Cyclohexyl-Based Chiral Auxiliaries

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Received November 27, 1991 (Revised Manuscript Received January 30, 1992)

Contents

I. Background

The field of asymmetric induction has undergone radical changes since the early 1970s when large numbers of research groups became interested in uncovering new and practical techniques for the control of absolute stereochemistry. Most reviews of asymmetric induction processes are constructed around the theme of one particular transformation (e.g., the Diels–Alder reaction), detailing the efficacy of various chiral auxiliaries and how the details of the transformation are altered by the added feature of control of absolute stereochemistry. An alternate approach is to compile information on a number of fundamentally different reactions as mediated by chiral auxiliaries with common features. For example, we have recently published a review of chiral auxiliaries with a C2 (or pseudo-C2) symmetry element. This organization serves to provide a summary of information relative to auxiliary design and calls attention to those design features that provide for consistently high levels of absolute stereochemical control throughout a broad range of reaction types.

This review has as its central theme chiral auxiliaries based upon the cyclohexane frame where the chirality of the auxiliary and thus its directing influence reside within this carbocycle. A large number of reaction types have been examined using chiral auxiliaries of this type, although those that have been explored with the readily available menthol (**1**, Figure 1) rarely provide what would be considered practical levels of control. On the other hand, auxiliaries that bear phenyl substituents such as Corey's 8-phenylmenthol (**2**) and our *trans*-2-phenylcyclohexanol (**3**) have provided levels of control that exceed 1000:1 and routinely afford >90% de. This review will concentrate on successful asymmetric induction reactions using **2** and **3** and similarly constituted chiral auxiliaries, providing the background perspective for the use of such auxiliaries in different reactions and for the design of new auxiliaries.

James K. Whitesell received his B.S. degree from The Pennsylvania State University in 1966 and the Ph.D. degree from Harvard University in 1971 under the direction of R. B. Woodward. After a 2-year postdoctoral stay at the Woodward Research Institute in Basel, Switzerland, he bagan his independent research at the University of Texas at Austin, where he currently holds the position of Professor of Chemistry. He conducts research on methods for the analysis and control of stereochemistry within complex molecular arrays and has made major contributions in the area of absolute stereochemical control through asymmetric induction. Recently, he has turned his attention to extending methods for the control of arrangements within molecules to fixing the relative orientations between molecules. Results in this latter area will have wide-ranging applications in material science.

II. Introduction

To be viewed as a true auxiliary for the control of absolute stereochemistry the stereodirector must be readily recoverable in reusable form. This requires for processes involving auxiliaries in stoichiometric quantities that the covalent connection to the substrate be a "hard" or a "soft" carbon–heteroatom bond. Chirality can be introduced either near or further from this heteroatom linkage, and since the directing influence of the auxiliaries might be presumed to be similar for different reactions at a specific distance from the auxiliary, we have divided this review into sections by the position at which chirality is introduced (α, β, etc.). Those processes that control chirality at two (or more centers) such as the Diels–Alder reaction are categorized by the center that is closest to the auxiliary (Figure 2). Only oxygen appears to have been employed to this point, although clearly other heteroatoms, such as nitrogen, could also be used.

In so far as possible, we have reported levels of control as de (diastereomeric excess) values when the ratio of diastereomeric products (with the auxiliary still attached) was determined, as ee (enantiomeric excess) when the ratio of enantiomers of the product freed of the auxiliary was determined by direct observation (e.g., by NMR with a chiral shift reagent), and as op (optically

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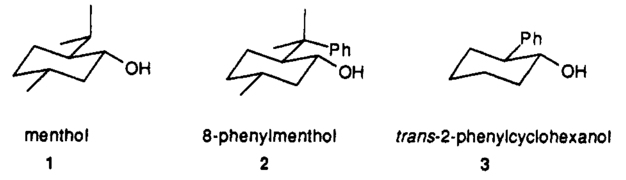


Figure 1.

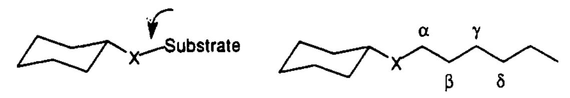


Figure 2.

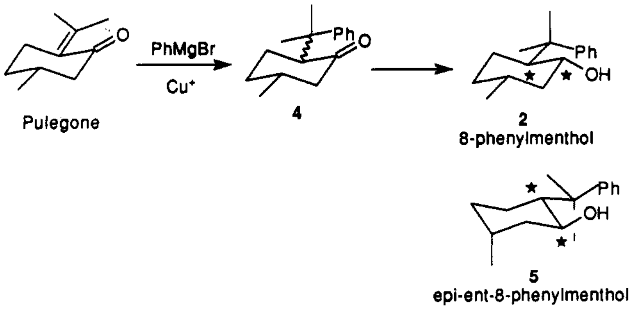


Figure 3.

pure) when optical rotation data was compared with values presumed to represent homogeneous samples. Absolute stereochemistry is shown for newly formed chiral centers only when it has been determined unambiguously.

III. Synthesis of Auxiliaries

Practical applications of asymmetric induction require that the auxiliaries not only be reusable but that they can also be readily obtained in the first place. All three of the auxiliaries menthol, 8-phenylmenthol, and *trans*-2-phenylcyclohexanol are reasonably stable and can be prepared in few steps from commercial materials. Menthol of high enantiomeric purity is available in both (+) and (–) forms from several suppliers (e.g.; Aldrich, (–)-menthol $22/100 g; (+)-menthol $67/50 g). The synthesis of (1*R*)-(+)-8-phenylmenthol, outlined in Figure 3 starts with (*R*)-(–)-pulegone which can be obtained inexpensively from Givadone. Conjugate addition provides a diastereomeric mixture of ketones (**4**) that undergoes relatively rapid equilibration under the dissolving metal reduction conditions that provide almost exclusively the trans relationship between the two chiral centers (*) that are generated in the sequence.[1] Unfortunately, control of the absolute stereochemistry of both of these centers is directed by the methyl-bearing stereocenter originating from pullegone and at practical temperatures for the reduction, an approximately 85:15 mixture is formed of 8-phenylmenthol (**2**) and the diastereomer that we have named *epi*-*ent*-8-phenylmenthol (**5**).[2] Since **5** is of opposite configuration at the carbinol carbon as well as the adjacent center (the "working end" of the auxiliary), it might be anticipated that this diastereomer would control with approximately the same level but opposite sense as **2**. This has been shown to be the case[1] and thus it is essential that complete separation of *epi*-*ent*-8-phenylmenthol from 8-phenylmenthol be effected. This separation is nontrivial as both **2** and **5** are liquids, but it can be accomplished chromatographically or by recrystallization of the derived α-chloroacetate esters.[3,4] Purification has also been achieved by recrystallization of the *N*-phenylcarbamates and subsequent hydrolysis under relatively vigorous conditions (10 equiv of NaOEt in EtOH, reflux, 28 h).[5]

Figure 4.

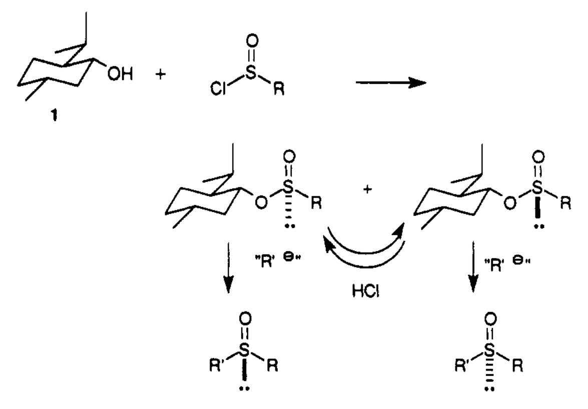
The enantiomer of **2**, (1*S*)-8-phenylmenthol can be obtained from (*S*)-(+)-pulegone which is, however, not readily available. A synthesis of (*S*)-(+)-pulegone was originally described by Corey in the original publication describing 8-phenylmenthol and latter improvements in this sequence have been made by others.

The synthesis of *trans*-2-phenylcyclohexanol as a racemic mixture is accomplished by copper-catalyzed opening of cyclohexene oxide by phenyl Grignard reagent.[6] Resolution into individual enantiomers is readily achieved by enantioselective, enzymatic hydrolysis of the acetate esters. The originally described procedure using pig liver acetone powder (PLAP)[7,8] can still be highly recommended as it can be effected on a large scale and this crude enzyme mixture is not as pH sensitive as purified enzymes that have also been used successfully.[7,9] PLAP has also been shown to be effective for the resolution of 2-(aryloxy)cyclohexanols, with levels of control in the selective hydrolysis between 90 and 99%.[10] A bacterial lipase from a *Pseudomonas* strain has been shown to be effective in resolving the enantiomers of a number of trans-2-substituted cyclohexanols[11] and an empirically derived rule has been developed to predict which enantiomer will be hydrolyzed faster.[12] The enantiomers of *trans*-2-phenylcyclohexanol have also been resolved chromatographically as para-substituted benzoate esters on a cellulose triacetate column (α for the *p*-nitrobenzoate; 3.12).[13] Hydroboration of 1-phenylcyclohexene with monoisopinocampheylborane provides an alternate route to a single enantiomer of *trans*-2-phenylcyclohexanol.[14]

Auxiliaries that are structurally related to 8-phenylmenthol and *trans*-2-phenylcyclohexanol can be prepared by substitution of other nucleophilic species in the conjugation–addition step to form the former or the ring-opening reaction of cyclohexene oxide in the synthesis of the latter. For the preparation of other 8-substituted menthols, however, the substituent must be stable to electron-transfer reduction conditions as this is the only practical technique yet available for the formation the trans stereochemistry. For example, the synthesis of the biphenyl analogue is hampered by substantial reduction of the "internal" aromatic ring.[15,16] By contrast, the synthesis of a variety of racemic 2-substituted cyclohexanols (including desmethyl-8-phenylmenthol) is straightforward.

IV. α Stereocenter

At first inspection it might appear that controlling stereochemistry at the position α to the heteroatom linker would be pointless as removal of the substrate would invariable entail destruction of the newly formed stereocenter (Figure 4). This is the case with carbon as the stereocenter but both sulfur and phosphorus ster-



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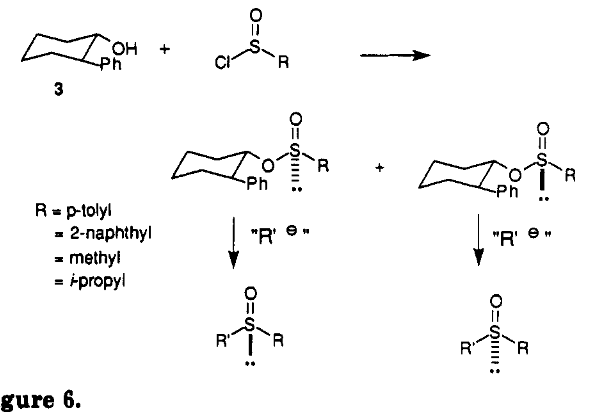


Figure 6.

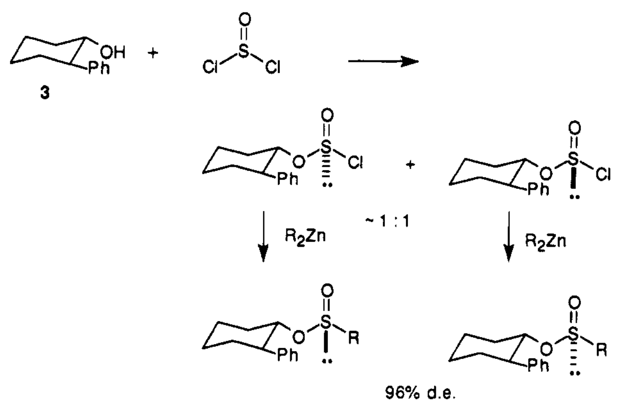
eochemistry have been controlled at this position and the substrate then released from the auxiliary. For example, the classical approach for the synthesis of resolved sulfoxides proceeds through addition of Grignard reagents to sulfinate esters of menthol (Figure 5). In this sequence, menthol serves more as a resolving agent than an inducer of asymmetry, providing separation of the two, diastereomeric sulfinate ester intermediates by crystallization.[17-19] However, in the case where R = *p*-tolyl, one diastereomer can be obtained through HCl-induced epimerization and crystallization.[20]

trans-2-Phenylcyclohexanol has been used in this scheme (Figure 6), providing for enhanced crystallinity of the intermediates and sufficient levels of resolution such that chromatographic separation is also an option.[21]

In more recent studies, however, it has been shown that reaction of alkyl organozinc reagents with an approximately 1:1 mixture of diastereomeric chloro sulfinate esters derived from *trans*-2-phenylcyclohexanol proceeds with both high conversion (and yield) as well as excellent absolute stereochemical control (Figure 7). Presumably, the intermediate chloro sulfinate esters are in rapid equilibrium relative to selective reaction of one with the nucleophile.[22]

Stereochemistry at phosphorus has also been controlled in an analogous fashion using menthol as a resolving agent for the separation of diastereomers (Figure 8).[23]

There are a number of sequences that control stereochemistry at the α position and then make use of this stereocenter for the control of a second reaction process. For example, lactone acetal diastereomers have been shown to equilibrate under recrystallization conditions, leading to high conversion to a single stereoisomer.



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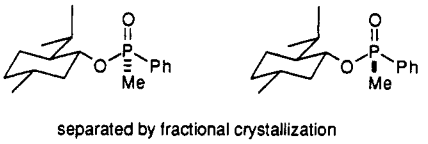

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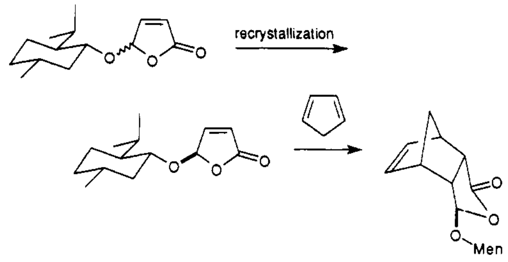

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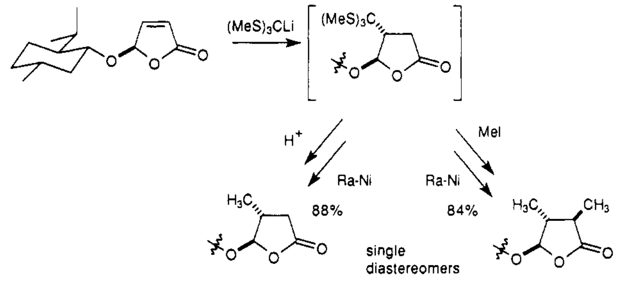
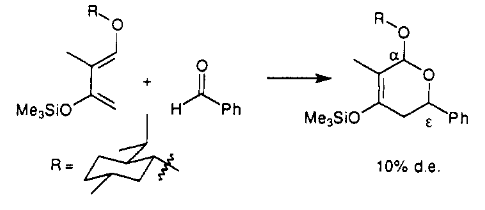


Figure 10.

Subsequent reaction of the unsaturated lactone as a dienophile in a Diels–Alder reactions affords greater than 96% de in the adduct (Figure 9).[24]

The stereochemistry set in the lactone above has also been used to control conjugate addition of nucleophiles (Figure 10).[25] High levels of stereocontrol have also been observed in the addition of both thiols[26] and amines[27] to a single diastereomeric lactone acetal formed from menthol. In all of these reactions, control of stereochemistry at the critical center is directed by the acetal carbon and only indirectly by the auxiliary that serves as a means of separating the acetal stereoisomers.

Cyclohexyl-based chiral auxiliaries have also been incorporated into the diene portion of the Diels–Alder reaction. For example, with the auxiliary as a substituent at the 1-position of the diene, chirality is controlled at this carbon as well as two addition centers (Figures 11[28] and 12[29]). In the first of these examples (Figure 11), the auxiliary can be readily released, although control of absolute stereochemistry at the ϵ



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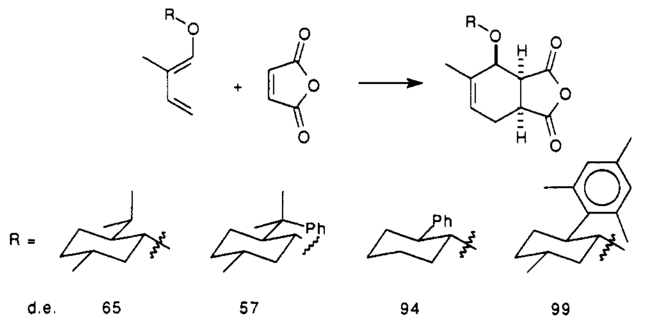

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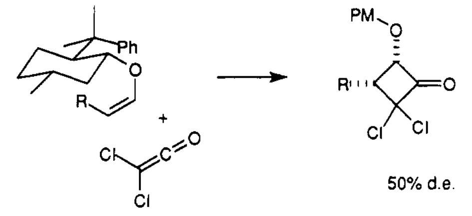

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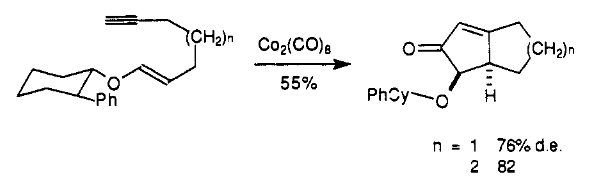


Figure 14.

Figure 15.

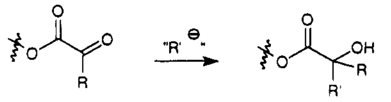
carbon is only minimal, while in the second (Figure 12), control varies from good to excellent, depending on the auxiliary, although release of the auxiliary has not been addressed.

In an alternate cycloaddition, reaction of an enol ether of 8-phenylmenthol and dichloro ketene provides moderate stereocontrol, but again with no ready method for release of the auxiliary (Figure 13).[30,31]

Control of multiple stereocenters has also been achieved in intramolecular Pauson–Khand bicyclizations, as illustrated in Figure 14.[32,33]

V. β Stereocenter

Control of stereochemistry at the β position to the auxiliary represents a more generally practical system than at the α center as release of the substrate need not directly involve the newly formed stereocenter and thus can be accomplished readily without loss of stereochemistry (Figure 15). Indeed, there are far more examples of control at this site than the others combined, possibly because it is also the *closest* site to the auxiliary where release of the substrate from the auxiliary is generally practical with recovery of both.



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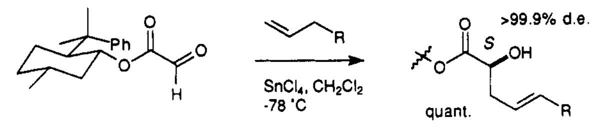

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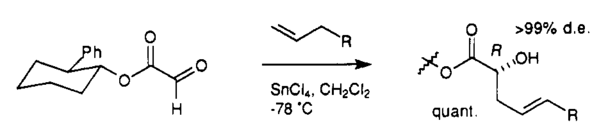

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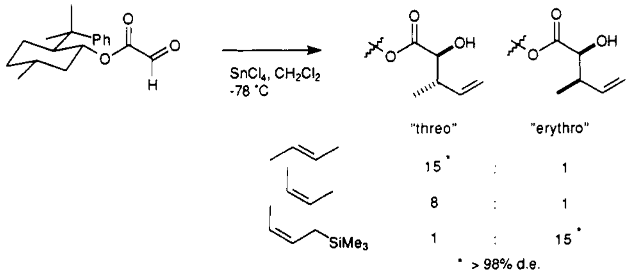


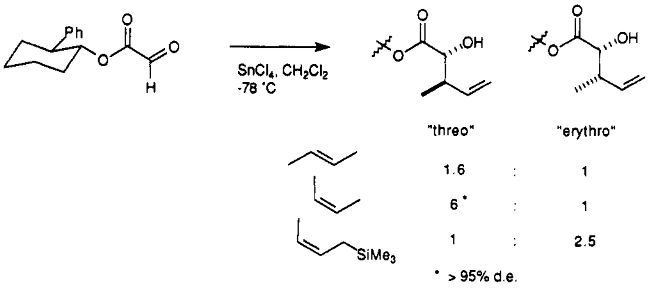
Figure 19.

While a variety of possible linkages between the substrate and the auxiliary are possible, the vast majority of studies have used a carboxylic acid ester. This section is divided into subheadings based on the reactivity character of the β atom as used in the stereocenter generating reaction (A, electrophilic; B, nucleophilic; C, cycloaddition; and D, miscellaneous).

A. Electrophilic Reactions

The highest levels of control that have so far been observed using cyclohexyl-based chiral auxiliaries have resulted from nucleophilic addition reactions to glyoxylate and substituted glyoxylate esters (Figure 16). The majority of these reactions involve either a Grignard reagent or an alkene as a nucleophile, although this classification merges with allylmetal species.

The reactions of the glyoxylate esters of both 8-phenylmenthol (Figure 17) and *trans*-2-phenylcyclohexanol (Figure 18) with terminal, monosubstituted alkenes proceed with exceptional high levels of stereochemical control in the product, homoallylic alcohols.[34,35] Useable levels of control are only obtained in the presence of a strong Lewis acid ($SnCl_4$ or $TiCl_4$) which must be present in equimolar quantities as it appears that complexation of the acid with the product deactivates the acid to the point where it is no longer effective. While these reactions appear similar in that both auxiliaries afford high levels of chemical and stereochemical yields, they provide opposite absolute directions of control. Unfortunately, no viable explanation for this dichotomy is yet available. Reaction of the glyoxylates with 1,2-disubstituted alkenes reveals more subtle differences between the directing effects of these auxiliaries (Figures 19 and 20). With all three alkenes it appears that only the *S* configuration at the carbinol carbon is formed with 8-phenylmenthol and only the *R* configuration with



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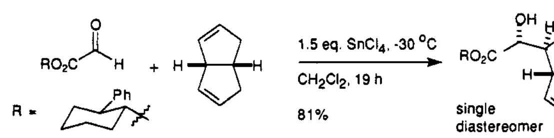

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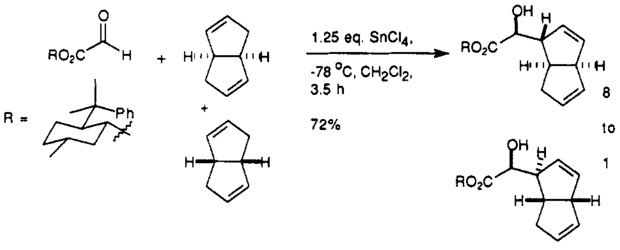

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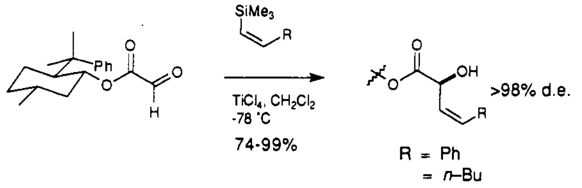

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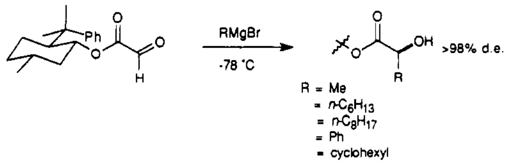

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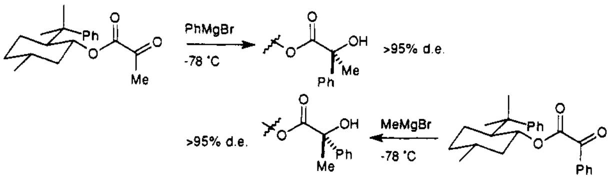

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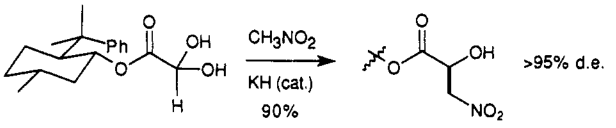

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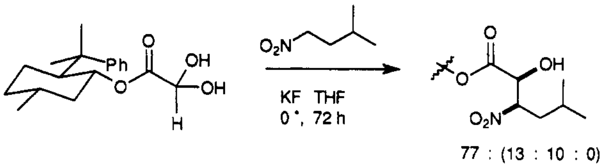

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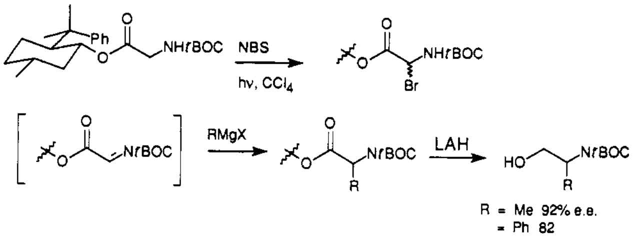

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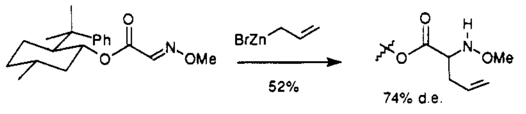


Figure 29.

trans-2-phenylcyclohexanol. Similar results were obtained from the reaction of 8-phenylmenthyl glyoxylate with (trimethylstanyl)-*cis*-2-butene using $TiCl_4$,[36] while lower levels of control (80:10:8:2) were observed with (trimethylstanyl)-*trans*-2-butene and BF_3 as the Lewis acid.[37,38]

These ene reactions of glyoxylates have been used for the synthesis of a number of natural products. The key steps in the routes to specionin and xylomollin both involve added stereocontrol features, with the first effecting breaking of molecular symmetry of an achiral diene (Figure 21)[39,40] and the second selecting between two enantiomers of the starting diene (Figure 22).[41]

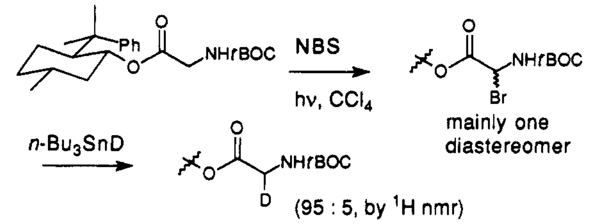
Vinyl silanes have also been used as nucleophilic partners for reaction with glyoxylates, affording allylic (in contrast to *homo*allylic) alcohols from reaction with 8-phenylmenthyl glyoxylate (Figure 23).[42]

A variety of other nucleophiles have been added to 8-phenylmenthyl and *trans*-2-phenylcyclohexanyl glyoxylates (and substituted glyoxylates) with high levels of absolute stereochemical control. For example, a variety of organomagnesium reagents, both alkyl and aryl, have been added to 8-phenylmenthyl glyoxylates with high levels of control (Figures 24 and 25).[43-45] The addition of an alkyl titinate[46] to the pyruvate of 8-phenylmenthol also proceeds with greater than 95% de.

Nitroalkanes have also been added to glyoxylates of these chiral auxiliaries. For example, the addition of nitromethane was shown to proceed with greater than 95% de with 8-phenylmenthyl glyoxylate hydrate (Figure 26).[47] Under proper conditions this process is reversible and a thermodynamic equilibrium can be established (Figure 27). The absolute and relative configuration of the stereocenters in the major adduct were deduced by single-crystal, X-ray analysis of the derived amino hydroxy ester.[48,49]

The addition of nucleophiles to nitrogen derivatives of the glyoxylate of 8-phenylmenthol proceeds with moderate control of stereochemistry (Figures 28[50] and 29[51]).

The sequence shown in Figure 30 is especially intriguing because it provide a high level of control at a stereocenter based upon D and H and because, in two reactions, control is exhibited in processes that are likely to involve radical reactions.[52] Enamines have also been added to imine derivatives of the glyoxylates of menthol and 8-phenylmenthol, but with less than satisfactory control (27 and 67% de).[53]



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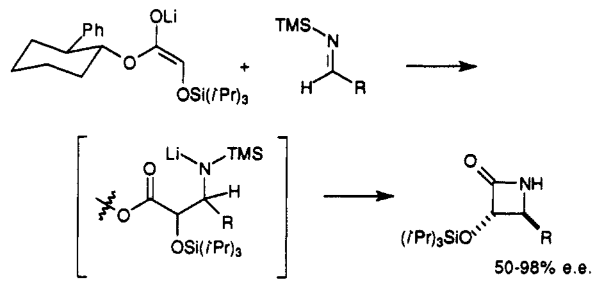

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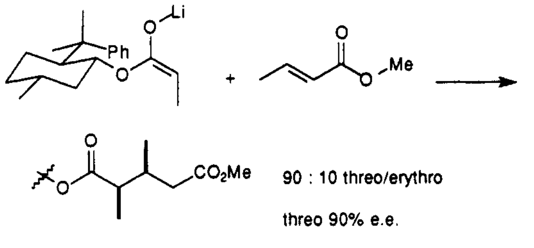

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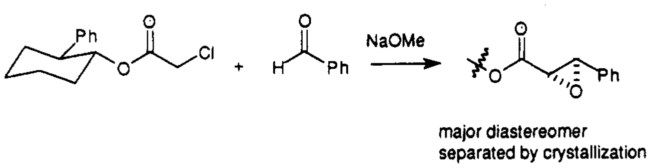


Figure 33.

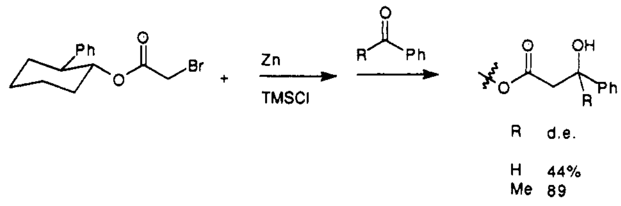
B. Nucleophilic Reactions

There are only a few schemes that employ the atom β to the heteroatom linker as a nucleophile and none of these achieve the exceptional levels of control exhibited by many of the reactions with the reverse electronic demand. While it is tempting to speculate on the basis of this observation as to the nature of the participation of the chiral auxiliary, and especially the phenyl substituent, in all of the reactions directed by 8-phenylmenthol and *trans*-2-phenylcyclohexanol there are too few examples to justify substantive conclusions. Nonetheless, it is clear from empirical analysis that electron deficiency in the substrate attached to these auxiliaries is important if useful levels of stereochemical control are to be achieved.

The most practically important of these reactions is that affording β-lactams (Figure 31), providing good to excellent levels of control with *trans*-2-phenylcyclohexanol as the auxiliary.[54,55]

Other, simple alkylations of simple enolates have been carried out with good levels of stereodirection (Figures 32,[56] 33,[57] 34,[58] and 35[59-61]).

Double alkylation resulting in formation of a cyclopropane derivative has also been accomplished with good stereochemical control using *epi*-*ent*-8-phenylmenthol (Figure 36).[62] A tandem double Michael sequence provided cyclic products with levels of control from 17 to 73% using a variety of 8-phenylmenthol analogues (Figure 37).[63]



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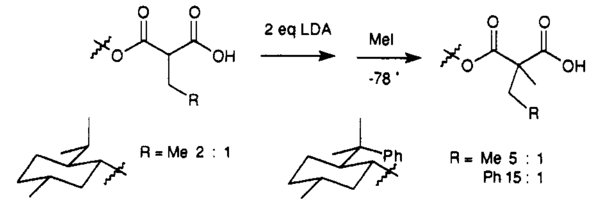

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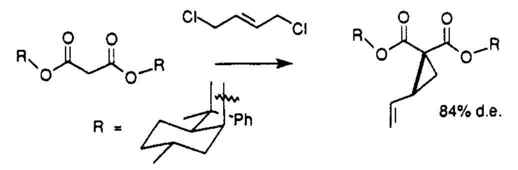


Figure 36.

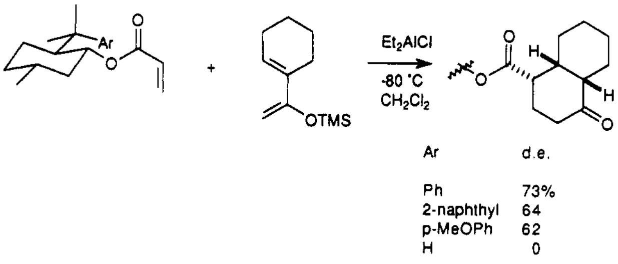


Figure 37.

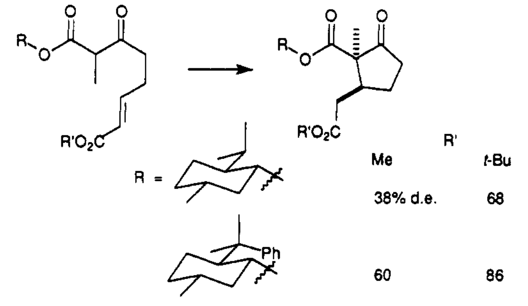


Figure 38.

An intramolecular alkylation with a Michael acceptor was shown by Stork to afford cyclopentanones with good asymmetric induction using 8-phenylmenthol (Figure 38).[64]

The lack of rigidity in the ester linkage between the substrate and the auxiliary as been addressed through the formation of lactone acetals from 8-phenylmenthone (Figure 39).[65,66] While little control is obtained in the formation of the acetal (1.3:1), separation of the two diastereomers can be accomplished by flash chromatography.

C. Cycloaddition Reactions

There are number of reactions that can be viewed as cycloaddition processes (regardless of how they may

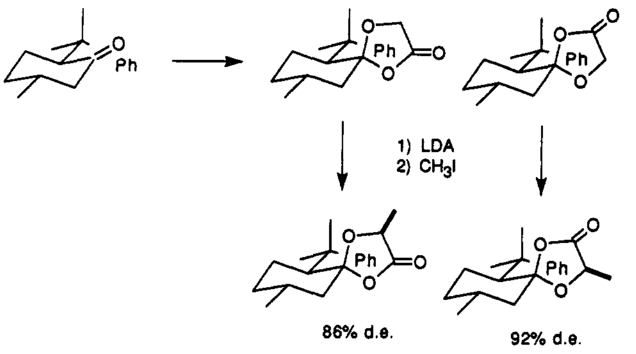


Figure 39.

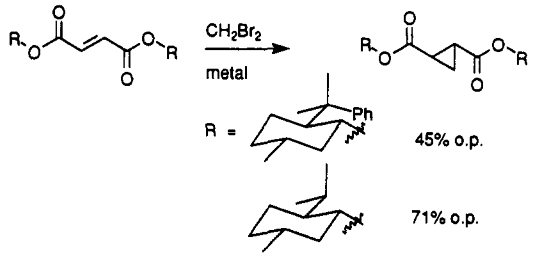


Figure 40.

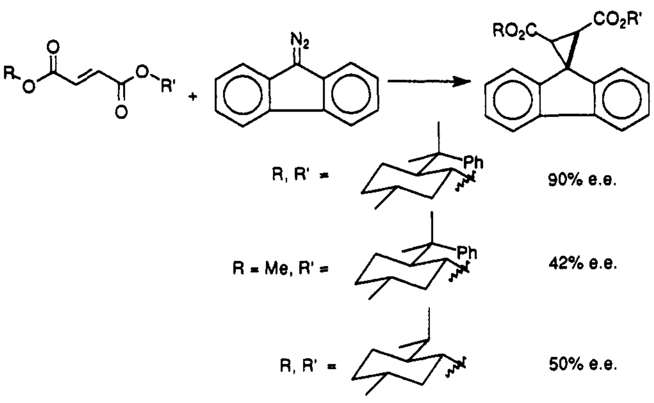


Figure 41.

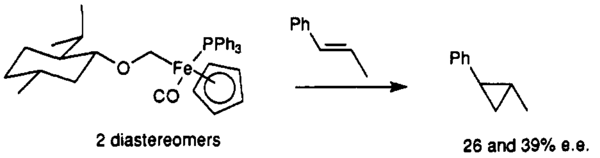


Figure 42.

actually occur) that employ cyclohexyl-based chiral auxiliaries. These reactions can provide for control at multiple centers formed in the reaction.

Two scenarios for cyclopropanation have been reported, and it interesting to note that the first is the only example where menthol represents a superior auxiliary to 8-phenylmenthol (Figures 40[67] and 41[68]). An early example of the formation of a cyclopropane using menthol as auxiliary provided only 26 and 39% ee starting with two different diastereomers (Figure 42).[69] Several schemes involving [2 + 2] cycloaddition induced by light have been reported. For example, for the Paternò-Büchi reaction a wide range of chiral auxiliaries was examined, with 8-phenylmenthol providing the highest level of control (Figure 43).[70-72] Because of the symmetry present in one starting material, these examples do not provide information on how regiocontrol of the reaction might be influenced by the auxiliary. However, in a previously reported study with an unsymmetrical partner for the phenylpyruvate, little regioselectivity was observed (Figure 44).[73]

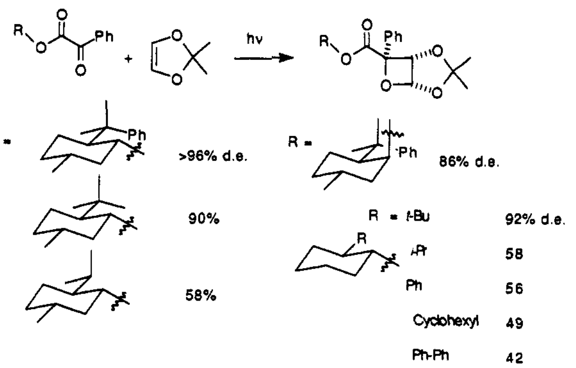


Figure 43.

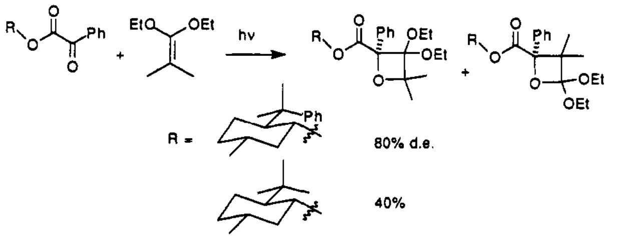


Figure 44.

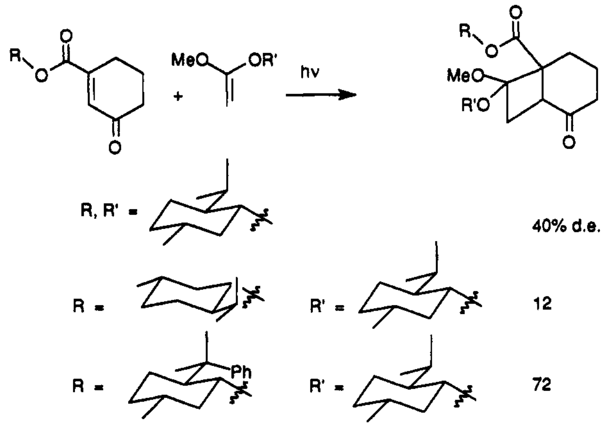


Figure 45.

In another example of [2 + 2] photocycloaddition, the influence of chiral auxiliaries on both partners for the reaction was examined. However, even in the "matched" case of directing effects, only moderate control was observed (Figure 45).[74,75] Other examples of [2 + 2] photoinduced cycloaddition have been reported, but levels of control remain below that required for practical application of this chemistry.[76,77]

Control of stereochemistry in Diels–Alder reactions using 8-phenylmenthol has been very successful, and indeed, the first use of this auxiliary developed by Corey was in the reaction of the acrylate ester with a substituted cyclopentadiene (Figure 46).[78] In the early 1960s asymmetric induction in the Diels–Alder reaction was studied with menthol as the auxiliary.[79-81] Extensive examinations of this reaction by Oppolzer established the endo selectivity to be on the order of 90% and the level of absolute direction to be 94% with 8-phenylmenthol as auxiliary (several other camphor-based auxiliaries were also examined[82]). Given the power of this process it is surprising that apparently little practical use has been made of this reaction. In

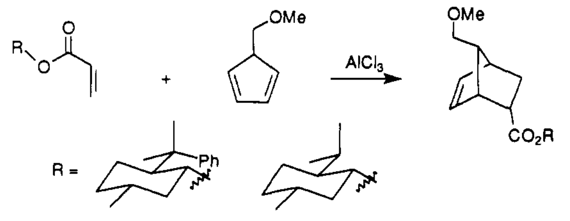


Figure 46.

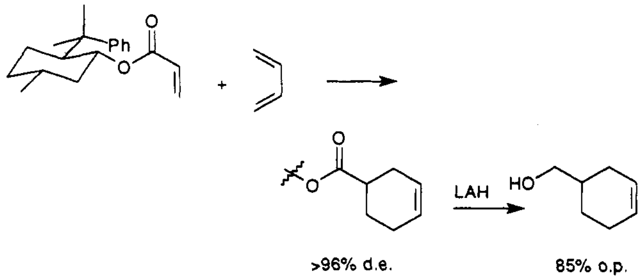


Figure 47.

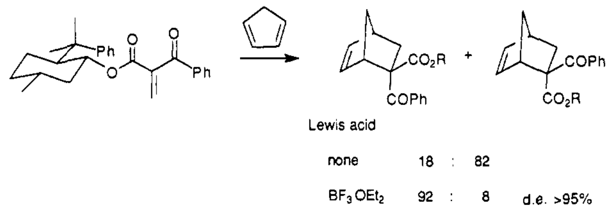


Figure 48.

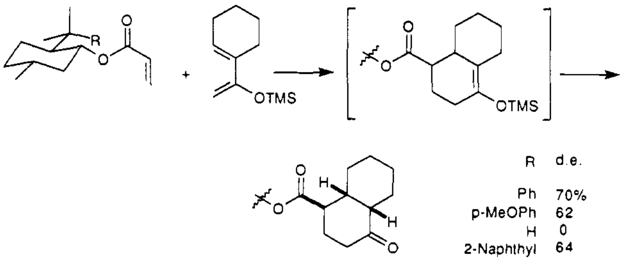


Figure 49.

one example, Martin has used this reaction in the synthesis of (+)-phyllanthocin, with control of absolute stereochemistry at the onset, as shown in Figure 47.[83] While the control exhibited in the cycloaddition reaction was very good (the minor diastereomer could not be detected), there was apparently substantial loss of stereochemical integrity in the subsequent reduction of the ester linkage. Other examples of Diels–Alder reactions directed by 8-phenylmenthol are illustrated in Figures 48[84] and 49[85] (lower levels of control were observed in similar reactions with menthol as auxiliary[86]). The experiments summarized in Figure 49 are interesting in that the "endo/exo" selectivity is reversed with and without the presence of a Lewis acid.

It is unlikely that the reaction shown in Figure 50 is a "true" heteroatom Diels–Alder reaction involving as it does the aromatic ring.[87] More likely is a stepwise process that involves an intermediate allylic cation derived by addition of the cyclopentadiene to the imine followed by bonding between the cation and the aromatic ring (use of menthol as an auxiliary afforded essentially no selectivity).

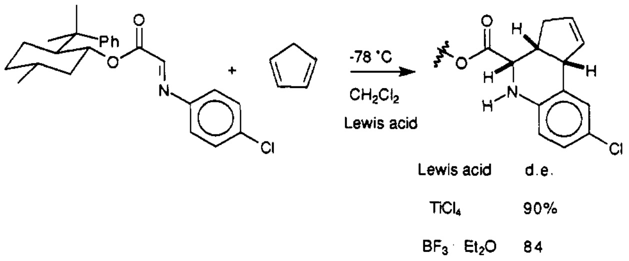


Figure 50.

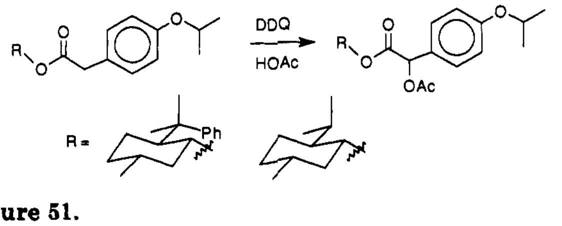


Figure 51.

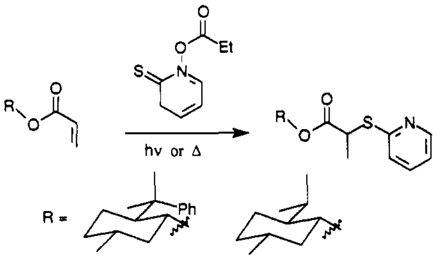


Figure 52.

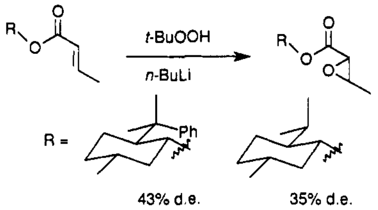


Figure 53.

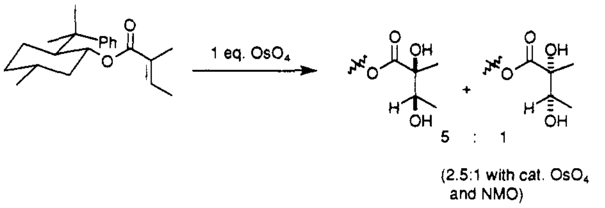


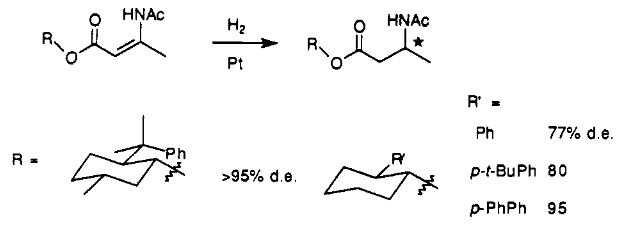
Figure 54.

D. Miscellaneous Reactions

1. Oxidations

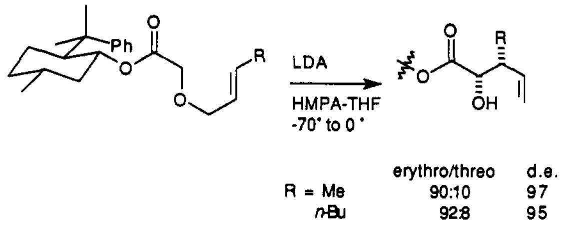
Control of stereochemistry in oxidations at the β position and at the β and γ positions has been obtained in several different reactions but none have practical levels of asymmetric induction. Oxidation with DDQ of the aryl acetates of menthol and 8-phenylmenthol afforded 20 and 62% de, respectively (Figure 51).[88] Radical addition to the acrylate esters of these auxiliaries afforded thioethers (Figure 52) with levels of control comparable to those in the previous example.[89]

Oxidation of acrylates to epoxides and a diol have also been carried out, but also with less than practical levels of control (Figures 53[90] and 54[91]).



R' =	
Ph	77% d.e.
p-t-BuPh	80
p-PhPh	95

Figure 55.



	erythro/threo	d.e.
R = Me	90:10	97
n-Bu	92:8	95

Figure 56.

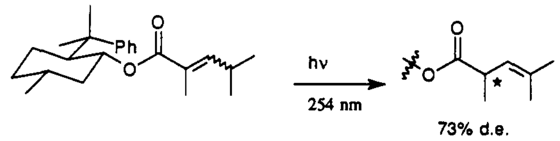


Figure 57.

2. Reductions

Excellent levels of asymmetric induction were obtained in the reduction of β-acetamidocrotonates using several cyclohexyl-based chiral auxiliaries.[92] As illustrated in Figure 55, the best results were obtained with 8-phenylmenthol and the *p*-biphenyl analogue of *trans*-2-phenylcyclohexanol, although the latter auxiliary was partly destroyed by reduction during the reaction. A single geometric isomer of the starting acetamidocrotonate was obtained except with (*p-tert*-butylphenyl)cyclohexanol.

3. Rearrangements

There are three examples where stereochemistry has been controlled by cyclohexyl-based auxiliaries in rearrangement reactions. The anionic, [2,3] Wittig rearrangement in Figure 56 represents a powerful complement to the ene reactions of glyoxylates as the strongly basic conditions required for the rearrangement contrast with the highly Lewis acidic media for the ene reactions.[93] Both relative (erythro/threo) and absolute stereochemical control were observed to be at practical levels.

Asymmetric induction has also been observed in a photochemically driven 1,3-hydrogen shift (Figure 57).[94]

A valuable method for overall control of stereochemistry at the position δ to the linker based on transfer of chirality from the β position has been developed by Burgess.[95] The key steps for stereocontrol are a formal 1,3-hydrogen shift followed by an allylic sulfoxide–sulfinate rearrangement (Figure 58).

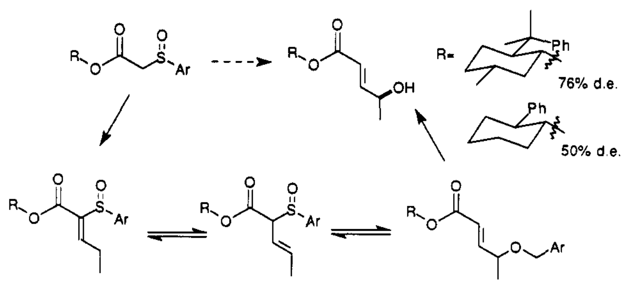
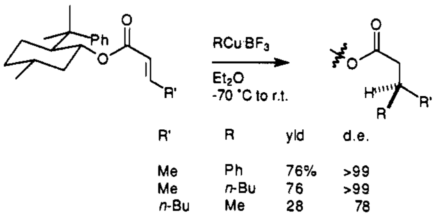
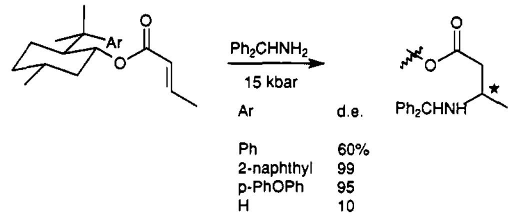


Figure 58.



R'	R	yld	d.e.
Me	Ph	76%	>99
Me	n-Bu	76	>99
n-Bu	Me	28	78

Figure 59.



Ar	d.e.
Ph	60%
2-naphthyl	99
p-PhOPh	95
H	10

Figure 60.

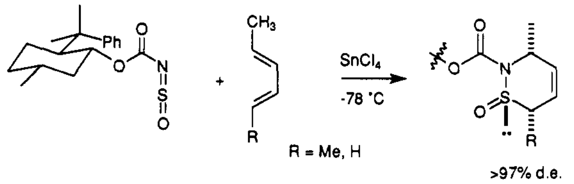


Figure 61.

VI. γ Stereocenter

A number of studies have examined control of stereochemistry at the position γ to the heteroatom linker through conjugate addition to α,β-unsaturated esters of cyclohexyl chiral auxiliaries. Initial investigations using menthol as the auxiliary afforded very low levels of control (<10% de).[96-98] Practical levels of control were first obtained by Oppolzer using 8-phenylmenthyl acrylates, as summarized in Figure 59.[99-101]

We have observed similar results using *trans*-2-phenylcyclohexanol as the chiral auxiliary for organocopper reagent additions to α,β-unsaturated esters, with control at the 96–98% de level.[102] Addition of cuprate reagents to monocrotonates of *trans*-1,2-cyclohexanediol has also been shown to afford control in the 72–88% de range.[103] Conjugate addition with absolute control has also been observed in the high-pressure addition of amines to these systems (Figure 60).[104]

Both ene and cycloaddition reactions *N*-sulfinylcarbamates proceed with high levels of asymmetric induction at the sulfur, γ to the linker, as well as at the δ carbon. For example, reaction of the *N*-sulfinylcarbamate of 8-phenylmenthol with 2,4-hexadiene and with pentadiene affords cycloadducts with practical levels of stereocontrol and, in the case of the unsymmetrical diene, regiocontrol (Figure 61).[105,106] These adducts can be further transformed by ring opening with attack at sulfur by Grignard reagents follow by [2,3] sulfoxide–sulfinate rearrangement, providing a facile route to aminols with excellent control of stereochemistry (Figure 62).

The ene reactions of the *N*-sulfinylcarbamate of *trans*-2-phenylcyclohexanol also proceeds with high levels of control at both carbon and at sulfur (Figure

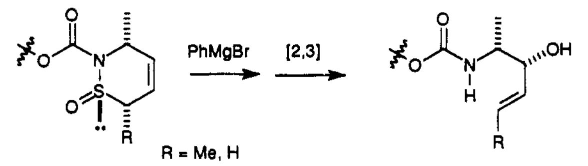


Figure 62.

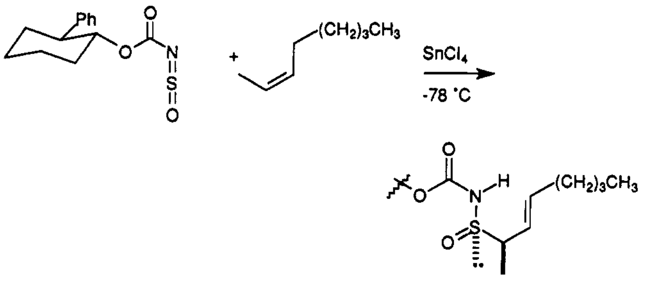


Figure 63.

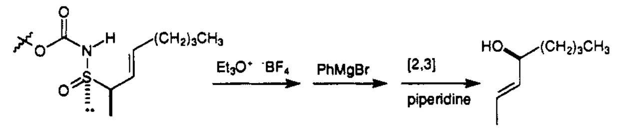


Figure 64.

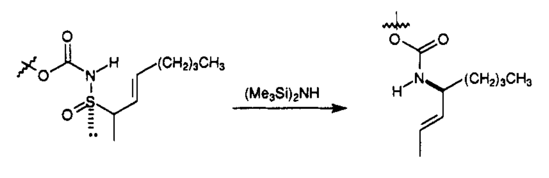


Figure 65.

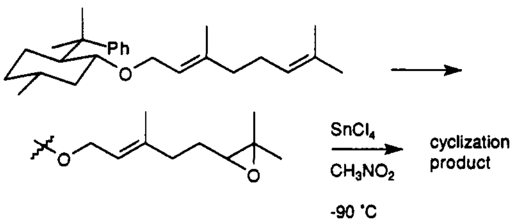


Figure 66.

63).[107] With unsymmetrical alkenes (such as 2-octene) the regiocontrol is excellent and only trans geometric isomers are produced from *cis*-alkenes. These unstable adducts can be transformed in a further three steps to allylic alcohols (Figure 64), or in one step to allylic amines (Figure 65).[108] Both processes providing for the net allylic functionalization of alkenes with net retention of the double bond regiochemistry and with greater than 90% ee. In the latter case, the product allylic amines are obtained as carbamates of *trans*-2-phenylcyclohexanol, affording the opportunity to further enhance stereochemical purity by both chromatographic and crystallization techniques.

VII. Remote Stereocenter

Only two examples have appeared that can be considered to represent control at a center more remote than γ to the linker (other than those already discussed, above, that control more proximate centers as well). Formation of the epoxide from the diene in Figure 66 occurred preferentially at the double bond remote from the oxygen, but with essentially no stereocontrol. However, Lewis acid catalyzed cyclization of this monoepoxide (to an unidentified product) proceeded more rapidly with one of the diastereomers, leading to 64% enrichment of the unreacted epoxide at 70% conversion.[109]

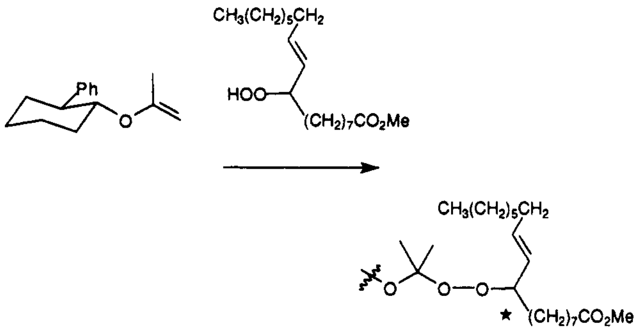


Figure 67.

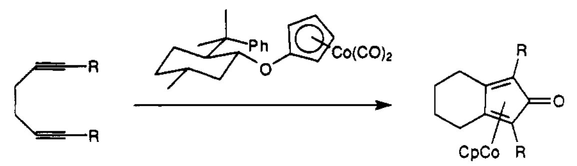


Figure 68.

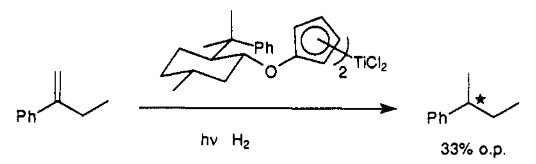


Figure 69.

Porter has shown that *trans*-2-phenylcyclohexanol can serve as an effective resolving agent for hydroperoxides Figure 67.[110,111] Baseline separation was obtained for the diastereomers of several hydroperoxide perketals using either normal or reverse-phase chromatography.

VIII. Catalytic Processes

Only two examples have so far appeared where cyclohexyl auxiliaries were involved as part of a chiral catalyst for asymmetric induction (Figures 68 and 69).[112] Unfortunately, the level of control was not at practical levels (0–34% de) in either case.

IX. Origin of Control

The high levels of control exhibited by 8-phenylmenthol and *trans*-2-phenylcyclohexanol has inspired numerous hypotheses as to the origin of the directing effect. Investigators active in the development of these auxiliaries including Corey, Oppolzer, and ourselves (as well as others, for related auxiliaries) have invoked models for absolute control with π stacking of the aromatic moiety of the auxiliary and that of the attached substrate during the course of the reaction.[113] Indeed, Corey's development of 8-phenylmenthol was the result of earlier observations on the control of stereochemistry during reduction of ketones at the C-15 position in prostaglandin precursors.[114] In these studies, π–π stacking was suggested as the reason for the relatively high levels of diastereoselection in the reduction of the biphenylurethane (Figure 70).[115]

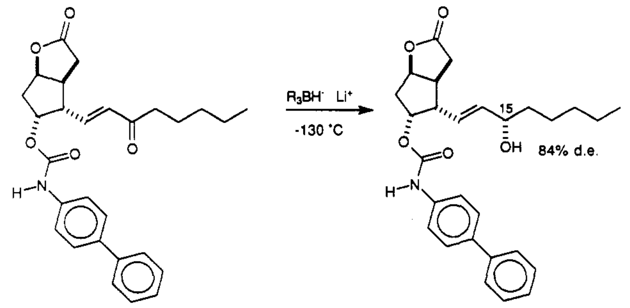


Figure 70.

While experimental evidence for the critical participation of the aromatic ring has been obtained,[116–118] it is still not clear what the precise nature of this interaction might be in the competing, diastereomeric transition states. Part of the difficulty that complicates an analysis of these matters centers around the number of degrees of freedom that are available in most substrates linked to these auxiliaries.[119] It is far too frequent that researchers in the area of asymmetric induction draw far reaching conclusions solely from the *direction* of control. Unfortunately, the elaborate models that often result from such "thought" experiments can draw no validity from the correspondence of prediction with observation as *any* model, no matter how inconsistent with solidly established, physical organic concepts, has a 50:50 chance of predicting correctly. As delineated more mathematically (and perhaps succinctly) some time ago by the crystallographer Kitaigorodskii:

$$V = (N/n) - 1$$

> The author believes that the value of a theory is zero if for explaining the experiment, the research had to introduce as many parameters as the number of values the experiment produced.[120]

X. References

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