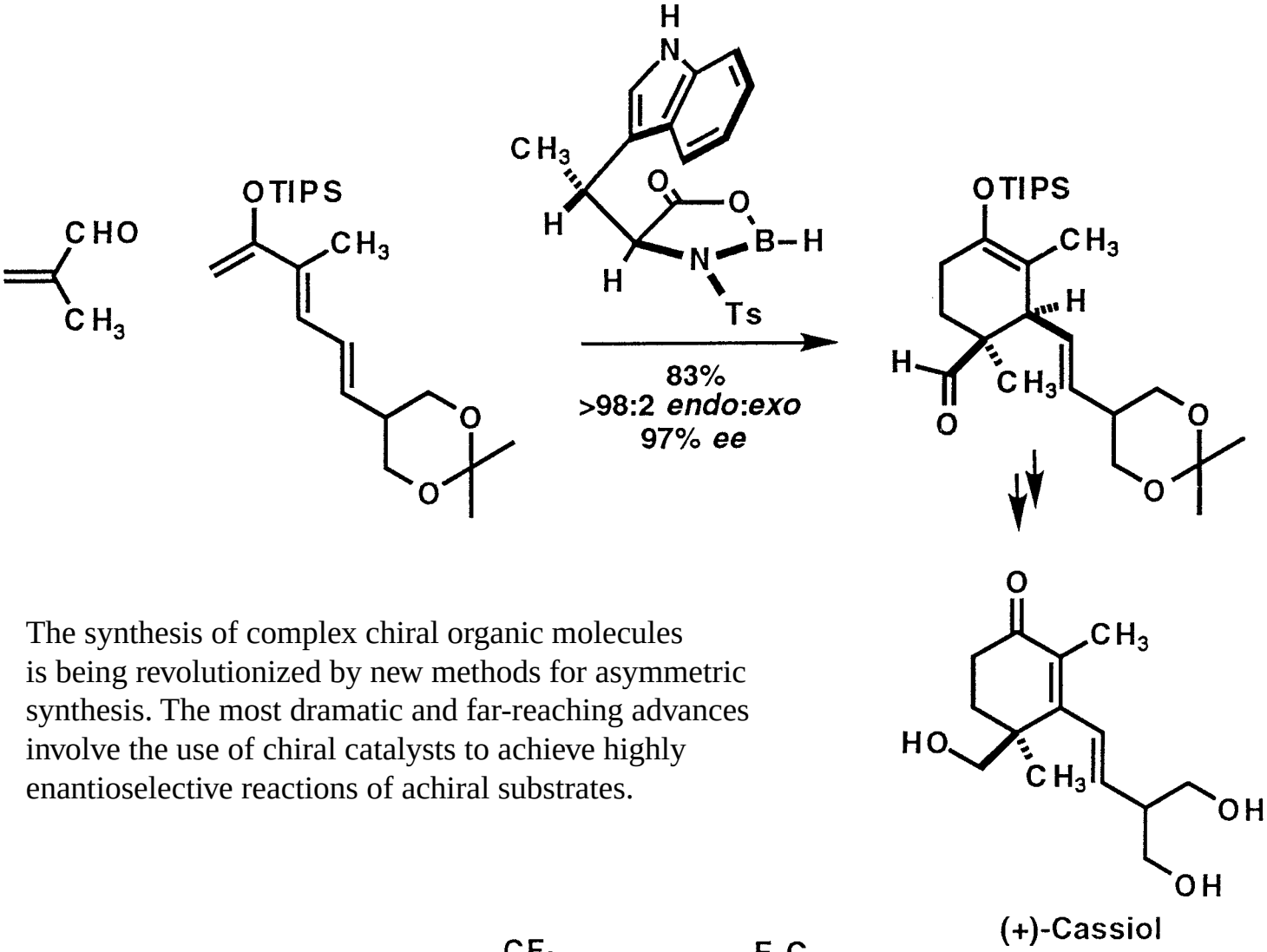
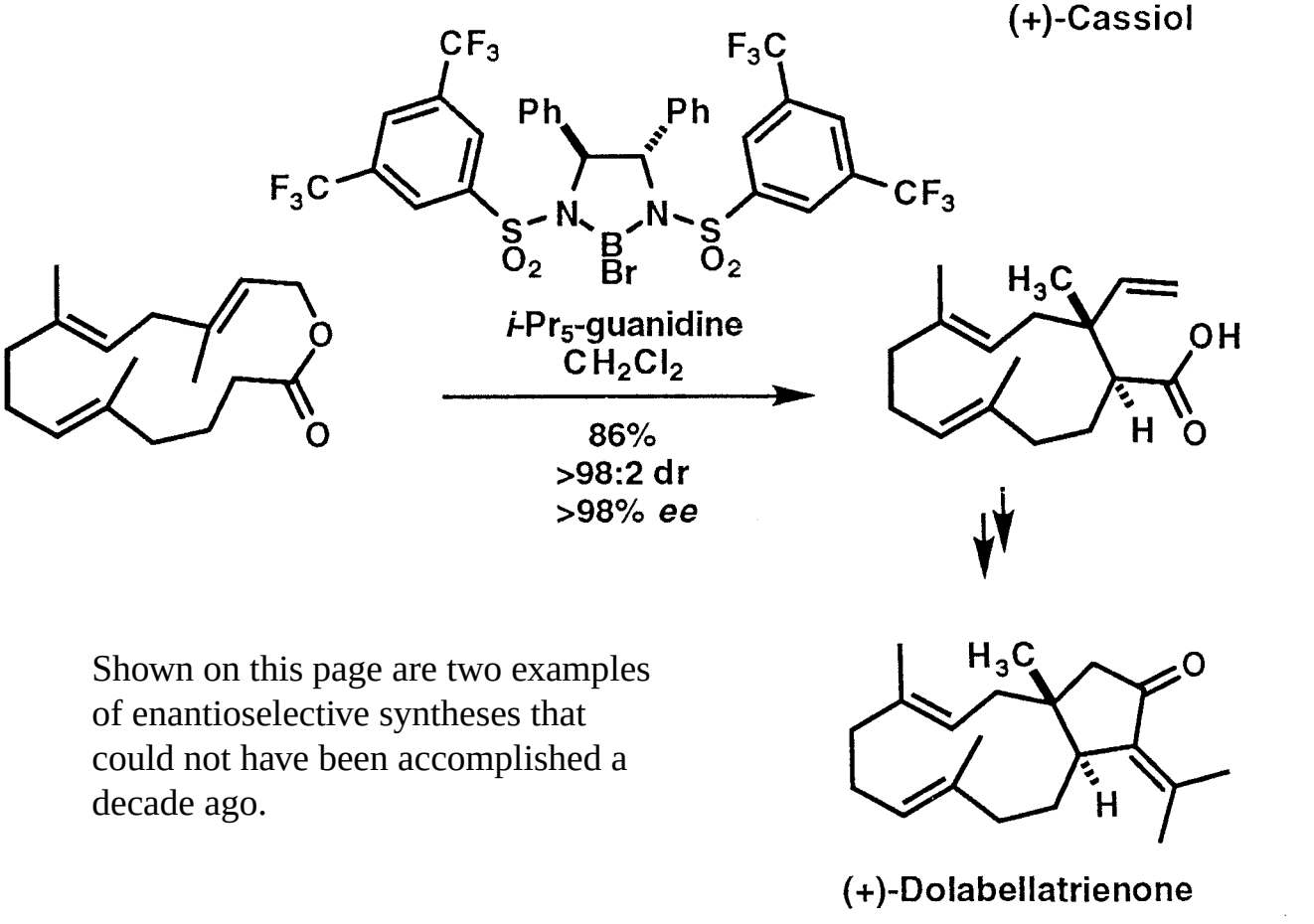


The synthesis of complex chiral organic molecules is being revolutionized by new methods for asymmetric synthesis. The most dramatic and far-reaching advances involve the use of chiral catalysts to achieve highly enantioselective reactions of achiral substrates.



Shown on this page are two examples of enantioselective syntheses that could not have been accomplished a decade ago.

The Catalytic Enantioselective Construction of Molecules with Quaternary Carbon Stereocenters

Elias J. Corey* and Angel Guzman-Perez

The catalytic asymmetric synthesis of structurally complex naturally occurring organic molecules and other highly useful chiral substances represents a new frontier for synthetic chemistry and an ideal testing ground for the remarkable new synthetic chiral catalysts, whose impact on all of chemistry promises to be profound. Catalytic enantioselective methodology provides a powerful new option for synthesis planning and execution, which complements the use of chiral starting materials, chiral controller groups (auxiliaries), or enzymic catalysis. The synthesis of complex molecules with quaternary (fully substituted) stereocenters, one of the most demanding tasks in multistep synthesis, presents simultaneously a challenge to catalytic enantioselective processes and an opportunity to demonstrate their power and potential. In addition, the problems that inevitably arise in the execution of a synthesis of a complex molecule provide a stimulus and a sense of direction for new discovery. In this article several of the most promising new catalytic enantioselective methods are reviewed from the point of view of their application to the construction of complex chiral molecules with quaternary stereocenters. It is safe to predict that this field of chemistry will grow enormously in the coming decades and will have great intellectual and practical impact.

Keywords: asymmetric catalysis · chirality · enantioselective addition · quaternary stereocenters · total synthesis

1. Introduction

Organic chemistry has undergone a revolution in the last two decades. The development of new and highly enantioselective processes has become a major focus of chemical synthesis, and the use of chiral catalysts is displacing chiral auxiliaries and reagents as the method of choice for asymmetric synthesis. An efficient chiral catalyst allows for large quantities of optically active product to be obtained on use of relatively small amounts of enantiopure material, without the need for the removal and recovery of a chiral auxiliary. Furthermore, the most practical catalytic methods utilize an inexpensive and readily available chiral ligand, and provide high and predictable enantioselectivity across a wide range of substrates.[1] The application of such catalytic asymmetric reactions to the synthesis of challenging natural products has assumed increasing importance not only to demonstrate their value, but also to understand these methods better and improve them, thereby increasing their generality. The asymmetric construction of molecules with quaternary carbon stereocenters, that is, carbon centers with four different nonhydrogen substituents, represents a very challenging and dynamic area in organic synthesis. The preparation of compounds containing these centers with *catalytic* enantioselective reactions is particularly demanding. This review presents a concise survey of some modern and highly selective methods for the catalytic construction of these compounds, using representative recent examples. The many excellent noncatalytic, diastereoselective, or biochemical methods will not be discussed here.[2]

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2. Catalytic Methods Applicable to the Direct Synthesis of All-Carbon-Substituted Quaternary Carbon Stereocenters

2.1. Robinson Annulation and Intramolecular Aldol Reaction Catalyzed by Amino Acids

The enantioselective version of the classical Robinson annulation has been applied to the synthesis of optically active diketones, which are useful in the preparation of a variety of terpenes and other natural products. The transformation involves the discrimination between two enantiotopic carbonyl groups in an intramolecular aldol reaction, which involves

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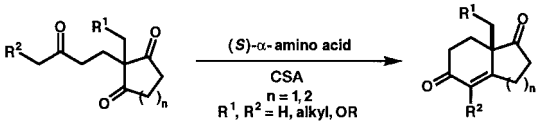
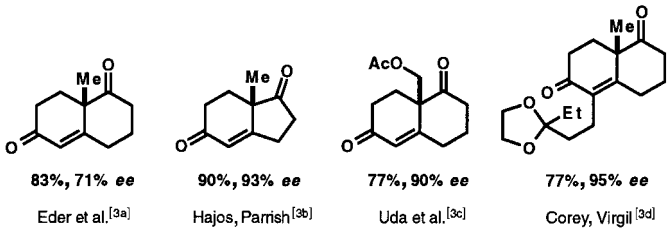
an enamine of the triketone and the chiral α-amino acid catalyst (Scheme 1). For example, the fused bicyclic compounds shown in Scheme 2, which include the Wieland–Miescher ketone, were prepared in this manner. The products could be recrystallized until optically pure.[3]



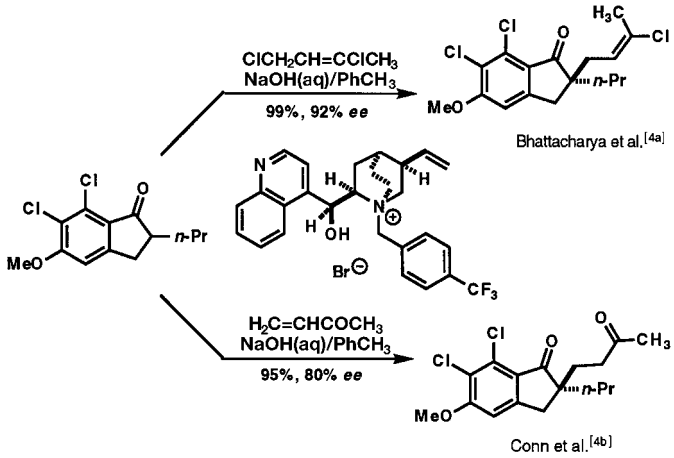
Scheme 1. Enantioselective aldol cyclization. CSA = (+)-camphorsulfonic acid.



Scheme 2. Chiral products from amino acid catalyzed cyclization of achiral precursors, including the Wieland–Miescher ketone (extreme left).

2.2. Alkylation and Michael Addition Reactions

Alkylations and Michael additions are useful and versatile reactions; however, few instances of highly enantioselective catalytic versions of these transformations for the synthesis of quaternary stereocenters have been demonstrated to date. A noteworthy example is the use of the phase-transfer catalyst *N*-(4-trifluoromethylbenzyl)cinchoninium bromide by Merck scientists for the synthesis of alkylated indanones as promising drug candidates (Scheme 3).[4]



Scheme 3. Enantioselective alkylation by phase-transfer catalysis.

2.3. Diels–Alder Reactions

The Diels–Alder cycloaddition is arguably one of the most useful and powerful transformations available to the synthetic chemist. Great effort has been devoted to the development of catalytic enantioselective versions of this reaction.[5] The enantioselective Diels–Alder reaction of 2-substituted acroleins is particularly interesting, because it provides products with a quaternary stereocenter. Scheme 4 presents a collection of Lewis acid catalysts (**1**–**10**) that have been applied successfully to the asymmetric Diels–Alder reaction of 2-substituted acroleins.[6]

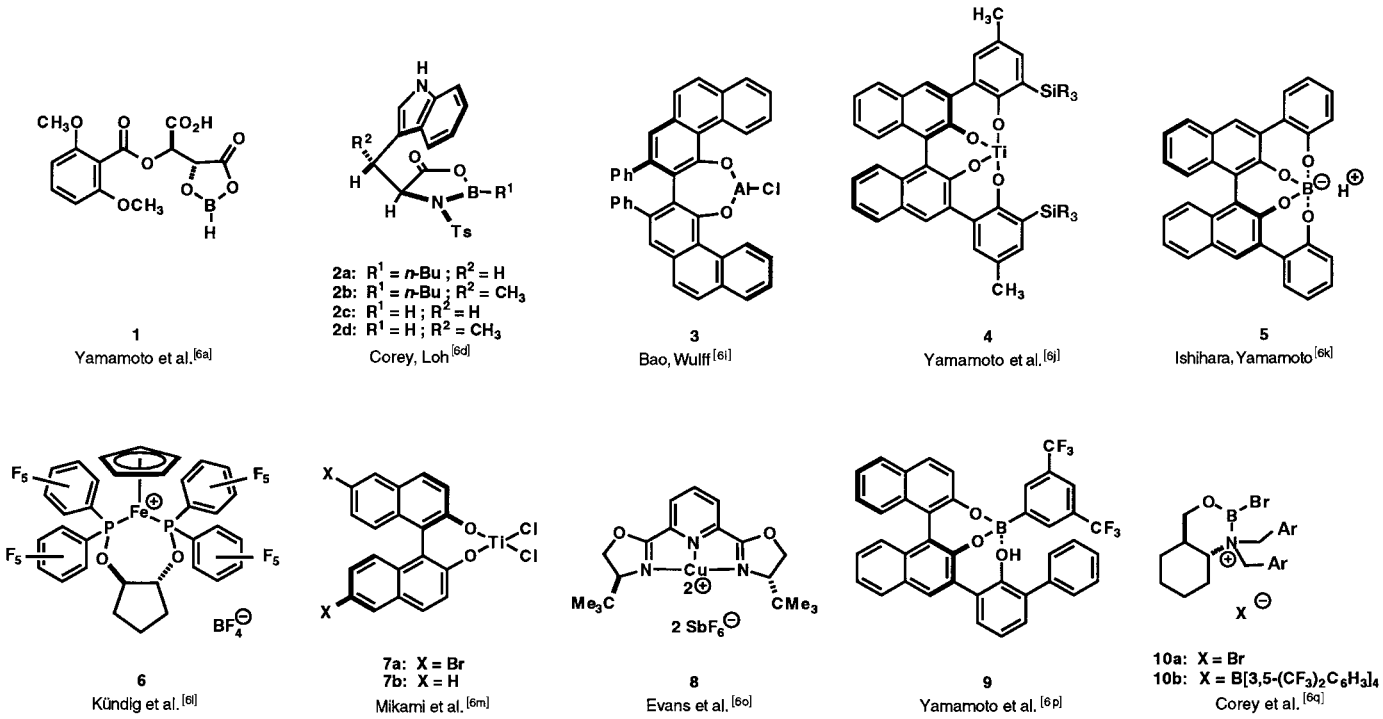
The asymmetric Diels–Alder reactions of 2-haloacroleins have attracted considerable attention not only because of the high reactivity and selectivity obtained with these dienophiles, but also because of the exceptional synthetic versatility of the resulting adducts.[6d] The excellent enantioselectivities resulting from the reactions of 2-bromoacrolein and 2-chloroacrolein with a variety of dienes are summarized in Scheme 5. In

Elias J. Corey, born 1928 in Methuen about 50 km north of Boston, studied Chemisty from 1945 to 1950 at the Massachusetts Institute of Technology, where he gained his doctorate for work on synthetic penicillins under John C. Sheehan. In January 1951 he joined the University of Illinois at Urbana-Champaign as an Instructor in Chemistry and was promoted to full Professor in 1956 at the early age of 27. Since 1959 he has been at Harvard University. His many scientific successes were crowned with the Nobel Prize for Chemistry in 1990. For as long as he can remember he has enjoyed study, adventure, and discovery.

E. J. Corey

A. Guzman-Perez

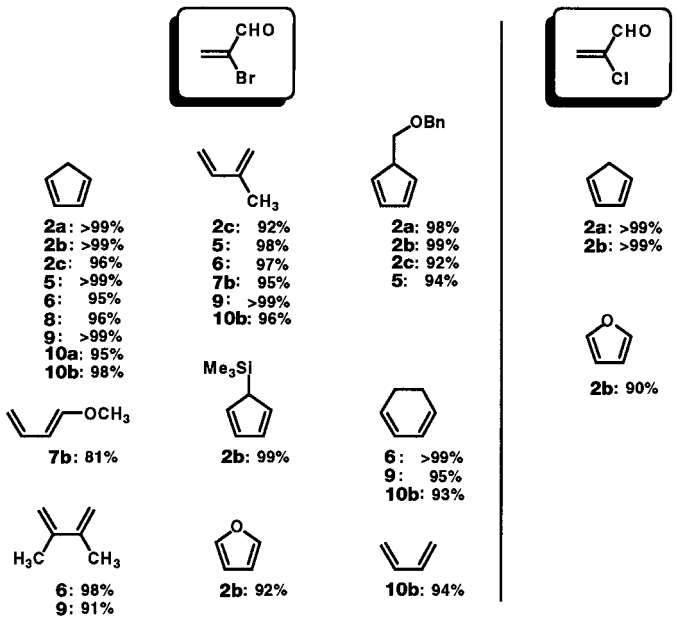
Angel Guzman-Perez was born in 1967 in Mexico City (Mexico) and obtained his Bachelor's degree in Chemistry at the National Autonomous University of Mexico. He worked for a year (1990–1991) at Syntex Research (Palo Alto, California, USA) in the medicinal chemistry department and then joined the Ph.D. program at Harvard University under the direction of Professor E. J. Corey to study new methods for the asymmetric synthesis of natural products. He received the Ph.D. degree in Chemistry in 1997 and now works in drug discovery at Pfizer Central Research (Groton, Connecticut, USA).



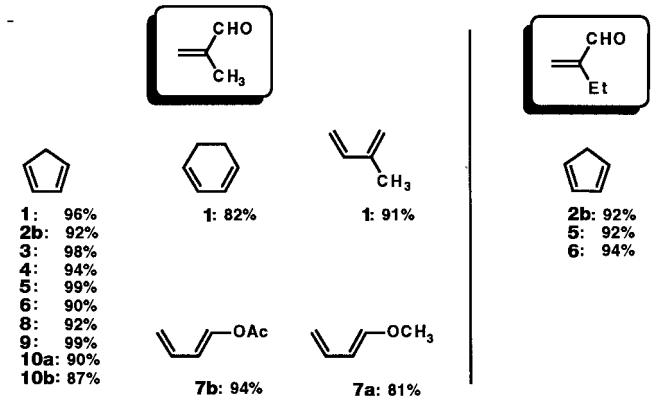
Scheme 4. Effective catalysts for the synthesis of Diels–Alder adducts with quaternary stereocenters. R = *o*-tolyl, Ar = 3,5-$Me_2C_6H_3$.

addition, 2-alkylacroleins such as 2-methylacrolein and 2-ethylacrolein produce favorable results with several dienes, but are less versatile than their 2-halo counterparts as shown in Scheme 6. Furthermore, certain 2,3-disubstituted acroleins afford promising selectivities in the reaction with cyclopentadiene (Scheme 7).

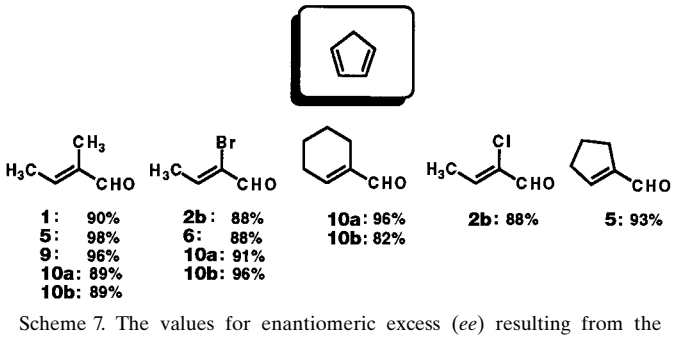
The application of these reactions to the total synthesis of natural products (especially with catalysts **2**) has recently commenced. For example, Marshall and Xie synthesized a



Scheme 5. The values for enantiomeric excess (*ee*) resulting from the asymmetric Diels–Alder reaction of 2-bromoacrolein and 2-chloroacrolein with several dienes on catalysis with the indicated compounds.

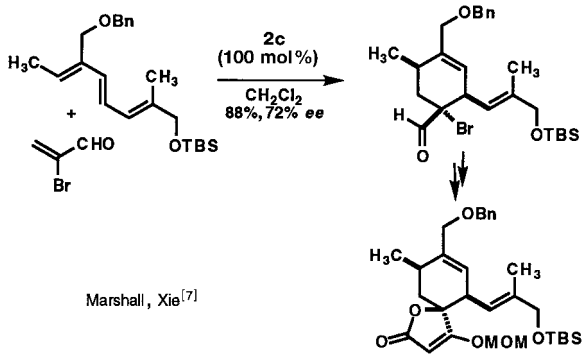


Scheme 6. The values for enantiomeric excess (*ee*) resulting from the asymmetric Diels–Alder reaction of 2-methylacrolein and 2-ethylacrolein with several dienes on catalysis with the indicated compounds.



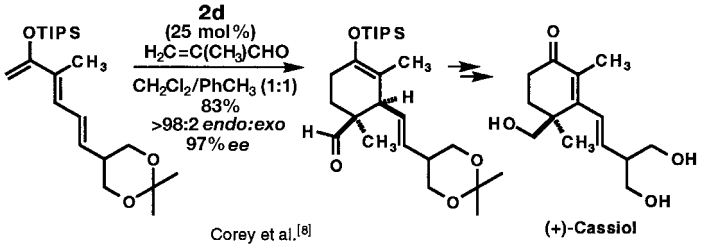
Scheme 7. The values for enantiomeric excess (*ee*) resulting from the asymmetric Diels–Alder reaction of several 2,3-disubstituted acroleins with cyclopentadiene on catalysis with the indicated compounds.

Diels–Alder cycloadduct bearing a quaternary stereocenter using stoichiometric amounts of catalyst **2c**, and converted it into the spirotetronate subunit of kijanolide (Scheme 8).[7]



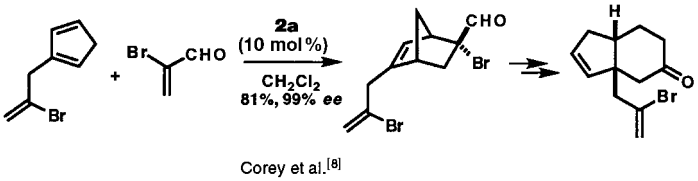
Scheme 8. Enantioselective Diels–Alder route to the spirotetronate unit of kijanolide. MOM = methoxymethyl, TBS = *tert*-butyldimethylsilyl.

Furthermore, the enantioselective Diels–Alder reaction between a trisubstituted electron-rich open-chain diene and 2-methylacrolein catalyzed by oxazaborolidine **2d** was used to accomplish an efficient synthesis of the potent antiulcer agent cassiol in 97% *ee* (Scheme 9). The high enantioselectivity of the key cycloaddition is the collective result of critical modifications to the substrate, catalyst, and reaction solvent.[8]



Scheme 9. Enantioselective total synthesis of (+)-cassiol. TIPS = triisopropylsilyl.

Finally, a Diels–Alder reaction involving catalyst **2a** was used as a key step in an especially simple enantioselective synthesis of gibberellic acid via the bicyclic ketone shown in Scheme 10.[8]



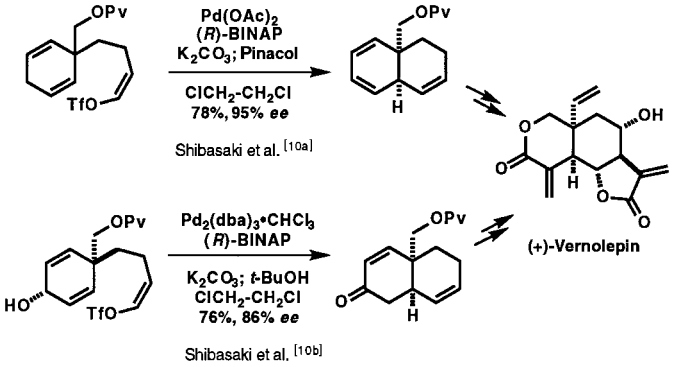
Scheme 10. Catalytic enantioselective Diels–Alder reaction for the synthesis of gibberellic acid.

2.4. Heck Reactions

The enantioselective version of the intramolecular Heck reaction is an extremely effective C–C bond construction. Its utility has already been demonstrated in the synthesis of several natural products containing quaternary stereocenters. Two general strategies have been applied in this field: the differentiation of enantiotopic olefinic bonds in molecules with prochiral quaternary centers and the differentiation of the enantiotopic faces of C–C double bonds.[9]

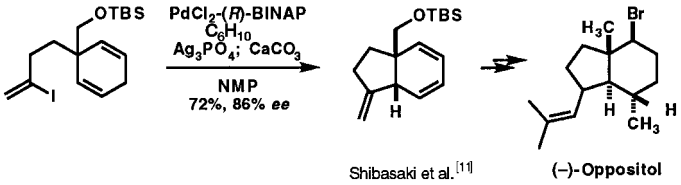
2.4.1. Heck Reactions That Differentiate between Enantiotopic Groups

The asymmetric synthesis of vernolepin has been accomplished in two ways by Shibasaki and co-workers (Scheme 11). The key step in both cases is the differentiation of enantiotopic C–C double bonds by an intramolecular Heck reaction.[10]



Scheme 11. Asymmetric intramolecular Heck reaction for the synthesis of vernolepin. BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, dba = dibenzylidenacetone, PV = pivaloyl.

Furthermore, the synthesis of a *cis*-hydrindan was accomplished employing a similar strategy as outlined in Scheme 12. The product of this Heck reaction allowed for the formal asymmetric synthesis of oppositol and prepinnaterpene. Interestingly, the use of an *endo*-vinyl iodide instead of the *exo*-vinyl iodide shown afforded product in only 3% *ee*.[11]

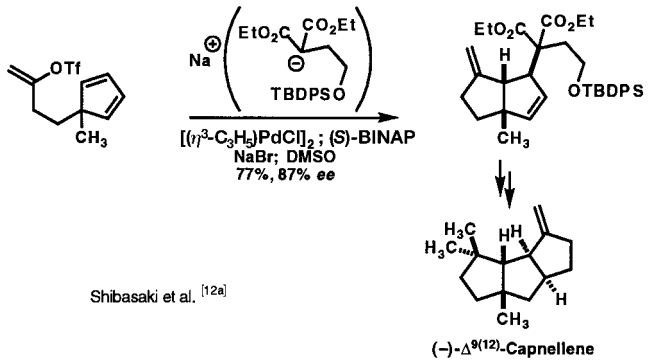


Scheme 12. Synthesis of (−)-oppositol. NMP = *N*-methyl-2-pyrrolidone.

The asymmetric Heck reaction has also been applied to the synthesis of compounds containing two fused five-membered rings by the use of prochiral cyclopentadienyl systems. The transformation initially generates a π-allylpalladium species, which is then trapped with a suitable nucleophile to complete the catalytic cycle. Nucleophiles that have been used for this purpose include acetate, an amine, and dicarbonyl-stabilized enolates. For example, in the synthesis of $\Delta^{9(12)}$-capnellene the π-allyl intermediate was captured with a malonate anion to provide the desired product of 87% *ee* with complete diastereo- and regioselectivity (Scheme 13).[12]

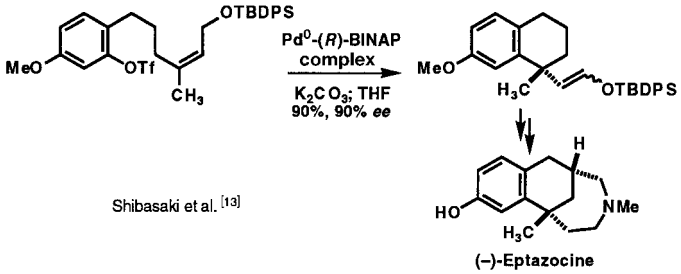
2.4.2. Heck Reactions That Differentiate between Enantiotopic Faces

The use of an intramolecular Heck reaction that differentiates between enantiotopic faces was demonstrated by Shibasaki and co-workers for the synthesis of eptazocine. The



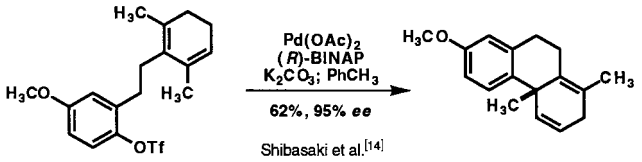
Scheme 13. Heck alkylation/cyclization route to (−)-capnellene. TBDPS = *tert*-butyldiphenylsilyl.

Z-olefinic substrate provided better results than the corresponding *E* isomer (Scheme 14).[13]



Scheme 14. Enantioselective synthesis of (−)-eptazocine.

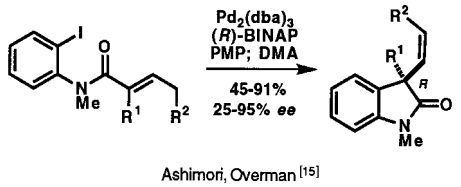
A synthetic intermediate in the synthesis of a number of diterpenes, including kaurene, abietic acid, and a bruceantin analogue, was prepared by a regio- and face-selective Heck reaction (Scheme 15).[14]



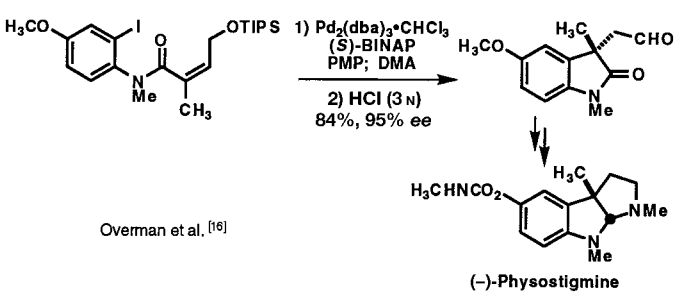
Scheme 15. Enantioselective route to hydrophenanthrenes.

Overman and Ashimori reported the construction of several 2-oxindoles from the corresponding aryl iodides through intramolecular Heck reactions. Either enantiomeric product, depending upon whether the HI scavenger used is Ag_3PO_4 or 1,2,2,6,6-pentamethylpiperidine (PMP), can often be obtained with good enantioselectivity by using a single enantiomer of BINAP (Scheme 16). The reason for this behavior is not known.[15]

The enantioselective synthesis of physostigmine was accomplished with the methodology outlined above. As observed by Shibasaki and co-workers in their eptazocine synthesis, the *Z* olefin provided better results than the corresponding *E* isomer (Scheme 17).[16, 17]



Scheme 16. Enantioselective route to 2-oxoindolines. DMA = *N*,*N*-dimethylacetamide, PMP = 1,2,2,6,6-pentamethylpiperidine. If PMP is used instead of $AgNO_3$, the *S* enantiomer is formed (74–99%, 63–81% *ee*).

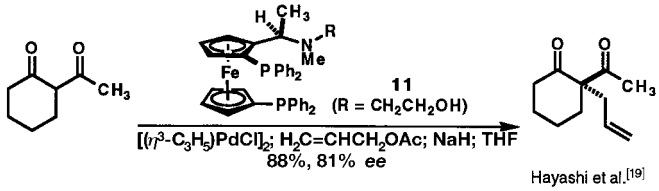


Scheme 17. Enantioselective route to (−)-physostigmine.

2.5. Palladium-Catalyzed Allylation Reactions[18]

2.5.1. Allylation Reactions That Differentiate between Enantiotopic Faces

The palladium-catalyzed allylation of active methine compounds employing a chiral ferrocene diphosphane ligand (**11**, R = CH_2CH_2OH) was reported by Hayashi and co-workers. For example, the sodium enolate of 2-acetylcyclohexanone undergoes a face-selective reaction with a chiral η^3-allylpalladium species generated in situ from allyl acetate and a catalytic Pd^0 complex with this ligand (Scheme 18). The high



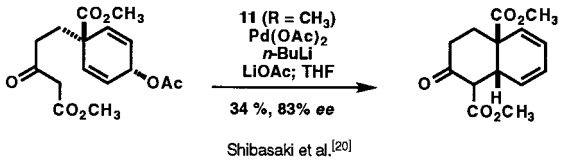
Scheme 18. Enantioselective alkylation of a 1,3-diketone.

enantioselectivity obtained with this ligand is ascribed to secondary attractive interactions between the terminal hydroxyl group of the ligand and the approaching prochiral enolate of the diketone.[20]

2.5.2. Allylation Reactions That Differentiate between Enantiotopic Groups

An intramolecular palladium-catalyzed allylation reaction was used by Shibasaki and co-workers to accomplish the differentiation of enantiotopic olefinic bonds in a molecule with a prochiral quaternary center. This strategy is reminiscent of the one discussed in the context of the Heck reaction (Section 2.4) and results in the enantioselective establishment of a quaternary stereocenter. The best results are obtained

with the indicated *trans* diastereomer of the substrate instead of the *cis* diastereomer, and with **11** (R = CH_3) as the ligand (Scheme 19).[20]



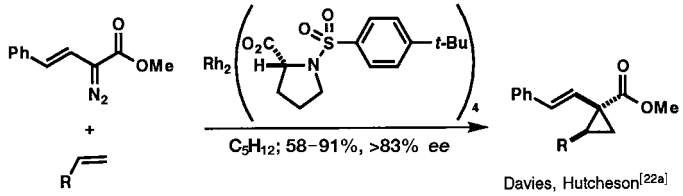
Scheme 19. Enantioselective intramolecular alkylation.

2.6. Rhodium-Catalyzed Cyclopropanation Reactions

The reaction of olefins with α-diazocarbonyl compounds in the presence of chiral rhodium or copper catalysts offers significant potential as a general method for the asymmetric synthesis of cyclopropanes. Rhodium(II) catalysts have been especially useful for the synthesis of optically active cyclopropanes containing quaternary stereocenters.[21]

2.6.1. Intermolecular Cyclopropanation Reactions

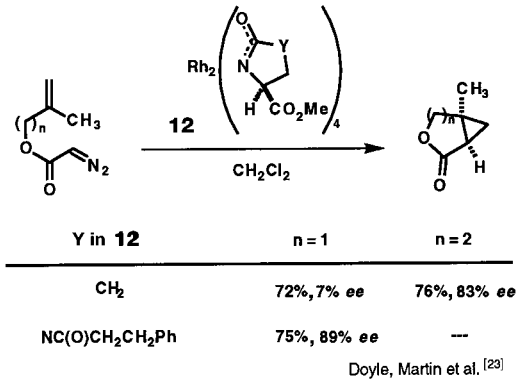
The intermolecular rhodium-catalyzed asymmetric cyclopropanations often result in products of good enantioselectivity but low *diastereoselectivity*. A noteworthy example of a rhodium-catalyzed intermolecular cyclopropanation that proceeds with both high diastereo- and enantiocontrol utilizes methyl (*E*)-2-diazo-4-phenylbut-3-enoate as shown in Scheme 20. The presence of a vinyl substituent on the diazo compound is essential for obtaining good selectivities in this reaction.[22]



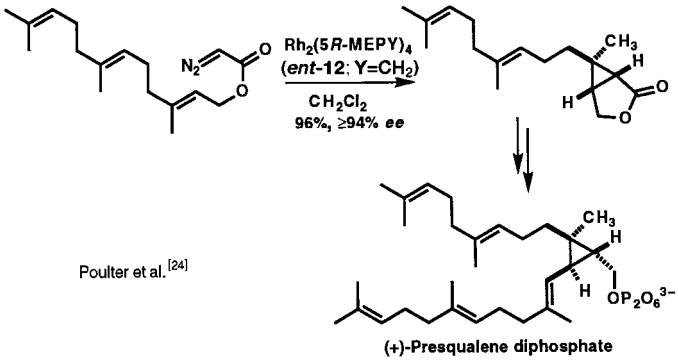
Scheme 20. Catalytic enantioselective intermolecular [2+1] cycloaddition.

2.6.2. Intramolecular Cyclopropanation Reactions

Unlike intermolecular cyclopropanations, the intramolecular reactions can only produce one diastereomer due to geometric constraints of the fused bicyclic product, and accordingly have seen substantially more use in synthesis. The enantioselective intramolecular reaction of a variety of alkenyl diazoacetates catalyzed by chiral rhodium carboxamides [Rh_2(5*S*-MEPY)$_4$] (**12**, Y = CH_2) and [Rh_2(4*S*-MPPIM)$_4$] (**12**, Y = NC(O)CH_2CH_2Ph) was studied by Doyle, Martin, and co-workers. Optically active bicyclic lactones containing quaternary stereocenters are obtained when 1,1-disubstituted and trisubstituted olefins are used in the reaction (Scheme 21).[23] This methodology was applied by Poulter and co-workers to the efficient asymmetric synthesis of presqualene diphosphate (Scheme 22).[24]



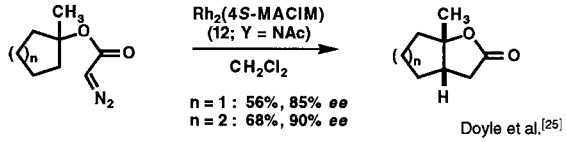
Scheme 21. Catalytic enantioselective intramolecular [2+1] cycloaddition.



Scheme 22. Enantioselective synthesis of (+)-presqualene diphosphate.

2.7. Rhodium-Catalyzed C–H Insertion Reactions

In addition to cyclopropanation reactions, rhodium(II) catalyzes the selective intramolecular insertion of diazoacetates into C–H bonds. The enantioselective version of this reaction[21a] allows for the differentiation of enantiotopic aliphatic C–H bonds of molecules with prochiral quaternary stereocenters. The resulting bicyclic lactones are obtained in high optical purity (Scheme 23).[25]



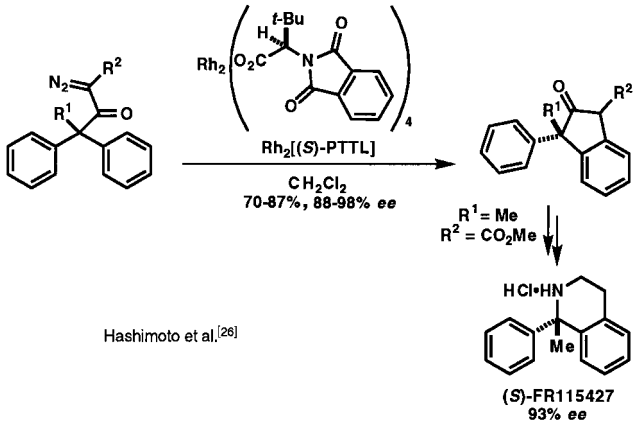
Scheme 23. Enantioselective cyclization by intramolecular C–H insertion.

In addition, an asymmetric rhodium-catalyzed aromatic C–H bond insertion has also been demonstrated and applied to the total synthesis of FR115427 (Scheme 24).[26]

3. Catalytic Methods Applicable to the Synthesis of Heteroatom-Substituted Quaternary Carbon Stereocenters

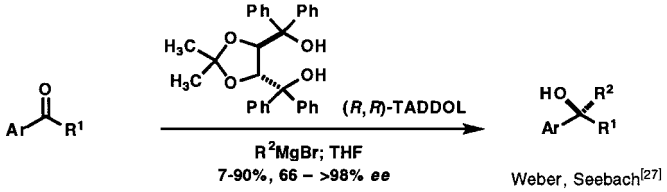
3.1. Addition of Carbon Nucleophiles to Ketones

A conceptually straightforward approach to the preparation of enantiopure tertiary alcohols is the addition of



Scheme 24. Enantioselective synthesis of (*S*)-FR115427.

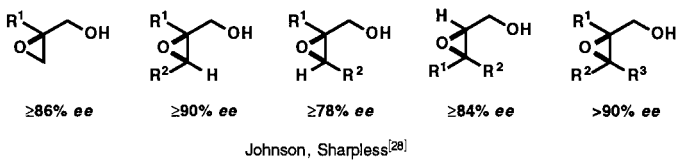
organometallic reagents to prochiral ketones in the presence of a chiral catalyst. This approach, which simultaneously forms a stereocenter and a C–C bond, has been realized for the synthesis of secondary alcohols from aldehydes. Recently, Seebach and Weber developed an effective asymmetric addition of alkyl Grignard reagents to ketones with stoichiometric amounts of (*R*,*R*)-TADDOL as shown in Scheme 25. The best results are obtained with alkyl aryl ketones. The chiral ligand was also used in substoichiometric amounts but this resulted in somewhat lower enantioselectivity.[27]



Scheme 25. Enantioselective carbonyl alklylation.

3.2. Katsuki–Sharpless Asymmetric Epoxidation Reactions (KSAE)

The KSAE of allylic alcohols is, to date, one of the most predictable and widely used catalytic asymmetric reactions. The reaction (employing diethyl or diisopropyl tartrate, *tert*-butylhydroperoxide, titanium(IV) isopropoxide, and molecular sieves in CH_2Cl_2 or toluene) provides 2,3-epoxy alcohols containing quaternary centers as shown in Scheme 26 in

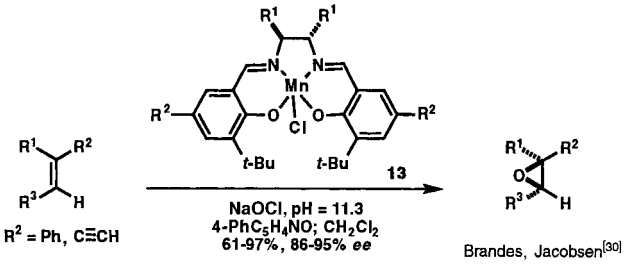


Scheme 26. Chiral 2,3-epoxy alcohols from Katsuki–Sharpless oxidation.

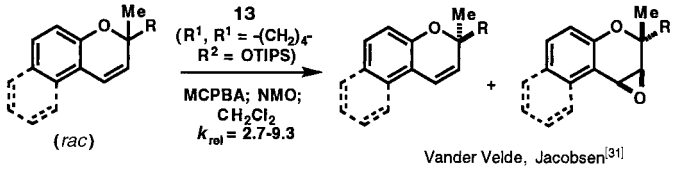
excellent enantioselectivity when 2-substituted, disubstituted, and trisubstituted allylic alcohols are used. The KSAE has been applied in numerous occasions to the synthesis of molecules containing quaternary stereocenters, and the topic has been extensively reviewed; consequently, it will not be discussed here.[28]

3.3. Jacobsen Epoxidation Reactions

The Jacobsen epoxidation of conjugated *cis*-disubstituted and trisubstituted olefins catalyzed by manganese–salen complexes (**13**) is highly enantioselective (Scheme 27).[29] Epoxides with quaternary stereocenters are obtained from the latter olefin class.[30] Furthermore, the kinetic resolution of racemic chromenes with the Jacobsen epoxidation exhibits promising relative rate (k_{rel}) values (Scheme 28).[31]



Scheme 27. Jacobsen enantioselective epoxidation.

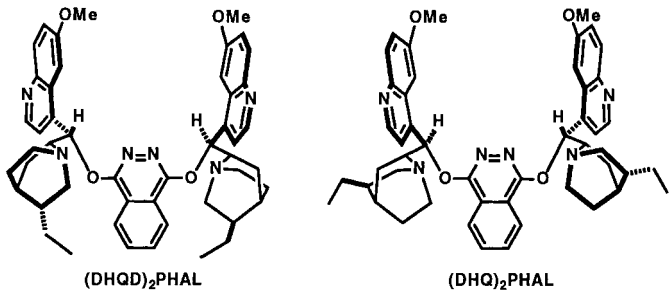


Scheme 28. Kinetic resolution by Jacobsen epoxidation. MCPBA = *m*-chloroperbenzoic acid, NMO = *N*-methylmorpholin-*N*-oxide.

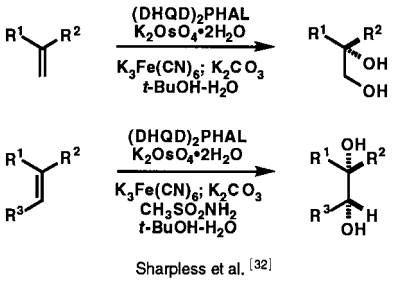
3.4. Sharpless Asymmetric Dihydroxylation Reactions

The cinchona alkaloid catalyzed asymmetric dihydroxylation (AD) has emerged as one of the most general methods for the enantioselective functionalization of olefins. The most common catalysts for the reaction are bis(cinchona) alkaloids such as the quinidine derivative $(DHQD)_2PHAL$ and its pseudo-enantiomer, the quinine derivative $(DHQ)_2PHAL$ (Scheme 29). Products containing quaternary stereocenters are typically obtained in high enantioselectivity by AD of 1,1-disubstituted and trisubstituted olefins (Scheme 30). A variety of groups can be tolerated on or near the olefinic carbons, such as ketone, ester, amide, halogen, sulfide, ether, carbamate, and silane functionalities. Furthermore, enynes and polyenes have been oxidized regio- and enantioselectively.[32] Although the AD of tetrasubstituted olefins is challenging, promising results have been reported (Scheme 31).[33]

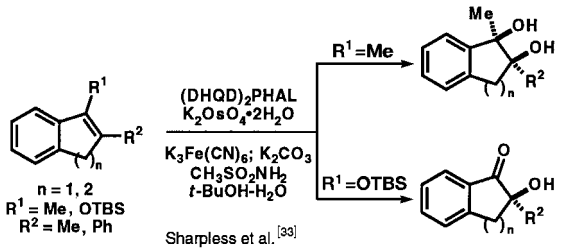
Applications to the synthesis of complex molecules have begun to emerge. A regioselective asymmetric dihydroxyla-



Scheme 29. Ligands for the Sharpless asymmetric dihydroxylation reaction.



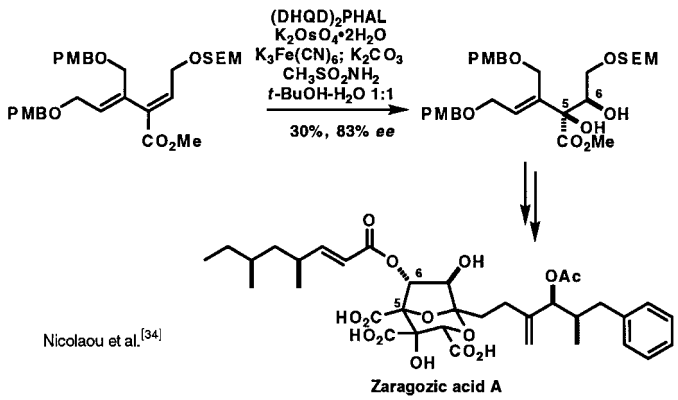
Scheme 30. Sharpless asymmetric dihydroxylation.



Scheme 31. Asymmetric dihydroxylation of tetrasubstituted olefins.

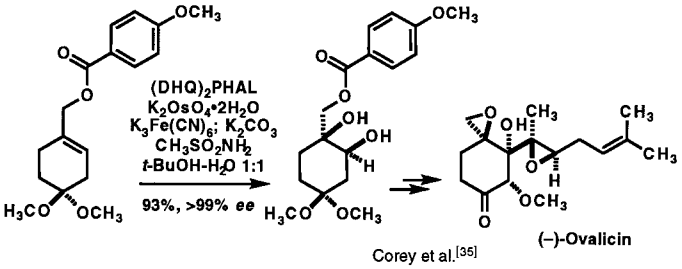
tion introduced the absolute stereochemistry in Nicolaou's synthesis of zaragozic acid A (Scheme 32).[34]

The key step in the synthesis of ovalicin is a novel application of the Sharpless asymmetric dihydroxylation in which a 4-methoxybenzoyl group is attached to the allylic alcohol substrate to produce a dramatic enhancement in enantioselectivity from 18% *ee* to greater than 99% *ee*



Scheme 32. Asymmetric dihydroxylation route to zaragozic acid A. In the asymmetric dihydroxylation, 44% of the starting material is recovered. PMB = *p*-methoxybenzyl, SEM = 2-(trimethylsilyl)ethoxymethyl.

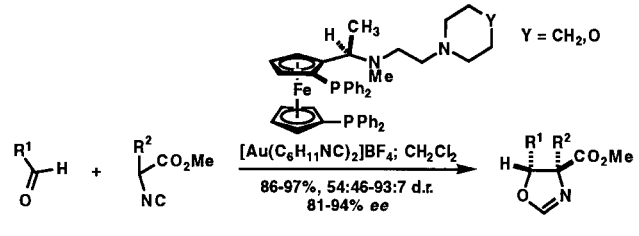
(Scheme 33).[35] The development of this novel application was guided by a mechanistic model recently proposed for AD, which predicted the specific binding of the 4-methoxybenzoyl unit of the substrate to the U-shaped binding pocket of the cinchona alkaloid/OsO_4 catalyst.[36] The reaction was extended to the highly selective dihydroxylation of a variety of allylic 4-methoxybenzoates, homoallylic 4-methoxyphenyl ethers, and other related compounds.[37, 38]



Scheme 33. Enantioselective synthesis of (−)-ovalicin.

3.5. Gold-Catalyzed Aldol Reactions

Aldol-type reactions form one of the most important classes of C–C bond forming transformations due to their ability to generate highly functionalized compounds. A noteworthy example of the catalytic enantioselective aldol processes that are currently becoming available to the synthetic chemist is the gold(I)-catalyzed reaction between α-isocyanocarboxylates and aldehydes.[39] In particular, methyl 2-alkylisocyanoacetates undergo this reaction in the presence of a gold(I) complex with chiral bis(phosphino)ferrocene ligands to afford the corresponding optically active 4-methoxycarbonyldihydrooxazoles (Scheme 34). These useful heterocycles can be hydrolyzed to enantiomerically enriched α-alkylserines and α-alkylthreonines.[40]



Scheme 34. Ito–Hayashi enantioselective route to dihydrooxazoles.

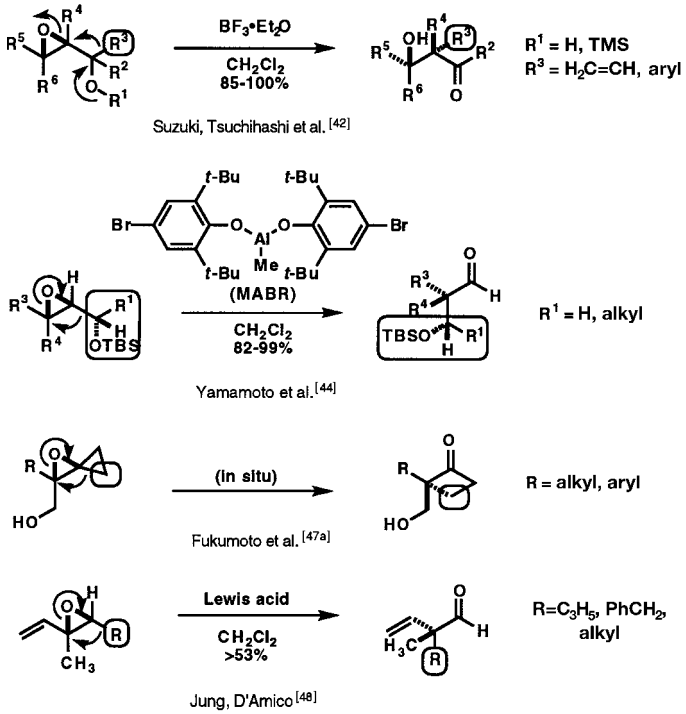
4. Methods Applicable to the Indirect Synthesis of Quaternary Carbon Stereocenters by a Catalytic Asymmetric Reaction Followed by Chirality Transfer

Intramolecular chirality-transfer reactions (also called self-immolative reactions), in which a chiral center is sacrificed as another is enantiospecifically created, are important for the construction of molecules containing quaternary stereocenters. Often in these approaches, a *catalytic enantioselective*

reaction is used to establish an initial chiral center. Subsequently, an *enantiospecific* intramolecular reaction, typically a rearrangement, destroys the original center and transfers the chirality to a newly created quaternary carbon atom. Commonly, a heteroatom-substituted stereocenter is destroyed at the expense of a less readily established all-carbon-substituted quaternary center.

4.1. Asymmetric Epoxidation—1,2-Rearrangement Strategies[41]

As discussed in Section 3.2, the KSAE of allylic alcohols is a general and predictable reaction that makes optically active 2,3-epoxy alcohols readily available. Consequently, the enantiospecific 1,2-rearrangement of these epoxides and their derivatives has been thoroughly studied and can be subdivided into four groups: the Suzuki–Tsuchihashi, Yamamoto, Fukumoto, and Jung variants (Scheme 35). The last three rearrangements are all mechanistically very similar but differ in the epoxide substituents, migrating group, and Lewis acid used.



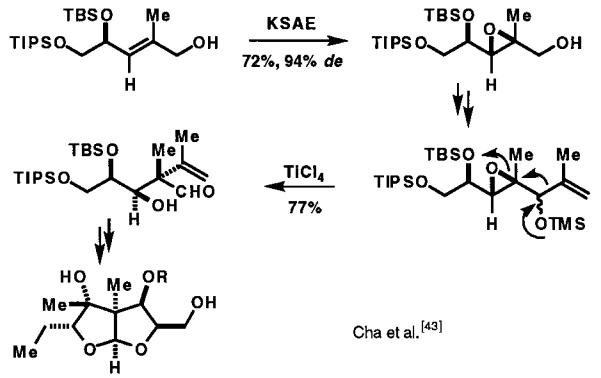
Scheme 35. Cationic rearrangements of chiral oxiranes.

4.1.1. Suzuki–Tsuchihashi Epoxide Rearrangements

The Suzuki–Tsuchihashi rearrangement is mechanistically similar to the pinacol rearrangement and results in the 1,2-migration of a vinyl or aryl group.[42] It was applied together with a KSAE to the synthesis of the bis(tetrahydrofuran) core of asteltoxin (Scheme 36).[43]

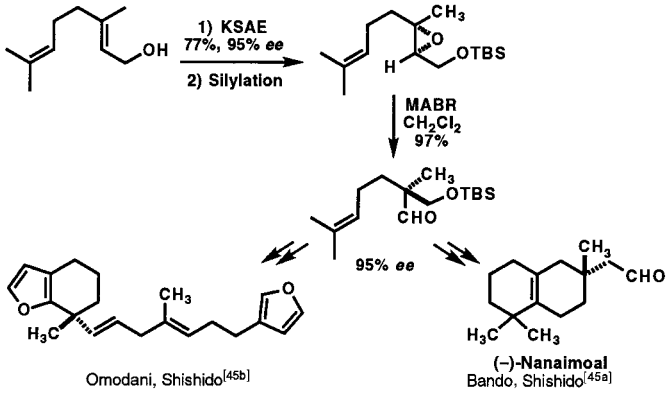
4.1.2. Yamamoto Epoxide Rearrangements

The Yamamoto rearrangement involves the 1,2-migration of a 1-(*tert*-butyldimethylsilyloxy)alkyl group, typically a 1-



Scheme 36. Enantioselective synthesis of a (+)-asteltoxin subunit.

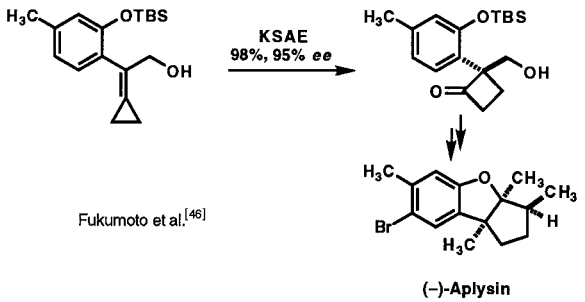
(*tert*-butyldimethylsilyloxy)methyl group.[44] A KSAE, followed by silylation and Yamamoto rearrangement, was utilized for the synthesis of nanaimoal and of the enantiomer of a naturally occurring marine furanoterpene (Scheme 37).[45]



Scheme 37. Synthesis of (−)-nanaimoal and the enantiomer of a natural marine furanterpene.

4.1.3. Fukumoto Epoxide Rearrangement

The Fukumoto variant is notable in that a stereospecific rearrangement occurs spontaneously during the KSAE of a 2-substituted 2-cyclopropylidenethanol. The natural product aplysin was synthesized in this manner (Scheme 38).[46, 47]

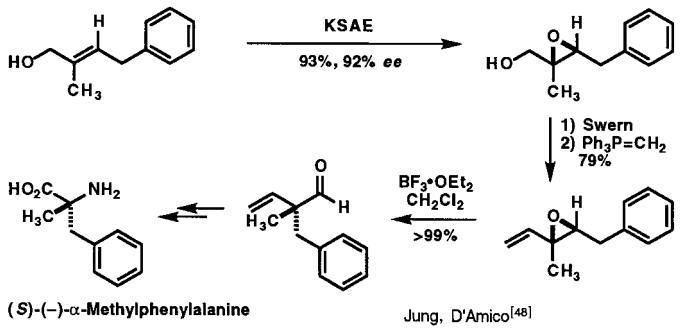


Scheme 38. Synthesis of (−)-aplysin.

4.1.4. Jung Epoxide Rearrangement

The Jung rearrangement of optically active vinyl epoxides is relatively flexible with respect to the migrating group. It was

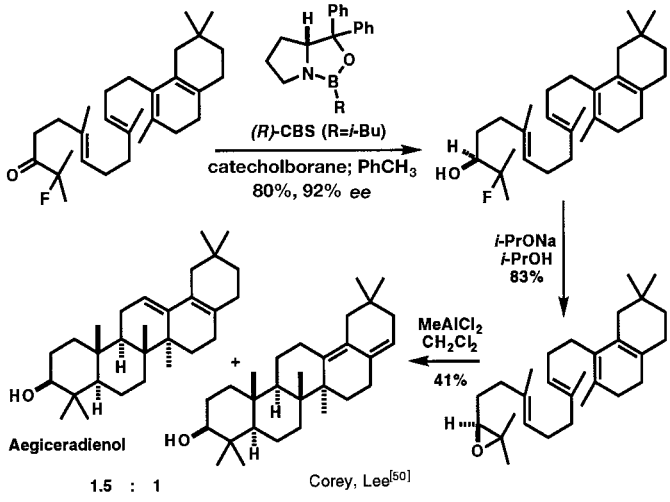
applied to the synthesis of (*S*)-(−)-α-methylphenylalanine as shown in Scheme 39.[48]



Scheme 39. Synthesis of (*S*)-(−)-α-methylphenylalanine by Jung rearrangement.

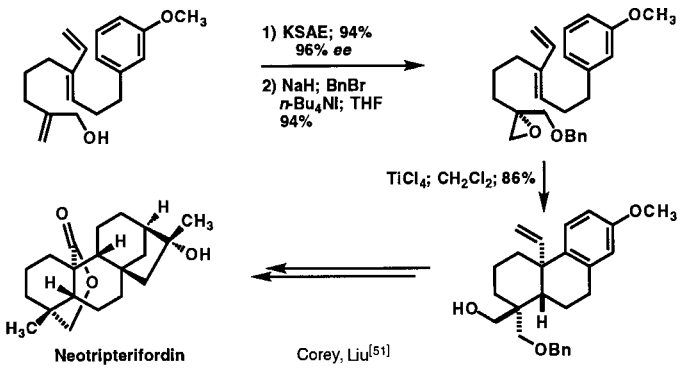
4.2. Chirality Transfer by Cationic Cyclization Reactions

The Lewis acid promoted olefin-cation cyclization[41] of optically active epoxides has been applied to the enantiospecific synthesis of molecules with quaternary stereocenters. For instance, the synthesis of β-amyrin, erythrodiol, and oleanolic acid was accomplished through the common intermediate aegiceradienol, itself a natural product, as shown in Scheme 40. Aegiceradienol was prepared stereospecifically by oxazaborolidine-catalyzed (CBS) reduction[49] of the indicated α-fluoroketone to provide the corresponding fluorohydrin in high enantiomeric purity, followed by ring-closure to the epoxide and enantiospecific olefin-cation cyclization. The latter reaction results in the formation of three new quaternary stereocenters, two new tertiary stereocenters, and three new rings in a single synthetic operation.[50]



Scheme 40. Enantioselective route to pentacyclic triterpenes.

Recently, the synthesis of neotripterifordin was accomplished by a Katsuki–Sharpless asymmetric epoxidation followed by a stereospecific olefin-cation double cyclization, which provided exclusively the indicated intermediate with three stereocenters in high yield (Scheme 41).[51, 52]

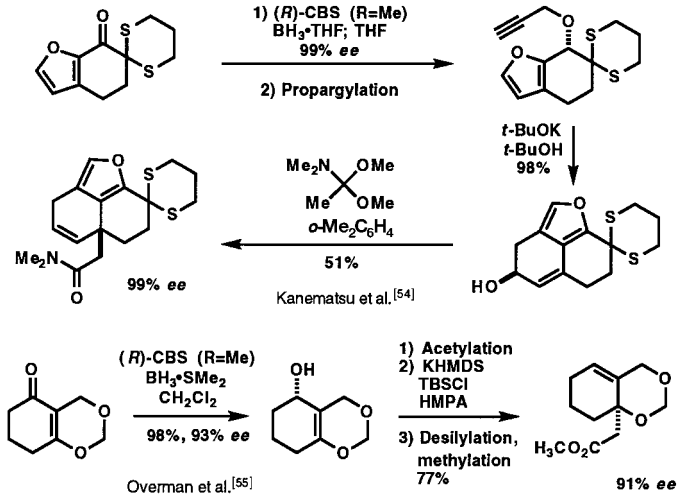


Scheme 41. Enantioselective synthesis of neotripterifordin.

4.3. Strategies Based on the Claisen Rearrangement[53]

4.3.1. Chirality Transfer by Claisen Rearrangements

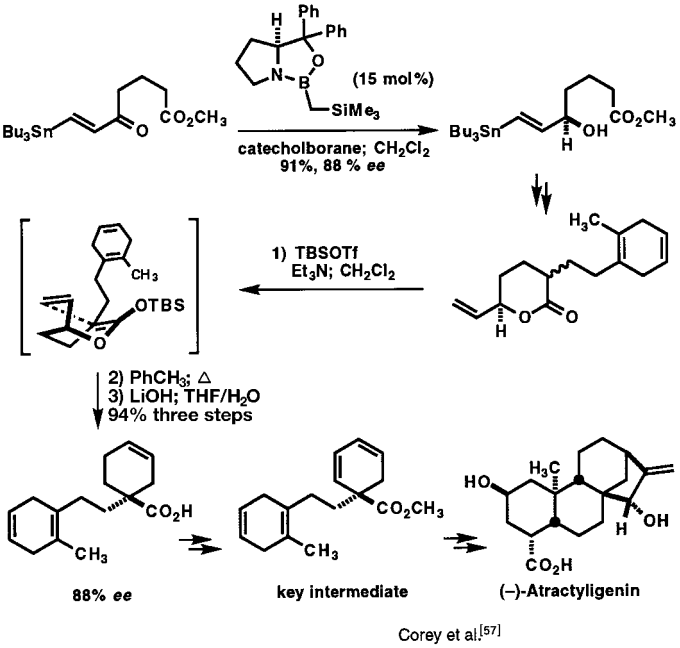
The Claisen rearrangement has been a mainstay of organic synthesis due to its wide applicability and high stereospecificity. Additionally, it is an excellent method for the transfer of chirality from an optically active secondary alcohol to a quaternary carbon center. This approach is especially useful, because several types of allylic alcohols are available by catalytic enantioselective reactions. For example, the preparation of a useful key intermediate for the synthesis of naturally occurring fused furans was accomplished by a sequence involving a highly enantioselective CBS reduction, a furan ring transfer reaction, and an enantiospecific Claisen rearrangement (Scheme 42).[54]



Scheme 42. Introduction of angular substituents by enantioselective CBS reduction followed by Claisen rearrangement. KHMDS = potassium bis(trimethylsilyl)amide.

Likewise, the basic skeleton of the cardenolides was stereospecifically synthesized by Overman and co-workers through the CBS reduction of a tetrasubstituted enone, followed by an Ireland–Claisen rearrangement of the resulting allylic alcohol (Scheme 42). The rearrangement proceeds with high stereochemical fidelity as evidenced by the high enantiomeric excess of the product.[55]

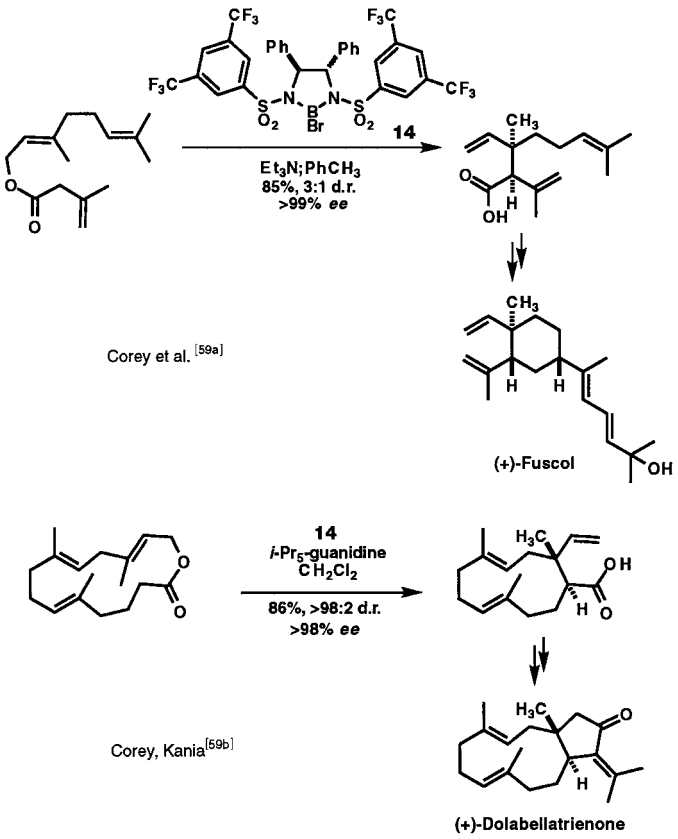
Furthermore, the challenging quaternary carbon center of a key intermediate for the synthesis of atractyligenin was established by the CBS reduction of a β-tri-*n*-butylstannyl enone followed by chirality transfer from the resulting secondary alcohol to the desired quaternary site by an Ireland–Claisen rearrangement (Scheme 43). The high enantioselectivity obtained in the CBS reduction is a result of remote steric interactions[56] between the β-tri-*n*-butylstannyl substituent of the enone and the trimethylsilylmethyl group on the boron atom of the catalyst, which strongly disfavor the minor diastereomeric reduction pathway.[57]



Scheme 43. Enantioselective synthetic route to (−)-atractyligenin.

4.3.2. *Claisen Rearrangements with Chiral Reagents*

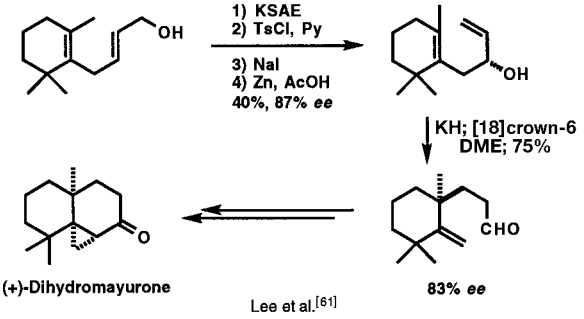
The Ireland–Claisen rearrangement of several allylic esters with chiral diazaborolidine reagent **14** results in substituted 4-alkenoic acids of high enantiomeric and diastereomeric purity.[58] This process has been utilized successfully to install the quaternary stereocenters in fuscol and dolabellatrienone (Scheme 44). Although these transformations require stoichiometric amounts of the chiral boron compound, the reagent is readily available and recyclable, and it provides outstanding results.[59]



Scheme 44. Asymmetric synthesis of cyclic diterpenoids by enantioselective Claisen rearrangement.

4.4. Strategies Based on Anionic Oxy-Cope Rearrangements

The anionic oxy-Cope rearrangement[60] is an alternative method for the transfer of chirality from a secondary alcohol to a quaternary stereocenter. For example, in a synthesis of dihydromayurone the stereochemistry of a secondary allylic alcohol is installed by KSAE. Subsequently, this alcohol undergoes anionic oxy-Cope rearrangement to generate a quaternary stereocenter through a putative chairlike transition state with approximately 95% stereochemical fidelity (Scheme 45).[61]



Scheme 45. Enantioselective synthesis of (+)-dihydromayurone by oxy-Cope rearrangement.

5. Summary and Outlook

The progress in the catalytic asymmetric synthesis of molecules containing quaternary carbon stereocenters, both by direct and indirect methods, has been astounding. Despite these impressive recent advances, many unsolved problems remain. These include limitations with regard to scope and frequent practical problems associated with catalyst preparation and use, especially on large scale. Nonetheless, continued exploratory research on catalytic enantioselective method-

ology and the underlying basis for enantioselectivity can be expected to provide new and powerful methods for the construction of a wide range of complex molecules.

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