1,3-Aminoalcohols and Their Derivatives in Asymmetric Organic Synthesis

Susan M. Lait,[†] Danica A. Rankic,[‡] and Brian A. Keay*[,‡]

Department of Chemistry and Biochemistry, University of Lethbridge, Lethbridge, Alberta, Canada T1K 3M4, and Department of Chemistry, University of Calgary, Calgary, Alberta, Canada T2N 1N4

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1. Introduction

Aminoalcohols have been used extensively in asymmetric synthesis, both as chiral ligands and auxiliaries. The two heteroatoms allow great flexibility, as one or both can be bound to a Lewis acid, transition metal, or achiral starting material. Syntheses[1] of and the role of 1,2-aminoalcohols and their derivatives[2,3] as chiral auxiliaries have been reviewed previously. While less abundant than the 1,2-aminoalcohols, 1,3-aminoalcohols have also contributed significantly to the advancement of asymmetric synthesis. Because they are often forgotten in favor of their more popular cousins, this review has been undertaken to demonstrate the breadth of chemistry using 1,3-aminoalcohols as sources of chirality. Many have found use as chiral ligands or auxiliaries, and there have also been applications as a resolving agent and as a phase transfer catalyst. For the purposes of this review, the chemistry of aminated sugars[4] (which are often simultaneously 1,2-, 1,3-, 1,4-, and, occasionally, 1,5-aminoalcohols) will only be discussed when they are acting specifically as 1,3-aminoalcohols.

This paper reviews the application of 1,3-aminoalcohols and their derivatives in asymmetric transformations for organic synthesis. It is broken into seven sections according to reaction classes in which 1,3-aminoalcohols are participants as chirality transfer agents. The review begins with the reactions of stabilized carbanions, followed by ring opening reactions, additions to carbonyls, pericyclic reactions, transition-metal-catalyzed reactions, and radical cyclizations. The last section describes the uses of 1,3-aminoalcohols and derivatives that do not fall into any of the aforementioned categories. Within each reaction class, a variety of 1,3-aminoalcohols will be introduced along with results spanning a wide range of substrates. It is important to note that this review will not cover the synthesis of 1,3-aminoalcohols extensively. The syntheses presented will be only of those 1,3-aminoalcohols that have proven to be applicable in asymmetric transformations. The review shows that 1,3-aminoalcohols and their derivatives have proven useful in asymmetric transformations and that there is still much room for research in this area.

2. Reactions of Stabilized Carbanions

In 1990 Denmark[5a] and co-workers investigated simple aminoalcohol **1a** as a chiral auxiliary for alkylation of phosphorus-stabilized carbanions. Reaction with $BnPOCl_2$ in Et_3N gave **2a** and **3a** in 49% and 28% yields, respectively. Addition of **2a** to *t*BuLi and quenching the resulting anion with various electrophiles gave **4a** (Scheme 1, Table 1). The best results were obtained using MeI; however, respectable diastereoselectivity was observed using Me_2SO_4, $ClCH_2OBn$, $BrCH_2CO_2Bn$, or allyl iodide. The relative stereochemistry of the alkylation products was determined by acid-catalyzed cleavage of the auxiliary followed by methylation with

* Corresponding author. E-mail: keay@ucalgary.ca. Phone: 1-403-220-5340. Fax: 1-403-284-1372.
[†] University of Lethbridge.
[‡] University of Calgary.

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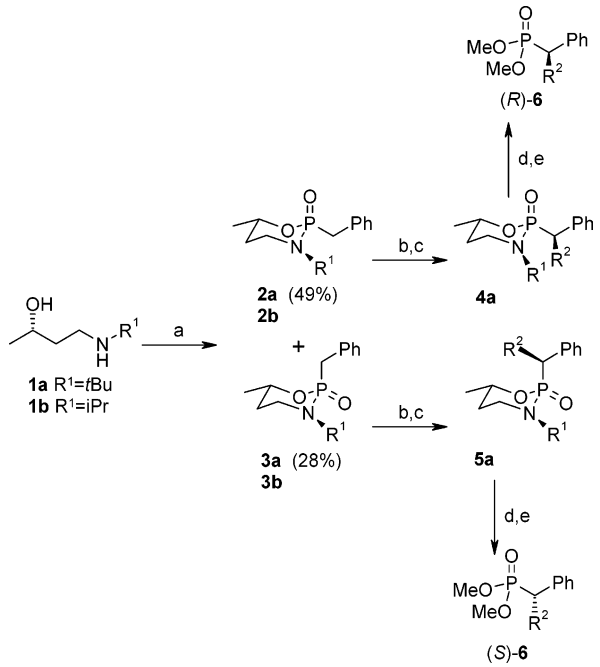
Susan M. Lait was born in Edinburgh, Scotland, in 1976 and moved to Ottawa, Ontario, Canada, in 1982. She received a B.Sc. degree in Applied Chemistry from the University of Guelph in 1999 and a Ph.D. in Organic Chemistry from the University of Calgary in 2004. Under the supervision of Prof. Brian A. Keay, her graduate research focused on synthesis of a 1,3-spiro-aminoalcohol and its application to asymmetric reactions. During her graduate studies, Dr. Lait developed a strong interest in chemical education; she is currently teaching introductory and organic chemistry at The University of Lethbridge in Alberta, Canada.

Danica A. Rankic was born in Calgary, Alberta, Canada, in 1982. She received her B.Sc. degree with distinction from the University of Calgary in 2004. She is currently in the third year of the Ph.D. program at the Univeristy of Calgary under the supervision of Dr. Brian A. Keay. The focus of her research is the development of novel 3,3′-disubstituted BINAP derivatives as ligands in transition-metal-catalyzed asymmetric processes.

Dr. Brian A. Keay was born in Toronto (1955) and received his Honors B.Sc. Co-op (1979) in Chemistry and Ph.D. (1983) in Organic Chemistry from the University of Waterloo, working with Prof. R. Rodrigo. After a Natural Sciences and Engineering Research Council of Canada (NSERC) postdoctoral fellowship with Prof. E. Piers (1983–85, University of British Columbia), he joined the faculty at the University of Windsor as an Assistant Professor (1985). In 1989, he moved to the University of Calgary, where he is now Professor and Head of the Department of Chemistry (since July 2002). He currently oversees a research group consisting of one postdoctoral fellow and seven graduate students. His research interests include the design and synthesis of asymmetric ligands for use as catalysts or substrate bound chiral auxiliaries with Lewis acids and transition metals, palladium-catalyzed polyene cyclizations, asymmetric intramolecular Diels–Alder reactions, and the synthesis of natural products.

Scheme 1[a]



[a] Reagents and conditions: (a) $BnPOCl_2$, Et_3N (2 equiv); (b) *t*BuLi, THF, −70 °C; (c) R^2X; (d) 6 N HCl; (e) CH_2N_2.

CH_2N_2 giving (*R*)-**6**. Surprisingly, it was noted that repeating this chemistry using the less sterically hindered aminoalcohol **1b** instead of **1a** gave superior diastereoselectivity; however, no yields were reported for these reactions (Table 1). Epimeric substrate **3a** gave the opposite enantiomer of the product, (*S*)-**6**, upon cleavage of the auxiliary from **5a**. Unfortunately, use of any electrophile other than MeI gave negligible diastereoselectivity upon reaction with **3a** (Scheme 1, Table 1).

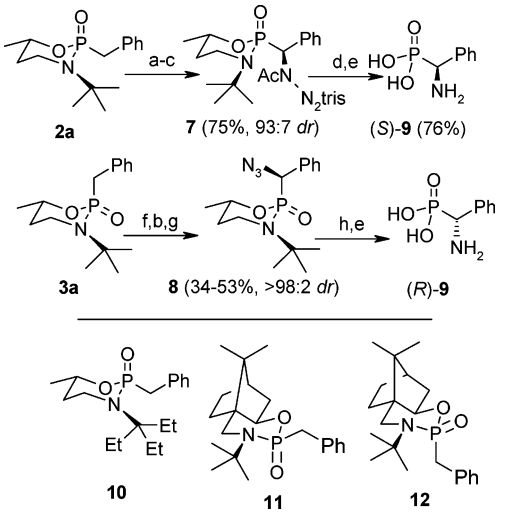
In an extension of this work, Denmark et al.[5b] also used **1a** as a chiral auxiliary for amination of phosphorus-stabilized carbanions. Formation of the anion of **2a** and quenching with trisylN_3 gave **7** in 75% yield with a 93:7 diastereomeric ratio (dr) (Scheme 2). Use of **3a** gave only one observable diastereomer of **8**, but the yield was much lower. As before, the two epimers, **2a** and **3a**, were complementary, giving opposite enantiomers of **9** upon cleavage of the auxiliary. Several other aminoalcohols were tested as auxiliaries in an unsuccessful attempt to find a system that could combine good yield and stereocontrol. Amination of **10** and **12** gave moderate stereocontrol (75:25 and 81:19 dr, respectively) though yields were 79−81%. On the other hand, amination of **11** gave only 30% yield even though only one diastereomer of the product was observed.

In 1993, Ahn et al. used camphor-based auxiliaries **13a**−**c** for enolate alkylation reactions.[6] Treatment of adducts **13a**−**c** with LDA generated *Z*-enolates which were quenched with alkyl halides to give alkylation products **14**−**16** with excellent diastereoselectivity (Table 2). Reduction of **14**−**16** with $LiAlH_4$ gave alcohols **17**−**19** in 73−81% yield alongside

Table 1. Alkylation of the Phosphorus-Stabilized Carbanions of 2a and 3a

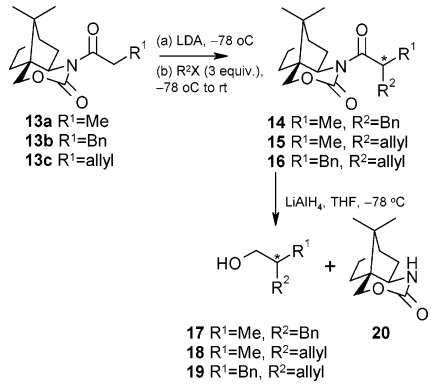
substrate	electrophile (R^2X)	yield (%)	dr
2a	MeI	85	95:5 (*R*)
2a	Me_2SO_4	67	92:8 (*R*)
2a	$BrCH_2CO_2Bn$	46	94:6 (*R*)
2a	$ClCH_2OBn$	74	92:9 (*R*)
2a	allyl iodide	86	90:10 (*R*)
2a	BnBr	70	84:16 (*R*)
2b	MeI	not reported	98:2 (*R*)
2b	BnBr	not reported	97:3 (*R*)
3a	MeI	96	83:17 (*S*)
3a	BnBr	96	55:45 (*S*)

Scheme 2[a]



[a] Reagents and conditions: (a) *n*BuLi, Et_2O, −78 °C; (b) trisylN_3, −78 °C; (c) Ac_2O, warm to rt, 8 h; (d) Al−Hg, EtOH; (e) 4 N HCl, dioxane, reflux; (f) KHMDS, THF, −78 °C; (g) AcOH; (h) H_2, 5% Pd/C, EtOH.

Table 2. Synthesis of Chiral Alcohols 17−19 by Alkylation of 13

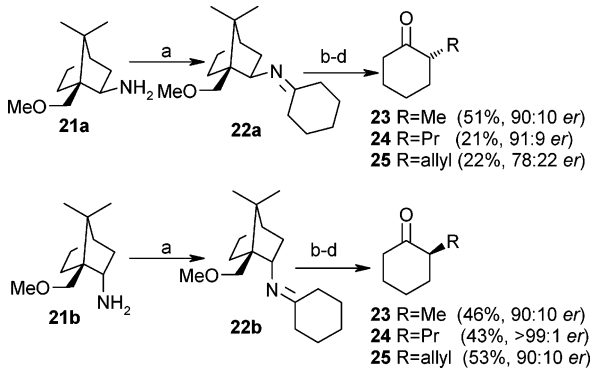


sm **13**	R^2X	product	yield (%)	dr	alcohol
a	BnBr	(2′*S*)-**14**	60	>99:1	(*S*)-**17**
b	MeI	(2′*R*)-**14**	81	>99:1	(*R*)-**17**
a	allyl iodide	(2′*S*)-**15**	61	>99:1	(*S*)-**18**
c	MeI	(2′*R*)-**15**	49	>99:1	(*R*)-**18**
b	allyl iodide	(2′*R*)-**16**	79	>99:1	(*R*)-**19**
c	BnBr	(2′*S*)-**16**	43	>99:1	(*S*)-**19**

90% recovered oxazinone **20**. By interchanging R^1 and R^2, Ahn et al. were able to prepare both enantiomers of the chiral alcohol using the same auxiliary.

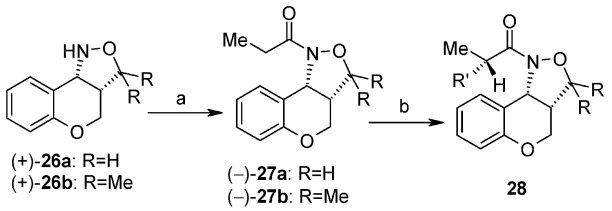
Methoxy derivative **21a** and its *endo* isomer **21b** have been used as chiral auxiliaries for alkylation of cyclohexanone.[7] Chiral imines **22** were prepared from auxiliaries **21** and cyclohexanone (Scheme 3). Enolates generated using LDA

Scheme 3[a]



[a] Reagents and conditions: (a) cyclohexanone, PhH, reflux, 8 h; (b) LDS, THF, −78 °C; (c) RX, THF, 0 or −10 °C; (d) citric acid, H_2O.

Table 3. Diastereoselective Alkylation of (−)-27a,b with Various Electrophiles (R′X)



Conditions and reagents: (a) CH_3CH_2COCl, Et_3N, CH_2Cl_2
(b) R'X, KHMDS, THF

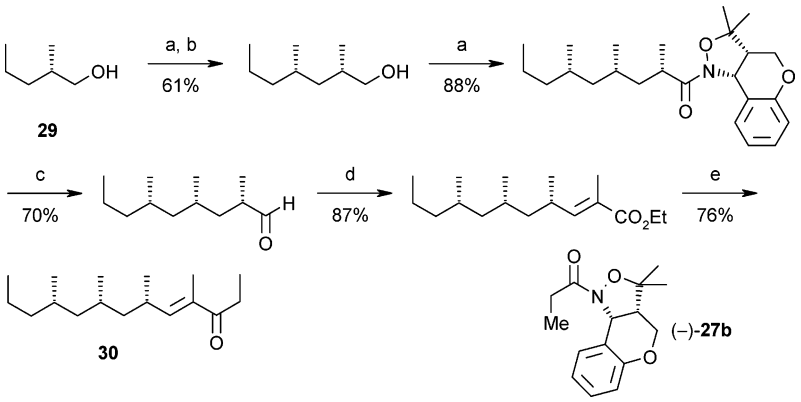
entry	(−)-**27**	R′X	yield (%)	dr
1	**a**	$PhCH_2Br$	94	98:2
2	**b**	$PhCH_2Br$	93	99:1
3	**a**	$CH_2{=}CHCH_2Br$	80	95:5
4	**b**	$CH_2{=}CHCH_2Br$	96	98:2
5	**a**	$CH_2{=}C(CH_3)CH_2Br$	91	98:2
6	**b**	$CH_2{=}C(CH_3)CH_2Br$	78	96:4
7	**a**	*n*-$C_5H_{11}I$	72	98:2
8	**a**	$C_6H_{11}CH_2OTf$	93	94:6
9	**b**	$C_6H_{11}CH_2OTf$	90	98:2

were subsequently quenched with alkyl halides. Hydrolytic workup gave 2-alkylcyclohexanones **23**−**25** in low to moderate yield. The reactions proceeded with moderate to excellent diastereoselectivity, and the two epimers of the auxiliary gave opposite enantiomers of the final product.

In 1995, Masamune reported a class of benzopyranoisoxazolidines used as chiral auxiliaries in the asymmetric α-alkylation of carboxylic acid derivatives.[8] Auxiliaries **26a** and **26b** were easily acylated to give **27a** and **27b**, respectively, by treating with the appropriate acid chloride and triethylamine (Table 3). Smooth α-alkylation was effected by deprotonation of the corresponding acyl amide. Addition of an electrophile gave amides **28**. Alkylation of the anion of **27** was not limited to common "reactive" electrophiles such as benzyl bromide, allyl bromide, or *n*-pentyl iodide. Interestingly, these anions were capable of reacting with *β*-branched triflates. Alkylation protocols involving the *N*-acyl anions of Evans' oxazolidinone,[9] Oppolzer's camphor sultam,[10] or other similar methods[11] tend to be unsuccessful in the reaction with *β*-branched triflates. Alkylation adducts could be reductively cleaved to afford either an aldehyde or an alcohol with concomitant recovery of the auxiliary. Additionally, the adducts could be treated with a nucleophile such as MeMgBr to generate a ketone and return the auxiliary.

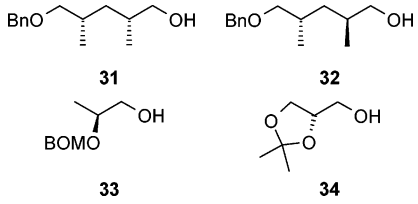
Abiko and Masamune showcased this methodology in 1996 through the first synthesis of (+)-siphonarienone (**30**),

Scheme 4[a]



[a] Reagents and conditions: (a) (1) Tf_2O, 2,6-*t*Bu_2pyridine; (2) K-enolate of (−)-**27b**, ether, HMPA; (b) $LiBH_4$−EtOH, ether; (c) DIBAL-H, ether, 0 °C; (d) ethoxycarbonylethylidenetriphenylphosphorane, toluene, reflux, 3 h; (e) (1) Me_3Al, MeNH(OMe)·HCl, benzene, reflux, 2 h; (2) EtMgBr, THF, rt, 2 h.

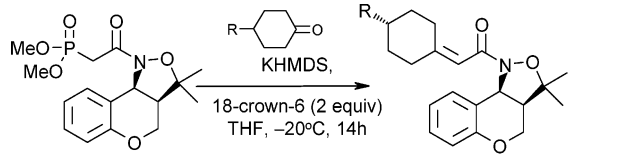
a marine polyketide-type natural product (Scheme 4).[12] This synthesis demonstrated the importance of the use of β-branched triflates as electrophiles. These electrophiles allow the introduction of fully reduced polypropionate structural units with the desired 1,3-syn relationship. High diastereoselectivities (dr > 99:1) accompany the alkylation steps in this synthesis. Although this synthesis relies on the homologation of chiral alcohol **29**, this methodology has been extended to more functionalized alcohols (**31**−**34**) as well.



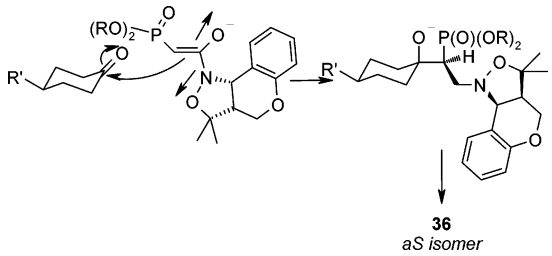
The use of chiral benzopyranoisoxazolidines was extended in 1996 to the synthesis of axially chiral olefins via an asymmetric Horner−Emmons reaction.[13] Deprotonation of chiral phosphonate **35** using KHMDS and 18-crown-6 provided an anion that readily reacted with a variety of 4-substituted cyclohexanones to afford axially chiral olefins **36** enriched in the *aS* isomer (Scheme 5). Separation of the diastereomers was achieved by either crystallization or chromatography. Cleavage of the chiral auxiliary can be done reductively or nucleophilically to afford alcohols, aldehydes, or ketones, as seen previously with the alkylation chemistry. The high diastereoselectivities reported were based on an anion conformer that minimizes dipole−dipole repulsions and on the bulky nucleophile adding preferentially to the equatorial side of the carbonyl group (Scheme 6).

Banks et al.[14] reported using fructose derivative **38** as a chiral auxiliary for several asymmetric reactions in 1998. An intramolecular nitrene insertion reaction was the key step in preparation of **38** from **37** (Scheme 7). Treatment of **38**

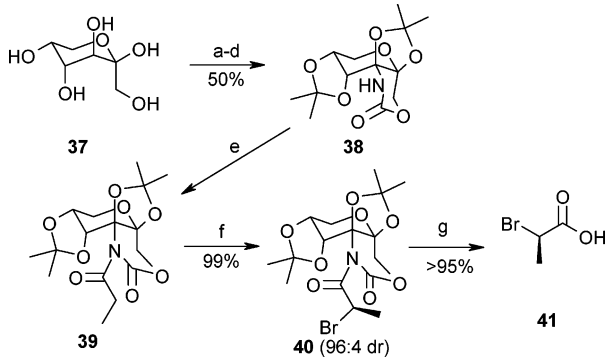
Scheme 5



Scheme 6



Scheme 7[a]



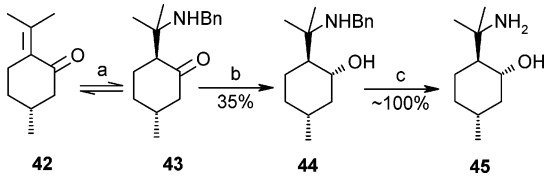
[a] Reagents and conditions: (a) acetone, conc H_2SO_4; (b) Cl_2CO, pyridine; (c) NaN_3, TBAB; (d) $(CHCl_2)_2$, reflux; (e) MeMgBr, Et_2O, 0 °C, EtCOCl; (f) NBS, THF, −78 °C; (g) LiOH, H_2O_2, 0 °C.

with propionyl chloride afforded **39** in excellent yield. Bromination of **39** using NBS gave better stereoselectivity, and **40** was formed in excellent yield with 96:4 dr. Cleavage of the auxiliary gave desired acid **41** in high yield.

3. Ring Opening Reactions

More work has been published describing the chemistry of 8-aminomenthol (**45**) and its derivatives than any other 1,3-aminoalcohol. This is likely due to their ease of preparation from commercially available (+)-pulegone (**42**) (Scheme 8). In 1987, He and Eliel[15] reported the synthesis of 8-aminomenthol (**45**) in three steps. Conjugate addition of benzylamine to (+)-pulegone (**42**) gave intermediate **43**, which was immediately reduced to benzyl derivative **44** in the presence of water to minimize formation and reduction of the imine byproduct. Purification by crystallization of the benzoate or *p*-toluate salt gave diastereomerically pure **44** in 35% yield. Removal of the benzyl protecting group gave aminoalcohol **45** in quantitative yield.

Scheme 8[a]



[a] Reagents and conditions: (a) $BnNH_2$; (b) $NaBH_4$, 4:1 EtOH/H_2O; (c) HCO_2NH_4, 10% Pd/C, MeOH.

In 2001, Pedrosa et al.[16] used menthol-based aminoalcohol **45** as a chiral auxiliary for intramolecular alkyllithium addition reactions. Oxazines **46** were prepared by condensation of **45** with a brominated benzaldehyde, reductive opening of the oxazine ring, and then condensation of the resulting aminoalcohol with a second aldehyde (Scheme 9). Treatment of **46a** with *t*BuLi in Et_2O at −90 °C and then warming to room temperature gave only dehalogenated product, showing that the halogen−metal exchange had been successful but that the resulting aryllithium had not opened the oxazine ring. On the other hand, when Et_2AlCl was added before warming to room temperature, addition product **46a** was formed. This protocol was applied to remaining oxazines **46** to produce aminoalcohols **47** in good yield (Table 4). In all cases, only one diastereomer of **47** was observed. Cleavage of the auxiliary gave amines **48** in moderate yield. From these amines, several alkaloids were synthesized. Enantiopure (*R*)-*O*-methyllophocerine (**49d**), (*R*)-*O*-methylarmepavine (**38f**), (*R*)-laudanosine (**38g**), and (*R*)-homolaudanosine (**38h**) were prepared by methylation of **48d**,**f**,**g** and **h**, respectively, while enantiopure (*S*)-calycotomine (**50e**) was made by hydrogenolysis of the benzyl group of **48e**.

This chemistry was also used for tandem 6-*exo*-carbolithiation ring opening reactions.[17] Oxazines **51** were prepared from **45** in the usual fashion (Scheme 10). Treatment of **51a**, **51g**, or **51h** with *t*BuLi and TMEDA at −90 °C and then warming to room temperature gave only debrominated starting material. Under the same conditions, however, **51b** gave 6-*exo* cyclization product **52b** with 77:23 dr, and **51f** gave **52f** as a single observable diastereomer (Table 5, method A). Cyclization of **51e** also proceeded under these conditions, and elimination of BnOH gave **53e** with 75:25 dr. The reaction conditions were then altered to force cyclization by adding the TMEDA immediately after the *t*BuLi (Table 5, method B). Again, **51a** and **51h** gave only debrominated starting material; however, **51b** gave **54b** as the 6-*exo* cyclization was followed by intramolecular opening of the oxazine ring. A single observable diastereomer of **54g** was also formed from **51g** using this method. Finally, TMEDA was removed entirely from the reaction protocol (Table 5, method C). In all cases, double cyclization products **54** were observed as the major diastereomer with minor formation of **55b** and **55h** in two cases.

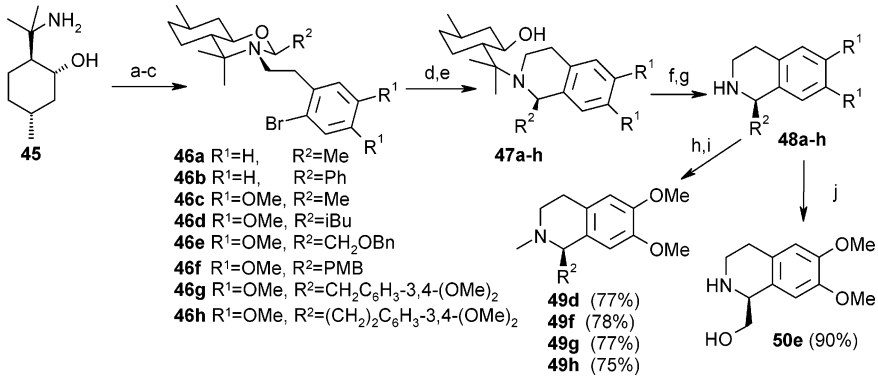
Table 4. Intramolecular Alkyllithium Addition to Oxazines 46 Giving Amines 48

	oxazine **46** (% yield)	addition product **47** (% yield)	amine **48** (% yield)
a	88	80	71
b	85	78	82
c	86	83	60
d	87	83	61
e	90	77	59
f	83	81	55
g	82	79	58
h	86	77	57

Pedrosa et al.[18] used **44** as a chiral auxiliary for Grignard additions in 1990 and 1996. Instead of the more typical nucleophilic attack on a carbonyl, the oxazine linking the substrate to the auxiliary was opened directly, allowing asymmetric synthesis of amines. Condensation of aldehydes with **44** gave thermodynamic diastereomers **56**−**64**, in which R^1 was equatorial (Scheme 11). The oxazine was then opened in an S_N2-like reaction by alkyl magnesium bromides, giving **65**. Alkyl magnesium iodides, on the other hand, reacted with retention at the electrophilic carbon, giving alkylation products **66** (Table 6; entries 3 and 10). The diastereoselectivity of these reactions was generally good for reagents other than cPrMgBr and EtMgX, which only worked well in one case (entry 15), and yields ranged from moderate to good. Removal of the auxiliary was achieved by elimination with P_2O_5 to give diene **67** and amine **68**. The benzyl group of the latter was removed by hydrogenolysis, giving excellent yields of amines **69**−**80**. These reactions proceeded without any apparent racemization (Table 6).

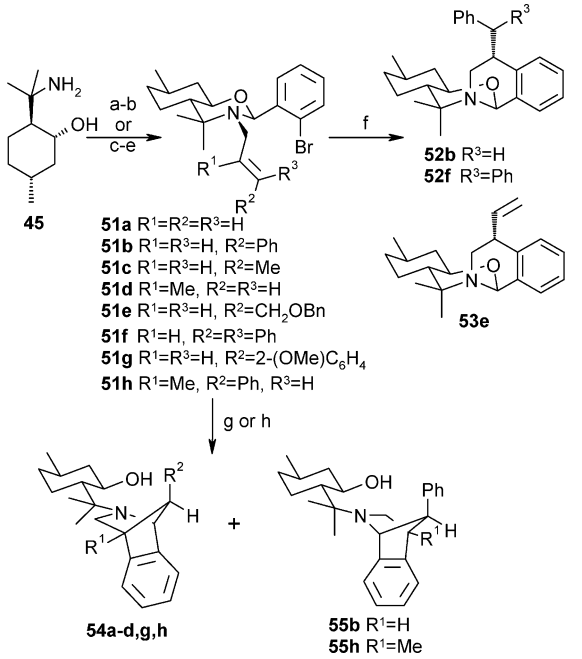
Oxazines **57** and **59**−**64** were also treated with Me_3Al to give similar addition products, and cleavage of the auxiliary by the same method gave chiral amines **69**−**71**, **74**, and **81**−**83** (Table 7).[18] Whereas the Grignard reagents reacted with inversion at the reacting carbon, the stereochemistry at that center was retained using Me_3Al. Thus, MeMgBr and Me_3Al were complementary reagents giving opposite enantiomers of amine using the same auxiliary.

Scheme 9[a]



[a] Reagents and conditions: (a) 2-bromobenzaldehyde or 2-bromo-4,5-dimethylbenzaldehyde, CH_2Cl_2, rt; (b) $NaBH_4$, $Et_2O{\cdot}BF_3$, THF, rt; (c) R^2CHO, 120 °C; (d) *t*BuLi (2.2 equiv), Et_2O, −90 °C; (e) Et_2AlCl, −90 °C to rt; (f) PCC; (g) KOH, MeOH, THF; (h) dimethylcarbonate, CH_2Cl_2; (i) $LiAlH_4$, Et_2O; (j) H_2, $Pd(OH)_2$/C, EtOH.

Scheme 10[a]



[a] Reagents and conditions: (a) 2-bromobenzaldehyde, CH_2Cl_2, rt; (b) $R^2R^3C{=}CR^1CH_2Br$, K_2CO_3, MeCN; (c) $R^2R^3C{=}CR^1CHO$, CH_2Cl_2, rt; (d) $NaBH_4$, EtOH; (e) 2-bromobenzaldehyde, 120 °C; (f) (method A) *t*BuLi (2.2 equiv), Et_2O, −90 °C, 5 min, then TMEDA (2 equiv), then warm to rt over 30 min; (g) (method B) *t*BuLi (2.2 equiv), TMEDA (2 equiv), Et_2O, −90 °C, then warm to rt, 15 h; (h) (method C) *t*BuLi (2.2 equiv), Et_2O, −90 °C, then warm to rt, 0.3−24 h.

Table 5. Intramolecular Alkyllithium Opening of Oxazines 51 to Cyclized Products 52−54

oxazine **51** (yield, %)	lithiation procedure[a]	major product	yield (%)	dr
a (88)	C	**54a**	80	≥98:2
b (91)	A	**52b**	98	77:23
b (91)	B	**54b**	97	77:23
b (91)	C	**54b**	90	76:24
c (89)	C	**54c**	5	≥98:2
d (63)	C	**54d**	35	≥98:2
e (65)	A	**53e**	66	75:25
f (72)	A	**52f**	45	≥98:2
g (74)	B	**54g**	81	≥98:2
g (74)	C	**54g**	95	≥98:2
h (72)	C	**54h**	69	87:13

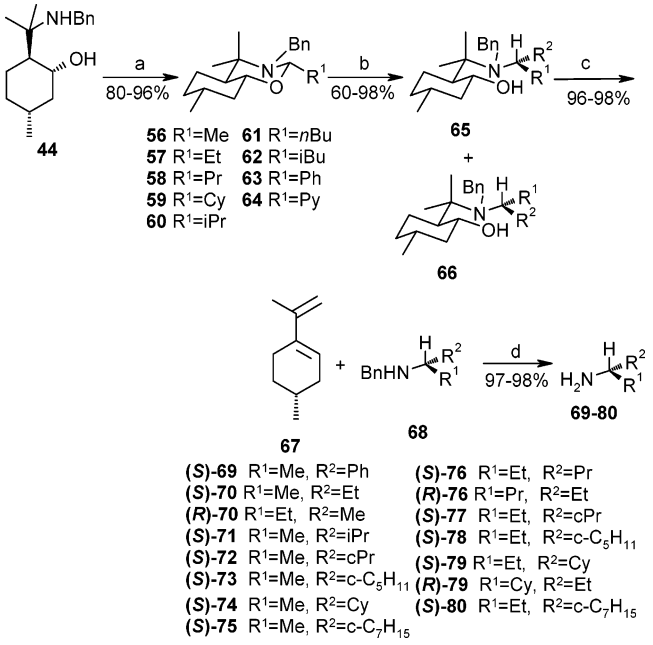
[a] For procedures, see Scheme 10.

4. Addition Reactions to Carbonyls

4.1. Hydride Reductions

"Darvon alcohol"[19] (+)-**84** was reacted with $LiAlH_4$ to generate chiral reducing agents **85** (Scheme 12). First to perform this reaction were Yamaguchi et al.,[20] who used **85** to reduce acetophenone (**86a**) to **87a** in 1972. Reaction with fresh reagent in Et_2O at −65 °C gave (*R*)-**87a** (88:12 er) quantitatively after 3 min whereas reaction with reagent that had been stirred overnight gave (*S*)-**87a** (83:17 er) with 40% conversion. Similar results were observed for reduction of other ketones although the enantioselectivity was not as good (Table 8). While some of the change in enantioselectivity was attributed to an increase in reaction homogeneity, the authors were unable to fully explain this unusual phenomenon. They postulated the existence of a rapidly formed *R*-selective reagent which could be converted to a more stable *S*-selective reagent over time. It should be noted that

Scheme 11[a]



[a] Reagents and conditions: (a) R^1CHO, PhH, reflux, 3−10 h; (b) R^2MgX, rt, 2 h; (c) P_2O_5, PhMe, reflux, 90 min; (d) H_2 (1 atm), 5% Pd/C, rt, 4−10 h.

Table 6. Synthesis of Amines 69−80 by Addition of Grignard Reagents to Oxazines 56−64

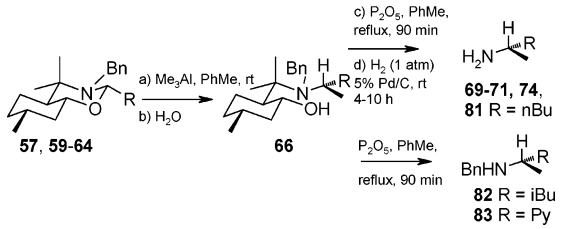
entry	sm	R^2MgX (R^2)	yield (%)	**65:66**	amine	yield (%)	er
1	**56**	PhMgBr	98	94:6	**69**	98	94:6 (*S*)
2	**56**	EtMgBr	85	65:35	**70**	94	64:36 (*S*)
3	**56**	EtMgI	86	41:59	**70**	92	58:42 (*R*)
4	**56**	*i*PrMgBr	62	95:5	**71**	92	>99:1 (*S*)
5	**56**	*c*-PrMgBr	96	59:41	**72**	67	>99:1 (*S*)
6	**56**	*c*-C_5H_{11}MgBr	81	98:2	**73**	96	98:2 (*S*)
7	**56**	CyMgBr	77	88:12	**74**	94	>99:1 (*S*)
8	**56**	*c*-C_7H_{15}MgBr	67	90:10	**75**	92	90:10 (*S*)
9	**57**	PrMgBr	80	94:6	**76**	93	94:6 (*S*)
10	**57**	MeMgI	89	9:91	**70**	94	90:10 (*S*)
11	**57**	*c*-PrMgBr	95	67:33	**77**	61	>99:1 (*S*)
12	**57**	*c*-C_5H_{11}MgBr	79	100:0	**78**	92	>99:1 (*S*)
13	**57**	CyMgBr	78	100:0	**79**	93	>99:1 (*S*)
14	**57**	*c*-C_7H_{15}MgBr	58	93:7	**80**	92	>99:1 (*S*)
15	**58**	EtMgBr	83	92:8	**76**	92	92:8 (*R*)
16	**59**	EtMgBr	60	60:40	**79**	93	60:40 (*R*)

N-methyl ephedrine has been used to generate a similar chiral reducing agent that provides higher selectivities for the reduction of aryl ketones.[21]

Five years later, Brinkmeyer and Kapoor[19] used this methodology to asymmetrically reduce acetylenic ketones **88** to propargylic alcohols **89** (Scheme 13). This chemistry was applied to the asymmetric synthesis of 11α-hydroxyprogesterone, a key intermediate in commercial production of hydrocortisone acetate.[22] Asymmetric reduction of **88g** using **85** (generated *in situ*) gave cyclization precursor **89g**, in which the key chiral center at C-11 has been set.

In 1980, Cohen et al.[23] expanded upon this work in their studies toward asymmetric synthesis of Vitamin E. They too prepared **85** from (+)-**84** and used it to reduce acetylenic ketones **90**−**93** (Table 9). In most cases, they were able to obtain propargylic alcohols **94**−**97** with modest to good enantiomeric ratios (er: 82:18 to 95:5); however, the reduction of (+)-**93** did not fare as well. Applying the strategy of matched and mismatched pairs, Cohen et al. took

Table 7. Synthesis of Amines 69−71, 74, and 81−83 by Reaction of Oxazines 57 and 59−64 with Me_3Al



sm	yield (%)	dr	cleaved amine	yield (%)	er
57	95	95:5	**70**	94	95:5 (*S*)
59	94	>99:1	**74**	96	>99:1 (*S*)
60	95	>99:1	**71**	79	>99:1 (*S*)
61	93	80:20	**81**	90	80:20 (*S*)
62	97	95:5	**82**	91	95:5 (*S*)
63	97	87:13	**69**	85	>99:1 (*S*)
64	90	67:33	**83**	50	>99:1 (*S*)

Scheme 12

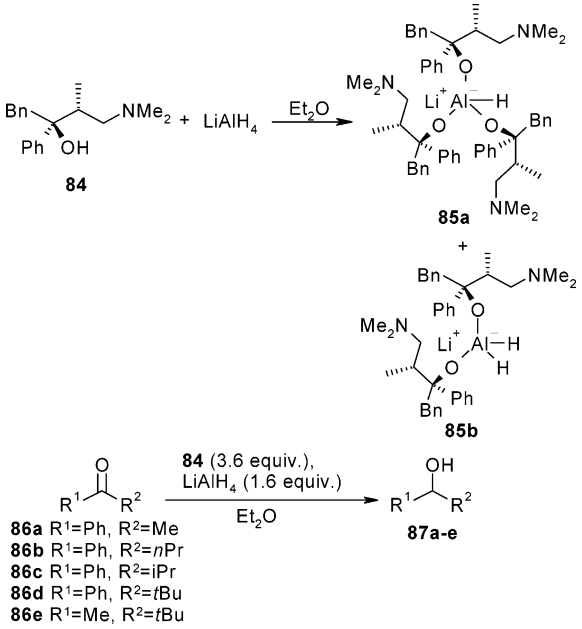


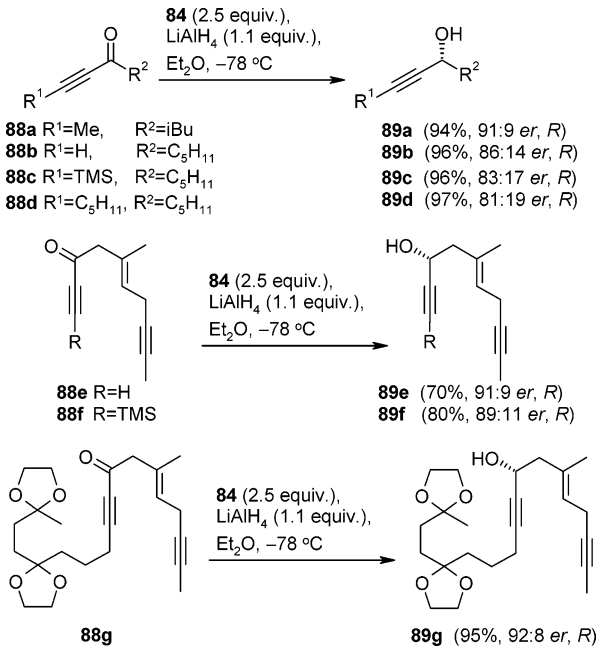
Table 8. Asymmetric Reduction of Ketones 86 to Alcohols 87 Using Reducing Agent 85

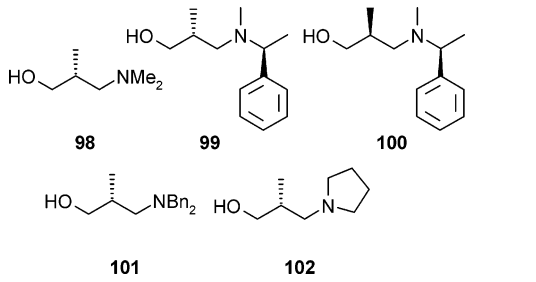
ketone **86**	temp (°C)	conversion (%)	er
a	0	100	84:16 (*R*)
a	rt	46	81:19 (*S*)
b	0	100	81:19 (*R*)
b	rt	50	80:20 (*S*)
c	0	100	65:35 (*R*)
c	rt	34	60:40 (*S*)
d	0	100	68:32 (*R*)
d	rt	43	64:36 (*S*)
e	0	100	64:36 (*R*)
e	rt	42	60:40 (*S*)

note of the fact that its enantiomer (−)-**93** gave the best selectivity observed. As such, they prepared *ent*-**85** from (−)-**84**, and sure enough, it reduced (+)-**93** with 95:5 er and 96% yield. They also prepared chiral reducing agents from 1,3-aminoalcohols **98**−**102** and $LiAlH_4$;[23] however, reduction of **90** using these reagents gave no better than 68:32 er.

Aminoalcohol **103** was used in 1999 as a chiral ligand for ketone reduction.[24] Complexation of **103** with BH_3 gave **104**, which was used *in situ* to catalyze reduction of ketones **86** to alcohols **87** (Scheme 14). Increasing reaction temperature from 0 to 50 °C improved the er of **87a** from 58:42 to 94:6, and ketones **86f**−**h** were thus reduced at elevated temperature.[25]

Scheme 13





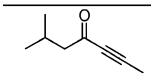
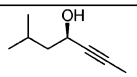
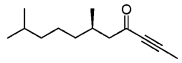
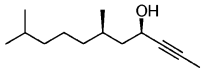
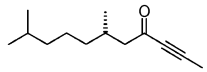
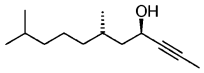
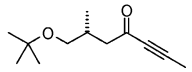
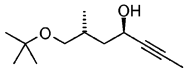
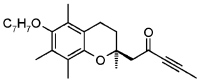
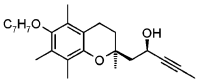
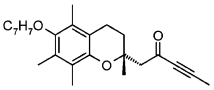
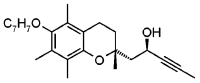
4.2. Aldol Reactions

In 1992, camphor derivative **103** was also used as a chiral auxiliary for aldol[26] reactions by first conversion into oxazinone **13a** (Scheme 15). Treatment of **13a** with $TiCl(OiPr)_3$ generated *Z*-enolates which were quenched with a variety of aldehydes to give aldol products **105a**−**f** with excellent diastereoselectivity.[26]

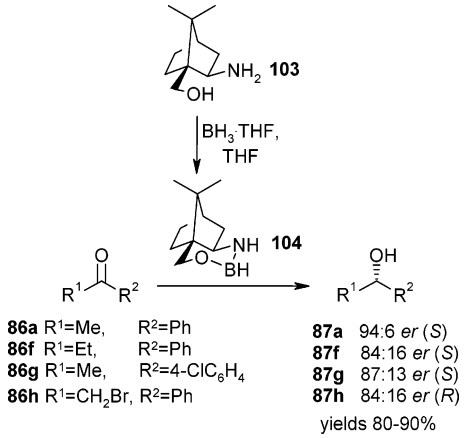
Similarly, oxazinone **108** was used as a chiral auxiliary for the aldol reaction in 1997.[27] Nitrene **107** was generated from **106**, and intramolecular insertion reactions resulted in a 1:1 mixture of **108** and **109**, allowing isolation of **108** in 36% yield (Scheme 16). Treatment of the corresponding propionamide **110** with Bu_2BOTf and quenching the resulting enolate with benzaldehyde gave *syn* aldol product **111** as a single diastereomer (Scheme 17). Use of excess Bu_2BOTf was also investigated in an attempt to prepare *anti* aldol product **112**; however, **113** was isolated instead. This was attributed to an intramolecular opening of the cyclic carbamate by the newly formed alcohol. Interestingly, treatment of **111** with excess Bu_2BOTf also gave **113** due to either a retroaldol−aldol sequence or epimerization followed by rearrangement.

Banks and co-workers[28] in 1994 used gulonic acid derivative **115** as a chiral auxiliary for asymmetric aldol reactions. An intramolecular nitrene insertion reaction was the key step in preparation of **115** from **114**, and treatment with propionyl

Table 9. Asymmetric Reduction of Ketones 90−93 with 85 to Alcohols 94−97

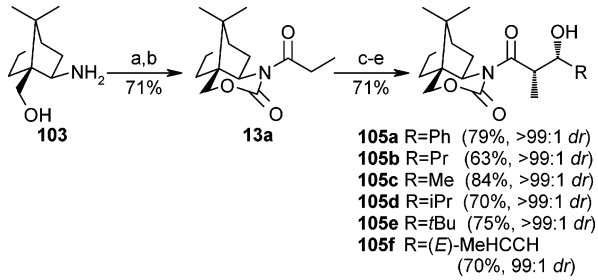
ketone	alcohol	yield (%)	*dr* or *er*
 **90**	 **94**	99	91;9 (*R*)
 (+)-**91**	 **95a**	78	82:18 (*R*)
 (-)-**91**	 **95b**	62	84:16 (*R*)
 **92**	 **96**	94	93:7 (*R*)
 (+)-**93**	 **97a**	87	67:33 (*R*)
 (-)-**93**	 **97b**	93	95:5 (*R*)

Scheme 14



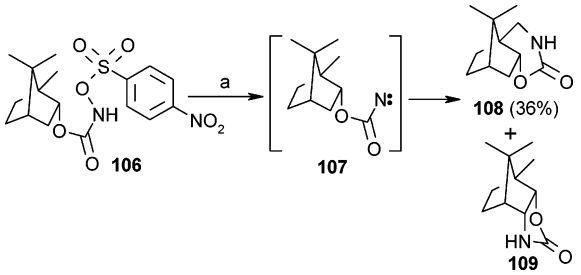
chloride then afforded amide **116** (Scheme 18). Reaction of **116** with LDA at −78 °C generated the enolate, which was quenched with benzaldehyde to give **117** in 88% yield with 91:9 dr. The minor diastereomer was the other *syn* product; no *anti* product was observed. Reductive cleavage of the auxiliary from **117** gave alcohol **118** in moderate yield.

Scheme 15[a]



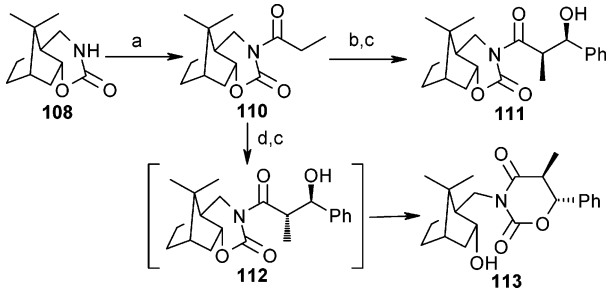
[a] Reagents and conditions: (a) $(Cl_3CO)_2CO$, ^-OH; (b) *n*BuLi, EtCOCl; (c) LDA, -78 °C; (d) $TiCl(OiPr)_3$ (3 equiv), −45 °C; (e) RCHO (2 equiv), −78 °C.

Scheme 16[a]



[a] Reagents and conditions: (a) $BnEt_3NCl$, $NaHCO_3$, CH_2Cl_2, H_2O, rt.

Scheme 17[a]



[a] Reagents and conditions: (a) EtMgBr, then EtCOCl, THF, −78 °C; (b) Bu_2BOTf, iPr_2NEt, CH_2Cl_2, 0 °C; (c) PhCHO, Ch_2Cl_2, −78 °C; (d) Bu_2BOTf (2.2 equiv), iPr_2NEt, CH_2Cl_2, 0 °C.

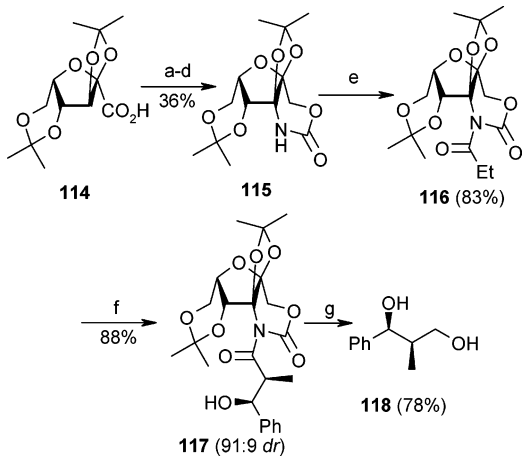
Four years later, Banks' group[14] reported fructose derivative **39** as a chiral auxiliary for aldol reactions (Scheme 19). LDA was used to generate the enolate, and quenching with benzaldehyde gave **119** in good yield with 89:11 dr. The minor diastereomer was the other *syn* product; no *anti* product was observed. Cleavage of the auxiliary gave acid **120** in high yield.

4.3. Nucleophilic Addition to Carbonyls

It has been demonstrated that aminoalcohol (+)-**84** can be treated with $LiAlnBu_4$ to make chiral alkylating agent **121** (Scheme 20). In 1980, Abenhaïm et al.[29] reacted **122** with **121** in hexanes at 0 °C to give **123** with up to 72:28 er. Preparation of **121** by reacting **84** with *n*BuLi followed by nBu_3Al gave the same result. While the enantioselectivity of this reaction left something to be desired, it is worth noting that **84** was more successful as a ligand than (-)-*N*-methyl ephedrine.

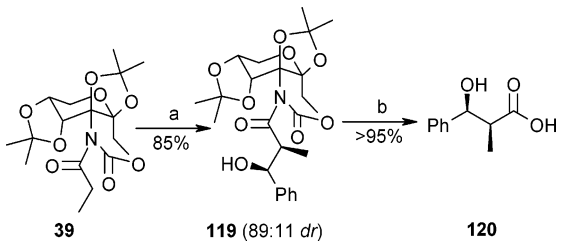
Five years later, Abenhaïm et al. improved greatly on the selectivity of this reaction.[30] Changing the lithium alkyl aluminate to $LiAliBu_3$ affected the enantioselective addition of an isobutyl group to α-ketoester **122** (Scheme 21). Compound **124** was generated in 95% yield with 93:7 er. To our knowledge, there have been no other reports of

Scheme 18[a]



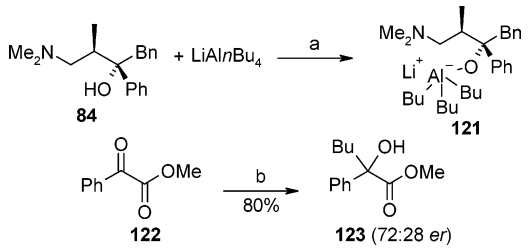
[a] Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C; (b) Cl_2CO (3 equiv), pyridine, PhMe, Et_2O; (c) NaN_3 (2 equiv), TBAB, CH_2Cl_2, H_2O; (d) $(CHCl_2)_2$, reflux; (e) *n*BuLi, hexanes, THF, −78 °C, EtCOCl; (f) LDA, THF, −78 °C, PhCHO; (g) $LiBH_4$, THF, H_2O, 0 °C.

Scheme 19[a]



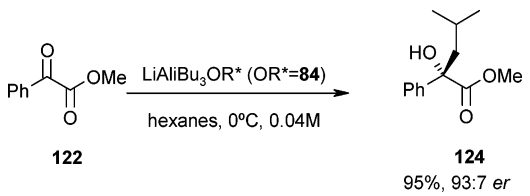
[a] Reagents and conditions: (a) LDA, THF, 0 °C, PhCHO; (b) LiOH, H_2O_2, 0 °C.

Scheme 20[a]



[a] Reagents and conditions: (a) hexanes; (b) **121** (1.05 equiv), $LiAlnBu_4$ (1.05 equiv), hexanes.

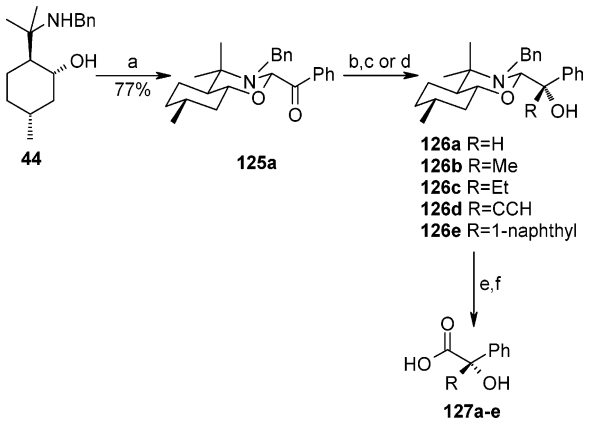
Scheme 21



enantioselective additions of lithium alkyl aluminates to α-ketoesters.

Aminoalcohol **44** has been condensed with phenylglyoxal to give oxazine **125a** in 77% yield (Scheme 22).[15] As such, **125a** was used as a chiral auxiliary for addition of various nucleophiles to its ketone functionality. In all cases, just one diastereomer of addition product **126** was observed by ^1H and ^{13}C NMR. Hydrolysis of the oxazine with dilute acid cleaved the auxiliary, and the resulting α-hydroxyaldehyde was oxidized to α-hydroxyacid **127**. No loss of optical purity was observed for **127b**−**d**; however, **127a** and **127e** showed

Scheme 22[a]



[a] Reagents and conditions: (a) PhCOCHO; (b) RMgBr (R═Me, Et, 1-naphthyl or CCH); (c) MeLi; (d) $NaBH_4$; (e) 1% $HCl_{(aq)}$, EtOH; (f) $NaClO_2$.

Table 10. Preparation of α-Hydroxyacids 127 from Auxiliary 125a

nucleophile	temp (°C)	product **127**	yield (%)	er
MeMgBr	20	**b**	44	99:1 (*S*)
MeMgBr	−70	**b**	not reported	99:1 (*S*)
MeLi	−70	**b**	47	97:3 (*S*)
EtMgBr	5	**c**	77	≥99:1 (*S*)
HC≡CMgBr	20	**d**	63	99:1 (*S*)
1-Np-MgBr	20	**e**	23	91:9 (*R*)
$NaBH_4$	5	**a**	48	90:10 (*S*)

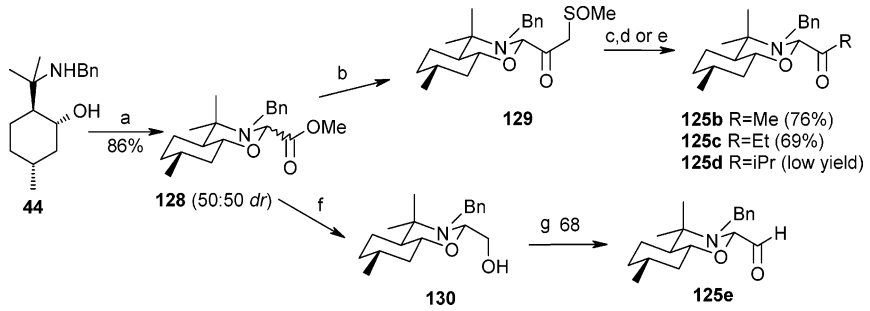
somewhat diminished values for ee (Table 10). This was attributed to partial racemization during the cleavage process.

In an expansion of this work, Eliel and He[31] reported the syntheses of oxazines **125b**−**e** in 1990 via an indirect approach, since the method used to prepare **125a** was not general (Scheme 23). Again, various nucleophiles were added to **125**, giving products **131**−**134**. Replacing the Ph group of **125a** with various alkyl groups resulted in reduced diastereoselectivity (Table 11, entries 1−6) even when the alkyl group was the sterically similar *i*Pr (entry 6). Given that similar diastereoselectivity was obtained when R = *i*Pr and when R = H, sterics at that site did not appear to play a key role in controlling the direction of addition of MeMgBr to the carbonyl carbon (entries 6 and 7). As a bonus, exchanging the R and R′ groups allowed access to enantiomeric pairs of cleavage products using only one enantiomer of the chiral auxiliary.

Eliel and He also reported[31] preparation of 8-methylaminomenthol (**139**, Scheme 24), from which ketone **140** was made. Reaction of **140** with nucleophiles was slightly less selective than the corresponding benzylated system (**125a**, Scheme 22), giving **127b** with 96:4 er (MeMgBr) or 98:2 er (MeLi) upon hydrolysis of the auxiliary. The yields of α-hydroxyacid were low (26−30%), which appeared to be an ongoing problem with the cleavage or oxidation protocol.

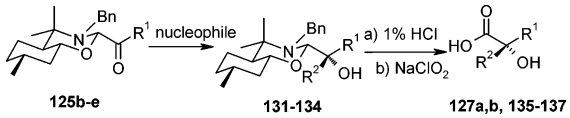
In 1984, Wade et al. reported that the addition of organometallic reagents (specifically organolithium and Grignard reagents) to 3-acylisoxazolines[32] could be achieved with high diastereoselectivity and an interesting metal dependent selectivity.[33] When ketones **141a** and **141b** were reacted with an excess of the organometallic compound, they provided diastereomeric alcohols **142a** and **142b**, respectively (Table 12). Diastereofacial selectivity is highly metal dependent with these compounds. Grignard reagents react with 3-acylisoxazolines via an s-*cis* conformation **143** brought

Scheme 23[a]



[a] Reagents and conditions: (a) $MeOCH(OH)CO_2Me$; (b) NaDMSO; (c) Al−Hg; (d) excess NaDMSO, MeI (1 equiv), then Al−Hg; (e) excess NaDMSO, excess MeI, then Al−Hg; (f) Vitride, PhMe; (g) DMSO, TFAA, Et_3N.

Table 11. Preparation of α-Hydroxyoxazines 131−134 from Oxazines 125b−e



sm **125**	nucleophile	R^1	R^2	major product	yield (%)	dr	cleavage product
b	$NaBH_4$	Me	H	**131a**	85−100	95:5 (*S*)	(*S*)-**135**
b	EtMgBr	Me	Et	**131b**	97	92:8 (*R*)	(*R*)-**136**
b	*i*PrMgCl	Me	*i*Pr	**131c**	∼100	96:4 (*R*)	(*R*)-**137**
b	PhMgBr	Me	Ph	**131d**	81	95:5 (*R*)	(*R*)-**127b**
c	MeMgBr	Et	Me	**132**	93	96:4 (*S*)	(*S*)-**136**
d	MeMgBr	*i*Pr	Me	**133**	∼100	94:6 (*S*)	(*S*)-**137**
e	MeMgBr	H	Me	**134a**	81	95:5 (*R*)	(*S*)-**135**
e	PhMgBr	H	Ph	**134b**	∼100	84:16 (*R*)	(*R*)-**127a**

Scheme 24

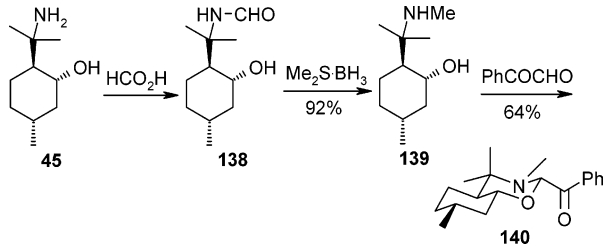
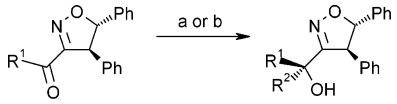


Table 12. Reaction of Ketones 141a,b with Organometallic Reagents To Give Diastereomeric Alcohols 142a,b



141a R^1 = Ph
141b R^2 = Me

142a R^1 = Ph, R^2 = Me
142b R^1 = Me, R^2 = Ph

conditions: (a) 3 equiv R^2Li, THF, –78°C
(b) 3 equiv R^1MgBr, CH_2Cl_2, –78°C

ketone	conditions	**142a**:**142b**	yield (%)
141a	a	99.5:0.5	94
	b	2:98	77
141b	a	1:99	82
	b	>99:1	71

about by magnesium chelation whereas organolithium reagents react with the free s-*trans* conformer **144** (Figure 1). In both cases, the nucleophile approaches the carbonyl carbon *anti* to the substituent at the 4-position of the ring. When the 4-position is free of substitutents, no diastereoselection is observed. In a later report, the reductions of these carbonyl compounds were also realized although the reductions were

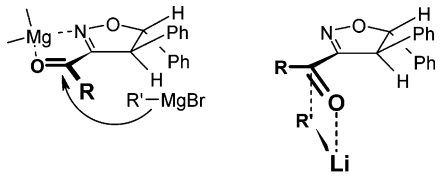
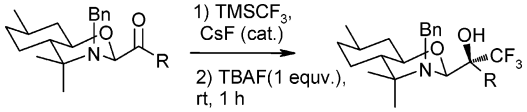


Figure 1. (A) Approach of Grignard reagents on the s-*cis* bound conformer **143**. (B) Approach of organolithium reagents on the free s-*trans* conformer **144**.

Table 13. Results from the Addition of $TMSCF_3$ to 145a−f



145a R=Ph
145b R=4-$OMeC_6H_4$
145c R=Furyl
145d R=Et
145e R=i-Pr
145f R=*n*-Bu

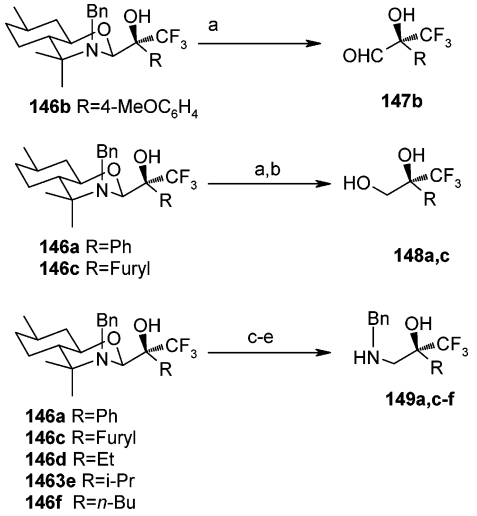
sm **145**	solvent catalyst	major product **146** (dr)	yield of major product **146** (%)
a	THF, CsF	**a** (>50:<1)	**a** (95)
b	THF, CsF	**b** (>50:<1)	**b** (93)
c	THF, CsF	**c** (>50:<1)	**c** (96)
d	THF, CsF	**d** (>50:<1)	**d** (90)
e	THF, CsF	**e** (>50:<1)	**e** (95)
f	THF, CsF	**f** (>50:<1)	**f** (94)

limited to the use of 9-BBN, as it provided the highest diastereoselection (≥92:8 dr).[34]

Pedrosa et al. recently (2006) described an efficient synthesis of enantioenriched trifluoromethylated aldehydes **147b**, 1,2-diols **148a,c**, and 1,2-aminoalcohols **149a,c−f** by diastereoselective addition of $TMSCF_3$ to 2-acyl-1,3-perhydrobenzoxazines **145a−f** (Table 13, Scheme 25).[35] Treatment of **145a−f** with $TMSCF_3$ in the presence of CsF gave **146a−f** with dr's ranging from 96:4 to >99:1 and yields ranging from 90 to 96% (Table 13). It should be noted that using TBAF catalytically resulted in lower yields and dr's. The chiral auxiliary was removed via three procedures, giving α-hydroxyaldehyde **147b**, 1,2-diols **148a,c**, or 1,2-aminoalcohols **149a,c−f** (Scheme 25).

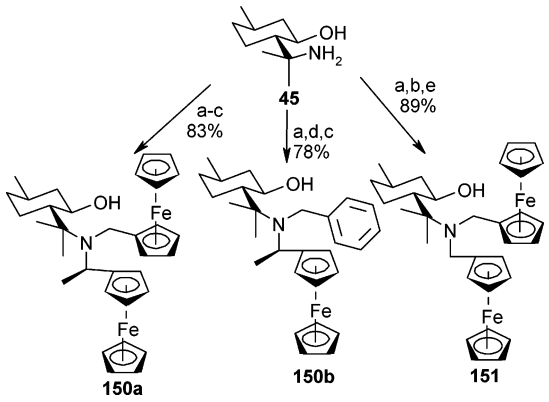
8-Aminomenthol derivatives have also been used as ligands for asymmetric dialkylzinc addition to aldehydes. Specifically, Pedrosa et al.[36] prepared ferrocenyl derivatives **150a**, **150b**, and **151** in good yield from **45** (Scheme 26). None of these compounds were effective ligands on their own; however, when pretreated with MeMgBr, the results

Scheme 25[a]



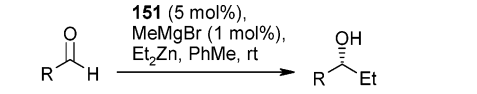
[a] Reagents and conditions: (a) 2% HCl/EtOH, reflux, 1 h; (b) $NaBH_4$, EtOH, 0 °C, 1.5 h; (c) AlH_3, THF, −10 °C to rt; (d) PCC, DCM; (e) NaOH.

Scheme 26[a]



[a] Reagents and conditions: (a) ferrocenecarboxaldehyde, CH_2Cl_2, rt; (b) ferrocenylCH_2NMe_3I, K_2CO_3, reflux; (c) MeMgBr, PhH, rt; (d) BnBr, K_2CO_3, MeCN, reflux; (e) DIBAL-H, PhMe, 0 °C.

Scheme 27

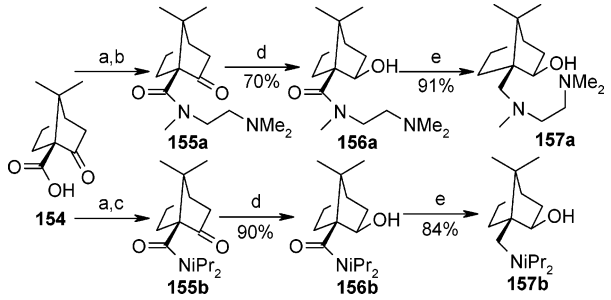


152a R=Ph	**153a** (87%,98:2 *er*, *S*)
152b R=*p*MeOC$_6$H$_4$	**153b** (65%, 85:15 *er*, *S*)
152c R=*p*ClC$_6$H$_4$	**153c** (76%, 97:3 *er*, *S*)
152d R=PhHC=CH	**153d** (78%, 95:5 *er*, *R*)
152e R=MeHC=CH	**153e** (70%, 84:16 *er*, *S*)
152f R=Me(CH$_2$)$_4$	**153f** (73%, 89:11 *er*, *S*)
152g R=ferrocenyl	**153g** (90%, 89:11 *er*, *R*)

were much better. Ligands **150a** and **b** both gave excellent yields of **153a** with moderate enantioselectivity (75:25 er for both ligands) while ligand **151** gave **153a** in good yield with 98:2 er. Given this success, **151** was used to catalyze Et_2Zn addition to a variety of aliphatic, aromatic, and organometallic aldehydes **152a**−**g**, giving alcohols **153a**−**g** with 80:20 to 98:2 er (Scheme 27).

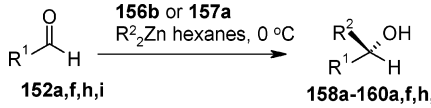
In 1988, Oppolzer and Radinov[37] used camphor-derived aminoalcohol **157a** as a chiral ligand for the addition of vinyl$_2$Zn to aldehydes. At the time, this was a significant advancement, as only Me_2Zn and Et_2Zn had been added to aldehydes with greater than 95:5 er. Formation of the acid chloride of **154** and substitution with MeHN(CH$_2$)$_2$NMe$_2$ gave amide **155a** (Scheme 28). Selective reduction of the

Scheme 28[a]



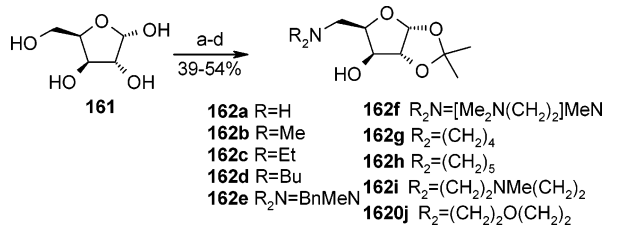
[a] Reagents and conditions: (a) $SOCl_2$, pyridine, rt; (b) PhH, MeHN(CH$_2$)$_2$NMe$_2$, 0 °C; (c) PhH, *i*Pr$_2$NH, 0 °C; (d) $NaBH_4$, MeOH; (e) $LiAlH_4$, THF.

Table 14. Aminoalcohol-Catalyzed Dialkylzinc Addition to Aldehydes 152



catalyst (mol %)	sm **152**	R^1	$R^2{}_2Zn$	product	yield (%)	er
157a (20)	**a**	Ph	Et	**158a**	85	96:4 (*S*)
156b (20)	**a**	Ph	Et	**158a**	68	95:5 (*R*)
157b (20)	**a**	Ph	Et	**158a**	35	91:9 (*R*)
157a (20)	**a**	Ph	Pr	**159a**	85	96:4 (*S*)
157a (2)	**a**	Ph	vinyl	**160a**	96	94:6 (*S*)
157a (2)	**f**	Me(CH$_2$)$_4$	vinyl	**160f**	88	94:6 (*R*)
157a (10)	**f**	Me(CH$_2$)$_4$	vinyl	**160f**	82	96:4 (*R*)
157a (20)	**f**	Me(CH$_2$)$_4$	vinyl	**160f**	90	>98:2 (*R*)
157a (2)	**h**	Me(CH$_2$)$_5$	vinyl	**160h**	86	94:6 (*R*)
157a (2)	**i**	cy	vinyl	**160i**	83	91:9 (*S*)

Scheme 29[a]

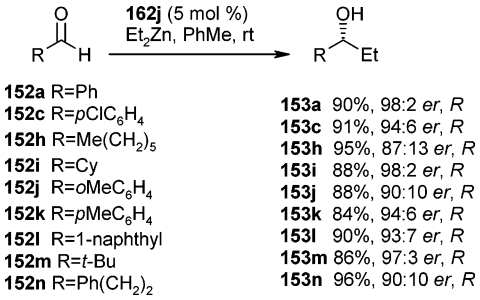


[a] Reagents and conditions: (a) acetone, H_2SO_4, $CuSO_4$; (b) 0.2% $HCl_{(aq)}$; (c) *p*TsCl, pyridine, $CHCl_3$; (d) R_2NH.

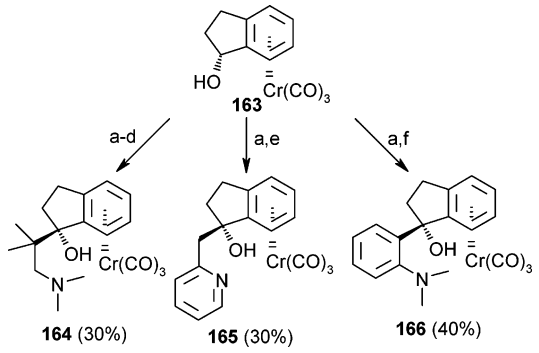
ketone with $NaBH_4$ in MeOH gave *exo* alcohol **156a**, and subsequent reduction with $LiAlH_4$ gave *exo* alcohol **157a**. Similarly, **156b** and **157b** were obtained using *i*Pr$_2$NH. When **156b** and **157b** were used as ligands for the addition of Et_2Zn to benzaldehyde (**152a**), the yields were low due to incomplete conversion. On the other hand, complete conversion was observed using aminoalcohol **157a** (Table 14). As good enantioselectivity was also observed, **157a** was then used as a ligand for addition of *n*Pr$_2$Zn to **152a** and of vinyl$_2$Zn to a variety of aldehydes. Yields and ee both varied from 82 to 96%, and it was noted that increasing the ligand loading increased the enantioselectivity of the reaction.

In 1994, Cho and Kim[38] prepared aminoalcohols **162** from α-D-xylose (**161**) and used them as ligands for asymmetric Et_2Zn addition reactions (Scheme 29). For addition to benzaldehyde (**152a**), **162j** offered the best chiral induction, giving **153a** with 98:2 er (Scheme 30). This ligand was therefore used for Et_2Zn addition to aldehydes **152c** and **152h**−**n**, giving alcohols **153c,h**−**n** in good yield with good to excellent enantioselectivity.

Scheme 30

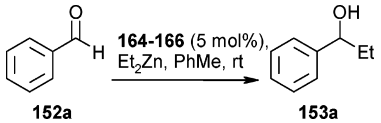


Scheme 31[a]



[a] Reagents and conditions: (a) Ac_2O, DMSO; (b) Me_2CBrCN, Zn, THF; (c) $LiAlH_4$, THF; (d) MeI, K_2CO_3, MeCN; (e) 2-methylpyridine, PhLi, THF; (f) *N*,*N*-dimethylaniline, *n*BuLi, TMEDA, THF.

Table 15. Asymmetric Addition of Et_2Zn to 152a Catalyzed by Complexes 164−166



catalyst	yield (%)	er
164	96	78:22 (*R*)
165	97	85:15 (*R*)
166	92	71:29 (*S*)

Brocard et al.[39] used aminoalcohol arene−chromium complexes **164**−**166** as chiral ligands for alkylzinc addition reactions in 1996. These complexes were prepared in 30−40% yield by oxidation of optically pure **163** and nucleophilic attack at the resulting ketone (Scheme 31). Addition of Et_2-Zn to benzaldehyde (**152a**) catalyzed by these chromium complexes proceeded with moderate to good enantioselectivity, with **165** giving the greatest asymmetric induction (85:15 er, Table 15). For comparison, the uncomplexed aminoalcohols gave little to no enantioselectivity. It was also noteworthy that complex **166** gave the opposite enantiomer of **153a** than **164** and **165**.

Costa and de Oliveira recently reported (2004) the synthesis of (+)- and (−)-*syn*-1,3-aminoalcohols **167a**−**e** as well as their use as catalysts in the enantioselective addition of diethyl zinc to benzaldehyde (Scheme 32).[40] Moderate to excellent enantioselectivities (77:23 to 95:5 er) were reported (Table 16). The configuration of the carbon bearing the hydroxyl moiety was found to influence the absolute stereochemistry of 1-phenylpropanol. At 20 mol % loading, catalyst (−)-**167c** was found to be the most efficient, giving (*S*)-1-phenylpropanol in 99% yield and 95:5 er (entry 5, Table 16).

Scheme 32

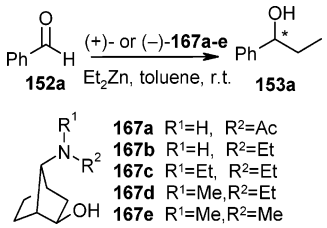
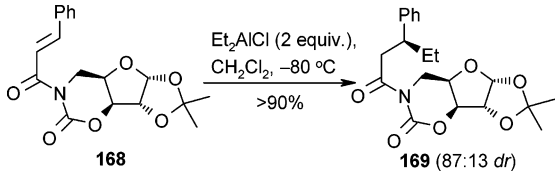


Table 16. Addition of Et_2Zn to Benzaldehyde 152a Catalyzed by Aminoalcohols 167a−e

entry	catalyst **167**	mol %	time (h)	yield (%)	er	config
1	(+)-**a**	20	3	71	82:18	*R*
2	(+)-**b**	20	8	62	77:23	*R*
3	(+)-**c**	8	18	94	93:7	*R*
4	(−)-**c**	8	18	90	89:11	*S*
5	(−)-**c**	20	1	99	96:4	*S*
6	(+)-**d**	20	1	96	93:7	*R*
7	(−)-**e**	8	20	91	89:11	*S*
8	(+)-**e**	8	20	93	91:9	*R*
9	(+)-**e**	20	1	98	93:7	*R*

Scheme 33



Finally, Kunz and Pees[41] in 1989 reported 1,4-addition of Et_2AlCl to **168**. Reaction of **168** with 2 equiv of Et_2AlCl at −80 °C gave **169** in good yield with 87:13 dr (Scheme 33).

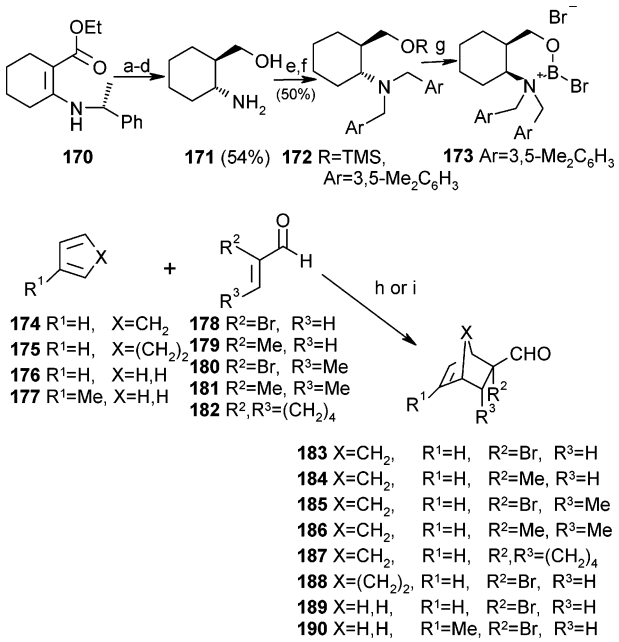
5. Pericyclic Reactions

5.1. Diels−Alder Reactions

An example of a cyclohexane-based 1,3-aminoalcohol as a source of chirality was reported by Corey et al.[42] in 1996. Lewis acid **173** was prepared *in situ* from aminoalcohol **172**, which was in turn was prepared by diastereoselective reduction of α,β-unsaturated ester **170**, removal of the chiral auxiliary, and substitution of the heteroatoms (Scheme 34). Pretreatment of Lewis acid **173** with $AgB[3,5\text{-}(CF_3)_2C_6H_3]_4$ encouraged dissociation of bromide from the boron, giving a more active catalyst (method B) than when no silver salt was included in catalyst formation (method A). When performing Diels−Alder reactions on the highly reactive cyclopentadiene (**174**), this pretreatment was not necessary to get high yields or enantioselectivity (Table 17). Less reactive dienes **175**−**177**, however, did not react using method A but gave excellent yields of adducts **188**−**190** using method B. In all cases, the adducts were formed with greater than 90:10 er.

Previously discussed aminoalcohol **45** has also been used as a chiral auxiliary for intramolecular Diels−Alder reactions of furan dienes (IMDAF reactions). The first example involved using acrylamide dienophiles.[43] Condensation of **45** with 3-furaldehyde followed by acylation with acryloyl chloride gave acrylamide **195** but no Diels−Alder adduct (Scheme 35). Repetition of this procedure using 2-furaldehyde, however, did not allow isolation of acrylamide **191a**. Instead, a mixture of the two *exo* Diels−Alder adducts **192a** and **193a** was obtained (Table 18). The product ratio and,

Scheme 34[a]



[a] Reagents and conditions: (a) $NaBH(OAc)_3$, MeCN, AcOH, 0 °C (81% de); (b) NaO*t*Bu, *t*BuOH, THF, rt; (c) $LiBH_4$, THF, reflux; (d) $Pd(OH)_2/C$, H_2 (300 psi), MeOH; (e) $Ba(OH)_2$, 3,5-dimethylbenzyl bromide, EtOH, reflux; (f) TMSCI, DMAP; (g) BBr_3; (h) (method A) **173**, CH_2Cl_2, −94 °C, then add dienophile, then add diene, −94 °C, 1 h; (i) (method B) **173**, CH_2Cl_2, −94 °C, then add $AgB[3,5\text{-}(CF_3)_2C_6H_3]_4$, CH_2Cl_2, then add dienophile, then add diene, −94 °C, 1 h.

Table 17. Diels−Alder Reactions Catalyzed by Lewis Acid 173

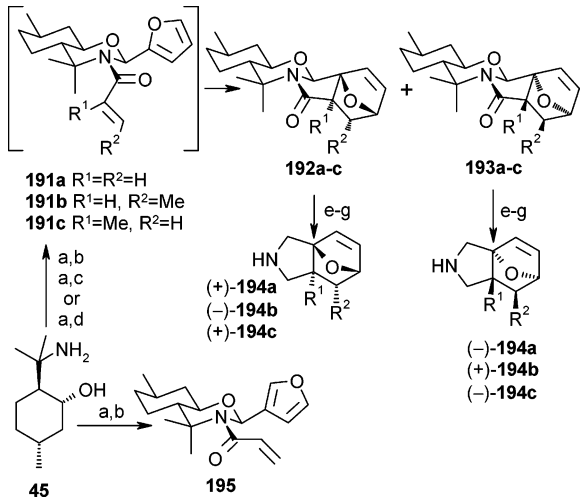
sm	sm	method[a]	product	yield[b] (%)	*exo*/*endo*[c]	er
178	**174**	A	**183**	99	94:6	98:2 (2*R*)[d]
178	**174**	B	**183**	99	91:9	99:1 (2*R*)[d]
179	**174**	A	**184**	99	88:12	95:5 (2*S*)[d]
179	**174**	B	**184**	98	89:11	94:6 (2*S*)[d]
180	**174**	A	**185**	99	>98:2	95:5[d,e]
180	**174**	B	**185**	99	>98:2	98:2[d,e]
181	**174**	A	**186**	88	>98:2	95:5[d,e]
181	**174**	B	**186**	97	>98:2	95:5[d,e]
182	**174**	A	**187**	99	>98:2	98:2[c,d]
182	**174**	B	**187**	97	>98:2	91:9[d,e]
178	**175**	B	**188**	99	4:96	97:3 (2*R*)[d]
178	**176**	B	**189**	99	n/a	97:3[e]
178	**177**	B	**190**	99	n/a	98:2 (*R*)

[a] For methods, see Scheme 34. [b] Isolated yield of *exo* + *endo* mixture. [c] Determined by ^1H NMR. [d] Determined by reduction to the primary alcohol ($NaBH_4$), conversion to the Mosher ester, and ^1H NMR. [e] Absolute stereochemistry of product not reported.

indeed, the major product depended on the solvent used for the acylation reaction. In CH_2Cl_2, **192a** was the major product (69:31 dr), but in hexanes, **193a** was the major product (78:22 dr). Use of a Lewis acid allowed the IMDAF reaction to proceed at lower temperature, improving the diastereoselectivity, and *in situ* addition of Et_2AlCl to **191a** in CH_2Cl_2 gave **192a** with 85:15 dr. This was also true for crotonamide **191b** and methacrylamide **191c**, which gave **192b** and **192c**, respectively, with 81:19 dr when treated with Et_2AlCl. Chromatographic separation of **192** and **193** followed by cleavage of the auxiliary (*vide supra*) allowed isolation of (+)- and (−)-**194** in 66−74% yield.

In 2005, Pedrosa et al. expanded on the use of chiral auxiliary **44** in IMDAF reactions by inserting a phenyl group as a linker between the chiral auxiliary **44** and the furan (Scheme 36).[44] This strategy provided the *exo* adducts

Scheme 35[a]

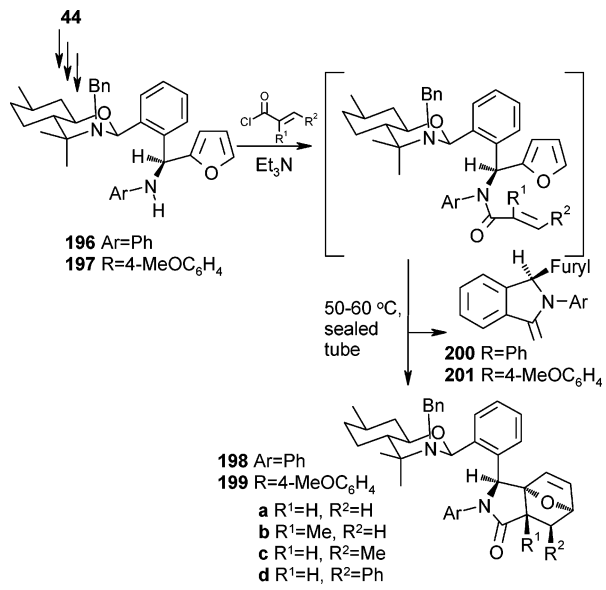


[a] Reagents and conditions: (a) 3-furaldehyde or 2-furaldehyde, PhH, rt; (b) acryloyl chloride, Et_3N, 0 °C; (c) crotonyl chloride, pyridine, 0 °C; (d) methacryloyl chloride, TMEDA, 0 °C; (e) $LiAlH_4$ (5 equiv), $AlCl_3$ (2 equiv), THF, −10 °C; (f) PCC; (g) KOH, MeOH, THF, rt.

Table 18. IMDAF Reaction of Acrylamides 191 Giving 192 and 193

sm **191**	solvent	LA (equiv)	temp (°C)	yield (%)	**192:193**
a	CH_2Cl_2	none	20	96	69:31
a	hexanes	none	20	96	22:78
a	hexanes	Et_2AlCl (2.0)	−23	96	80:20
a	CH_2Cl_2	Et_2AlCl (2.0)	−23	96	85:15
b	hexanes	none	20	82	24:76
b	CH_2Cl_2	Et_2AlCl (2.0)	−23	83	81:19
c	hexanes	none	20	89	45:55
c	CH_2Cl_2	Et_2AlCl (2.0)	−23	92	81:19

Scheme 36

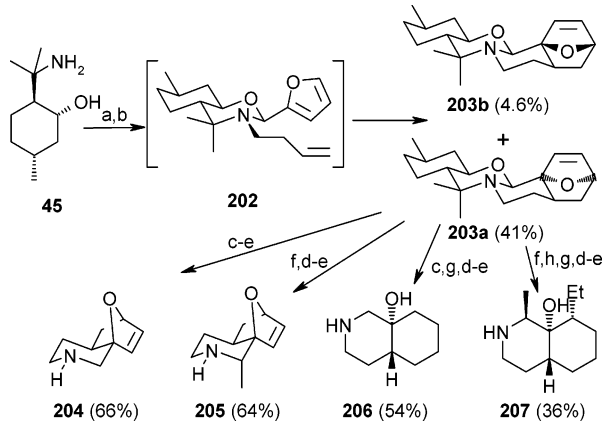


198a−d and **199a−d** as single diastereomers in the IMDAF reactions (Table 19). In all cases, except for the reaction of **196** with acryloyl chloride, isoindolone **200** and **201** were isolated in 10−15% yields. The advantage of this sequence over previous work (Scheme 35) is that it allowed for the recovery of chiral auxiliary **44** since it could be removed easily by hydrolysis with 2% HCl in EtOH after hydrogena-

Table 19. IMDAF Reactions with 196 and 197 Containing a Phenyl Linker

sm	acyl chloride	amide time (h)	IMDAF time (h)	pdt	yield (%)
196	acryloyl	5	24	**198a**	55
196	methacryloyl	115	48	**198b**	33
196	crotonoyl	0.25	36	**198c**	37
196	cinnamoyl	0.25	24	**198d**	35
197	acryloyl	16	48	**199a**	73
197	methacryloyl	120	48	**199b**	49
197	crotonoyl	0.25	48	**199c**	51
197	cinnamoyl	24	24	**199d**	36

Scheme 37[a]



[a] Reagents and conditions: (a) $H_2C{=}CHCH_2CH_2Br$, K_2CO_3, PhMe, reflux; (b) 2-furaldehyde, reflux, 4 days; (c) $LiAlH_4$ (5 equiv), $AlCl_3$ (2 equiv), THF, −10 °C; (d) PCC; (e) KOH, MeOH, THF; (f) Me_3Al, PhMe, rt; (g) PtO_2, H_2, EtOH; (h) Et_3Al, PhMe, rt.

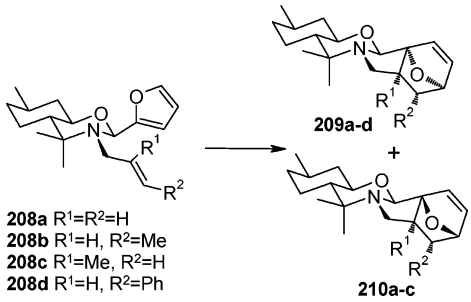
tion of the double bond in the oxabicyclo rings of compounds **198** and **199** and removal of the benzyl group.

In addition to their work with acrylamides, Pedrosa et al. studied IMDAF reactions using unactivated dienophiles. In 1998, they reported[45] the synthesis of enantiopure substituted decahydroisoquinolines via this method. Alkylation of **45** followed by condensation with neat 2-furaldehyde gave a 9:1 mixture of **203a** and **203b** via intermediate **202** (Scheme 37). Chromatographic separation of the diastereomers gave **203a**, which, upon cleavage of the auxiliary, could be converted to epoxyisoquinoline **204** or **205** or decahydroisoquinolines **206** or **207**. Minor diastereomer **203b** could be used to prepare the opposite enantiomers of **204**−**207**.

In 2000, Pedrosa et al.[46] reported the synthesis of enantiopure substituted tetrahydroepoxy-isoindolines via similar chemistry. Alkylation of **45** followed by condensation with 2-furaldehyde gave intermediate amine **208**, which immediately underwent IMDAF reactions to give adducts **209** and **210** (Table 20). The diastereoselectivity for reactions of **208a**−**c** was 94%, and **208d** gave only one observable diastereomer. After purification of the major diastereomer **209a**−**d**, cleavage of the auxiliary (*vide supra*) allowed access to enantiopure tetrahydroepoxyisoindolines **211** or **212** (Scheme 38). The IMDAF reaction of **213a**−**d** was not as diastereoselective and provided mixtures of **214** and **215a**−**d**, but chromatography allowed for separation of the diastereomers of the product (Table 21). Cleavage of the auxiliary (*vide supra*) then provided enantiopure tetrahydroepoxyisoindoline **211**, **216**, or **217**. The latter two compounds were formed as a separable mixture of diastereomers (Scheme 39).

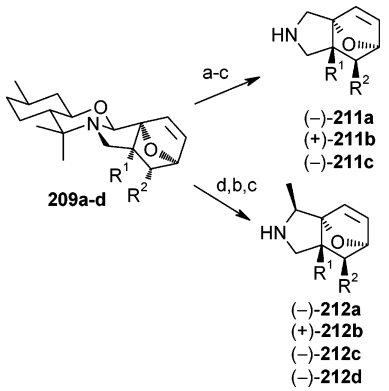
Intramolecular Diels−Alder reactions using an acyclic diene were also reported (Table 22).[43] While ring strain

Table 20. IMDAF Reaction of Amines 208 Giving 209 and 210



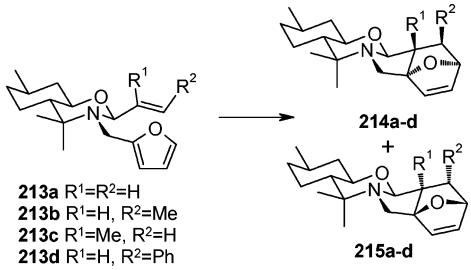
amine **208**	yield (%)	products (ratio, %)
a	93	**209a** (97), **210a** (3)
b	80	**209b** (97), **210b** (3)
c	60	**209c** (97), **210c** (3)
d	50	**209d** (100)

Scheme 38[a]



[a] Reagents and conditions: (a) $LiAlH_4$ (5 equiv), $AlCl_3$ (2 equiv), THF, −10 °C; (b) PCC, CH_2Cl_2; (c) KOH, MeOH, THF; (d) Me_3Al, PhMe, rt.

Table 21. IMDAF Reaction of Amines 213 Giving 214 and 215

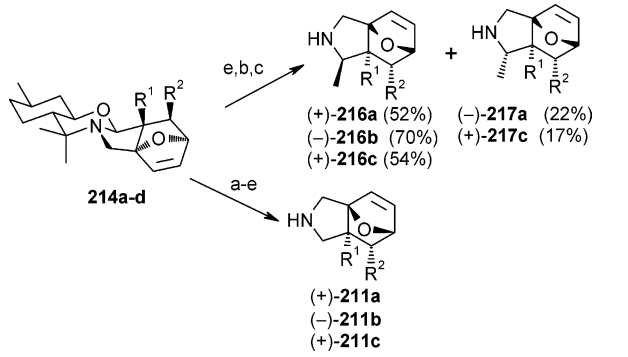


amine **213**	yield (%)	products (ratio, %)
a	96	**214a** (90), **215a** (10)
b	80	**214b** (77), **215b** (23)
c	85	**214c** (91), **215c** (9)
d	73	**214d** (86), **215d** (14)

prevented formation of any *endo* adducts in the IMDAF reactions (Scheme 35), this was not the case for acrylamide **218**, which gave a mixture of *exo* diastereomers **219** and **220** and *endo* diastereomers **221** and **222**. Adding Et_2AlCl altered the distribution of diastereomers but did not improve the *exo*/*endo* ratio. The diastereoselectivity of the *exo* products was increased to 67% de, but there was no significant increase in the diastereoselectivity of the *endo* products.

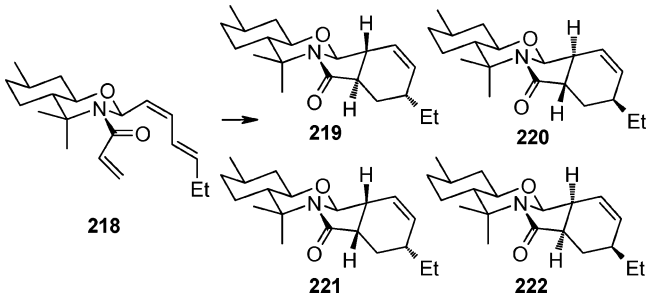
By switching to styrene-type dienes **223**, the use of this chiral auxiliary was extended to the synthesis of enantiopure 3a,4,9,9a-tetrahydrobenz[*f*]isoindolines **229**.[47] These targets were chosen because the skeleton is common to several

Scheme 39[a]



[a] Reagents and conditions: (a) $LiAlH_4$ (5 equiv), $AlCl_3$ (2 equiv), THF, −10 °C; (b) PCC, CH_2Cl_2; (c) KOH, MeOH, THF; (d) Me_3Al, PhMe, rt; (e) MeMgI, Et_2O, rt.

Table 22. Intramolecular Diels−Alder Reaction of Acrylamide 218 Giving 219−222



solvent	LA (equiv)	temp (°C)	yield (%)	**219:220:221:222**
PhMe	none	110	83	32:22:34:12
hexanes	none	20	96	23:24:39:8
CH_2Cl_2	Et_2AlCl (2.0)	−23	90	45:9:35:11

compounds with interesting biological activity.[48] Precursors **224** were prepared from **45** in the usual fashion (Scheme 40). Because styrenes are less active dienes, **224** had to be heated in order to undergo cyclization. In a survey of solvents, refluxing PhMe and DMF were found to give complete conversion and good yields of Diels−Alder adducts in which the newly formed double bond had migrated to regenerate the aromatic ring. For acrylamides **224a**−**e**, mixtures of *exo* adducts **225** and **226** were obtained with dr ranging from 75:25 to 96:4 (Table 23). No *endo* adducts were observed. Amide **224f** showed minimal reactivity even when refluxed in PhMe for 22 h, possibly due to steric congestion. This was not a problem for **224g**, which gave only one diastereomer of the Diels−Alder adduct; however, the 1,3-hydrogen shift which migrates the double bond was less diastereoselective, resulting in mixtures of **225g** and **227g**. Cleavage of the auxiliary from major products **225** gave enantiopure 3a,4,9,9a-tetrahydrobenz[*f*]isoindolines **229**. Interestingly, **224h** did not undergo a Diels−Alder reaction. Instead, an ene reaction gave **228h** as a single observable diastereomer (Scheme 40). Cleavage of the auxiliary from this product gave pyrrolidine **230**.

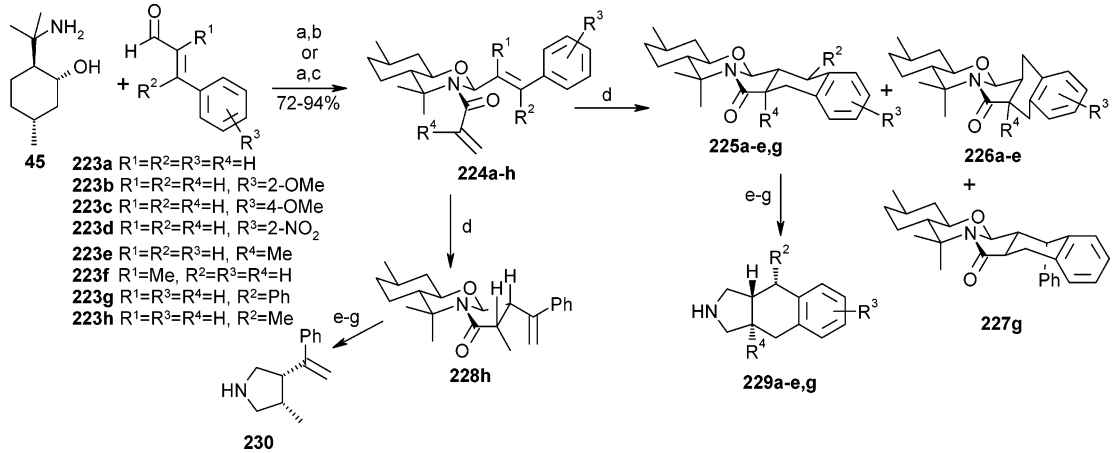
Table 23. Intramolecular Diels−Alder Reaction of Amides 224 Giving 225−227

sm **224**	solvent	yield (%)	products (%)	cleavage product **229**	yield[a] (%)
a	PhMe	88	**225a** (80) **226a** (20)	**a**	54
a	DMF	81	**225a** (86) **226a** (14)	**a**	54
b	PhMe	86	**225b** (86) **226b** (14)	**b**	70
b	DMF	82	**225b** (81) **226b** (19)	**b**	70
c	PhMe	81	**225c** (89) **226c** (11)	**c**	73
c	DMF	78	**225c** (96) **226c** (4)	**c**	73
d	PhMe	85	**225d** (85) **226d** (15)	**d**	51
d	DMF	90	**225d** (83) **226d** (17)	**d**	51
e	PhMe	75	**225e** (75) **226e** (25)	**e**	69
e	DMF	84	**225e** (90) **226e** (10)	**e**	69
f	PhMe	5[b]	*c*	*c*	
g	PhMe	86	**225g** (82) **227g** (18)	**g**	74
g	DMF	83	**225g** (90) **227g** (10)	**g**	74
h	PhMe	90	**228h** (100)	**172**	67

[a] Isolated yield of cleavage product in three steps from **225** or **228**. [b] Recovery of **224f** was 85%. [c] Not reported.

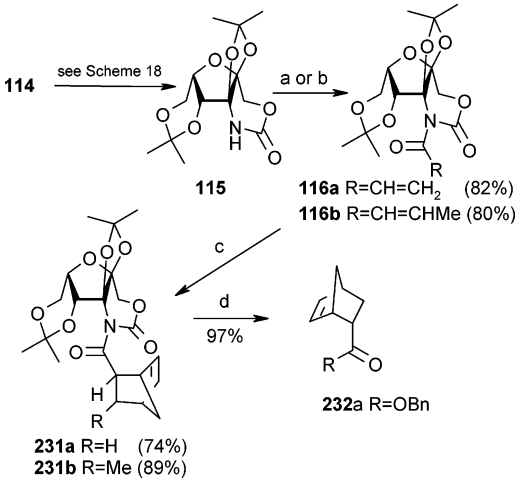
In 1994, Banks et al.[28] prepared dienophiles **116a,b** from sugar **114** and used them in Lewis-acid-catalyzed Diels−Alder reactions (Scheme 41). Reaction of **116a** with cyclopentadiene at −78 °C gave **231a** in a 97:3 ratio of *endo*/*exo*

Scheme 40[a]



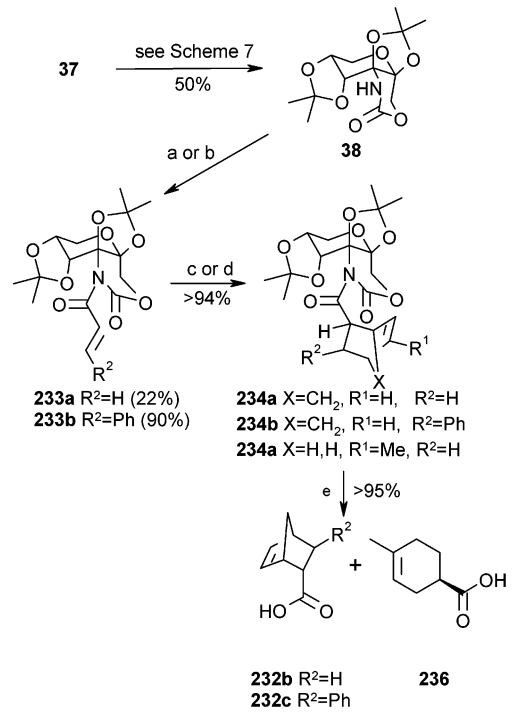
[a] Reagents and conditions: (a) PhMe, reflux; (b) acryloyl chloride, Et_3N, CH_2Cl_2, 0 °C; (c) methacryloyl chloride, TMEDA, CH_2Cl_2, 0 °C; (d) solvent, reflux, 3−4 h; (e) $LiAlH_4$ (5 equiv), $AlCl_3$ (2 equiv), THF, −10 °C; (f) PCC; (g) KOH, MeOH, THF, rt.

Scheme 41[a]



[a] Reagents and conditions: (a) MeMgBr, THF, acryloyl chloride; (b) *n*BuLi, hexanes, THF, −78 °C, crotonyl chloride; (c) Et_2AlCl (1.4 equiv), cyclopentadiene (10 equiv), CH_2Cl_2, −20 or −78 °C; (d) LiOBn, THF, −78 °C to rt.

Scheme 42[a]

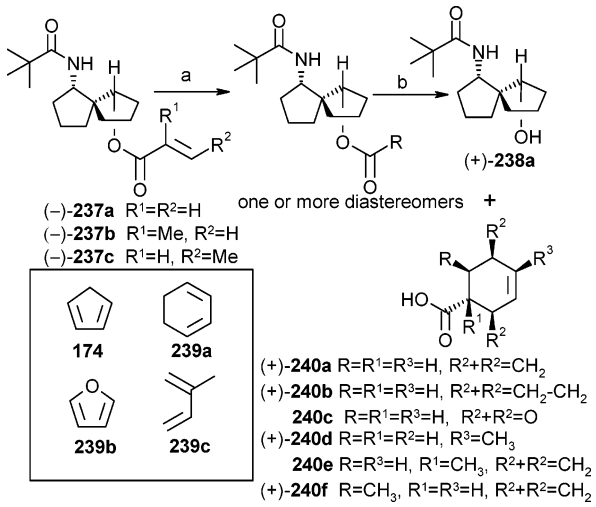


[a] Reagents and conditions: (a) MeMgBr, Et_2O, 0 °C, acryloyl chloride; (b) MeMgBr, Et_2O, 0 °C, cinnamoyl chloride; (c) Et_2AlCl (1.4 equiv), cyclopentadiene (10 equiv), CH_2Cl_2, −20 or −78 °C; (d) Et_2AlCl (1.4 equiv), isoprene (10 equiv), CH_2Cl_2, −78 °C; (e) LiOH, H_2O_2, 0 °C.

isomers with 91:9 dr for the major *endo* adduct. Improved stereoselectivity was observed for **116b**, which reacted with cyclopentadiene at −20 °C to give **231b** in a 98:2 ratio of *endo*/*exo* isomers with 97:3 dr for the major *endo* adduct. Cleavage of the chiral auxiliary gave **232** with between 99:3 and 98:2 er.

Additionally, Banks and co-workers[14] have also reported fructose derivative **38** as a chiral auxiliary for several asymmetric reactions. Dienophiles **233** were prepared from **38** (Scheme 42). While cinnamate **233a** formed in good yield, acrylate **233a** could only be obtained in poor yield. Nonetheless, they were used in Lewis-acid-catalyzed Diels−Alder reactions (Scheme 42). Reaction of **233a** with cyclopentadiene at −78 °C gave exclusively *endo* isomers of **234a** with 93:7 dr. Use of acyclic diene isoprene under the same conditions produced **235a** in excellent yield with 87:13 dr. Offering less stereoselectivity, cinnamate **233b** reacted with cyclopentadiene at −20 °C to give **234b** in an 80:20 ratio of *endo*/*exo* isomers with 82:18 dr for the major *endo* adduct. Cleavage of the auxiliary from **234a**, **234b**, and **235** gave high yields of acids **232b**, **232c**, and **236**, respectively.

Scheme 43[a]



[a] Reagents and conditions: (a) 2 equiv of BCl_3, **239**; (b) NaOH, MeOH, reflux, 1 day.

In 2000, Keay et al. reported the asymmetric synthesis of (+)-(1*R*,5*S*,6*S*)-6-(2,2-dimethylpropamido)spiro[4.4]nonan-1-ol (**238a**) and its use as chiral auxiliary in a variety of Diels−Alder reactions (Scheme 43).[49] Dienophiles **237a**−**c** could easily be prepared by treating **238a** with acryloyl chloride, methacryloyl chloride, or *trans*-crotonyl chloride, respectively, in the presence of triethylamine. Treatment of dienophiles **237a**−−**c** with a variety of dienes at −78 °C with 2 equiv of BCl_3 gave Diels−Alder adducts in yields of 74−82% (Scheme 43, Table 24). Dienophile (−)-**237a** gave solely the *endo* adducts in 99:1 dr when reacted with cyclopentadiene and cyclohexadiene. Lower *endo*/*exo* ratios and diastereoselectivities were observed with adducts **240c** when furan was used as the diene. The Diels−Alder reaction of isoprene with (−)-**237a** provided acid (+)-**240d** in good yield (79%) and excellent enantioselectivity (92%). Dienophile (−)-**237b** was found to react with cyclopentadiene to afford only the *endo* isomer **240e** but with low diastereoselectivity. It is possible that the *cis*,*trans* geometry of the aminoalcohol chiral auxiliary did not block one side of the diene enough to give good facial selectivity. Dienophile (−)-**237c** reacted with cyclopentadiene in a good *endo*/*exo* ratio and good diastereoselectivity to afford acid (+)-**240f** in 93:7 er. It is important to note that saponification of the ester linkage in the Diels−Alder adducts returned the chiral auxiliary and final product with no loss of chirality. The aminoalcohol could easily be separated by chromatography and subsequently recycled.

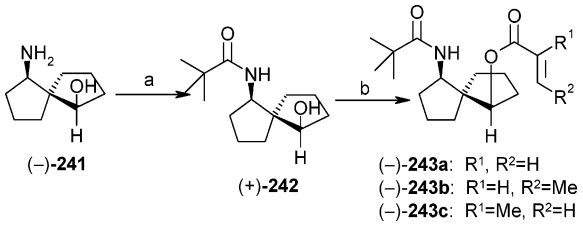
The epimer of **238a**, compound **241**, was reported in 2003 (Scheme 44) to investigate the effect that the *cis*,*cis* geometry would have on diastereoselectivity in Diels−Alder reactions.[50] *Cis*,*cis*-aminoalcohol **241** was *N*-acylated with pivalic anhydride to provide chiral auxiliary **242**, which was subsequently esterified with unsaturated acid chlorides to form dienophiles **243a**−**c** (Scheme 44). Pretreatment of

Table 24. Diels−Alder Reactions of Dienophiles (−)-237a, (−)-237b, and (−)-237c with Dienes 239

dienophile **237**	diene **239**	yield (%)	*endo*/*exo*	dr	product (er)	*R* or *S*
(−)-**a**	**a**	70	100:0	>99:1 (*endo*)	(+)-**240a** (>99:1)	*R*
(−)-**a**	**b**	82	100:0	>99:1 (*endo*)	(+)-**240b** (>99:1)	*R*
(−)-**a**	**c**	74	2:1	90:10 (*endo*) 89:11 (*exo*)	**240c**[a]	
(−)-**a**	**d**	79	n/a	n/a	(+)-**240d** (96:4)	*R*
(−)-**b**	**a**	72	100:0	60:40 (*endo*)	**240e**[a]	
(−)-**c**	**a**	81	8:1	93:7 (*endo*) 82:18 (*exo*)	(+)-**240f** (93:7)	*R*

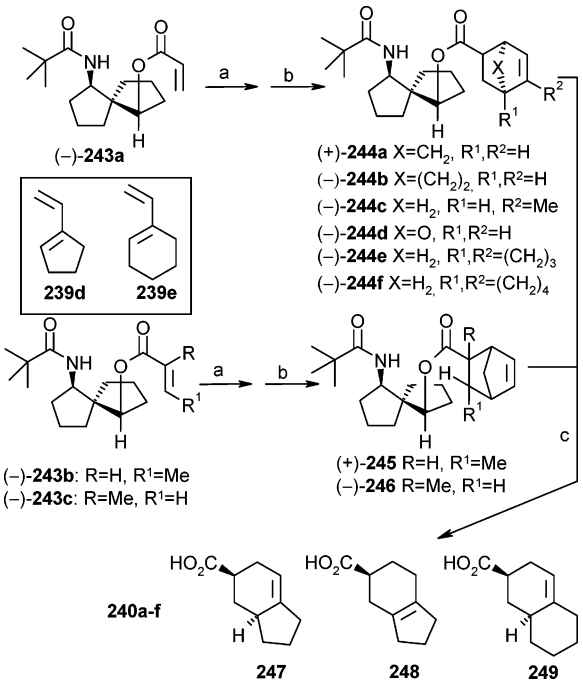
[a] er not reported

Scheme 44[a]



[a] Reagents and conditions: (a) pivalic anhydride, pyridine, CH_2Cl_2, rt; (b) acryloyl chloride, Et_3N, CH_2Cl_2 or LHMDS, THF, crotonyl or methacryloyl chloride.

Scheme 45[a]



[a] Reagents and conditions: (a) 2 equiv of BCl_3, CH_2Cl_2, −78 °C; (b) **239**, −78 °C, 8−14 h; (c) MeOH, 5 M NaOH, reflux.

dienophiles **243** with 2 equiv of BCl_3 followed by addition of diene **174** or **239** gave Diels−Alder adducts **244** in fair to excellent yields (50%−99%) and dr (89:11 to 99:1) (Scheme 45, Table 25). Even the less reactive crotonate and methacrylate esters **243b**,**c** reacted with cyclopentadiene with reasonable selectivity, providing **245** and **246**, respectively (92:8 dr and 90:10 dr, respectively, for the major products, Table 25). Chiral auxiliary **242** was easily cleaved from the Diels−Alder adducts by treatment with NaOH in MeOH at reflux, followed by acidification to afford free carboxylic acids **240a**−**f** and **247**−**249** without epimerization or isomerization (Table 25).

Interestingly, *cis*,*cis*-amidoalcohol (+)-**242** gave predominantly *endo* adducts having the *R*-configuration α to the carboxylic acid. This was in contrast to the reaction of the epimeric *cis*,*trans*-amidoalcohol (−)-**238a**, which gave *endo* adducts having the *S*-configuration at that site. Thus, even though the spiro and amido centers had the same sense of chirality, changing the stereochemistry at C-1 led to products that were enantiomeric after cleavage of the auxiliary (Scheme 46). This is not only an interesting piece of information; it has a practical application. It has already been shown that *cis*,*cis*-amidoalcohol **242** can be prepared from *cis*,*trans*-amidoalcohol **238a**.[50] Jones oxidation of **242** gave the amidoketone (not shown), from which **238a** was originally prepared by reduction with DIBAL-H.[49a] Only one enantiomer of aminoalcohol **241** (Scheme 44) is needed from the resolution to allow the preparation of both diastereomeric auxiliaries, thereby giving access to both enantiomers of a desired Diels−Alder adduct. Because the auxiliaries are complementary and readily interconverted, both enantiomers of the Diels−Alder adduct can therefore be prepared from either enantiomer of **241**.

5.2. 1,3-Dipolar Cycloadditions

Compound **44** was used as a chiral auxiliary by Breau et al.[51] in 1998 for 1,3-dipolar cycloadditions of nitrile oxides. Condensation of **44** with acrolein gave oxazine **247**, which was reacted with acetonitrile oxide to give **248** with 95:5 dr (Scheme 47). No yield was reported, nor was the auxiliary cleaved.

Pedrosa et al. have also turned their attention to the application of aminoalcohol **45** as an auxiliary for intramolecular [3 + 2] cycloadditions[52] by converting **45** into aldehydes **249a**−**d**. Decarboxylative condensation of **249** with *N*-substituted aminoacids gave unstabilized azomethine ylides **250**, which underwent spontaneous intramolecular [3 + 2] cycloaddition reactions to give products **251**−**253** and, in some cases, byproducts **254**, in which the oxazine ring had been hydrolyzed (Table 26). Cleavage of the auxiliary from **251d** gave **255d**, which was analyzed by X-ray crystallography to confirm its absolute configuration and thus the stereochemical outcome of the cycloadditions (Scheme 48).

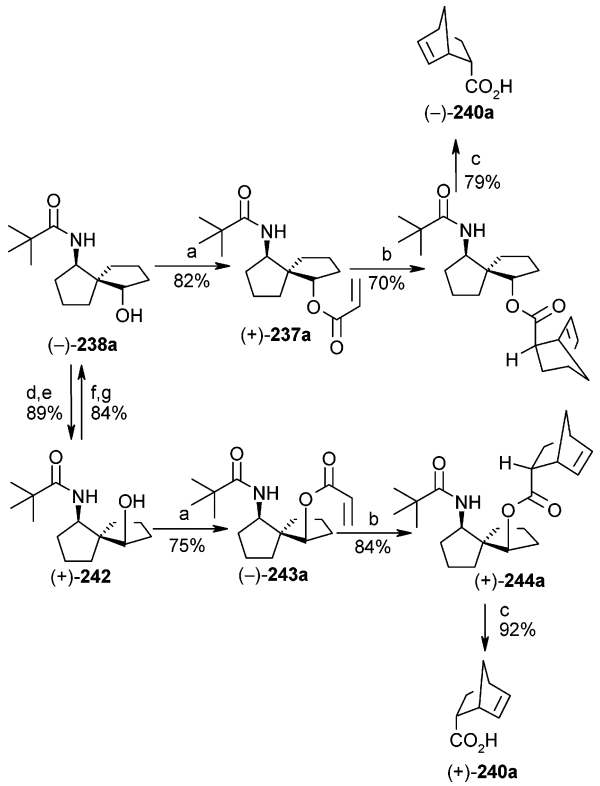
Similarly, reaction of aldehydes **249** with *N*,*N*′-disubstituted hydrazines gave azomethine imines[53] **256**, which also underwent spontaneous intramolecular [3 + 2] cycloadditions, this time giving products **257**−**258** as single observable diastereomers in all cases (Table 27). The relative stereochemistries of **257a**−**f** and **258a**−**d** were determined by ^{1}H NMR, COSY, and NOESY. Cleavage of the auxiliary was not reported; however, it could presumably be accomplished by the standard method (*vide supra*).

In 1998, Breau and co-workers[54] used 8-aminomenthol derivative **259** as a chiral auxiliary for 1,3-dipolar cycload-

Table 25. Diels−Alder Reaction of Chiral Dienophiles (−)-243a−c with Dienes 239

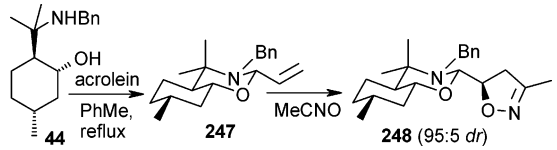
dienophile **243**	diene	product yield (%)	*endo*/*exo*	*dr*	cleavage product (yield, %)	*er*
(−)-**a**	**174**	(+)-**244a** (84)	>99:1	>99:1	**240a** (92)	>99:1 (*R*)
(−)-**a**	**239a**	(−)-**244b** (99)	>99:1	>99:1	**240b** (93)	>99:1 (*R*)
(−)-**a**	**239b**	(−)-**244d** (73)	2:1	>99:1 (*endo*) >99:1 (*exo*)	**240c** (72)	
(−)-**a**	**239c**	(−)-**244c** (78)	n/a	>99:1	**240d** (77)	>99:1 (*R*)
(−)-**a**	**239d**	(−)-**244e** (94)	>99:1	>99:1	**247:248** [3:1] (82)	>99:1 (*R*)
(−)-**a**	**239e**	(−)-**244f** (50 [98])	>99:1	93:7	**240i** (73)	93:7 (*R*)
(−)-**b**	**174**	(+)-**245** (63 [90])	7:1	93:7 (*endo*)	**240f** (75)	93:7 (*R*)
(−)-**c**	**174**	(−)-**246** (64 [74])	1:4	88:12 (*endo*) 90:10 (*exo*)	**240e** + epimer (46)	88:12 (*endo*) 90:10 (*exo*)

Scheme 46[a]



[a] Reagents and conditions: (a) acryloyl chloride, Et_3N, CH_2Cl_2; (b) cyclopentadiene (**174**), BCl_3 (2 equiv), CH_2Cl_2, −78 °C; (c) 5 M $NaOH_{(aq)}$, MeOH, reflux; (d) MsCl, pyridine, 0 °C to rt; (e) 3:1 dioxane/10% $NaOH_{(aq)}$, reflux, 3−5 days; (f) Jones; (g) DIBAL-H, THF, −78 °C.

Scheme 47

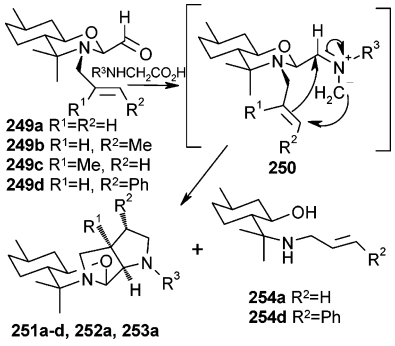


ditions with nitrile oxides. As direct tosylation of **45** gave *O*-tosylation as well as the desired *N*-tosylation, the alcohol was first protected as a silyl ether. Subsequent tosylation and deprotection afforded **259** in 75% yield from **45** (Scheme 49). Condensation of **259** with acrolein diethyl acetal in the presence of $F_3B{\cdot}OEt_2$ produced **260** with 98:2 dr. Reaction of **260** with MeCNO and PhCNO gave **261a** and **261b**, respectively, with good diastereoselectivity and in good yield.

5.3. Claisen Rearrangements

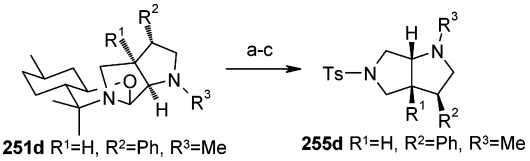
Denmark and Marlin used aminoalcohol **1a** as a chiral auxiliary for carbanion-assisted Claisen rearrangements in

Table 26. Intramolecular 1,3-Dipolar Cycloaddition of Azomethine Ylides 250



sm **249**	R^3	base	solvent	temp (°C)	products (% yield)
a	Me	none	DMF	90	**253a** (94)
b	Me	none	DMF	90	**253b** (78)
c	Me	none	DMF	90	**253c** (90)
d	Me	none	DMF	90	**253d** (56) **254d** (18)
d	Me	Et_3N	DMF	153	**251d** (76)
a	Ph	none	DMF	90	**252a** (34) **254a** (30)
a	Ph	none	PhMe	110	**252a** (70)
a	Bn	Et_3N	DMF	90	**253a** (38) **254a** (46)

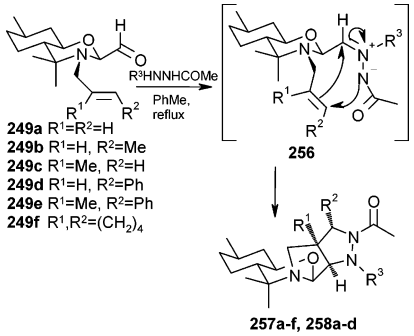
Scheme 48[a]



[a] Reagents and conditions: (a) AlH_3, THF, −10 °C; (b) PCC, NaOAc; (c) NaOH, TsCl, THF.

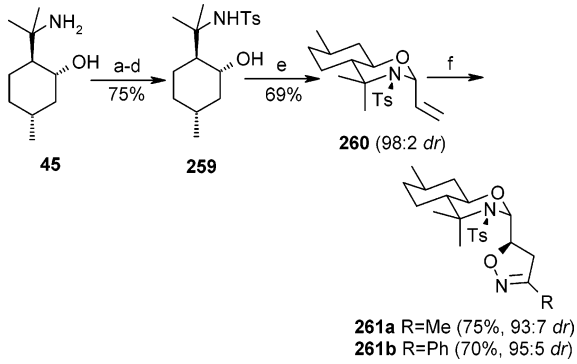
1987.[55] Reaction of **1a** with PCl_3, *N*-methylmorpholine, and propargyl alcohol **262** gave allenyl phosphoramidates **263** and **264** in 20% and 54% yields. After separation of the two isomers, addition of sodium allyloxide gave **265** in 54% yield (Scheme 50). Treatment of **265** with KDMSO in 3:1 DMSO/THF gave Claisen rearrangement product **266** in 62% yield but with no observable asymmetric induction. Premixing the KDMSO with LiCl, however, improved both the yield and degree of asymmetric induction, giving **266** in 78% yield and 90:10 dr. Use of LiDMSO as a base gave the same diastereoselectivity, supporting the importance of the lithium cation. Conversion of **266** to a TBDMS enol ether, ozonolysis with oxidative workup, and methylation of the resulting carboxylic acid with CH_2N_2 gave (*S*)-**267** (Scheme 50). Interestingly, use of epimeric substrate **268**, prepared from

Table 27. Intramolecular 1,3-Dipolar Cycloaddition of Azomethine Imines 256



aldehyde **249**	R^3	product	yield (%)
a	Me	**257a**	94
b	Me	**257b**	80
c	Me	**257c**	90
d	Me	**257d**	92
e	Me	**257e**	45
f	Me	**257f**	42
a	Ph	**258a**	82
b	Ph	**258b**	16
c	Ph	**258c**	18
d	Ph	**258d**	78

Scheme 49[a]



[a] Reagents and conditions: (a) *n*BuLi, Et_2O, −78 °C; (b) TBSCI, Et_2O, −78 °C to rt; (c) TsCl, Et_3N, CH_2Cl_2, reflux; (d) TBAF·$3H_2O$, THF, rt; (e) acrolein diethyl acetal, $Et_2O{\cdot}BF_3$, Et_2O, 0 °C, 4 h; (f) RCNO (10 equiv).

263, gave the opposite enantiomer of product, (*R*)-**267**, upon cleavage of the auxiliary from **269** (Scheme 51).

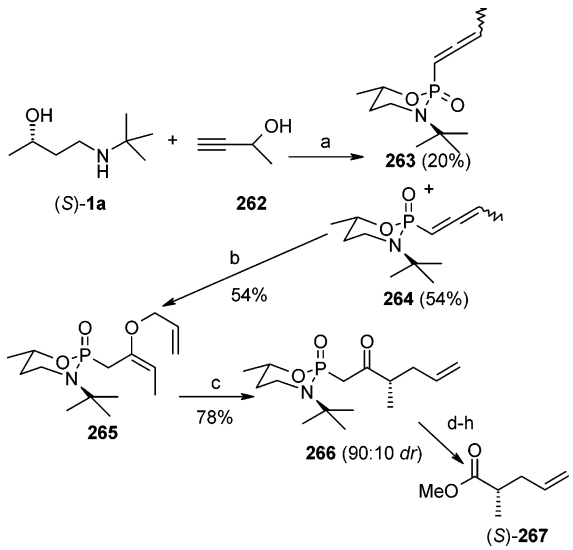
5.4. Intramolecular Alder–Ene Reaction

Following from their work on IMDAF reactions (*vide supra*), Pedrosa et al. recently reported (2005) the use of **45** as a chiral auxiliary in the intramolecular Alder−Ene reaction.[56] Chiral perhydro-1,3-benzoxazines **271** were synthesized via condensation of **45** with an appropriate unsaturated aldehyde followed by *N*-alkylation with the appropriate unsaturated acid chloride (Scheme 52). Substrates **271a**−**e** were heated to afford Alder−Ene adducts **272a**−**e** diastereoselectively and in good to excellent yields (Table 28). Compound **271f** afforded diastereomers **272f** and **273f** in a 70:30 ratio. Compound **271g** underwent the Alder−Ene reaction to give a 1:1 ratio of adducts **272g** and **273g**. Cleavage of the chiral auxiliary and subsequent *N*-tosylation of **272a**−**g** gave enantiopure *cis*-3,4-disubstituted pyrrolidines **274a**−**g** from **271a**−**g** with yields of 16−54%.

5.5. Intramolecular [2 + 2] Photocycloadditions

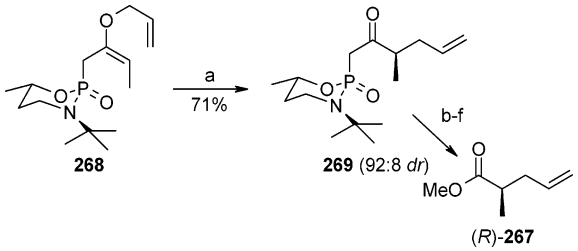
In 2003, Pedrosa and co-workers described the use of chiral perhydro-1,3-benzoxazines **275** as chiral templates for

Scheme 50[a]



[a] Reagents and conditions: (a) PCl_3, *N*-methylmorpholine; (b) NaH, allyl alcohol, *t*BuOH, THF; (c) KDMSO (2−2.5 equiv), LiCl (6 equiv), 3:1 DMSO/THF, rt, 4 h; (d) KHMDS; (e) TBSCl; (f) O_3, MeOAc; (g) H_2O_2/HCO_2H; (h) CH_2N_2.

Scheme 51[a]



[a] Reagents and conditions: (a) KDMSO (2−2.5 equiv), LiCl (6 equiv), 3:1 DMSO/THF, rt, 4 h; (b) KHMDS; (c) TBSCl; (d) O_3, MeOAc; (e) H_2O_2/HCO_2H; (f) CH_2N_2.

intramolecular [2 + 2] photocycloadditions.[57] Perhydro-1,3-benzoxazines **275a**−**c** were synthesized in a two-step protocol from (-)-8-aminomenthol (**45**) (Scheme 53). When an acetonitrile solution of perhydro-1,3-benzoxazines **275a**−**c** was irradiated, they afforded cyclization adducts **276a**−**c** as single diastereomers (Scheme 53). It is interesting to note that only these geminally disubstituted olefins provided complete facial selectivity. Cleavage of the chiral auxiliary from photocyclization adducts **276a**−**c** followed by *N*-tosylation afforded enantiopure nitrogen heterocycles **277a**−**c** in modest to good yields (46−75%).

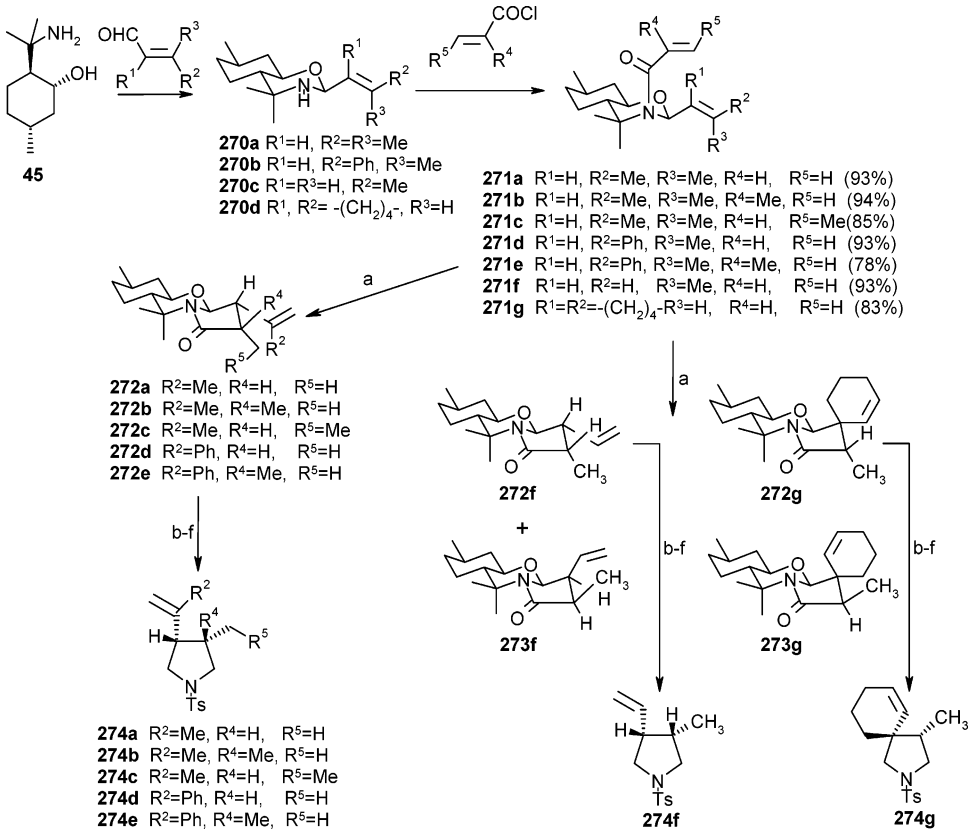
6. Transition-Metal-Catalyzed Reactions

6.1. Palladium

6.1.1. Allylic Alkylations

In 2002, Korostylev et al.[58] reported synthesis of aminophosphite **278** (Scheme 54). Complexation of **278** with $Rh(CO)_2Cl_2$ and observation of the resulting ν(CO) frequency in the IR and the ^1J(P,Rh) coupling constant in the ^{31}P NMR indicated a strong π-acceptor ability for the phosphorus atom. Unfortunately, use of **278** as a ligand for Pd-catalyzed allylic alkylation of **276** with dimethyl malonate afforded **277** in extremely poor yield. Compound **278** was outperformed by phosphites **279**−**281**, derived from 1,2-iminoalcohols. All three of these ligands gave much higher yields (86−95%)

Scheme 52[a]

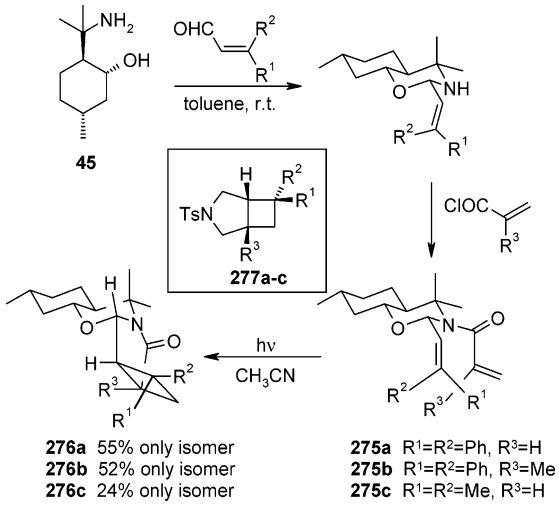


[a] Reagents and conditions: (a) PhMe, reflux; (b) AlH_3, THF, −10 °C; (c) H_3O^+; (d) PCC, CH_2Cl_2, rt; (e) 2.5 M KOH in THF−MeOH−H_2O; (f) TsCl, DIEA.

Table 28. Intramolecular Ene Reactions of Perhydro-1,3-benzoxazines 271

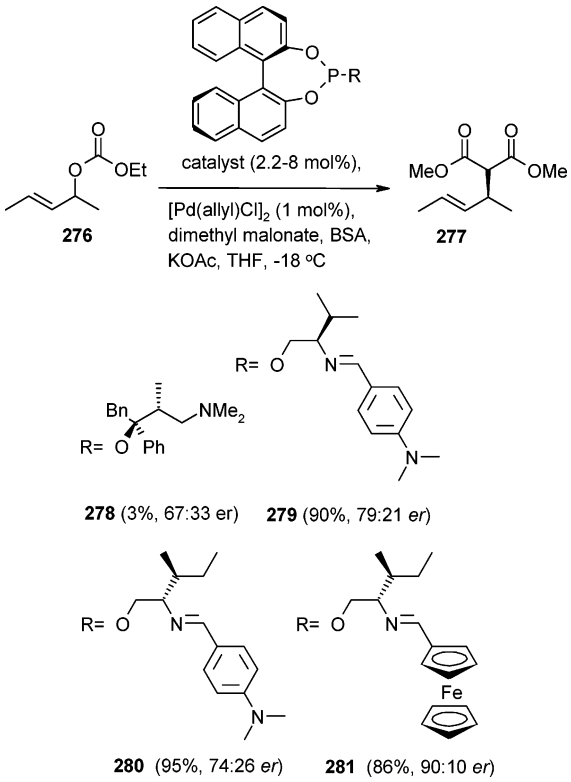
amide **271**	time (h)	yield (%)	products (%)
a	5	95	**272a** (100)
b	10	92	**272b** (100)
c	30	86	**272c** (100)
d	3	90	**272d** (100)
e	15	90	**272e** (100)
f	45	88	**272f** (72), **273f** (28)
g	60	85	**272g** (45), **273g** (55)

Scheme 53



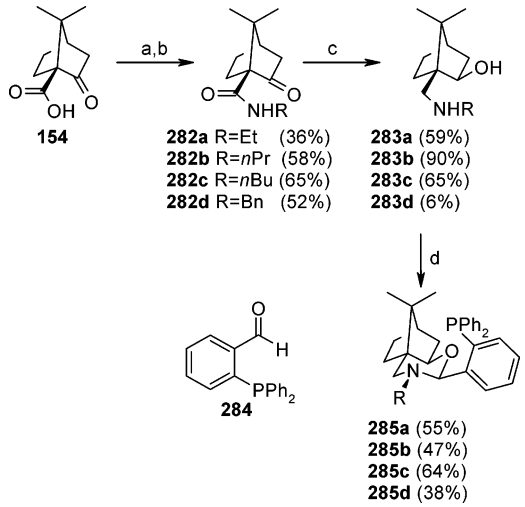
than **278**. Ligand **281** provided the highest enantioselectivity for this transformation, affording **277** in 90:10 er.

Scheme 54



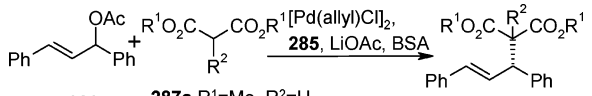
Mino et al.[59] reported a synthesis of phosphinooxazinanes **285a**−**d** by condensation of aminoalcohols **283a**−**d** (made from **282a**−**d** starting with **154**) with 2-diphenylphosphinobenzaldehyde in 2001 (**284**, Scheme 55). These ligands

Scheme 55[a]



[a] Reagents and conditions: (a) $SOCl_2$, pyridine; (b) RNH_2, Et_3N; (c) $LiAlH_4$; (d) **284**, *p*TsOH, pyridine, heat.

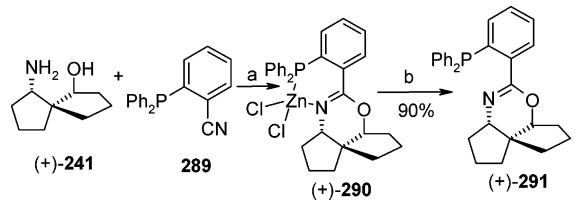
Table 29. Pd-Catalyzed Allylic Alkylation of 287 with 286 Using Ligands 285



286 **287a** R^1=Me, R^2=H; **287b** R^1=Et, R^2=H; **287c** R^1=Et, R^2=Me; **288a-c**

ligand **285**	Nu **287**	solvent	temp (°C)	pdt **288**	yield (%)	er
a	**a**	THF	rt	**a**	85	82:18
b	**a**	THF	rt	**a**	98	90:10
c	**a**	THF	rt	**a**	82	87:13
d	**a**	THF	rt	**a**	13	61:39
b	**a**	PhMe	rt	**a**	81	93:7
b	**a**	PhMe	−20	**a**	50	97:3
b	**b**	PhMe	−20	**b**	73	96:4
b	**c**	PhMe	rt	**c**	59	80:20

Scheme 56[a]

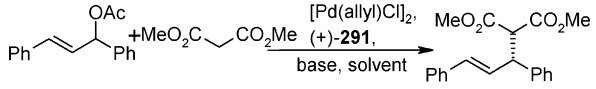


[a] Reagents and conditions: (a) $ZnCl_2$, PhCl, reflux, 6 days; (b) 2,2′-dipyridyl, $CHCl_3$, rt, 1 h.

were then applied to asymmetric Pd-catalyzed allylic alkylation reactions of **286** and **287**; ligand **285c** was shown to give the best yield and enantioselectivity (Table 29). The enantioselectivity was further improved by switching to a less polar solvent and lowering reaction temperature, although both of these measures resulted in reduced yield.

Keay et al. reported the synthesis of spirooxazine (+)-**291** from the *cis*,*cis*-aminoalcohol (+)-**241** in 2004 (Scheme 56).[60] It was found that (+)-**291** was effective as ligand in the Pd-catalyzed allylic alkylation of 1,3-diphenylallyl acetate **286** with dimethyl malonate **287a** (Table 30) to give **288a**. A series of hydride bases were employed, and NaH was found to be the best choice. The alkylation could proceed in as little as 30 min in THF at 0 °C in 99% yield and 95:5 er. Use of the more polar solvent dimethyl ether gave better

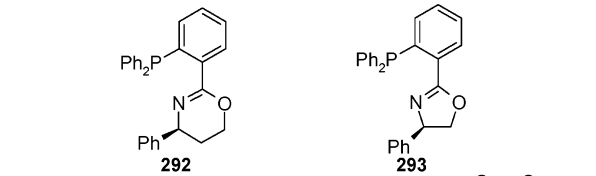
Table 30. Pd-Catalyzed Alkylations of Allylic Acetate 286 with Dimethyl Malonate (287a) Using (+)-291 as a Chiral Ligand



286 **287a** **288a**

base	solvent	temp (°C)	time	yield (%)	er
LiH	THF	25	48 h	62	90:10 (*S*)
LiH	DME	25	48 h	61	93:7 (*S*)
NaH	CH_2Cl_2	0	4 h	96	94:6 (*S*)
NaH	THF	0	30 min	99	95:5 (*S*)
NaH	DME	0	90 min	75	96:4 (*S*)
NaH	1,4-dioxane	25	60 min	78	90:10 (*S*)
NaH	MeCN	25	24 h	68	93:7 (*S*)
KH	CH_2Cl_2	25	48 h	86	90:10 (*S*)
KH	THF	0	60 min	91	94:6 (*S*)
KH	DME	0	90 min	62	93:7 (*S*)
KH	1,4-dioxane	25	60 min	63	90:10 (*S*)
Cs_2CO_3	THF	25	48 h	77	90:10 (*S*)

Table 31. Asymmetric Pd-Catalyzed Allylic Alkylation of Acetates 286 and 294 with 287a Using Ligands 292−293



286 R=Ph **294** R=Me **287a** **288a** R=Ph **277** R=Me

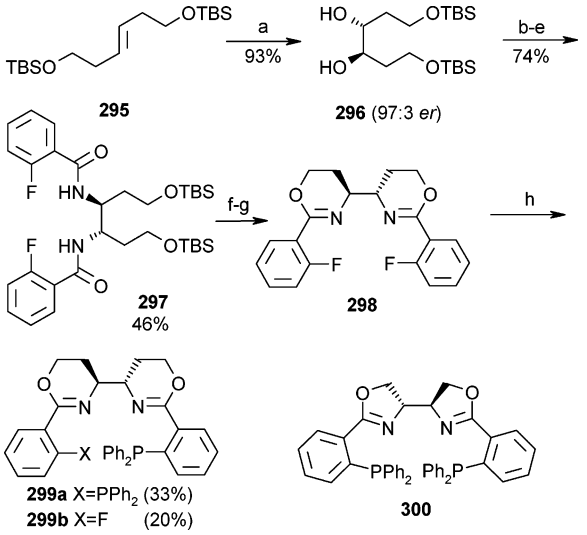
ligand	acetate	product	time (h)	yield (%)	er
292	**286**	**288a**	48	80	99:1 (*R*)
293	**286**	**288a**	1	99	99:1 (*S*)
292	**294**	**277**	168	58	77:23 (*R*)
293	**294**	**277**	24	97	75:25 (*S*)

enantioselectivity (91%) but with slightly slower reaction time and yield: 90 min and 75%, respectively (Table 30). Interestingly, the suspension with **287a** and LiH had to be refluxed for 2 h and then cooled to reaction temperature prior to adding **286** and the Pd−ligand complex. If this was not done, no alkylation occurred. Also, no reaction occurred if Li_2CO_3 was used instead of LiH. The use of KH did not noticeably improve the alkylation er's.

In 2000, Zehnder et al.[61] compared phosphinooxazine **292** (derived from a 1,3-aminoalcohol) with phosphinooxazoline **293** (derived from a 1,2-aminoalcohol). Both ligands were used for asymmetric Pd-catalyzed allylic alkylation reactions, giving excellent enantioselectivity for alkylation of **286** but only moderate selectivity for alkylation of **294** (Table 31). While oxazine **292** generated **277** with an equal or slightly higher er, it was not nearly as efficient as oxazoline **293**; reaction times were significantly longer and yields were higher even though neither alkylation went to completion.

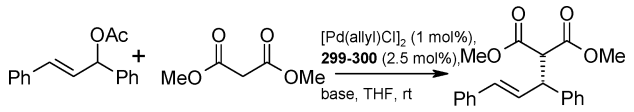
A bis(phosphinooxazine) ligand analogous to Phos-Biox (**300**) was reported by Lee et al. in 1999.[62] Asymmetric dihydroxylation of alkene **295** gave diol **296** in good yield with 97:3 er (Scheme 57). Functional group manipulation afforded diamide **297**, which was cyclized to bisoxazine **298**. Substitution of PPh_2 groups for the fluorides gave a mixture of mono- and disubstituted products **299**, both of which were used as ligands for Pd-catalyzed allylic alkylation of **286**

Scheme 57[a]



[a] Reagents and conditions: (a) $(DHQD)_2PHAL$, OsO_4, $K_3Fe(CN)_6$, K_2CO_3, $MeSSO_2HN_2$, *t*BuOH, H_2O, 0 °C; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C; (c) NaN_3, DMF, 105 °C; (d) H_2, $Pd/CaCO_3$, EtOH, rt; (e) 2-fluorobenzoyl chloride, Et_3N, CH_2Cl_2, 0 °C; (f) HF-pyridine, MeCN, rt; (g) Tf_2O, *i*Pr_2EtN, −78 °C to rt; (h) $KPPh_2$, THF, rt.

Table 32. Asymmetric Pd-Catalyzed Allylic Alkylation of Acetate 287a with 286a Using Ligands 299−300



286 R=Ph **287a** **288a** R=Ph

ligand	base	yield (%)	er (%)
299a	NaH[a]	66	92:8
299a	BSA/KOAc[b]	99	82:18
299b	NaH[a]	>99	98:2
299b	BSA/KOAc[b]	>99	97:3
300	NaH[a]	>99	99:1
300	BSA/KOAc[b]	96	97:3

[a] Premixed 1.5 equiv of NaH with 2 equiv of **287a**. [b] 3 equiv of BSA and 1 mol % KOAc.

with **287a** (Table 32). Under most reaction conditions tested, bis(phosphinooxazine) **299a** generated **288a** with moderate to good enantioselectivity but significantly lower than that of **288a** generated using bis(phosphinooxazoline) **300**. Fluorinated monophosphine **299b**, on the other hand, gave **288a** in excellent yield with enantioselectivity comparable to that obtained using **300**.

In 1996, Evans and Brandt[63] prepared β-pinene-derived phosphinooxazines **301**, which were also applied to asymmetric Pd-catalyzed allylic alkylation reactions (Scheme 58). In the reaction of **286** and **287a** in THF, excellent yields (94−97%) were obtained using ligands **301**; however, the enantioselectivity was much higher using **301a** (98:2 er) than **301b** (82:18 er).[63a] Reaction in CH_2Cl_2 improved the yield to 99%, and (*S*)-**288a** was still obtained with 98:2 er. It was also noted that both 1,3-oxazine ligands offered superior turnover rates over those of the corresponding 1,3-oxazolines under analogous conditions.

Three years later, vinylogous sulfonates **302** and **303** were also employed as substrates for Pd-catalyzed allylic alkylations using **301a** as a ligand (Table 33).[63b] The vinylogous sulfonate was presented as an improved leaving group over the more common acetate and carbonates, and products **304**

Scheme 58

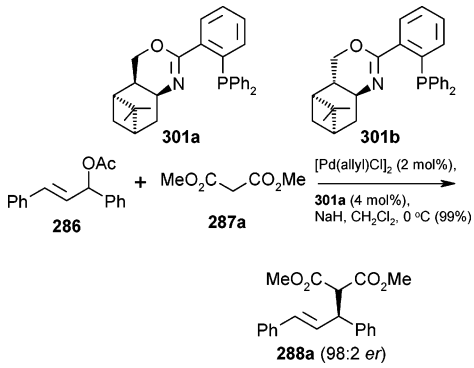
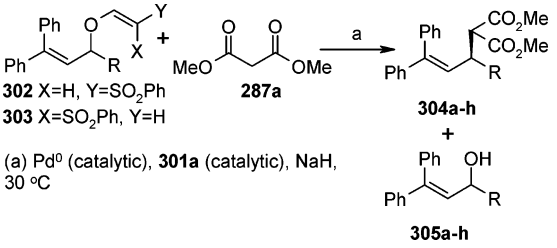


Table 33. Pd-Catalyzed Asymmetric Allylic Alkylation of Vinylogous Sulfonates 302−303 with 287a Using Ligand 301a



sm	R	yield of **304** (%)	er of **304**	yield of **305** (%)
302a	Me	89	95:5 (*S*)	6
303a	Me	94	95:5 (*S*)	3
302b	Et	73	97:3 (*S*)	18
303b	Et	80	97:3 (*S*)	11
302c	Pr	59	98:2 (*S*)	23
303c	Pr	75	98:2 (*S*)	10
302d	Bu	63	97:3 (*S*)	24
303d	Bu	78	96:4 (*S*)	12
302e	CH_2OBn	36	97:3 (*S*)	54
303e	CH_2OBn	61	97:3 (*S*)	30
302f	$(CH_2)_2OBn$	59	99:1 (*S*)	14
303f	$(CH_2)_2OBn$	58	99:1 (*S*)	10
302g	$(CH_2)_3OTBS$	63	98:2 (*S*)	30
303g	$(CH_2)_3OTBS$	78	97:3 (*S*)	12
302h	$(CH_2)_4OTBS$	65	96:4 (*S*)	14
303h	$(CH_2)_4OTBS$	76	96:4 (*S*)	9

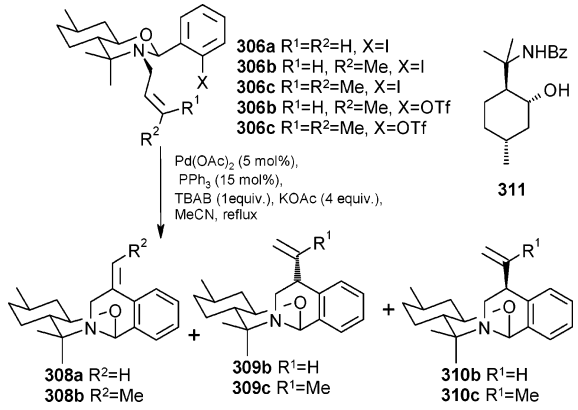
were obtained with excellent enantioselectivity. The yields were not as impressive, and alcohols **305** were also obtained in all cases. The first microwave-accelerated asymmetric allylic alkylation reaction with ≥95:5 er was also reported when **303d** gave **304d** in 78% yield with 95:5 er in 4 min.

6.1.2. Heck Reactions

Aminoalcohol **45** has also been used as a chiral auxiliary for intramolecular Heck reactions.[64] Precursors **306**, **307**, and **312** were prepared from **45** in the usual fashion. Reaction with catalytic Pd and PPh_3 in refluxing MeCN gave cyclization products **308**−**310** and **313**−**316** (Tables 34 and 35). While all but one reaction cyclized exclusively 6-*exo* (**312b** gave a small amount of 7-*endo* product **315b**), **306a** was the only precursor to give just one product. Use of triflates **307** instead of iodides **306** further reduced diastereoselectivity in the cyclization step and regioselectivity in the elimination of Pd (entries 3 and 5) as well as promoting formation of decomposition product **311**. Use of $AsPh_3$ as a ligand instead of PPh_3 was noted to increase formation of enamine products **316** (entries 7, 9, and 11).

Kündig and Meier[65] prepared phosphinooxazines in 1999 for asymmetric Heck chemistry. Ligands **318** were prepared

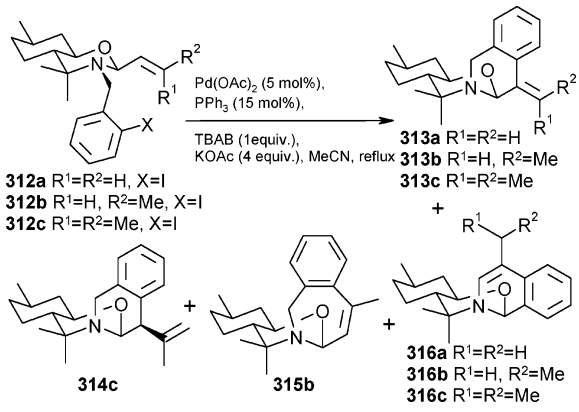
Table 34. Intramolecular Pd-Catalyzed Heck Reaction of 306−307



entry	precursor	products (yield, %)
1	**306a**	**308a** (85)
2	**306b**	**308b** (72)**, 310b** (12)
3	**307b**	**308b** (29), **309b** (29), **310b** (29)[a]
4	**306c**	**309c** (16)**, 310c** (64)
5	**307c**	**309c** (20), **310c** (40)[b]

[a] Also isolated degradation product **311** in 14% yield. [b] Also isolated degradation product **311** in 25% yield.

Table 35. Intramolecular Pd-Catalyzed Heck Reaction of 312a−c



entry	precursor	products (yield, %)
1	**312a**	**313a** (10), **316a** (90)
2	**312a**[a]	**313a** (22), **316a** (78)
3	**312b**	**313b** (69), **316b** (23), **315b** (8)
4	**312b**[a]	**313b** (26), **316b** (64), **315b** (10)
5	**312c**	**313c** (70), **316c** (16), **314c** (14)
6	**312c**[a]	**313c** (57), **316c** (34), **314c** (9)

[a] Used $AsPh_3$ as ligand instead of PPh_3.

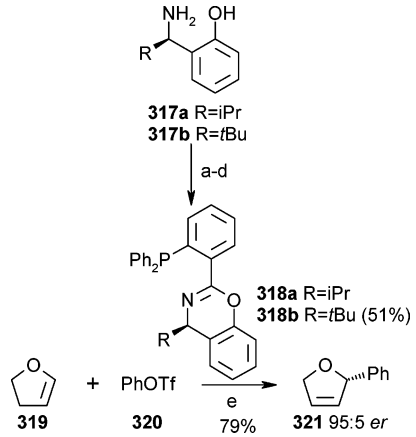
from optically pure aminoalcohols **317** by acylation of the amine, cyclization to the oxazine, and displacement of a fluoride group with $KPPh_2$ (Scheme 59). While both ligands **318** were prepared, only **318b** was used in the Heck reaction between dihydrofuran **319** and phenyltriflate (**320**), producing dihydrofuran **321** in 79% yield with 95:5 er.

6.2. Rhodium

6.2.1. Hydrosilylation

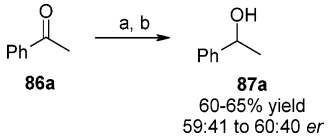
Korostylev et al.[58] performed a Rh-catalyzed hydrosilylation of **86a** using **278** as a ligand that gave acceptable yields between 60 and 65%, but the selectivity was poor (Scheme 60). When the Rh/ligand ratio was 1:1, (*R*)-**87a** was formed

Scheme 59[a]



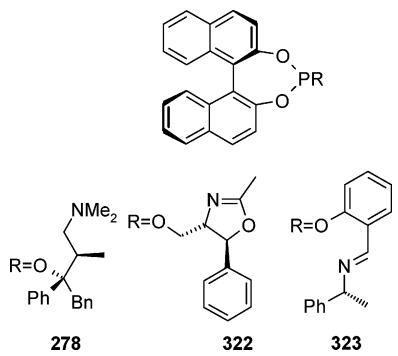
[a] Reagents and conditions: (a) 2-fluorobenzoyl chloride, Et_3N, CH_2Cl_2, 0−20 °C, 20 h; (b) Tf_2O, CH_2Cl_2, 0 °C; (c) Et_3N, 0−20 °C; (d) $KPPh_2$ (1.1 equiv), 18-crown-6 (1.3 equiv), THF, 0−20 °C; (e) $[Pd_2(dba)_3dba]$ (1.5 mol %), **318b** (5 mol %), iPr_2EtN, THF, 70 °C, 4 days.

Scheme 60[a]



[a] Reagents and conditions: (a) $[Rh(COD)Cl]_2$ (1 mol %), **278** (1−2 mol %), H_2SiPh_2, PhMe, 0 °C; (b) MeOH, K_2CO_3 or *p*TsOH.

with 60:40 er; when the Rh/ligand ratio was 1:2, (*S*)-**87a** was formed with 59:41 er. In terms of both yield and enantioselectivity, ligand **322** outperformed **278**, giving **87a** in 74% yield and 79:21 er. While 1,3-iminoalcohol-derived phosphite **323** was also prepared and complexed with $Rh(CO)_2Cl_2$ to show strong π-acceptor ability, it was not tested in any reaction.



6.2.2. Catalytic Hydrogenation

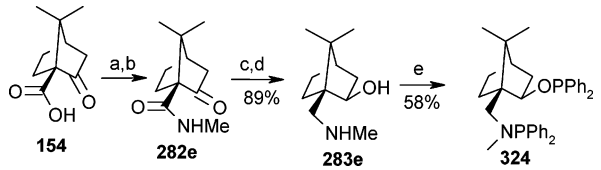
Camphor-based aminoalcohols have also been used as skeletons for phosphine ligands. In 2000, Yeung et al.[66] made *exo* aminoalcohol **283e**. Reaction of **283e** with 2 equiv of Ph_2PCl in the presence of Et_3N provided aminophosphine phosphinite **324** (Scheme 61). This ligand was used in the Rh-catalyzed hydrogenation of enamines **325** giving chiral amidoesters **326** with 95−100% conversion and moderate to good enantioselectivity (Scheme 62).

6.3. Titanium

6.3.1. Trimethylsilylcyanation

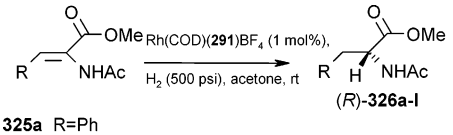
In 1991, Oguni et al.[67] used 1,2-amino- and 1,3-iminoalcohols as ligands for Ti-catalyzed trimethylsilylcyanation

Scheme 61[a]



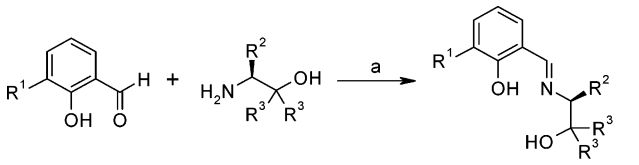
[a] Reagents and conditions: (a) $SoCl_2$, pyridine; (b) $MeNH_3Cl$, pyridine; (c) $NaBH_4$, MeOH, −20 °C; (d) Bh_3·THF; (e) Ph_2PCl, Et_3N, PhH.

Scheme 62



325a	R=Ph	**326a**	89:11 *er*
325b	R=2-ClC_6H_4	**326b**	71:29 *er*
325c	R=3-ClC_6H_4	**326c**	93:7 *er*
325d	R=4-ClC_6H_4	**326d**	92:8 *er*
325e	R=4-FC_6H_4	**326e**	90:10 *er*
325f	R=4-AcOC_6H_4	**326f**	90:10 *er*
325g	R=3-Me-4-AcOClC_6H_4	**326g**	88:12 *er*
325h	R=4-MeOC_6H_4	**326h**	91:9 *er*
325i	R=4-$NO_2C_6H_4$	**326i**	95:5 *er*
325j	R=4-MeC_6H_4	**326j**	81:19 *er*
325k	R=2-Furyl	**326k**	92:8 *er*
325l	R=3,4-(OCH_2CH_2)C_6H_3	**326l**	88:12 *er*

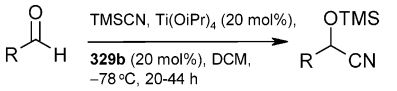
Scheme 63[a]



327a R[1]=H	**328a** R[2]=iPr, R[3]=H	**329a** R[1]=R[3]=H, R[2]=iPr
327b R[1]=*t*Bu	**328b** R[2]=iPr, R[3]=Ph	**329b** R[1]=*t*Bu, R[2]=iPr, R[3]=H
	328c R[2]=iBu, R[3]=H	**329c** R[1]=*t*Bu, R[2]=iPr, R[3]=Ph
		329d R[1]=*t*Bu, R[2]=iBu, R[3]=H

[a] Reagents and conditions: (a) Na_2SO_4 (5 equiv), MeOH, reflux, 18−72 h.

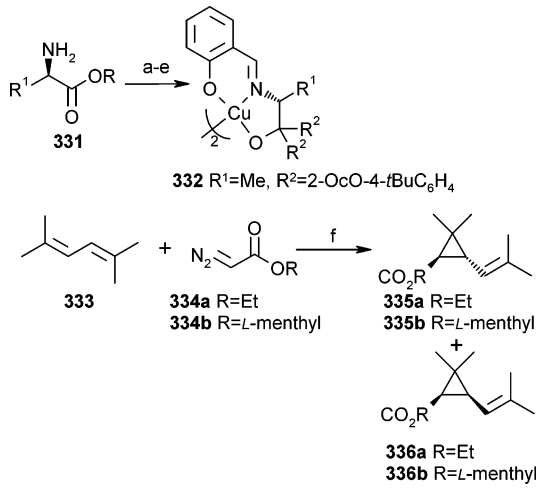
Scheme 64



152a	R=Ph	**330a**	67% (93:7 *er*, *R*)
152b	R=4-MeOC_6H_4	**330b**	62% (95:5 *er*, *R*)
152i	R=Cy	**330i**	72% (83:17 *er*, *R*)
152k	R=4-MeC_6H_4	**330k**	68% (85:15 *er*, *R*)
152o	R=2-naphthyl	**330o**	76% (87:13 *er*, *R*)
152p	R=2-thiophenyl	**330p**	60% (90:10 *er*, *R*)
152q	R=$(CH_2)_{10}$Me	**330q**	48% (83:17 *er*, *R*)

of aldehydes. Condensation of aldehydes **327** with amino-alcohols **328** gave ligands **329** (Scheme 63). Reaction conditions were optimized using substrate **152a**, and ligand **329b** was found to give the highest enantioselectivity for **330a**. Trimethylsilylcyanation of the remaining aldehydes proceeded with moderate yields, and enantioselectivity varied from moderate to good (Scheme 64). It should be noted that **329a** gave the opposite sense of chiral induction to the other three ligands, presumably due to its lack of a bulky *t*Bu group *ortho* to the phenol. Ligands **329** were also observed to accelerate the reaction, and trimethylsilylcyanation of **152a** proceeded six times faster catalyzed by the **329b**−Ti complex than by Ti(O*i*Pr)$_4$ alone.

Scheme 65[a]



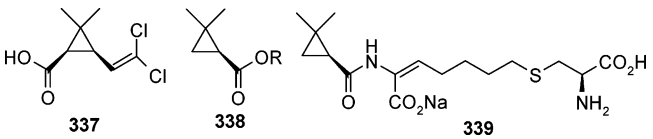
[a] Reagents and conditions: (a) R^2MgX; (b) H_2O; (c) salicaldehyde; (d) $Cu(OAc)_2$; (e) NaOH.

6.4. Copper

6.4.1. Carbenoid Reactions

Aratani prepared copper complexes **322** in 1985 that are derived from both a 1,3-iminoalcohol and a variety of 1,2-aminoalcohols. Addition of Grignard reagents to aminoacids **331**, condensation with salicylaldehyde, and complexation with copper afforded chelates **332** (Scheme 65).[68] These complexes were then used to catalyze formation of the copper carbenoid from **334a**, which reacted with diene **333** to give ethyl *trans*-chrysanthemate **335a**. A wide variety of alkyl (R^1 = Me, Bn, *i*Pr, *i*Bu) and aryl (R^2 = Ph, 2-MeOC_6H_4, 2-BuOC_6H_4, 2-BuO-4-MeC_6H_4, 2-BuO-4-PrC_6H_4, 2-BuO-4-*t*BuC_6H_4, 2-OcO-4-*t*BuC_6H_4) substituents were tested, and the enantioselectivity of the reaction increased as the bulk of the R^2 groups increased. The highest er obtained was 85:15 with catalyst **332**, in which R^1 = Me and R^2 = 2-OcO-4-*t*BuC_6H_4. Using (*R*)-**332**, a wide variety of alkyl diazoacetates **334** were studied (R = Et, *i*Pr, Cy, *t*Bu, 2-Oc, CHMePh, CMe_2Ph, CMe_2*i*Pr, CMe*i*Pr_2, L-menthyl, D-neomenthyl, L-adamantyl). Generating the carbenoid of **334b** gave **335** with the highest enantioselectivity; a 93:7 mixture of **335b** and **336b** was obtained with 97:3 dr for **335b**.

Cyclopropane carboxylic acids **337** and **338** were also synthesized using this chemistry. These acids are precursors to natural products such as cilastatin (**339**). Using (*S*)-**332**, an 85:15 mixture of *cis*/*trans* **337** was obtained, and the *cis* isomer was formed with 95:5 er. Using (*R*)-**332**, **338** was obtained in 96:4 er. Finally, Aratani reacted **322** and **334a** with alkenes **340**−**346** to study the stereoselectivity in the formation of cyclopropanes **347**−**353** (Table 36).

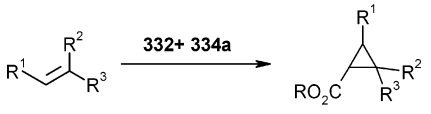


7. Radical Cyclizations

7.1. Tin-Mediated Cyclizations

The preparation of **44** from **45** by hydrogenolysis of the benzyl group has already been described (Scheme 8). This allows two different groups to be attached at the nitrogen,

Table 36. Synthesis of Cyclopropanes 347−353 by 332-Catalyzed Carbenoid Insertion into Alkenes 340−346

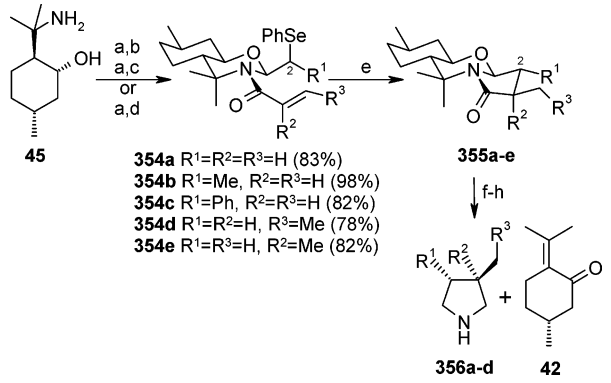


340 R^1=R^2=H, R^3=Ph **347**
341 R^1=R^2=H, R^3=$(CH_2)_5CH_3$ **348**
342 R^1=R^3=Pr, R^2=H **349**
343 R^1=PMP, R^2=H, R^3=Me **350**
344 R^1=H, R^2=R^3=Ph **351**
345 R^1=H, R^2=Me, R^3=Ph **352**
346 R^1=R^2=R^3=Me **353**

catalyst **332**	alkene	pdt	*cis*/*trans*[a]	*cis* dr[a]	*trans* dr[a]
(*R*)	**340**	**347**	14:86	77:23 (1*S*,2*R*)	85:15 (1*S*,2*S*)
(*S*)	**340**	**347**	18:82	89:11 (1*R*,2*S*)	90:10 (1*R*,2*R*)
(*R*)	**341**	**348**	17:83	73:27 (1*S*,2*R*)	88:12 (1*S*,2*S*)
(*S*)	**341**	**348**	22:78	82:18 (1*R*,2*S*)	92:8 (1*R*,2*R*)
(*R*)	**342**	**349**	n/a	n/a	91:9 (2*S*,3*S*)
(*S*)	**342**	**349**	n/a	n/a	92:8 (2*R*,3*R*)
(*R*)	**343**	**350**	9:91	72:28[b]	90:10[b]
(*S*)	**343**	**350**	12:88	80:20[b]	90:10[b]
(*R*)	**344**	**351**	n/a	n/a	88:12 (*S*)
(*S*)	**344**	**351**	n/a	n/a	82:18 (*R*)
(*R*)	**345**	**352**	40:60	93:7[b]	84:16[b]
(*S*)	**345**	**352**	36:64	84:16[b]	79:21[b]
(*R*)	**346**	**353**	79:21	(1*S*,3*R*)[c]	(1*S*,3*S*)[c]
(*S*)	**346**	**353**	77:23	(1*R*,3*S*)[c]	(1*R*,3*R*)[c]

[a] Detemined by GC (R = L-menthyl). [b] Absolute stereochemistry not reported. [c] de not reported.

Scheme 66[a]



[a] Reagents and conditions: (a) PhSeCHR^{1}CHO, CH_2Cl_2, rt; (b) acryloyl chloride, Et_3N, 0 °C; (c) crotonyl chloride, pyridine, 0 °C; (d) methacryloyl chloride, TMEDA, 0 °C; (e) Bu_3SnH, AIBN, PhH, reflux; (f) $LiAlH_4$ (5 equiv), $AlCl_3$ (2 equiv), THF; (g) PCC; (h) KOH, MeOH, THF.

and the auxiliary can be used to control the stereochemical outcome of an intramolecular reaction between these two groups.

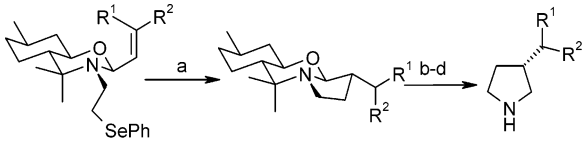
In 1996, Pedrosa et al. applied this strategy to an intramolecular 5-*exo*-trig radical cyclization.[69] Condensation of **45** with a Se-substituted aldehyde followed by acylation afforded selenides **354** in good to excellent yield (Scheme 66). Sn-mediated radical cyclization of these precursors gave **355** (Table 37). Moderate diastereoselectivity was observed in most cases; however, **354e** gave only one observable diastereomer of **355e**. The ratio of epimers at C2 of **354b** (Scheme 66) was found to be irrelevant, as either epimer gave the same result as a 1:1 mixture. Chromatography allowed separation of the diastereomers, and reductive opening of the oxazine followed by oxidation of the alcohol and retro-1,4-addition gave pyrrolidines **356** in moderate yield. Oddly, no auxiliary removal was reported for the

Table 37. 5-*exo*-trig Radical Cyclization of Selenides 354 to Pyrrolidines 356

sm **354**	pdt **355**	yield[a] (%)	C2 ratio[b] (*R*/*S*)	dr[b]	pyrrolidine **356**	yield[c] (%)
a	**a**	94	n/a	81:19	**a**	55
b	**b**	87	59:41	82:18 (2*R*)	**b**	64
				82:18 (2*S*)		
c	**d**	82	only *R*	72:28	**d**	62
d	**d**	84	n/a	81:19	**d**	55
e	**e**	81	n/a	≥99:1	*d*	*d*

[a] Combined yields of diastereomers (after separation by chromatography). [b] Determined by ^{1}H NMR. [c] Isolated yield of **356** from major diastereomer of **355**. [d] Not reported.

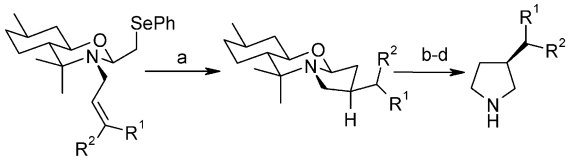
Scheme 67[a]



357a R^1=R^2=H (66%) **358a** 82% (56:44 *dr*) (*S*)-**356a** 60%
357d R^1=H, R^2=Me (89%) **358d** 85% (61:39 *dr*) (*S*)-**356d** 52%
357e R^1=H, R^2=Ph (90%) **358e** 90% (53:47 *dr*) (*S*)-**356e** 49%
357f R^1=R^2=Me (77%) **358f** 89% (>99:1 *dr*)* (*R*)-**356f** 62%

[a] Reagents and conditions: (a) Bu_3SnH, AIBN, PhH, reflux; (b) $LiAlH_4$ (5 equiv), $AlCl_3$ (2 equiv), THF; (c) PCC; (d) KOH, MeOH, THF. * indicates other diastereomer from that shown above.

Scheme 68[a]



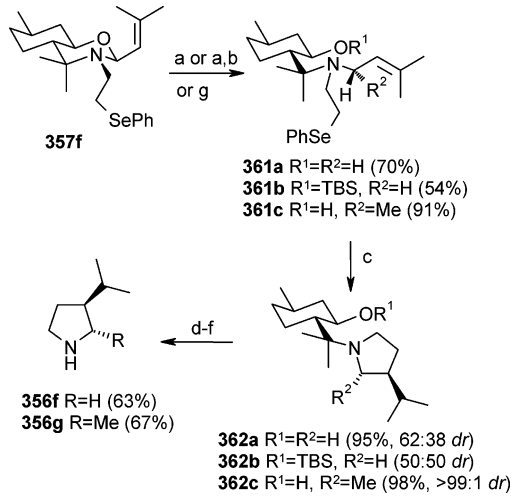
359a R^1=R^2=H (96%) **360a** 84% (68:32 *dr*) (*R*)-**356a** (60%)
359d R^1=H, R^2=Me (97%) **360d** 89% (65:35 *dr*) (*R*)-**356d** (52%)
359e R^1=H, R^2=Ph (84%) **360e** 90% (48:42 *dr*) (*R*)-**356e** (51%)
359f R^1=R^2=Me (84%) **360f** 90% (66:34 *dr*) (*S*)-**356f** (not reported)

[a] Reagents and conditions: (a) Bu_3SnH, AIBN, PhH, reflux; (b) $LiAlH_4$ (5 equiv), $AlCl_3$ (2 equiv), THF; (c) PCC; (d) KOH, MeOH, THF.

diastereomerically pure **355e**. (+)-Pulegone (**42**) was also recovered and could be recycled to resynthesize **45** (Scheme 8).

Three years later, Pedrosa et al.[70] also reported the synthesis of pyrrolidines **356** by 5-*exo*-trig radical cyclization of selenides **357** and **359**. Condensation of **45** with a Se-substituted aldehyde, reductive opening of the oxazine, and condensation of the resulting amine with α,β-unsaturated aldehydes gave selenides **357** in moderate to excellent yield. Sn-mediated radical cyclization of these precursors gave **358** (Scheme 67). In most cases, while good yields were obtained, the diastereoselectivity of these reactions was poor. A notable exception to this rule was dimethyl-substituted **357f**, which gave only one observable diastereomer of **358f**. After separation of the diastereomers of **358**, cleavage of the auxiliary (*vide supra*) proceeded to give pyrrolidines **356** in moderate yields. Condensation of **45** with the same Se-substituted aldehyde followed by alkylation with allylic bromides gave selenides **359** in good to excellent yield. Sn-mediated radical cyclization of these precursors gave **360** in good yield but with poor diastereoselectivity (Scheme 68). Separation of the diastereomers was again achieved by column chromatography, and subsequent cleavage of the auxiliary (*vide supra*) gave pyrrolidines **356** in moderate yields. While **45** was not a particularly effective auxiliary in most of these cyclizations, it also functioned as a resolving

Scheme 69[a]



[a] Reagents and conditions: (a) DIBAL-H, 0 °C; (b) TBSCl, DMF; (c) Bu_3SnH, AIBN, PhH, reflux; (d) PCC; (e) KOH, MeOH, THF; (f) R′RC═$CHCH_2Br$, K_2CO_3, MeCN, reflux; (g) MeMgI, Et_2O.

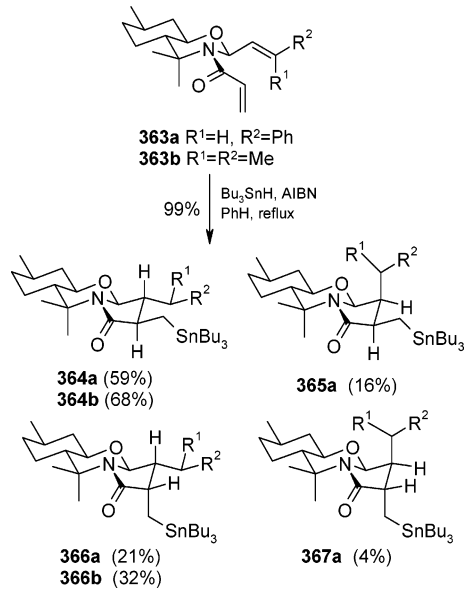
agent, and enantiopure pyrrolidines could be obtained by chromatographic separation of the diastereomers of cyclization product prior to auxiliary cleavage.

In another variation on this theme, both reagents for a 5-*exo*-trig radical cyclization were attached to the nitrogen atom of **45** while the alcohol was either left unsubstituted or protected as a silyl ether (Scheme 69).[71] Reductive opening of oxazine **357f** gave **361a**, which, upon reaction with Bu_3SnH and AIBN, gave **362a** in good yield but low de. TBS ether **361b** was prepared from **361a**, and its cyclization to **362b** gave no observable diastereoselectivity, which supported the theory that hydrogen bonding of the alcoholic proton may have played a role in the small amount of stereoselectivity that was observed.[71] When oxazine **357f** was opened with MeMgI, **361c** was obtained as a single diastereomer. Unlike **361a** and **361b**, **361c** reacted with excellent diastereoselectivity upon treatment with Bu_3SnH and AIBN, giving **362c** as a single observable diastereomer. Cleavage of the auxiliary (*vide supra*) from **362a** and **362c** gave pyrrolidines **356f** and **356g** in moderate yield.

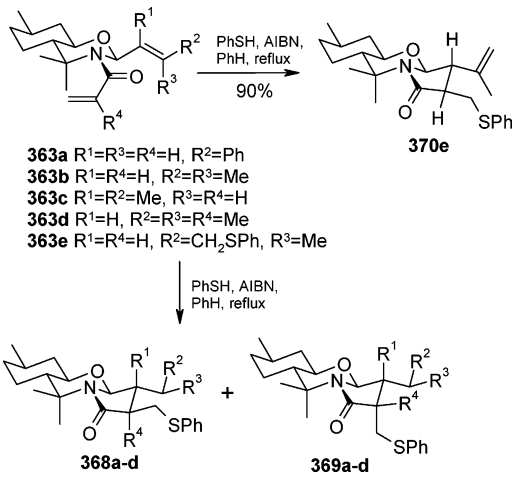
In 1999, Pedrosa et al.[72] also reported use of **45** as a chiral auxiliary for the synthesis of pyrrolidines **356** via radical cyclizations not involving selenides. Treatment of oxazine **363a** with Bu_3SnH and AIBN gave a mixture of **364a**−**367a** while oxazine **363b** gave only **364b** and **366b** under the same reaction conditions (Scheme 70). In both cases, the diastereomers were separated by chromatography and, as with Pedrosa's other work in this area, cleavage of the auxiliary gave pyrrolidines **356** and (+)-pulegone (**42**, *vide supra*), as the initial reduction step also cleaved the Bu_3Sn group.

Pedrosa et al. 's most recent contribution to asymmetric synthesis of pyrrolidines involved the use of sulfanyl radicals in a study of 5-*exo*-trig cyclizations using derivatives of **45** as chiral auxiliaries.[73] As before, oxazines **363** were prepared by condensation of **45** with an aldehyde followed by acylation with an acid chloride (*vide supra*). Pure diastereomers were obtained except for **363e**, which was a mixture of *E*- and *Z*-isomers. Refluxing **363a** with PhSH and AIBN in benzene gave an inseparable mixture of diastereomers. Better selectivity was obtained for reaction of **363b**, and the major product was identified as **368b**. No diastereoselectivity was observed for the reaction of **363c** which gave an equimolar mixture of products while **363d** gave a 7:3 mixture

Scheme 70



Scheme 71



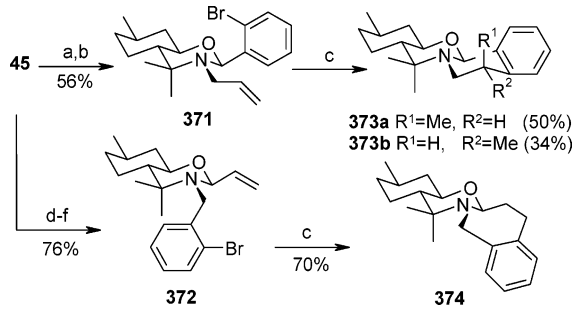
of **368d** and **369d**. By far, the best result was obtained for the mixture of (*E*)- and (*Z*)-**363e** which gave only one diastereomer of product **370e** in good yield (Scheme 71). Not only was this reaction stereoselective, it was also catalytic in thiol, proceeding to completion even when only 0.3 equiv of PhSH was added.

As precursors for more radical cyclizations,[74] oxazines **371** and **372** were prepared from **45** in 56% and 76% yields, respectively (Scheme 72). Unfortunately, **45** was not a particularly effective auxiliary. Treatment of **371** with Bu_3SnH and AIBN gave 6-*exo* cyclization products **373a** and **373b** in a 3:2 ratio alongside 16% yield of debrominated starting material. Interestingly, **372** gave 7-*endo* cyclization product **374** in 70% yield under the same conditions.

7.2. Yang Photocyclization Reactions

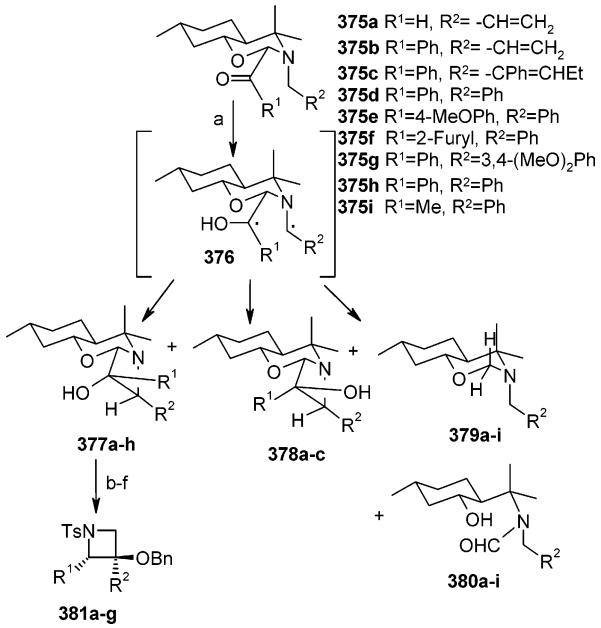
An example of a radical cyclization not involving Sn-generated radicals is the use of **45** as a chiral auxiliary in the Yang photocyclization in the synthesis of azetidin-3-ol derivatives **381** (Scheme 73).[75] In 2005, Pedrosa and coworkers focused on the photocyclization of chiral perhydro-1,3-benzoxazines **375**. A 0.02 M solution of perhydro-1,3-oxazine in MeOH, benzene, or MeCN was irradiated. The resultant cycloadducts were separated by column chroma-

Scheme 72[a]



[a] Reagents and conditions: (a) allyl bromide, K_2CO_3, MeCN, rt; (b) 2-bromobenzaldehyde, PhMe, reflux; (c) Bu_3SnH, AIBN, PhH, heat; (d) 2-bromobenzaldehyde, CH_2Cl_2, rt; (e) $NaBH_4$, $Et_2O{\cdot}BF_3$, THF; (f) acrolein, PhMe, reflux.

Scheme 73[a]



[a] Reagents and conditions: (a) *hν*, 0.02 M solution in solvent; (b) NaH, BnBr, THF; (c) $LiAlH_3$, $AlCl_3$, ThF; (d) PCC, CH_2Cl_2, rt; (e) KOH, THF−MeOH−H_2O; (f) TsCl, DIEA.

tography. The stereochemistry of the products was then determined by COSY and NOESY experiments. *N*-Allyl derivatives **375a**−**c** were found to cyclize to give two diastereomers: **377a**−**c** as the major and **378a**−**c** as the minor diastereomer (Scheme 73, Table 38). In contrast, the *N*-benzyl derivatives **375d**−**g** gave only one diastereomer, **377d**−**g**. Observed byproducts **379a** and **380** arose from Norrish Type I fragmentation. Cleavage of the chiral auxiliary followed by *N*-tosylation gave azetidin-3-ol derivatives **381**.

8. Miscellaneous Uses of 1,3-Aminoalcohols

8.1. Synthesis of Chiral Phosphorothioates

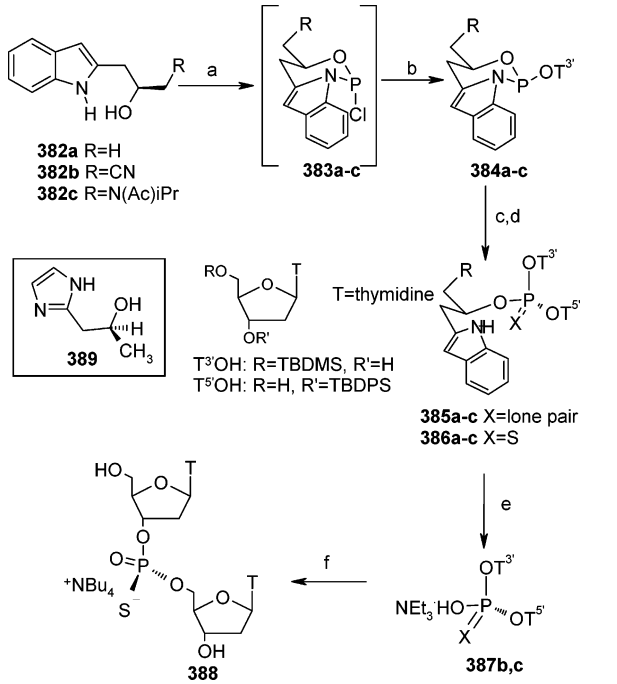
Oligonucleotide phosphorothioates **388** (PS-Oligos) are of interest to many groups due to their therapeutic potential (Scheme 74).[76] As previous procedures for the preparation of PS-Oligos **388** always resulted in mixtures of 2^n diastereomers where *n* is equal to the number of internucleotidic phosphorothioate linkages, in 1999, Just et al. developed a

Table 38. Yang Photocyclizations of Perhydro-1,3-benzoxazines 375

sm **375**	solvent	temp (°C)	time (h)	yield[a] (%)	product ratio[b] (%)	byproducts
a	MeOH	25	35			**379a** (15)
						380a (5)
a	C_6H_6	25	35	40	**377a** (68)	**379a** (2)
					378a (32)	**380a** (9)
a	MeCN	25	35	50	**377a** (82)	**379a** (2)
					378a (18)	**380a** (8)
a	MeCN	5	56	32	**377a** (83)	**379a** (2)
					378a (17)	**380a** (16)
b	MeCN	25	7	56	**377b** (79)	**380b** (20)
					378b (21)	
c	MeCN	25	5	27[c]	**377c** (94)	**380c** (4)
					378c (6)	
d	MeCN	25	4	60	**377d** (>96)[d]	**380d** (6)
e	MeCN	25	5	58	**377e** (>96)[d]	**380e** (11)
f	MeCN	25	3	55	**377f** (>96)[d]	**380f** (7)
g	MeCN	25	4	56	**377g** (>96)[d]	**380g** (13)
h	MeCN	25	9	6		**380h** (40)
i	MeCN	25	43			**379i** (25)

[a] Yields refer to pure diastereomers (**378** and **379**) after flash chromatography. [b] Determined by ^1H NMR. [c] 29% enamine byproduct. [d] Only one diastereomer was detected by ^1H NMR.

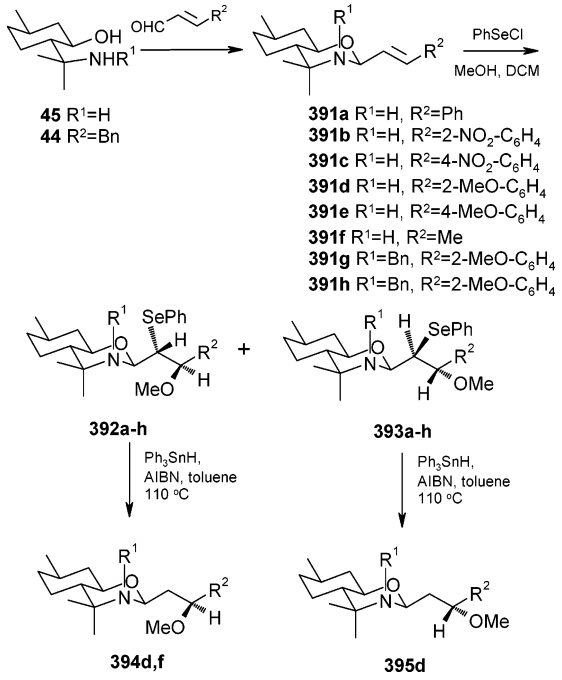
Scheme 74[a]



[a] Reagents and conditions: (a) PCl_3, Et_3N, CH_3CN or THF, 0−60 °C; (b) T3′OH, 0 °C, 22−32% (2 steps); (c) T5′OH, DBU; (d) Beaucage's reagent, 74−78%; (e) 28% NH_4OH, 50 °C, 0.5 h; (f) TBAF, DMF.

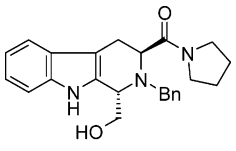
method for the preparation of oligonucleotide phosphorothioates **388** (PS-Oligos) using indoles **382a**−**c** as starting materials (Scheme 74).[77] Mixing **382a**−**c** with PCl_3 provided **383a**−**c**, which were immediately treated with T3′OH, giving **384a**−**c**. Treatment with a second sugar provided ring opened products **385a**−**c**, which were immediately reacted with Beaucage's reagent to give phosphorothioates **386a**−**c**. Hydrolysis of the indole moiety in **386b** and **c** was effected with 28% ammonium hydroxide, giving **388** after removal of the silyl protecting groups from **387** with TBAF. Interestingly, the indole in **386a** could not be removed under a variety of conditions, which resulted in the authors preparing

Scheme 75



the **b** and **c** series in Scheme 74. Cleavage of the indole moiety in the **b** series was accomplished by the classical β-elimination of a cyanoethyl group,[78] while in the **c** series, the indole is removed via neighboring group participation.[79] Initial work by Just et al. employing imidazooxazaphosphorine **389** was unsuccessful due to its unexpected high reactivity along with difficulties in preparing starting materials.[80]

In 2000, Just and co-workers also developed chiral auxiliary **390** for the stereoselective synthesis of **388**.[81] Compound **390** was found to be very selective when synthesizing **388**, giving a 40:1 ratio of the R_P-isomer to the R_P-isomer. Auxiliary **390** was found to be particularly attractive, as it can be derived from tryptophan, an inexpensive and readily available amino acid. It was also demonstrated that this methodology was compatible with solid-phase synthesis of PS-Oligos.



390

8.2. Regio- and Stereoselective Methoxyselenenylation Reactions

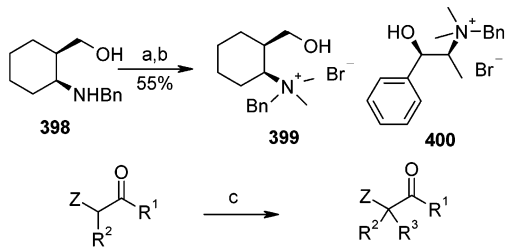
Pedrosa et al. have recently (2006) shown that 2-vinylperhydro-1,3-benzoaxazines **391a**−**h** undergo regio- and stereoselective methoxyselenenylation reactions (Scheme 75).[82] The starting olefins **391a**−**h** are easily prepared by condensation of (−)-8-aminomenthol derivative **45** or **44** with α,β-unsaturated aldehydes. Treatment of **391a**−**h** with PhSeCl in MeOH/CH_2Cl_2 afforded either one diastereomer **392a**−**f,h** or a mixture of diastereomers **392d,e,g,h** and **393d,e,g,h** (Table 39). Subsequent deselenenylation on **392d,f** and **393d** was accomplished by treatment with Ph_3-SnH and AIBN in refluxing toluene to give **394d,f** and **395d**, respectively.

Table 39. Regio- and Stereoselective Methoxy-selenenylation Reactions with 391a−h

sm **391**	temp (°C)	time (h)	yield (%)[a]	products (ratio)[b]
a	−15	24		
a	22	48	93	**392a** (>96)
b	22	168	70[c]	**392b** (>96)
c	22	168	71[d]	**392c** (>96)
d	22	24	95	**392d** (58)
				393d (42)
d	22	72	93	**392d** (35)
				393d (65)
d	−15	24	98	**392d** (>96)
e	22	24	96	**392e** (50)
				393e (50)
e	−15	48	96	**392e** (>96)
f	22	72	89	**392f** (>96)
g	22	96	76[e]	**392g** (81)
				393g (19)
g	4	168	42[f]	**392g** (88)
				393g (12)
h	22	108	75[g]	**392h** (50)
				393h (50)
h	−15	168	60[h]	**392h** (>96)

[a] Yields refer to pure compounds after column chromatography. [b] Determined by ^{1}H NMR or the reaction mixtures. [c] 22% of **391b** was recovered. [d] 0% of **391c** was recovered. [e] 16% of **391g** was recovered. [f] 51% of **391g** was recovered. [g] 20% of **391h** was recovered. [h] 31% of **391h** was recovered.

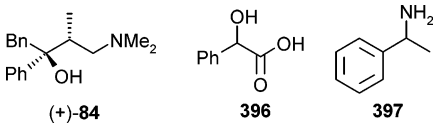
Scheme 76[a]



[a] Reagents and conditions: (a) H_2CO, HCO_2H; (b) MeBr; (c) R^3X (1.1 equiv), **399** (5 mol %), 10% $NaOH_{(aq)}$, $CHCl_3$, 0 °C.

8.3. Resolving Agents

Aminoalcohol (+)-**84** was reported in 1997 as a resolving agent for mandelic acid (**396**), although it was not as efficient as α-methylbenzylamine (**397**).[83]



8.4. Chiral Phase Transfer Catalyst

In 1979, Saigo et al.[84] prepared (−)- and (+)-**399** from optically pure (+)- and (−)-**398** (Scheme 76). This was the only example found of a 1,3-aminoalcohol-based chiral phase transfer catalyst. Application of **399** to asymmetric alkylation of activated methylene compounds **401**−**404** gave **405**−**408** with enantioselectivities comparable to those obtained using commercially available 1,2-aminoalcohol-derived chiral phase transfer catalyst **399** (Table 40). Saigo[84] and Fiaud[85] reported only the optical rotation of their alkylation products; however,

Table 40. Asymmetric Alkylation of Doubly Activated Methylene Compounds 401−404 to 405−408 Using Chiral Phase Transfer Catalysts 399 and 400

catalyst	sm	R^3	pdt	yield (%)	$[\alpha]_D$[a] (deg)	lit.[b] $[\alpha]_D$ (deg)	er[c]
(−)-**400**	**401**	allyl	**405a**	85	−8.2	−100.4 (*S*)[d]	54:46 (*S*)
(−)-**399**	**401**	allyl	**405a**	84	−7.4	−100.4 (*S*)[d]	54:46 (*S*)
(+)-**399**	**401**	allyl	**405a**	79	+7.7	−100.4 (*S*)[d]	54:46 (*R*)
(+)-**399**	**401**	Bn	**405b**	71	+4.7	−51 ± 19[e]	54:46[f]
(+)-**399**	**402**	allyl	**406**	68	+18.2	+254 (*S*)[g]	53:47(*S*)
(−)-**400**	**402**	allyl	**406**	90	−23.5	+254 (*S*)[g]	55:45 (*R*)
(−)-**399**	**403**	Me	**407**	65	+1.7	−16.09 (*R*)[h]	55:45 (*S*)
(−)-**399**	**404**	allyl	**408**	86	+0.4	*i*	

[a] All optical rotations measured in $CHCl_3$. [b] Maximum reported optical rotation for enantiopure product. [c] For clarity, enantiomeric excesses have been calculated from the reported optical rotations. [d] See ref 86. [e] Reported value was −3.558° for material with 7 ± 3% ee; see ref 87. [f] Absolute stereochemistry of product not reported. [g] See ref 88. [h] See ref 89. [i] No literature value could be found.

calculation of the ee of the products shows that there was still a great deal of room to improve the asymmetric induction in these reactions.[86−89] It is worthy to note that work done by Saigo and Fiaud represents the first attempts at asymmetric alkylation of carbonyl compounds using chiral phase transfer catalysis. This transformation can now be facilitated enantioselectively by a wide variety of phase transfer catalysts, many of which are based on cinchona alkaloid frameworks.[90]

9. Summary

While frequently overlooked in favor of the more common 1,2-aminoalcohols, a wide variety of 1,3-aminoalcohols and their derivatives have been used for asymmetric induction in organic synthesis. They range from small linear compounds to multicyclic structures and heterocyclic derivatives. Some are derived from common natural products such as menthol, camphor, and sugars while others are entirely synthetic in structure. 1,3-Aminoalcohols have been used as chiral auxiliaries for Diels−Alder reactions and other cycloadditions, for sigmatropic rearrangements, for aldol reactions and alkylation of anions, for radical cyclizations, and for addition of organometallic reagents to ketals and carbonyl groups. They have been chelated to transition metals and other catalysts including B, Al, Zn, Ti, Pd, Cu, and Zn species. The resulting chiral catalysts have been used for Diels−Alder reactions, for allylic alkylation and Heck reactions, for carbenoid cyclopropanation reactions, for reduction of enamines and carbonyl groups, for trimethylsilylcyanations, and for addition of organometallic reagents to carbonyl groups. 1,3-Aminoalcohols have a rich history in asymmetric organic synthesis and, given their usefulness and adaptability, they will likely have a rich future as well.

10. Acknowledgments

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