cis-1-Amino-2-indanol in Drug Design and Applications to Asymmetric Processes

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1. Introduction

Natural products generally exist as a single enantiomer as a consequence of the inherent chirality of the enzymes that produce them. Furthermore, enzymes, receptors, and other binding sites in biological systems recognize compounds with a specific chirality. Enantiomers of a chiral molecule can display different biological activities, and in extreme cases, one enantiomer is an active drug and the other exhibits fatal toxicity. As a consequence of the FDA's 1992 directive on stereoisomers, studies on therapeutic profiles of single enantiomers of several drugs were launched. As an example, racemic oxybutynin, commercialized as Ditropan, is prescribed for the treatment of urinary incontinence and exhibits classical antimuscarinic side effects, such as dry mouth.[1] Biological investigations showed that (*S*)-oxybutynin displayed an improved therapeutic profile compared to its racemic counterpart.

The increased development of single-enantiomer pharmaceuticals and interest in asymmetric synthesis has enhanced the need for convenient methods for the preparation of enantiopure materials.[2,3] In the search of easily accessible chiral templates for asymmetric transformations, chiral amino alcohols derived from α-amino acids were generally identified as versatile reagents for the generation of enantiopure compounds and have been extensively and successfully utilized as chiral auxiliaries and ligands in asymmetric reactions. Amino alcohols that are not derived from the chiral pool sometimes offer additional advantages in terms of structural diversity and conformational properties.[4−6] Among those, *cis*-1-amino-2-indanol (**1**) played a crucial role in the development of active pharmaceutical ingredients. Since its discovery as a valuable HIV-PR inhibitor ligand, many asymmetric methodologies have emerged which utilize **1** as a constrained phenyl glycinol surrogate. Both its sterically bulky indane structure and the conformationally restricted *cis*-aminoindanol moiety create an effective chiral discrimi-

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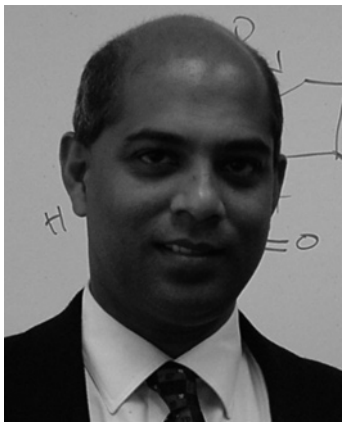
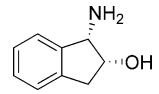
Dr. Isabelle Gallou was born in 1974 in Paris, France. She received her "Diplôme d'Ingénieur" in Chemistry and Chemical Engineering in 1999 from the Ecole Supérieure de Chimie Physique Electronique de Lyon. She obtained her Ph.D. in 2002 under the guidance of Professor T. V. RajanBabu at the Ohio State University where she worked on the development of selective palladium- and rhodium-catalyzed processes for the asymmetric synthesis of structurally relevant synthons. She then joined Boehringer Ingelheim Pharmaceuticals, Inc. in the department of Chemical Development under the direct supervision of Drs. Vittorio Farina and Chris Senanayake. She was involved in the design of innovative and practical processes, which were implemented on kilogram scale. In particular, she developed expertise in the fields of chiral amines and unsymmetrical ureas. Dr. Gallou's research interests include catalysis and asymmetric reactions for C–C and C–N bond formations as well as mechanistic study and the development of practical processes for large-scale production of active pharmaceutical ingredients and intermediates.



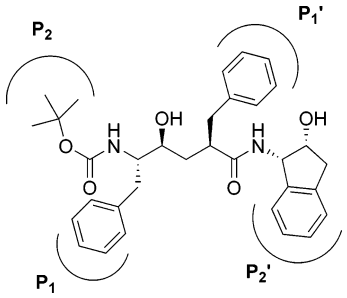
Dr. Chris H. Senanayake was born in Sri Lanka and obtained his Ph.D. under the guidance of Professor James H. Rigby at Wayne State University at 1987 where he worked on the total synthesis of complex natural products. During his postdoctoral fellowship with Professor Carl R. Johnson, he worked on the total synthesis of polyol systems such as amphotericin B and compactin analogues, and the synthesis of C-nucleotide precursors. After a brief stay at Dow Chemical, he joined the Merck Process Research Group in 1990, where he obtained a prestigious Merck Management Award in chemistry. In 1996, he joined Sepracor, Inc., as Director of Chemical Process Research. He was responsible for the design and development of economical processes for the commercialization of pharmaceutical drugs. In 2002, he joined Boehringer Ingelheim Pharmaceuticals, Inc., and became Vice President of Chemical Development in 2005. Dr. Senanayake's research interests include the development of new asymmetric methods on catalytic, enzymatic, and mechanistic studies. He has published and lectured in the area of practical asymmetric synthesis and on the development of drugs in an economical and practical manner. Dr. Senenayake is an Editorial Advisory Board member of the Organic Process Research & Development Journal.

native environment in which highly diastereo- or enantioselective reactions can be achieved. Furthermore, as both enantiomers of **1** are readily accessible and now commercially available, both enantiomers of a target molecule can be easily prepared.[4−6]



(1*S*,2*R*)-**1**

Figure 1. *cis*-1-Amino-2-indanol.



L-685,434 (**2**)

Figure 2. Structure of HIV-PR inhibitor L-685,434.

The present review focuses on the importance of *cis*-1-amino-2-indanol (Figure 1) as a chiral template in the development of new methodologies for the asymmetric synthesis of organic compounds.[7−9]

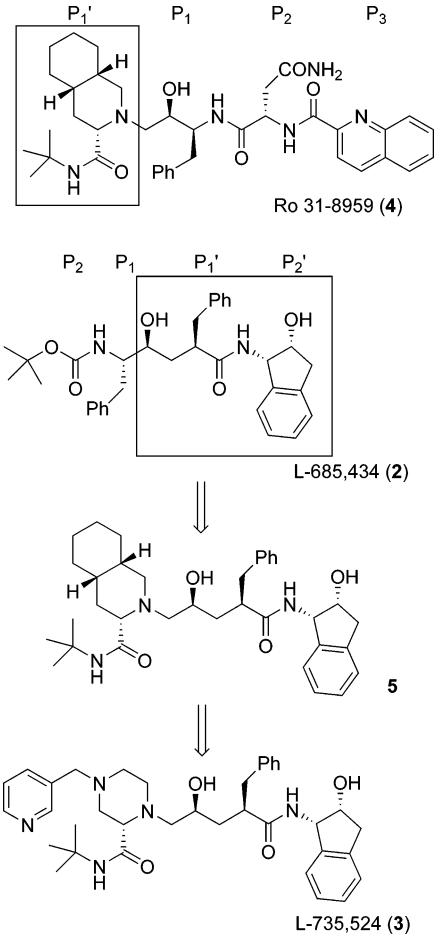
2. *cis*-1-Amino-2-indanol in Drug Design

cis-Aminoindanol was first introduced as a chiral amino alcohol P_2' ligand in a human immunodeficiency virus protease (HIV-PR) inhibitor series (at Merck). This led to the discovery of potent inhibitor L-685,434 (**2**). This compound displayed enzyme inhibitory potency (IC_{50}) of 0.3 nM and antiviral potency (CIC_{95}) of 400 nM. Crystallographic experiments of enzyme−inhibitor complexes revealed that the indane hydroxyl group acted as carbonyl surrogate, which seemed to indicate that conformationally constrained β-hydroxy amines could be generally useful as amino acid replacements (Figure 2).[10]

The aqueous insolubility of L-685,434 was later addressed by introducing polar, hydrophilic substituents at the *para* position of the P_1' phenyl ring.[11−13] These compounds indeed displayed improved solubilities as well as improved antiviral potencies. Further structure−activity relationship studies led to a *pseudo*-C_2-symmetric inhibitor and several hydroxyl ethylene isosteres. These compounds either displayed poorer enzyme inhibitory and antiviral potencies than **2** or were found extremely potent but still lacked adequate aqueous solubility and acceptable pharmacokinetic profile.[14−19]

In 1994, the design and pharmacological properties of orally bioavailable HIV-PR inhibitor L-735,524 (**3**) was disclosed, and it eventually became known as therapeutic agent Indinavir and commercialized as Crixivan.[20−26] Merck researchers hypothesized that the bioavailability of L-685,-434 could be improved by incorporating a basic amine into the backbone of this inhibitor series. In fact, replacement of the *N*-Boc and phenyl moieties P_2/P_1 ligands of **2** by the decahydroisoquinoline *tert*-butyl amide P_2'/P_1' ligand of potent HIV-PR inhibitor Ro 31-8959 (**4**, Saquinavir) enhanced aqueous solubility of the series. Despite the high enzyme inhibitory potency of the resulting **5** (IC_{50} = 7.6 nM) and its favorable pharmacokinetic profile, this novel inhibitor displayed low-antiviral potency (CIC_{95} = 400 nM). Systematic modification of the decahydroisoquinoline ring

Scheme 1

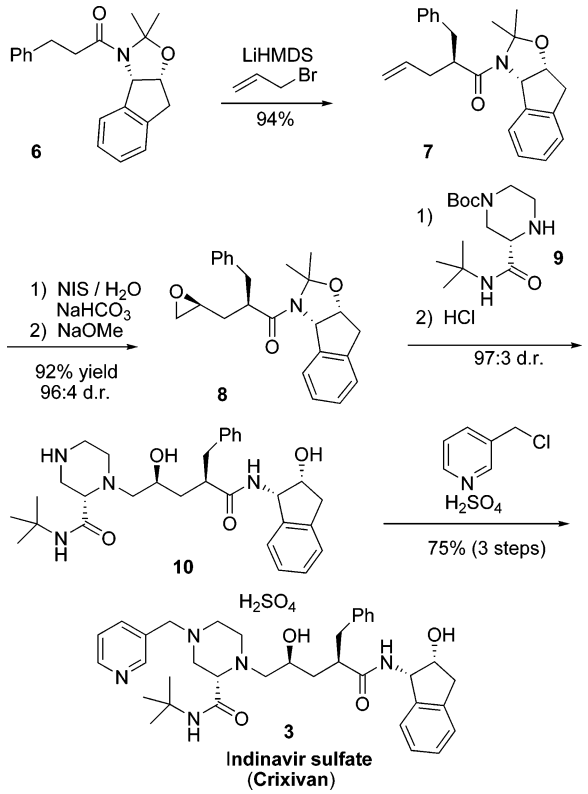


by 3-pyridylmethylpiperazine finally led to the discovery of L-735,524, which possessed high enzyme inhibitory and antiviral potencies ($IC_{50} = 0.35$ nM, $CIC_{95} = 25-100$ nM), as well as a good pharmacokinetic profile. Improvement in formulation with the sulfate salt of **3** gave increased aqueous solubility and oral bioavailability (Scheme 1).[20]

Although it contains 5 chiral centers with 32 possible stereoisomers, only a single stereoconformation of Indinavir confers the desired therapeutic effect. The industrial production of Crixivan took advantage of the chirality of (1*S*,2*R*)-aminoindanol to set the two central chiral centers of **3** by an efficient diastereoselective alkylation-epoxidation sequence.[21] The lithium enolate of amide **6** was reacted with allyl bromide to give **7** in 94% yield and 96:4 diastereoselective ratio. Treatment of a mixture of olefin **7** and *N*-chlorosuccinimide in isopropyl acetate/aqueous sodium carbonate with an aqueous solution of sodium iodide led to the desired iodohydrin in 92% yield and 97:3 diastereoselectivity. The resulting compound was converted to the epoxide **8** in quantitative yield. Subsequent epoxide opening with piperazine **9** in refluxing methanol and Boc-deprotection gave **10** in 94% yield. Finally, treatment of piperazine derivative **10** with 3-picolyl chloride in sulfuric acid afforded Indinavir sulfate in 75% yield from epoxide **8** and 56% yield for the overall process (Scheme 2).[21-26]

Continuing efforts in the search for more effective protease inhibitors led to the discovery of several drug candidates which displayed comparable enzyme-inhibitory effects and antiviral potencies to Indinavir.[27-36] In particular, Samuelsson and co-workers[33-36] designed a new C_2-symmetric HIV-PR inhibitor, on the basis of X-ray crystal structures, which

Scheme 2



indicated that the HIV-protease existed as a C_2-symmetric dimer. The peptidomimetic scaffold of this new class of inhibitors was based on D-mannitol and duplication of the C-terminus. Compound **11** was found roughly equipotent to Indinavir ($K_i = 0.4$ nM, Figure 3).[33-36]

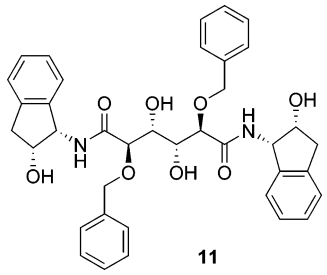


Figure 3. C_2-symmetric HIV-PR inhibitor.

Researchers at DuPont also took advantage of the *cis*-aminoindanol moiety to develop a new series of potent, selective, and orally bioavailable aggrecanase inhibitors.[37] Aggrecanase is mainly responsible for a degenerative joint disease. Preliminary studies identified **12** as a very potent and selective aggrecanase inhibitor ($IC_{50} = 12$ nM), with excellent oral bioavailability and pharmacokinetic profile.[38] Subsequent work at Bristol-Myers-Squibb led to the discovery of **13**, in which the potentially metabolically labile hydroxyphenyl has been replaced by a biphenyl group. This new inhibitor displayed remarkably increased potency ($IC_{50} = 1.5$ nM) and selectivity over **12** and represented a fresh lead in development of new medication for degenerative joint disease (Figure 4).[39,40]

More recently, *cis*-aminoindanol was found a valuable substituent in malarial Plasmepsin inhibitors. Malaria is one of the most serious infectious diseases in the world. Malaria parasites use hemoglobin as a source of nutrients during their

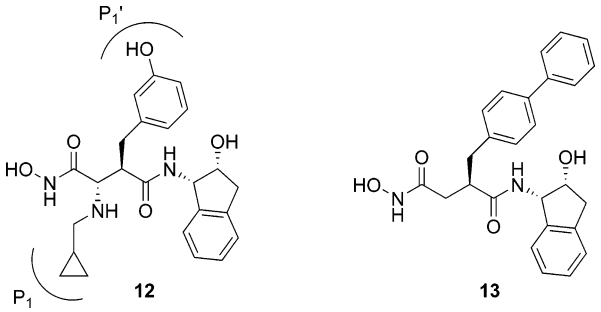


Figure 4. Aggrecanase inhibitors.

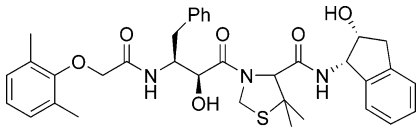


Figure 5. Malarial Plasmepsin inhibitor KNI-10006.

growth and maturation in red blood cells. In the most lethal parasite, *Plamodium falciparum*, four aspartic proteases, plasmepsin (Plm) I, II, IV, and histo-aspartic protease (HAP), have been identified in the food vacuole. These enzymes are responsible for the hemoglobin degradation pathway, and Plm I and II initiate the degradation process.[41] A series of dipeptide-type inhibitors containing allophenylnorstatine-dimethylthioproline scaffold were designed and synthesized.[42] Among these compounds, KNI-10006 (**14**), which has an aminoindanol at the P_2' position, was found to inhibit Plm II with a remarkable K_i value of 0.5 nM. Replacement of the aminoindanol moiety by aminoindan or 1-amino-2-cyclohexanol led to decreased affinity. Therefore, both the hydroxyl group and the indane platform of aminoindanol of KNI-10006 are important for its tight binding (Figure 5).[42]

However, achieving selectivity versus the highly homologous human aspartic protease cathepsin D (Cat D) has emerged as a major challenge. Hallberg and co-workers[43,44] designed a series of nonpeptidic C_2-symmetric inhibitors with high affinities to both Plm I and II ($K_i = 0.5-37$ and $6-181$ nM, respectively), and all inhibitors demonstrated a unique selectivity versus the human Cat D (K_i > 2000 nM). Modeling studies starting from a 3D structure of Plm II complexed with pepstatin A suggested that 1,2-dihydroxyethylene, which had successfully been used in HIV-1 protease inhibitors, could provide an alternative tetrahedral intermediate mimicking scaffold in Plm II inhibitors (Figure 6).[43,44]

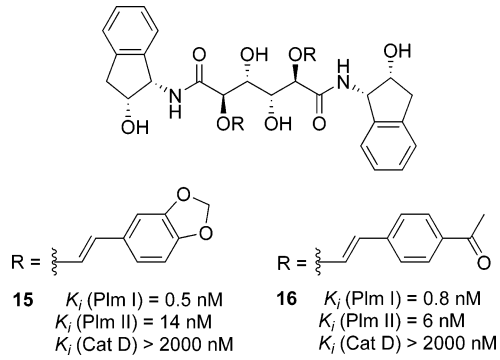


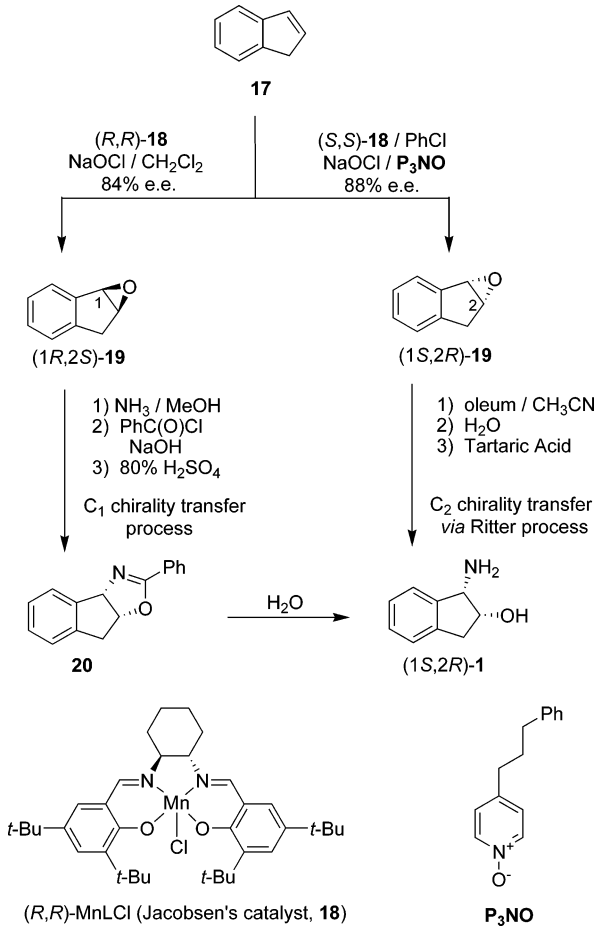
Figure 6. Nonpeptidic C_2-symmetric malarial Plasmepsin inhibitors.

3. Practical Syntheses of Enantiopure *cis*-1-Amino-2-indanol

Early syntheses of enantiopure *cis*-aminoindanols relied either on starting materials from the chiral pool or on chemical or enzymatic resolution of racemic intermediates.[11,45−55] Advances in catalytic asymmetric epoxidation and asymmetric dihydroxylation of prochiral olefin[56−62] enabled the development of truly practical asymmetric syntheses of *cis*-1-amino-2-indanols.[63−68]

Research groups at Sepracor[64,65] and Merck[66−68] independently developed similar strategies to access *cis*-(1*S*,2*R*)-aminoindanol. Both processes utilized Jacobsen's Mn-(salen) catalyst (MnLCl, **18**)[56−58,69] for indene epoxidation, followed

Scheme 3



by chirality transfer of the C−O bond of indene oxide **19** to obtain enantiopure *cis*-(1*S*,2*R*)-aminoindanol (Scheme 3).

Researchers at Sepracor demonstrated the preparation of (1*R*,2*S*)-indene oxide **19** from readily available indene **17** in the presence of 1.5 mol % of (*R*,*R*)-MnLCl/13% NaOCl in dichloromethane in 83% yield and 84% enantiomeric excess (Scheme 3). Chiral indene oxide **19** was then subjected to nucleophilic opening with ammonia to provide *trans*-aminoindanol, which was transformed without isolation to its benzamide under Schotten−Baumann conditions (83% ee, > 99.5% ee after recrystallization). The optically pure *trans*-benzamidoindane was then converted to the optically pure benzaoxazoline **20** by exposure to 80% H_2SO_4, followed by addition of water to give *cis*-1-amino-2-indanol.[64,65] The sequence was demonstrated on multi-kilogram scale to prepare optically pure (1*R*,2*S*)-**1** in 40% yield from indene.

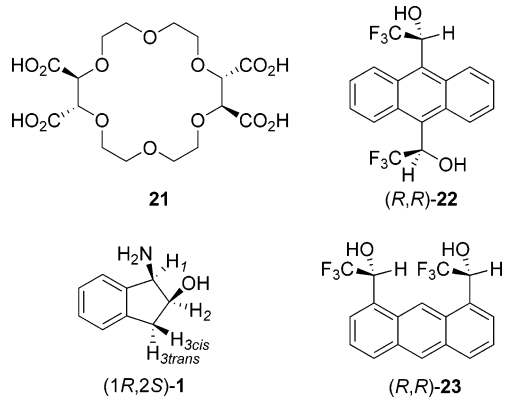


Figure 7. Examples of Chiral Solvating Agents for enantiomeric discrimination of *cis*-aminoindanol.

A complementary approach to the synthesis of (1*R*,2*S*)-**1** was developed by Merck and used (*S*,*S*)-MnLCl catalyst in a hypochlorite medium to provide (1*S*,2*R*)-indene oxide **19**. Addition of an axial ligand, such as commercially available phenyl propyl pyridine *N*-oxide (P_3NO), to the (*S*,*S*)-MnLCl-NaOCl-PhCl system, resulted in a highly activated and stabilized catalyst for indene epoxidation.[68,70−72] This reagent mixture was demonstrated on a multi-kilogram scale to afford indene oxide in 89% yield with an optical purity of 88% ee.[68] Intermediate **19** was then converted without isolation to *cis*-aminoindanol in a stereo- and regioselective manner using the Ritter acid as an oleum (21% SO_3-H_2SO_4). This led to chiral *cis*-1-amino-2-indanol **1** in 80% yield.[21,66,73,74] (Scheme 3).

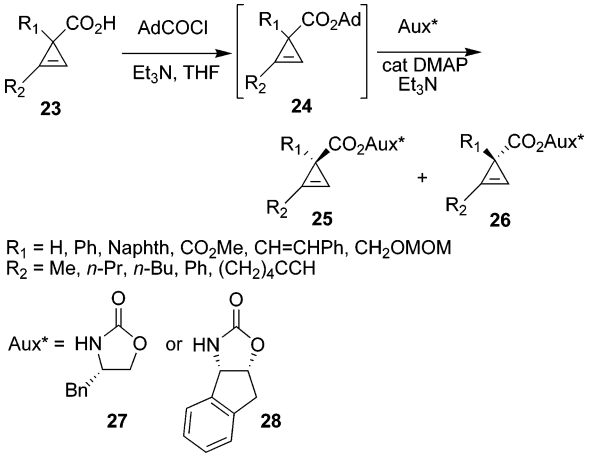
Despite these highly practical and cost-effective processes, the suitability of a bioconversion process for the production of *cis*-aminoindanol continues to be explored alongside further optimization of these chemical syntheses.[51]

4. cis-1-Amino-2-indanol in NMR Chiral Solvating Agents' Studies

Chiral solvating agents (CSA) are used to determine the composition of a mixture of enantiomers by NMR.[75,76] The chiral reagent can form association complexes with the enantiomers in solution, and the diastereomeric complexes thus formed may have different chemical shifts. In addition, the association constants of the two enantiomers with the chiral reagent are often different. This will cause different time-averaged solvation environments that may contribute to chiral recognition in the NMR spectrum. Chiral solvating agents work for a wide range of compounds, including amines and alcohols. Because of its rigid platform and dual functionality, *cis*-aminoindanol is an ideal template to test chiral solvating agents' efficiency (Figure 7).

Wenzel and co-workers[76,77] studied the utility of chiral crown ether **21** as an enantiomeric discriminating agent. The carboxylic acid groups of **21** can discriminate neutral amines. An acid−base reaction occurs between the carboxylic acid groups of **21** and amines and produces ammonium salts, which then associate with the crown cavity.[77] When **21** is mixed with racemic *cis*-aminoindanol in methanol-d_4, certain resonances in the ^{1}H NMR spectrum show downfield shifts that are consistent with protonation of the amino group. An excellent enantiomeric discrimination was observed in the ^{1}H NMR of the primary amine of **1** in the presence of an equimolar amount of **21** (74.1 Hz for H_1 and 30.5 Hz for H_7). The magnitude of the enantiomeric discrimination for the hydrochloride salt of *cis*-aminoindanol is fairly comparable (48.9 Hz for H_1 and 34.8 Hz for H_7).[77]

Scheme 4



Virgili and co-workers studied the enantiorecognition of *cis*-aminoindanol by (*R*,*R*)-α,α′-bis(trifluoromethyl)-9,10-anthracenedimethanol **22**.[78] The examination of the bidentate associations between **22** and **1** revealed that the *cisoid* conformation of **22** is responsible for the separation of the NMR signals. When 1 equiv of **22** on a 3:1 mixture of (1*R*,2*S*)-**1** and (1*S*,2*R*)-**1** was used, mean differentiation was observed for H_1 and H_3. Protons H_{3cis} and H_{3trans} are more shielded in (1*S*,2*R*)-**1**, while H_1 in (1*R*,2*S*)-**1** is the most shifted to higher fields.[78] Virgili and co-workers later found that (*R*,*R*)-**23** gave similar enantiodiscrimination as (*R*,*R*)-**22**, but (*R*,*R*)-**23** also enantiodifferentiates nuclei not separated by (*R*,*R*)-**22**, for example, the signal of H_2.[79]

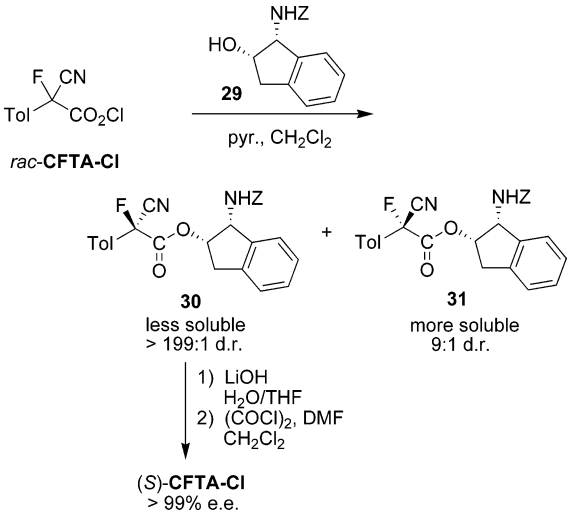
5. cis-1-Amino-2-indanol as Resolving Agent

5.1. Separation of Carboxylic Acids by Preparation of Diastereomeric *cis*-Aminoindanol Esters

Despite the unusual properties of cyclopropenes that make them interesting synthons, methods that produce enantiomerically enriched cyclopropenes are rare and cyclopropenes with quaternary centers unknown. Fox and co-workers recently devised a simple and inexpensive resolution for obtaining numerous derivatives of cyclopropene carboxylic acids in enantiomerically pure form.[80] A number of chiral alcohols such as (−)-menthol or quinidine were screened, but none of the diastereomeric esters were separable by chromatography. Computational screening of various auxiliaries using molecular mechanics indicated that chiral oxazolidinones could be excellent resolving groups for the cyclopropene carboxylic acids because of the difference in the relative orientation of the alkene and oxazolidinone substituents for the diastereomers. Indeed, a variety of cycloprop-2-ene carboxylic acids can be resolved through conversion to diastereomeric *N*-aryl-oxazolidinones and separated by column chromatography to provide gram quantities of diastereomerically pure cyclopropenes. In the cases where the oxazolidinone of (*S*)-phenylalaninol or (*S*)-phenylglycinol failed to provide good separation, the oxazolidinone of *cis*-(1*S*,2*R*)-1-amino-2-indanol proved an excellent resolving agent (Scheme 4).[80]

The chiral derivatizing agent α-cyano-α-fluoro-*p*-tolylacetic acid (CFTA) was found particularly effective from

Scheme 5



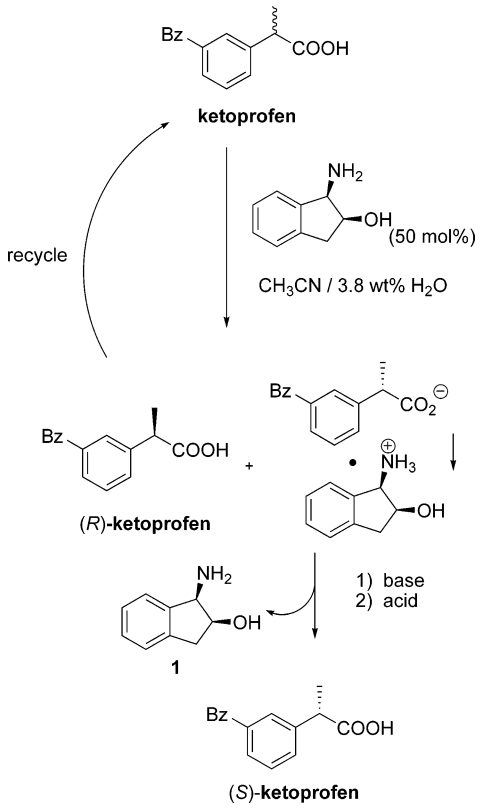
the viewpoint of both reactivity and NMR resolution ability. A very convenient method for obtaining optically pure (*S*)-CFTA by fractional recrystallization was recently disclosed.[81] A mixture of the diastereomeric CFTA esters was prepared from racemic CFTA chloride and (1*R*,2*S*)-*N*-carbobenzyloxy-*cis*-1-amino-2-indanol. Hydrolysis of the less soluble ester followed by conversion to the acid chloride led to (*S*)-CFTA-Cl in 99% ee (Scheme 5).[81]

5.2. Chiral Discrimination of 2-Arylalkanoic Acids

Production of enantiomerically pure α-arylpropanoic acids, also known as profens, is of critical importance to the pharmaceutical industry as they constitute a major class of antiinflammatory agents. Resolution with chiral amines is one of the most practical approaches for the preparation of optically pure α-arylpropanoic acids. Examples of efficient chiral amines include brucine, quinidine, cinchonidine, morphine, ephedrine, and α-(1-naphthyl)ethylamine. For instance, racemic ibuprofen[82] and ketoprofen[83] were resolved (*S*)-α-methylbenzylamine and (−)-cinchonidine, respectively. However, most of these chiral amines are either expensive, difficult to recover, available in only one enantiomeric form, or substrate-specific.

Enantiopure *cis*-1-amino-2-indanols have been demonstrated to effectively overcome these limitations. Not only are both enantiomers of *cis*-1-amino-2-indanol rapidly accessible via an inexpensive process, but also they have been shown to be extremely effective in the resolution of a number of 2-arylalkanoic acids,[84−86] including ketoprofen, flurbiprofen, and ibuprofen.[84] In the case of ketoprofen,[84] use of (1*R*,2*S*)-1-amino-2-indanol allowed for the selective crystallization of (*S*)-ketoprofen in the presence of (*R*)-ketoprofen (Scheme 6). Similarly, (*R*)-ketoprofen was shown to selectively precipitate with (1*S*,2*R*)-1-amino-2-indanol in the presence of (*S*)-ketoprofen. Extensive solubility studies led to the following observations: (a) diastereomeric salts of (*R*)- and (*S*)-ketoprofen with aminoindanols exhibited larger differences in solubility than diastereomeric salts of (*R*)- and (*S*)-ketoprofen with other chiral amines, (b) diastereomeric salts of (*R*)- and (*S*)-acids with aminoindanol displayed large differences in solubility for a wide range of chiral acids, and (c) a catalytic amount of water in acetonitrile had a significant impact on the rate of crystallization, leading to higher yields of the precipitating diastereoisomer. Finally, the undesired

Scheme 6



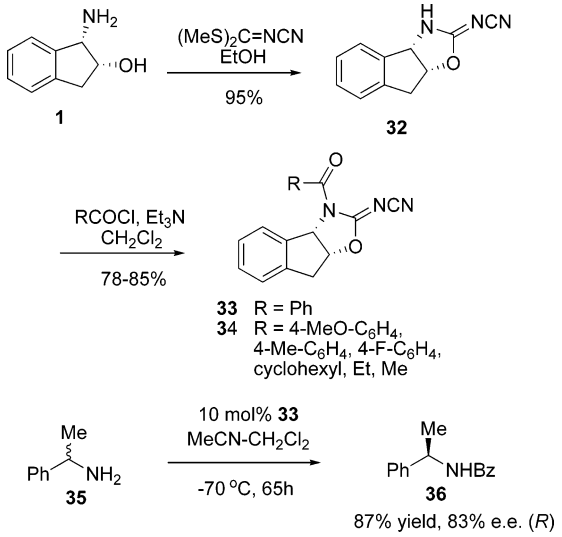
isomer ((*R*)-ketoprofen in Scheme 6) can be racemized and recycled, and enantiopure *cis*-aminoindanol can be easily recovered for reuse.[84]

5.3. Enantioselective Acetylation of Racemic Secondary Alkylamines

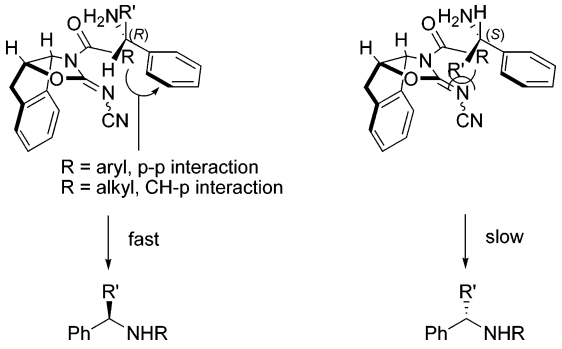
A new *cis*-aminoindanol-derived (*N*-cyanoimino)oxazolidine acetylating agent was developed by Tanaka and co-workers and applied to the kinetic resolution of secondary alkylamines.[87] Chiral acetylating agents **33** and **34** were readily prepared from (1*R*,2*S*)-1-amino-2-indanol by reaction with *S*,*S*′-dimethyl *N*-cyanodithioiminocarbonate followed by acetylation (78−85% yield, 2 steps). Kinetic resolution of racemic 1-phenylethylamine using 10 mol % of **33** at −70 °C led to (*R*)-*N*-benzoyl-1-phenylethylamine **36** in 87% yield and 83% ee. Chiral **32** was easily recovered by column chromatography (Scheme 7). The *N*-acyl transfer was activated by the strong electron-withdrawing *N*-cyanoimino moiety of **33**. Interestingly, no aminolysis of the oxazolidine ring of **33** was observed. Other acetylating agents **34** (R = 4-MeO−C_6H_4, 4-Me-C_6H_4, 4-F-C_6H_4, Me) were shown to efficiently resolve **35** at low temperature (−70 °C for R = aryl and −20 °C for R = Me), leading to protected secondary alkylamines in moderate to good enantioselectivities (65−78% ee). Kinetic resolution of a variety of racemic secondary alkylamines using a catalytic amount of **33** was also examined. It was rapidly established that a phenyl group in amines was essential to achieve high selectivities. Replacement of the methyl group of **35** by larger groups decreased the reaction rate but led to similar selectivities.[87]

To explain the stereochemical outcome of the reaction, Tanaka and co-workers speculated that the *N*-cyanoimino groups in **33** would prefer an opposite orientation to the amide carbonyl in order to minimize unfavorable dipole−

Scheme 7



Scheme 8



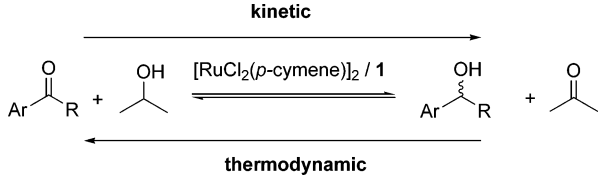
dipole interaction. In this conformation, the *Re*-face of the carbonyl group would be shielded by the large and conformationally rigid indane ring, thus, favoring the approach of the amine from the *Si*-face. Overlap of the amine phenyl ring with the carbonyl aryl or alkyl group of **33** would create a stabilizing $\pi-\pi$ or CH$-\pi$ interaction, respectively, in which case, the approach of the (*S*)-isomer would suffer from steric interaction between R′- and *N*-cyanoimino groups (Scheme 8).[87]

5.4. Kinetic Resolution of Secondary Aryl Alcohols

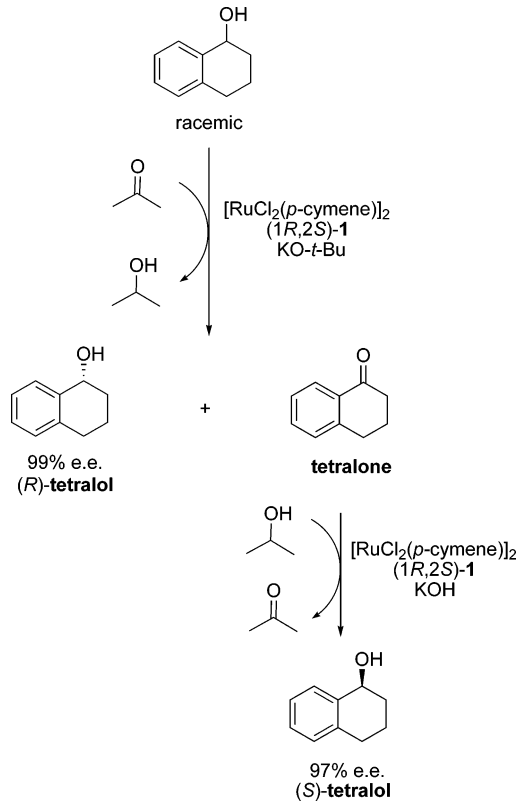
A novel kinetic resolution of secondary aryl alcohols using an enantiopure *cis*-1-amino-2-indanol-derived catalyst was disclosed by Faller.[88] The investigation was based on earlier findings by Wills[89] that stereochemically rigid (1*R*,2*S*)-1-amino-2-indanol was a powerful ligand for the asymmetric ruthenium-catalyzed transfer hydrogenation of aryl ketones using 2-propanol, leading to high enantioselectivities (up to 98%). The stereoselectivity of the reaction was obtained primarily by kinetic discrimination of enantiofaces of the prochiral ketone, but thermodynamic factors favoring the reverse process were not negligible (Scheme 9).[90−92] Thus, it was argued that an asymmetric transfer hydrogenation catalyst should be capable of dehydrogenation as well as hydrogenation.

Since Wills's hydrogenation catalyst provided an excellent route to (*S*)-aryl alcohols from aryl ketones, Faller decided to expand the scope of this catalyst to the kinetic resolution of racemic aryl alcohols to prepare (*R*)-aryl alcohols. Results

Scheme 9



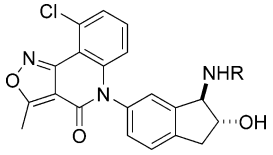
Scheme 10



showed that products can be obtained with enantiomeric purities in the 90−99% range.[88] In situations where the asymmetric transfer hydrogenation of a given ketone led to moderate enantioselectivity, the enantiomeric purity of the resulting alcohol could be enhanced via a subsequent asymmetric dehydrogenation with the antipode of the catalyst.[93] On the other hand, when applied to the kinetic resolution of (±)-tetralol and (±)-indanol, the [$RuCl_2$(*p*-cymene)]$_2$-(1*R*,2*S*)-1-amino-2-indanol-KO-*t*-Bu combination in acetone yielded the corresponding (*R*)-alcohols in 99% ee, aryl ketones and 2-propanol. In turn, reduction of 1′-tetralone and 1′-indanone using the same catalytic system in 2-propanol led to (*S*)-alcohols in 97% ee (Scheme 10). These studies provide a compelling demonstration of the generally unappreciated notion that a single enantiomer of a catalyst can lead to both antipodes of the same product with high levels of stereoselectivities.[88]

5.5. Crystallization-Induced Dynamic Resolution

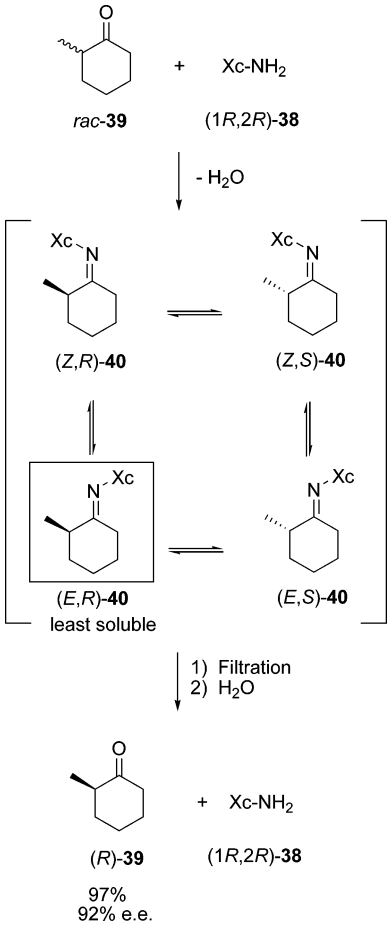
Researchers at Eli Lilly have disclosed the significance of the *trans*-6-nitro-1-amino-2-indanol template in a new class of resistant neoplasms inhibitors of type **37** (Figure 8). Unfortunately, multidrug resistance remains an important issue in chemotherapy, where cells may become cross-resistant to a wide range of drugs with different structures and cellular targets. Compounds of type **37**, which contain a bulky and constrained platform isomeric to *cis*-1-amino-



37

Figure 8. Resistant neoplasms inhibitor.

Scheme 11



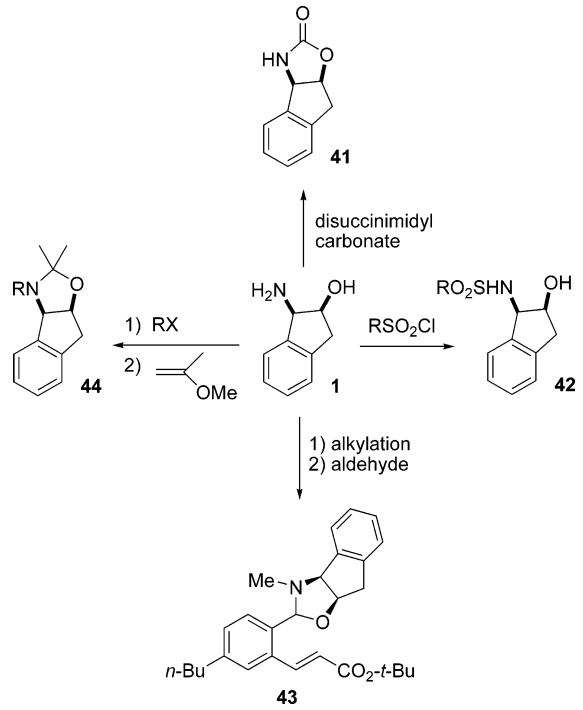
2-indanol, were shown to selectively inhibit intrinsic and/or acquired resistance conferred in part or in total to the 190 kDa multidrug resistance protein commonly referred to as MRP1.[94]

Compound **38** was recently identified as a valuable chiral auxiliary in the preliminary studies on the Crystallization-Induced Dynamic Resolution (CIDR) of imines.[95] This resolution/deracemization process provided a practical access to large quantities of nonracemic, α-epimerizable, unfunctionalized ketones and aldehydes. For example, crystalline imines of epimerizable 2-methylcyclohexanone **39** were formed, and **40** was found to exist as a 3:1 solution mixture of *E*/*Z* imine isomers with a 1:1 diastereoselective ratio. In the case of ketone **39**, equilibration in methanol afforded the best results, where imine (*E*,*R*)-**40** is the least soluble crystalline product. Filtration and hydrolysis under acidic conditions gave (*R*)-1-methylcyclohexanone in 97% yield and 92% ee, and the chiral auxiliary was recovered (Scheme 11).[95]

6. *cis*-1-Amino-2-indanol-Derived Chiral Auxiliaries

Conformationally constrained *cis*-aminoindanols and its derivatives have been utilized as chiral auxiliaries in a number of asymmetric reactions. The availability of both *cis*-enantiomers, the high levels of asymmetric induction attained, and the ease of recovery are all assets to the development of efficient and practical processes with those auxiliaries.

Scheme 12



Rigid *cis*-1-amino-2-indanol-derived oxazolidinone **41** was first introduced by Ghosh as a useful chiral auxiliary in the asymmetric *syn*-aldol reaction.[96,97] Later, the C-2 hydroxyl moiety of aminoindanol **42** was shown a valuable handle in the aldol reaction as well.[98,99] Askin utilized the rigid tricyclic aminoindanol acetonide as a chiral platform for the asymmetric synthesis of HIV-1 protease inhibitor **2**.[15] Scientist at Merck used *N*,*O*-acetal **43** as a Michael acceptor for 1,4 addition of lithium diphenyl cuprate or aryllithium to α,*β*-unsaturated esters, where the selectivity is controlled by the neighboring chiral auxiliary (Scheme 12).[100] Effective removal and recovery of these chiral auxiliaries was carried out under mild hydrolysis conditions.[96,97,100]

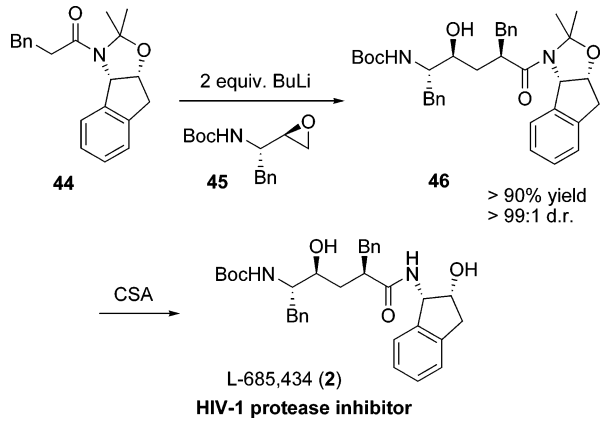
6.1. Alkylation and Electrophilic Amination Reactions

A concise and practical synthesis of HIV-1 protease inhibitor **2** was developed by Askin.[15] Diastereoselective alkylation of (*Z*)-lithium enolate of amide **44** with amino epoxide **45** occurred from the less hindered *β*-face and led to intermediate **46** in >90% yield and >99:1 d.r. The amino alcohol was deprotected by treatment with camphorsulfonic acid and gave **2** in good yield (Scheme 13).

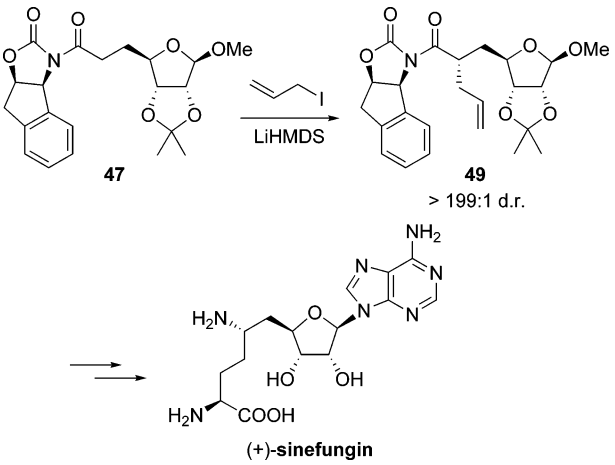
This alkylation strategy was successfully implemented to the diastereoselective synthesis of a number of biologically active compounds,[21,23,36,101,102] including the orally active HIV protease inhibitor Crixivan (>195:5 d.r.),[21,23] and nucleoside antibiotic (+)-sinefungin (>199:1 d.r.).[101] The C-6 amine stereochemistry of (+)-sinefungin was set by a highly diastereoselective allylation of (1*S*,2*R*)-1-amino-2-indanol-derived oxazolidinone **47** (Scheme 14).[101]

The low reactivity of glycine enolate with unactivated alkyl halides to form α-amino acids could be overcome by

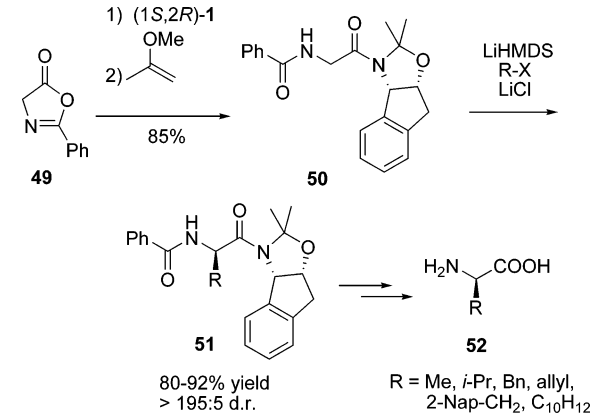
Scheme 13



Scheme 14



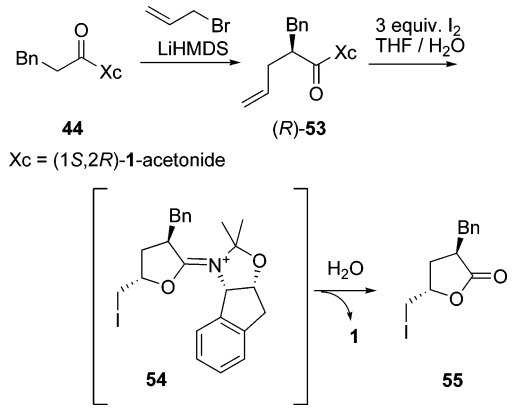
Scheme 15



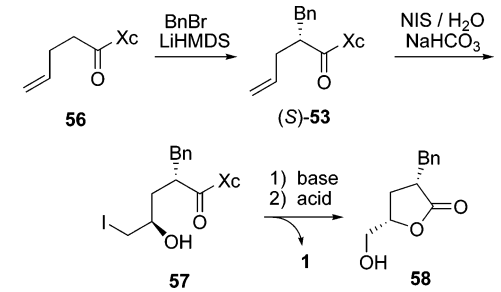
stabilizing the nucleophile using *cis*-aminoindanol-derived hippuric acid **50**. This key substrate was readily prepared from commercially available azalactone **49** by a one-pot operation (85% yield, 2 steps). The reaction of lithium enolate of amide acetonide **50** with a wide range of alkyl halides proceeded in moderate yields (>60%) and excellent diastereoselectivities (>195:5 d.r.). A 25% increase in yield was achieved by using lithium chloride as an additive in order to facilitate the dissociation of the amide enolate from the aggregated state and thus enhance its reactivity (Scheme 15). Reactions with secondary halides remained low-yielding, presumably because of competing elimination reaction.[103]

The methodology was extended by Askin to the asymmetric syntheses of *syn*- and *anti*-2,4-substituted-γ-butyrolactones in a stereoselective fashion[24] (Schemes16 and 17).

Scheme 16



Scheme 17



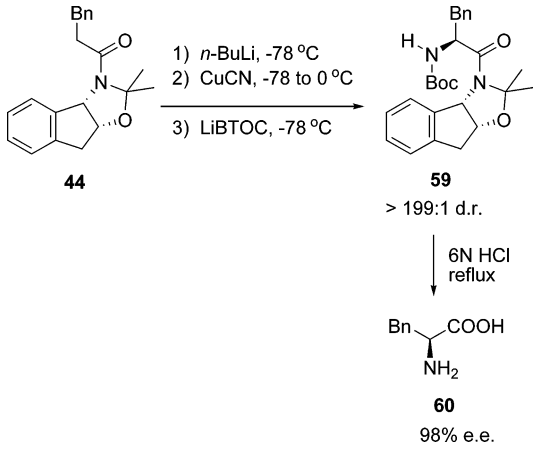
Amide **44** was diastereoselectively allylated (94% yield, 96:4 d.r.), and the resulting olefin (*R*)-**53** was then subjected to Yoshida's unbuffered condition (I_2/THF/H_2O) to give iodolactone **55** in 97:3 *anti*/*syn* ratio.[104] The efficient 1,3 chirality transfer was consistent with a highly ordered imidate transition state **54** wherein the $A_{1,3}$ strain between the iminium indanol substituent and the benzyl group shifts the latter in a *pseudo*-axial orientation, which resulted in a high preference for the formation of thermodynamically less stable *anti*-2,4-substituted-lactone **55**. Pro-(2*S*)-diastereomer **53** was prepared in high yields with excellent diastereoselectivity by reversal of the order of introduction of the benzyl and allyl groups. Interestingly, exposure to the buffered iodohydrin process (NIS/H_2O, $NaHCO_3$) resulted in the formation of the 2,4-*syn*-product **57** with outstanding selectivity (197:3 d.r.). Epoxide formation in a basic medium followed by acid-mediated lactonization gave *syn*-2,4-disubstituted-γ-butyrolactone **58**.[24]

A novel asymmetric synthesis of α-amino acids via electrophilic amination has been demonstrated by Zheng and Armstrong.[105] Transmetalation of lithium enolate **44** with copper(I) cyanide was necessary to generate a reactive amide cuprate, which then added efficiently to the lithium *tert*-butyl-*N*-tosyloxycarbamate (LiBTOC) electrophile. Electrophilic amination of chiral cuprates with LiBTOC provided an expedient approach to α-amino acids with predictable absolute configuration in high enantiomeric purity and good yield (Scheme 18).

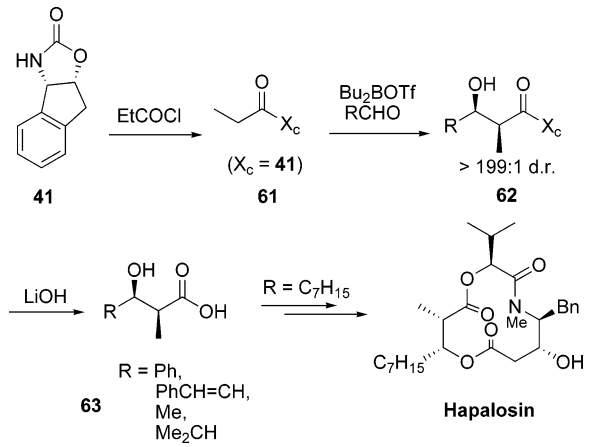
6.2. Aldol and Homoaldol Reactions

With proper choice of chiral template of *cis*-aminoindanol **1** and aldehyde, all four possible *syn*- and *anti*-aldol products can be prepared with predictable stereochemistry. Both boron and titanium enolate methodologies were successfully applied to the stereoselective syntheses of several biologically active compounds,[101,106−109] such as Hapalosin (Scheme 19), and

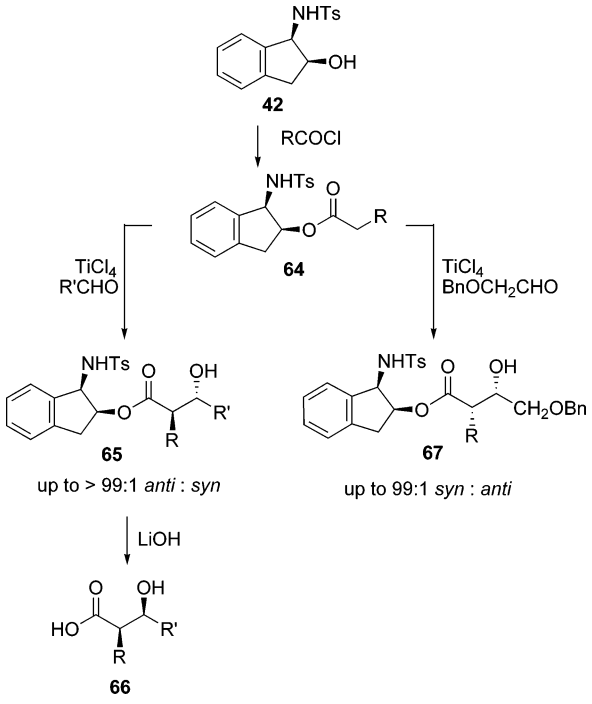
Scheme 18



Scheme 19



Scheme 20



natural product synthons,[96,98,110,111] such as *anti*-α-methyl-*β*-hydroxy acid **66** (Scheme 20).

Aldol condensation using boron enolate of **61** with various aldehydes proceeded with complete *syn* diastereofacial selectivity (Scheme 19). As both enantiomers of the chiral

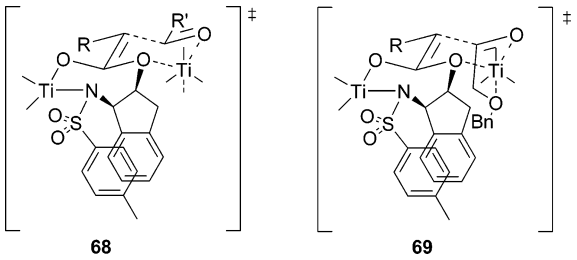
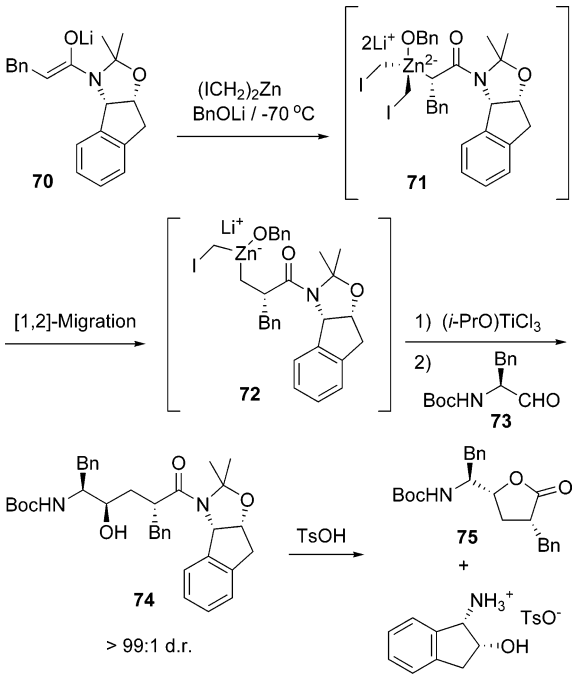


Figure 9. Proposed transition states by titanium chelation.

Scheme 21



auxiliary were readily available, both enantiomers of the *syn*-aldol could be prepared with equal asymmetric induction.[96,101]

When titanium enolate of ester **64** was added to a solution of aldehyde, precomplexed with titanium tetrachloride, the *anti*-aldol product **65** was obtained in excellent diastereoselectivities.[98] Hydrolysis of **65** afforded *anti*-α-methyl-*β*-hydroxy acid **66** as a pure enantiomer, and *cis*-1-*p*-tolylsulfonamido-2-indanol was recovered without loss of optical purity.[98] In contrast, reaction of titanium enolate of **64** with bidentate oxyaldehydes proceeded with excellent *syn*-diastereoselectivity (Scheme 20).[99] The stereochemical outcome was rationalized by a Zimmerman−Traxler-type transition states **68** and **69**.[112] Assuming a *Z*-geometry for titanium enolate of **64** and a seven-membered metallacycle with a chairlike conformation, a model was proposed where a second titanium metal coordinated to the indanol and aldehyde oxygens in a six-membered chairlike conformation. Aldehydes which were not precomplexed with titanium tetrachloride did not react, thus, corroborating the involvement of two titanium centers (Figure 9). A chelating substituent on the aldehyde would alter the transition state and consequently the stereochemical outcome of the condensation, leading to *syn*-aldol products.[98,99,112]

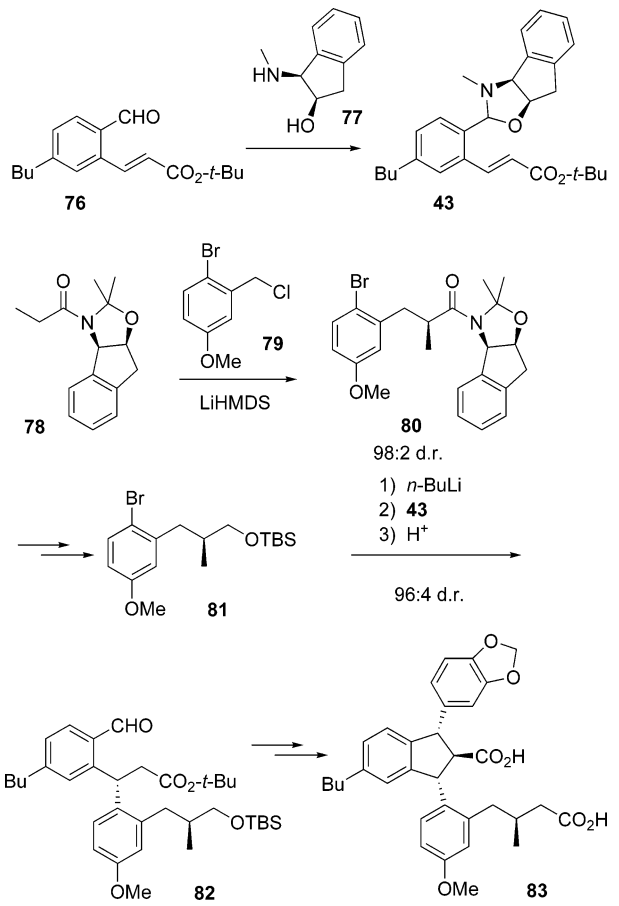
An elegant tandem *1,2-migration/homoaldol* protocol for the synthesis of highly functionalized *syn*-2,4-*γ*-butyrolactones took advantage of aminoindanol acetonide as a powerful chiral auxiliary for stereocontrolled 1,6 asymmetric induction (Scheme 21).[113,114] Lithium enolate **70** was reacted with bis(iodomethyl) zinc in the presence of lithium benzyl-

alkoxide. Armstrong and Williams hypothesized that the higher order alkoxy zincate **71**, in which the α-center has been set, underwent a 1,2-migration with remarkable retention of stereoselectivity to give alkoxy zincate **72**. The stereoselective migration, which proceeded in a remarkable >99:1 d.r., set the absolute configuration of the α-center. Zinc homoenolate **72** was then transmetalated with (*i*-PrO)-$TiCl_3$ and subjected to homoaldol reaction with *N*-(*tert*-butoxycarbonyl)phenylalaninal. Homoaldol **74** was obtained in 59% yield and >99:1 d.r. for the overall two-step transformation. Treatment of γ-hydroxyamide **74** with *p*-toluenesulfonic acid induced cyclization to lactone **75** in good yield. Pure *p*-toluenesulfonate salt of *cis*-(1*S*,2*R*)-aminoindanol crystallized from the reaction mixture and was recovered by simple filtration. Thus, asymmetric induction in two disparate transformations was achieved by *cis*-aminoindanol acetonide as the single chiral controlling element.[113,114]

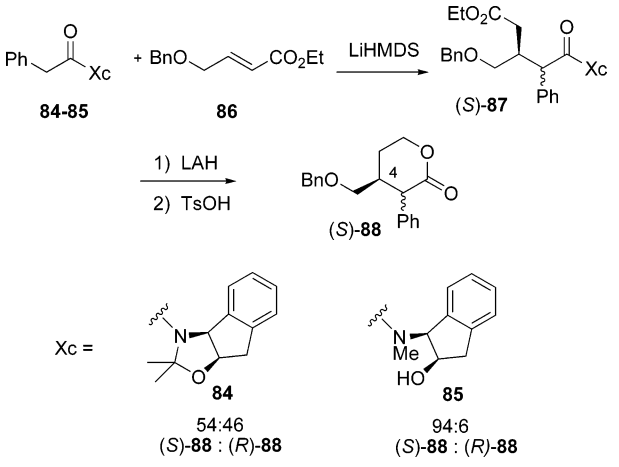
6.3. Conjugate Addition

cis-Aminoindanol was the chiral auxiliary of choice for both the stereoselective alkylation and the chiral Michael addition steps of Merck's asymmetric synthesis of endothelin receptor antagonist **83**. Aldehyde **76** was treated with (1*S*,2*R*)-*N*-methyl-1-amino-2-indanol to yield *N*,*O*-acetal **43** quantitatively. The aryllithium generated from **81** was added at low temperature to Michael acceptor **43** followed by acidic workup. Aldehyde **82** was obtained in 92% overall yield from **76** and 96:4 d.r. In comparison, conjugate addition to dimethyl acetal of **76** using external chiral additives led to diastereoselectivities that would not exceed 84:16 d.r. (Scheme 22). [100,115,116] *cis*-Aminoindanol was also used successfully as chiral auxiliary on Michael donors. Michael adducts from the reaction of chiral amide enolates **84** and **85** with α,β-unsaturated ester **86** and the resultant adducts were reduced and cyclized to δ-lactones **88** in order to determine the facial selectivity. Interestingly, acetonide **84** did not lead to significant diastereofacial discrimination, whereas **85** afforded lactone **88** with high 4-(*S*)-selectivity (Scheme 23).[117]

Scheme 22



Scheme 23



6.4. Metal Chelation

Secondary α-hydroxy acids were readily accessed by reduction of α-ketoesters bearing *cis*-1-arylsulfonamido-2-indanol derivatives as a chiral auxiliary in high yields and good-to-excellent diastereoselectivities (from 4:1 to >99:1 d.r.) using bulky alkyl hydrides. Indeed, reduction of **89** using l-selectride and zinc chloride afforded α-hydroxy ester **91** in 96% yield and >99:1 diastereomeric ratio. Hydrolysis under mild conditions released the chiral auxiliary and produced essentially optically pure α-hydroxy acids **92**. The high degree of stereoselection was attributed to metal chelation of the carbonyl oxygens, which locks **89** in an s-*cis* conformation. The vicinal toluenesulfonamide most probably shields the *Re*-face and, consequently, leads to the preferential hydride attack from the *Si*-face (Scheme 24).[118]

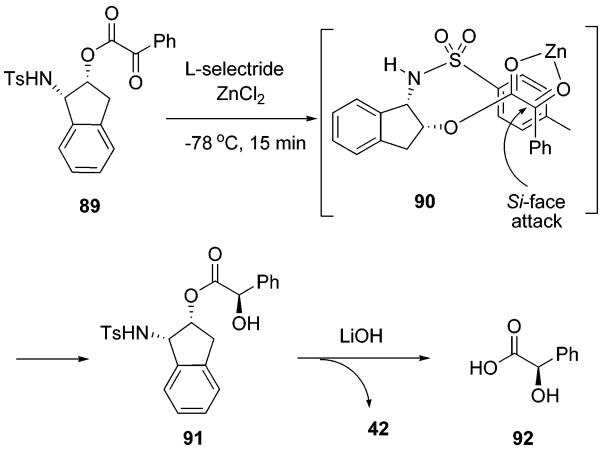
A thorough investigation was led by researchers at Sepracor on the advantage of using the C-1 amine or C-2 alcohol of *cis*-aminoindanol as a chiral handle. Hydroxy acid (*S*)-**93**, a key component of muscarinic receptor antagonist (*S*)-oxybutynin, was generated by diastereoselective cyclohexyl or phenyl Grignard addition to the appropriate ketoester or ketoamide, followed by removal of aminoindanol unit (Scheme 25).[119,120] Phenyl Grignard addition to ketoamide **94** and ketoester **94** proceeded via magnesium coordination and led to high diastereoselectivities. In the case of cyclohexyl Grignard addition, zinc chloride was a necessary additive in order to achieve good degrees of diastereoselection. Interestingly, *N*-tosyl-derived ketoester **96** provided the most expedient avenue to the preparation of optically pure (*S*)-acid **93**.

6.5. Pericyclic Reactions

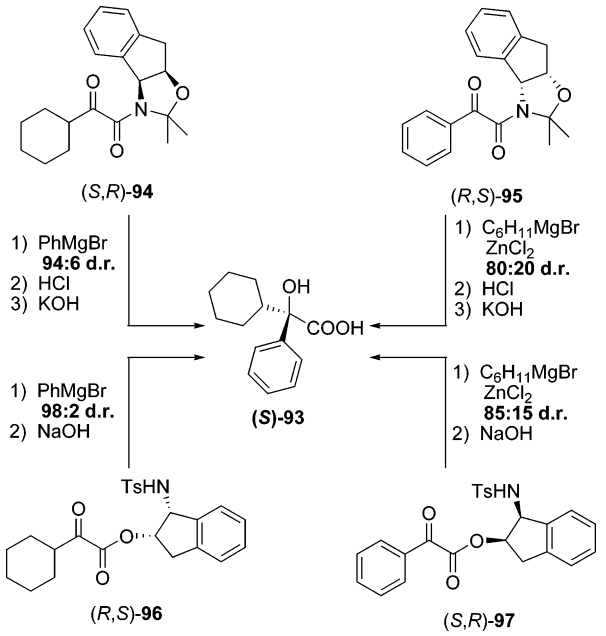
6.5.1. Diels–Alder Reaction

Pioneering work by Evans has shown that very high levels of diastereofacial discrimination could be achieved in the

Scheme 24



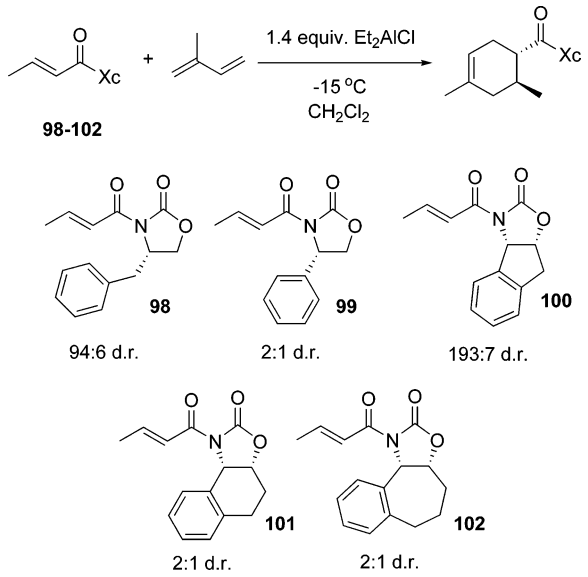
Scheme 25



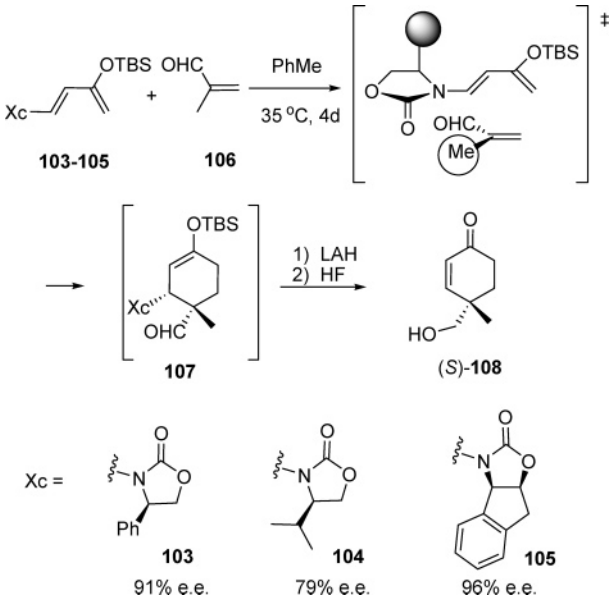
Diels−Alder reaction of isoprene using oxazolidinone **98** (94:6 d.r.). Use of phenyl glycinol derivative **99** gave reduced diastereoselectivity (2:1 d.r.).[121,122] The low level of selectivity of **99** was envisioned to result from the rotational freedom of the phenyl group which can adopt a more or less sterically demanding conformation. Conformationally constrained phenyl glycinol analogue **100** was subjected to Evans Diels−Alder reaction conditions (1.4 equiv Et_2AlCl, −15 °C, CH_2Cl_2) and gave excellent *endo*- and diastereoselectivities (193:7 d.r.). Homologous six- and seven-membered ring-containing systems **101** and **102** led to low levels of asymmetric induction (2:1 d.r.), thereby demonstrating the importance of the rigidity of the aminoindanol platform (Scheme 26).[123] In another example of *cis*-aminoindanol as chiral auxiliary on dienophiles, use of titanium tetrachloride as the Lewis acid resulted in high degrees of diastereoselection (*endo*/*exo* ratios superior to 99:1 and 96:4 d.r.).[124]

cis-Aminoindanol was also shown to be an excellent chiral auxiliary when attached to the diene moiety. Cycloaddition of readily accessible and stable 1-(2-oxazolidinon-3-yl)-3-siloxy-1,3-butadienes **103**−**105** with α-substituted acrolein **106** proceeded in quantitative yields and in excellent *endo*-selectivities. Crude cycloadducts were transformed directly into cyclohexenone **108**. The asymmetric induction was

Scheme 26



Scheme 27

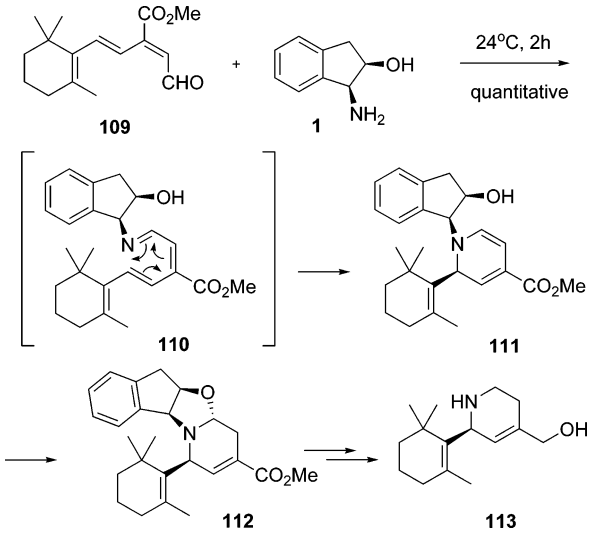


rationalized by considering the favored *endo*-transition state. The carbamate carbonyl is expected to adopt a position away from the dienyl moiety in order to avoid steric interaction with the hydrogen at C-2. In this conformation, the oxazolidinone substituent blocks one face of the diene. The higher diastereoselectivity obtained with diene **105** is believed to originate from more efficient steric shielding by the indanyl group compared to isopropyl or phenyl groups (Scheme 27).[125]

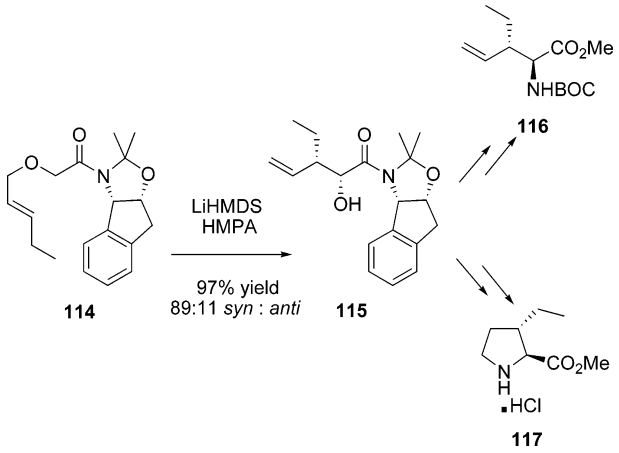
6.5.2. Claisen Rearrangement

The versatility of *cis*-aminoindanol as chiral auxiliary has been considered in various Claisen rearrangements[126,127] and was found to be particularly efficient in the 6π-azaelectrocyclization reaction.[127−129] Indeed, the reaction of (*E*)-3-carbonyl-2,4,6-trienal **109** with enantiopure *cis*-aminoindanol **1** proceeded under remarkably mild conditions to produce pentacyclic piperidine **112** as a single isomer. The reaction was thought to proceed via isomerization of dihydropyridine intermediate **111** toward the thermodynamically more stable aminoacetal **112** (Scheme 28).[127]

Scheme 28



Scheme 29



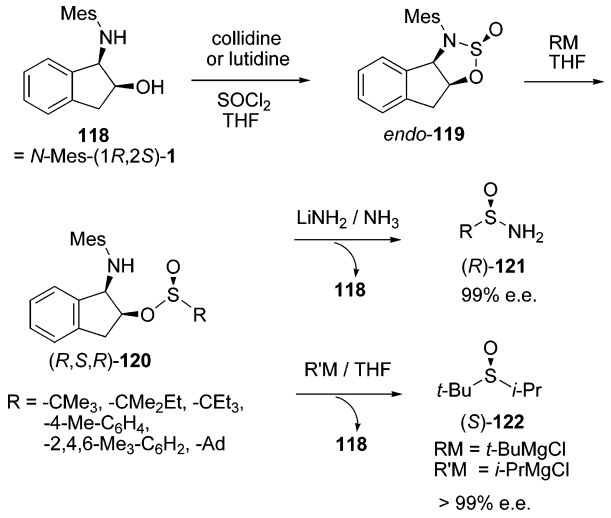
6.5.3. Wittig Rearrangement

The diastereoselectivity of the [2,3]-Wittig rearrangement of α-allyloxy amide enolates such as **114** was shown to be a function of the counterion with *syn*-selectivity increasing from K < Na < Li < Zr (Scheme 29).[130] Although zirconium enolates led to the highest diastereoselectivities (94:6 *syn*/*anti*), the reaction conversion was found moderate (73% yield). Optimal results were observed using a LiHMDS/HMPA combination, and **115** was obtained in 97% yield and 89:11 *syn*/*anti* selectivity. The scope of this methodology was extended to olefins bearing different substitution patterns. In general, *trans*-substituted olefins exhibited excellent *syn*-diastereoselectivities, whereas *cis*-olefins afforded low diastereofacial discrimination (1:2 *syn*/*anti*). Unsubstituted allyl ethers led to diastereoselectivities greater than 98%. The utility of this process was demonstrated by conversion of **115** to functionalized acyclic and cyclic α-amino esters **116** and **117**.

6.6. Other Electrophiles

Enantiopure sulfinamides have proved a powerful tool for the asymmetric synthesis of chiral amines[131−136] and were efficiently utilized in the preparation of natural products and potential drugs such as (*R*)-didesmethylsibutramine.[137] A general method for the modular synthesis of optically pure aryl and tertiary alkyl sulfinamide auxiliaries was developed

Scheme 30



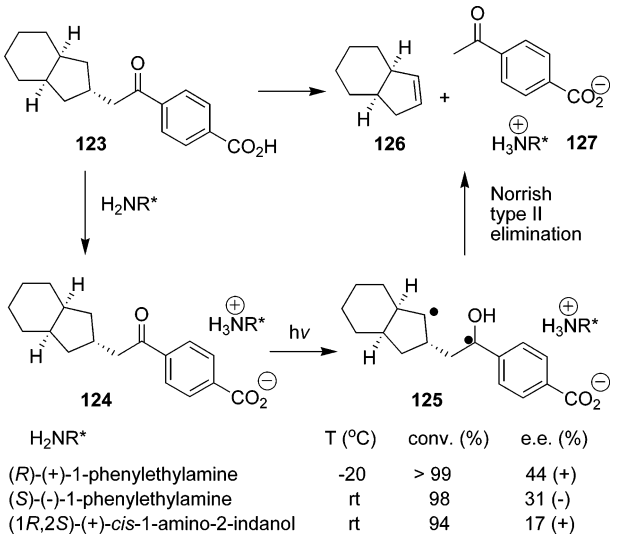
by Senanayake and co-workers from *N*-sulfonyl-1,2,3-oxathiazolidine-2-oxides.[138] Reaction of *N*-Mes-(1*R*,2*S*)-**1** (**118**), containing the conformationally constrained indane platform and an arylsulfonyl group as N-activator, with thionyl chloride and 3,5-lutidine in THF, provided oxathiazolidine oxide **119** in excellent 97:3 *endo*/*exo* selectivity. The activated N−S bond was cleaved chemoselectively with a variety of organometallic reagents with inversion of configuration at the sulfur atom. Subsequent mild displacement of the O−S bond with a nitrogen nucleophile also proceeded with inversion of configuration at the sulfur atom and led to enantiopure sulfinamides **121** in good overall yield. Enantiopure aminoindanol **118** was recovered and readily recycled (Scheme 30).[138−140] The base/solvent combination used in the formation of oxathiazolidine oxide was shown to have a pronounced effect on the *endo*/*exo* outcome. In fact, complete reversal of selectivity was obtained by reaction of *N*-Ts-(1*R*,2*S*)-**1** with thionyl chloride using 2,6-di-*tert*-butylpyridine in THF, leading to a 2:98 *endo*/*exo* ratio, which gave access to the (*S*)-enantiomer of **121**. The methodology thus afforded both enantiomers of sulfinamides **121** in 99% ee from one enantiomer of the indane platform and was proved amenable to multi-kilogram scale production.[138]

The same strategy was successfully applied to the synthesis of enantiopure sulfoxides, which are often used as chiral controllers for C−C bond formations or as ligands in catalytic asymmetric processes.[141] The O−S bond of **120** was displaced by a carbon nucleophile to give enantiopure sulfoxides (Scheme 30). Indeed, treatment of individual diastereoisomers of **120** (R = *t*-BuMgCl) with isopropylmagnesium chloride provided the corresponding enantiomers of **122** in excellent yield and optical purity, with remarkable recovery of enantiopure **118**. In addition to alkyl−alkyl chiral sulfoxides, this powerful process gave access to either enantiomers of alkyl−aryl and aryl−aryl sulfoxides in high enantioselectivity (>90% ee).[141]

6.7. Solid State Ionic Chiral Auxiliary

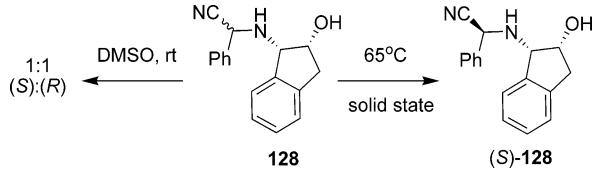
Scheffer and co-workers described their strategy for the synthesis of enantiomerically enriched alkenes by irradiation of ammonium salts of prochiral carboxylic acid-containing photoreactant in the crystalline state.[142] Since ionic auxiliaries (ammonium ions in this case) are optically pure, these salts crystallize in chiral space groups. This provides the asym-

Scheme 31



H_2NR^*	T (°C)	conv. (%)	e.e. (%)
(*R*)-(+)-1-phenylethylamine	-20	> 99	44 (+)
(*S*)-(-)-1-phenylethylamine	rt	98	31 (-)
(1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol	rt	94	17 (+)

Scheme 32



metric medium in which to carry out the photoreaction. The dense packing of the crystal prevents large conformational motions and ensures that only one conformational diastereomer of the photoreactant will be present. In other words, the molecule is pre-organized for abstraction of only one of the diastereotopic γ-hydrogen atoms. Upon photolysis, the chiral auxiliary attached to the aromatic ring of the aryl ketone is lost as part of the Norrish type II cleavage process, leaving the enantiomerically enriched olefin behind. Experimentally, in the presence of different chiral auxiliaries, enantiomeric excess was induced in *cis*-3a,4,5,6,7a-hexahydro-1*H*-indene **126**, although only to a moderate extend (Scheme 31). These low to moderate ee values were tentatively explained by the fact that Norrish type II photoelimination breaks one molecule into two, thus, destroying the original crystal lattice. In addition, photoproduct **126** is a liquid and softens the solid-state medium, and therefore, the topochemical control decreases as the reaction proceeds.[142]

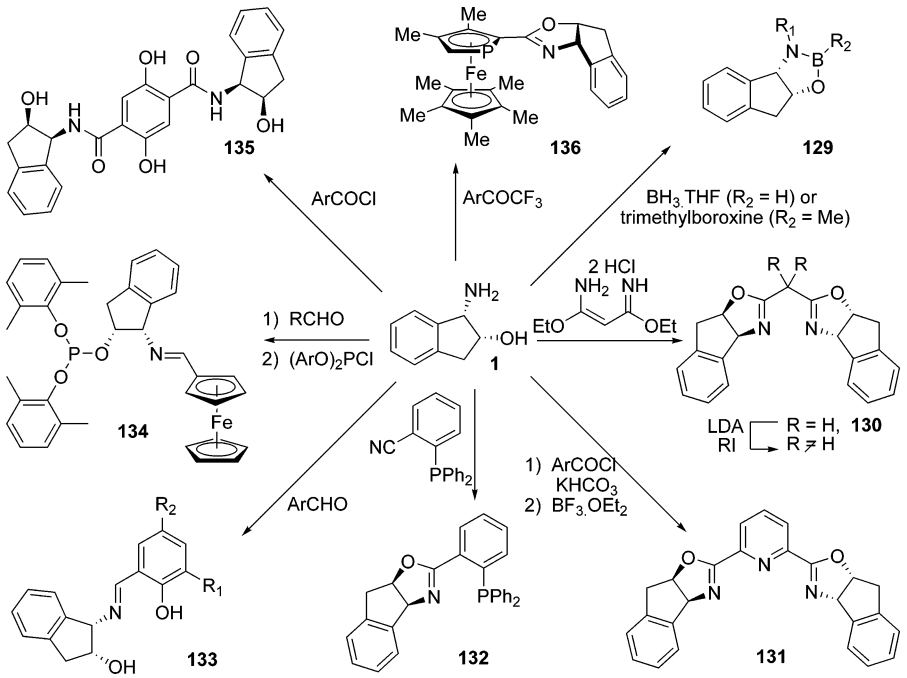
A more successful use of *cis*-aminoindanol in the solid state was recently disclosed by Hattori and Yamaura.[143] A diastereomeric mixture of the α-amino nitrile prepared by the Strecker reaction of benzaldehyde, (1*S*,2*S*)-1-amino-2-indanol, and cyanotrimethylsilane epimerized in DMSO at room temperature to give a 1:1 mixture of the (*S*)- and the (*R*)-configurations at the α-position to the nitrile moiety. In contrast, the same mixture epimerized in the solid state at 65°C to give a single diastereomer (Scheme 32).[143]

7. *cis*-1-Amino-2-indanol-Derived Ligands in Asymmetric Catalysis

The conformationally constrained indanyl platform has emerged as a particularly valuable backbone in a variety of catalytic processes leading to high levels of asymmetric induction. This includes catalytic asymmetric carbon−hydrogen, carbon−carbon, and carbon−heteroatom bond-forming reactions. Ligand derivatives of **1** include oxazaborolidines, bis(oxazolines)[144] and pyridine bis(oxazoline) **131**, phosphinooxazoline **132**, Schiff bases, triazolium salts, aryl phosphate **134**, benzoquinone **135**, and phosphaferrocene-oxazoline **136** (Scheme 33).[145] *cis*-1-Amino-2-indanol **1** itself was shown to be an efficient ligand in reduction of carbonyls.[88,146−149]

Oxazaborolidines of *cis*-aminoindanol (**129**) were developed for reduction of carbonyls and were shown to be of value in the reduction of imines.[150−154] *B*-Hydrogen oxazaborolidines were prepared in situ from **1** and BH_3·THF, while stock solutions of *B*-methyl oxazaborolidines were obtained by reaction with trimethylboroxine.[150−154]

Scheme 33



The extremely versatile class of aminoindanol-derived chiral bis(oxazoline) ligands were developed by Davies, Senanayake, and co-workers[155,156] and Ghosh and co-workers[144,157] independently to study the effect of conformational rigidity of ligands in the catalytic asymmetric Diels−Alder reaction.[158−162] These ligands were later found equally efficient for asymmetric hetero-Diels−Alder reactions,[163,164] conjugate additions,[165] and conjugate radical additions.[166] Inda-box ligand **130** (R = H) was obtained by condensation of **1** with the appropriate amide enol ether dihydrochlorate.[157] More constrained inda-box ligands (R ≠ H) were prepared either by Ritter type reaction of **1** with the corresponding dinitriles in the presence of trifluoromethanesulfonic acid[167] or by dialkylation of **130** with the corresponding alkyl iodides.[160]

Chiral pybox ligands were synthesized as ligands for the asymmetric cyclopropanation of styrene.[156] In-pybox ligand **131** was prepared by reaction of **1** with 2,6-pyridine dicarbonyl dichloride in the presence of potassium hydrogen carbonate in isopropyl acetate followed by cyclization of the bis-hydroxyamide with $BF_3{\cdot}Et_2$ at 120 °C.[168]

In light of the remarkable results obtained with the ligands described above, several new classes of aminoindanol-containing ligands were recently disclosed which take advantage of the rigidity and steric bulk of the indanyl platform. Among those, phosphinooxazoline **132**, prepared by reaction of **1** with diphenylphosphinobenzonitrile, was studied as a possible ligand for the asymmetric allylic alkylation of small acyclic allyl acetate substrates.[169]

Aminoindanol-derived Schiff bases **133** were developed as tridentate ligands for the chromium-catalyzed hetero-Diels−Alder reaction between weakly nucleophilic dienes and unactivated aldehydes.[170] The generality of the utility of these Schiff bases, readily obtained by condensation of **1** with the corresponding aldehyde, was later demonstrated in the hetero-Diels−Alder reaction between Danishefsky's diene and chiral aldehydes,[171] as well as in the inverse electron-demand, hetero-Diels−Alder reaction of α,β-unsaturated aldehydes with alkyl vinyl ethers,[172] and in hetero-ene reactions.[173] More recently, these tridentate Schiff bases have been successfully applied to the quinone Diels−Alder reaction[174] for the asymmetric synthesis of (−)-colombiasin A.[175] They also proved efficient ligands for asymmetric oxidations.[176,177]

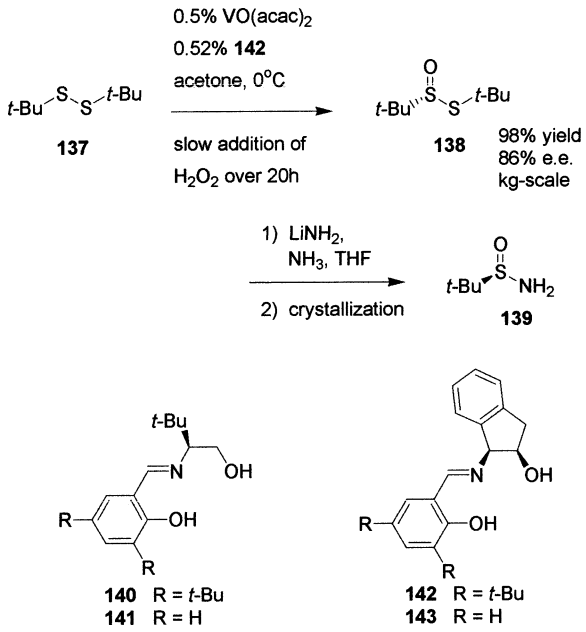
Aminoindanol-derived triazolium salts were developed as extremely efficient catalysts for the enantioselective intramolecular Stetter reaction and were later applied for the synthesis of optically pure α-chloroesters.[178−182]

Aryl phosphate **134** was studied as a possible ligand in the palladium-catalyzed allylic alkylation and allylic sulfonation reactions. This P,N-ligand was easily accessed by condensation of ferrocenealdehyde followed by reaction with bis(2,6-dimethylphenyl)chlorophosphite.[183]

Benzoquinone **135** was reported as one of a new class of amino alcohol-derived benzoquinones tested in the palladium-catalyzed 1,4-dialkylation of 1,3-dienes. These ligands were prepared by reaction of **1** with C_2-symmetric 1,4-diallyloxy-2,5-benzenedicarboxylic acid chloride followed by allyl deprotection.[184]

Bidentate phosphaferrocene-oxazoline **136**, generated by acylation with the corresponding phosphaferrocene trifluoroacetate followed by oxazoline formation, has proved to be a highly efficient ligand for asymmetric induction in the copper-catalyzed conjugate addition of diethylzinc to α,β-unsaturated ketones.[185]

Scheme 34

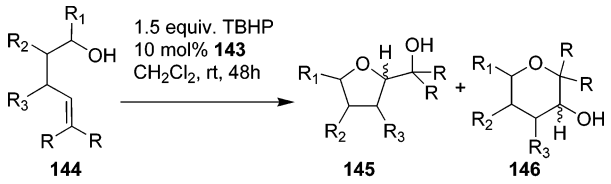


7.1. Asymmetric Oxidations

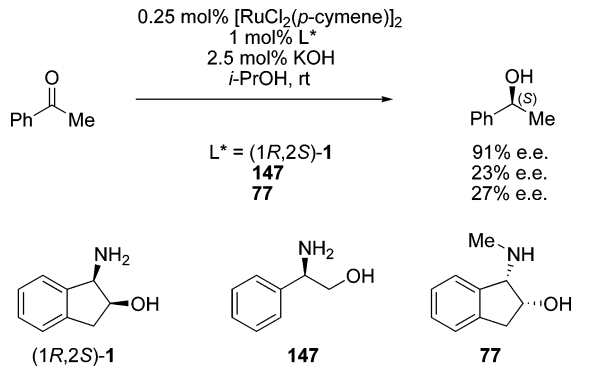
Enantiopure sulfinamides have proven extremely versatile chiral ammonia equivalents for the asymmetric synthesis of chiral amines. Ellman first introduced *tert*-butylsulfinamide in 1997.[186] Enantiomerically pure **139** was first synthesized in two steps from the inexpensive petroleum byproduct di-*tert*-butyl disulfide **137** in 68% yield. Asymmetric oxidation of **137** proceeded with high enantioselectivity and conversion using $VO(acac)_2$/ligand **140** and hydrogen peroxide in chloroform. After purification of the thiosulfinate ester **138**, displacement with $LiNH_2$ provided **A** in analytically and enantiomerically pure form by simple recrystallization (Scheme 34).[187] Scalability and reproducibility (>1 mol) issues arose due to the following: (a) ligand **140** is derived from *tert*-butyl glycinol (the (*S*)-enantiomer is expensive and the (*R*)-enantiomer is not commercially available), (b) use of chloroform (toxic) to achieve high conversion and enantioselectivity, (c) the biphasic system chloroform/water is sensitive to the vessel shape and rate of stirring, and (d) necessary purification of thiosulfinate **138** by bulb-to-bulb distillation. A new homogeneous oxidation was therefore developed.[176] It proceeded efficiently, independent of the reaction scale and can be performed at high concentrations using the relatively nontoxic acetone as solvent. This homogeneous oxidation was found to proceed with sufficiently high conversion and fidelity that no purification of **138** was necessary to prepare **139** by direct addition of $LiNH_2$. Finally, optimization of the ligand source led to the selection of ligand **142**. Both enantiomers of **142** are readily accessible in one step from commercially available, enantiomerically pure *cis*-1-amino-2-indanol and 3,5-di-*tert*-butylsalicylaldehyde. These significant improvements overcame the scalability problems of the original synthesis of **139** and was run on a large kilogram scale (Scheme 34).

In a very detailed study, Hartung and co-workers described the (Schiff-base)vanadium(V) complex-catalyzed oxidation of substituted bis(homoallylic)alcohols for the stereoselective synthesis of functionalized tetrahydrofurans.[177] Oxidation of

Scheme 35



Scheme 36



secondary or tertiary 1-substituted 5,5-dimethyl-4-penten-1-ols, using *tert*-butyl hydroperoxide (TBHP) as primary oxidant and vanadium(V) complex, prepared from tridentate Schiff-base ligand **141** and $VO(OEt)_3$, as catalyst, provided 2,5-*cis*-configured tetrahydrofurans in good yield and moderate-to-good diastereoselectivity (61:39 to 98:2 d.r.). In addition, by the use of the same oxidation system, 2- or 3-substituted 5,5-dimethyl-4-penten-1-ols led to *trans*-disubstituted oxolanes (81:19 to 98:2 d.r.). Finally, oxidation of 4-penten-1-ols (i.e., substrates with monosubstituted olefinic π-bonds) gave *trans*-disubstituted tetrahydrofurans as major product (60:40 to 98:2 d.r.) regardless of the substitution on the alkenol chain (Scheme 35).

7.2. Reduction of Carbonyls

7.2.1. Transfer Hydrogenation

cis-Aminoindanols have been shown to be excellent ligands for asymmetric transfer hydrogenation.[88,89,146] Reduction of acetophenone in 2-propanol in the presence of 0.25 mol % of $[RuCl_2(p\text{-cymene})]_2$, 1 mol % (1*R*,2*S*)-*cis*-1-amino-2-indanol, and 2.5 mol % of potassium hydroxide proceeded in 70% yield and 91% ee (*S*). Enantioselectivities were considerably lower with phenylglycinol (23% ee) or *N*-methyl-*cis*-aminoindanol (27% ee) as ligands. These results strongly suggested that a stereochemically rigid backbone enhanced the degree of asymmetric induction and that a primary amine function in the ligand was essential (Scheme 36).

Mechanistic studies[147] tended to demonstrate that the hydrogen transfer proceeds via a six-center transition state similar to that proposed by Noyori with monotosylated diamine complexes of ruthenium(II) (Figure 10).[188]

Excellent results have also been obtained using the CATHy (catalytic asymmetric transfer hydrogenation) catalyst and aminoindanol/pentamethylcyclopentadienylrhodium. Since this catalyst's structure is similar to Noyori's catalyst, the

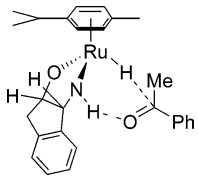
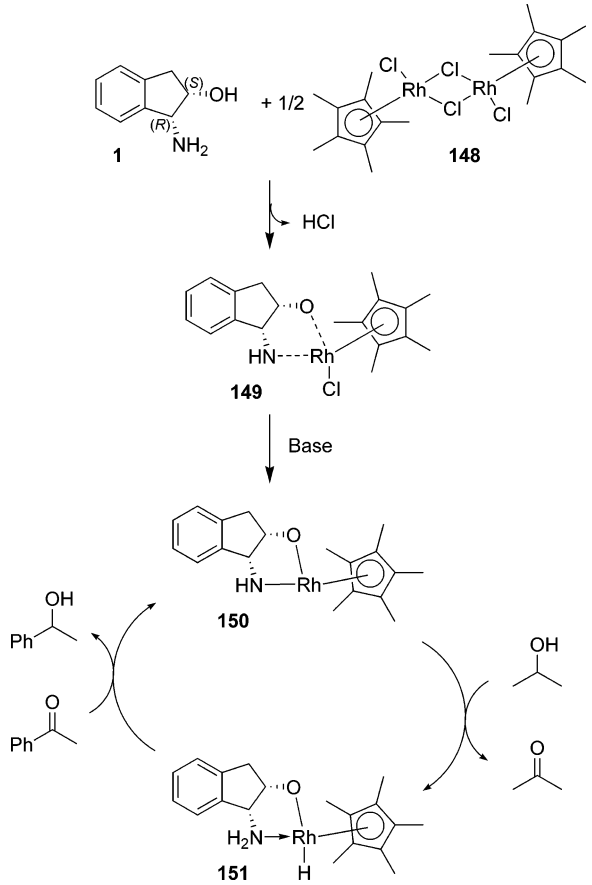


Figure 10. Proposed transition state for the transfer hydrogenation to carbonyls.

Scheme 37



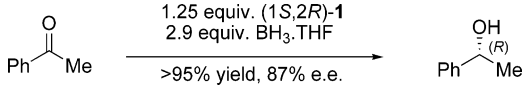
metal−ligand bifunctional mechanism is considered to be valid as well.[149] In the presence of base, the catalytic species **150** is formed from precursor **149** by HX removal. This active catalytic species **150** facilitates the H-transfer from the solvent 2-propanol to the substrate ketone through the formation of intermediate **151** and acetone. The catalyst is restored by reduction of the ketone (Scheme 37).[149]

A thorough study of this catalyst system was made by Gavriilidis. It appears that this rhodium catalytic system gives faster reaction rate than Wills's ruthenium catalyst, although a slightly lower conversion is obtained.[149] The enantioselectivity was found to decrease with conversion. The effects of various reaction parameters were investigated, and the results indicated that the catalyst can be deactivated by high temperature and air atmosphere. Also, the use of acetone was found to decrease the reaction rate. Overall, this catalytic system was found highly efficient both in terms of economics (low catalyst usage and cheap, readily available ligand) and in terms of efficiency (consistent high-quality product).[149]

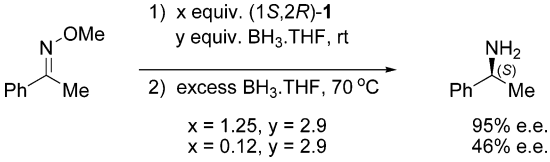
7.2.2. Borane Reduction

Since the discoveries of Itsuno[189] and Corey,[190] remarkable advances have been made in the enantioselective reduction

Scheme 38



Scheme 39



of prochiral ketones using amino alcohol-derived oxazaborolidines.[191,192] In most cases, these amino alcohols were obtained from chiral pool sources. Consequently, extensive synthetic manipulations were often necessary to access their unnatural antipode. Didier and co-workers were first to examine the potential of *cis*-aminoindanol as a ligand for the asymmetric oxazaborolidine reduction of ketones.[45] Several acyclic and cyclic amino alcohols were screened for the reduction of acetophenone (Scheme 38), and *cis*-aminoindanol led to the highest enantioselectivity (87% ee).

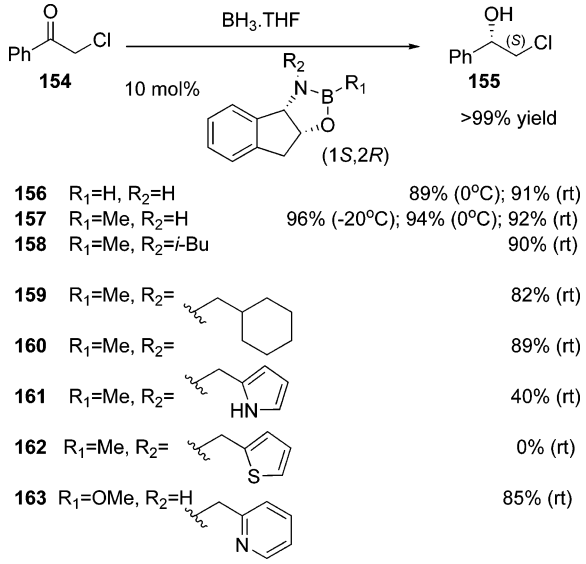
Interestingly, Didier also studied the reduction of *anti*-acetophenone oxime methyl ether (Scheme 39)[45] and again observed that *cis*-aminoindanol yielded one of the highest selectivities (95% ee). However, a stoichiometric amount of amino alcohol was needed to achieve high degrees of asymmetric induction. Use of a catalytic amount of amino alcohol resulted in a considerable decrease in product enantioselectivity.

Researchers at Sepracor later disclosed the use of a new class of chiral oxazaborolidines derived from *cis*-aminoindanol in the enantioselective borane reduction of α-haloketones.[150,151] The *B*-hydrogen oxazaborolidine ligand **156** was prepared in situ from *cis*-aminoindanol **1** and BH_3·THF.[152] Stock solutions of *B*-methyl oxazaborolidine **157**−**162** were obtained by reaction of the corresponding *N*-alkyl aminoindanol with trimethyl boroxine.[150,151] *B*-Methyl catalyst **157** was found to be more selective (94% ee at 0 °C) than the *B*-hydrogen catalyst **156** (89% ee at 0 °C), and enantioselectivities with **157** increased at lower temperatures (96% ee at −20 °C). The catalyst structure was modified by introduction of *N*-alkyl substituents. As a general trend, reactivities and selectivities decreased as the steric bulk or the chelating ability of the *N*-alkyl substituent increased (Scheme 40).

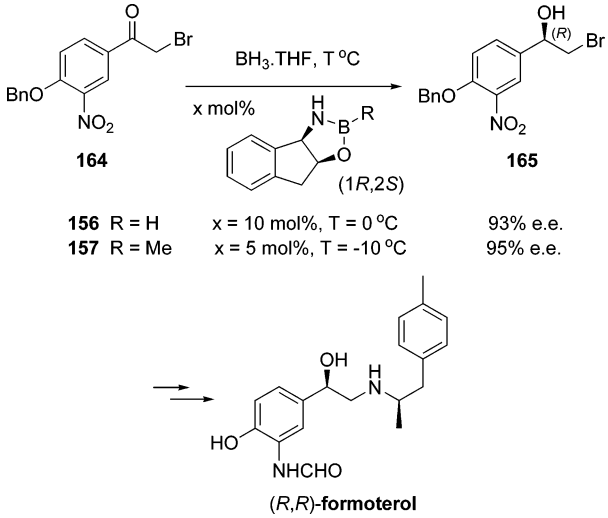
Borane reduction of a variety of aromatic ketones using 5−10 mol % of *B*-methyl catalyst **157** proceeded in >95% yield and in 80−97% ee. α-Haloketones were generally more reactive (90−97% ee) than simple ketones which required higher temperatures (0 °C compared to −20 °C) to react to completion and led to lower enantioselectivities (80−90% ee).[150] A complementary study by Umani-Ronchi and co-workers[193] described the borane reduction of cyclic and acyclic ketones using catalyst **156**. All products were obtained in >89% yield and >85% ee. Cyclic and hindered ketones led to the highest enantioselectivities (up to 96% ee) at room temperature.

More recently, Jones and co-workers investigated the utility and applicability of *B*-OMe oxazaborolidine **163**.[154] They prepared the *B*-OMe complex in situ from inexpensive borate esters. The results show that all the borate esters used in situ performed as effectively as the isolated catalyst. Also, inexpensive trimethyl borate could be used instead of

Scheme 40



Scheme 41



trimethyl boroxine for the reduction of acetophenone with comparable enantioselectivity (for the one-pot and the two-step process). Finally, they found that **163** and the traditional **157** *B*-Me catalyst, both generated in situ, have significant endurance during iterative reaction sequences (up to 12), allowing for in situ recycling.[154]

This methodology was successfully applied to the asymmetric synthesis of (*R*,*R*)-formoterol, a potent β_2-agonist for the treatment of asthma and bronchitis.[194−196] Reduction of bromo ketone **164** was a key step in the synthesis (Scheme 41). An extensive study, involving varying temperatures, boron sources, and phenylglycinol catalyst backbones, was undertaken in order to determine the optimal conditions for the reaction.[196] Experimental data clearly demonstrated that each catalyst had its own optimal conditions with respect to temperature, boron source, and additives. Conformationally rigid oxazaborolidine catalysts, containing the tetraline or indane backbone, proved to be the most effective in the reduction of **164**. The highest selectivity was achieved using a stock solution of catalyst **157** at −10 °C (96% ee). Although lower selectivity was obtained with the in situ prepared **156** at 0 °C (93% ee), this catalyst was chosen for the large-scale process as its preparation was easier, less time-consuming, and involved inexpensive reagents. On a multi-

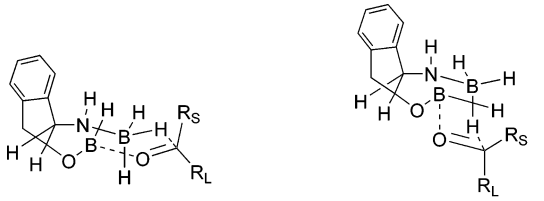
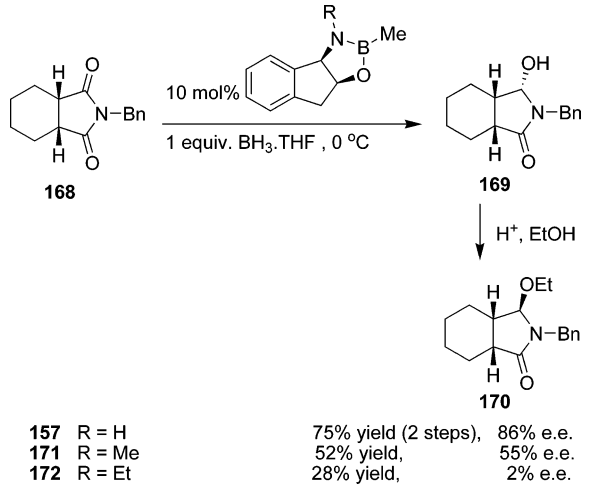


Figure 11. Proposed transition states for borane reduction.

Scheme 42



kilogram scale, bromohydrin **165** could be isolated in 85% yield by crystallization, which directly enriched its enantiopurity to >99% ee.

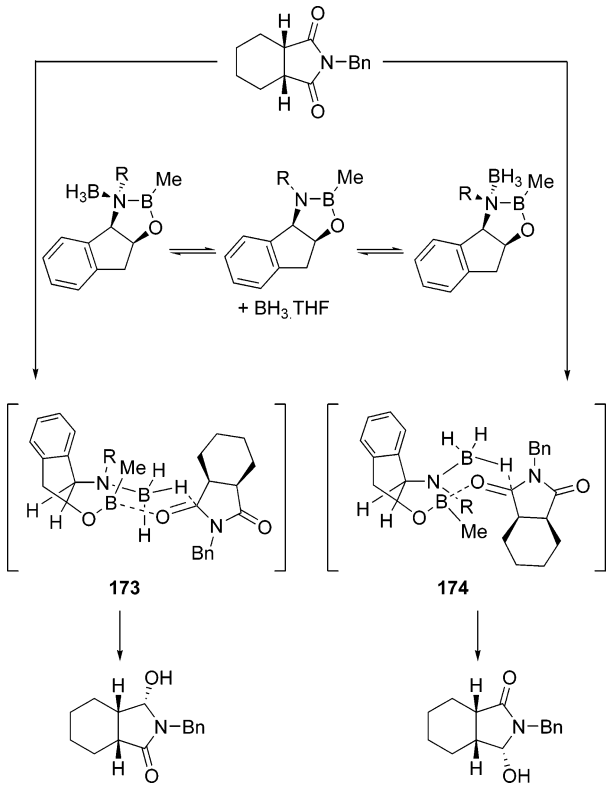
The proposed mechanism of reduction involves the coordination of a borane molecule to the nitrogen of the oxazaborolidine in a *trans*-relationship to the indanyl substituent. The ketone coordinates to the boron center of the oxazaborolidine, *cis* to the coordinated borane, in a possible boatlike transition state **166** or chairlike transition state **167** (Figure 11). In both cases, intramolecular hydride attack occurs from the *Re*-face of the carbonyl.[190,193]

Mechanistic studies by Jones and co-workers excluded the possibility of dimeric catalytic species, as a linear dependence was observed between the catalyst's enantiopurity and the reaction's enantioselectivity.[154,197−199] The test reaction was the desymmetrization of *meso*-imide **168** using chiral oxazaborolidine catalysts derived from *cis*-(1*R*,2*S*)-1-amino-2-indanol. The sense of the enantioselectivity of the reduction was established by conversion of hydroxy lactam **169** to the known ethoxy lactam **170** (Scheme 42).[199]

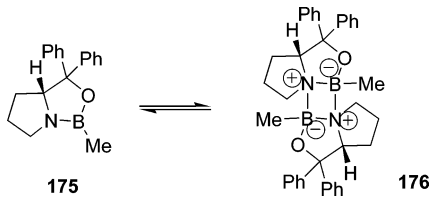
The decreasing enantioselectivity with increasing *N*-alkyl steric bulk was rationalized by assuming the model described above (Figure 11). As mentioned earlier, the key feature of this model is the coordination of borane on the least hindered *exo*-face of the oxazaborolidine. This coordination is reversible, and large substituents on the nitrogen can displace the equilibrium to *endo*-face coordination, therefore, diminishing the sense of asymmetric induction (Scheme 43).[199]

These results prompted Jones and co-workers to investigate further mechanistic details of reactions of catalyst **171**. Bearing in mind that the key feature of this catalyst system is the equilibrium that coexists between the monomeric **175** and the dimeric **176** forms of oxazaborolidine (Scheme 44), the latter of which breaks down to the active monomeric form **175** in the presence of a coordinating solvent such as

Scheme 43



Scheme 44



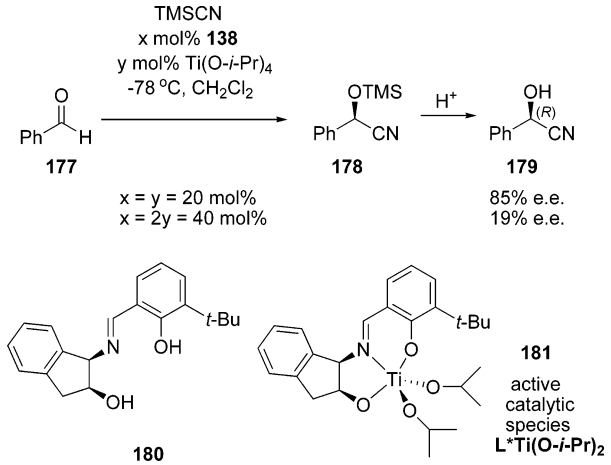
THF,[190] they studied the dependency of the enantioselectivity of the asymmetric reduction of acetophenone with solvent and borane.[154] They found BH_3•DMS in THF or Et_2O to be the optimal hydride and solvent source for ketone reduction using catalyst **171**. A strong correlation of the monomer/dimer ratio and high selectivities in THF and Et_2O was observed and lent further support to the hypothesis that the predominance of the monomeric form **175** is essential for achieving high enantioselectivities.[154]

7.3. Addition to Carbonyls

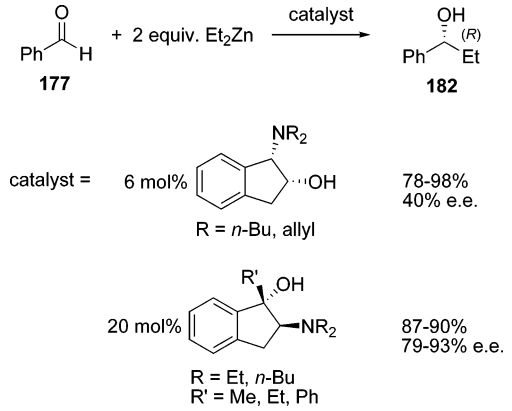
7.3.1. Trimethylsilylcyanide Addition

Tridentate salen ligands derived from enantiopure *cis*-aminoindanol were prepared in an effort to explain the relationship between the ligand structure and the enantioselectivity in the Ti(IV)-Schiff base-catalyzed asymmetric addition of trimethylsilylcyanide to benzaldehyde.[200] The nature and position of substituents on the Schiff base phenyl ring were shown to have a great influence on the reactivity and selectivity of the reaction. An enantiomeric excess of 85% was reached using 20 mol % of a 1:1 complex of Ti(O-*i*-Pr)$_4$ and tridentate ligand **180** (Scheme 45). Modification of the titanium/ligand ratio to 1:2 resulted in a considerable loss in enantioselectivity (19%). These observations are in accordance with Oguni's studies[201] which identified L*Ti(O-*i*-Pr)$_2$ **181** as the active species and determined bis(Schiff

Scheme 45



Scheme 46



base) compounds L^*_2Ti to be inactive toward the catalytic hydrocyanation of aldehydes.

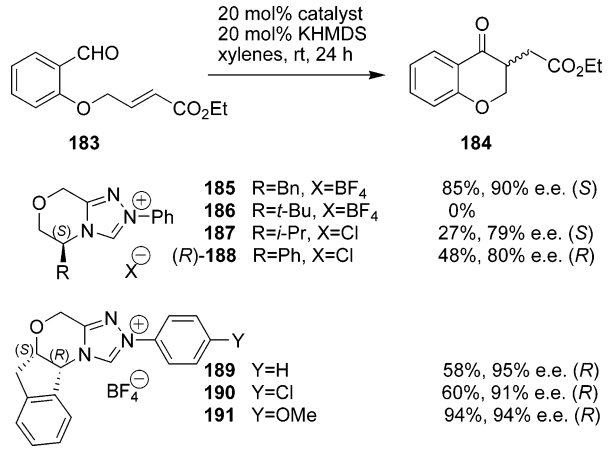
7.3.2. Diethylzinc Addition

In parallel to their investigations on the asymmetric reduction of ketones, Umani-Ronchi and co-workers examined the utility of *cis*-aminoindanol derivatives as catalysts in the addition of diethylzinc to aldehydes.[193] When *N*-dibutyl or *N*-diallylaminoindanol were used as catalysts, secondary alcohols could be obtained in high yields, but the enantioselectivities remained low, in the 40−50% range (Scheme 46). Interestingly, several recent studies[202,203] have taken advantage of alternative isomers of aminoindanol: both *cis*- and *trans*-*N*-disubstituted-2-amino-1-indanol were found to give high yields but moderate enantiomeric excesses (56−80% ee);[202] high degrees of enantioselection in the diethylzinc addition to aliphatic and aromatic aldehydes were eventually achieved by introducing an alkyl or aryl substituent at C-1 of *trans*-*N*-disubstituted-2-amino-1-indanol (up to 93% ee).[203] Optimal results were obtained with bulky groups at the hydroxy-bearing carbon and at the nitrogen (R = Ph, R′ = *n*-Bu), which led to the formation of (*R*)-1-phenylpropanol in 90% yield and 93% ee (Scheme 46).

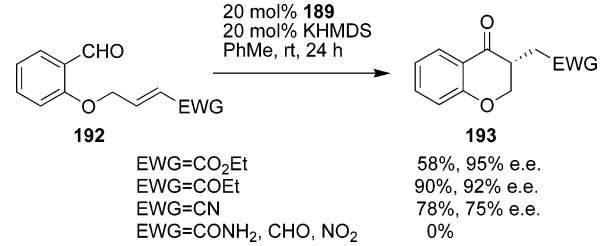
7.3.3. Umpolung Reactions

Umpolung reactivity of functional groups is a powerful methods for reversing the normal mode of reactivity.[204] The Stetter reaction, which requires a catalytic amount of thiazolium salts in the presence of a weak base, takes advantage of umpolung of the aldehyde reactivity and results

Scheme 47



Scheme 48



in an acyl anion equivalent attacking an electron-deficient olefin. This transformation provides access to 1,4-dicarbonyl systems.[205] In addition, if the Michael acceptor is a prochiral alkene, this reaction generates a new stereocenter. Rovis and co-workers reported a highly enantioselective intramolecular Stetter reaction using a family of chiral triazolium salts, which includes **185**−**191** (Scheme 47).[178]

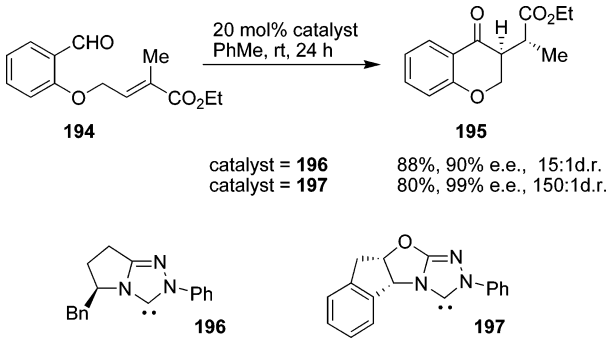
Under optimized conditions (KHMDS as base and xylenes as solvent at room temperature), the reactivity of structurally similar carbenes was studied. *tert*-Leucine-derived catalyst **186** proved inactive in the intramolecular Stetter reaction due to steric congestion. The benzyl catalyst **185** was found superior to both valine- and phenylglycine-derived catalysts **187** and **188**. Aminoindanol-derived catalyst **189** showed optimal selectivities, with reduced yields. Electronic tuning of the phenyl ring of the triazole nitrogen to produce a more electron-rich complex **191** led to improved yields with excellent enantioselectivity (Scheme 47).[178] Substitution on the phenyl ring of **1** is tolerated and leads to subtle differences in reactivity (80−95% yield) and enantioselectivity (84−97% ee). Furthermore, sulfur and nitrogen atoms in place of the oxygen in the tether are well-tolerated.[178]

Finally, different Michael acceptors were evaluated.[179] It resulted in the observation that the reactivity and selectivity of substrates containing different electron-deficient double bonds varied significantly under identical conditions.[179] While α,β-unsaturated aldehydes, amides, and nitro compounds did not yield any cycloadduct, α,β-unsaturated esters, ketones, and nitriles led to Stetter products in high yield and enantioselectivity (Scheme 48).[179,180]

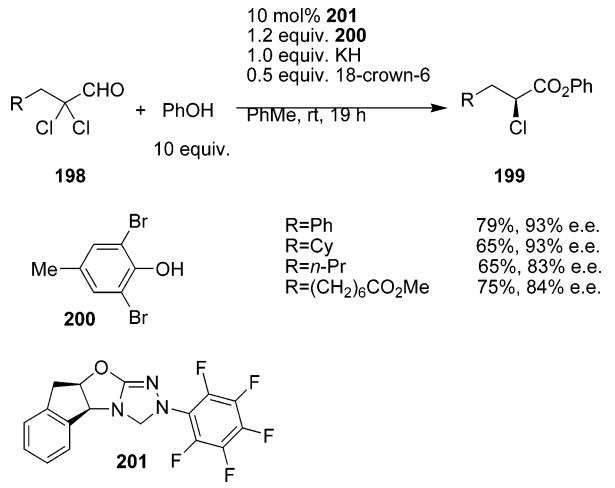
Subjecting α,α-disubstituted Michael acceptors to the asymmetric Stetter reaction using triazolinylidene carbene **197** resulted in a highly enantioselective conjugate addition (99% ee) and a diastereoselective intramolecular proton transfer (150:1 d.r.) (Scheme 49).[181]

In an extension of this work, Rovis and co-workers decribed the efficiency of the *cis*-aminoindanol-derived

Scheme 49



Scheme 50



triazolinylidene carbene **201** as catalyst for the in situ generation of chiral α-haloenolates of 2,2-dichloroaldehydes and their reaction with phenol to produce α-chloroesters in good yield and enantioselectivity. Although limited to aldehydes lacking α-branching, the reaction was found robust, allowing for the synthesis of a wide range of phenolic esters (Scheme 50).[182]

7.4. Asymmetric Alkylations

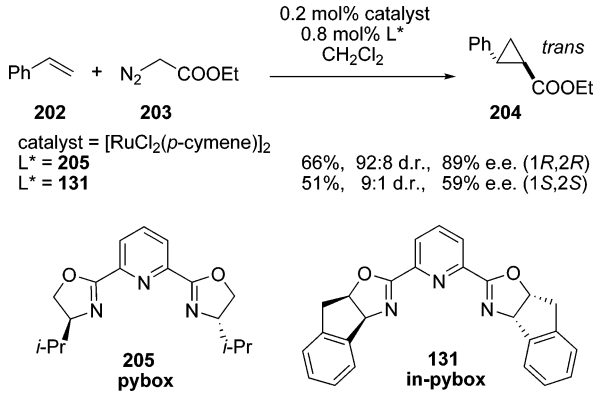
7.4.1. Catalytic Asymmetric Cyclopropanation

Davies and co-workers have explored the role of ligand conformation in the ruthenium(II)-catalyzed cyclopropanation of styrene.[156] This study was based on results reported by Nishiyama in which the catalyst prepared in situ from pyridine-bis(oxazoline) **205** and $[RuCl_2(p\text{-cymene})]_2$ was found to be highly active and selective in the reaction of ethyl diazoacetate with styrene (66% yield, 92:8 d.r. and 89% ee of major *trans*-isomer).[206] Several ligands hindered on the oxazoline ring, including **131**, were tested, and poorer yields and selectivities were obtained (for **131**, 50% yield, 9:1 d.r. and 59% ee of major *trans*-isomer), which indicated unfavorable steric interactions between styrene and the Ru(in-pybox)−carbene complex (Scheme 51).[156]

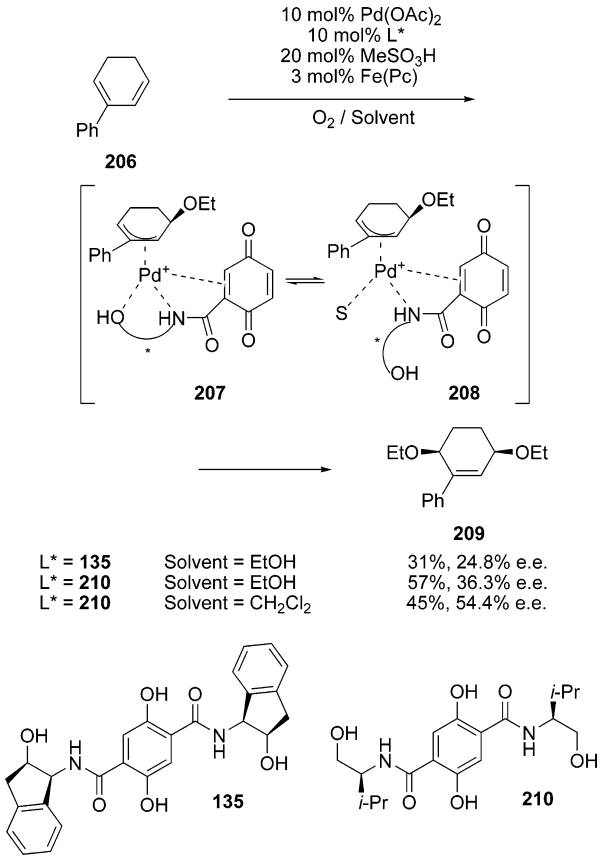
7.4.2. Asymmetric 1,4-Dialkylation of 1,3-Dienes

The potential of asymmetric induction of chiral benzoquinones containing β-amino alcohols as ligands in palladium(II) catalysis was demonstrated by Bäckvall and coworkers, although enantioselectivities remained low.[184] A variety of β-amino alcohols were tested as ligand components in the 1,4-dialkylation of 1,3-dienes, and it became clear that

Scheme 51



Scheme 52

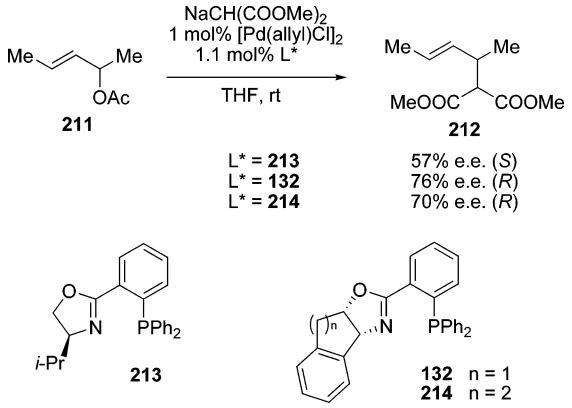


introducing a substituent on the β-carbon resulted in decreased selectivities, whereas introduction of bulky groups on the α-carbon enhanced enantioselectivities (Scheme 52). It was hypothesized that the hydroxyl group was coordinating to the palladium center, which brought the sterically demanding group at the α-position of the amide closer to the π−allyl. This intermediate **207** is in equilibrium with the noncoordinated complex **208**, which should result in lower levels of asymmetric induction. Sterically demanding groups at the β-carbon would indeed favor the noncoordinated intermediate. The effect of the solvent seemed to confirm this suggested mechanism, as the use of nonpolar, noncoordinating solvents led to higher enantioselectivities.[184]

7.4.3. Allylic Alkylation

Helmchen and co-workers reported phosphinooxazoline (PHOX) ligands to be particularly efficient for the palladium-catalyzed allylic alkylations.[169,207] Although P,N-chelate

Scheme 53



ligand **213** furnished excellent results with large acyclic substrates (e.g., 1,3-diphenylallyl acetate) up to 99% ee, reaction on small acyclic substrates (e.g., 1,3-dimethylallyl acetate) gave low enantioselectivities. Taking into account the many aspects of the allylic alkylation mechanism, it was argued that bulkier substituents on the oxazoline ring would lead to improved enantiofacial discrimination of small acyclic substrates. Indeed, constrained ligands **132** and **214** led to considerably increased enantioselectivities (Scheme 53), which were further optimized by running the reaction at lower temperatures (**214** led to 89.5% ee at −40 °C).[169]

A series of chiral P,N-bidentate aryl phosphite ligands were recently studied for the allylic alkylation of small acyclic substrates (Figure 12). In this case, the rigid indanyl

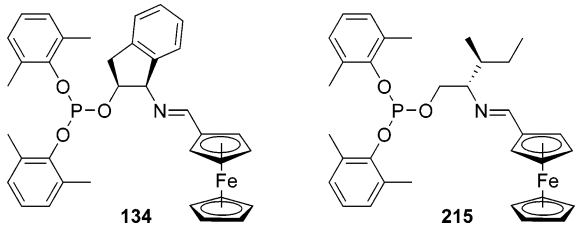


Figure 12. P,N-Bidentate aryl phosphite ligands.

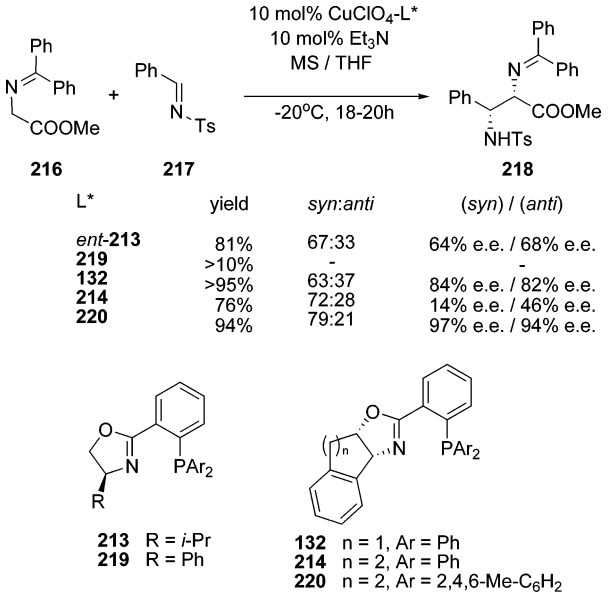
backbone led to moderate enantioselectivities (50% ee using **134** in THF) compared to ligand **215** (69% in THF and 82% in CH_2Cl_2).[183] The fact that the allylic alkylations could be performed at room temperature and did not necessitate lower reaction temperatures to achieve high selectivities is particularly noteworthy. These ligands were also tested in the allylic sulfonation reaction, and the same trends in enantioselectivities were observed.[183]

7.4.4. Mannich Reaction

Studies using the tetrahydronaphthol backbone as chiral auxiliary or as ligand in catalysis often showed that the relative flexibility of the six-membered ring was highly detrimental to the achievement of good levels of asymmetric induction, such as in the Diels−Alder reaction[123] or in the addition of diethyl zinc to benzaldehyde.[208] However, it led to similar or slightly improved selectivities compared to the more rigid indanol platform in the borane reduction of carbonyls[196,208,209] and the addition of Grignard reagents to ketones.[120]

In a recent publication, Jørgensen and co-workers described the first enantioselective Lewis acid-catalyzed Mannich reaction of imino glycine alkyl esters with imines as a new approach to optically active α,β-diamino acid

Scheme 54



derivatives.[210] In the course of the study, copper(I) complexes of phosphine-oxazoline ligands were found to be the most effective catalysts for the transformation. Among, the P,N-ligands tested, those derived from (1*R*,2*S*)-1-amino-2-hydroxy-1,2,3,4-tetrahydronaphthalene gave the most encouraging results in terms of *syn/anti* selectivities. Although **214** led to improved diastereoselectivities compared to **132**, enantioselectivities were much poorer. Rapid steric and electronic tuning of the phosphine aryl substituents yielded the novel ligand **220**, which gave the diamine adduct **218** in a remarkable 79:21 *syn/anti* selectivity and 97% ee for the *syn*-isomer (Scheme 54).[210]

Spectroscopic ^{1}H NMR investigations revealed that only **216** coordinated to the Lewis acid. It was therefore assumed that the catalyst activates **216** by coordination followed by deprotection by the base to give the chiral ligand Cu(I)-stabilized imino glycine alkyl ester anion. Mechanistic studies gave the geometry of **221**−**224** derived from ligands **214** and **220** as tetrahedral around the copper center (Figure 13).[210] Semiempirical PM3 calculations showed that inter-

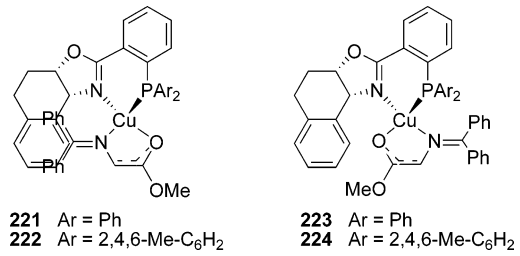


Figure 13. Possible coordination modes.

mediate **221** is <1 kcal/mol less stable than **223**, whereas 222 was found 12.4 kcal/mol more stable than **224**. The remarkable gap in energy differences correlates and accounts for the difference in enantioselectivities obtained experimentally with ligands **214** and **220** (20% ee and 97% ee, respectively). The relative stability of **222** compared to **224** was attributed to steric repulsion in **224** between the 2- and 6-methyl substituents of the phosphine aryl groups of the chiral ligand with the phenyl groups of the benzophenone imine. The same methyl substituents of the phosphine aryl groups apparently shield the *Re*-face of the carbon atom of

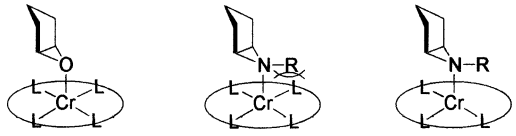
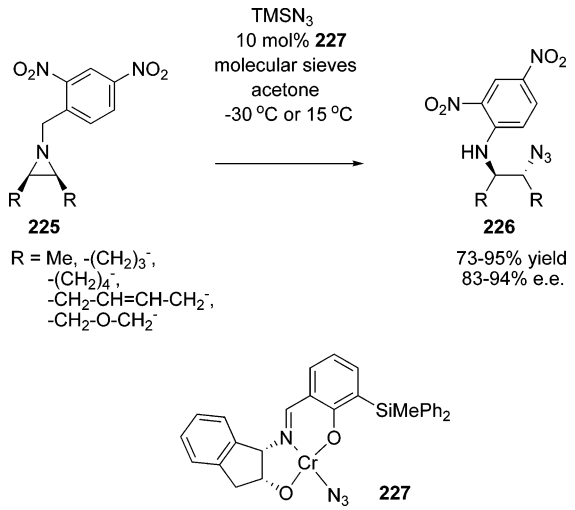


Figure 14. Schematic illustration of the possible advantage of tridentate ligands over tetradentate ligands for the activation of aziridines.

Scheme 55



225 **226** **227**

R = Me, -$(CH_2)_3$-, -$(CH_2)_4$-, -CH_2-CH=CH-CH_2-, -CH_2-O-CH_2-

73-95% yield
83-94% e.e.

216 which acts as a nucleophile. Indeed, the proposed preferred approach of imine **217** from the *Si*-face of benzophenone imine **216** accounts for the diastereo- and enantioselectivities observed (Figure 13).[210]

7.4.5. Azide Addition

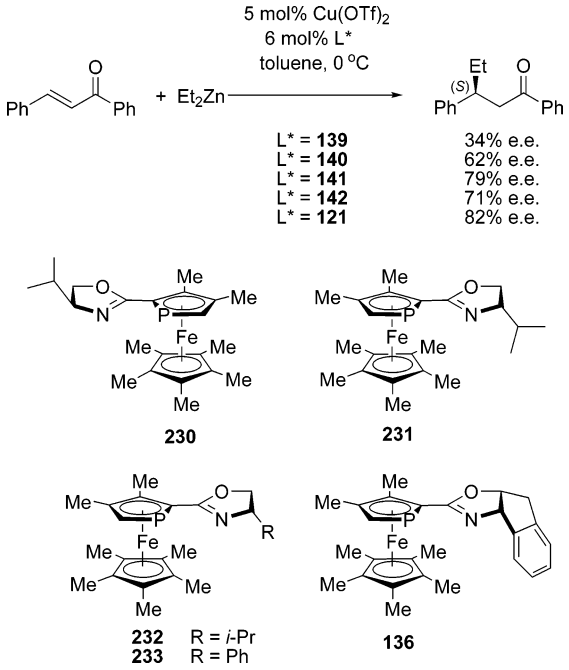
Tridentate Schiff base chromium(III) complexes were identified as the optimal catalysts for the enantioselective ring opening of *meso*-aziridines by $TMSN_3$.[211] Indeed, preliminary studies have shown that, although the (salen)-chromium complexes catalyzed the reaction to some extent, they consistently led to low enantioselectivities (<14% ee). It was rationalized that the diminished reactivity and selectivity of the salen complexes with aziridines compared to epoxides was due to the steric hindrance created by the *N*-substituent of the coordinated aziridine. As expected, improved results were observed using tridentate ligands on the chromium center, as they offer a less hindered coordination environment (Figure 14).[211]

Extensive optimization studies identified highly electron-deficient 2,4-dinitrobenzyl-substituted aziridines as the most reactive substrates, chromium as the metal of choice, and indanol-derived Shiff bases as the most effective ligands. In this ring-opening process, catalyst **227** provided the highest selectivities. When these optimized conditions were used, a variety of aziridines were selectively opened in a very efficient manner (Scheme 55).[211] This reaction can provide an easy access to C_2-symmetric 1,2-diamines, a valuable class of chiral auxiliaries, and even to less accessible non-C_2-symmetric 1,2-diamines because of the differentially protected amines of the ring-opened products.

7.5. Conjugate Addition

A new class of phosphaferrocene-oxazoline ligands was recently disclosed by Fu and applied to the copper-catalyzed asymmetric conjugate addition of diethylzinc to acyclic

Scheme 56

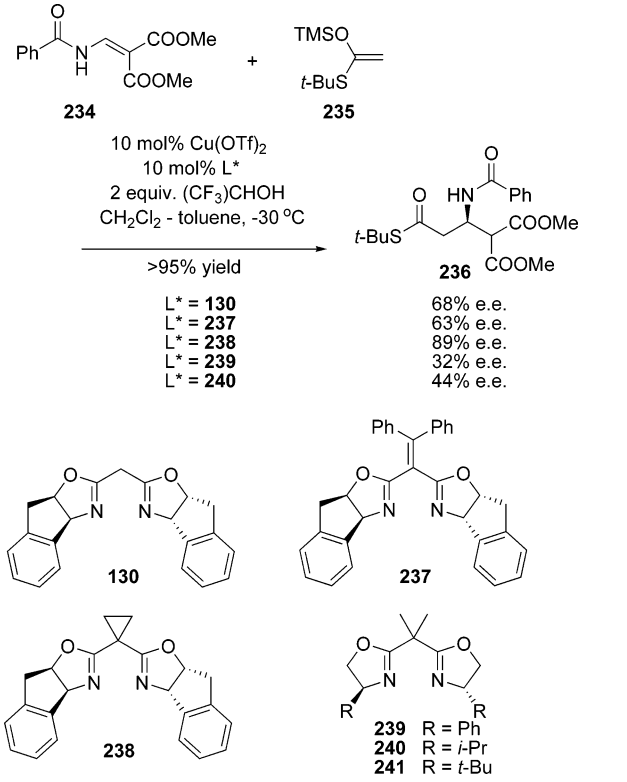


enones with good enantioselectivity. The substitution pattern on the phosphoryl ring, as well as on the oxazoline, was shown to have an enormous impact on the selectivity. Ligands **230** and **231**, which share the same absolute configuration in the oxazoline, provide the (*S*)-1,4-adduct preferentially. This observation led to the conclusion that the stereochemistry at the oxazoline, and not the planar chirality of the phosphaferrocene, was responsible for the stereochemistry of the conjugate addition. Introduction of a phenyl group at C-5 of the phosphoryl ring further enhanced the enantioselectivity of the reaction. The best result was obtained with the *cis*-aminoindanol-derived ligand **136** (Scheme 56).[185] The reaction conditions were optimized by using Cu(I)OTf instead of $Cu(II)(OTf)_2$, and diethylzinc addition to chalcone with **136** as ligand gave the 1,4-adduct in 87% ee.

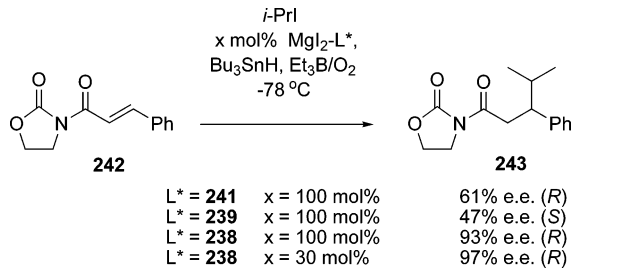
Sibi studied the copper-catalyzed conjugate addition of silylketene acetals to β-enamidomalonates using chiral bisoxazolines as ligands.[165] Addition of neutral nucleophile *O*,*S*-ketene silyl acetal **235** to malonate **234** was performed with 10 mol % of Lewis acid $Cu(OTf)_2$ and 10 mol % of bisoxazolines **130** and **237**−**240** as chiral source. When ligand **238** was used, β-amino acid derivative **236** was obtained in 96% yield and 89% ee (Scheme 57). A working model for the conjugate addition was proposed where the copper metal coordinates the malonate carbonyls and the addition occurs from the *Si*-face of the olefinic bond. However, other chelation modes can be speculated, involving the amido functional group in six- or eight-membered rings.[165]

The enantioselective conjugate radical addition using chiral bis(oxazoline)-based Lewis acid was also studied by Sibi and Porter.[166] Stoichiometric amounts of metal−ligand complexes derived from a number of box-ligands and a variety of Lewis acids including MgI_2 and $Zn(OTf)_2$ were examined in the addition to β-substituted, α,β-unsaturated *N*-oxazolidinone compounds. The enantioselectivity of product **243**, which ranged from 37% to 82% ee., was dramatically improved (up to 93% ee) using rigid aminoindanol-derived inda-box ligands (Scheme 58).[212] Catalytic amounts

Scheme 57



Scheme 58



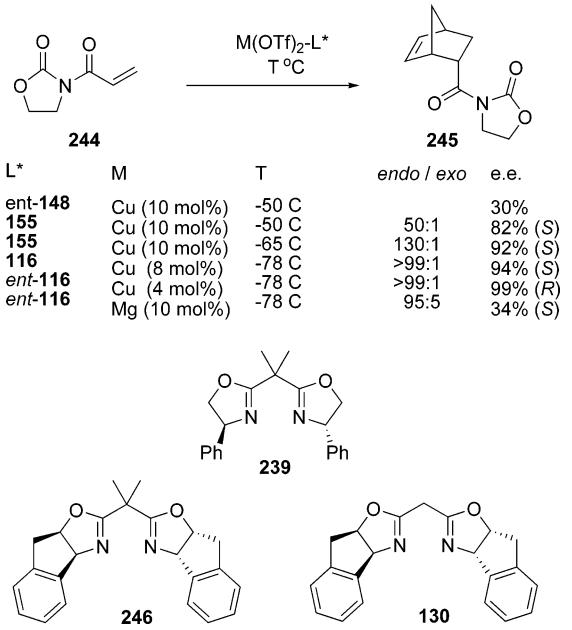
(5−30 mol %) of the MgI_2-**238** catalyst retained excellent enantioselectivity levels (90−97% ee). The reaction could be performed at room temperature with little loss of selectivity (93% ee using 30 mol % of **238**). In comparison, conjugate radical addition to pyrazole derivatives using Zn(OTf)$_2$−box-ligand complexes led to moderate enantioselectivities.[213] It is still unclear why pyrazole and oxazolidinone templates gave products of opposite configuration using the same chiral Lewis acid.

7.6. Pericyclic Reactions

7.6.1. Diels–Alder

Inda-box ligands were applied to the metal-catalyzed asymmetric Diels−Alder reaction of cyclopentadiene with α,β-unsaturated *N*-oxazolidinones by Davies and Senanayake[155,156] and Ghosh[157] independently. Conformationally constrained inda-box ligand **246** displayed excellent selectivity level (82% ee) compared to phe-box ligand **239** (30% ee) in the copper-catalyzed Diels−Alder reaction.[155] In addition, Ghosh has shown that the use of magnesium as Lewis acid led to moderate and reversed enantioselectivities compared to copper Lewis acid (Scheme 59).[157] These results have been rationalized using a square planar conformation of copper and s-*cis*-conformation of the dienophile proposed

Scheme 59



by Evans,[158] which results in a preferential *endo*-*Si*-face attack of the diene. For magnesium Lewis acids, a Corey−Ishihana transition state would explain the reversal of selectivity as magnesium adopts a tetrahedral geometry, favoring the diene attack from the less hindered *endo*-*Re*-face (Figure 15).[159]

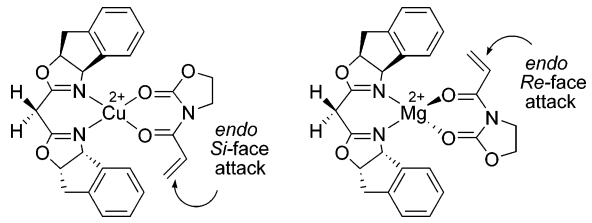
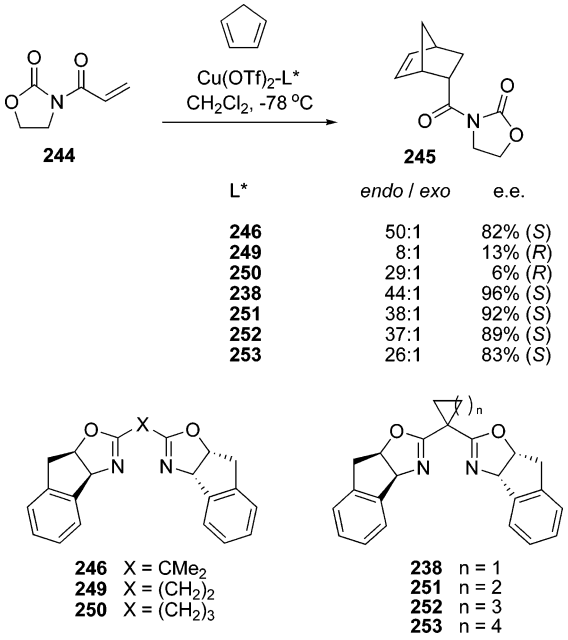


Figure 15. Proposed transition states for the copper- and magnesium-catalyzed asymmetric Diels−Alder reaction.

The ligand bite angle and its impact on the enantioselectivity were examined by Davies, Senanayake, and coworkers.[155,156,160] In a first series of experiments, such ligands as **246**, which form a six-membered copper chelate, were found to be the most selective. It was postulated that ligands **249** and **250** were far less selective because of the increased flexibility of the seven- and eight-membered metal chelates formed with copper.[155] Modification of ligand **246** to increase the bite angle (calculated in the increasing order **243** < **246** < **252** < **251** < **238**) resulted in higher *endo*/*exo* selectivities as well as *endo*-enantioselectivities of cycloadduct **244** (Scheme 60).[156,160] The orientation of the C-8 proton of the aminoindanol moieties in the "chiral pocket" of the copper complex was believed to play an important role on the stereoselectivity of the Diels−Alder reaction.[160] Another explanation raised the possibility that a larger bite angle would altogether change the coordination around the copper center, away from the idealized square planar model.[160]

Ghosh improved the utility of inda-box ligands in the Diels−Alder reaction by using cationic aqua complex derived from **130** and Cu(ClO$_4$)·6H$_2$O. The complex had the considerable advantage of being air-stable, and reaction of **244** and cyclopentadiene at −78 °C for 11h using 10 mol % of aqua complex afforded cycloadduct **245** in 88% yield,

Scheme 60



>99:1 *endo*/*exo* selectivity and 98% ee (*S*). Cryogenic temperatures were not necessary to achieve high levels of enantioselectivity as the same reaction could be run at 0 °C, which allowed for completion of the reaction within 1 h, to give **245** in similar yield (91%) with little loss of selectivity (98:2 *endo*/*exo*, 95% ee (*S*)).[161]

The importance of the rigid aminoindanol backbone in asymmetric catalytic Diels−Alder reactions is a subject of continued interest.[162,214] A recent example immobilized the copper−inda-box complex onto mesoporous silica in the context of continuous large-scale production of chiral compounds.[162] When 10 mol % of this catalyst was used (Figure 16), the Diels−Alder reaction between **244** and

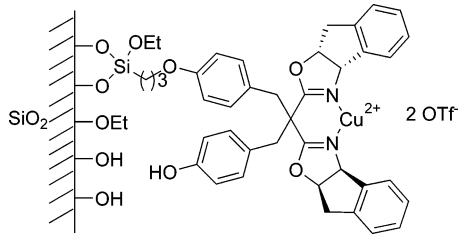
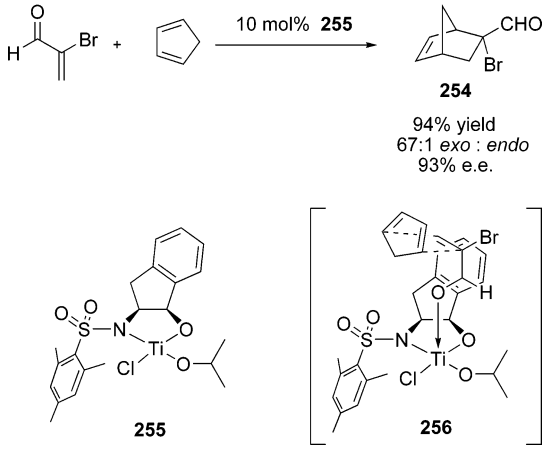


Figure 16. Immobilized copper−inda-box catalyst.

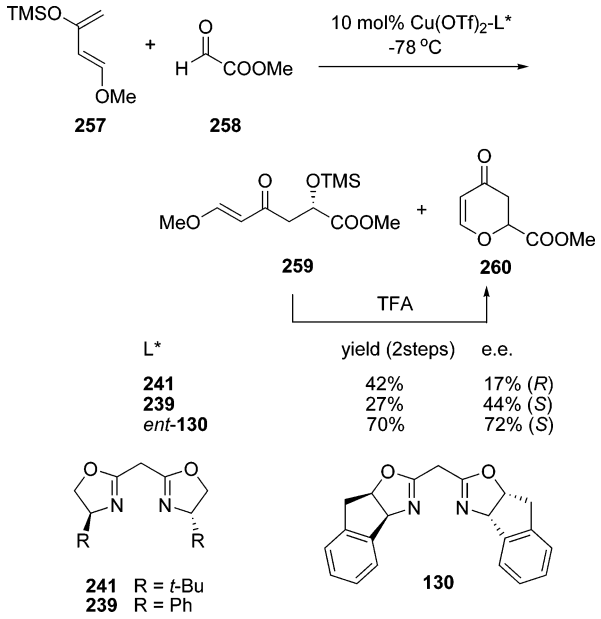
cyclopentadiene proceeded in 99% yield, 17:1 *endo*/*exo* selectivity, and 78% ee of *endo* cycloadduct. The catalyst could easily be recovered and reused several times without significant loss of diastereoselectivity (15:1 *endo*/*exo* selectivity after the fifth reuse) or enantioselectivity (72% ee after the fifth reuse).[162] The same remarkable reactivity was observed with a number of diene/dienophile partners.

Isomers of *cis*-1-amino-2-indanol have attracted considerably less attention, even though improved asymmetric inductions have been reported on several occasions. For example, Corey and co-workers envisioned that *cis*-2-amino-1-indanol-derived titanium complex **254** could provide high selectivities in the Diels−Alder reaction of 2-bromoacrolein and cyclopentadiene.[215] When 10 mol % of titanium catalyst **254** was used, synthetically versatile (*R*)-bromoaldehyde adduct **255** was obtained in 94% yield, 67:1 *exo*/*endo*

Scheme 61



Scheme 62

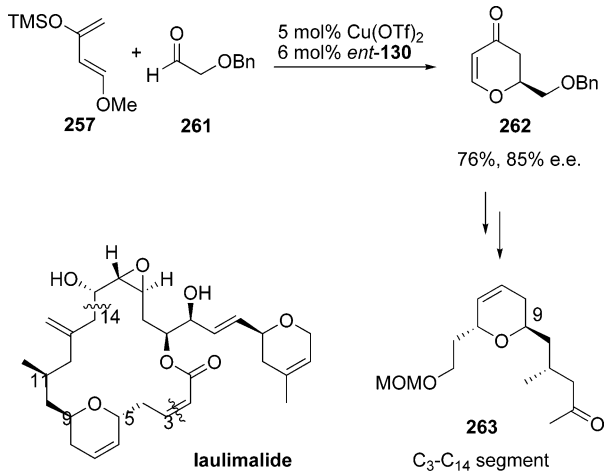


diastereoselectivity, and 93% ee. The absolute stereochemical outcome of the reaction is consistent with the proposed transition state assembly **256** in which the dienophile coordinates at the axial site of the metal, proximal to the indane moiety through π-attractive interactions. In this complex, the π-basic indole and the π-acidic dienophile can assume a parallel orientation facilitated by the octahedral geometry of the transition metal. The aldehyde would then react through a preferential *s-cis*-conformation (Scheme 61).[215]

7.6.2. Hetero-Diels–Alder

The asymmetric hetero-Diels−Alder reaction using inda-box ligands was first investigated by Ghosh and co-workers.[163] Danishefsky's diene and glyoxylate esters were reacted using copper triflate as Lewis acid. The reaction gave a mixture of Mukaiyama aldol **259** and pyranone derivative **260** after standard workup. Treatment of the crude mixture with trifluoroacetic acid allowed for ring-closing of **259** and led to **260** as the sole product. Aminoindanol-derived ligand *ent*-**130** afforded the highest yields and enantioselectivities (Scheme 62). As observed for the Diels−Alder reaction, use of magnesium triflate as Lewis acid resulted in largely decreased and reversed enantioselectivities.[163]

Scheme 63

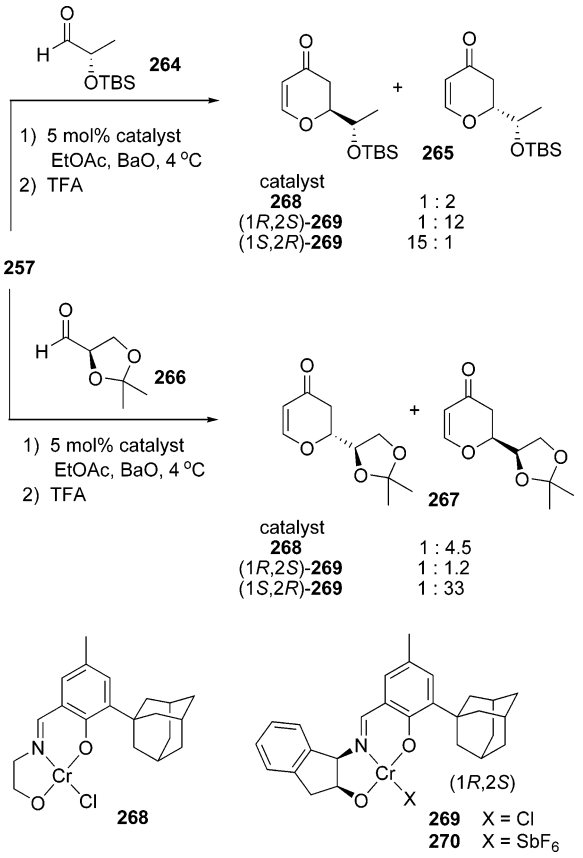


The synthetic utility of this methodology was demonstrated in the asymmetric construction of the C_3-C_{14} segment of antitumor macrolide laulimalide. When $Cu(OTf)_2$-*ent*-**130** was used as catalyst, Danishefsky's diene reacted with benzyloxyacetaldehyde **261** to provide cycloadduct **262** in 76% yield and 85% ee. Standard synthetic manipulations on dihydropyran **262** led to the C_3-C_{14} segment of laulimalide (Scheme 63).[164]

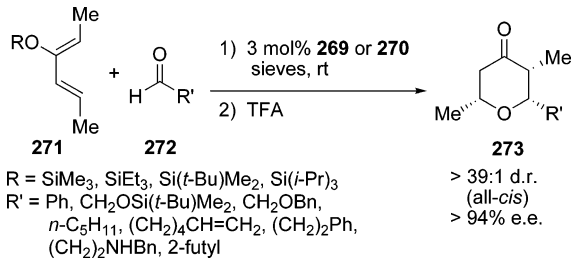
Jacobsen and co-workers investigated the diastereoselective hetero-Diels−Alder reaction between Danishefsky's diene and chiral aldehydes catalyzed by chromium−Schiff base complexes.[171] A variety of chiral aldehydes underwent the doubly diastereoselective reaction using catalysts **269** and **270** in good yield (up to 99%), satisfactory diastereomeric ratio (about 10:1 for unhindered aldehydes), and excellent enantiomeric excess of the major diastereoisomer (>97% ee). In the case of congested aldehydes, tridentate indane-derived catalysts were far less effective, leading to dihydropyrans in moderate yields (44−58%) and selectivities (<4:1 d.r.). While the reaction of **257** and **266**, using achiral complex **268** as catalyst, gave **267** in a relatively high 1:4.5 diastereomeric ratio, the matched catalyst/substrate system using (1*S*,2*R*)-**269** provided the highest level of diastereoselectivity (1:33) of the study (Scheme 64). With judicious choice of chiral aldehyde and catalyst enantiomer, any of the four possible diastereoisomers of dihydropyranone can be synthesized with high selectivity.[171] This methodology was successfully applied by Burke to the enantioselective synthesis of the $C_{20}-C_{32}$ segment of the Phorboxazoles.[216]

In a complementary study, Jacobsen and co-workers utilized their new chromium complex of aminoindanol-derived Schiff bases to perform an efficient hetero-Diels−Alder reaction between less nucleophilic mono-oxygenated dienes and unactivated achiral aldehydes. This reaction provided enantiomerically enriched dihydropyrans with three defined stereogenic centers in one step (Scheme 65).[170] The best results were obtained using catalysts **269**−**270**, which bear a very large adamantyl group. In all cases, reaction of dienes **271** with various aldehydes gave excellent all-*cis* diastereoselectivities (>39:1 d.r.). In addition, all aliphatic aldehydes led to remarkable enantioselectivities (>94% ee). The tetrahydropyranone formed from benzaldehyde was obtained with a lower level of enantioselectivity (65% ee using **269** and 81% ee using **270**). In general, reactions with hexafluoroantimonate catalyst **270** were faster and more enantioselective than with chloride **269**. With the exception

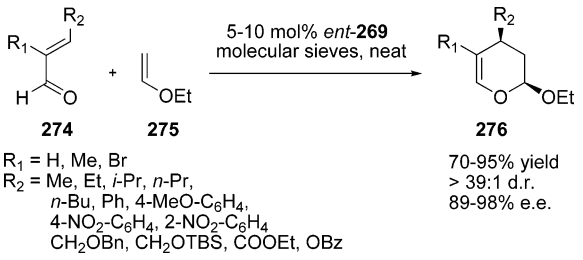
Scheme 64



Scheme 65



Scheme 66



of aromatic aldehydes, where use of acetone as solvent was critical, solvent-free conditions gave satisfactory results. This method provided highly efficient access to several interesting synthons, which, by further elaboration of the double bond, would ultimately lead to tetrahydropyran derivatives with 5 defined stereogenic centers.

Chromium complex **269** was also shown to efficiently catalyze the inverse electron-demand, hetero-Diels−Alder reaction of α,β-unsaturated aldehydes with alkyl vinyl ethers (Scheme 66).[172] While the uncatalyzed process required elevated temperatures and pressures to give dihydropyrans in good yields but poor *endo*/*exo* selectivities, the reaction

proceeded at room temperature in the presence of 5 mol % of **269** and 4 Å molecular sieves in dichloromethane of *tert*-butyl methyl ether with excellent diastereoselectivity (*endo*/*exo* >96:4) and promising enantioselectivities (72−78% ee). Optimal results were achieved using a solvent-free system and excess vinyl ether. Both reactivity and selectivity decreased with increasing steric bulk of alkyl group on the vinyl ether (Et > *n*-Pr > *n*-Bu ∼ *i*-Bu), and *tert*-butyl vinyl ether was completely unreactive. The cycloaddition of ethyl vinyl ether with a wide variety of α,β-unsaturated aldehydes bearing aliphatic and aromatic β-substituents proceeded with high selectivity (>39:1 d.r., 89−98% ee). Only 5 mol % of catalyst were necessary except in the case of sterically more demanding substituents (R = *i*-Pr, aromatics) which required 10 mol % of catalyst loading. Substitution could also be introduced in the α-position of the unsaturated aldehyde, and cycloadducts were obtained with similar high selectivities.[172]

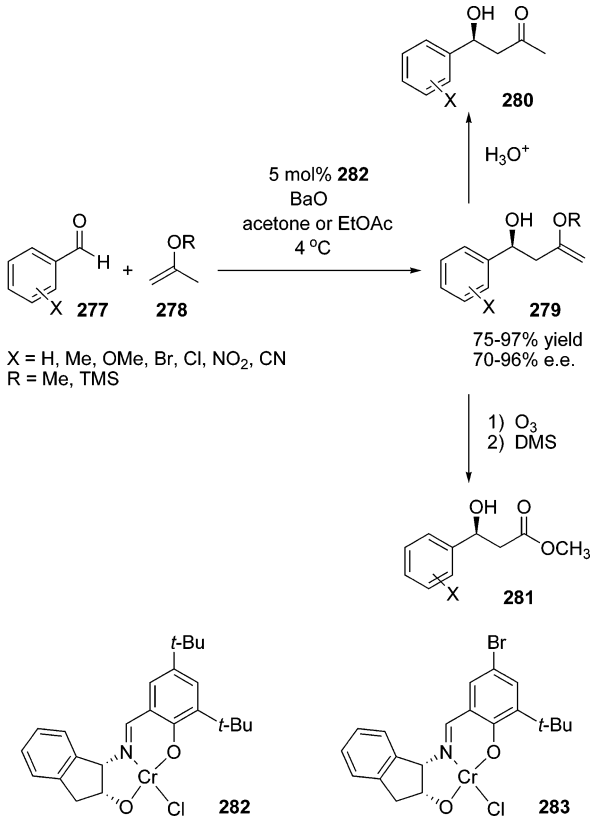
The above results were particularly remarkable in light of the few precedents which only involved chelation of oxabutadienes bearing oxygen-containing,electron-withdrawing groups by a two-point binding catalyst, which would easily explain the enantioface discrimination. In contrast, Jacobsen's tridentate chromium catalyst **269** is a one-point binding complex which activated the unsaturated aldehyde and discriminated its enantiotopic faces through simple chelation to the carbonyl. In efforts to understand the source of stereoinduction, the crystal structure of **269** was analyzed, and the catalyst was shown to exist in the solid state as a dimeric structure bridged through a single molecule of water and bearing a terminal water ligand on each chromium center. On the basis of preliminary solution molecular weight and kinetic studies, it was proposed that the dimeric species was maintained in the catalytic cycle and that dissociation of one terminal water ligand would open one coordination site for substrate binding. These mechanistic studies not only explained the crucial need for molecular sieves in the reaction, but also clearly indicated that the role of **269** is comparable to activation of the aldehyde by a Lewis acid.[172]

7.6.3. Hetero-ene Reaction

The generality of the activation of aldehydes for reaction with weak nucleophiles, using tridentate Schiff base chromium(III) complexes, was further demonstrated by the successful and highly selective ene-reaction of alkoxy- and silyloxyalkenes with aromatic aldehydes.[173] The ene-reaction of 2-methoxypropene or 2-trimethylsilyloxypropene with a number of substituted benzaldehydes catalyzed by **282** in acetone or ethyl acetate proceeded in high yields (75−97%) and good-to-excellent enantioselectivities (70−96% ee, with >85% ee in the majority of cases). Catalysts **269** and **183** were also effective in the ene-reaction, but enantioselectivities were 2−5% lower. Interestingly, chiral (salen)CrCl complexes afforded good yields of ene-reaction but considerably poorer selectivities (<30% ee). β-Hydroxy enol ethers thus obtained were readily transformed into β-hydroxy ketone and β-hydroxy ester derivatives (Scheme 67).[173]

The crystal structure of **283** revealed that the complex existed as a dimeric species where the two chromium centers are bridged through the indane oxygen and each chromium metal bears one molecule of water (Figure 17). It was therefore proposed, as for the inverse electron-demand, hetero-Diels−Alder reaction, that the barium oxide desiccant removed one molecule of bound water from the catalyst

Scheme 67



dimer, which opened one coordination site for binding of the substrate carbonyl.[173]

8. *cis*-2-Amino-3,3-dimethyl-1-indanol

Saigo designed and demonstrated the general utility of *cis*-2-amino-3,3-dimethyl-1-indanol as a chiral auxiliary in a variety of carbon−carbon and carbon−heteroatom bond-formation reactions and as ligands in several catalytic processes.[217−221] Racemic *cis*-2-amino-3,3-dimethyl-1-indanol **287** was prepared in three steps from 3,3-dimethyl-1-indanone by oxime formation followed by sequential reduction of the keto and imino functional groups. The resolution of **287** was performed using (*S*)-mandelic acid. Salt (+)-**289** crystallized from ethanol and recrystallization followed by treatment with an alkaline solution gave optically pure (1*R*,2*S*)-**287** in 35% yield. The enantiomeric (1*S*,2*R*)-**287** was obtained in 37% yield from the crystallization/recrystallization filtrates by successive treatment with base and (*R*)-mandelic acid, followed by filtration of the crystalline (−)-**289** and treatment of the salt with alkali (Scheme 68).[217,218]

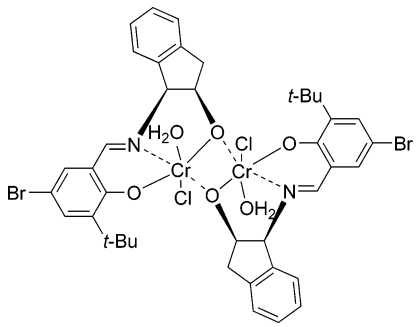
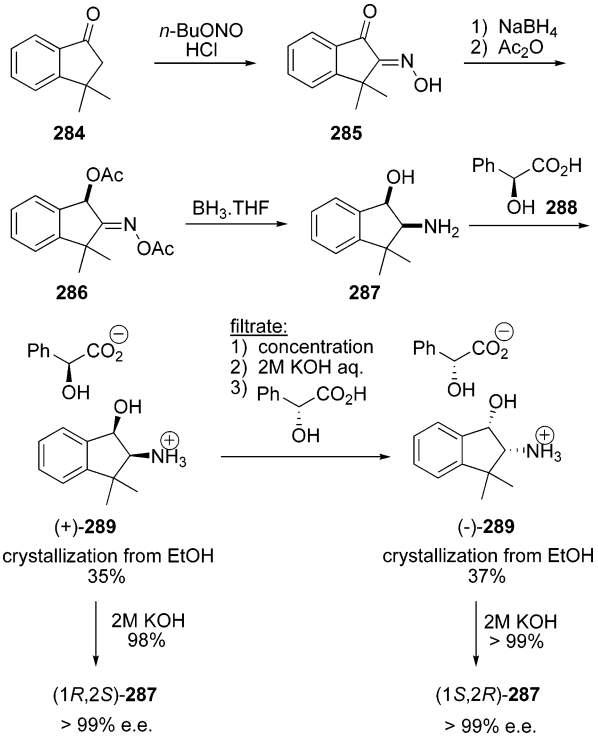
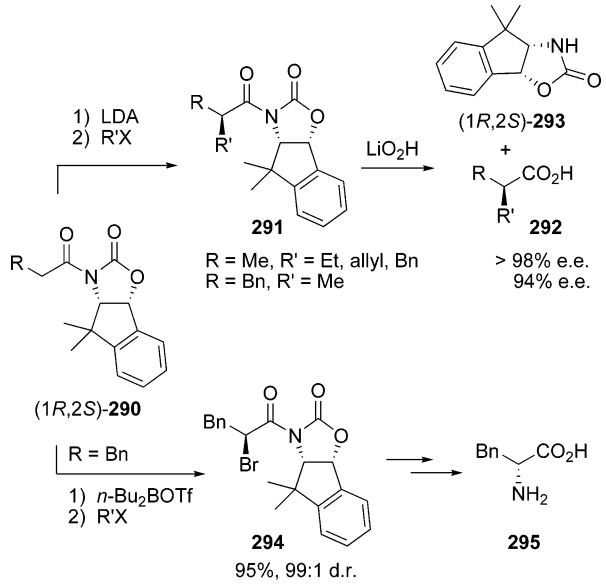


Figure 17. X-ray crystal structure of catalyst **283**.

Scheme 68



Scheme 69



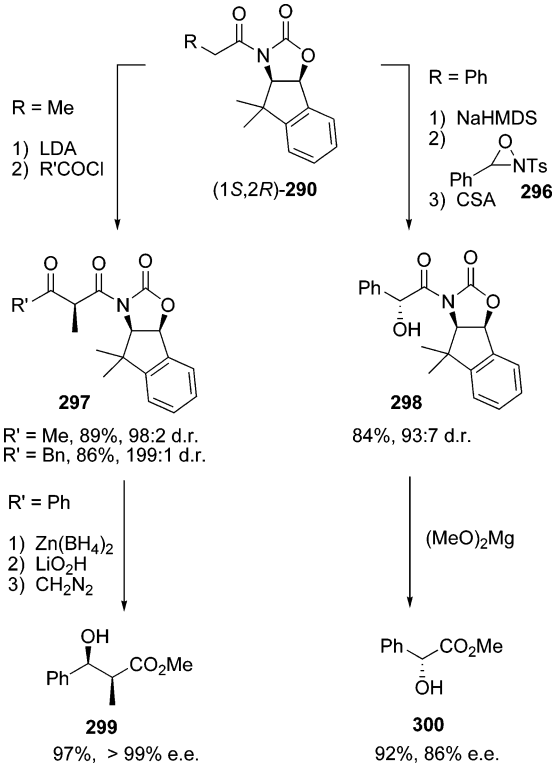
8.1. *cis*-2-Amino-3,3-dimethyl-1-indanol-Derived Chiral Auxiliaries

8.1.1. Electrophilic Additions

The diastereoselective alkylation of *N*-acyloxazolidinones enolates were first examined. Lithium enolates of **290** were reacted with a variety of alkyl halides, and alkylation products were formed with excellent diastereoselectivities (97:3 to 199:1 d.r.). Hydrolysis gave optically pure carboxylic acids, and the chiral auxiliary was recovered almost quantitatively.[217,218] Highly diastereoselective bromination was also achieved by reaction of the boron enolate of **290** with NBS (99:1 d.r.) to ultimately access optically pure amino acids (Scheme 69).[218]

Diastereoselective acylation of the imide enolates of **290** proceeded smoothly, and the corresponding β-keto carboximides were obtained in good yield and excellent >98:2 d.r. The acylated products could be converted to β-hydroxy carboximides in high *syn/anti* selectivity (96:4 in the case of R = Ph) by treatment with zinc borohydride. Recrystallization afforded optically pure *syn*-products. Hydrolysis followed by methylation led to chiral β-hydroxy esters in good yield and >99% ee (Scheme 70). In addition, reaction of the sodium enolate of **290** with 2-(*p*-toluenesulfonyl)-3-phenyloxyaziridine followed by acidic quenching led to the hydroxylated product with high diastereoselectivity (93:7 d.r.). Treatment with magnesium methoxide gave (*R*)-methyl mandelate in 86% ee, and the chiral auxiliary **293** was recovered (Scheme 70).[218]

Scheme 70



The stereochemical outcome of these electrophilic additions is consistent with a transition state in which the metal chelates the oxazolidinone carbonyl and the enolate oxygen. Reaction with an electrophile would therefore occur at the less hindered diastereotopic face of the (*Z*)-enolate, away from the shielding methyl groups of the auxiliary (Figure 18). As both enantiomers of oxazolidinone **293** are equally available, the direction of the asymmetric induction can be controlled by proper choice of the absolute stereochemistry of the chiral auxiliary.[218]

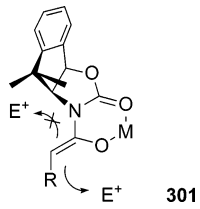
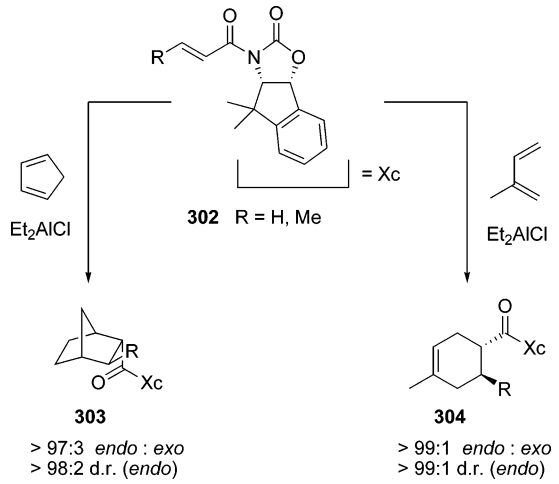


Figure 18. Chelating model for electrophilic additions.

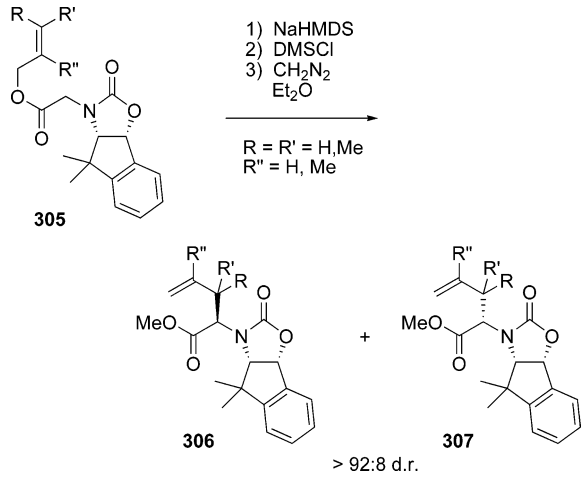
8.1.2. Pericyclic Reactions

Saigo and co-workers reasoned that, by analogy, high levels of diastereofacial discrimination could be achieved in

Scheme 71



Scheme 72



the Lewis acid-mediated Diels−Alder reaction of dienes with oxazolidinone **293**-derived dienophiles. Indeed, excellent regio- (*endo*/*exo*) and diastereoselectivities were reached in the Diels−Alder reaction of **302** with cyclic and acyclic dienes using Et_2AlCl as the activator (Scheme 71).[219] The selectivities obtained actually surpassed those reported with *cis*-1-amino-2-indanol **1** as the chiral auxiliary (193:7 d.r.).[123] The additional bulk introduced in the rigid backbone by the vicinal methyl groups proved an asset to improved stereocontrol.

cis-2-Amino-3,3-dimethyl-1-indanol was also employed as chiral auxiliary for the asymmetric Ireland−Claisen rearrangement of allyl carboxylates. Preliminary studies on the racemic system demonstrated the potential of the process, as unoptimized reaction conditions (NaHMDS, TMSCl in THF) led to the rearranged products in a promising 84:16 diastereomeric ratio. The reaction solvent was shown to affect the selectivity, and slightly improved results (87:13 d.r.) were obtained in Et_2O. It also appeared that the diastereoselectivity depended on the bulkiness of the silane used. Smaller silylating agents such as dimethylsilane chloride (DMSCl) gave better selectivities (93:7 d.r.). The Ireland−Claisen rearrangement of several enantiopure allyl carboxylates was carried out, and the corresponding products were obtained with high diastereoselectivity (Scheme 72).[220]

A six-membered chairlike transition state was proposed in which the (*E*)-ketene silyl acetal is placed in the opposite direction to the oxazolidinone carbonyl in order to avoid

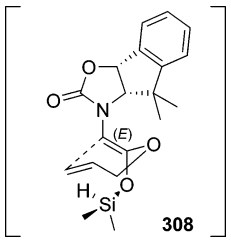
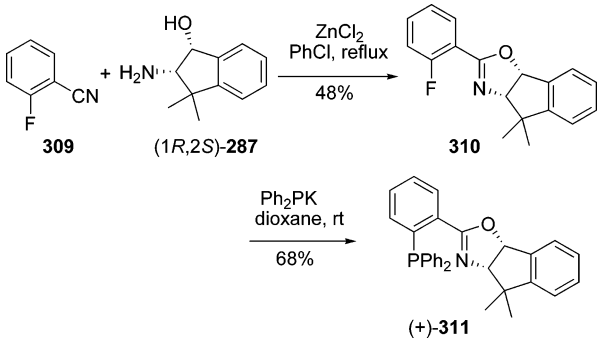
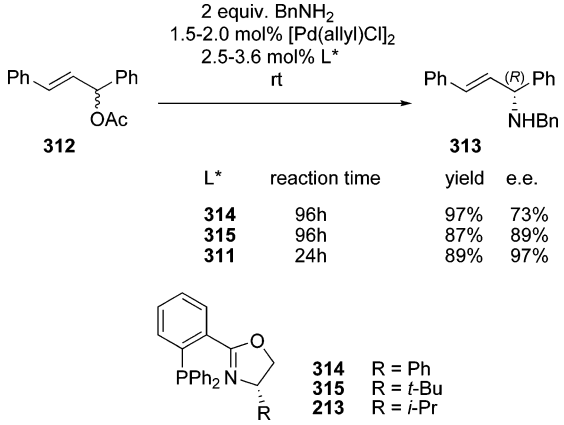


Figure 19. Proposed transition state for the diastereoselective Ireland−Claisen rearrangement.

Scheme 73



Scheme 74

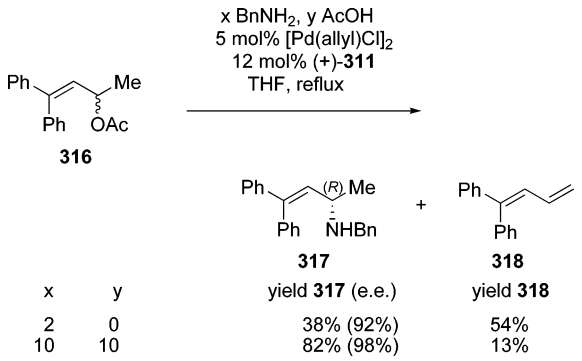


dipole moment repulsion, with the allylic moiety oriented away from the hindered indane backbone. This transition state not only accounts for the direction of the asymmetric induction but also explains the better results observed with smaller silylating groups (Figure 19).[220]

In continuing work, Saigo and co-workers synthesized phosphorus-containing oxazoline **311** derived from *cis*-2-amino-3,3-dimethyl-1-indanol and studied the utility of this new ligand in palladium- and rhodium-catalyzed asymmetric processes.[221−223] The chiral ligand was rapidly prepared by condensation of optically pure (1*R*,2*S*)-**287** with 2-fluoronitrile in the presence of a catalytic amount of zinc chloride followed by reaction with potassium diphenylphosphide (Scheme 73).[221]

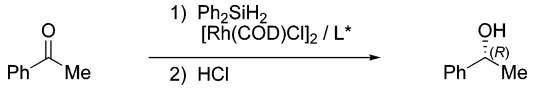
Ligand (+)-**311** was first tested in the palladium-catalyzed allylic amination reaction. Preliminary studies on 1,3-bisphenyl-2-propen-1-yl acetate **312** showed that phosphine-oxazoline **311** was a more effective ligand than the parent ligands **314**−**315** with shorter reaction time and better enantioselectivity (Schemes 74 and 75).[221,224] Other 1,3-bis(*p*-substituted-aryl)-2-propen-1-yl acetates were also converted to the corresponding amines with excellent selectivity (>95% ee). The amination reaction of 1-alkyl-3,3-diphenyl-

Scheme 75



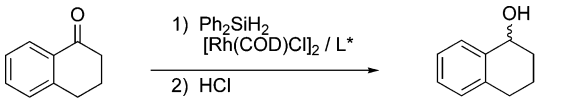
x	y	yield **317** (e.e.)	yield **318**
2	0	38% (92%)	54%
10	10	82% (98%)	13%

Scheme 76



L*	yield	e.e.
213	95%	82%
(+)-**311**	84%	94%

Scheme 77



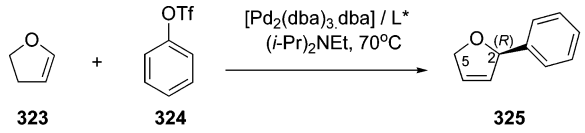
L*	yield	e.e.
213	70%	59% (*R*)
(+)-**311**	89%	89% (*R*)
(-)-**311**	97%	92% (*S*)

2-propen-1-yl acetates was examined, and addition of acetic acid to the reaction system was found to be necessary to minimize the competing elimination reaction and to achieve high enantioselectivities.[221] In the case of **316** (alkyl = methyl), the allylic amination with 2 equiv of benzylamine led to a mixture of allylamine **317** (38% yield, 92% ee) and elimination product **318** (54% yield). Addition of 10 equiv of acetic acid resulted in a faster reaction, decreased elimination product formation (13%), and higher enantiomeric excesses of **317** (98% ee). Increased amounts of benzylamine (10 equiv) were necessary to achieve high chemical yields of allylic aromatic product, probably to balance the acidity of the medium which may lead to ligand decomposition.

Encouraged by these successful results, Saigo and coworkers tested ligand **311** in the rhodium-catalyzed hydrosilylation of ketones.[222] Asymmetric hydrosilylation of acetophenone and tetralone using **311** as a chiral source led to considerably improved enantioselectivities (94% and 89% ee, respectively) compared to reactions performed with valinol-derived, phosphorus-containing oxazoline **213** (82% and 59%, respectively).[225,226] The equal accessibility of the two enantiomers of the *cis*-2-amino-3,3-dimethyl-1-indanol backbone in **311** represented an additional advantage over oxazoline **213**. The latter is derived from an amino alcohol of the chiral pool, which enantiomers are not equally available. When (−)-**311** was used, (*S*)-tetralol was easily obtained in 97% yield and 92% ee (Schemes 76 and 77).[222]

Phosphine-oxazoline **311** also proved a valuable ligand in the palladium-catalyzed asymmetric Heck reaction.[223] Although slightly less selective than ligand **315**,[227] the Heck

Scheme 78



L*	yield	e.e.
315	87%	97% (*R*)
(+)-**311**	81%	96% (*R*)

coupling of aryl and alkenyl triflates using **311** as ligand proceeded with high asymmetric induction (>90% ee) in all cases. Furthermore, both enantiomers of Heck reaction product can easily be obtained by proper choice of the ligand enantiomer (Scheme 78). Low yields were observed with bulky alkenes and were attributed to the rigid methyl groups of **311**, which ensure high stereoselection but may also hinder the approach of the alkene in the coordination sphere of the metal. Finally, in contrast to BINAP ligand which led to a 2,3- and 2,5-dihydro-2-phenylfuran mixture, phosphine-oxazolines were shown to have a low tendency to promote carbon−carbon bond migration. In the case of phosphine-oxazoline **311**, no migration was observed.[223]

9. Conclusion

The scope of applications of *cis*-aminoindanol has grown substantially since its discovery as a ligand for HIV-protease inhibitors and the development of a practical industrial process for the synthesis of either *cis*-isomers in enantiopure form. The remarkable properties of the rigid indane platform have been extensively utilized in the past decade in an ever-increasing number of asymmetric methodologies.

cis-1-Amino-2-indanol-based chiral auxiliaries have proven effective in various carbon−carbon and carbon−heteroatom bond formations, in particular in electrophilic additions, aldol and homoaldol reactions, conjugate additions, and pericyclic reactions. Examples of the utility of these chiral auxiliaries include the syntheses of α-amino acids, γ-lactones, sulfinamides, sulfoxides, natural products, and pharmaceutical drugs in a highly stereoselective fashion. The industrial process for Crixivan is an especially notable illustration of the remarkable properties of *cis*-aminoindanol. The availability of optically active *cis*-1-amino-2-indanol, the high levels of asymmetry it induces, and its easy recovery and recycling are considerable assets to the development of practical and economical large-scale processes.

The explosion of new aminoindanol-derived ligands disclosed in the past few years is the unmistakable mark of recognition and appreciation of the indanyl platform as a valuable backbone in the field of catalytic asymmetric synthesis. The emergence of related and novel structural designs and their success in achieving improved selectivities clearly reveals the continuing interest in the synthetic potential of conformationally constrained amino alcohols.

10. References

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