Asymmetric Creation of Quaternary Carbon Centers

Kaoru Fuji

Institute for Chemical Research, Kyoto University, Uji, Kyoto-fu 611, Japan

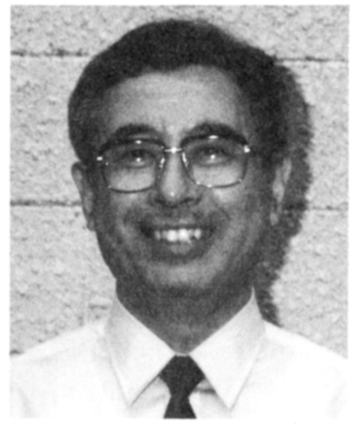
Received December 8, 1992 (Revised Manuscript Received June 4, 1993)

Contents

I. Introduction

The biological world including its human component can be regarded as a chiral world in the chemical sense. It happens usually in nature that one enantiomer exhibits biological activity whereas the other enantiomer does not. A number of biologically active natural products contain quaternary carbon atom(s). Interest in synthesizing them in an optically active form is reflected in the explosive increase in the number of new development for the chiral construction of quaternary carbons that have been published in this decade. This article will consider the asymmetric creation of quaternary carbon centers not only through carbon–carbon-bond-forming reactions but also through the functional group transformation of *meso* compounds. The nature of the quaternary carbon considered in this article is limited to one with four different carbon substituents. Syntheses of α-substituted amino acids, tertiary alcohols, and related subjects have been omitted.

Asymmetric syntheses can be divided into two types, enantioselective syntheses and diastereoselective syntheses. According to Izumi,[1] a reaction is described as enantioselective if the reaction is carried out on an achiral molecule using an enantioselective reagent or catalyst. In the case of diastereoselective synthesis, "if a molecule contains a center of chirality and a center of prochirality, the molecule can be divided by a plane in such a way that the parts on either side of the plane are diastereotopically related to each other. If the reaction results in the conversion of the center of prochirality into a new center of chirality, the reagent may attack from either side of this diastereotopically reacting plane, with the result that diastereoisomers are formed." This definition proposed by Izumi has proven useful for classifying asymmetric synthesis although modifications are necessary.

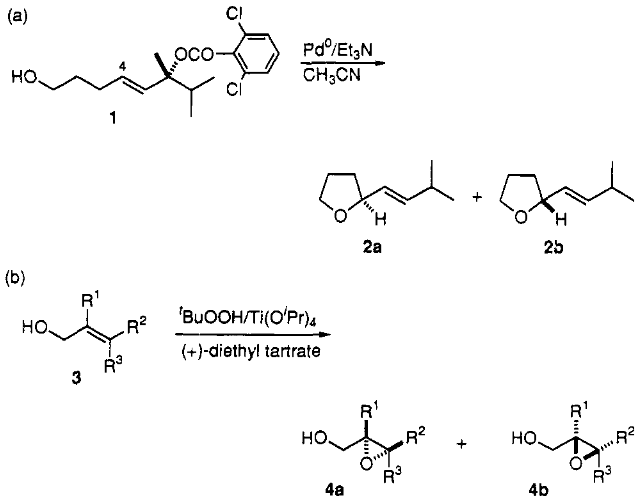


Kaoru Fuji was born in 1939 in Osaka, Japan, and received both his B.A. and Ph.D. degrees from Kyoto University. He was appointed Assistant Professor of the Institute for Chemical Research, Kyoto University, in 1967. After a postdoctoral stay with James P. Kutney at the University of British Columbia in Canada (1971–1973), he was promoted to the rank of Associate Professor in 1973, and Professor in 1983. During that time, he joined P. Gassman's group at the University of Minnesota as a research fellow (1981–1982). Dr. Fuji has been the recipient of silver medal from the pharmaceutical society of Japan and held a visiting position at Université Louis Pasteur de Strasbourg, France (1991). His research interests include the development of synthetic methodology, natural product synthesis, and design and synthesis of antitumor compounds. Programs are active in the areas of use of chiral leaving groups for an asymmetric induction, asymmetrization of symmetrical compounds, memory of chirality.

Consider the cyclization of the (*R*)-alcohol **1** affording the 2-substituted tetrahydrofuran **2a** (Scheme 1a).[2] Since the possible products **2a** and **2b** exist as the enantiomers but not as the diastereomers, the reaction can be regarded as an enantioselective synthesis of the 2-substituted tetrahydrofuran. According to Izumi's definition this reaction cannot be classified as an enantioselective reaction, because the *re* face and the *si* face at the C-4 of the reacting substrate **1** are not enantiotopic but diastereotopic to each other. In this reaction, *one of the two possible diastereotopic faces was selected to give an enantiomer*. The Katsuki–Sharpless oxidation of the achiral alcohol **3** gave **4a** using (+)-diethyl tartrate as a chiral source with an 90–95% enantiomeric excess (ee) in good yield (Scheme 1b).[3] In this reaction, *one of the enantiotopic faces was selected to give an enantiomer*. Thus, both the reactions shown in Scheme 1 involve *enantioselectivity*.

0009-2665/93/0793-2037$12.00/0

Scheme 1



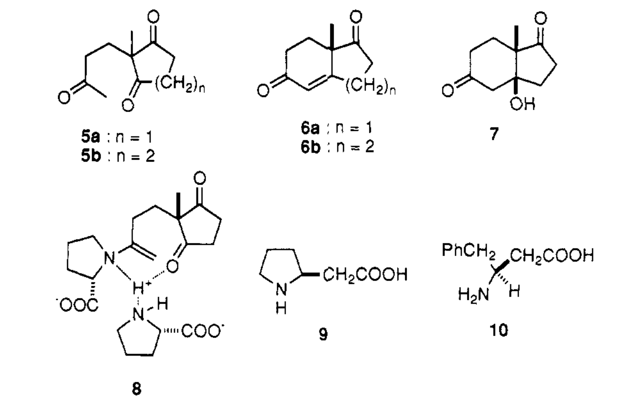
On the other hand, *one of the diastereotopically reacting planes of the substrate 1 was selected* in the Stork's reaction and *one of the enantiotopically reacting planes of 3 was selected* in the Katsuki–Sharpless oxidation. In this article, "enantioselective" and "diastereoselective" will be used to describe unequal quantities in the enantiomeric products and in the diastereomeric products, respectively. The terms, "enantiodifferentiating" and "diastereodifferentiating" will be used to discriminate the prochiral center(s) in the substrates. Thus, both enantioselective reactions and diastereoselective reactions can be further divided into two classes, enantio- and diastereodifferentiating reactions.

II. Enantioselective Creation

A. Enantiodifferentiating Reactions

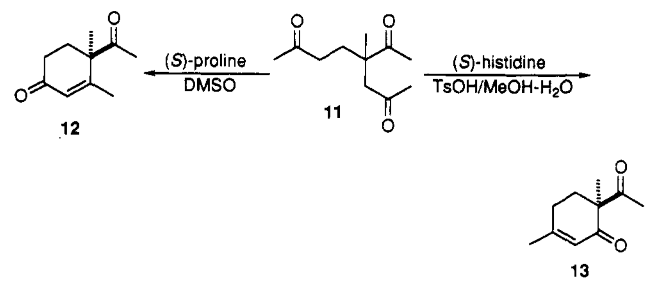
1. Abiological Methods

a. Animo Acid-Catalyzed Aldol Reactions. An interesting intramolecular aldol cyclization of the achiral triketone **5a** using an optically active amino acid as a catalyst was reported in 1971.[4] Thus the treatment of **5a** or **5b** with (*S*)-proline in CH_3CN afforded (*S*)-**6a** [84% optical purity (op)] or (*S*)-**6b** (71% op) in 87% or 71% yield, respectively. Another investigation of the same cyclization demonstrated that the intermediate aldol **7** (93% op) was obtained in nearly quantitative yield when dimethylformamide (DMF) was used as the solvent.[5] Detailed studies on the dilution effect of (*S*)-proline indicated a three-center hydrogen-bonded structure (**8**) as transition state.[6a] A nonlinear relationship, supporting transition structure **8**, between the enantiomeric purity of (*S*)-proline and that of the product **6a** was observed in this type of cyclization.[6b] Interestingly, when the (*S*)-β-amino acids **9** and **10** were used as catalysts, **5a** afforded the enantiomer of **6a**.[7] An experimental procedure, which affords optically active **6b** in 100-g quantities, has also been reported.[8] This cyclization was extended to the acyclic ketone **11**.[9] Although enantiomeric excess (ee) was moderate, interesting solvent effects were observed. A cyclohexenone **12** was obtained in dimethyl sulfoxide (DMSO)



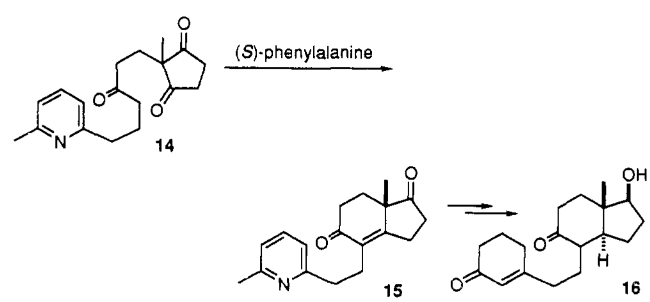
in the presence of (*S*)-proline, whereas with (*S*)-histidine as catalyst in a protic solvent **11** was converted into **13** (Scheme 2).

Scheme 2



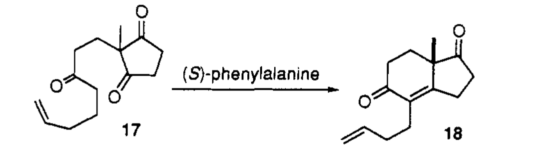
Since the amino acid-catalyzed cyclization is a simple and versatile method of producing the optically active bicyclo[4.4.0] or bicyclo[4.3.0] system, a number of synthetic applications have been reported. A beautiful example involves cyclization of the pyridine derivative **14** with (*S*)-phenylalanine, affording **15** (86% op; 82% yield) (Scheme 3).[10] The diketone **15** was converted

Scheme 3



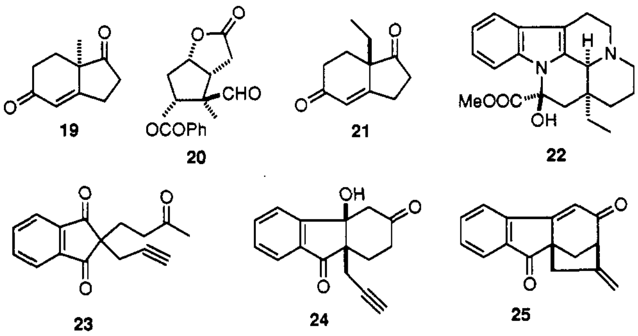
into a key intermediate **16** used for the syntheses of estrone and 19-norsteroids. Optically active diketone **18** (76% ee) was obtained from the triketone **17** with (*S*)-phenylalanine as a catalyst (Scheme 4).[11] In these

Scheme 4



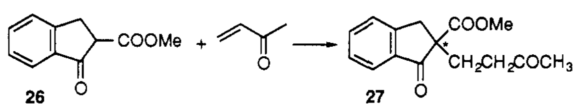
cyclizations, phenylalanine was shown to be a better catalyst than proline which was used in the original asymmetric cyclization.[3]

The diketone **19** (96% op), obtained from the achiral triketone **5a** with (*R*)-proline in 72% yield, served as a starting material for the synthesis of a key intermediate **20** in the 12-methylprostaglandin synthesis.[12] (+)-Vincamine (**22**) was synthesized from **21**.[13] The L-proline-catalyzed cyclization of **23** provided **24** (89%), which served as a starting material for the gibban structure compound **25**.[14] Enantioselectivities were not reported for these compounds.



b. Michael Additions and Alkylations. Bergson reported the first example of the chiral construction of a quaternary carbon center using a Michael addition under the influence of a chiral amine.[15] Thus, the addition of methyl 1-oxo-2-indancarboxylate (**26**) to methyl vinyl ketone in the presence of a catalytic amount of (*R*)-2-(hydroxymethyl)quinuclidine (**28**) gave **27**. Although both the degree of asymmetric induction and the absolute configuration of the product were not determined, this paper was significant in that it opened up a new avenue for catalytic asymmetric synthesis. A number of papers followed, and the pertinent results are compiled in Table 1. Interesting but fruitless attempts included the use of polymer-bound chiral catalysts (entries 3–5), in which a dramatic decrease in ee was observed in each case.[17]

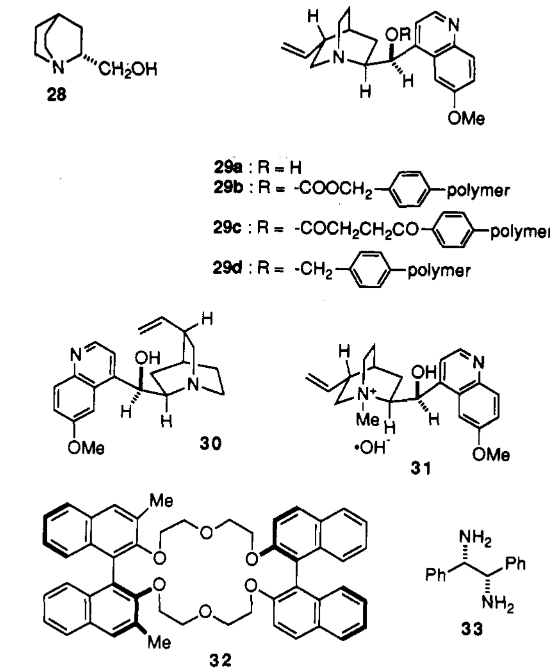
Table 1. Asymmetric Michael Addition of Methyl 1-Oxo-2-indancarboxylate (26) to Methyl Vinyl Ketone in the Presence of Chiral Catalysts Affording 27



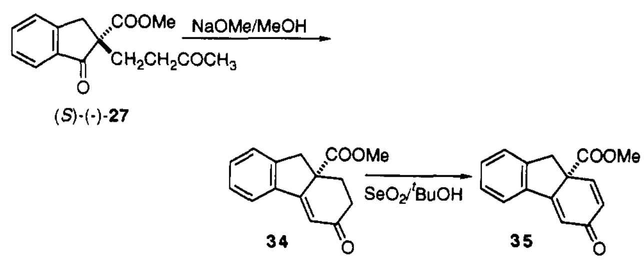
entry	catalyst	solvent	temp, °C	configuration	yield, %	% ee	ref
1	**28**[a]	benzene	22	*b*	*c*	*b*	15
2	**29a**	toluene	room temp	*b*	*c*	68	16
3	**29b**	toluene	room temp	*b*	91	8	17
4	**29c**	toluene	room temp	*b*	66	11	17
5	**29d**	toluene	room temp	*b*	99	2	17
6	**29a**	CCl_4	−21	*S*	99	76	18
7	**30**	CCl_4	−21	*R*	100	69	18
8	**31**	toluene	25	*S*	100	15	18
9	KO^{t}Bu/**32**	toluene	−78	*R*	48	99	19
10	$Co(acac)_2$/**33**	toluene	−50	*R*	50	66	20

[a] 57% ee. [b] Not determined. [c] Not described.

The *S* configuration of (−)-**27** was determined from the CD spectrum of **35**, obtained from (−)-**27** in two steps via **34** (Scheme 5).[18] The highest degree of ee so far (99%) was realized, when ^{t}BuOK/**32** was used as a catalyst in toluene at −78 °C in 48% yield (entry 9).[19] Raising the reaction temperature brought the ee down to 67% (75% yield). Although the chiral diamine **33** was a poor catalyst (5.8% ee; 18% yield), the complex

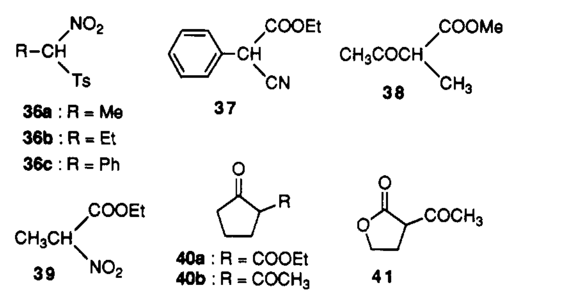


Scheme 5



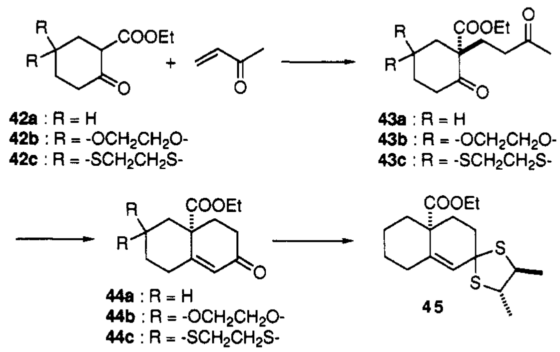
with $Co(acac)_2$ was shown to be moderately active providing **27** (66% ee; 50% yield).[20]

The Michael donors **36–41** were added to methyl vinyl ketone with quinine (**29a**) as a catalyst to afford the corresponding products containing a chiral quaternary carbon atom.[16] Their ee's were not reported. Quinine

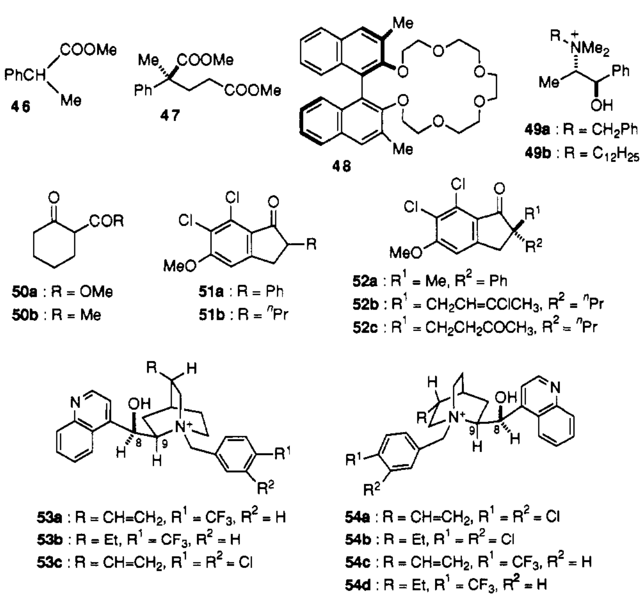


methohydroxide (**31**) catalyzes the Michael addition of the cyclohexanone derivatives **42a–c** to methyl vinyl ketone providing the corresponding products **43a–c** in quantitative yield and with an op of ~20%.[18] Cyclization of **43a–c** under the acidic (for **43a**) or the basic (for **43b** and **43c**) conditions gave **44a–c**, respectively. The absolute configuration of the major enantiomer at this stage was determined using their CD and ORD spectra. Treatment of **44a** with (*S*)-butane-2,3-dithiol gave **45**, the ee of which was determined from the ^{13}C NMR spectrum. The ee's of **44b** and **44c** were similarly determined (Scheme 6). Methyl 2-phenylpropionate (**46**) was added to methyl acrylate using KNH_2 complexed to a chiral crown ether **48** as catalyst. The (*S*)-**47** was obtained in 80% yield with 83% ee.[19] A chiral

Scheme 6



phase-transfer catalyst, (−)-*N*-benzyl-*N*-methylephedrinium bromide (**49a**), was introduced for the alkylation of the cyclohexanone derivatives **42a** and **50a,b**.[21] Although the yield for each alkylation was good, the ee was not significant. Benzylation of **42a** under phase-transfer conditions with **49b** afforded the corresponding benzylated product with low ee (~7%).[22] Methylation of 6,7-dichloro-5-methoxy-2-phenyl-1-indanone (**51a**) provided **52a** in 95% yield (up to 94% ee) using **53a** as a catalyst.[23] Methyl chloride showed an even better selectivity than methyl bromide or methyl iodide. Alkylation of **51b** with 1,3-dichloro-2-butene under similar conditions with **54c** as the phase-transfer catalyst afforded **52b** (99% ee; 99% yield).[24] The (*S*)-2,2-disubstituted indanone **52c** (80% ee) was prepared from **51b** by the Michael addition to methyl vinyl ketone in 95% yield under similar reaction conditions. The catalysts **54a–d**, epimeric at C-8 and C-9 to the cinchonine derivative **53**, yielded the *R* enantiomer of **52c** with 20–40% ee and similar yields.[25]



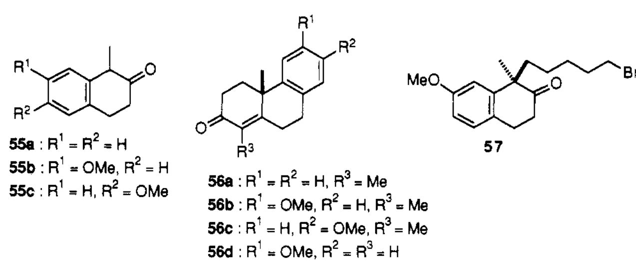
A one-step synthesis of the optically active tricyclic ketones **56a–d** from **55a–c** via a Michael addition followed by a Robinson annelation under phase-transfer conditions using chiral catalysts has appeared.[26] The results are summarized in Table 2. The two asymmetric centers C-8 and C-9 in the catalysts again determine the absolute stereochemistry of the products. The catalyst **54c** was effective in the alkylation of **55b** with 1,5-dibromopentane to provide a 74% yield of **57** with >70% ee.[26] The Michael addition of α-phenyl cyclic

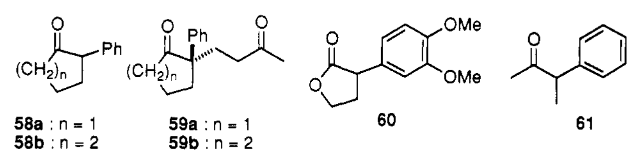
Table 2. Enantioselective Robinson Annelation under the Phase-Transfer Conditions

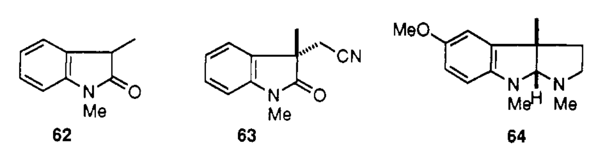
substrate	enone	catalyst	product	configuration	yield, %	% ee
55a	EVK[a]	**54d**	**56a**	*S*	64	77
55b	EVK	**54d**	**56b**	*S*	77	70
55b	MVK[b]	**54d**	**56d**	*S*	50	61
55c	EVK	**54d**	**56c**	*S*	81	81
55c	EVK	**54c**	**56c**	*S*	70	73
55c	EVK	**53a**	*ent*-**56c**	*R*	66	69
55c	EVK	**53b**	*ent*-**56c**	*R*	85	73

[a] Ethyl vinyl ketone. [b] Methyl vinyl ketone.

ketones **58a** and **58b** to methyl vinyl ketone proceeded smoothly to give the corresponding diketones **59a** and **59b**, respectively, with ~85% ee, when **54c** was the catalyst. The Michael addition of **60** and **61** was attempted but yielded a disappointingly low ee. The alkylation of an oxindole **62** with chloroacetonitrile under phase-transfer conditions afforded (*S*)-**63** in good yield in the presence of a variety of cinchoninium salts.[27] The best results (78% ee) were obtained from **53c**. (−)-Esermethole (**64**) was synthesized from (*S*)-**63**.

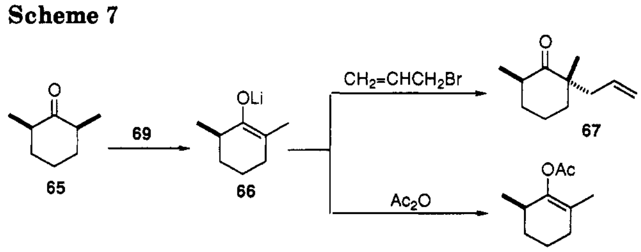




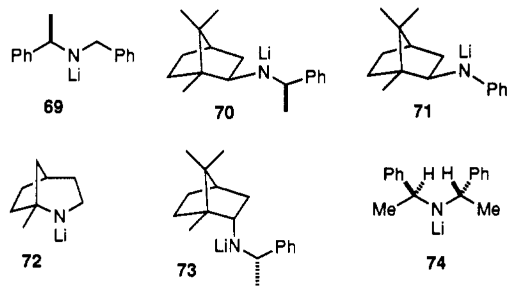


Deprotonation of the *meso*-ketone **65** with the chiral base **69** produced a chiral enolate **66** which was alkylated with allyl bromide to afford a 2,2-disubstituted ketone **67** (25% ee; 65% yield) (Scheme 7).[28] Quenching of

Scheme 7



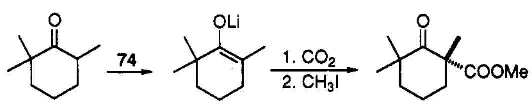
the chiral enolate **66** using acetic anhydride yielded the enol acetate **68** with 29% ee. Optically active enol acetate was obtained with the chiral bases **70–73**. Optimum results (74% ee) were obtained using **71** which resulted in the (*R*)-isomer. It is interesting to note that the base **70** gives the (*S*)-isomer with 65% ee.



69 70 71 72 73 74

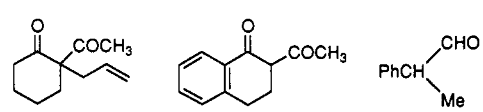
A similar but conceptually different chiral creation of a quaternary carbon center α to a carbonyl group has also been reported.[29] Deprotonation of 75 with a chiral base 74 in ether gave an achiral enolate 76, the carboxylation of which provided (*R*)-77 (67% ee; >95% yield) after methylation (Scheme 8). Changing the solvent to THF decreased the ee dramatically.

Scheme 8



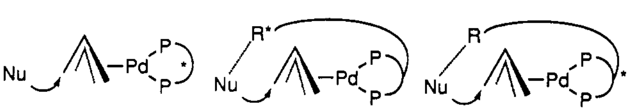
75 76 77

c. Catalytic Methods. Carbon–carbon-bond formation using chiral palladium catalysts has been a particularly active field lately. The catalytic chiral allylation of **50b** with allyl phenyl ether using [(2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)]bis[diphenylphosphine] (DIOP) produced **78** (~10% ee) in quantitative yield.[30] Compounds **79** and **80** afforded the corresponding allylated product in good yield with a low ee. The absolute configuration of the products was not determined. An imaginary model for the low



78 79 80

enantioselectivity is given in Figure 1a, where the

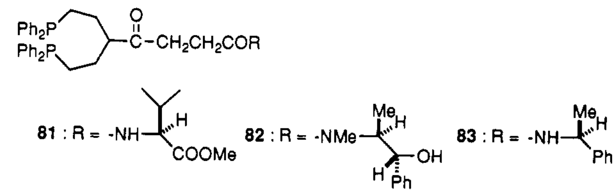


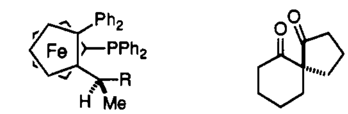
a b c

Figure 1.

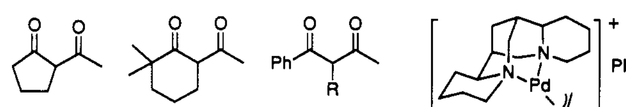
transfer of chirality from the chiral ligand must be poor due to the large distance between the inducing moiety on the ligand and the developing asymmetric center.[30] The phosphine ligand with a chiral pendant may overcome this shortcoming, since it can be expected to interact with the nucleophile as shown in Figure 1b. A chiral phosphine ligand **81** was shown to be effective in the palladium-catalyzed allylation of **50b** giving **78** (52% ee).[31] The chiral ligands **82** and **83** were found to be less effective than **81**. As an extension of this study, the chiral phosphine ligands shown in Figure 1c were developed. Thus, the allylation of 2-acetylcyclohexanone (**50b**) afforded (*S*)-(+)-**78** (81% ee; 88% yield) with a chiral ferrocenylphosphine **84** as ligand.[32] The absolute configuration of the (+)-**78** was determined to be *S* by its conversion to the known diketone **85**.[33]

Surprisingly, 2-acetylcyclopentanone (**86**) yielded an almost racemic product. Other chiral ferrocenylphosphine ligands with the β-(2-hydroxyethyl)amino group gave optically active **78** but with a lower ee. The allylation of the carbonyl compounds **79**, **80**, and **87–89** with **84** as catalyst were also performed affording the corresponding products with 80–22% ee. The cationic





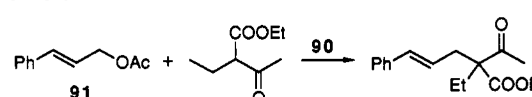
84 : R = -NMe(CH2CH2OH) 85



86 87 88 : R = Me 89 : R = ^{i}Pr 90

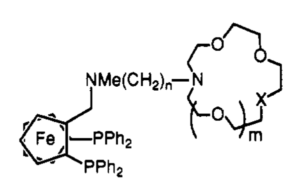
complex [(Pd(η^3-C_3H_5)(sparteine)] PF_6 (**90**) was shown to be a good catalyst precursor for the asymmetric allylation of methyl malonate.[34] The attempted construction of a chiral quaternary carbon with this catalyst proved fruitless (Scheme 9). The reaction of **91** with **92** afforded **93** with only 5% ee.

Scheme 9



91 92 93

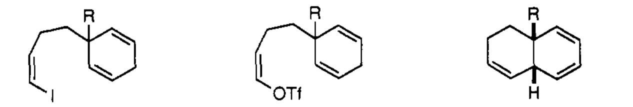
The chiral ferrocenylphosphine ligands **94a–e** modified by crown ethers were synthesized and used in the palladium-catalyzed allylation of 2-acetylcyclohexanone (**50b**).[35] The chiral ligand **94d** was shown to be among the most effective at inducing chirality in the allylation product (*R*)-**78** (75% ee). Other diketones **86** and **88** afforded the corresponding allylated product (65% and 72% ee).



94a : n = 2, m = 1, X = O
94b : n = 2, m = 2, X = O
94c : n = 2, m = 3, X = O
94d : n = 2, m = 2, X = NMe
94e : n = 3, m = 2, X = O

An interesting enantiotopic group differentiation between double bond by a Heck-type reaction was reported. The palladium-catalyzed cyclization of the prochiral alkenyl iodides **95a–c** using (*R*)-[[1,1′-dinaphthalene]-2,2′-diyl]bis[diphenylphosphine] (BINAP) afforded the *cis*-decalin derivatives **97a–c** (35–

45% ee; ~70% yield).[36] A silver salt was necessary in order to get good yield of the products.[37] It was shown that Ag_3PO_4 improved the ee of the products **97a** and **97b** to 69% and 80% ee, respectively.[38] Alkenyl triflates **96a–d** afforded the corresponding *cis*-decalins **97a–d** (~90% ee; 35–60% yield).[39] A silver salt is unnecessary



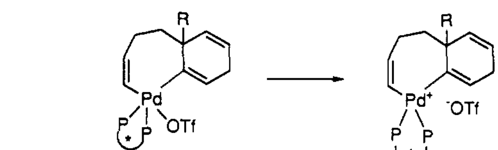
95a : R = COOMe
95b : R = $CH_2OTBDMS$
95c : R = CH_2OAc

96a : R = COOMe
96b : R = $CH_2OTBDMS$
96c : R = CH_2OAc
96d : R = CH_2OCO^tBu

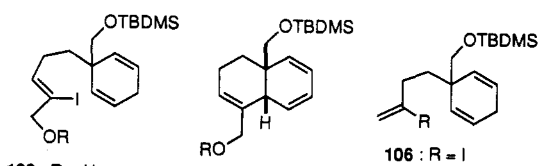
97a : R = COOMe
97b : R = $CH_2OTBDMS$
97c : R = CH_2OAc
97d : R = CH_2OCO^tBu

in this case, because **98** is immediately transformed into the 16-electron Pd^+ intermediate **99** under the reaction conditions (Scheme 10). An enantiodifferentiating Heck reaction of an alkenyl iodide **100** gave **103** in 71% ee in the presence of Ag_3PO_4. Cyclization of **101** under similar reaction conditions provided **104** (83% ee; 63% yield) along with **103** (92% ee; 35% yield). The acetate **105** (87% ee) was obtained from **102** in 67% yield.[39] (*R*)-BINAP has been used as a chiral catalyst for all the cases described above. An application of this type of cyclization to give the bicyclo[4.3.0] system has also been reported.[40] Treatment of the iodide **106** with $PdCl_2$[(*R*)-BINAP], Ag_3PO_4, and $CaCO_3$ resulted in the formation of the *cis*-hydridan **108** (86% ee; 55% yield). The alkenyl triflate **107** gave

Scheme 10



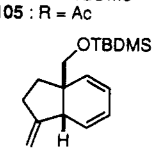
98 **99**



100 : R = H
101 : R = TBDMS
102 : R = Ac

103 : R = H
104 : R = TBDMS
105 : R = Ac

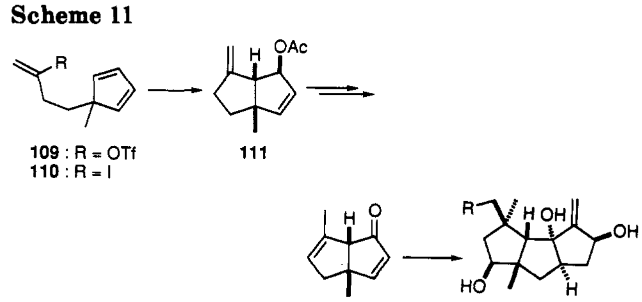
106 : R = I
107 : R = OTf



108

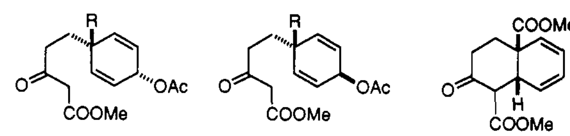
less satisfactory results (73% ee; 63%). A similar reaction of **109** with $Pd(OAc)_2$, (*S*)-BINAP, and tetrabutylammonium acetate provided **111** (80% ee; 89% yield) (Scheme 11).[41] The same product was obtained from the corresponding iodide **110** but with less satisfactory ee and yield. The optically active bicyclic diene **111** was converted into **112**. Since the racemic bicyclic ketone **112** was converted into (±)-$\Delta^{9(12)}$-capnellene-3β,8β,10α-triol (**113**) and (±)-$\Delta^{9(12)}$-capnellene-3β,8β,10α,14-tetrol (**114**),[42] the synthesis of optically active **112** formally constitutes a total synthesis of these sesquiterpenoids in optically active form.

Scheme 11



109 : R = OTf
110 : R = I
111
112
113 : R = H
114 : R = OH

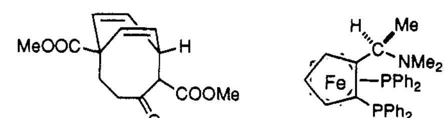
The intramolecular palladium-catalyzed cyclization of the β-keto ester **115** with (*R*)-(*S*)-1-[1-(dimethylamino)ethyl]-1′,2-bis(diphenylphosphino)ferrocene (BPPFA) (**121**) provided **119** (34%; 83% ee) and **120** (51%).[43] The ee of the latter was not reported. Other chiral ligands, (*S*,*S*)-(1,2-dimethyl-1,2-ethanediyl)bis[diphenylphosphine] (chiraphos) and (*S*)-BINAP, gave poorer results both in yield and % ee. Although the same type of cyclization occurred with **116–118**, again less satisfactory results were obtained.



115 : R = COOMe
116 : R = CH_2OAc

117 : R = COOMe
118 : R = CH_2OAc

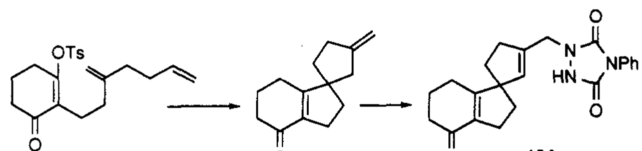
119



120 **121**

An interesting double cyclization giving a chiral quaternary carbon was reported.[44] Cyclization of **122** with DIOP and $Pd(OAc)_2$ in benzene afforded **123** (45% ee; >90% yield), the latter was determined for the cycloadduct **124** by ^{1}H NMR analysis using $Yb(tfc)_3$ as a chiral shift reagent (Scheme 12). The absolute

Scheme 12



122 **123** **124**

configuration of the product was not reported. The palladium-catalyzed cyclization of **125** in the presence of (*R*)-BINAP and Ag_3PO_4 gave (*S*)-**126** (71% ee; 81% yield).[45] Interestingly, when the cyclization was conducted in the presence of 1,2,2,6,6-pentamethylpiperidine (PMP) (*R*)-**126** (66% ee; 77% yield) (Scheme 13) was formed. Applications of this method to the synthesis of a variety of spiroindoles are summarized in Table 3. The silver–amine-promoted cyclizations gave contrasting enantiomers in all cases.

Homochiral rhodium(II) carboxylate **127** was employed in the intramolecular cyclization of diazoketone

Scheme 13

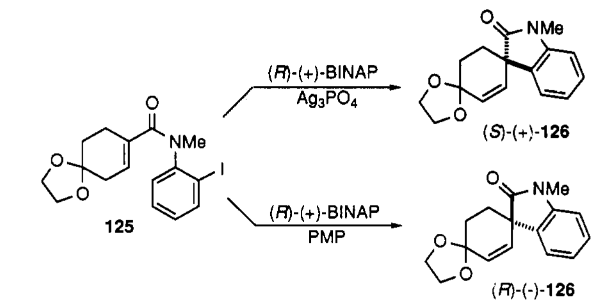
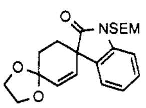
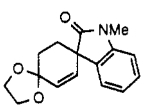


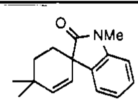
Table 3. Asymmetric Synthesis of Spirocyclic Compounds from the Corresponding Aryl Iodides



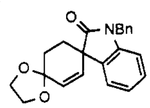
Ag : 76%, (*S*), 65% ee
R_3N : 74%, (*R*), 75% ee



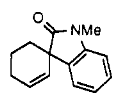
Ag : 81%, (*S*), 71% ee
R_3N : 77%, (*R*), 66% ee



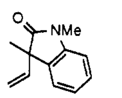
Ag : 99%, (*S*), 72% ee
R_3N : 89%, (*R*), 71% ee



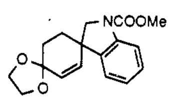
Ag : 91%, (*S*), 41-50% ee
R_3N : 66%, (*R*), 66% ee



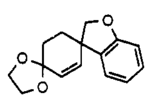
Ag : 74%, (*S*), 79-81% ee
R_3N : 45%, (*R*), 89-95% ee



Ag : 88%, (-), 63% ee
R_3N : 91%, (+), 25% ee

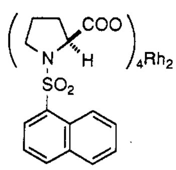


Ag : 90%, (+), 64% ee
R_3N : 68%, (-), 8% ee

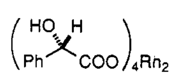


Ag : 91%, (+), 49-55% ee
R_3N : 66%, (-), 0-7% ee

129 affording **130** (33% ee; 80% yield) Scheme 14.[46]

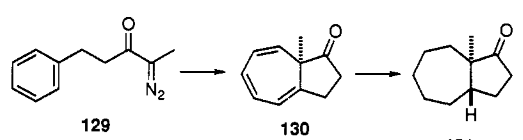


127



128

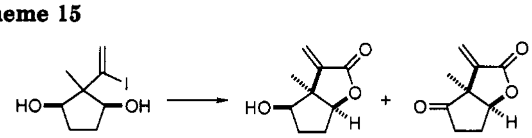
Scheme 14



129 130 131

The absolute configuration of **130** was determined by its conversion to the known ketone **131**. Another rhodium salt **128** gave less satisfactory results (25% ee). Treatment of **132** with $Pd(OAc)_2$, Ag_2O, and (*R*)-BINAP under 1 atm of CO pressure provided α-methylene lactones **133** (57% ee; 44% yield) and **134** (42% ee; 5% yield) Scheme 15).[47]

Scheme 15

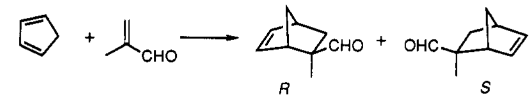


132 133 134

Various chiral catalysts for the Diels–Alder cycloaddition of cyclopentadiene and methacrolein have been reported since Koga's first paper.[48] Table 4 summarizes the results. A variety of chiral alkoxyaluminum dichlorides including **135** and **136** were tested as catalysts in order to deduce the stereochemical relationships between the catalyst and the absolute configuration of the products.[54] The same type of catalysts prepared from $EtAlCl_2$ with chiral diols were studied in detail to give some light on the experimental parameters.[51] The chiral catalyst **138** is among the best both in terms of ee and wide applicability.[50] The results for the creation of quaternary carbons with **138** as well as another borane catalyst **142**[55] are listed in Table 5. The chiral catalyst **135** was used in the cycloaddition of cyclopentadiene with dienophiles **143–145** without any particular enantioselectivity.[56] The chiral titanium complex **146** was shown to be an effective catalyst in the Diels–Alder reaction.[57] The reactions of **147a–c** with methacrolein in the presence of **146** afforded **148a–c**, respectively, (71–86% ee; 43–82% yield).

The one-step chiral construction of the steroid skeleton **152** by the Diels–Alder cycloaddition of **150** and **151** has been reported (Scheme 16).[58] A variety of

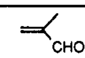
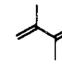
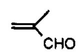
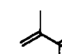
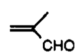
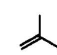
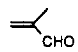
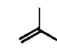
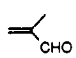
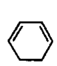
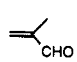
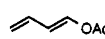
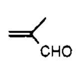
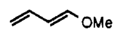
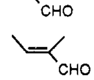
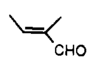
Table 4. Enantioselective Diels–Alder Cycloaddition of Cyclopentadiene and Methacrolein with Chiral Catalysts Giving the *exo*-Adducts



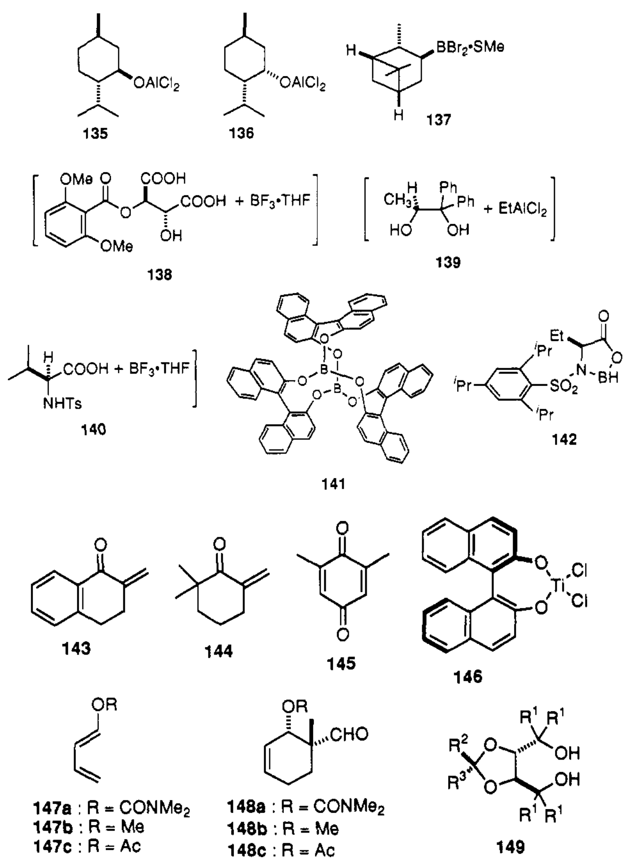
catalyst	configuration of major product	yield, %	% ee	ref
135	*S*	69	72	48
136	*R*	72	66	48
137	*R*	68[a]	29	49
138	*R*	85[a]	96	50
139	*R*	90	86	51
140	*R*	95	64	52
141	*R*	85[a]	90	53

[a] *Exo*/*endo* = 9:1.

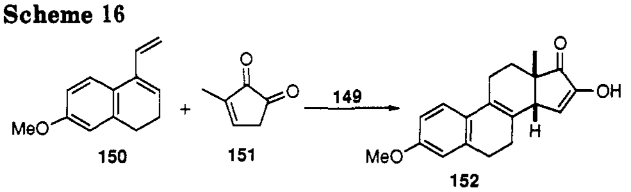
Table 5. Enantioselective Diels–Alder Reactions Catalyzed by 138 or 142

entry	dienophile	diene	catalyst	yield, %	ismer ratio	% ee[a]	ref
1			138	61		97	50
2			142	73		74	55
3			138	65	98/2[b]	91	50
4			142	58	99/1[b]	65	55
5			138	40	93/7[c]	82	50
6			142	84	99/1[d]	71	55
7			142	43	98/2[d]	58	55
8			138	91	3/97[c]	90	50
9			142	85	8/92[c]	51	55

[a] For the major isomer. [b] Ratio of regioisomers. [c] *Endo*/*exo* ratio. [d] Determined by ^1H NMR analysis.



Scheme 16



chiral titanium catalysts prepared from the chiral diol **149** and $TiCl_2(O^iPr)_2$ were tested and the results are listed in Table 6.

Table 6. Diels–Alder Reaction of 150 with 151 Using 149 as a Chiral Ligand Giving 152

	chiral ligand 149			product 152		
entry	R¹	R²	R³	yield, %	% ee	configuration
1	Ph	Me	Me	64	45	13-*S*,14-*R*
2	Ph	Me	Ph	71	49	13-*R*,14-*S*
3	*a*	Me	Me	60	78	13-*R*,14-*S*
4	*b*	Me	Me	76	70	13-*S*,14-*R*
5	*b*	Et	Et	77	79	13-*S*,14-*R*

[a] Naphthalene-1-yl. [b] 3,5-Dimethylphenyl.

d. Miscellaneous Reactions. Detailed studies on the enantioselective carbenoid cyclopropanation of olefins with alkyl diazoacetate catalyzed by chiral cobalt(II) complexes **153** and **154** have been reported.[59,60] Examples involving the creation of a quarternary carbon are compiled in Table 7. The attempted conjugate addition of a chiral sulfonium ylide **155** to **156** afforded a cyclopropyl derivative **157** in 49% yield with a disappointingly low ee (Scheme 17).[61]

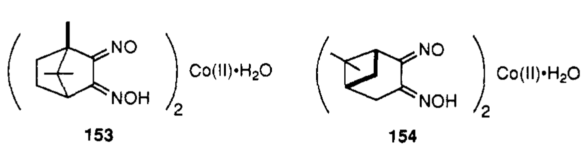
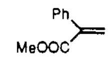
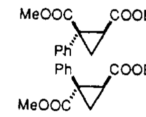
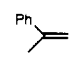
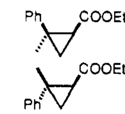
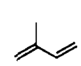
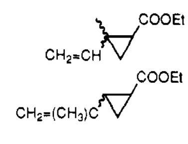
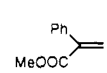
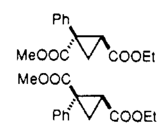
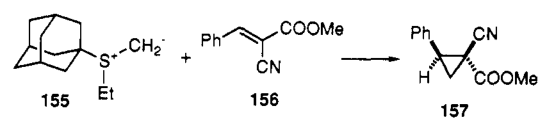


Table 7. Asymmetric Cyclopropanation of Olefins with Ethyl Diazoacetate

olefin	catalyst	yield, %	product	% ee ([α]d)	ref
	95	92		37 71	59
	95	97		(+35.4°)[a] (+145°)[a]	59
	95	*b*		(+115°) (+145°)	59
	96	95		26 42	60

[a] Absolute configuration was not determined. [b] Not reported.

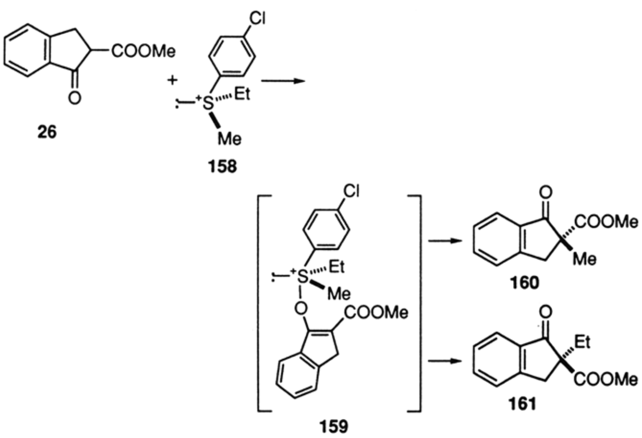
Scheme 17



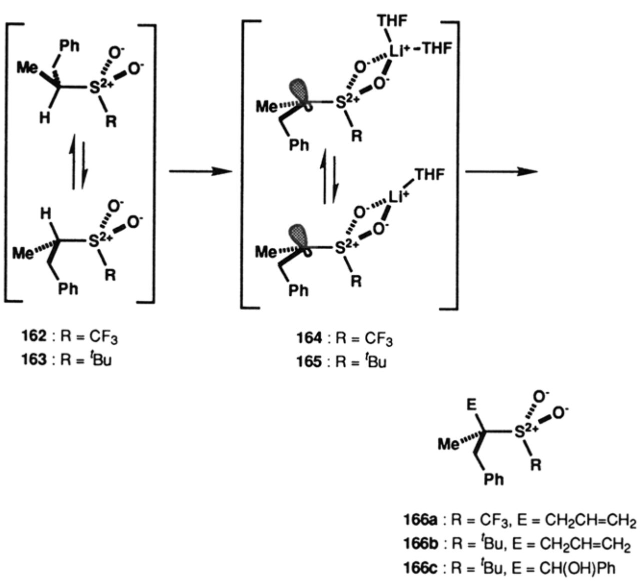
The alkylation of **26** with a chiral sulfonium salt **158** was reported to give **160** (4% ee; 30% yield) and **161** (10% ee; 44% yield).[62] Although the ee was quite low, it is interesting to note that the methylated product **160** has the opposite chirality to the ethylated product **161**. An S–O sulfurane intermediate **159** was proposed for this alkyl transfer reactions, since the (*R*)-sulfonium salt **158** gave (*R*)-**160** and (*S*)-**161** (Scheme 18).

Deprotonation of the (*S*)-sulfone **162** with ^{n}BuLi in THF generated the corresponding lithio sulfone **164**.[63] The rate of racemization of **164** was measured in the presence of *N,N'*-dimethyl-*N,N'*-dipropylurea to determine an extrapolated half-life of 3 h at −105 °C. Thus, the lithio sulfone **164** was shown to be configurationally rather stable at very low temperatures. Allylation of **164**, generated using ^{t}BuLi, with allyl iodide in THF at −70 °C gave (*R*)-**166a** (≥95% ee; 79% yield) (Scheme 19). The same reaction with the (*S*)-sulfone **163** afforded the corresponding homoallylic sulfone (*R*)-**166b** (80%; 92% ee). Reaction of lithio sulfone **165** with benzaldehyde gave a 3:2 mixture of hydroxy sulfones (*S,R*)- and (*S,S*)-**166c** (84%), each with 92% ee.

Scheme 18

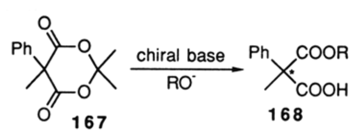


Scheme 19

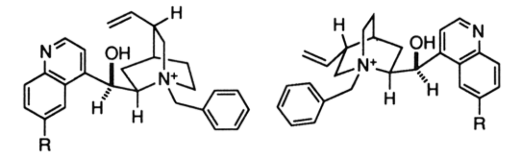


The differentiation of the enantiotopic carbonyl groups in the hydrolysis of **167** was reported.[64] Treatment of **167** with an alkoxide together with a chiral quaternary ammonium cation (**169** or **170**) in toluene followed by acid hydrolysis afforded a chiral monoester **168**. The *pro-S* carbonyl group in **167** was attacked by an alkoxide ion with **169a** and **169b** and *vice versa* with **170a** and **170b**. Selected examples are summarized in Table 8.

Table 8. Asymmetric Monoesterification of 167



reaction conditions			product 168		
chiral base	RO	temp, °C	yield, %	% ee	selectivity
169a	MeO	-50	88	4	*pro-S*
169b	MeO	-50	89	27	*pro-S*
170a	MeO	-50	92	8	*pro-R*
170b	MeO	-50	73	34	*pro-R*
170b	MeO	-78	100	37	*pro-R*
169b	EtO	-78	90	45	*pro-S*
169b	^{n}PrO	-78	91	51	*pro-S*
169b	^{n}BuO	-50	69	45	*pro-S*
170b	^{n}BuO	-78	77	40	*pro-R*

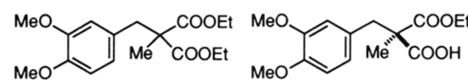


169a : R = H
169b : R = OMe
170a : R = H
170b : R = OMe

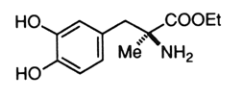
2. Biological Method

Discrimination of enantiotopic groups using enzymes has occupied an important position in the creation of quaternary carbon centers. Studies have been mainly focused on the enantiodifferentiating hydrolysis of 2,2-disubstituted malonates using pig liver esterase (PLE) and the enantiodifferentiating reduction of symmetrical diketones by microorganisms.

a. Hydrolysis of Diesters. The first successful example of the hydrolysis of the disubstituted malonate ester with PLE was the enantioselective synthesis of (*R*)-**172** from dimethyl malonate **171**.[65] Although the ee is only moderate (~59% ee), the optically active half-ester (*R*)-**172** is an important starting material for the synthesis of the antihypertensive (*S*)-α-methyl-DOPA (**173**). Other results are summarized in Table



171 **172**

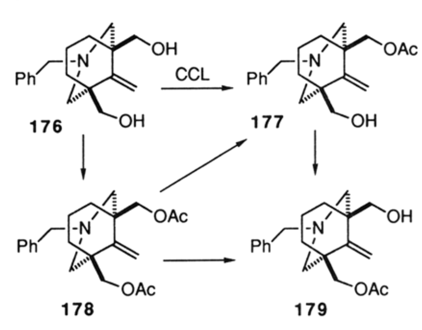


173

9. An interesting reversal of enantiodifferentiation from *pro-S* to *pro-R* in the hydrolysis was observed. This depended on the chain length of the alkyl substituents.[67] The tendency was notable on the hydrolysis of the dimethyl esters (entries 11–17). Chymotrypsin was shown to be a better enzyme in the hydrolysis of ethyl 2-benzyl-2-methylmalonate to give the corresponding (*R*)-half ester with >98% ee.[67] The same was true for the corresponding methyl ester. Detailed studies on the effect of DMSO have shown that the ratio of the (*R*)-enantiomers of the monoesters increased with increasing the concentration of DMSO in the PLE-catalyzed hydrolysis of 2,2-disubstituted methyl malonates.[73]

An interesting enantiodifferentiating hydrolysis of diacetate **178** was reported (Scheme 20).[74] PLE, porcine

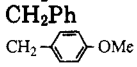
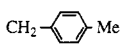
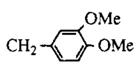
Scheme 20



pancreas lipase (PPL), and *Candida cylindracea* lipase (CCL) catalyzed hydrolysis of **178** to afford the optically active monoacetate in 64–80% ee in low yield. The

Table 9. Enantioselective Hydrolysis of 2,2-Disubstituted Malonates 174 with PLE

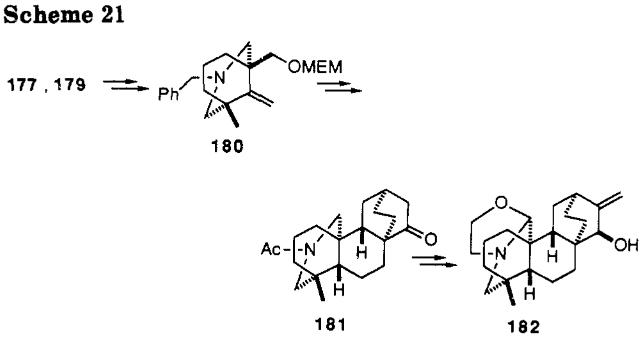
174 175

entry	malonate 174 R¹	R²	product 175 yield, %	% ee	configuration	ref
1	Et	Et	*a*	20	*S*	66
2	Et	Et	*b*	15	*S*	67
3	Et	ⁿPr	*a*	8	*S*	66
4	Et	ⁿPr	*b*	10	*S*	67
5	Et	ⁿBu	*a*	38	*S*	66
6	Et	ⁿBu	*b*	25	*S*	67
7	Et	ⁿPentyl	*b*	10	*R*	67
8	Et	ⁿOctyl	*b*	5	*S*	67
9	Et	Ph	*a*	86	*S*	66
10	Et	CH_2Ph	*b*	23	*R*	67
11	Me	Et	*b*	73	*S*	67
12	Me	ⁿPr	*b*	52	*S*	67
13	Me	ⁿBu	*a*	50	*S*	66
14	Me	ⁿBu	*b*	58	*S*	67
15	Me	ⁿPentyl	*b*	46	*R*	67
16	Me	ⁿHexyl	*b*	87	*R*	67
17	Me	ⁿHeptyl	*b*	88	*R*	67
18	Me	CH_2Ph	*a*	*c*	*R*	68
19	Me	CH_2Ph	*b*	16	*R*	67
20	Me	CH_2Ph	*d*	45[e]	*R*	69
21	Me		*d*	82[e]	*R*	69
22	Me		95	96	*R*	70, 71
23	Me		*d*	93[e]	*R*	69
24	Me	CH_2Br	*f*	46	*c*	72
25	Me	CH_2OH	37	6	*S*	72
26	Me	CH_2OMe	86	21	*S*	72
27	Me	$CH_2OTBDMS$	49	95	*R*	72
28	Me	CH_2OCH_2Ph	90	67	*R*	72
29	Me	CH_2O^tBu	90	96	*R*	72

[a] Not specified but good yield. [b] 90–98%. [c] Not determined. [d] 85–100%. [e] Performed in the buffer containing 50% DMSO. [f] Not specified.

(−)-acetate **177** was obtained with PLE or PPL, while (+)-acetate **179** was obtained with CCL. Transesterification of the diol **176** with vinyl acetate using CCL in benzene produced (−)-**177** (100% ee; 32% yield). Both of (−)- and (+)-monoacetates **177** and **179** were converted into the same azabicyclo[3.3.1]nonane **180**, which was further transformed to **181**. Since **181** had been transformed into naturally occurring atisine (**182**),[75] synthesis of the optically active **181** constituted the first total synthesis of naturally occurring atisine (**182**) (Scheme 21).

Scheme 21



b. Reduction of Diketones. Some early brilliant work on the total synthesis of optically active 17β-estradiol 3-methyl ether (**186**) involved the enantiodifferentiating reduction of diketone **183** by a microorganism (Scheme 22).[76] Incubation of the dione **183** in *Bacillus thuringiensis* culture afforded **184** in almost pure enantiomeric form in 60–70% yield, whereas *Saccharomyced uvarum* converted **183** into **185**. The latter was transformed into **186**. Extensive studies were reported on the selection of the microorganism for the selective reduction of **183** into **184** or **185**.[77]

Scheme 22

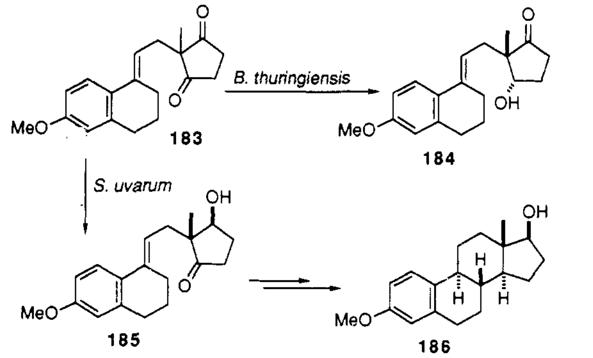
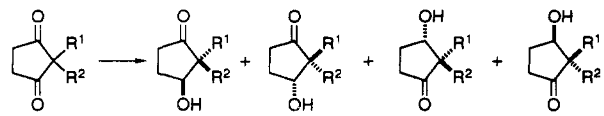
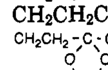
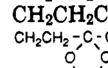


Table 10. Enantioselective Synthesis of 2,2-Disubstituted 3-Hydroxycyclopentanones with Bakers' Yeast (*Saccharomyces cerevisiae*)



187 188 189 190 191

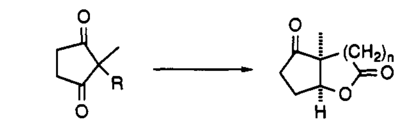
entry	substrate R¹	R²	yield, % (% ee) 188	190	ref(s)
1	Me	$CH_2CH_2CH_3$	60 (98)		78, 79
2	Me	$CH_2CH{=}CH_2$	68 (98)	8 (98)	78, 79
3	Me	$CH_2CH{=}CH_2$	65 (90)[a]		80, 81
4	Me	$CH_2C{\equiv}CH$	40 (98)	20 (98)	78, 79
5	Me	$CH_2C{\equiv}CH$	65 (*b*)[a]		81
6	Me	$CH_2C(CH_3){=}CH_2$	75 (98)		78
7	Me	CH_2CH_2CN	68 (98)	3 (98)	78
8	Me				82
9	Me	$CH_2CH_2CO(CH_2)_3COOMe$		92 (*b*)	83
10	Et	$CH_2CH_2COCH_3$			84
11	Et		*b*		82
12	Et	$CH_2CH_2COCH_2CH_2SPh$	*b*	53 (100)[c]	85
13	Et	$CH_2CH_2COCH_2CH$-$(OTHP)CH_3$	*a*	70 (100)	86

[a] *Dipodusucus* sp. was used. [b] Not specified. [c] *Schizosaccharomyces* sp. was used.

A number of 2,2-disubstituted 1,3-cyclopentanediones were reduced with Bakers' yeast (*Saccharomyces Cerevisiae*) to afford the corresponding hydroxy ketones with high ee.[78–86] The reported results are summarized in Table 10. It is interesting that the diketones with a long alkyl chain give the (2*R*,3*S*)-alcohol **190** diastereoselectively (entries 9 and 12), while those with a shorter chain yielded the other diastereoisomer **188** as major product (entries 1–7). The ee was high in every case. Neither **189** nor **191**, enantiomeric to **188** or **190**, respectively, was obtained from the microbial reduction.

The rate and enantioselectivity of the reduction of 187 [R^1 = Me, R^2 = $(CH_2)_2CO(CH_2)_3COOMe$] was dramatically increased by the addition of either allyl alcohol or α,β-unsaturated carbonyl compounds.[83] This enhancement was not limited to *Schizosaccharomyces pombe* but was also demonstrated with *Schizosaccharomyces malidevorans*, *Saccharomyces cerevisiae*, and *Saccharomyces uvarum*. Cyclopentane-1,3-diones with a carboxyl or an ester moiety at C_2 afforded lactones directly. Reduction of **192** with *Dipodascus albidus*[81] or **193** with bakers' yeast[79] gave rise to the γ-lactone **195** with high ee in 64% or 9% yield, respectively (Scheme 23). The δ-lactone **196** of 100% ee was

Scheme 23

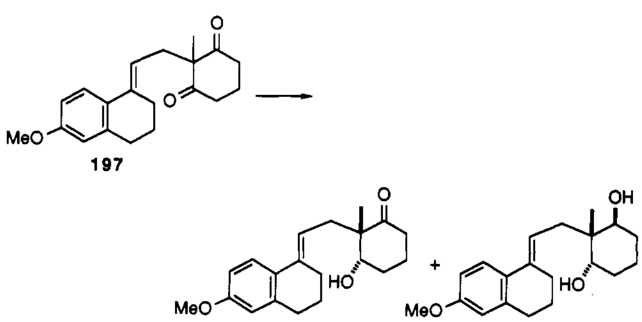


192 : R = CH_2COOH 195 : n = 1
193 : R = CH_2COOMe 196 : n = 2
194 : R = CH_2CH_2COOMe

obtained in 52% yield from **194** with bakers' yeast.[79]

An early example of an enantiodifferentiating reduction of 2,2-disubstituted cyclohexane-1,3-dione includes the transformation of **197** into **198** (Scheme 24).[87]

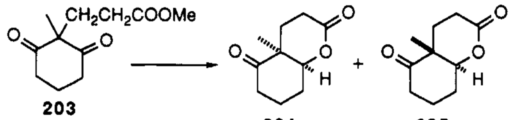
Scheme 24



197 198 199

The diol **199** was obtained as a byproduct. Neither the yield or ee was specified. Cyclic 1,3-diones **200** were also reduced with bakers' yeast.[79,88,89] The results are compiled in Table 11. The larger the ring size, the lower the yield. Thus, no reduction was observed with the 9-membered diketone after 48 h.[89] The diketo ester **203** afforded **204** and **205** in 7% and 13% yield with a recovery of 60% starting material (Scheme 25).[79]

Scheme 25

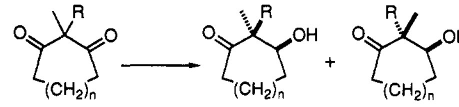


203 204 205

(2*S*,3*S*)-2-Allyl-3-hydroxy-2-methylcyclopentanone (**206**) obtained by the bakers' yeast reduction of the corresponding diketone was utilized as a chiral starting material for the syntheses of (8*R*,15*S*)-8-methylprostaglandin C_2[90] and anguidine.[91,92]

An interesting reduction of bicyclic diketones with baker's yeast has also been reported. The diketones **207** and **208** provided **209** (99.5% ee; 59% yield)[93] and **210** (100% ee; 71% yield),[94] respectively. A ketone **211**

Table 11. Reduction of 2,2-Disubstituted Cyclic 1,3-Diones with Bakers' Yeast[a]

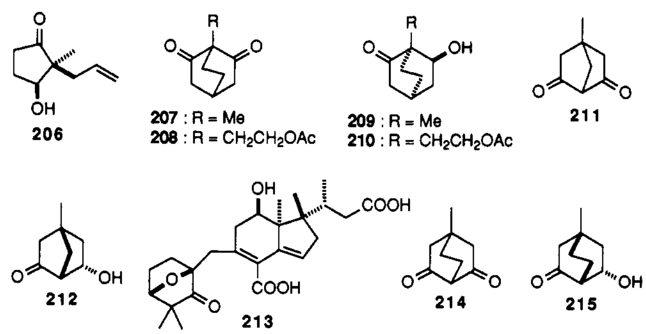


200 201 202

n	substrate R	yield, % 201	yield, % 202	recovered dione, %	ref(s)
1	$CH_2CH_2CH_3$	18	62	15	79, 88
1	$CH_2CH{=}CH_2$	36	44	15	79, 88
1	$CH_2C{\equiv}CH$	20	55	20	79, 88
1	$CH_2C(CH_3){=}CH_2$	20	29	20	79
1	CH_2CH_2CN	15	34	30	79
1	$(CH_2)_3C(CH_3){=}CH_2$	18	57	10	88
2	$CH_2CH_2CH_3$	0.2	10	75	88
2	$CH_2CH{=}CH_2$	20		60	88
2	$CH_2C{\equiv}CH$	43	17	30	88
2	$CH_2C(CH_3){=}CH_2$	22	18	50	88
3	$CH_2CH{=}CH_2$	4	1	75	88
4	$CH_2CH{=}CH_2$			80	88

[a] >98% ee for each product.

with a bicyclo[2.2.1]ring system afforded **212** (82.5% ee; 55% yield), which was used for the synthesis of the optically active glycinoeclepin A (**213**),[95] a potent hatching stimulus for the soybean cyst nematode from the dried root of the kidney bean.[96] 4-Methylbicyclo[2.2.2]octane-2,6-dione (**214**) was also reduced with bakers' yeast to give **215** (98% ee; 58% yield).[93]



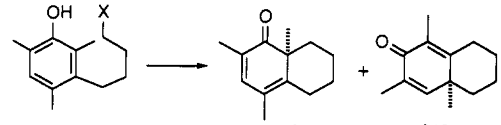
206 207 : R = Me 208 : R = CH_2CH_2OAc 209 : R = Me 210 : R = CH_2CH_2OAc 211 212 213 214 215

B. Diastereodifferentiating Reactions

1. Use of Chiral Nucleofuges

The intramolecular alkylation of a phenol **216**, containing a chiral leaving group, gave bicyclic ketones **217** and **218** under basic conditions (Scheme 26).[97,98]

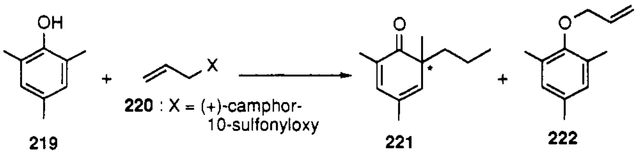
Scheme 26



216 : X = (+)-camphor-10-sulfonyloxy 217 218

Lithium butoxide in refluxing *tert*-butyl alcohols led to the highest optical yields of **217** (19% ee; 70% yield) and **218** (13% ee; 9% yield). The intermolecular version of this reaction is shown in Scheme 27. The reaction of 2,4,6-trimethylphenol (**219**) with allyl (+)-camphor-10-sulfonate (**220**) gave **221** (8% ee; 22%) along with an allyl ether **222**. Though the ee's were not exciting, these reactions are very important because they dem-

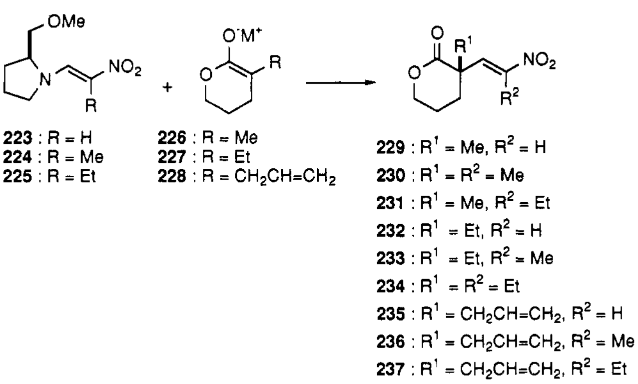
Scheme 27



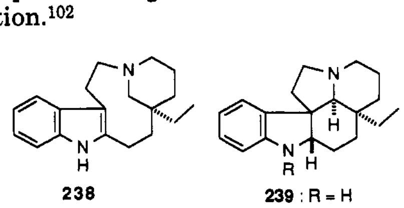
onstrate for the first time asymmetric induction by a chiral leaving group.

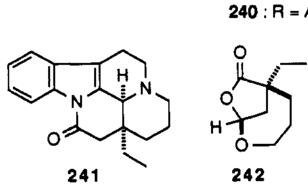
A successful asymmetric synthesis of quaternary carbon centers using a chiral leaving group has been reported (Scheme 28).[99,100] The actual process involves

Scheme 28



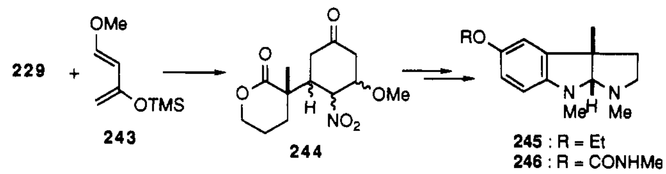
an addition–elimination reaction. The reaction of a nitro enamine **223** with an enolate **226** of the α-substituted δ-lactone yielded the corresponding product **229**. Zinc(II) as a countercation gave a better yield (99%) and ee (86%) than lithium (30% ee; 81% yield). This was generally true for other combinations of nitro enamines **223–225** with the enolates **226–228**. The ee's from zinc enolates lay in the 96–82% range, but dropped to 30–45% with lithium enolates. The lactone **232** is an ideal chiral building block for the synthesis of *Aspidosperma* alkaloids such as a (+)-quebrachamine (**238**), (−)-aspidospermidine (**239**), and (+)-demethoxyaspidospermine (**240**) and *Hunteria* alkaloid, (−)-eburnamonine (**241**), because all of these alkaloids have common structural feature involving a quaternary carbon bearing an ethyl group, and C_1, C_2, and C_3 units as a non-tryptamine part readily accessible from **232**. In fact, the chiral syntheses of all of these four alkaloids were accomplished starting from **232**.[101,102] The bicyclic acetal **242**, a pivotal intermediate for the synthesis of (−)-eburnamonine (**241**), was prepared from L-glutaric acid in more than 10 steps with an overall 13% yield.[103] The acetal **242** was synthesized from **232** in 74% yield in two steps involving the Nef reaction followed by acetalization.[102]



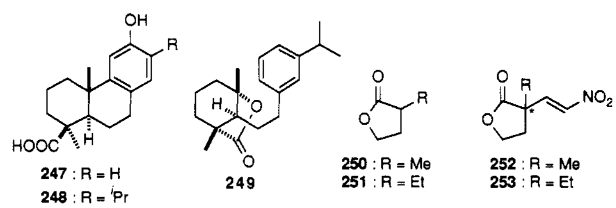


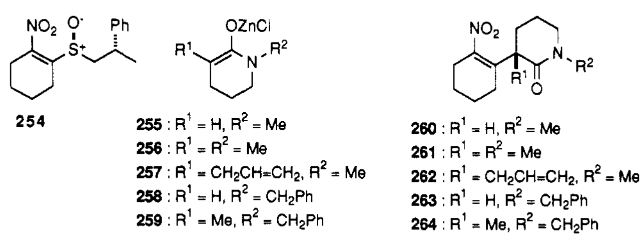
(−)-Physostigmine (**246**) was synthesized from the chiral α,α-disubstituted γ-lactone **229** via (−)-eserethole (**245**) (Scheme 29).[104] The Diels–Alder cyclization of

Scheme 29



229 with the Danishefsky's diene **243** provided **244**. Although the cyclic adduct **244** was a diastereoisomeric mixture, the regiochemistry was controlled perfectly due to the electronic nature of the diene as well as the dienophile. The same lactone **229** was shown to be a useful starting material for the synthesis of optically active tricyclic diterpenoids such as (+)-podocarpic acid (**247**) and (+)-lambertic acid (**248**).[105,106] A unique secodehydroabietane **249** was synthesized from the enantiomer of **229**.[107] The γ-lactones **250** and **251** were used in the chiral nitroolefination with **223** to afford **252** and **253** in good yield but with poor ee's (15% and 63%).[99,100]





A cyclic nitroolefin **254** possessing a chiral sulfinyl group at the β-position was shown to be a good substrate for chiral induction through an addition–elimination process.[108] The enolates **255–259** of the 6-membered

Table 12. Nitroolefination of Lactams with 254

enolate	countercation	product	yield, %	% ee
255	Li^+	**260**	70	44
255	Zn^{2+}	**260**	87	87
256	Li^+	**261**	95	85
256	Zn^{2+}	**261**	93	99
257	Li^+	**262**	97	89
257	Zn^{2+}	**262**	96	99
258	Li^+	**263**	91	86
259	Zn^{2+}	**264**	91	86
265	Zn^{2+}	**269**	82	43
266	Li^+	**270**	89	33
266	Zn^{2+}	**270**	91	84
267	Zn^{2+}	**271**	96	73
268	Zn^{2+}	**272**	94	81

lactams attack the β-position of an α,β-unsaturated nitro group in **254** followed by elimination of the sulfinyl group to afford the corresponding nitro lactams **260–264**. It should be noted that the nitroolefins **260** and

263 were obtained in 87% ee and 86% ee, respectively, although they were supposed to be readily epimerized due to an extremely labile hydrogen prone to enolization. The same type of reaction occurs with γ-lactam enolates **265–268**, giving the corresponding products **269–272**. These results are given in Table 12. Zinc enolates generally gave higher ee's than the lithium enolates. The nitroolefin **270** has the total framework including two nitrogens necessary for the construction of (−)-physostigmine (**246**). The chiral synthesis of (−)-physostigmine (**246**) was reported using **270** as starting material.[109]

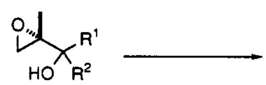
265 : R = H
266 : R^1 = Me
267 : R^1 = Et
268 : R^1 = $CH_2CH{=}CH_2$

269 : R = H
270 : R^1 = Me
271 : R^1 = Et
272 : R^1 = $CH_2CH{=}CH_2$

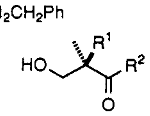
2. Intramolecular Chiral Transfer Reactions

Intramolecular chiral transfer reactions, particularly reactions involving the 1,2-shift of a carbon–carbon bond, are important for constructing chiral quaternary carbons. Since this type of reaction is stereospecific, a product with high ee is obtained when the starting material has a high degree of ee. Chiral epoxides have been frequently used in this type of reaction. The chiral epoxy alcohols **273–275** were converted into the product **276–278** in good yields, when treated with $BF_3{\cdot}OEt_2$ in dichloromethane (Scheme 30).[110] The ee's (87%) of the products were the same as those of the starting material, indicating a 100% chiral transfer efficiency.

Scheme 30



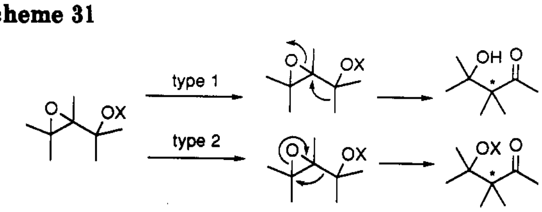
273 : R^1 = Tol, R^2 = CH_2CH_2Ph
274 : R^1 = Tol, R^2 = C≡CH
275 : R^1 = $C(SiMe_3){=}CH_2$, R^2 = CH_2CH_2Ph



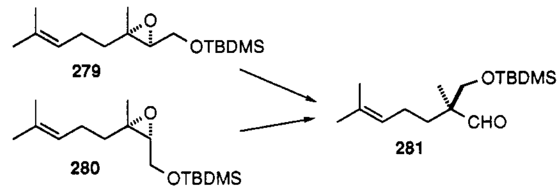
276 : R^1 = Tol, R^2 = CH_2CH_2Ph
277 : R^1 = Tol, R^2 = C≡CH
278 : R^1 = $C(SiMe_3){=}CH_2$, R^2 = CH_2CH_2Ph

Two types of acid-catalyzed rearrangements of epoxides to carbonyl groups are possible as shown in Scheme 31. The transformation illustrated in Scheme 30 is an example of type I. The successful asymmetric creation of a quaternary carbon center through a type II rearrangement has been reported.[111] Both (2*S*,3*S*)-**279** and (2*R*,3*S*)-**280** gave **281** of *S* configuration at the newly created quaternary carbon (Scheme 32). A 100% chiral transfer was observed for both substrates.

Scheme 31

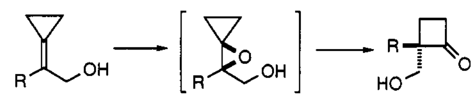


Scheme 32



A Katsuki–Sharpless asymmetric epoxidation of the cyclopropylidene alcohols **282a–c** in the presence of either diethyl or diisopropyl D-(−)-tartrate afforded the unstable spiroepoxides **283a–c**, respectively, which underwent a spontaneous rearrangement under the reaction conditions to yield the corresponding chiral cyclobutanes **284a–c** in moderate to good yield (Scheme 33).[112] The ee's of the products depend upon the chiral induction in the epoxidation step, which ranged from 73% to 96%. (+)-α-Cuparenone (**285**) was synthesized from the enantiomer of **284c**. A similar rearrangement of **286** furnished **284a** of high ee in good yield, from the enantiomers of which (−)-frontalin (**287**) was prepared.[113] Chirality transfer from a secondary alcohol **288** using an anionic oxy-Cope rearrangement created a chiral quaternary carbon center in the product **289**.[114] The yield was 75% and the efficiency of the chirality transfer was 95%.

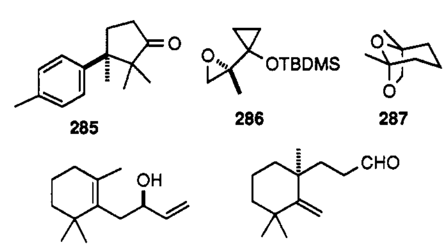
Scheme 33



282a : R^1 = Me
282b : R^1 = alkyl
282c : R^1 = Tol

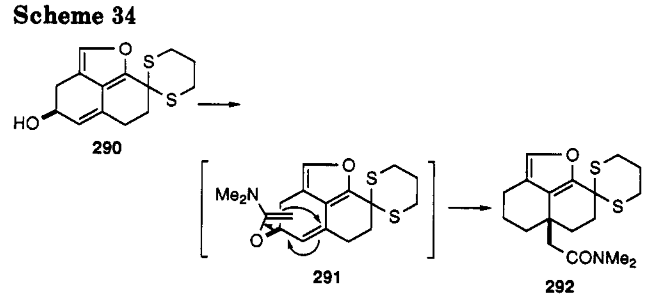
283a : R^1 = Me
283b : R^1 = alkyl
283c : R^1 = Tol

284a : R^1 = Me
284b : R^1 = alkyl
284c : R^1 = Tol

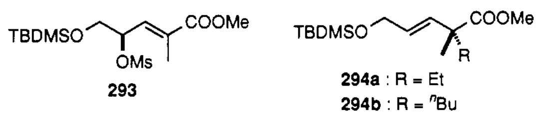


The Claisen rearrangement of the optically active secondary alcohol **290** by treatment with *N*,*N*-dimethylacetamide dimethyl acetal in refluxing *o*-xylene proceeded smoothly to produce **292** in 51% yield with 100% chirality transfer via **291** (Scheme 34).[115] A 1,3-

Scheme 34



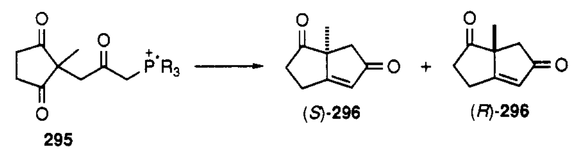
chirality transfer from a mesylate **293** of an optically active secondary alcohol was reported.[116] Treatment of **293** with $EtCu(CN)Li \cdot BF_3$ or $^{n}BuCu(CN)Li \cdot BF_3$ afforded **294a** or **294b** in 92% or 97% yield, respectively. A nearly quantitative transfer of chirality was observed.



3. Miscellaneous Reactions

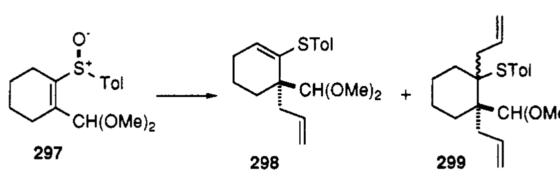
An interesting diastereodifferentiation between the two carbonyl groups in **295** by an intramolecular Wittig reaction has been reported (Scheme 35).[117,118] (+)-(*R*)-

Scheme 35



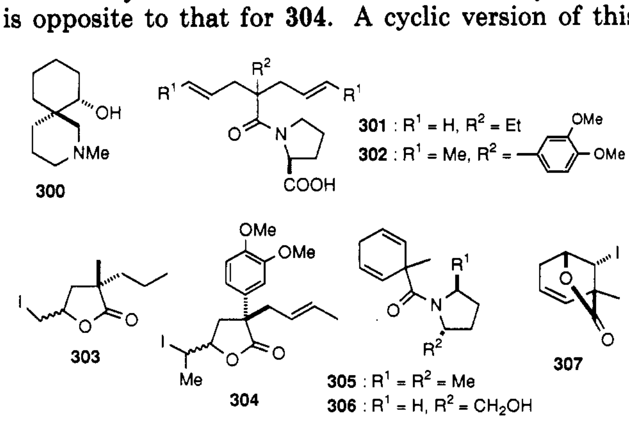
Cyclohexyl-*O*-anisylmethyl phosphonium salt afforded (*S*)-**296** with the highest ee (77%) of the various chiral phosphonium salts examined. Unfortunately further development of this work has not yet been reported. A chiral sulfoxide **297** underwent a Pummerer-type reaction on treatment with allylmagnesium bromide to yield **298** with 96% ee in 60% yield along with the diallyl compound **299** (23%) (Scheme 36).[119] The former was

Scheme 36



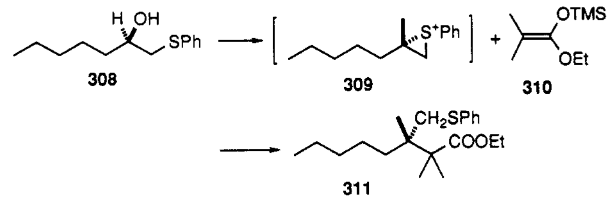
converted into (−)-sibirine (**300**), an alkaloid isolated from *Nitraria sibirica*.

Iodolactonization of **301** and **302** in aqueous THF afforded **303** (24% ee; 96%) and **304** (16% ee; 38%), respectively.[120] Although ee's are low for both reactions, it is worthy of note that the enantioselectivity for **303** is opposite to that for **304**. A cyclic version of this



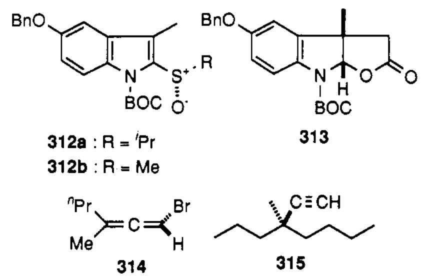
reaction involving **305** and **306** has also been reported.[121] A low level of enantioselectivity (30% ee from **305** and 42% ee from **306**) in the product **307** was observed. Treatment of a tertiary alcohol **308** (86% ee) with $TiCl_4$ afforded an intermediate episulfonium ion **309**, which

Scheme 37



reacted with ketene silyl acetal **310** yielding **311** in 71% yield with 83% ee (Scheme 37).[122]

The reaction of optically active 2-(alkylsulfinyl)indole **312a** (≥97% ee) with dichloro ketene followed by reduction with tributyltin hydride afforded indoline butyrolactone **313** (70–75% ee; 37% yield).[123] Essentially racemic **313** was obtained when the chiral sulfoxide **312b** with 93% ee was used. Optically active **313** was converted into (−)-physostigmine. A chiral allenic bromide **314** gave **315** (>99% ee; 71% yield) with (*n*-BuCuBr)MgCl·LiBr in THF.[124]



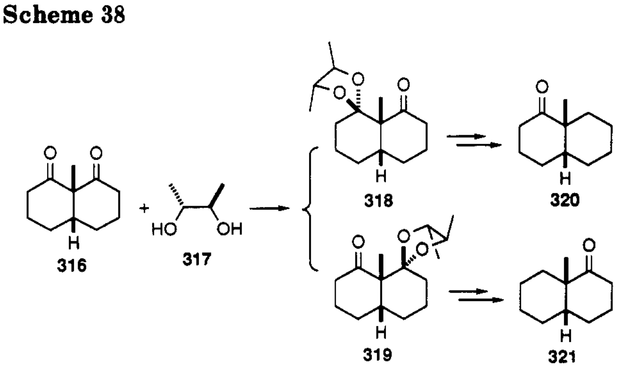
III. Diastereoselective Creation

A. Enantiodifferentiating Reactions

Achiral substrates as well as chiral reagents are needed for diastereoselective synthesis using enantiodifferentiating reactions. Only a few reactions whereby a chiral quaternary carbon is created belong to this category.

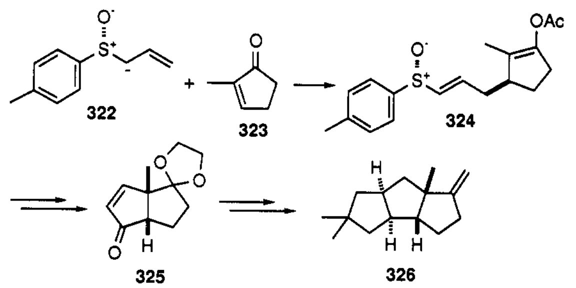
The enantiotopically differentiating monoacetalization of prochiral diketone **316** with (2*R*,3*R*)-2,3-butanediol (**317**) afforded the diastereomeric monoacetals **318** and **319** in 74% and 8% yields, respectively.[125] The acetal was converted into a ketone either **320** or its enantiomer **321** (Scheme 38). The Michael addition of

Scheme 38

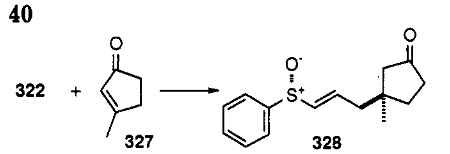


a chiral sulfinylallyl anion **322** and 2-methyl-2-cyclopentenone (**323**) followed by *in situ* *O*-acetylation with acetyl chloride provided **324** in 84% yield and 95% op at C-3.[126] The enol acetate **324** was transformed into (+)-hirsutene (**326**) (isolated from *Coriolus consors*) via **325** possessing a chiral quaternary carbon center (Scheme 39). Addition of **322** to 3-methyl-2-cyclopen-

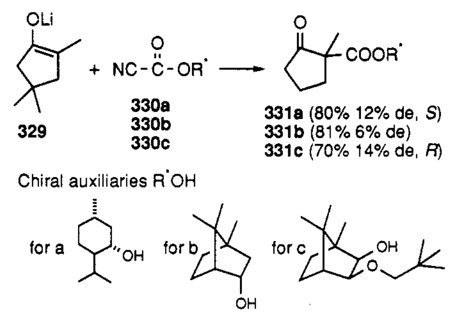
Scheme 39



Scheme 40



Scheme 41



tenone (327) afforded 3,3-disubstituted cyclopentenone 328 (80% yield) with 90% diastereoselectivity (Scheme 40).

Acylation of the achiral lithium enolate 329 with chiral cyanoformate 330a–c provided the corresponding β-keto esters 331a–c in good yield but with poor diastereoselectivity (Scheme 41).[127]

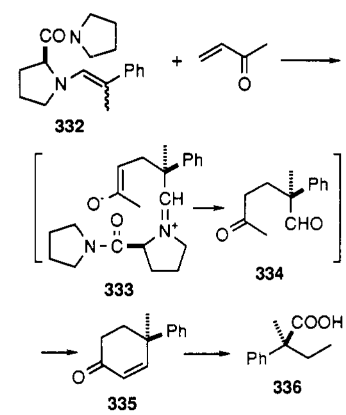
B. Diastereodifferentiating Reactions

1. Alkylation of Chiral Enamines

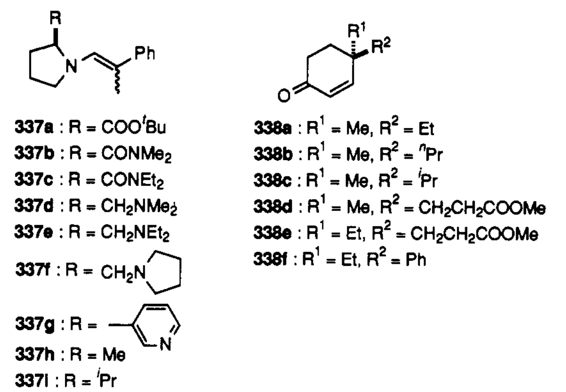
Alkylation of ketones and aldehydes through enamines is one of the most important methods of carbon–carbon-bond formation. The Michael-type addition of the chiral enamine 332 to methyl vinyl ketone in methanol provided 333 diastereoselectively. The *in situ* hydrolysis of 333 with acetic acid afforded 4,4-disubstituted cyclohexenone 335 (36.5% op) *via* the aldehyde 334 in 48% overall yield from the enamine 332 (Scheme 42).[128,129] The absolute configuration of 335 was determined by its conversion to the known acid 336.[130] The optical yield of 335 increased to 49.1% in methanol–benzene (1:9). A number of chiral proline derivatives 337a–i were screened without any remarkable increase in optical yield.[128,129,131] Chiral 4,4-disubstituted cyclohexenones 338a–f were prepared in the similar manner.[128,132] The enantiomeric excesses of these compounds were not determined.

(+)-Mesembrine (341), an antipode of naturally occurring (−)-mesembrine, was synthesized by this method (Scheme 43).[133,134] Thus, the chiral enamine 339 was converted into 340 in 38% yield by the alkylation with methyl vinyl ketone followed by acid treatment in a one-pot reaction. Transformation of

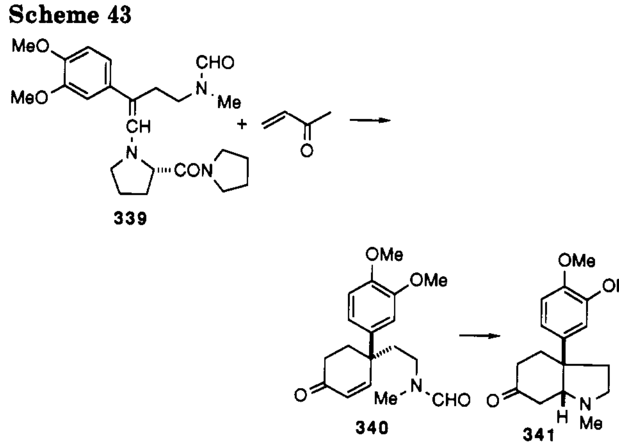
Scheme 42



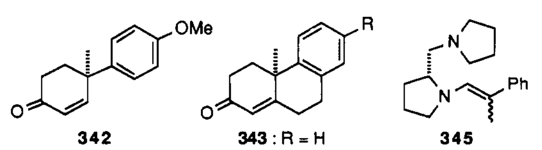
340 to (+)-mesembrine (341) was effected with ethanolic hydrochloric acid in 70% yield, although the ee was not



Scheme 43

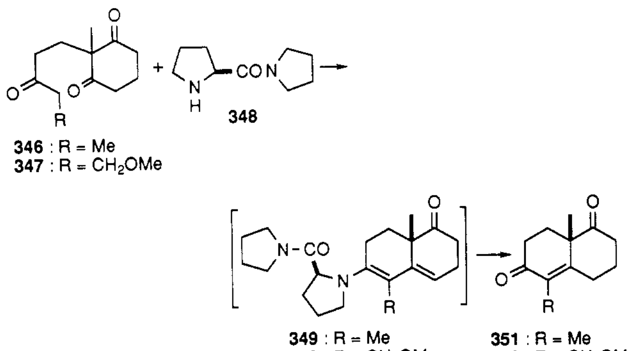


reported. (*R*)-335 and (*R*)-342[135] were transformed to the key intermediates 343 and 344 required for the total synthesis of optically active diterpenoids and steroids.[135] Naturally occurring (*S*)-(+)-podocarpic acid (247) was synthesized from the enantiomer of 335 prepared from (*R*)-enamine 345.[136] The reaction of the triketones 346

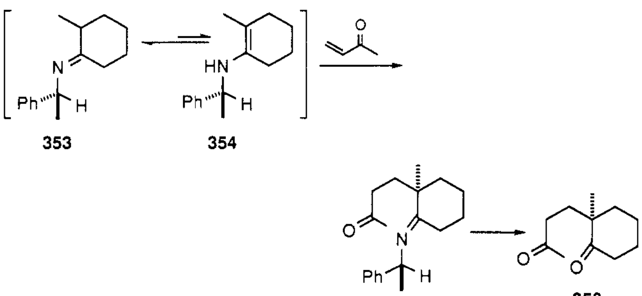


and 347 with a chiral amine 348 provided 351 and 352 in 43% and 21% yield. The reaction proceeded *via* the dienamines 349 and 350. The op for these bicycle ketones 351 and 352 was ~49% (Scheme 44).[137]

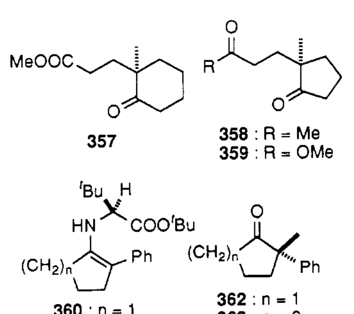
Scheme 44


346 : R = Me
347 : R = CH2OMe
348
349 : R = Me
350 : R = CH2OMe
351 : R = Me
352 : R = CH2OMe

Scheme 45


353 354 355 356

The chiral enamine **354** derived from α-methylcyclohexanone was converted into **355** on alkylation with methyl vinyl ketone by the azeotropic removal of water in the presence of *p*-TsOH in toluene. The acid hydrolysis of **355** formed from **353** gave **356** (91% ee; 89% overall yield) (Scheme 45).[138] The reactive nucleophilic species of this reaction is the enamine **354**. Cyclic ketones **357** (90% ee; 81% yield), **358** (89% ee; 83% yield), and **359** (90% ee; 79% yield) were prepared in the similar manner. This type of deracemizing alkylation reaction has been further developed and applied to the syntheses of a number of optically active natural products having quaternary carbons. These studies by a group of French CNRS researchers are not included in this article because their recent review is available.[139]


357
358 : R = Me
359 : R = OMe
360 : n = 1
361 : n = 2
362 : n = 1
363 : n = 2

Metalation of a chiral cyclic imine **360** followed by methylation with methyl iodide afforded (*S*)-2-methyl-2-phenylcyclopentanone (**362**) (94% ee; 62% overall yield) after hydrolysis.[140] The corresponding 6-membered ketone **363** was obtained in a similar manner from **361** (96% ee; 40% yield).

Addition of a Grignard reagent to a chiral α,β-unsaturated aldimine **364** in THF afforded an intermediate **366**, which yielded the 1,2-disubstituted cyclohexanecarboxaldehyde **367** by alkylation followed by acid hydrolysis (Scheme 46).[141] The Grignard addition proceeds via a chelated cyclic transition state **365** with *s-cis* conformation, in which the attack of the Grignard reagent takes place from the opposite side of the *tert*-butyl substituent resulting in an α-configuration of the R^1 substituent. The fixed *Z* configuration of the intermediate magnesioenamine **366** suffers the second alkylation from the α-side due to the bulky *tert*-butyl group to afford the product **367** with R^1 and R^2 *cis* to each other. Table 13 lists results of the three-step synthesis of other cyclohexanecarboxaldehydes. This process gives products with >90% ee in moderate isolated yield. It is interesting that the diastereomer **368** of **367** (R^1 = Ph, R^2 = Me) was obtained in 49% yield with 91% ee, when the reaction mixture was refluxed for several hours before the addition of methyl iodide. Starting with the addition of vinylmagnesium bromide the 5-membered aldimine **369** was transformed into **370** using a similar sequence of reactions to those for **364**. The addition of phenylmagnesium bromide to **369** followed by methylation afforded a mixture of **371** (15%, unknown ee) and **372** (82% ee; 62% yield). Heating the reaction mixture before methylation afforded **372** (91% ee; 49% yield) as the sole product. A total synthesis of (+)-ivalin (**373**) was reported, using a Grignard addition–alkylation reaction as the key step.[142] Thus, aldimine **374** gave **375** (95% ee; 35% yield) and **377** (22%), after reduction with $NaBH_4$. The alcohol **375** was converted into (+)-ivalin (**373**) *via* **376**.

Scheme 46

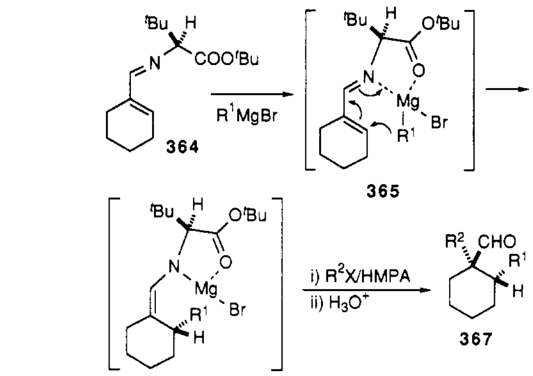
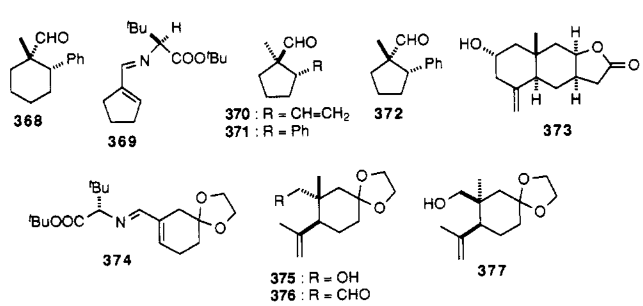
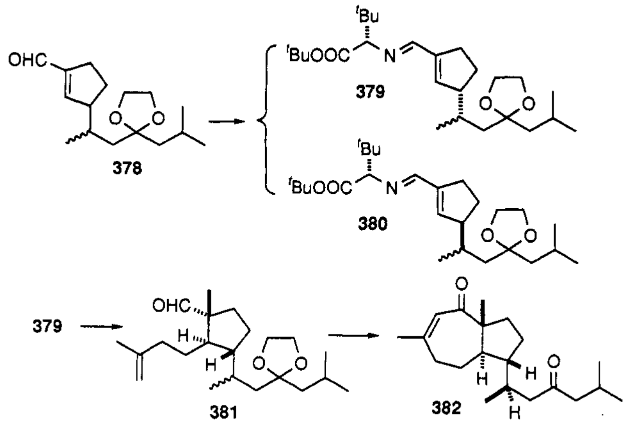

364 365 366 367

Table 13. Asymmetric Synthesis of Cyclohexanecarboxaldehydes 367

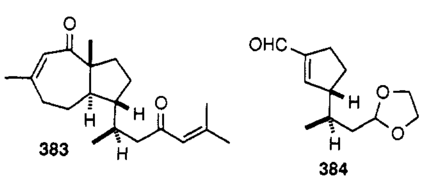
entry	R^1MgBr	R^2X	yield, %	% ee
1	PhMgBr	CH_3I	55	91
2	CH_2=CHMgBr	CH_3I	67	93
3	CH_2=CHMgBr	$PhCH_2I$	67	93
4	CH_2=CHMgBr	CH_2=$CHCH_2Br$	63	93
5	CH_2=CHMgBr	C_2H_5I	65	93
6	CH_2=CHMgBr	CH_3OCH_2Cl	52	93


368 369
370 : R = CH=CH2
371 : R = Ph
372 373 374
375 : R = OH
376 : R = CHO
377

Scheme 47

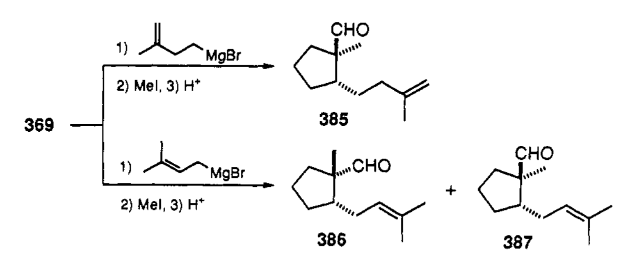


Another application of Koga's method to natural product synthesis includes (−)-reiswingin A (**382**) (Scheme 47).[143,144] The condensation of the racemic aldehyde **378** with (L)-*tert*-leucine *tert*-butyl ester afforded a mixture of **379** and **380** in 94% yield. Addition of 3-methyl-3-butenylmagnesium bromide followed by methylation and acid hydrolysis gave the aldehyde **381** in 32% yield with a 50% recovery of optically active **378**. The aldehyde was converted into (−)-reiswingin A (**382**). This synthesis permitted the assignment of the configuration at C-13 and the absolute stereochemistry of the natural product. (−)-Reiswingin B (**383**) was synthesized from **384** using a similar sequence of reactions to those used for (−)-reiswingin A (**382**).[144] An interesting difference in the stereo-



chemical outcome was observed in the double alkylation reactions.[145] Addition of (3-methyl-3-butenyl)magnesium bromide to **369** followed by methylation and hydrolysis provided **385** in 94%, whereas the reaction starting with the addition of (3-methyl-2-butenyl)-magnesium bromide gave a 7:1 mixture of **386** and **387** in 40% yield (Scheme 48). The ee's of these products

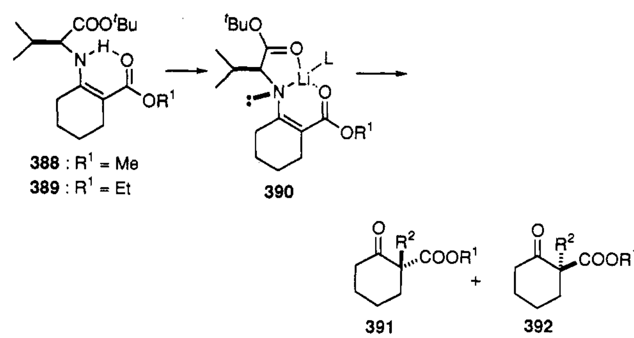
Scheme 48



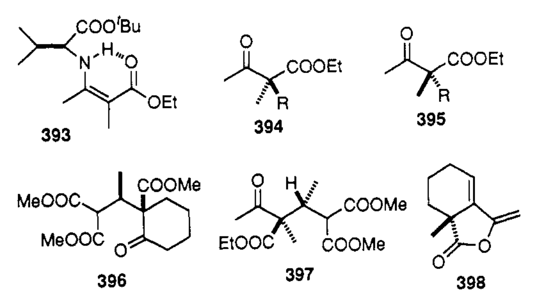
were not reported.

A practical method for the alkylation of β-dicarbonyl compounds via lithio enamines has appeared (Scheme 49).[146] An enamine **388** prepared from methyl 1-methyl-2-oxocyclohexanecarboxylate with (*S*)-valine *tert*-butyl ester was treated with LDA in toluene at −78 °C to afford a lithiated species **390** (R^1 = Me). After the addition of HMPA (1.0 equiv) the reaction mixture was stirred at −78 °C for 1 h and then alkylated with

Scheme 49



methyl iodide, yielding **391** ($R^1 = R^2$ = Me) in 57% yield and 99% ee. The enantiomer **392** ($R^1 = R^2$ = Me) was obtained in 63% yield and 92% ee, when THF (2.0 equiv) was added instead of HMPA. Table 14 summarizes the results including the interesting change in absolute stereochemistry of the product through changing the additive (entries 1–8). The lithium species **390** can be alkylated with Michael acceptors (entries 14–21).[148,149] Examination of the effect of various additives on the alkylation of **388** showed that strong electron-donating ligands tended to give **391** ($R^1 = R^2$ = Me) preferentially, whereas the weaker ligands afforded **392** ($R^1 = R^2$ = Me) resulting from the underside attack. The intermediate **390** (R = Me) with the trans-fused chelated 5/6-ring juncture was assumed to be responsible for the reversal of the diastereoface differentiation.[150] The underside attack of the alkylating agent is heavily suppressed by the bulky and strongly ligating HMPA. The weakly ligating additives are replaced by the entering alkyl halide[151] so that the halogen is coordinated to lithium before alkylation takes place. This leads to the preferential α-side attack. Various Lewis acids were screened in order to improve the yield and ee of this reaction.[149] Chlorotrimethylsilane was found to give satisfactory results with nonactivated Michael acceptors such as methyl vinyl ketone and ethyl acrylate (entries 18–21). The acyclic enamine **393** underwent a similar alkylation to that of **389** to give either **394** or its enantiomer **395**.[146,148,149] The effect of



additives was exactly similar to that for the cyclic enamines **388** and **389**. A cyclohexanone derivative **396** (99% ee) with contiguous quaternary and tertiary carbon centers was prepared via the asymmetric Michael addition of **388** on methyl ethylidenmalonate in 86% yield.[152] Conversion of **391** ($R^1 = R^2$ = Me) into a chiral diene **398**, a plausible precursor for the synthesis the kaurane-type diterpenoid, was reported.[153] The acyclic enamine **393** gave **397** in 94% yield with 99% ee.[152] The enamine **399** of a 7-membered β-keto ester was alkylated using Koga's method[143] to provide **400**–**403** in 65–76% yield with >96% ee (Scheme 50).[154]

Table 14. Asymmetric Alkylation of Enamines 388 and 389 in Toluene

entry	substrate	additive (equiv)	product (R^1, R^2)	yield, %	% ee	ref
1	**388**	HMPA (1.0)	**391** (Me, Me)	57[a]	99	146
2	**388**	THF (2.0)	**392** (Me, Me)	63	92	146
3	**388**	HMPA (1.0)	**391** (Me, $CH_2CH{=}CH_2$)	71[a]	76	146
4	**388**	dioxolane (1.2)	**392** (Me, $CH_2CH{=}CH_2$)	56	56	146
5	**388**	HMPA (1.0)	**391** (Me, CH_2Ph)	77	99	146
6	**388**	dioxolane (1.6)	**392** (Me, CH_2Ph)	48	71	146
7	**388**	HMPA (1.0)	**391** (Me, CH_2COOMe)	59	70	146
8	**388**	TMA (3.0)	**392** (Me, CH_2COOMe)	78	74	146
9	**389**	HMPA	**391** (Et, CH_2Ph)	83	>95	147
10	**389**	HMPA	**391** (Et, 2-naphthyl-CH_2)	83	>95	147
11	**389**	HMPA	**391** (Et, *p*-$BrC_6H_4CH_2$)	72	>95	147
12	**389**	HMPA	**391** (Et, *m*-$ClC_6H_4CH_2$)	82	>95	147
13	**389**	HMPA	**391** (Et, CH_2COOMe)	68	59	147
14	**389**	none	**392** (Et, $CH_2CH(COO^tBu)_2$)	59	33	148
15	**389**	none[b]	**392** (Et, $CH_2CH(COO^tBu)_2$)	86	95	148
16	**389**	HMPA (4.0)	**391** (Et, $CH_2CH(COO^tBu)_2$)	73[c]	92	148
17	**389**	THF (8.0)	**392** (Et, $CH_2CH(COO^tBu)_2$)	87[d]	76	148
18	**389**	TMSCl (5.0)[b]	**391** (Et, $CH_2CH_2COCH_3$)	67[e]	90	149
19	**389**	HMPA (1.0) TMSCl (5.0)	**392** (Et, $CH_2CH_2COCH_3$)	48[d]	60	149
20	**389**	TMSCl (5.0)[b]	**391** (Et, CH_2CH_2COOMe)	53[e]	57	149
21	**389**	HMPA (1.0) TMSCl (5.0)	**392** (Et, CH_2CH_2COOMe)	23[d]	77	149

[a] At −55 °C. [b] In THF. [c] At −105 °C. [d] At −95 °C. [e] At −100 °C.

Scheme 50

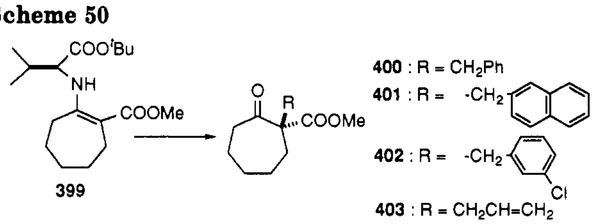
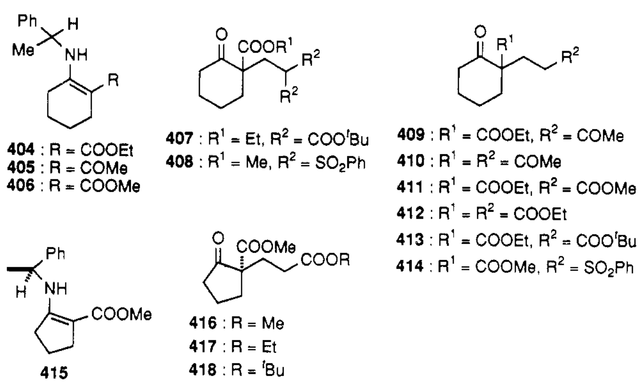


Table 15. Diastereoselective Alkylation of Chiral Enamines 404–406

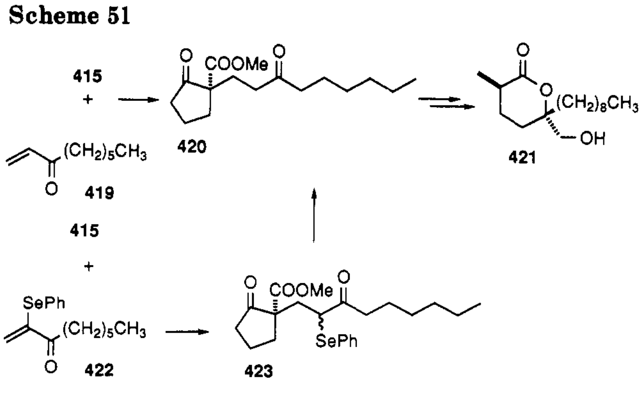
product (*R*/*S*)	substrate (*R*/*S*)	reaction conditions	yield, %	% ee	ref
407 (*R*)	**404** (*R*)	in toluene	65	>95	155
408 (*R*)	**406** (*S*)	in THF	90	50	156
409 (*R*)	**404** (*R*)	in toluene	50	79	155
409 (*S*)	**404** (*S*)	in ether/$ZnCl_2$	80	79	157
410 (−)	**405** (*R*)	in toluene	58	65	155
411 (*S*)	**404** (*S*)	in ether/$MgBr_2$	76	80	157
412 (*R*)	**404** (*R*)	in CH_3CN/Co(acac)$_2$	29	89	155
412 (*S*)	**404** (*S*)	in ether/$MgBr_2$	80	79	157
412 (*S*)	**404** (*S*)	in THF/11 kbar	31	84	157
413 (*S*)	**404** (*S*)	in ether/$MgBr_2$	60	90	157
413 (*S*)	**404** (*S*)	in THF/14 kbar	31	84	157
414 (*S*)	**406** (*S*)	in THF/14 kbar	85	94	156

The chiral enamines **404–406** were alkylated with various electrophiles to give **407–414** after hydrolysis.[155-157] Either Lewis acid catalysts or high pressure promoted the alkylation.[156,157] The pertinent results are summarized in Table 15. The reaction of the 5-membered (*S*)-enamine **415** with alkyl acrylates and the $MgBr_2$ as a Lewis acid in ether afforded **416** (70% ee; 50% yield), **417** (65% ee; 50% yield), and **418** (85% ee; 45% yield).[157] A high pressure of 14 kbar was also effective for this transformation in THF to yield **417** and **418** with ~85% ee in fair yield. Interestingly the steric bulk of the alkyl group in the acrylates had no effect on the diastereoselectivity under high-pressure conditions, while selectivity increased significantly with the *tert*-butyl acrylate under the $MgBr_2$-catalyzed conditions. Addition of **415** to the hexyl vinyl ketone **419** proceeded smoothly in ether with $ZnCl_2$ to give **420**

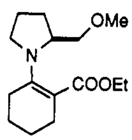


(70% ee; 82% yield) after a hydrolytic workup (Scheme 51).[158] An activated α,β-unsaturated ketone **422** un-

Scheme 51



derwent a Michael reaction with **415** in the absence of a Lewis acid catalyst to afford **423** in 55% yield. The phenylselenyl group was reductively removed with Bu_3SnH in the presence of AIBN to give **420** with 70% ee. The diketone **420** was further transformed into (−)-malyngolide (**421**). The alkylation of a chiral enamine **424** was attempted with poor results both in yield and ee.[159]



424

2. Alkylation of Chiral Enolates and Related Carbanions

The most important contribution in this area involves the alkylation of chiral bicyclic lactams developed by Meyers and co-workers. The first paper reporting this elegant method for the creation of a chiral quaternary carbon center appeared in 1984.[160] Condensation of (S)-valinol (**425**) with 3-benzoylpropionic acid **426** afforded a single diastereomer of **427** (Scheme 52). The alkylation of the bicyclic lactam **427** *via* its enolate produced the *endo* isomer **428** predominantly. The second alkylation of **428**, either as an *endo–exo* mixture or diastereomerically pure, provided **429** from the *endo* attack of the alkylating agent in 50–90% yield. Refluxing **429** with 10% sulfuric acid in butanol yielded the α,α-disubstituted esters **430** with >95% ee. The scope of this method has been expanded rapidly and a number of chiral structural units **431–439** having a quaternary carbon shown in Table 16 were synthesized.

Scheme 52

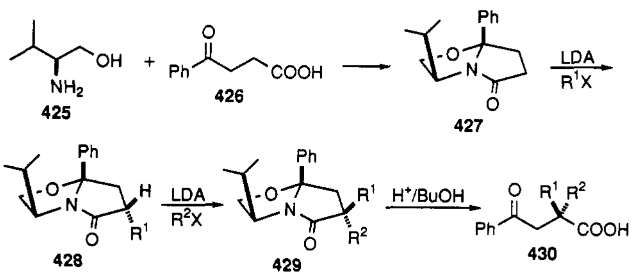
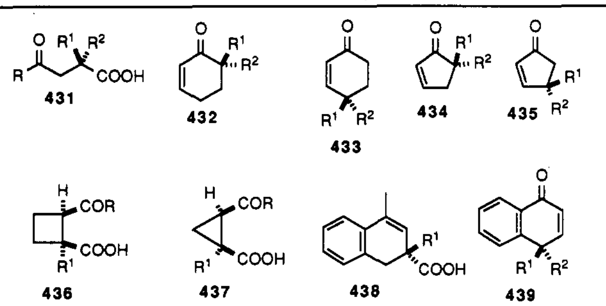


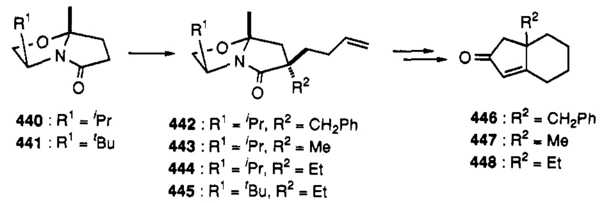
Table 16. Chiral Structural Units with a Quaternary Carbon Center Prepared from Meyer's Bicyclic Lactams



We shall not report these results in detail, because a review article appeared recently.[161]

After their review had appeared, an asymmetric synthesis of hydrinden-2-ones **446–448** using bicyclic lactam technology was reported.[162] Bicyclic lactam **440** was alkylated with 4-bromo-1-butene followed by another alkylation to afford **442–444** in >90% yield (Scheme 53). The reported diastereoselectivity was modest for **442** (7.5:1) and **443** (6.9:1) and poor for **444** (2:1). Ethylation of **441** increased the *endo/exo* ratio only slightly to 3:1. The major diastereomers of **443** and **445** were separated and converted into the optically pure hydrinden-2-ones **447** and **448**, respectively. Separation of the major isomer of **442** was carried out at a later stage.

Scheme 53



Scheme 54

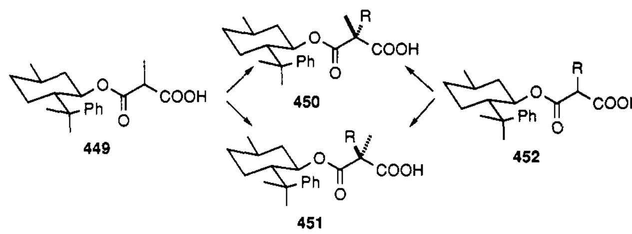


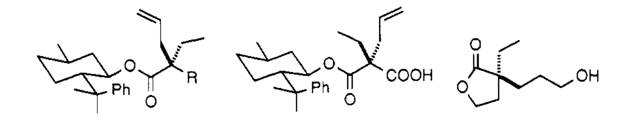
Table 17. Alkylation of Half-Esters 449[163]

alkylating agent	yield, %	ratio 450:451
EtI	83	4:1
^{n}PrI	72	4:1
$CH_2{=}CHCH_2I$	77	7:1
$CH_2{=}C(Me)CH_2I$	91	6:1
$PhCH_2Br$	72	12:1
2-$NO_2C_6H_4CH_2Br$	94	10:1
4-$NO_2C_6H_4CH_2Br$	95	8:1[a]
3,4-$(MeO)_2C_6H_3CH_2Br$	75	12:1
4-$MeOC_6H_4CH_2Br$	71	12:1
2-$MeOC_6H_4CH_2Br$	73	16:1

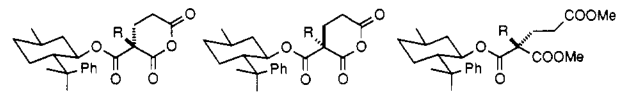
[a] Reference 164.

The diastereodifferentiating alkylation of a dianion formed from the chiral half-ester **449** gave a variety of disubstituted half-esters **450** and **451**, with the former as the major isomer (Scheme 54).[163,164] The results are listed in Table 17. It is interesting that methylation of **452** (R = Et, ^{n}Pr, and CH_2Ph) afforded **450** as the major isomer as in the case of the alkylation of **449**.[163,165] The products **450** were converted into optically active α-alkyl α-amino acids. The alkylation of the half-esters of the monosubstituted malonic acids with several chiral secondary alcohols was tested to improve the diastereomeric ratio of the products without much success.[164] Allylation of **452** (R = Et) gave a 2.6:1 mixture of **453** and **455** in quantitative yield. This mixture was separated after homologation followed by esterification to give **454**, which was then converted into the chiral precursors **242**[101-103] and **456**[101,102] used for the total synthesis of *Aspidosperma*- and *Hunteria*-type indole alkaloids.[164,165]

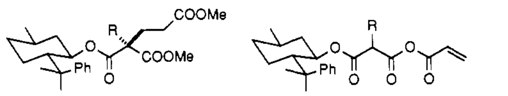
Treatment of **449** with acryloyl chloride in the presence of DMAP and diisopropylamine in THF gave a mixture of **457a** and **458a**, which was further converted into a mixture of **459a** and **460a**.[166] Addition of lithium perchlorate imporved both the yield and diastereoselectivity of the products **459a** and **460a** to 63% and 87:13, respectively. The same reaction with **452** (R = Et) afforded **459b** and **460b** in the ratio of 23:77 (>65%) which was determined after further conversion. The overall reaction involves esterification giving **461a** or **461b** followed by an intramolecular Michael addition under the reaction conditions. The contrasting diastereodifferentiation between **449** and **452** (R = Et) was ascribed to the difference in conformation between the intermediate enolates **462** and **463**, formed from **449** and **452** (R = Et), respectively.



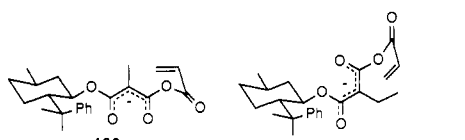
453 : R = COOH
454 : R = CH_2COOMe
455
456



457a : R = Me
457b : R = Et
458a : R = Me
458b : R = Et
459a : R = Me
459b : R = Et

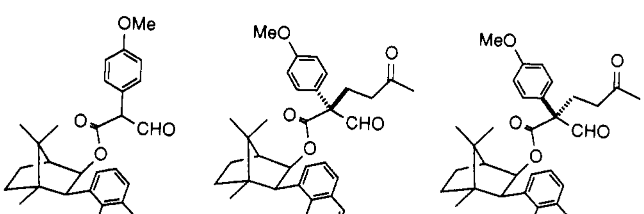


460a : R = Me
460b : R = Et
461a : R = Me
461b : R = Et

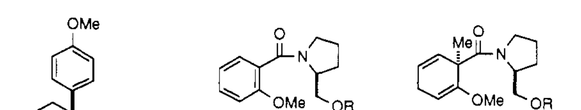


462
463

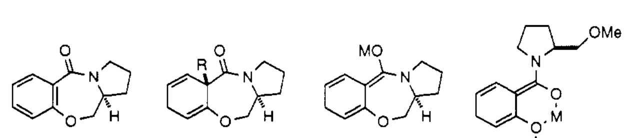
The Michael addition of **464** to methyl vinyl ketone under basic conditions furnished a diastereomeric mixture of **465** and **466**.[167] The highly selective formation of **564** was observed using potassium carbonate as base in dimethoxymethane with a trace of water giving **465** and **466** in 95:5 in 76% combined yield. (+)-*O*-Methyljoubertiamine (**467**) was synthesized from **465**.



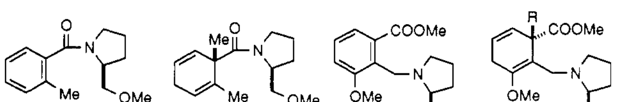
464
465
466



467
468a : R = H
468b : R = Me
468c : R = CH_2OMe
469a : R = H
469b : R = Me
469c : R = CH_2OMe



470
471
472
473



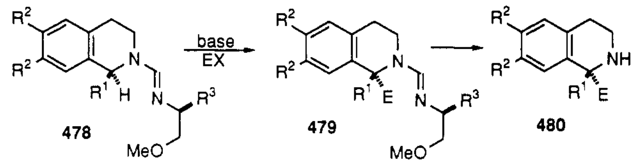
474
475
476
477

The Birch reduction of **468a–c** followed by methylation of the resulting amide enolate afforded **469a–c**, respectively, with a very high diastereomeric excess (260:1) in 82–85% yield.[168] In contrast to **468a**, the cyclic analog **470** gave **471** with the opposite absolute stereochemistry at the newly created quaternary center.[169] This inversion of the sense of asymmetric induction was ascribed to the difference in the geometry of the amide enolate.[168] The (*E*)-enolate **472** derived from **470** undergoes alkylation with β-selectivity. The (*Z*)-enolate **473** may be generated from **468a–c** because of the powerful chelating effect of the ring methoxy group. Alkylation of **473** occurs with α-selectivity. This presumption was supported by the fact that the reductive alkylation of **474**, which has no chelating substituent on the ring, afforded **475** with a high diastereoselectivity (>99:1) in 90% yield. Further development of this reductive alkylation has been reviewed by Schultz in 1990.[170] Alkylation of **476** giving **477** was reported after his review had appeared.[171] The diastereoselectivities were improved by evaporation of ammonia prior to alkylation. The results are summarized in Table 18.

Table 18. Reductive Alkylation of 476

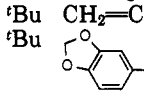
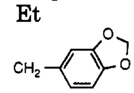
product 477, R	yield, %	diastereomer distribution
Me	83	20:1
Et	84	15:1
^{n}Pr	75	15:1
CH_2Ph		2:1
$CH_2CH{=}CH_2$	74	2:1
$CH_2C{\equiv}CH$	50	20:1
CH_2CN	54	20:1

Scheme 55



478
479
480

Table 19. Alkylation of 478 To Produce 480 with a Quaternary Carbon Center

starting material 478				product 480	
R¹	R²	R³	EX^a	yield, %	% ee
CH_2Ph	OMe	^{i}Pr	MeI	90	76
Me	OMe	^{t}Bu	$PhCH_2Cl$	88	86
Me	OMe	^{t}Bu	$CH_2{=}CH{-}CH_2Cl$	44	76
Me	OMe	^{t}Bu		60	83
Me	OMe	^{i}Pr	$ClCH_2CH_2CH_2Br$		74
Et	H	^{t}Bu	$PhCH_2Cl$	87	83
CH_2Ph	H	^{i}Pr	MeI	71	76
CH_2Ph	H	^{t}Bu	EtI	85	81
Et	H	^{t}Bu	^{i}PrI	56	86
	OMe	^{t}Bu	CO_2	53	82

^{a} See Scheme 55.

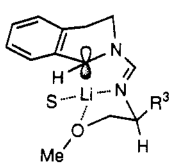
The chiral formamidines **478** of 1-substituted tetrahydroisoquinolines were deprotonated using ^{n}BuLi or ^{s}BuLi to form the corresponding lithiated species, which were alkylated with a variety of electrophiles to give the 1,1-disubstituted formamidines **479** (Scheme 55). Chiral 1,1-disubstituted tetrahydroisoquinolines **480** were obtained from **479** on treatment with hydrazine.[172] The results are compiled in Table 19. It has been well demonstrated that the alkylation of the chiral formamidines **478** (R^1 = H) of unsubstituted isoquin-

Table 20. Effect of the Substituent in Chiral Auxiliary of 478 (R^1 = Et, R^2 = H) on Selectivity

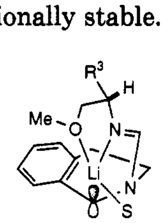
R^3 in 478	EX[a]	% de of 479
Me	$PhCH_2Cl$	0–4
Ph	MeI	44–56
^iPr	MeI	73–75
^tBu	$PhCH_2Cl$	84–88

[a] See Scheme 55.

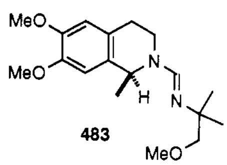
oline proceeded at the β-face to give the (*S*)-1-substituted product 478 (R^1 = alkyl).[173] The second electrophilic attack of EX takes place at the α-face to produce 479 as shown in Scheme 55. In order to shed light on the sterically diverse outcome of the alkylation, the effect of varying the substituent R^3 in 478 (R^1 = Et, R^2 = H) was studied.[174] As seen in Table 20, diastereoselectivity increased substantially as the size of R^3 increased. It was also demonstrated in the corresponding experiments that a modest drop in diastereoselectivity occurred in the first alkylation even for the methyl group. These results were rationalized by assuming that the lithiated species 481 and 482 were involved in the first and the second alkylations, respectively. Optically active 483 with an achiral formamidine was benzylated to afford the racemic dialkylated product 484 after removal of the amidine moiety.[175] This suggests that the intermediate anionic species are not configurationally stable.



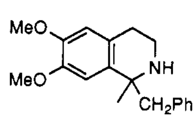
481



482



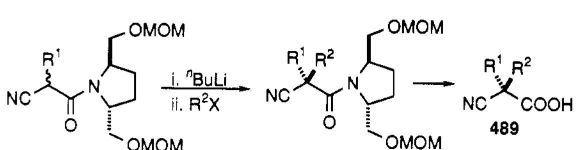
483



484

Methylation of chiral β-keto ester 485 led to a diastereomeric mixture 486 at C-2.[127] Results are listed in Table 21. The diastereomeric mixture 487 was deprotonated using ^nBuLi and alkylated to furnish 488 in good yield with a high diastereomeric excess (de) (Scheme 56).[176] The chiral auxiliary was easily removed

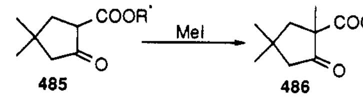
Scheme 56



by successive treatment with hydrochloric acid and potassium carbonate to afford the α,α-dialkylated cyanoacetic acid 489 in good yield as summarized in Table 22.

Diastereodifferentiating alkylation of an anionic species, derived from 490 and 491, with THF proceeded smoothly in the presence of 9-BBN triflate to give the corresponding products 492 (67%, >95% de) and 493

Table 21. Diastereodifferentiating Methylation of 485 Yielding 486



485 486

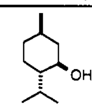
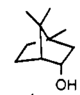
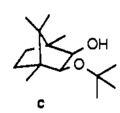
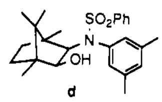
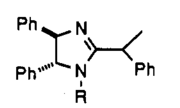
chiral auxiliary	yield, %	% de	configuration at C-2 of the excess isomer
 a	42	18	*R*
 b	81	16	
 c	70	58	*S*
 d	60	62	*R*

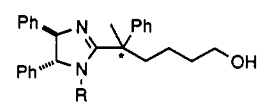
Table 22. Preparation of Optically Active 489

		488		489	
487 (R^1)	R^2X (R^2)	yield, %	% de	yield	configuration
Me	Et	96	90	75	*R*
Me	$CH_2{=}CHCH_2$	96	90	83	*R*
Me	$PhCH_2$	96	85	84	*R*
Et	Me	96	80	73	*S*
$CH_2{=}CHCH_2$	Me	94	84	87	*S*
$PhCH_2$	Me	94	84	92	*S*

(48%, 64% de).[177] The stereochemistry at the newly created carbon center was not reported.



490 : R = H
491 : R = $CH_2CH{=}CH_2$



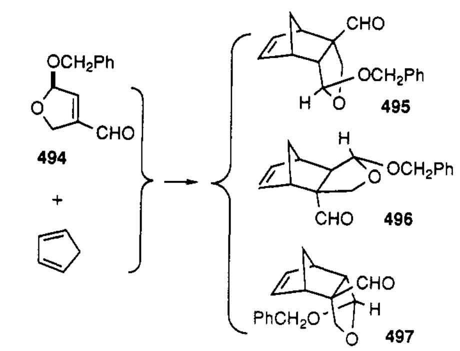
492 : R = H
493 : R = $CH_2CH{=}CH_2$

3. Diels–Alder Cycloadditions

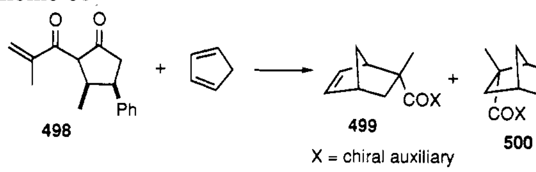
2(*R*)-(Benzyloxy)-2,5-dihydro-4-furanecarboxaldehyde (494), prepared from D-arabinose, served as a chiral dienophile for the Diels–Alder reaction with cyclopentadiene at −20 °C to afford a diastereomeric mixture of 495, 496, and 497 (82:18:<1) in quantitative yield (Scheme 57).[178] The relative yield of 495 decreased as the temperature increased. Diastereoselective Diels–Alder cycloadditions between chiral α,β-unsaturated *N*-acyloxazolidinones and dienes have been reported.[179] An isolated example of the creation of a quaternary carbon center was included in this paper. This is shown in Scheme 58. The reaction of 498 with cyclopentadiene in the presence of diethylaluminum chloride gave a mixture of 499 and 500 with a poor *endo*/*exo* selectivity (4:1) and diastereofacial selectivity (5:1) in ~80% yield. The structure of the major isomer was not determined.

Asymmetric Diels–Alder cycloadditions of the chiral (*E*)-2-cyanocinnamates 501a–d with cyclopentadiene were reported (Scheme 59).[180,181] A high degree of

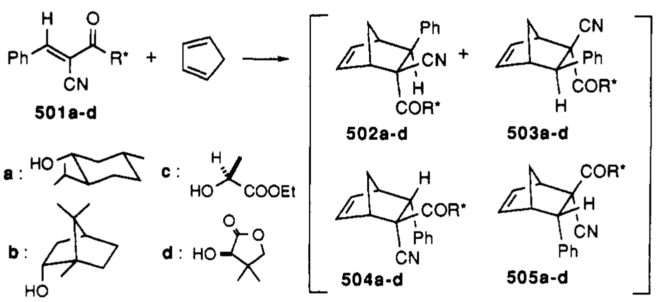
Scheme 57



Scheme 58



Scheme 59

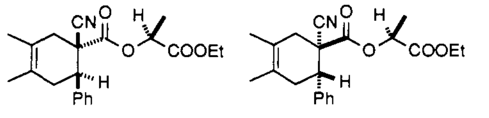


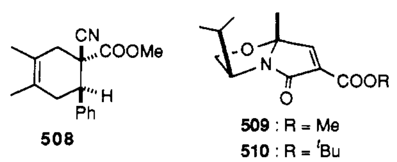
diastereodifferentiation was realized with the esters of α-keto alcohols such as (*S*)-ethyl lactate and (*R*)-pantolactone in the presence of titanium tetrachloride. Results are listed in Table 23. The titanium tetra-

Table 23. Diels–Alder Reactions between Cyclopentadiene and Dienophiles 501a–d

dieno-phile	Lewis acid (equiv)	conversion %	(502 + 503): (504 + 505)	502: 503
501a	$AlCl_3$(0.75)	90	80:20	36:64
501b	$AlCl_3$(0.75)	94	78:22	33:67
501c	$TiCl_4$(0.5)	99	88:12	2:98
501d	$TiCl_4$(0.75)	94	85:15	99:1

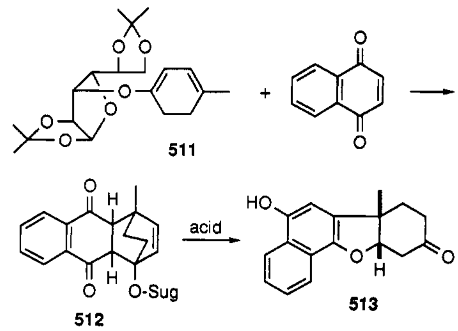
chloride catalyzed cycloaddition of **501c** with 2,3-dimethylbutadiene gave a 95:5 mixture of **506** and **507** in good yield.[182] Optically pure cyclohexene derivative **508** was obtained from **506** by base hydrolysis followed by methylation with diazomethane. The similar sequence of reactions with **501d** yielded the enantiomer of **508**.





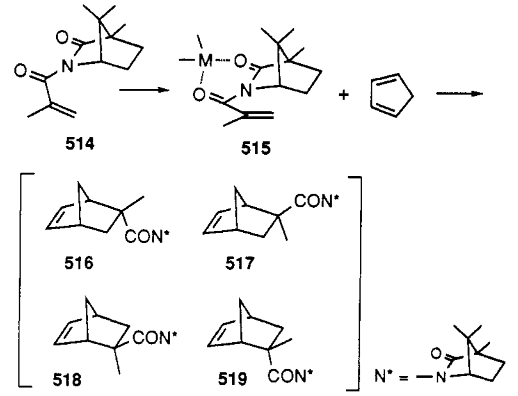
It was shown that Meyer's chiral bicyclic lactams **509** and **510** were versatile dienophiles for Diels–Alder reactions.[183] The details are included in Meyer's review.[161] The reaction of chiral alkoxycyclohexadiene **511** with 1,4-naphthoquinone gave **512**, which was further converted into **513** of 95% ee on acid treatment (Scheme 60).[184]

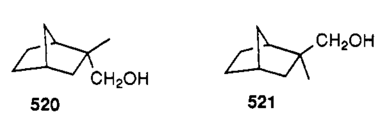
Scheme 60



Four products **516–519** (82:9:5:4) were obtained in 98% yield from the Diels–Alder cyclization of **514** and cyclopentadiene in the presence of methylaluminum dichloride (Scheme 61).[185] The major product **516** arises from an *endo* addition to the *s-trans*-rotamer **515** from the less hindered *si*-face which is opposite to the one-carbon bridge of the camphor system. The *endo* addition from the *re*-face gives **519**. The products **517** and **518** were formed via the *exo*/*re* and the *exo*/*si* addition, respectively. Thus, the ratio of *endo* addition (**516** + **519**) to *exo* addition (**517** + **518**) was 86:14. This was confirmed by converting the reaction mixture into a mixture of two alcohols **520** and **521** (86:14). Discrimination between *si*- and *re*-face addition (π-facial selectivity) can be evaluated as 87:13 from the ratio of the combined yield of (**516** + **518**) and (**517** + **519**). The results of the Diels–Alder cycloaddition of chiral dienophile **514** with various dienes are summarized in Table 24.

Scheme 61

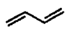
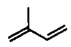
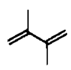
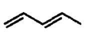
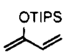
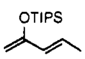
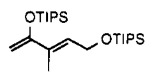




4. Use of Chiral Acetals

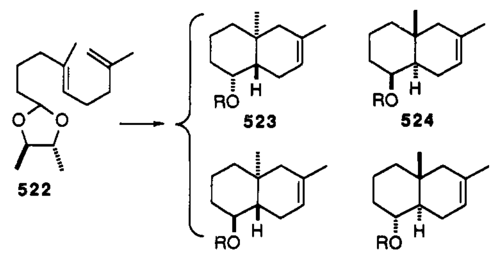
Cyclization of the optically active acetal **522** with stannic chloride in benzene afforded the axial hydroxy ethers **523** and **524** (52%) and the equatorial ethers **525** and **526** (21%) (Scheme 62).[186,187] Diastereomeric ratios

Table 24. Diels–Alder Cycloadditions of 514 at −78 °C in the Presence of Methylaluminum Dichloride[a]

diene	π-facial selectivity	*endo*/*exo*	yield, %
	91:9[b]	90:10[c]	93
	85:15[d]		61
	90:10		79
	95:5		82
	90:10	67:33	63
	57:43[e]		89
	50:50[e]	87:13	91
	88:12[f,g]	>98:2	95

[a] All the data were taken from the Table I in the original paper (ref 185). [b] Should be 87:13 (see this text). [c] Should be 86:14 (see this text). [d] At −30 °C. [e] Diethylaluminum chloride was employed. [f] Titanium tetrachloride was employed. [g] At −20 °C.

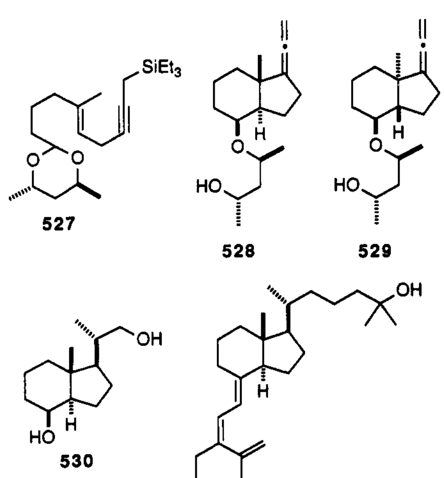
Scheme 62



522 523 524 525 526

R = CHMeCH(OH)Me

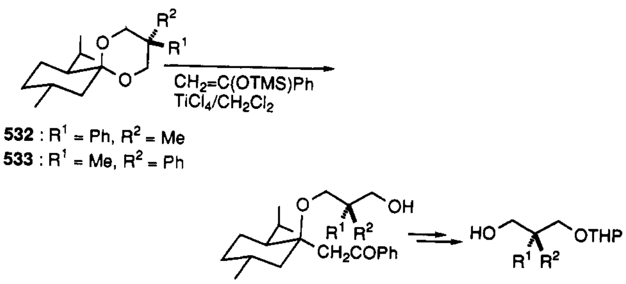
were determined to be 92:8 for **523** to **524** and 8:92 for **525** to **526**. Treatment of the optically active acetal **527** with titanium tetrachloride in dichloromethane afforded **528** (82%) and **529** (9%).[188] The former was converted into a key intermediate **530** for the synthesis of 1α,25-dihydroxyvitamin D_3 (**531**). A highly stereo-



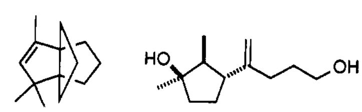
527 528 529 530 531

selective cleavage of the equatorial C–O bond in the reaction of the acetals **532** and **533** with acetophenone enol trimethylsilyl ether in the presence of titanium chloride to give **534** and **535** in 85–95% yield with >95% de was observed (Scheme 63).[189] Each product was further converted into **536** and **537**, enantiomeric at the quarternary carbon center, in 75–78% yield.

Scheme 63



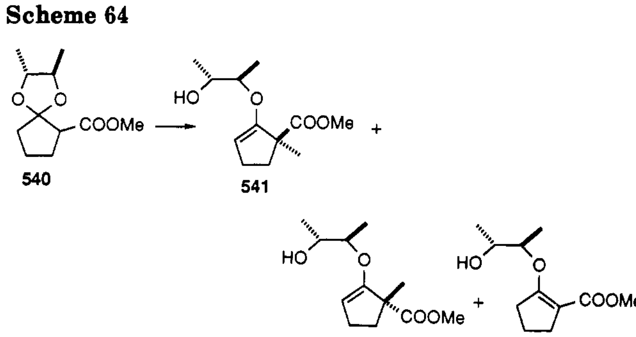
A highly diastereoselective synthesis of 1,1-disubstituted cyclopropanes was reported by two groups independently.[190,191] The preparation involves the Simmons–Smith cyclopropanation of homochiral acetals of α,β-unsaturated ketones or aldehydes. The results obtained by the two groups are summarized in Table 25. The major product of entry 9 served as a starting material for the chiral synthesis of (+)-modhephene (**538**).[195] (−)-Chokol A (**539**) was synthesized from the major product of entry 6, which established the absolute configuration of **539**.[197]



538 539

Methylation of an enolate prepared from **540** with LDA (1 molar equiv) afforded **541** (11%), **542** (7%), and **543** (28%) along with a 46% recovery of starting material (Scheme 64).[198] Yields of **541** and **542** increased

Scheme 64

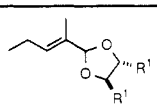
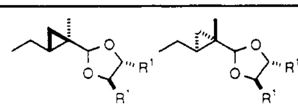
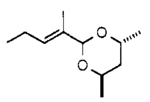
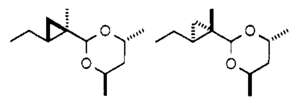
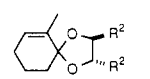
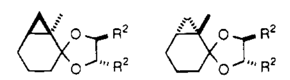
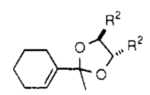
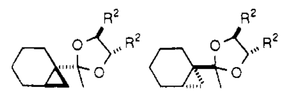
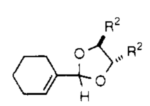
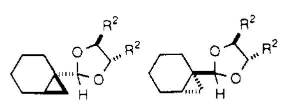
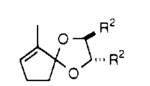
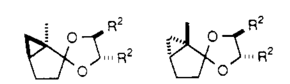
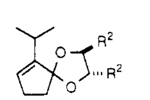
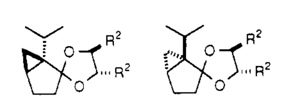
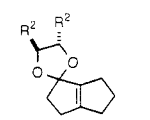
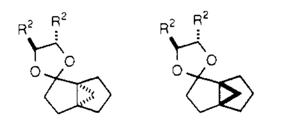
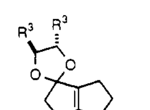
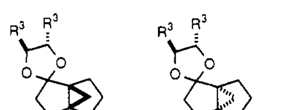
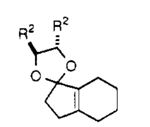
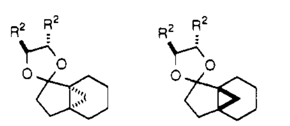
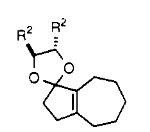
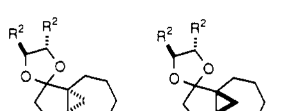
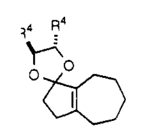
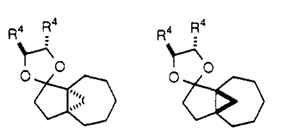
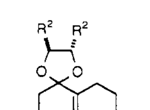
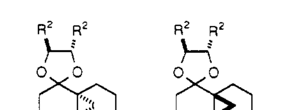


540 541 542 543

to 59% and 32%, respectively, as the amount of LDA to 5 molar equiv increased. A variety of chiral acetals of β-keto esters were alkylated under the same reaction conditions. As shown in Table 26, diastereoselectivities are generally high, although the yields are moderate. In all cases an enol ether similar to **543** was obtained as a byproduct in 10–30% yield.

Carbocupration of the chiral cyclopropene **544** constitutes an interesting method for the asymmetric creation of a quaternary carbon center. The reaction

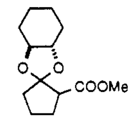
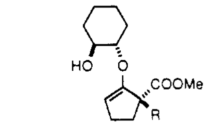
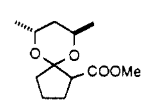
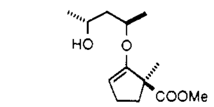
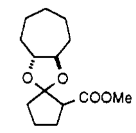
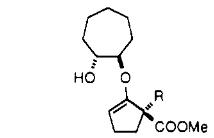
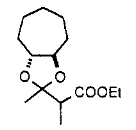
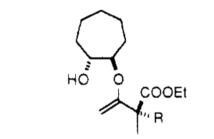
Table 25. Diastereodifferentiating Cyclopropanation of Homochiral Acetals

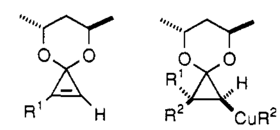
entry	acetal[a]	product[a]	yield, %	diastereomer ratio	ref
1			81	19:1	190, 192
2			69	7:1	192
3			99	20:1	191, 193
4			88	14:1	191, 193
5			70	2:1	193
6			88	9:1	193
7			54	9:1	193
8			78	9:1	193, 194
9			84	8:1	195
10			90	7:1	193, 194
11			84	9:1	193, 194
12			62	16:1	196
13			92	7:1	193, 194

[a] R^1 = COO^{i}Pr; R^2 = CH_2OCH_2Ph; R^3 = CH_2OMe; R^4 = Ph.

of **544** with Me_2CuLi in THF/DME afforded the chiral copper reagent **546** and **550** in 89% yield in the ratio of 94:4.[199] The chiral copper reagents **547–549** were prepared from **545** in a similar manner in good yield with high diastereoselectivity. The α-disubstituted carboxylic acids **551–553** were obtained from **546**.

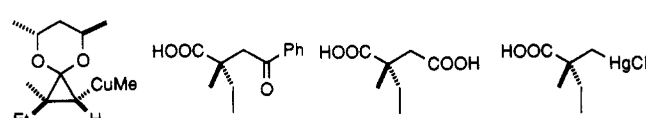
Table 26. Asymmetric Alkylation of Chiral Acetals of β-Keto Esters

acetal	product
	 R = Me (57%, 92% de) R = $^n C_9H_{19}$ (66%, 99% de)
	 57%, 73% de
	 R = Me (54%, >99% de) R = $^n C_9H_{19}$ (74%, >99% de)
	 R = CH_2Ph (78%, >99% de) R = $CH_2CH{=}CH_2$ (48%, >99% de)



546 : R^1 = Et, R^2 = Me
547 : R^1 = Ph, R^2 = Me
548 : R^1 = Ph, R^2 = Et
549 : R^1 = Ph, R^2 = ^{n}Bu

544 : R^1 = Et
545 : R^1 = Ph

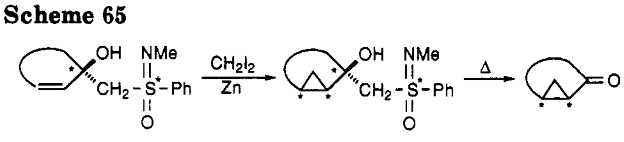


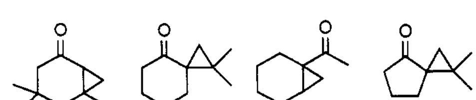
550 **551** **552** **553**

5. Miscellaneous Reactions

The chiral sulfur moiety has occasionally been employed as an auxiliary. An interesting example includes the chiral β-hydroxysulfoximine-directed cyclopropanation shown in Scheme 65.[200] Both enantiomers of the cyclopropyl ketones **554–557** were prepared by this method.

Scheme 65

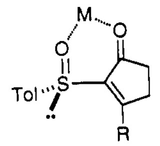




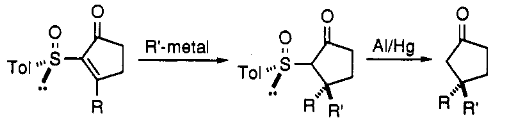
554 **555** **556** **557**

The addition of an organometallic reagent to enantiomerically pure sulfoxides **558a** and **558b** afforded the 3,3-disubstituted 2-sulfinylcyclopentanone **559**, which was directly subjected to reductive desulfination

Scheme 66



to give 3,3-disubstituted cyclopentanones **560**[201a] (Scheme 66). Preferential β-attack of the reagents was rationalized by the chelate model shown in Figure 2,



558a : R = Tol
558b : R = Me
559
560

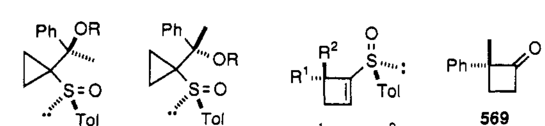
Figure 2. Chelate model for the β-attack of the organometallic reagents.

which suffers nucleophilic addition from the side of the less bulky nonbonding electron pair of sulfur.[201b] Yields and % ee of selected products **560** are listed in Table 27.

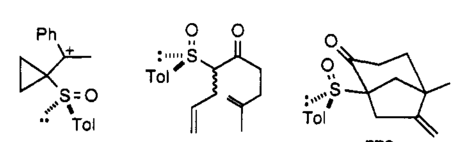
Table 27. Asymmetric Synthesis of 3,3-Disubstituted Cyclopentanones 560

substrate	R'M	yield, %	% ee
558a	Me_2CuLi	58	78
558a	Me(PhS)CuMgBr	77	73
558a	^{n}Bu(PhS)CuMgBr	69	81
558b	Tol_2CuLi	53	90–93
558b	^{n}Bu(PhS)CuMgCl	79	53
558b	^{n}Bu(^{t}BuO)CuMgCl	61	88

An interesting rearrangement of a chiral cyclopropyl sulfoxide to a cyclobutanone was reported.[202] When a diastereomeric mixture of **561** and **564** was refluxed in benzene in the presence of a catalytic amount of *p*-TsOH, a 1,2-asymmetric rearrangement took place to afford **567** in 88% yield. α,α-Disubstituted cyclobutanone **569** with 94% ee was obtained on reduction with acetyl chloride followed by treatment with titanium tetrachloride–lead hydroxide. The rearrangement of either diastereomer **561** or **564** produced the single isomer **567**. Refluxing of the mesylate **562** or **565** in benzene also provided **567** as a single isomer,[203] whereas the tosylates **563** and **566** underwent stereospecific rearrangement to afford **568** and **567**, respectively. The difference in stereochemical outcome of this rearrangement was rationalized by the involvement of the carbenium ion **570** as the reactive intermediate for the alcohols and mesylates, whereas a concerted mechanism was proposed for the tosylates.

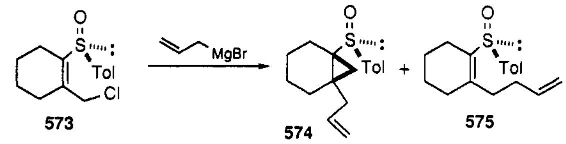


561 : R = H
562 : R = Ms
563 : R = Ts
564 : R = H
565 : R = Ms
566 : R = Ts
567 : R[1] = Ph, R[2] = Me
568 : R[1] = Me, R[2] = Ph
569



570 571 572

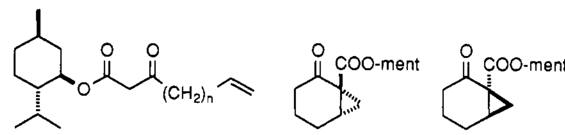
Scheme 67



573 574 575

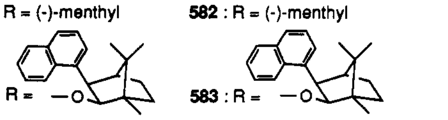
The manganese(III)-based oxidative radical cyclization of a diastereomeric mixture **571** afforded a bicyclic ketone **572** in 44% yield as the single stereoisomer.[204] Addition of allylmagnesium bromide to a chiral α,β-unsaturated sulfoxide **573** produced the cyclopropane **574** (66%) as a single diastereomer along with a coupling product **575** (16%) as shown in Scheme 67.[205]

The diazo insertion–homoconjugate addition with menthyl ester **576** catalyzed by copper bronze afforded a 1:1 mixture of **578** and **579** in 53% yield.[206] The corresponding reaction of **577** gave a 1:1 mixture of cyclopentanones **580** and **582** in 61% yield. Screening a variety of metal–ligand combination using **584** as a substrate led to the discovery that [mono(tetraphenylporphyrinato)]RhCl[207] was an efficient catalyst giving **581** and **583** in a ratio of 89:11 in 64% yield.[208] The diazoketone **585** afforded a 66:34 mixture of **587** and **588** in 94% yield using bis(*N-tert*-butylsalicylaldiminato)copper(II)[209] as catalyst. The diastereomeric ratio increased to 80:20 with some sacrifice in yield (64%), when [1,3-bis(diphenylphosphino)propane]$PdCl_2$[210] was used. The same tendency was observed for the conversion of **586** to **589** and **590**. Naturally occurring (+)-isoneonepetalactone (**591**) was synthesized from **587**.[208] Cyclopropanation of **584** with a chiral copper catalyst **592** was attempted unsuccessfully.[211]

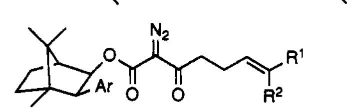


576 : n = 3
577 : n = 2
578
579

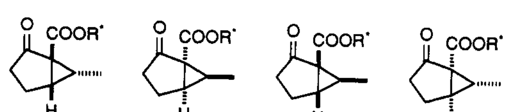
580 : R = (-)-menthyl
582 : R = (-)-menthyl



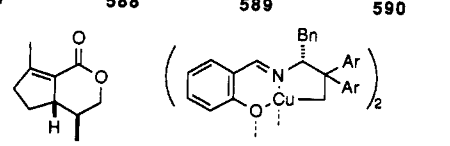
581 : R =
583 : R =



584 : R[1] = R[2] = H
585 : R[1] = H, R[2] = Me
586 : R[1] = Me, R[2] = H

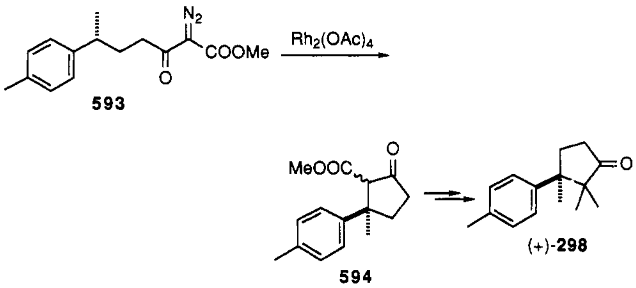


587 588 589 590



591 592

Scheme 68



Scheme 69

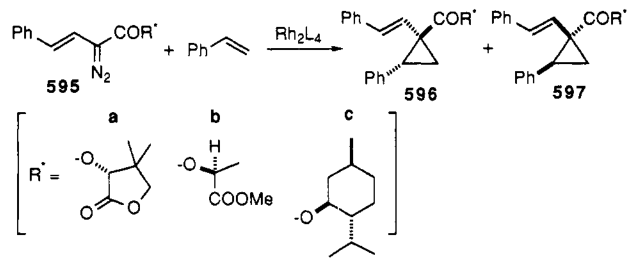


Table 28. Rhodium(II)-Catalyzed Asymmetric Cyclopropanation

substrate	ligand	major isomer (% de)	yield, %
595a	CH_3COO	**596** (89)	91
595a	(*S*)-PhCH(OH)COO	**596** (17)	89
595a	(*R*)-PhCH(OH)COO	**596** (81)	95
595a	$CH_3(CH_2)_6COO$	**596** (91)	84[a]
595b	CH_3COO	**597** (67)	83
595c	CH_3COO	(3)[b]	81

[a] At 0 °C. [b] Stereochemistry was not determined.

The rhodium-catalyzed intramolecular C–H insertion of the optically active diazoketone **593** proceeded smoothly to give **594** in 67% yield with nearly 100% stereoselectivity at the newly created quaternary carbon center.[212] This was confirmed by the synthesis of (+)-α-cuparenone (**298**) (Scheme 68). The rhodium-catalyzed reaction of chiral vinyl diazoesters **595a–c** with styrene afforded cyclopropanes **596** and **597** in good yield[213] (Scheme 69). The highest diastereoselectivity was observed with **595a**. Double diastereodifferentiation between the chiral ligand and carbenoid auxiliary was clearly evident in this reaction. The selected examples are listed in Table 28.

The asymmetric synthesis of 1,1,2-trisubstituted 1,2-dihydronaphthalenes **604** has been reported.[214,215] The process involves tandem addition to chiral naphthyl oxazolines (Scheme 70). The addition of alkyllithium to chiral oxazolines **598–601** generates a lithiated species **602**, which can be trapped with methyl iodide to afford **603** with good diastereoselectivity. Conversion of **603** into the chiral dihydronaphthalenes **604** was effected by successive treatment with magic methyl or Meerwein reagent, sodium borohydride, and finally oxalic acid. The results of tandem addition are listed in table 29. Trapping **602** (R = Me, $R^1 = R^2 = R^3$ = H) with methyl chloroformate gave the corresponding product **603** (COOMe instead of Me) in good yield and ee. 2-Substituted naphthalene **605** undergoes the same type of tandem addition to give a diastereomeric mixture of **606** and **607**. The results are summarized in Table 30.[215,216] Various chiral oxazolines listed in Table 31 were used as a substrate to gain insight into the mechanism of this asymmetric induction. It turned out that the selectivity of the nucleophilic addition was determined by the C-4 stereocenter in the oxazolines.[215]

Scheme 70

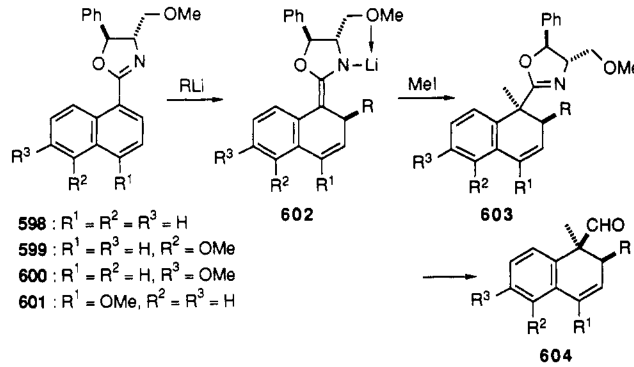


Table 29. Asymmetric Tandem Addition to Chiral 1-Substituted Naphthalenes 598–601 Giving 603 (Scheme 70)

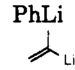
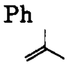
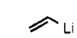
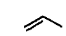
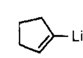
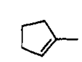
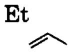
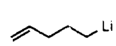
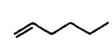
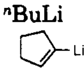
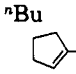
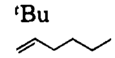
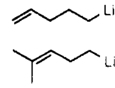
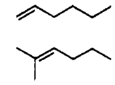
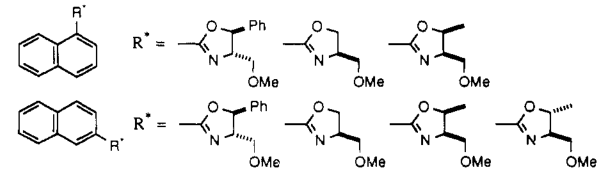
		dihydronaphthyloxazolines **603**		
oxazoline	RLi	% yield	R	diastereomeric ratio
598	^{n}BuLi	97	^{n}Bu	94:6
598	^{t}BuLi	98	^{t}Bu	74:26
598	PhLi	99	Ph	83:17
598		75		88:12
598		79		90:10
598		73		89:11
598	EtLi	92	Et	94:6
599		80		80:20
599		80		95:5
599	^{n}BuLi	95	^{n}Bu	97:3
600		50		85:15
601	^{n}BuLi	95	^{n}Bu	97:3
601	^{t}BuLi	95	^{t}Bu	65:35
601		90		97:3
601		90		97:3

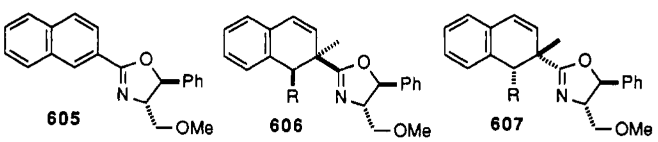
Table 30. Asymmetric Tandem Addition to Chiral 2-Substituted Naphthalene 605

RLi	temp, °C	time, h	yield, %	ratio (**606**:**607**)
^{n}BuLi	−78	2	85	98:2
^{n}BuLi	−78	2	92[a]	98:2
MeLi	−30	15	67	91:9
PhLi	−30	5	89	90:10
^{t}BuLi	−100	1.5	74	76:27

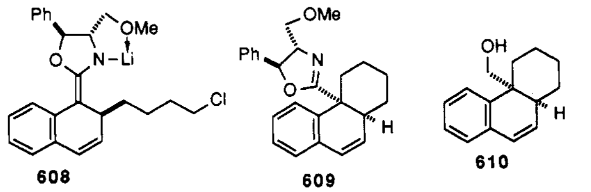
[a] HMPA (1.0 equiv) added.

Table 31. List of Chiral Oxazolines





605 606 607

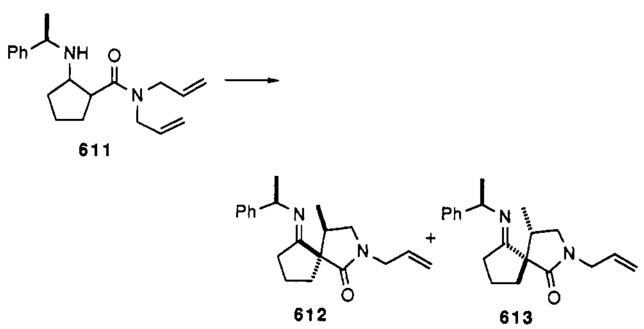


608 609 610

An intramolecular version of this reaction has been reported.[217] Thus, the addition of 1-chloro-4-lithiobutane to 598 ($R^1 = R^2 = R^3 = H$) in THF at -78 °C afforded **608**, which was further converted by warming to room temperature *in situ* to give an annulated product **609** in 75% yield. The carbinol **610** of 96% ee was prepared from **609**.

Thermolysis of **611** proceeded smoothly to afford a 77:23 mixture of **612** and **613** in 90% yield (Scheme 71).[218] Acid hydrolysis of each diastereomer produced

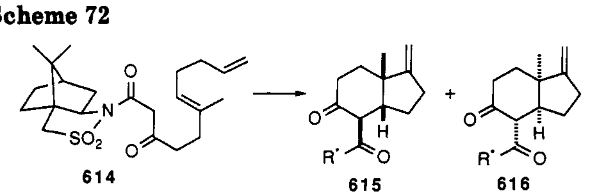
Scheme 71



611 612 613

the corresponding spiroketone enantiomeric to each other. Diastereodifferentiating free-radical cyclizations promoted by manganese(III) have also been reported. A sultam derivative **614** provided **615** (49%) and **616** (17%) on treatment with $Mn(OAc)_3$ and $Cu(OAc)_2$ in acetic acid (Scheme 72).[219] Another example includes

Scheme 72

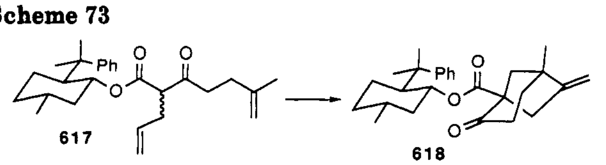


614 615 616

R* = D-camphor sultam

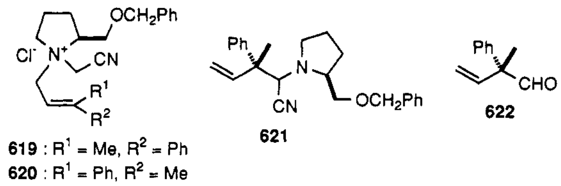
the cyclization of **617** to **618** in 90% yield and 86% de (Scheme 73).[220]

Scheme 73



617 618

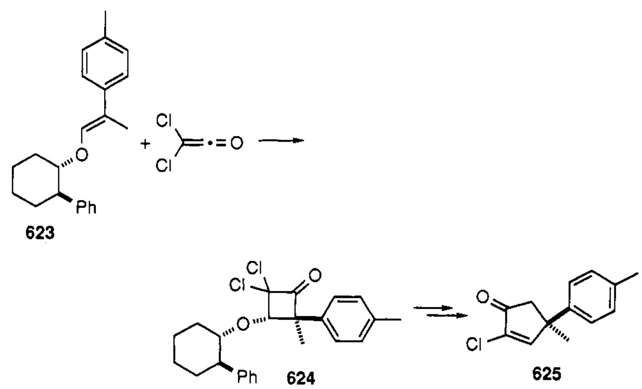
A [2,3]-sigmatropic rearrangement of the anion derived from **619** proceeded in THF–DMSO to afford **622** in 44% yield with 90% ee *via* **621**. The corresponding *Z*-isomer **620** afforded the enantiomer of **622** with 36% ee in 35% yield.[221] The [2 + 2]-cycloaddition



619 : R^1 = Me, R^2 = Ph
620 : R^1 = Ph, R^2 = Me
621 622

reaction of **623** with dichloroketene proceeded smoothly to give **624** in 92% yield and >90% de. (-)-α-Cuparenone and (+)-β-cuparenone were prepared from the cyclopentenone **625** derived from **624** (Scheme 74).[222]

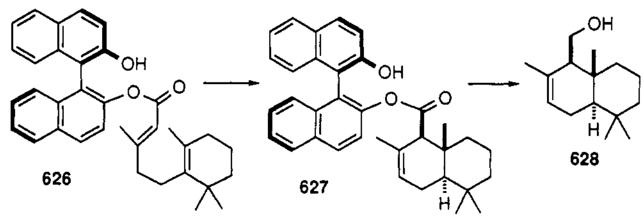
Scheme 74



623 624 625

Cyclization of the chiral binaphthyl ester **626** in the presence of stannic chloride followed by the reduction of the resulting bicyclic ester **627** with lithium aluminum hydride afforded (-)-drimenol **628** with low ee (~20%) (Scheme 75).[223]

Scheme 75



626 627 628

IV. An Overview of Reviews on Related Topics

An unexpectedly large number of examples for the asymmetric creation of quaternary carbon centers were revealed on searching the literature. However, most of them are isolated examples in the tables, revealing both the scope and limitation of certain reactions. I have endeavored to cover all papers relating to the present topics in this review and apologize for any omissions. For the convenience of readers, useful review articles—some of which are mentioned in the text—are listed below.

(1) Martin, S. F., Methodology for the Construction of Quaternary Carbon Centers. *Tetrahedron* **1980**, *36*, 419–460.

(2) Sih, C. J.; Chen, C.-S. Microbial Asymmetric Catalysis. Enantioselective Reduction of Ketones. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 570–578.

(3) Tomioka, K.; Koga, K. Asymmetric Control in the Construction of Quaternary Carbon Centers and Its Application to the Total Synthesis of Natural Products. *J. Synth. Org. Chem. Jpn.* **1986**, *44*, 545–557 (in Japanese).

(4) Agami, C. Mechanism of the Proline-Catalyzed Enantioselective Aldol Reaction, Recent Advances. *Bull. Soc. Chim. Fr.* **1988**, *3*, 499–507.

(5) Zhu, L.-M.; Tedford, M. C. Application of Pig Liver Esterases (PLE) in Asymmetric Synthesis. *Tetrahedron* **1990**, *46*, 6587–6611.

(6) Csuk, R.; Glanzer, B. I. Baker's Yeast Mediated Transformations in Organic Chemistry. *Chem. Rev.* **1991**, *91*, 49–97.

(7) Fuji, K.; Node, M. Chiral Nitroolefins for Enantioselective Reactions. *Synlett* **1991**, 603–610.

(8) Romo, D.; Meyers, A. I. Chiral Non-Racemic Bicyclic Lactams. Vehicles for the Construction of Natural and Unnatural Products Containing Quaternary Carbon Centers. *Tetrahedron* **1991**, *47*, 9503–9569.

(9) d'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. The Asymmetric Michael Addition Reactions Using Chiral Imines. *Tetrahedron: Asymmetry* **1992**, *3*, 459–505.

Finally, it should be mentioned that all of the articles in July/August 1992 issue of *Chemical Reviews* deal with asymmetric syntheses.

References

(1) Izumi, Y. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 871.
(2) Stork, G.; Poirier, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 1073.
(3) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.
(4) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496.
(5) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.
(6) (a) Agami, C.; Levisalles, J.; Puchot, C. *J. Chem. Soc., Chem. Commun.* **1985**, 441. (b) Puchot, C.; Samuel, O.; Duñach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353.
(7) Buchschacher, P.; Cassal, J.-M.; Fürst, A.; Meier, W. *Helv. Chim. Acta* **1977**, *60*, 2747.
(8) Gutzwiller, J.; Buchschacher, P.; Fürst, A. *Synthesis* **1977**, 167.
(9) Terashima, S.; Sato, S.; Koga, K. *Tetrahedron Lett.* **1979**, 3469.
(10) (a) Danishefsky, S.; Cain, P. *J. Am. Chem. Soc.* **1975**, *97*, 5282. (b) Danishefsky, S.; Cain, P. *J. Am. Chem. Soc.* **1976**, *98*, 4975.
(11) Shimizu, I.; Naito, Y.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 487.
(12) Grieco, P. A.; Fukamiya, N.; Miyashita, M. *J. Chem. Soc., Chem. Commun.* **1976**, 573.
(13) Takano, S.; Sato, S.; Goto, E.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1986**, 156.
(14) Takano, S.; Kasahara, C.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1981**, 635.
(15) Langström, B.; Bergson, G. *Acta Chem. Scand.* **1973**, *27*, 3118.
(16) Wynberg, H.; Helder, R. *Tetrahedron Lett.* **1975**, 4057.
(17) Hermann, K.; Wynberg, H. *Helv. Chim. Acta* **1977**, *60*, 2208.
(18) Hermann, K.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2238.
(19) Cram, D. J.; Sogah, G. D. Y. *J. Chem. Soc., Chem. Commun.* **1981**, 625.
(20) Brunner, H.; Hammer, B. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 312.
(21) Fiaud, J.-C. *Tetrahedron Lett.* **1975**, 3495.
(22) Julia, S.; Ginebreda, A.; Guixer, J.; Tomás, A. *Tetrahedron Lett.* **1980**, *21*, 3709.
(23) (a) Dolling, U.-H.; Davis, P.; Grabowski, J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446. (b) Hughes, D. L.; Dolling, U.-H.; Ryan, K. M.; Schoenewaldt, E. F.; Grabowski, E. J. J. *J. Org. Chem.* **1987**, *52*, 4745.
(24) Bhattacharaya, A.; Dolling, U.-H. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 476.
(25) Conn, R. S. E.; Lovell, A. V.; Karady, S.; Weinstock, L. M. *J. Org. Chem.* **1986**, *51*, 4710.
(26) Nerinchx, W.; Vandewalle, M. *Tetrahedron: Asymmetry* **1990**, *1*, 265.
(27) Lee, T. B. K.; Wong, G. S. K. *J. Org. Chem.* **1991**, *56*, 872.
(28) Simpkins, N. S. *J. Chem. Soc., Chem. Commun.* **1986**, 88.
(29) Hogeveen, H.; Menge, W. M. P. B. *Tetrahedron Lett.* **1986**, *27*, 2767.
(30) Fiaud, J. C.; Hibon de Gournay A.; Larcheveque, M.; Kagan, H. B. *J. Organometal. Chem.* **1978**, *154*, 175.
(31) Hayashi, T.; Kanehira, K.; Tsuchiya, H.; Kumada, M. *J. Chem. Soc., Chem. Commun.* **1982**, 1162.
(32) Hayashi, T.; Kanehira, K.; Hagihara, T.; Kumada, M. *J. Org. Chem.* **1988**, *53*, 113.
(33) Würthrich, H. J.; Siewinski, A.; Schaffner, A.; Jeger, O. *Helv. Chim. Acta* **1973**, *56*, 239.
(34) Togni, A. *Tetrahedron: Asymmetry* **1991**, *2*, 683.
(35) Sawamura, M.; Nagata, H.; Sakamoto, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2586.
(36) Sato, Y.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 4738.
(37) Abelman, M. M.; Oh, T.; Oveman, L. E. *J. Org. Chem.* **1987**, *52*, 4130.
(38) Sato, Y.; Sodeoka, M.; Shibasaki, M. *Chem. Lett.* **1990**, 1953.
(39) Sato, Y.; Watanabe, S.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 2589.
(40) Sato, Y.; Honda, T.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 2593.
(41) Kagechika, K.; Shibasaki, M. *J. Org. Chem.* **1991**, *56*, 4093.
(42) Shibasaki, M.; Mase, T.; Ikegami, S. *J. Am. Chem. Soc.* **1986**, *108*, 2090.
(43) Takemoto, T.; Nishikimi, Y.; Sodeoka, M.; Shibasaki, M. *Tetrahaedron Lett.* **1992**, *33*, 3531.
(44) Carpenter, N. E.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5846.
(45) Ashimori, A.; Overmann, L. E. *J. Org. Chem.* **1992**, *57*, 4571.
(46) Kennedy, M.; McKervey, M. A.; Maguire, A. R.; Roos, G. H. P. *J. Chem. Soc., Chem. Commun.* **1990**, 361.
(47) Suzuki, T.; Uozumi, Y.; Shibasaki, M. *J. Chem. Soc., Chem. Commun.* **1991**, 1593.
(48) Hashimoto, S.; Komeshima, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 437.
(49) Bir, G.; Kaufmann, D. *Tetrahedron Lett.* **1987**, *28*, 777.
(50) Furuta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. *J. Org. Chem.* **1989**, *54*, 1481.
(51) Rebiere, F.; Riant, O.; Kagan, H. B. *Tetrahedron: Asymmetry* **1990**, *1*, 199.
(52) Sartor, D.; Saffrich, J.; Helmchen, G. *Synlett* **1990**, 197.
(53) Kaufmann, D.; Boese, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 545.
(54) Takemura, H.; Komeshima, N.; Takahashi, I.; Hashimoto, S.; Ikota, N.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1987**, *28*, 5687.
(55) Takasu, M.; Yamamoto, H. *Synlett* **1990**, 194.
(56) Northcott, C.; Valenta, Z. *Can. J. Chem.* **1987**, *65*, 1917.
(57) Mikami, K.; Terada, M.; Motoyama, Y.; Nakai, T. *Tetrahedron: Asymmetry* **1991**, *2*, 643.
(58) Quinkert, G.; del Grosso, M.; Bucher, A.; Bauch, M.; Döring, W.; Bats, J. W.; Dürner, G. *Tetrahedron Lett.* **1992**, *33*, 3617.
(59) Nakamura, A.; Konishi, A.; Tatsuno, Y.; Otsuka, S. *J. Am. Chem. Soc.* **1978**, *100*, 3443.
(60) Nakamura, A.; Konishi, A.; Tsujitani, R.; Kudo, M.; Otsuka, S. *J. Am. Chem. Soc.* **1978**, *100*, 3449.
(61) Trost, B. M.; Hammen, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 962.
(62) Kobayashi, M.; Uemura, K.; Watanabe, N.; Matsuyama, H. *Chem. Lett.* **1985**, 1067.
(63) Gais, H.-J.; Hellmann, G. *J. Am. Chem. Soc.* **1992**, *114*, 4439.
(64) Hiratake, J.; Shibata, K.; Baba, N.; Oda, J. *Synthesis* **1988**, 278.
(65) Iriuchijma, S.; Hasegawa, K.; Tsuchihashi, G. *Agric. Biol. Chem.* **1982**, *46*, 1907.
(66) Schneider, M.; Engel, N.; Boensmann, H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 66.
(67) Björkling, F.; Boutelje, J.; Gatenbeck, S.; Hult, K.; Norin, T.; Szmulik, P. *Tetrahedron* **1985**, *41*, 1347.
(68) Francis, C. J.; Jones, J. B. *J. Chem. Soc., Chem. Commun.* **1984**, 579.
(69) Björkling, F.; Boutelje, J.; Gatenbeck, S.; Hult, K.; Norin, T. *Tetrahedron Lett.* **1985**, *26*, 4957.
(70) Fadel, A.; Canet, J.-L.; Salaun, J. *Tetrahedron Lett.* **1989**, *30*, 6687.
(71) Canet, J.-L.; Fadel, A.; Salaün, J. *J. Org. Chem.* **1992**, *57*, 3463.
(72) Luyten, M.; Müller, S.; Herzog, B.; Keese, R. *Helv. Chim. Acta* **1987**, *70*, 1250.
(73) Björkling, F.; Boutelje, J.; Gatenbeck, S.; Hult, K.; Norin, T.; Szmulik, P. *Biorg. Chem.* **1986**, *14*, 176.
(74) Ihara, M.; Suzuki, M.; Fukumoto, K.; Kabuto, C. *J. Am. Chem. Soc.* **1990**, *112*, 1164.
(75) Pelletier, S. W.; Parthasarathy, P. C. *Tetrahedron Lett.* **1963**, 205.
(76) Gibian, H.; Kieslich, K.; Koch, H.-J.; Kosmol, H.; Rufer, C.; Schröder, E.; Vössig, R. *Tetrahedron Lett.* **1966**, 2321.
(77) Kosmol, H.; Kieslich, K.; Vössing, R.; Koch, H.-J.; Petzoldt, K.; Gibian, H. *Liebigs Ann. Chem.* **1967**, *701*, 198.
(78) Brooks, D. W.; Grothaus, P. G.; Irwin, W. L. *J. Org. Chem.* **1982**, *47*, 2820.
(79) Brooks, D. W.; Mazdiyasni, H.; Grothaus, P. G. *J. Org. Chem.* **1987**, *52*, 3223.
(80) Schwarz, S.; Schaumann, J.; Truckenbrodt, G.; Weber, G.; Meyer, M.; Schick, H.; Welzel, H.-P. *Z. Chem.* **1979**, *19*, 450.

(81) Schwarz, S.; Truckenbrodt, G.; Meyer, M.; Zepter, R.; Weber, G.; Carl, C.; Wentzke, M.; Schick, H.; Welzel, H.-P. *J. Prakt. Chem.* **1981**, *323*, 729.
(82) Zhou, W.; Zhuang, Z.; Wang, Z. *Huaxue Xuebao* **1982**, *40*, 666; *Chem. Abstr.* **1983**, *98*, 31097q.
(83) Lanzilotta, R. P.; Bradley, D. G.; Beard, C. C. *Appl. Microbiol.* **1975**, 427.
(84) Zhou, W.; Huang, T.; Wang, C. *K'o Hsueh T'ung Pao* **1980**, *25*, 561; *Chem. Abstr.* **1980**, *93*, 200713s.
(85) Dai, W.; Zhou, W. *Tetrahedron* **1985**, *41*, 4475.
(86) Zhuang, Z.; Zhou, W. *Tetrahedron* **1985**, *41*, 3633.
(87) Kogan, L. M.; Gulaya, V. E.; Torgov, I. V. *Tetrahedron Lett.* **1967**, 4673.
(88) Brooks, D. W.; Mazdiyasni, H.; Chakrabarti, S. *Tetrahedron Lett.* **1984**, *25*, 1241.
(89) Brooks, D. W.; Mazdiyasni, H.; Sallay, P. *J. Org. Chem.* **1985**, *50*, 3411.
(90) Schwarz, S.; Depner, W. J.; Schaumann, J. *Tetrahedron* **1982**, *38*, 1261.
(91) Brooks, D. W.; Grothaus, P. G.; Palmer, J. T. *Tetrahedron Lett.* **1982**, *23*, 4187.
(92) Brooks, D. W.; Grothaus, P. G.; Mazdiyasni, H. *J. Am. Chem. Soc.* **1983**, *105*, 4472.
(93) Mori, K.; Nagano, E. *Biocatalysis* **1990**, *3*, 25.
(94) Kitahara, T.; Miyake, M.; Kido, M.; Mori, K. *Tetrahedron: Asymmetry* **1990**, *1*, 775.
(95) Watanabe, H.; Mori, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2919.
(96) Masamune, T.; Fukuzawa, A.; Furusaki, A.; Ikura, M.; Matsue, H.; Kaneko, T.; Abiko, A.; Sakamoto, N.; Tanimoto, N.; Murai, A. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1001 and references cited therein.
(97) Duggan, P. G.; Murphy, W. S. *J. Chem. Soc., Chem. Commun.* **1974**, 263.
(98) Duggan, P. G.; Murphy, W. S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 634.
(99) Fuji, K.; Node, M.; Nagasawa, H.; Naniwa, Y.; Terada, S. *J. Am. Chem. Soc.* **1986**, *108*, 3855.
(100) Fuji, K.; Node, M.; Nagasawa, H.; Naniwa, Y.; Taga, T.; Machida, K.; Snatzke, G. *J. Am. Chem. Soc.* **1989**, *111*, 7921.
(101) Node, M.; Nagasawa, H.; Fuji, K. *J. Am. Chem. Soc.* **1987**, *109*, 7901.
(102) Node, M.; Nagasawa, H.; Fuji, K. *J. Org. Chem.* **1990**, *55*, 517.
(103) Takano, S.; Yonaga, M.; Ogasawara, K. *Heterocycles* **1982**, *19*, 1391.
(104) Node, M.; Hao, X.; Fuji, K. *Chem. Lett.* **1991**, 57.
(105) Node, M.; Hao, X.; Nagasawa, H.; Fuji, K. *Tetrahedron Lett.* **1989**, *30*, 4141.
(106) Hao, X.; Node, M.; Fuji, K. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1505.
(107) Fuji, K.; Zheng, S.; Node, M.; Hao, X. *Chem. Pharm. Bull.* **1991**, *39*, 202.
(108) Fuji, K.; Node, M.; Abe, H.; Itoh, A.; Masaki, Y.; Shiro, M. *Tetrahedron Lett.* **1990**, *31*, 2419.
(109) Node, M.; Itoh, A.; Masaki, Y.; Fuji, K. *Heterocycles* **1991**, *32*, 1705.
(110) Shimazaki, M.; Hara, H.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1987**, *28*, 5891.
(111) Maruoka, K.; Ooi, T.; Nagahara, S.; Yamamoto, H. *Tetrahedron* **1991**, *47*, 6983.
(112) Nemoto, H.; Ishibashi, H.; Nagamochi, M.; Fukumoto, K. *J. Org. Chem.* **1992**, *57*, 1707.
(113) Nemoto, H.; Yamada, T.; Ishibashi, H.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3149.
(114) Lee, E.; Shin, I.; Kim, T. *J. Am. Chem. Soc.* **1990**, *112*, 260.
(115) Kanematsu, K.; Nishizaki, A.; Sato, Y.; Shiro, M. *Tetrahedron Lett.* **1992**, *33*, 4967.
(116) Ibuka, T.; Tanaka, M.; Nishii, S.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 1596.
(117) Trost, B. M.; Curran, D. P. *J. Am. Chem. Soc.* **1980**, *102*, 5699.
(118) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 4929.
(119) Imanishi, T.; Kurumada, T.; Maezaki, N.; Sugiyama, K.; Iwata, C. *J. Chem. Soc., Chem. Commun.* **1991**, 1409.
(120) Takano, S.; Murakata, C.; Imamura, Y.; Tamura, N.; Ogasawara, K. *Heterocycles* **1981**, *16*, 1291.
(121) Hart, D. J.; Huang, H.; Krishnamurthy, R.; Schwartz, T. *J. Am. Chem. Soc.* **1989**, *111*, 7507.
(122) Toshimitsu, A.; Hirosawa, C.; Tanimoto, S. *Chem. Lett.* **1992**, 239.
(123) Marino, J. P.; Bogdan, S.; Kimura, K. *J. Am. Chem. Soc.* **1992**, *114*, 5566.
(124) Caporusso, A. M.; Consoloni, C.; Lardicci, L. *Gazz. Chim. Ital.* **1988**, *118*, 857.
(125) Duthaler, R. O.; Maienfisch, P. *Helv. Chim. Acta* **1982**, *65*, 635.
(126) Hua, D. H.; Sinai-Zingde G.; Venkataraman, S. *J. Am. Chem. Soc.* **1985**, *107*, 4088.
(127) Kunisch, F.; Hobert, K.; Welzel, P. *Tetrahedron Lett.* **1985**, *26*, 5433.
(128) Yamada, S.; Otani, G. *Tetrahedron Lett.* **1969**, 4327.
(129) Otani, G.; Yamada, S. *Chem. Pharm. Bull.* **1973**, *21*, 2112.
(130) Otani, G.; Yamada, S. *Chem. Pharm. Bull.* **1973**, *21*, 2119.
(131) Sone, T.; Hiroi, K.; Yamada, S. *Chem. Pharm. Bull.* **1973**, *21*, 2331.
(132) Otani, G.; Yamada, S. *Chem. Pharm. Bull.* **1973**, *21*, 2125.
(133) Yamada, S.; Otani, G. *Tetrahedron Lett.* **1971**, 1133.
(134) Otani, G.; Yamada, S. *Chem. Pharm. Bull.* **1973**, *21*, 2130.
(135) Sone, T.; Terashima, S.; Yamada, S. *Chem. Pharm. Bull.* **1976**, *24*, 1273.
(136) Sone, T.; Terashima, S.; Yamada, S. *Chem. Pharm. Bull.* **1976**, *24*, 1288.
(137) Hiroi, K.; Yamada, S. *Chem. Pharm. Bull.* **1975**, *23*, 1103.
(138) Pfau, M.; Revial, G.; Guingant, A.; d'Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273.
(139) d'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymmetry* **1992**, *3*, 459.
(140) Hashimoto, S.; Koga, K. *Tetrahedron Lett.* **1978**, 573.
(141) Kogen, H.; Tomioka, K.; Hashimoto, S.; Koga, K. *Tetrahedron* **1981**, *37*, 3951.
(142) (a) Tomioka, K.; Masumi, F.; Yamashita, T.; Koga, K. *Tetrahedron Lett.* **1984**, *25*, 333. (b) Tomioka, K.; Masumi, F.; Yamashita, T.; Koga, K. *Tetrahedron* **1989**, *45*, 643.
(143) Snider, B. B.; Yang, K. *Tetrahedron Lett.* **1989**, *30*, 2465.
(144) Snider, B. B.; Yang, K. *J. Org. Chem.* **1990**, *55*, 4392.
(145) Snider, B. B.; Yang, K. *J. Org. Chem.* **1992**, *57*, 3615.
(146) Tomioka, K.; Ando, K.; Takemasa, Y.; Koga, K. *J. Am. Chem. Soc.* **1984**, *106*, 2718.
(147) Georg, G. I.; Guan, X.; Kant, J. *Bioorg. Med. Chem. Lett.* **1991**, *2*, 125.
(148) Tomioka, K.; Ando, K.; Yasuda, K.; Koga, K. *Tetrahedron Lett.* **1986**, *27*, 715.
(149) Tomioka, K.; Seo, W.; Ando, K.; Koga, K. *Tetrahedron Lett.* **1987**, *28*, 6637.
(150) Tomioka, K.; Ando, K.; Takemasa, Y.; Koga, K. *Tetrahedron Lett.* **1984**, *25*, 5677.
(151) Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1967**, *98*, 567.
(152) Tomioka, K.; Yasuda, K.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1987**, 1345.
(153) Huang, P. Q.; Zhou, W. S. *Tetrahedron: Asymmetry* **1991**, *2*, 875.
(154) Georg, G. I.; Guan, X. *Tetrahedron Lett.* **1992**, *33*, 17.
(155) Brunner, H.; Kraus, J.; Lautenschlager, H.-J. *Monatsh. Chem.* **1988**, *119*, 1161.
(156) Pinheiro, S.; Guingant, A.; Desmaële, D.; d'Angelo, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1003.
(157) Guingant, A.; Hammami, H. *Tetrahedron: Asymmetry* **1991**, *2*, 411.
(158) Guingant, A. *Tetrahedron: Asymmetry* **1991**, *2*, 415.
(159) Hodgson, A.; Marshall, J.; Hallett, P.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2169.
(160) Meyers, A. I.; Harre, M.; Garland, R. *J. Am. Chem. Soc.* **1984**, *106*, 1146.
(161) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503.
(162) Meyers, A. I.; Snyder, L. B. *Synlett* **1991**, 863.
(163) Ihara, M.; Takahashi, M.; Niitsuka, H.; Taniguchi, N.; Yasui, K.; Fukumoto, K. *J. Org. Chem.* **1989**, *54*, 5413.
(164) Ihara, M.; Takahashi, M.; Taniguchi, N.; Yasui, K.; Niitsuka, H.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 525.
(165) Ihara, M.; Yasui, K.; Taniguchi, N.; Fukumoto, K. *Heterocycles* **1990**, *31*, 1017.
(166) Ihara, M.; Taniguchi, N.; Suzuki, S.; Fukumoto, K. *J. Chem. Soc., Chem. Commun.* **1992**, 976.
(167) Taber, D. F.; Mack, J. F.; Rheingold, A. L.; Geib, S. J. *J. Org. Chem.* **1989**, *54*, 3831.
(168) Schultz, A. G.; Sundararaman, P.; Macielag, M.; Lavieri, F. P.; Welch, M. *Tetrahedron Lett.* **1985**, *26*, 4575.
(169) Schultz, A. G.; Sundararaman, P. *Tetrahedron Lett.* **1984**, *25*, 4591.
(170) Schultz, A. G. *Acc. Chem. Res.* **1990**, 207.
(171) Schultz, A. G.; Taylor, R. E. *J. Am. Chem. Soc.* **1992**, *114*, 3937.
(172) Meyers, A. I.; Gonzalez, M. A.; Struzka, V.; Akahane, A.; Guiles, J.; Warmus, J. S. *Tetrahedron Lett.* **1991**, *32*, 5501.
(173) Meyers, A. I. *Tetrahedron* **1992**, *48*, 2589.
(174) Meyers, A. I.; Warmus, J. S.; Gonzalez, M. A.; Guiles, J.; Akahane, A. *Tetrahedron Lett.* **1991**, *32*, 5509.
(175) Meyers, A. I.; Guiles, J.; Warmus, J. S.; Gonzalez, M. A. *Tetrahedron Lett.* **1991**, *32*, 5504.
(176) Hamamoto, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 2463.
(177) Dalko, P. I.; Langlois, Y. *Tetrahedron Lett.* **1992**, *33*, 5213.
(178) Sundin, A.; Frejd, T.; Magnusson, G. *Tetrahedron Lett.* **1985**, *26*, 5605.
(179) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.
(180) Avenoza, A.; Cativiela, C.; Mayoral, J. A.; Peregrina, J. M.; Sinou, D. *Tetrahedron: Asymmetry* **1990**, *1*, 765.
(181) Cativiela, C.; Mayoral, J. A.; Avenoza, A.; Peregrima, J. M.; Lahoz, F. J.; Gimeno, S. *J. Org. Chem.* **1992**, *57*, 4664.
(182) Avenoza, A.; Cativiela, C.; Mayoral, J. A.; Peregrina, J. M. *Tetrahedron: Asymmetry* **1992**, *3*, 913.
(183) Busacca, C. A.; Meyers, A. I. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2299.
(184) Bird, C. W.; Lewis, A. *Tetrahedron Lett.* **1989**, *30*, 6227.
(185) Boeckman, R. K., Jr.; Nelson, S. G.; Gaul, M. D. *J. Am. Chem. Soc.* **1992**, *114*, 2258.
(186) Johnson, W. S.; Harbert, C. A.; Stipanovic, R. D. *J. Am. Chem. Soc.* **1968**, *90*, 5279.

(187) Johnson, W. S.; Herbert, C. A.; Ratcliffe, B.; Stipanovic, R. D. *J. Am. Chem. Soc.* **1976**, *98*, 6188.
(188) Johnson, W. S.; Elliott, J. D.; Hanson, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 1138.
(189) Harada, T.; Hayashima, T.; Wada, I.; Iwa-ake, N.; Oku, A. *J. Am. Chem. Soc.* **1987**, *109*, 527.
(190) Arai, I.; Mori, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 8254.
(191) Mash, E. A.; Nelson, K. A. *J. Am. Chem. Soc.* **1985**, *107*, 8256.
(192) Mori, A.; Arai, I.; Yamamoto, H. *Tetrahedron* **1986**, *42*, 6447.
(193) Mash, E. A.; Nelson, K. A. *Tetrahedron* **1987**, *43*, 679.
(194) Mash, E. A.; Nelson, K. A. *Tetrahedron Lett.* **1986**, *27*, 1441.
(195) Mash, E. A.; Math, S. K.; Flann, C. J. *Tetrahedron Lett.* **1988**, *29*, 2147.
(196) Mash, E. A.; Torok, D. S. *J. Org. Chem.* **1989**, *54*, 250.
(197) Mash, E. A. *J. Org. Chem.* **1987**, *52*, 4142.
(198) Kato, K.; Suemune, H.; Sakai, K. *Tetrahedron Lett.* **1992**, *33*, 247.
(199) Isaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **1990**, *112*, 7428.
(200) Johnson, C. R.; Barbachyn, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 4290.
(201) (a) Posner, G. H.; Kogan, T. P.; Hulce, M. *Tetrahedron Lett.* **1984**, *25*, 383. (b) Posner, G. H.; Mallamo, J. P.; Hulce, M.; Frye, L. L. *J. Am. Chem. Soc.* **1982**, *104*, 4180.
(202) Hiroi, K.; Nakamura, H.; Anzai, T. *J. Am. Chem. Soc.* **1987**, *109*, 1249.
(203) Hiroi, K.; Anzai, T.; Ogata, T.; Saito, M. *Tetrahedron Lett.* **1990**, *31*, 239.
(204) Snider, B. B.; Wan, B. Y.; Buckman, B. O.; Foxman, B. M. *J. Org. Chem.* **1991**, *56*, 328.
(205) Imanishi, T.; Ohra, T.; Sugiyama, K.; Ueda, Y.; Takemoto, Y.; Iwata, C. *J. Chem. Soc., Chem. Commun.* **1992**, 269.
(206) Taber, D. F.; Saleh, S. A.; Korsmeyer, R. W. *J. Org. Chem.* **1980**, *45*, 4699.
(207) Ogoshi, H.; Setsune, J.; Omura, T.; Yoshida, Z. *J. Am. Chem. Soc.* **1975**, *97*, 6461.
(208) Taber, D. F.; Amedio, J. C., Jr.; Krishna, R. *J. Org. Chem.* **1988**, *53*, 2984.
(209) Charles, R. G. *J. Org. Chem.* **1957**, *22*, 677.
(210) Sugi, Y.; Bando, K. *Chem. Lett.* **1976**, 727.
(211) Dauben, W. G.; Hendricks, R. T.; Luzzio, M. J.; Ng, H. P. *Tetrahedron Lett.* **1990**, *31*, 6969.
(212) Taber, D. F.; Petty, E. H.; Raman, K. *J. Am. Chem. Soc.* **1985**, *107*, 196.
(213) Davies, H. M. L.; Cantrell, W. R., Jr. *Tetrahedron Lett.* **1991**, *32*, 6509.
(214) Barner, B. A.; Meyers, A. I. *J. Am. Chem. Soc.* **1984**, *106*, 1865.
(215) Meyers, A. I.; Roth, G. P.; Hoyer, D.; Barner, B. A.; Laucher, D. *J. Am. Chem. Soc.* **1988**, *110*, 4611.
(216) Meyers, A. I.; Hoyer, D. *Tetrahedron Lett.* **1984**, *25*, 3667.
(217) Meyers, A. I.; Licini, G. *Tetrahedron Lett.* **1989**, *30*, 4049.
(218) Cossy, J.; Bouzide, A.; Pfau, M. *Tetrahedron Lett.* **1992**, *33*, 4883.
(219) Zoretic, P. A.; Weng, X.; Biggers, C. K.; Biggers, M. S.; Casper, M. L.; Davis, D. G. *Tetrahedron Lett.* **1992**, *33*, 2637.
(220) Snider, B. B.; Zhang, Q. *Tetrahedron Lett.* **1992**, *33*, 5921.
(221) Hiroi, K.; Nakazawa, K. *Chem. Lett.* **1980**, 1077.
(222) Greene, A. E.; Charbonnier, F.; Luche, M.-J.; Moyano, A. *J. Am. Chem. Soc.* **1987**, *109*, 4752.
(223) Lee, E.; Cho, J. H. *Bull. Kor. Chem. Soc.* **1989**, *10*, 323.