme 30).

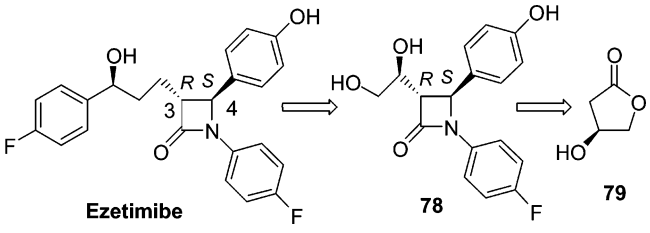
Chemists at Schering-Plough have developed a novel and efficient enantio- and diastereoselective synthesis of Ezetimibe, a cholesterol absorption inhibitor. The key to this novel synthesis was the development of a one-step formation of the *trans*-β-lactam **78** from a chiral aldol condensation of the lithium dianion of 3-(*R*)-hydroxy-γ-lactone **79** and an imine ($Ar^1CH{=}NAr^2$), as shown in Scheme 31.[33]

First, conversion of hydroxy-γ-lactone **79** to its corresponding lithium dianion **80** with 2 equiv of LDA followed by addition to an imine produced two adducts (*S*,*S*,*R*)-**81** and (*S*,*S*,*S*)-**81** together with a small amount of two cyclized products (*trans*- and *cis*-**82**), as shown in Scheme 32. The

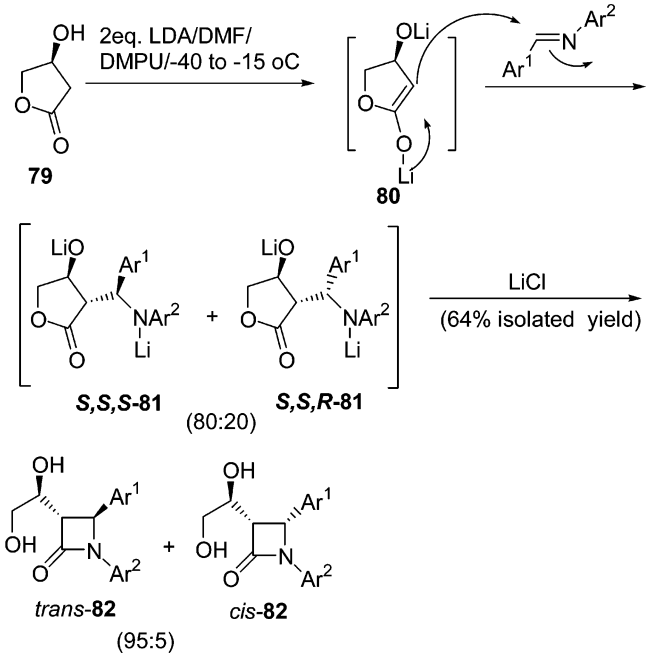
Scheme 30



Scheme 31



Scheme 32

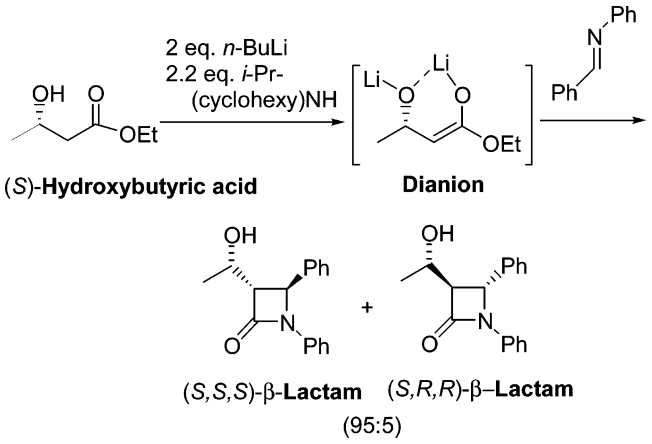


addition of lithium enolate **80** to an imine took place exclusively from the opposite side of the alkoxide group to give the (*S*)-configuration. However, the diastereoselectivity at the benzylic position was only 80:20 in favor of the desired *SSS*-isomer. Initially, the cyclization to form the β-lactam could not be completed under the reaction conditions. The addition of lithium chloride drove the cyclization to completion. It was speculated that some stable lithium aggregates may account for the incomplete cyclization and that addition of a different lithium salt may be able to break the stable aggregates and increase the reactivity.[34,35] It was also observed that (*S*,*S*,*S*)-**81** cyclized four times faster than **(***S*,*S*,*R*)-**81**, enhancing the ratio of *trans* to *cis* from 80:20 to >87:13. The desired product was isolated by a simple filtration to give the *trans* β-lactam in 64% yield and a 95:5 ratio of *trans*/*cis* on a 300 g scale (Scheme 32). The *trans*-**82** was converted into Ezetimibe in several steps.

Interestingly, a cationic effect on the diastereoselectivity was observed for this aldol condensation. For example, addition of 1 equiv of Et_2Zn to the lithium dianion **80** gave an 11:89 ratio of (*S*,*S*,*S*)-**81**/(*S*,*S*,*R*)-**81** while addition of a mixture of NaHMDA and LiHMDA reversed the ratio to 86:14. Therefore, either the *trans*- or the *cis*-isomer can be obtained depending upon which additive is introduced.

For comparison, the same absolute stereochemistry at the *β*-lactam ring of the major product was obtained when an open-chain 3-hydroxybutyrate was used as a starting material despite the opposite stereochemistry for the side-chain alcohols (Scheme 33).[36] Thus, treatment of ethyl (*S*)-3-

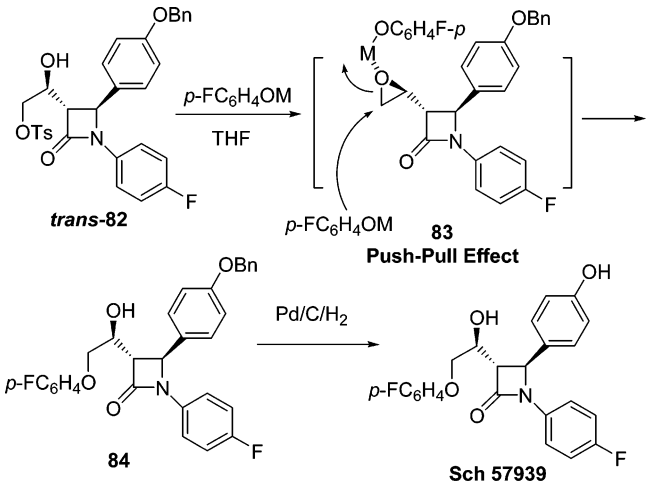
Scheme 33



hydroxybutyrate with 2 equiv of LiN(cyclohexyl)Pr-*i* followed by addition of the resulting dianion to benzylideneaniline gave a mixture of (*S*,*S*,*S*)-*β*-lactam and (*S*,*R*,*R*)-*β*-lactam in a 95:5 ratio.

Chemists at Schering-Plough have also converted *trans*-**82** into an Ezetimibe analogue (SCH 57939) (Table 3).[37]

Table 3. Cation Effect

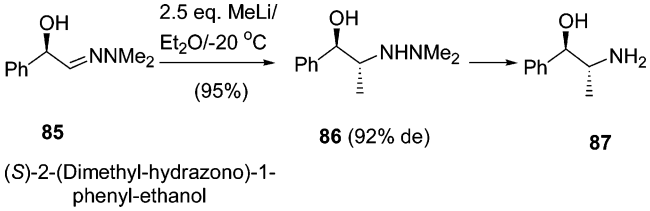


Entry	M	Yield, **84**
1	Na	10%
2	Li	43%
3	ZnBr	67%

Thus, conversion of the terminal alcohol in *trans*-**82** to a leaving group followed by a displacement with 4-FC_6H_4-OM gave the desired product **84**. Again, a strong cationic effect was observed. For example, sodium 4-fluorophenoxide gave a very slow reaction at 65 °C with less than 10% of the desired ether. Calcium 4-fluorophenoxide gave only a trace of ether **84** even at elevated temperatures. The use of lithium 4-fluorophenoxide improved the yield to 43%, but a long reaction time was still required (95% conversion at 60 h). The best yield (67%) was obtained with 4-FC_6H_4OZnCl. Presumably, a "push-and-pull" effect accounts for the high yield with the organozinc reagent.[38] In all of the reactions carried out, epoxide **83** was found to be the intermediate.

Claremon et al. of Merck Sharp & Dohme Research Laboratories reported high *threo* diastereoselectivity in the addition of organolithium to the aldehyde dimethylhydrazone (Scheme 34).[39] Addition of 2.5 equiv of MeLi to (*S*)-2-

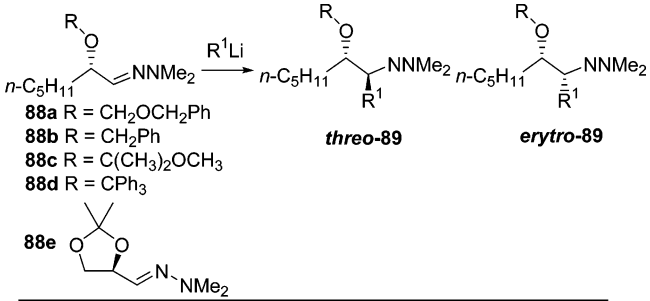
Scheme 34

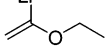
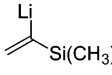


(dimethylhydrazono)-1-phenylethanol (**85**) produced hydrazine **86** in 92% de and 95% yield. The amino alcohol **87** was obtained after removal of the hydrazine group.

The above methodology was used to prepare a number of amino alcohols in high yields and excellent diastereoselectivity, as summarized in Table 4.[39] For example, treatment

Table 4. Diastereocontrolled Organolithium Addition to Hydrazones



entry	Hydrazone	RLi	**89** Yield%	*threo:erythro-89*
1	**88a**	MeLi	95	97:3
2	**88a**	PhLi	95	>98:2
3	**88b**	MeLi	98	97:3
4	**88b**	PhLi	93	>98:2
5	**88b**	*t*-BuLi	98	>98:2
6	**88b**		94	>98:2
7	**88c**	PhLi	93	>98:2
8	**88c**		85	>98:2
9	**88c**		88	98:2
10	**88d**	MeLi	85	1:10
11	**88e**	MeLi	95	3:1
12	**88e**	MeLi	75	6:1
13	**88e**	MeLi (CuI, 0.1eq)	96	1:3

of different ether-protected hydrazones (**88a**−**e**) with 1.5−2.5 equiv of R_1Li gave alkylated product **89** in 85−98% yields and 94−96% de. It is worth noting that use of the

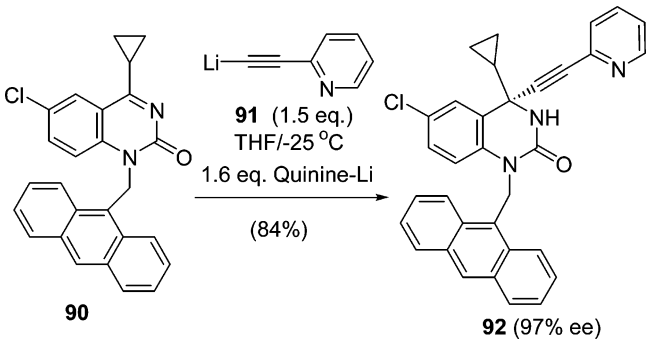
trityl protecting group switched the *threo*/*erythro* selectivity from about 98:2 to 1:10. The selectivity also varied when **88e** was used as a substrate. This synthetic method provided a general access to various amino alcohols.

3.2. Alkynylation of Imines and Ketones

Recently, chiral mediator-promoted additions of lithium acetylides to prochiral imines and ketones have been used to establish key chiral centers in enantioselective syntheses of HIV-1 non-nucleoside reverse transcriptase inhibitors.[40−48] Researchers at both Merck and Dupont Pharmaceuticals have developed a number of highly effective chiral mediators for this type of addition. In collaboration with scientists at Cornell University, they have also elucidated the reaction mechanisms and aggregation states of lithium species.

Two syntheses discussed below involved the addition of Li acetylides to cyclic *N*-acyl ketimines for the establishment of the quaternary benzylic chiral centers.[41,42] First, Huffman of Merck used a stoichiometric amount of quinine to induced the enantioselective addition of Li acetylide **91** to a cyclic *N*-acyl ketimine **90**, producing the (*S*)-enantiomer **92** in 84% yield and 97% ee (Scheme 35).[41] One equivalent of lithium

Scheme 35

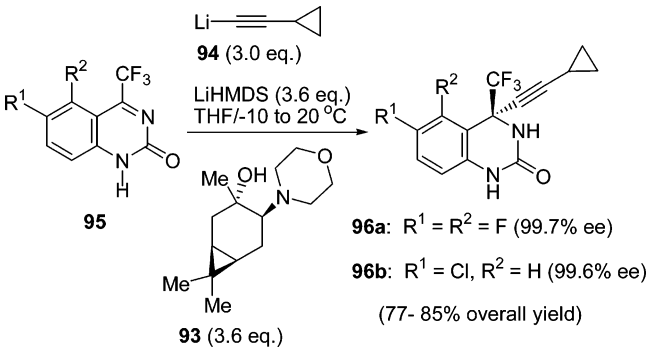


base was required to neutralize the hydroxyl group in quinine. The opposite (*R*)-enantiomer could be obtained in high enantioselectivity using quinidine as a chiral ligand. There is a metal cation effect on the enantioselectivity. For example, lithium salts of both acetylene and alcohol, generated with BuLi or LiHMDS, gave better enantioselectivity than either sodium or magnesium salts produced from sodium (NaHMDS) or magnesium (EtMgBr). THF is a better solvent than either toluene or diethyl ether. Under the reaction conditions, a bulky 9-anthrylmethyl was apparently required to protect the distal nitrogen in order to obtain high enantioselectivity.

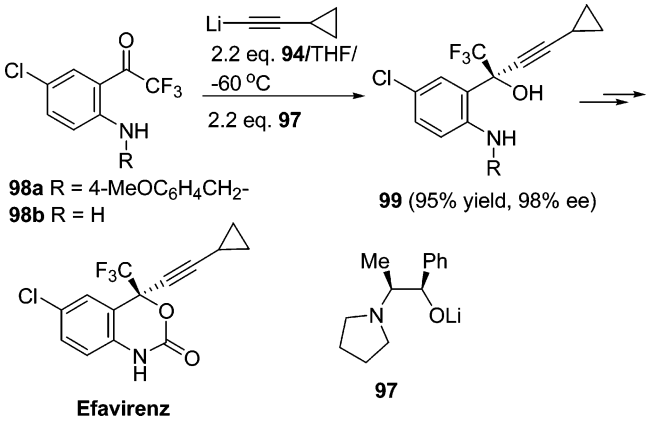
For enantioselective addition of Li cyclopropylacetylide **94** to a similar imine **95**, Parsons et al. of Merck have developed a (+)-3-carene amino alcohol-based ligand (**93**).[41] Three equivalents of **94** and 3.6 equiv each of **93** and LiHMDS are required to give **96** in >99.6% ee. The (+)-3-carene-derived amino alcohol **93** ligand could be recovered in 92% yield and recycled directly (Scheme 36).

Furthermore, Merck chemists developed a class of chiral amino alcohol-based ligand for enantioselective addition of Li acetylide to prochiral ketones in the synthesis of Efavirenz (Scheme 37).[43] Thus, addition of 2.2 equiv of Li acetylide **94** to trifluoromethyl benzoketone **98** in the presence of 2.2 equiv of a lithium amino alcohol derivative gave a chiral tertiary alcohol product (**99**) in 95% yield and 98% ee. While quinine was not effective for this type of addition, (1*R*,2*S*)-*N*-pyrrolidinylnorephedrine (**97**) was found to be the best chiral mediator. An extensive optimization of the reaction

Scheme 36



Scheme 37



conditions was carried out, and the best procedure is as follows: use of 2 equiv of Li acetylide and 2 equiv of Li alkoxide followed by equilibration of the resulting acetylide−alkoxide solutions at temperatures above −40 °C prior to the addition of the ketoaniline. Among the bases tried (LiHMDS, BuLi, and LDA), LiHMDS gave the best result (Scheme 37).

Merck chemists also collaborated with Collumn's group at Cornell on the mechanism of this type of acelylide addition. Based on ^{6}Li, ^{13}C, and ^{15}N NMR spectroscopy studies in solution and X-ray crystallography in the solid state, they proposed a cubic 2:2 tetramer formed from Li acetylide and Li alkoxide to be the active intermediate (Figure 5).[42−45]

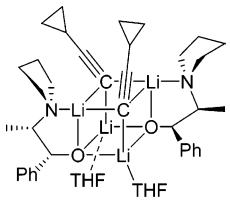
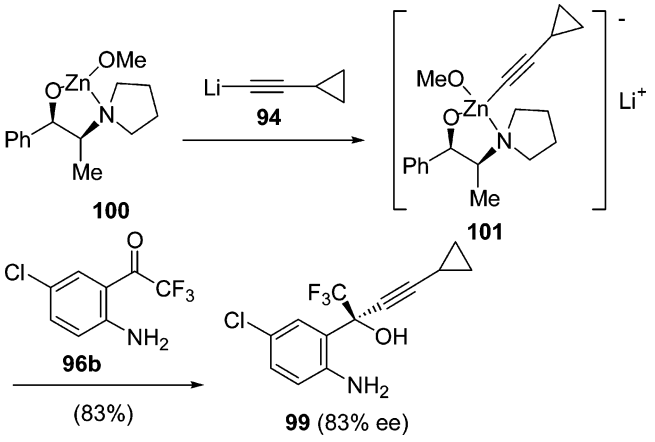


Figure 5.

An *N*-protection step of the aniline group in the ketone and a deprotection step were required in the above addition in order obtain high enantioselectivtiy. To streamline the synthesis, Merck chemists developed an organozinc-mediated addition of Li acetylide to an *N*-unprotected prochiral ketone (Scheme 38).[44] Treatment of lithium acetylide **94** with the cyclic aminoalkoxide zincate **100** formed the "ate" complex **101**. Addition of the zinc−lithium "ate" complex **101** to free aniline trifluoromethyl benzoketone **96b** afforded the chiral tertiary alcohol **99** in 83% ee and 83% yield. The formation

Scheme 38



of a zinc adduct lowers the basicity yet still maintains the nucleophilicity of the acetylide. This procedure is the most efficient synthesis of Efavirenz and has been scaled up in the pilot plant (Scheme 38).[44]

A similar lithium acetylide, **102**, could also be used to open a chiral epoxide, with complete retention of the chiral center, to form a secondary alcohol **103** in 99% ee (Scheme 39).[49]

Scheme 39

3.3. Addition to Chiral Esters

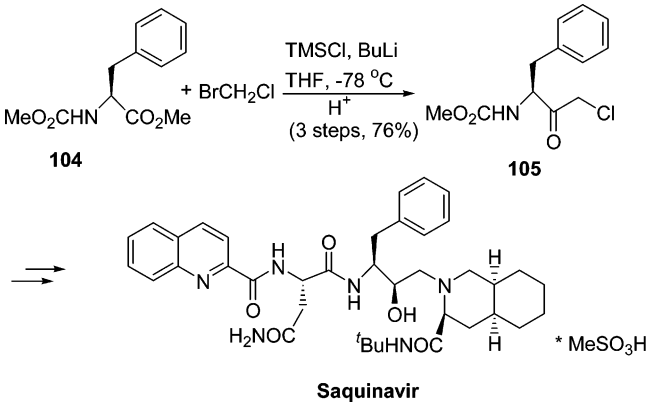
This part of the review will focus on addition of organolithium reagents to esters bearing chiral centers as a template. Under basic conditions, the chiral center α to the carbonyl has a tendency to racemize. However, addition of alkyllithiums or lithium amides to chiral esters has been proven to retain the configuration at either the α or the β carbon. The weak basicity and the strong coordination ability of the lithium cation account for this retention of the chiral centers. All the substrates discussed in this section are α-amino esters, and only 1 equiv of organolithium addition was observed to give ketone derivatives.

In the synthesis of Saquinavir, a tetrapeptide mesylate salt and the first HIV protease inhibitor, chemists at Roche have developed an addition of chloromethyllithium to the *N*-protected α-amino ester **104** for the preparation of the center moiety, i.e., the *N*-protected chloromethyl ketone **105** (Scheme 40).[50] The chloromethyllithium was generated in situ at −78 °C from $BrCH_2Cl$ and BuLi. After an acidic workup, the chloromethyl ketone **105** was obtained in 76% yield with retention of the α-chiral center. The chloromethyl ketone **105** was converted into Saquinavir in several steps.

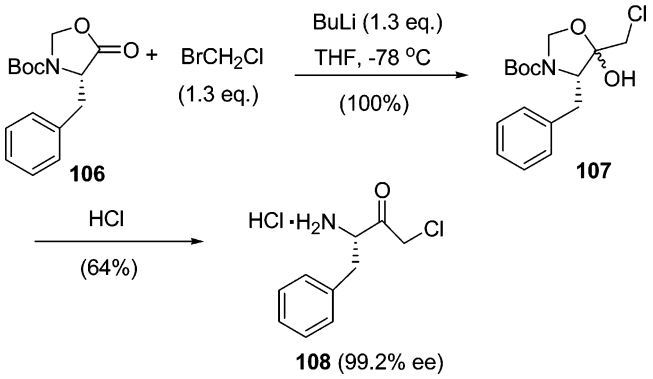
Similarly, Izawa et al. of Ajinomoto used chloromethyllithium to add to the *N*-protected 3-oxazolidin-5-one **106** for the preparation of *N*-protected 5-chloromethyl-5-hydroxy-3-oxazolidines **107** (Scheme 41).[51]

Cbz-protected substrate **109** worked well for this addition to give hemiketal **110** with retention of the chiral center (Scheme 42).[51] Both the resulting oxazolidines **107** and **110** were readily converted into α-aminoalkyl-α′-chloromethyl ketone derivatives **108** and **111**.

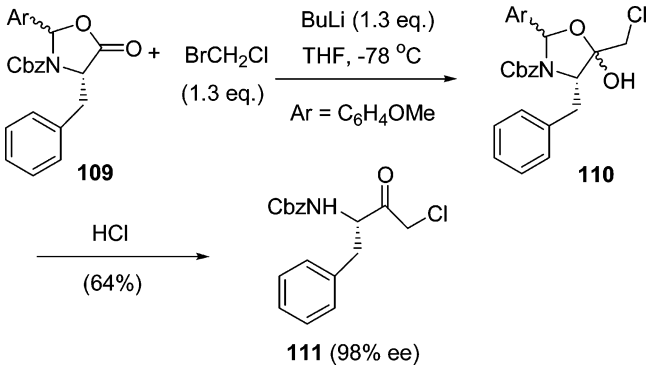
Scheme 40



Scheme 41



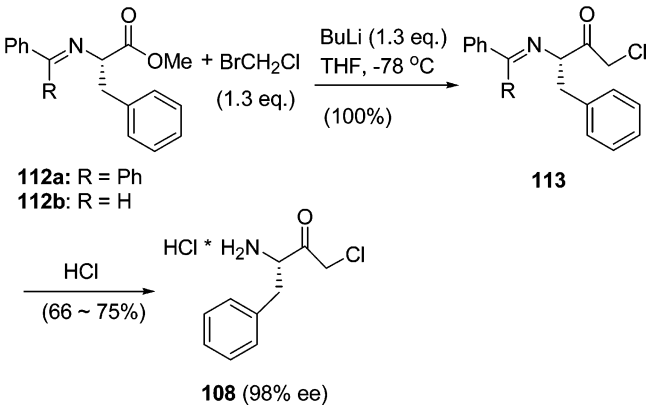
Scheme 42



Furthermore, Izawa used an imine as a protecting group for the amino group in the addition of $ClCH_2Li$ to an amino ester group for the preparation of one-carbon-homologated chloroketone **108** (Scheme 43).[52] In this case, a chemoselective addition of $ClCH_2Li$ to the carbonyl group was achieved in the presence of an imine group to give **113** in 100% yield and retention of the chiral center. Both *N*-diphenylmethylene- and *N*-benzylidene-protected amino acid esters worked well to give, after hydrolysis, the desired product **108** in >98% ee and good isolated yields (Scheme 43).[52]

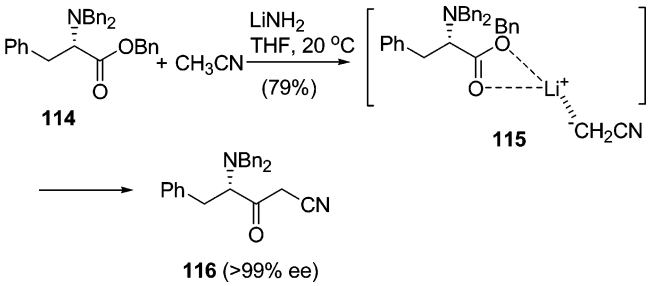
The fact that reaction stops at the ketone stage indicates the formation of a stable chelation intermediate. In addition, the weak basicity of the chloromethyllithium does not promote the enolization of the starting ester, resulting in a complete retention of the chiral center at the α-position. α-Aminoalkyl-α′-chloromethyl ketones are useful intermediates for the preparations of serine protease and hydroxyethyl isostere subunits found in many renin and HIV protease inhibitors.

Scheme 43



Chang et al. of Abbott have reported an addition of cyanomethyllithium to an amino ester for the preparation of a 2-carbon homologated aminoketone derivative (Scheme 44).[53] Thus, addition of $LiNH_2$ to a mixture of amino ester

Scheme 44



114 and CH_3CN gave aminoketone **116** in >99% ee and with retention of the chiral center. It was found that lithium amide gave better chiral retention than the corresponding sodium amide.[53] Two key factors may have contributed to this difference: (1) deprotonation of acetonitrile with lithium amide is kinetically faster than extraction of the α-proton; and (2) there may be a strong chelation between lithium cation and carboxylic oxygen, as shown by intermediate **115**, thus activating the carbonyl group. The activation would therefore favor the nucleophilic addition of cyanomethyl anion to the carbonyl over the deprotonation of the α-proton. The *β*-keto nitrile product **116** could be converted into a protease inhibitor Ritonavir (Norvir) (Scheme 44).

4. Organolithium Reagents in Chiral Aldol Condensations

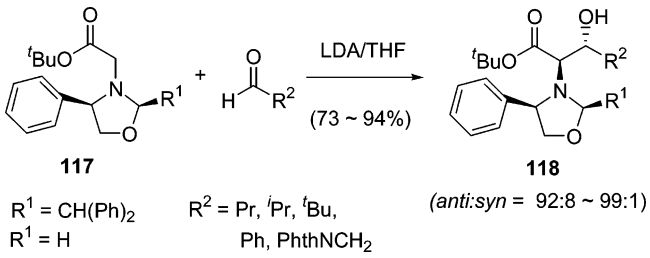
Enantioselective aldol condensations can be divided into chiral auxiliary-induced, Lewis acid-mediated, and catalytic asymmetric reactions. While a vast number of reactions have been reported in the past two decades, this review will focus on industrial application of additions of lithium enolates to aldehydes. Enantioselective aldol and Michael additions of chiral lithium amides and amines were reviewed previously.[54−55]

4.1. Chiral Auxiliary-Induced Aldol Reactions

Chiral auxiliaries can be attached to either the nucleophiles (such as esters or imides) or the electrophiles (aldehydes or ketones). They are generally removed at the end of the synthesis when they are attached to the carbonyl bonds, as either amides or esters (auxiliary-induced). The chiral centers become part of the molecules when they are attached to other parts of either the nucleophiles or electrophiles (chiral-pool approach).

Iwanowicz et al. of Bristol-Meyers Squibb have converted the nitrogen of an α-amino ester into an oxazolidine auxiliary (**117**) and applied it to *anti*-selective aldol reactions (Scheme 45).[56] Enolization of the ester functional group with LDA

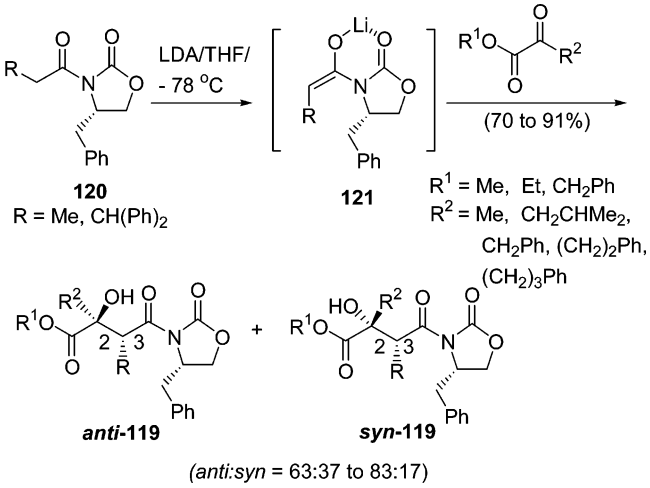
Scheme 45



followed by addition to various aldehydes afforded predominantly *anti*-diastereomers **118** in good to excellent yields. Furthermore, it was observed that bulkier substituents on the oxazolidines gave better diastereo- and enantioselectivity. For example, the lithium enolate of a less sterically hindered glycine ester produced a mixture of all four possible diastereomers. A bulky ester group (*t*-Bu) is necessary for the high selectivity. Removal of the chiral auxiliaries gave the chiral *β*-hydroxy-α-amino acids of the *erythro*-stereoisomer.

Jacobson et al. of DuPont-Merck used Evan's auxiliary for the synthesis of a variety of 2-hydroxy-2,3-disubstituted succinates **119** (Scheme 46).[57] Thus, a number of lithium

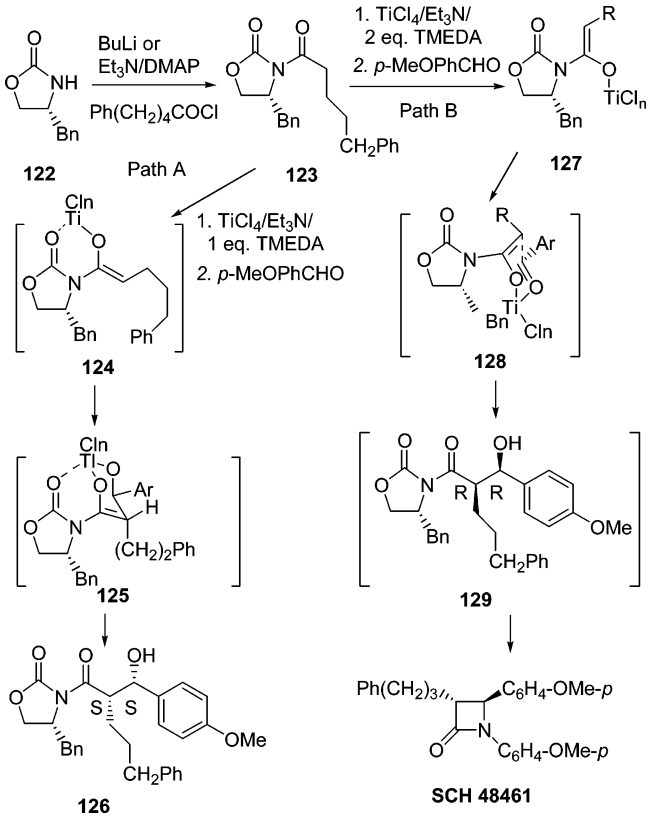
Scheme 46



enolates (**121**) generated from the Evan's auxiliary amide **120** and LDA in THF were added to the ketone functional group of α-keto esters to give 2,3-trisubstituted adducts in good yield. The enantioselectivity at the C-3 position was exclusive because the *Z*-enolate reacted preferentially from the *Si* face. However, the diastereoselectivity at C-2 was only modest (63:37 to 83:17). For comparison, addition of lithium, boron, and titanium enolates of Evans' chiral imides to α-keto esters were examined.[57]

In a related titanium-promoted aldol condensation, chemists at Schering-Plough used Evan's auxiliary for the synthesis of azetidinone-based cholesterol absorption inhibitor SCH 48461 (Scheme 47).[58] Treatment of the oxazolidinone auxiliary **122** with BuLi followed by phenylvaleryl

Scheme 47



chloride afforded the *N*-acyloxazolidinone **123**. For the Ti-promoted aldol condensation, either the (*S*,*S*)- or the (*R*,*R*)-hydroxy adduct can be obtained as major product. The use of 1 equiv of TMEDA in combination with $TiCl_4$ resulted in (*S*,*S*)-adduct **126** following reaction Path A. First, formation of a six-membered ring titanium enolate complex **124** followed by addition of the enolate to a benzaldehyde from the opposite side of the existing benzyl group on the oxazolidinone auxiliary gave a trioxo-titanium complex (**125**) with the phenylpropyl group situated at the equatorial position of the newly formed chair form. On the other hand, the use of 2 equiv of TMEDA gave (*R*,*R*)-adduct **129** as major product via intermediate **128** (Path B). The (*R*,*R*)-adduct **129** was converted into the desired β-lactam product (SCH 48461) in good yield (Scheme 47). This synthesis was scaled up in the pilot plant and produced API on hundred kilo scale for clinical supply.

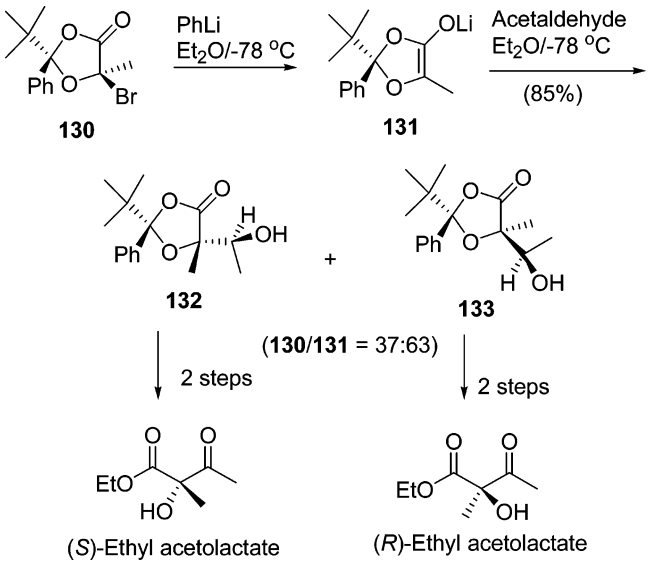
Greiner et al. of Rhone Poulenc Agrochimie have developed a synthesis of both enantiomers of ethyl acetolactate through an aldol condensation of sterically hindered dioxolanone with acetaldehyde (Scheme 48).[59] First, generation of a lithium enolate of 2-*tert*-butyl-5-methyl-2-phenyl-1,3-dioxolan-4-one (**131**) via a halogen metal exchange starting from bromo-dioxolanone **130** followed by addition to an acetaldehyde formed two of the four possible diastereomers **132** and **133** in a 37:63 ratio. The pair of diastereomers were separated and converted into the corresponding enantiomerically pure ethyl acetolactates.

4.2. Lewis Acid-Promoted Aldol Additions to Chiral Aldehydes

Two related Lewis acid-mediated additions of Li enolates to α-hydroxy aldehydes are discussed below.

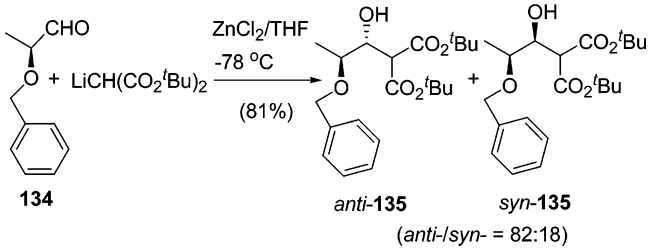
Marumoto et al. of Sankyo Co. have reported $ZnCl_2$-promoted diastereoselective aldol condensations of the

Scheme 48



lithium enolate of malonate ester to various α-alkoxy aldehydes **134** for the preparations of *anti*-1,2-diols **135** (Scheme 49).[60] It was observed that the bigger the ester group, the better the diastereoselectivity. For example, when the alkyl group was changed from methyl to a more bulky

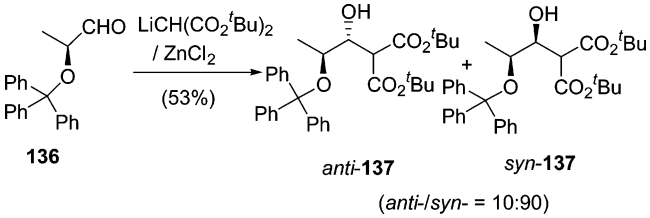
Scheme 49



isopropyl or phenyl group, higher *anti*-selectivity was obtained. Direct aldol condensation in the absence of any Lewis acids gave products in lower diastereoselectivity (*anti*/*syn* = 60:40) and lower yield (71%). Introduction of $BF_3 \cdot OEt_2$ resulted in higher diastereoselectivity (*anti*/*syn* = 91:9), although in lower yield (52%). Other Lewis acids such as $MgBr_2$ or $ZnBr_2$ gave poorer diastereoselectivity. Lowering the reaction temperature from −78 to −98 °C in the presence of $ZnCl_2$ increased the selectivity from 82:18 to 87:13 and the yield from 81% to 89%.

Surprisingly, the *anti*/*syn* selectivity was reversed from 82:18 to 10:90 when the substrate was changed from benzyl-protected **134** to 2-trityl-protected α-hydroxyaldehyde **136** (Scheme 50).[60]

Scheme 50



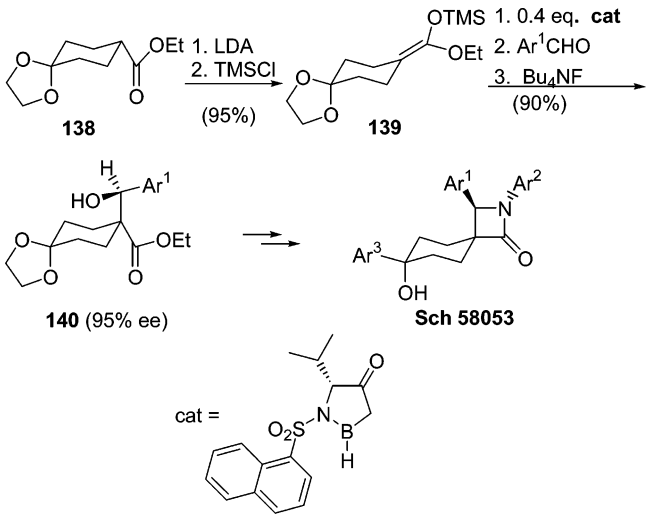
4.3. Chiral Lewis Acid-Catalyzed Aldol Condensations

Chiral Lewis acid-catalyzed Mukaiyama aldol condensations have been reported as a powerful method for the

preparation of β-hydroxy esters.[61] A successful industrial application of this type of catalytic reaction will have a major economical impact on the cost of goods due to the use of a small amount of catalyst.

Chemists at Schering-Plough have reported the first process using chiral Lewis acid-catalyzed Mukaiyama aldol condensation for the synthesis of SCH 58053, a cholesterol absorption inhibitor.[62] As shown in Scheme 51, enolization

Scheme 51



of the spiro ester **138** with LDA followed by trapping with TMSCl gave the TMS ketene acetal **139** in 95% isolated yield. A slow addition of the TMS ketene acetal to a mixture of benzaldehyde and 0.4 equiv of D-valine sulfonamide oxazaborolidine gave, after a Bu_4NF workup, the β-hydroxy ester **140** in 90% isolated yield and 95% ee. The D-valine sulfonamide oxazaborolidine catalyst was hydrolyzed, converted into the corresponding sodium salt, separated from the product via layer splitting, and recovered in 87% yield. The recovered procatalyst was converted into the oxazaborolidine in situ, by treatment with 1 equiv of BH_3·THF and recycled 9 times without loss of any enantioselectivity. The hydroxy ester, **140**, was converted into the corresponding spiro-β-lactam, SCH 58053 (Scheme 51). This route was scaled up and prepared several kilos of API for studies.

5. Organolithium Reagents in Chiral Conjugate Additions

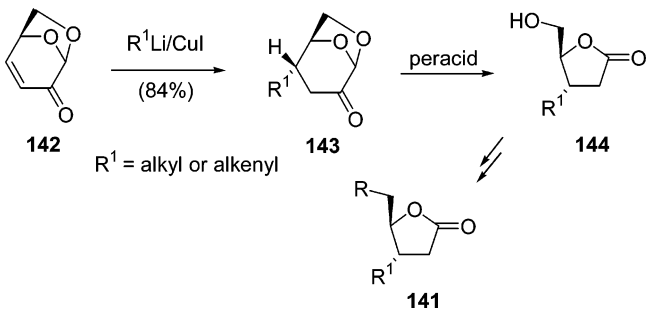
Chiral conjugate additions have been used in a number of asymmetric processes. The chiral templates can be placed on either Michael donors, Michael acceptors, chiral ligands, or chiral catalysts. Both carbon and nitrogen nucleophiles are used for conjugate enantioselective additions. While this review will focus on industrial applications, Michael additions have been reviewed previously.[55]

5.1. Conjugate Additions to Chiral Michael Acceptors

The chiral centers in the Michael acceptors discussed here end up as part of the molecule.

Ebata et al. of Japan Tobacco Inc. have reported a process for the synthesis of *trans*-3,4-disubstituted-γ-lactones **141**, using Michael addition of alkyl- or alkenyllithium to a chiral levoglucosenone **142** (Scheme 52).[63] Thus, addition of RLi in the presence of a copper halide to a bicyclic enone **142**

Scheme 52



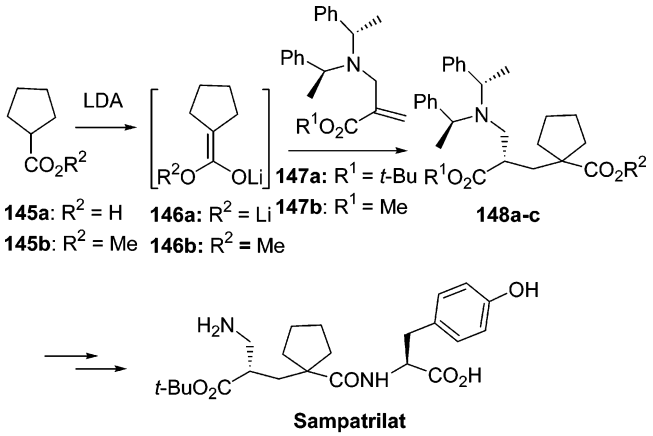
gave a Michael addition product **143** in 84% yield and high stereoselectivity. The organometallic reagents approach from the opposite side of the existing chiral center, resulting in a *trans*-adduct. Alkyl- or alkenylmagnesium could also be used in the addition reaction (Scheme 52). The bicyclic intermediate **143** was oxidatively opened with a peracid to afford the desired *trans*-3,4-disubstituted-γ-lactones **144**.

5.2. Auxiliary-Induced Asymmetric Conjugate Additions

The use of chiral auxiliaries has been demonstrated to be an effective method for asymmetric induction in conjugate additions. The chiral auxiliary can be placed on either a chiral acceptor or a chiral donor.

In the synthesis of intermediates for neutral endopeptidase inhibitors and inhibitors of zinc metalloprotease such as samptrilat, Dunn et al. of Pfizer England have reported an addition of lithium spiro enolate to chiral 2-aminomethylacrylates (Table 5).[64] Di-((*S*)-α-methylbenzyl)amine was used

Table 5. Chiral Michael Addition



Entry	148	R^1	R^2	148 Yield	148 de
1	a	*t*-Bu	H	83%	99%
2	b	Me	H	86%	94%
3	c	*t*-Bu	Me	50%	80%

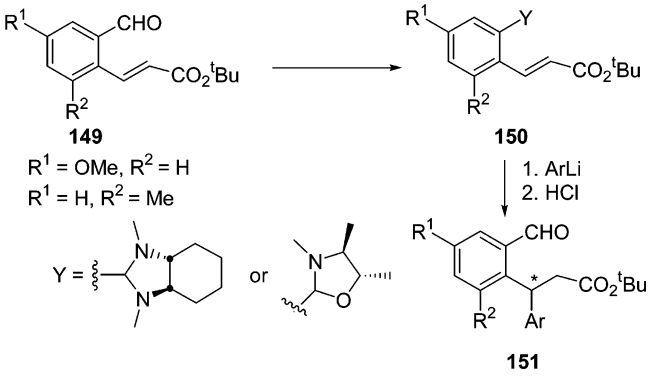
as a chiral auxiliary on the methylacrylate to induce the conjugate addition. Study of the effects of the R^1 group on the acrylate and R^2 on the Michael donor indicated that the size of the R^1 group has little impact on the stereoselectivity. However, R^2 has a major impact. For example, conversion of cyclopentanecarboxylic acid **145a** to its corresponding dianion Li enolate **146a** followed by addition to chiral

aminomethylacrylates **147a** or **147b** produced (*S*,*S*,*S*)-glutarates **148a** and **148b** in 83−86% yield and 94−99% de. On the other hand, Michael addition of the lithium enolate of methyl cyclopentanecarboxylate **146b** to **147a** gave a glutarate diester **148c** in only 50% yield and 80% de. Apparently, the aggregation state of the dianion enolate (R^2 = H) is different from that of the lithium enolate of the methyl ester.

Several Merck process groups used Michael additions for the preparation of a key intermediate in the synthesis of an endothelin receptor antagonist. In the first approach, they attached a chiral auxiliary to an aldehyde in the aromatic moiety of the Michael acceptor. In the second approach, they have developed a chiral-ligand-promoted conjugate addition (see section 5.5).

First, the benzaldehyde moiety in the Michael acceptors (**149**) was converted into different chiral imidazolidine or oxazolidine auxiliaries (**150**) by reacting with either chiral diamines or amino alcohols (Scheme 53).[9,65] Addition of

Scheme 53



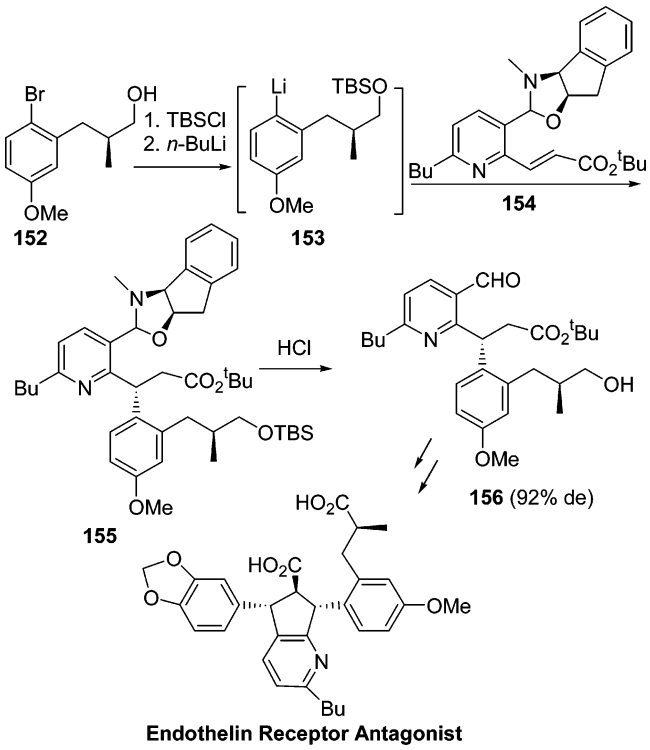
aryllithium reagents to the chiral Michael acceptors (**150**) proceeded very well to give, after hydrolysis, the desired addition product in high enantioselectivity.

Similarly, the use of an oxazolidine auxiliary derived from *cis*-aminoindanols produced a Michael adduct **155**.[65a] Thus, in situ protection of the hydroxyl group in **152** with TBSCl followed by a halogen−lithium exchange generated ArLi species **153**. Addition of the resulting ArLi **153** to chiral Michael acceptor **154** afford adduct **155** in 92% de. Both the chiral auxiliary and the TBS groups were hydrolyzed with HCl to give Michael adduct **156** in 92% overall yield and 92% de. The free aldehyde **156** was converted into one of the endothelin receptor antagonists as shown in Scheme 54.

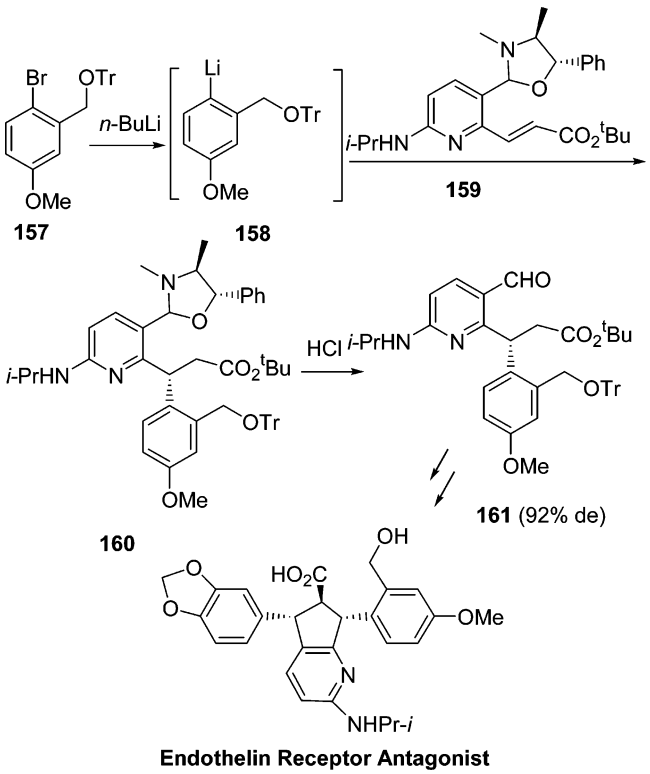
In the preparation of another analogue of an endothelin receptor antagonist, chemists at Merck have used imidazolidine as an auxiliary for a Michael addition following a similar sequence (Scheme 55).[65b] Thus, generation of an aryllithium reagent (**158**) by reacting ArBr (**157**) with BuLi followed by addition of **158** to chiral Michael acceptor **159** produced adduct **160** in 92% ee. A simultaneous hydrolysis of both the chiral auxiliary and the trityl group with HCl afforded the desired antagonist in 81% overall yield. This type of addition is practical and applicable to a wide variety of structurally complex chiral β,β-diaryl propanoates on large scale because it employs readily available and inexpensive chiral auxiliaries.

Smitrovich et al. of Merck have reported an addition of a chiral Michael donor to methyl acrylate for the asymmetric synthesis of 3-aryl-δ-lactones (Scheme 56).[66] Thus, enolization of chiral ketone **162** with LiHMDS followed by addition to a methyl acrylate derivative in the presence of TMEDA afforded the Michael adduct **164** in high diastereoselectivity. Although the exact induction mechanism was not known, the existing chiral centers and the Li alkoxide must have contributed to the high diastereoselectivity. The Michael adduct was subsequently converted into a disubstituted δ-lactone (**165**) in 99.8% ee (Scheme 56).

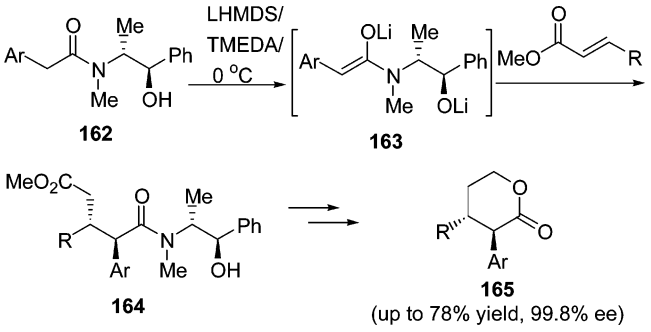
Scheme 54



Scheme 55

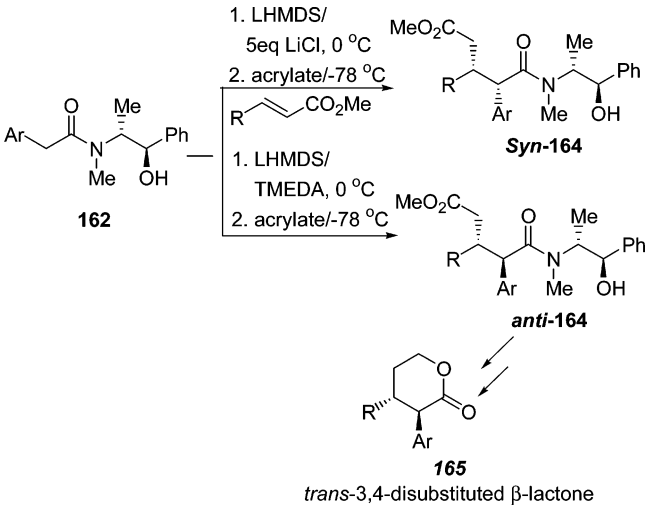


Scheme 56



Furthermore, Smitrovich et al. at Merck have shown that the stereochemical outcome can be changed dramatically in the presence of LiCl. For example, Michael reaction of lithium enolates of pseudoephedrine **163** in the absence of LiCl gives predominantly the *trans*-**165**.[67] In contrast, the *syn*-**165** is the predominant product in the presence of LiCl (Scheme 57).

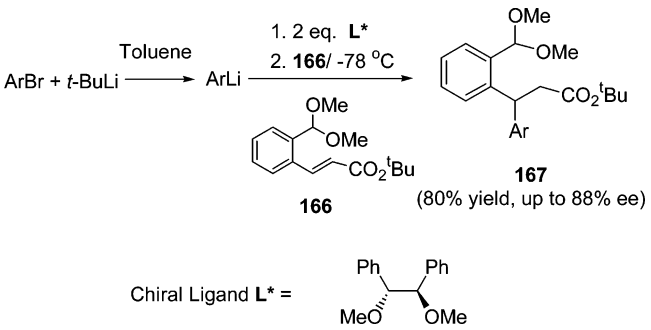
Scheme 57



5.3. Chiral Additive-Mediated Conjugate Addition

To improve process efficiency, chemists at Merck have developed a chiral-ligand-promoted addition of aryllithium to an achiral Michael acceptor for the synthesis of an endothelin receptor antagonist (Scheme 58).[68] To induce the

Scheme 58

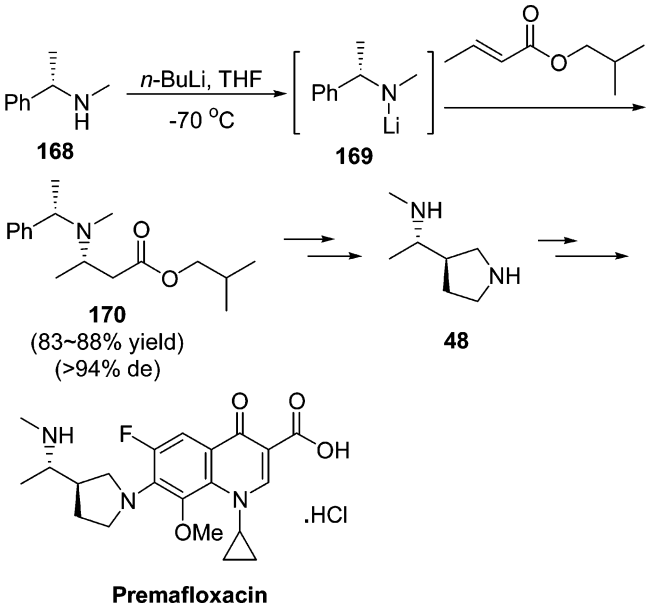


chiral center, they have introduced an external ligand such as diamines, diethers, or amino ethers. The aldehyde group on the aromatic ring was protected as dimethylacetal. Addition of ArLi reagents generated from the reaction of arylbromides and *t*-BuLi to α,*β*-unsaturated *tert*-butyl arylacrylate derivative **166** in the presence of 2 equiv of chiral ligands gave *β*,*β*-diaryl propanoates **167**. For example, use of 2 equiv of a C_2 symmetric chiral diether in toluene at −78 °C produced the Michael adduct **167** in 88% ee and 80% yield (Scheme 58).[68]

5.4. Addition of Lithium Chiral Nitrogen Nucleophiles to Michael Acceptors

In the synthesis of *N*-methyl-*N*-{(1*S*)-1-[(3*R*)-pyrrolidin-3-yl]ethyl}amine (**48**), a key intermediate in the preparation of the antibiotic premafloxacin, McWhorter et al. from Pfizer used an asymmetric Michael addition of a chiral lithium amide to isobutyl crotonate to set the first stereocenter (Scheme 59).[14] Thus, conversion of chiral diamine **168** to

Scheme 59



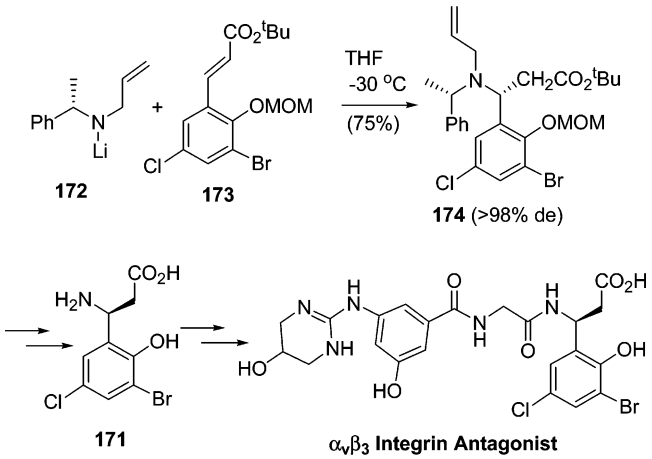
its corresponding lithium amide **169** followed by addition to and isobutyl acrylate derivative gave *β*-amino Michael adduct **170** in 83−88% yield and greater than 94% de (Scheme 59). The chiral auxiliary was removed, and the resulting intermediate was converted into monosubstituted pyrrolidine **48**. This synthesis is complimentary to the chiral alkylation approach discussed in Scheme 16.

Recently, a group of scientists at Pfizer reported an asymmetric Michael addition for the synthesis of (*S*)-*β*-amino acid ester, **171**, a key intermediate in the route to an $\alpha_v\beta_3$ Integrin Antagonist.[69] As shown in Scheme 60, Michael addition of lithium *N*-(*S*)-α-methlybenzyl-*N*-allyl amide (**172**) to *tert*-butyl cinnamate (**173**) at −30 °C in THF gave the protected *β*-amino acid ester (**174**) in 75% yield and >98% de. The allyl group was removed successfully using Pd-$(PPh_3)_4$. However, the debenzylation to **171** with $Pd(OH)_2$ was accompanied by the undesired dehalogenation of the aromatic ring.

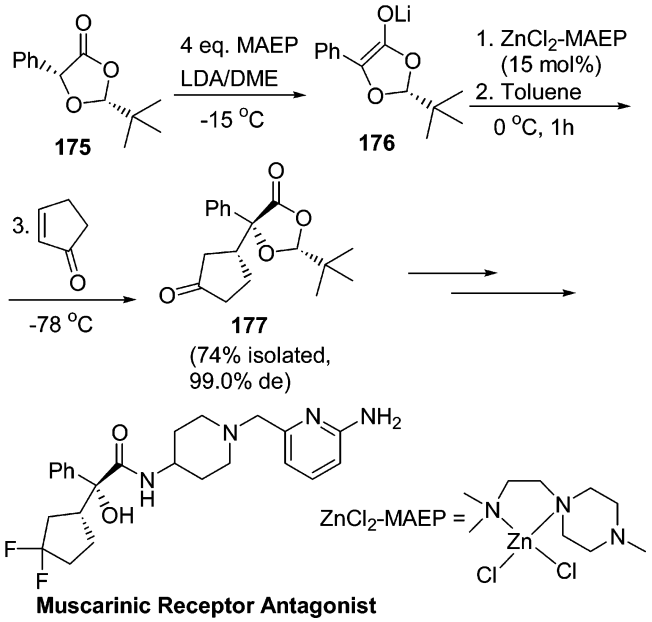
5.5. Catalytic Asymmetric Conjugate Addition

Process chemists at Merck have developed a $ZnCl_2$-MAEP-catalyzed diastereoselective Michael addition and applied it to the synthesis of a muscarinic receptor antagonist (Scheme 61).[70] Enolization of dioxolane **175** with LDA followed by addition to 2-cyclopenten-1-one in the presence of 15% of $ZnCl_2$-MAEP afforded the adduct **177** in 74%

Scheme 60



Scheme 61



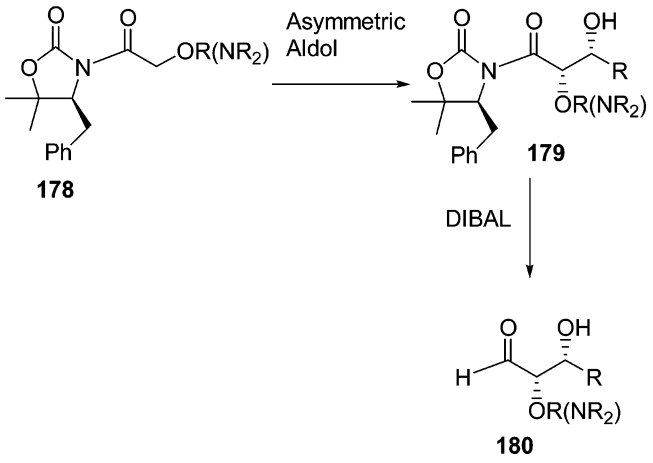
yield and 99.0% de. It was believed that the unsymmetrical triamine ligand 1-(2-dimethylaminoethyl)-4-methylpiperazine (MAEP) stabilizes the lithium enolate. A homogeneous reaction mixture was required prior to the addition of cyclopentenone for high selectivity. This synthesis was scaled up and prepared multi-kilograms of the muscarinic receptor antagonist (Scheme 61).

6. Miscellaneous Reactions

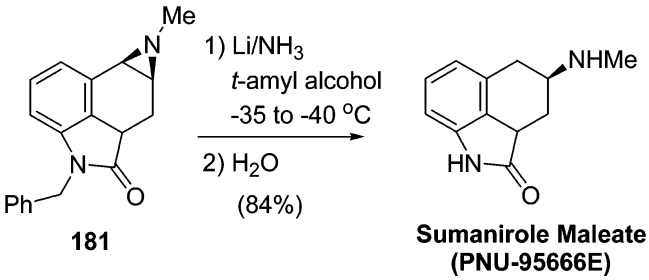
Recently, Davies has published a series of chiral auxiliary-induced Michael additions and aldol condensations:[71] for example, use of (*S*)-*N*-acyl-4-benzyl-5,5-dimethyloxazolidin-2-one for the synthesis of α,*β*-dihydroxy or α-amino-*β*-hydroxy acid derivatives (Scheme 62). Those reactions can be potentially useful for drug synthesis.

Joshi's group at Pfizer has developed a dissolving metal (lithium) reaction to simultaneously remove a benzyl group on an amide nitrogen and regioselectively open a benzylic aziridine for the synthesis of Sumanirole (PNU-95666E).[72] As shown in Scheme 63, the aziridine **181** was treated with lithium metal, ammonium gas, and *tert*-amyl alcohol at −35 to −40 °C to give, after an aqueous workup, the desired Sumanirole Maleate in 84% yield. Notice that the aziridine

Scheme 62



Scheme 63



was regioselectively opened at the benzylic position. Lithium, sodium, and potassium work similarly for the reduction in liquid ammonium. However, lithium was selected for the scale-up for its better molar solubility in liquid ammonium and higher reduction potential compared to the cases of both sodium and potassium. Joshi's group has addressed both process and safety issues, including the hazardous analysis, the physical form of lithium metal, and the lithium addition apparatus, and scaled up the process in the plant on 50 kg scale to produce API for phase III clinical studies.

7. Conclusion

In the past two decades, industrial chemists have developed many asymmetric syntheses using organolithium reagents. Some of the processes have been scaled up in the plant and produced active pharmaceutical ingredients for clinical studies, and some have been commercialized to produce marketed products on multi-kilo scale. Most lithium reagents, such as BuLi, LDA, PhLi, and LiHMDS, are commercially available on a large scale. In addition, a variety of other lithium species can be generated in situ in excellent yields, and those lithium species can be transmetalated to other organometallic reagents. Industrial chemists have applied literature precedents to their asymmetric processes. However, as we have attempted to show in this review, they have also invented new asymmetric procedures for their processes and scaled the processes up in the plant. The catalytic addition of Li acetylides to ketones for the synthesis of the HIV inhibitor Efavirenz, and the chiral-ligand-promoted alkylation of doubly benzylic carbon for the synthesis of an anticancer agent, Sarasar, are two examples.

Development of efficient and practical asymmetric pharmaceutical API processes will continue to be the focus of industrial research. Organometallic, particularly organolithium, reagents will play an important role in establishing

asymmetric centers. With a better understanding of the reaction mechanisms and the development of novel methods by both academic institutions and industrial companies, there will be more new inventions of practical and efficient asymmetric processes for the synthesis of complex drug candidates.

8. Acknowledgments

We thank Drs. Kenneth Mathews, Paitoon Rashatasakhon, and Robert Orr for their proofreading of the manuscript.

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CR040694K