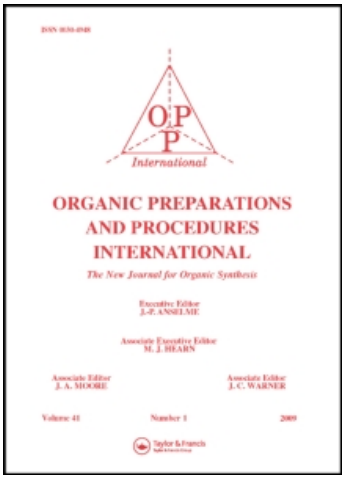

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REAGENT-CONTROLLED ASYMMETRIC DIELS-ALDER REACTIONS. A REVIEW

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REAGENT-CONTROLLED ASYMMETRIC DIELS-ALDER REACTIONS. A REVIEW

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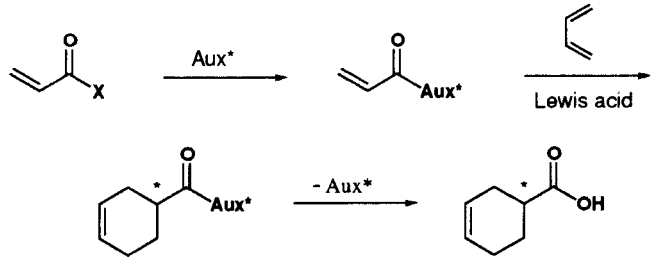
INTRODUCTION

The versatility of the Diels-Alder reaction[1] arises from high regio- and stereoselectivity, as well as from the possible use of numerous dienes and dienophiles bearing a large variety of functional groups. This versatility is further increased by intramolecular[2] and hetero Diels-Alder reactions.[3]

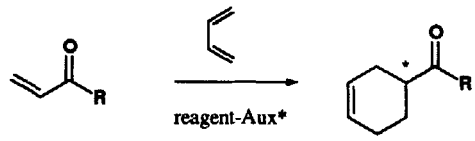
The Diels-Alder reaction has been of significant use in the synthesis of natural products.[4] In recent years, there has been an emphasis on asymmetric synthesis and an enormous amount of work has been devoted to the development of asymmetric Diels-Alder reactions.[4] In an asymmetric Diels-Alder reaction, the stereochemistry of the product can be dictated by the absolute stereochemistry of a chiral auxiliary residing either in the substrate or in some reagent. In the former case (*substrate-control*), success has been achieved in utilizing a variety of chiral auxiliaries as part of either the diene or the dienophile.[4] However, there is an inherent limitation to substrate control which cannot be avoided. Separate steps are needed in the incorporation and subsequent removal of the chiral auxiliary as well as the need for stochiometric amounts of chiral auxiliary in substrate-controlled methods (Eq. 1). These limitations coupled with the fact that partial racemization may occur in the removal of the chiral auxiliary, make the alternate method, *reagent-control*, more attractive. Evidently, *reagent-* and *substrate-control* can be utilized simultaneously in double asymmetric induction to enhance enantioselectivity.[5]



(1)

In *reagent-controlled* asymmetric Diels-Alder reactions, the source of the chiral center is part of the reagent (Eq. 2). This approach not only eliminates the need for the incorporation and removal of the chiral auxiliary but also has the potential that only catalytic amounts of the chiral source need be used. This review will cover the chiral Lewis acid approach in asymmetric Diels-Alder reactions.[6] It is not intended to be a comprehensive treatise of chiral Lewis acids, but rather to serve as a survey for chemists whose main interest lies in the application of this methodology for asymmetric syntheses. Rapid development in this area began with the work of Koga in 1979, in which a Diels-

Alder reaction was catalyzed by a chiral alkoxyaluminum Lewis acid.[7]



(2)

I. DIELS-ALDER REACTIONS

1. Boron-Based Lewis Acids

Several ligands have been used to generate chiral boron Lewis acids (Fig. 1). Chiral Lewis acid **1-6** have been modified *via* boron-oxygen or boron-nitrogen bonds. These Lewis acids are readily generated and following a reaction, the ligands can be easily recovered. The propeller compound **1** is a C_3-symmetric tetradecacyclic diborate compound.[8] The structure was determined by X-ray structural analysis. Monoacylated tartaric acid has been used to generate the chiral (acyloxy)borane catalyst **2**.[9,10] Boron Lewis acids have also been modified by amino acid derivatives to form **3**, **4**, and **5**.[11-13] Compound **6** is unique in that it incorporates an ammonium salt moiety.[14] The chiral Lewis acids **7-9** incorporate a boron atom *via* a boron-carbon bond.[15-17] The synthesis of these catalysts were more involved and the recovery of chiral source has not been developed to date.

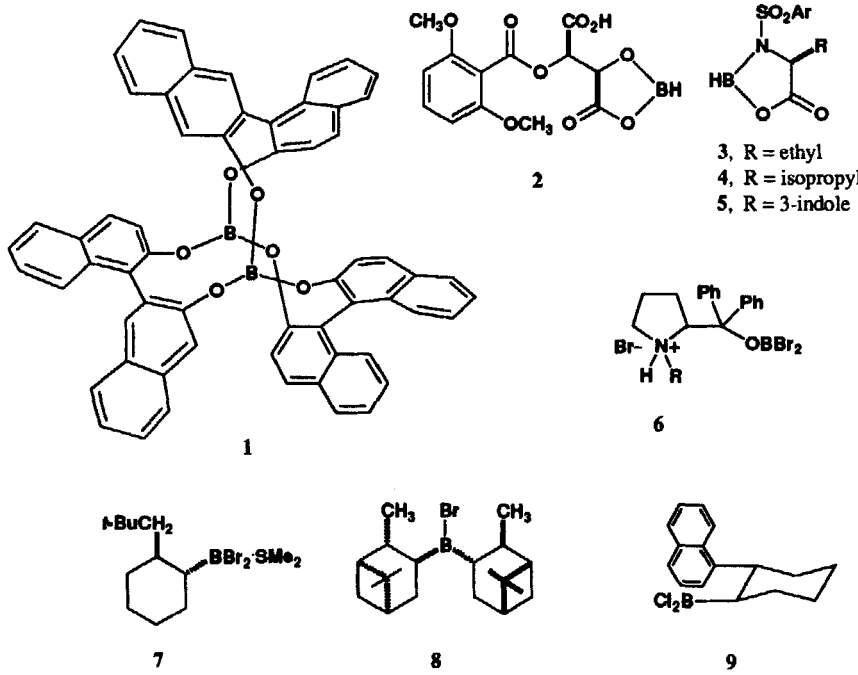
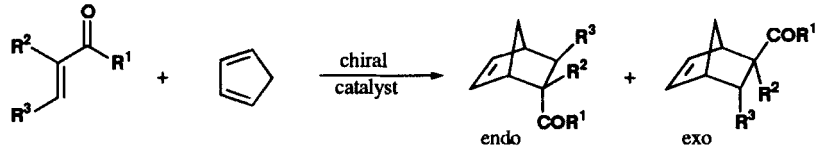


FIG. 1

The efficacy of these chiral catalysts has been examined on a limited number of dienes and dienophiles. To date, the highly selective cycloaddition reactions involve more reactive dienophiles.

The usual test cases have been acrolein and methyl acrylate derivatives as illustrated in Eq.3. and the results are summarized in Table 1. With the exception of catalysts **6** and **7**, good to excellent enantioselectivites and yields were obtained.



(3)

TABLE 1. Asymmetric Diels-Alder Reactions: Boron-Based Lewis Acids

Entry	Catalyst	Dienophile	Diene	*endo:exo*	%ee	Yield(%)	Ref.
1	0.10 Eq. **2**	CH_2=CHCHO	CPD	88:12	90	84	10
2	0.10 Eq. **2**	CH_2=CH(CH_3)CHO	CPD	11:89	96	85	10
3	0.10 Eq. **2**	CH_2=CH(CH_3)CHO	CHD	93:7	82	40	10
4	0.10 Eq. **2**	CH_2=CH(CH_3)CHO	DMBD	-	97	61	10
5	0.20 Eq. **8**	CH_2=CH(CH_3)CHO	CPD	1:99	97	84	13
6	0.03 Eq. **1**	CH_2=CH(CH_3)CHO	CPD	3:97	90	85	8
7	0.05 Eq. **5**	CH_2=CH(Br)CHO	CPD	4:96	99	95	14
8	0.10 Eq. **2**	CH_3CH_2=CHCHO[a]	CPD	90:10	2	53	10
9	0.10 Eq. **3**	CH_3CH_2=CHCHO[a]	CPD	93:7	54	52	11
10	1.0 Eq. **4**	CH_3CH_2=CHCHO[a]	CPD	97:3	72	58	12
11	0.20 Eq. **8**	CH_3CH_2=CHCHO[a]	CPD	58:42	70	80	13
12	0.10 Eq. **2**	CH_3CH_2=CH(CH_3)CHO[a]	CPD	3:97	91	90	10
13	0.10 Eq. **3**	CH_3CH_2=CH(CH_3)CHO[a]	CPD	8:92	51	85	11
14	1.0 Eq. **4**	CH_3CH_2=CH(CH_3)CHO[a]	CPD	1:99	64	95	12
15	0.10 Eq. **3**	CH_2=CH(CH_3)CHO	DMBD	-	74	73	11
16	0.10 Eq. **9**	CH_2=CHCO_2CH_3	CPD	*endo*	97	97	15
17	0.10 Eq. **9**	CH_3CH_2=CHCO_2CH_3[a]	CPD	*endo*	93	91	15
18	0.10 Eq. **9**	CH_2=CHCO_2CH_3	CHD	*endo*	86	83	15
19	0.08 Eq. **6**	CH_2=CHCO_2CH_3	CPD	96:4	31	-	17
20	0.08 Eq. **7**	CH_3CH_2=CHCO_2CH_3[a]	CPD	-	<28	-	16
21	0.10 Eq. **2**	CH_2=CHCO_2H	CPD	96:4	78	93	9

a) *trans*-isomer. b) CPD-cyclopentadiene. c) CHD-cyclohexadiene. d) DMBD-2,3-dimethylbutadiene

Substituent patterns on the dienophile influence the diastereoselectivity as well as the enantioselectivity of the reaction. Dienophiles without α-substituents were *endo*-selective and those examined with α-substituents (Br, CH_3) were *exo*-selective. The diastereoselectivity of α-substituted dienophiles was also diene dependent. Cycloadditions of methacrolein and cyclopentadiene were *exo*-selective (entries 5, 12-14) but with cyclohexadiene, the reaction was *endo*-selective (entry 3). In both of these cases, high enantioselectivities were observed. β-Substituted dienophiles, on the other hand,

had little effect on the diastereoselectivities but can have marginal to significant effect on enantioselectivity (entries 8-14, 17).

For catalysts **1-5**, the chiral ligand significantly lowers the Lewis acidity thus limiting the choice to the more reactive dienophiles. For example, acrolein-derived dienophiles are highly reactive and allow the Diels-Alder reaction to proceed at -78°, leading to high enantioselectivities. The more active catalyst **9** can catalyze cycloaddition of methyl acrylate and methyl crotonate at -78° as well as leading to high enantioselectivities and yields (entries 16-18). There has been one example of a successful Diels-Alder reaction involving a carboxylic acid dienophile catalyzed by **2** to afford high *endo* selectivity with 78% ee (entry 21). Catalytic systems **2** and **9** show promise for further development of a more substrate general catalyst. Catalyst **2** was readily generated from tartrate derivatives, whereas **9** had to be resolved.

Kelly[18] and Yamamoto[19] independently developed an asymmetric Diels-Alder reaction of juglone promoted with chiral boron Lewis acids. The boron Lewis acid was asymmetrically modified by binaphthol derived compound **10**[18] or diol **13**[19], to obtain enantioselectivities as high as 90+% ee range (Figs. 2 and 3). The proposed intermediates **11** and **14** are consistent with the results of the

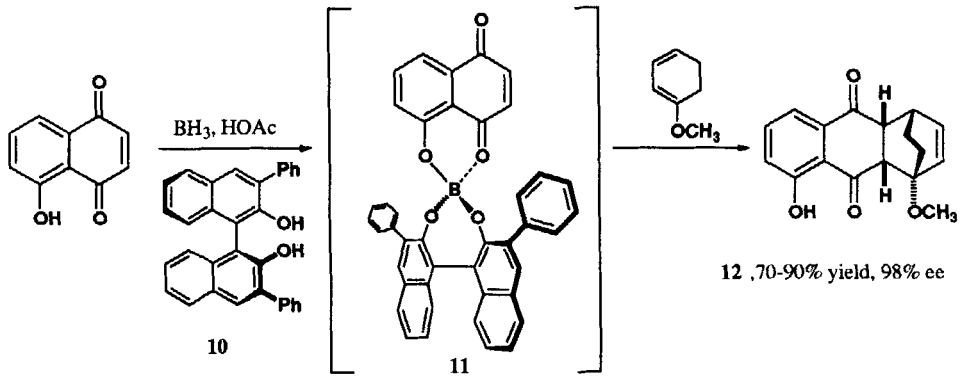


FIG. 2

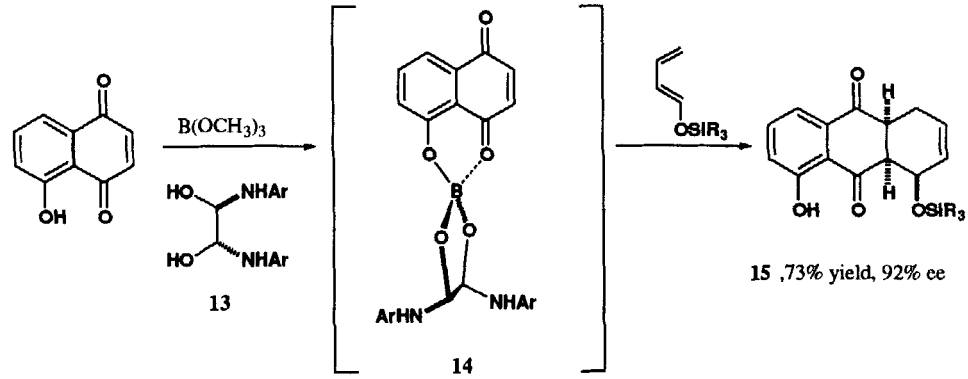


FIG. 3

reaction. This approach constitutes a beautiful utilization of the structural features of the substrate. The hydroxyl group of juglone aided in organizing the reacting complex. The phenyl substituent in **10** and the aromatic group in **13** were necessary for high enantioselectivities.

2. Aluminum-based Lewis Acids

Aluminum Lewis acids have been modified with various chiral ligands. Fig. 4 illustrates some representative chiral ligands and Table 2 summarizes the results of the Diels-Alder reactions. The ligands that have been examined were chiral alcohols (**16** and **17**),[7,20-22] chiral diols (**18-23**),[22-24] as well as mono- and bis-sulfonamides (**24** and **25**).[24,25]

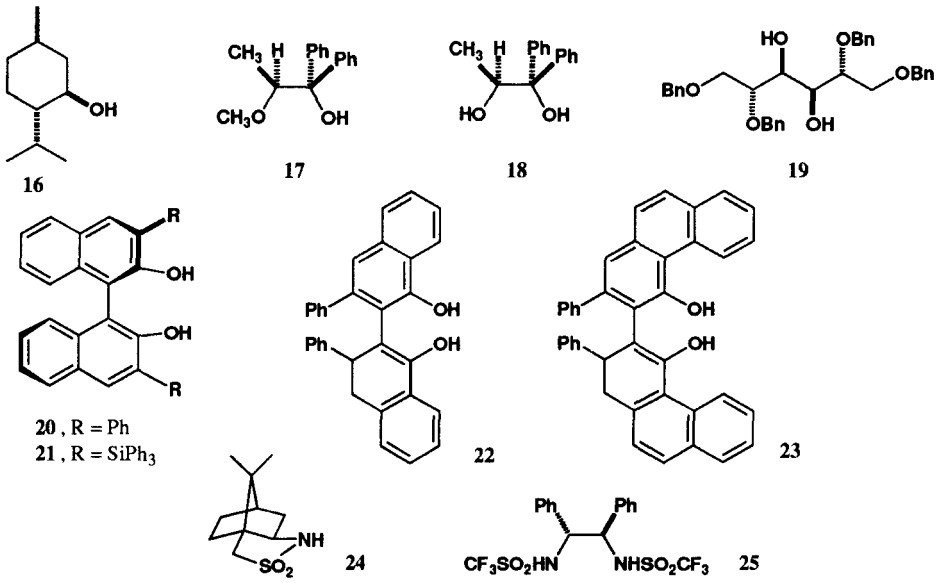
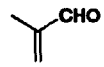
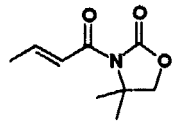
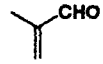
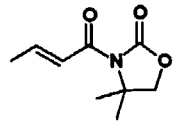
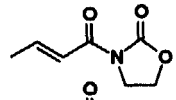
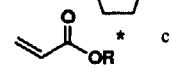
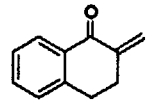
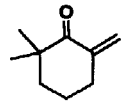


FIG. 4

$EtAlCl_2$ modified with alcohol **16** and diol **18** catalyzes the Diels-Alder reaction of methacrolein and cyclopentadiene. The enantioselectivities were in the 70% range (entries 1 and 3). The same reaction modified by alcohol **17** gave low enantioselectivity (entry 2). However, chiral diols **19** and **20** gave excellent enantioselectivities with oxazolidinone dienophiles (entries 4-6), although the *endo*-selectivities were lower than expected. When two equivalents of $EtAlCl_2$ to chiral diols were utilized, higher ee as well as improved *endo-exo* ratios were observed. Chiral diols **20** and **21** are improved versions of 1,1-binaphth-2-ol ligand. The pendant R group was designed to face toward the reacting dienophile. Similarly, diols **22** and **23** are designed to direct the bulky aryl group toward the reacting dienophile. Aluminum Lewis acids modified with diols **21** and **22** gave low selectivities (entries 7 and 8). The larger biphenanthrol **23** on the other hand gave high selectivity and yields (entry 9). In order to keep the dienophile concentration low for the highest ee, the dienophile was added over 3 hrs period *via* a syringe pump.

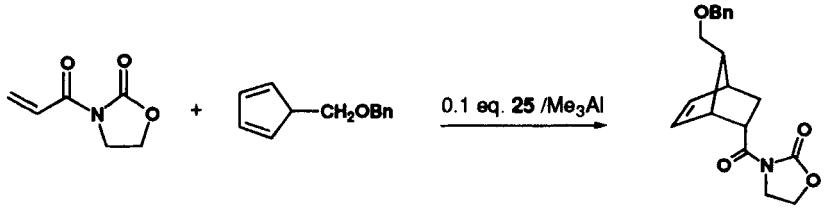
TABLE 2. Asymmetric Diels-Alder Reactions: Aluminum-Based Lewis Acids

Entry	Equiv	Ligand/LA	Dienophile	Diene	*endo*:*exo*	%ee	Yield	Ref.
1	0.15	**16**/$EtAlCl_2$			2:98	72	69	7
2	0.10	**17**/$EtAlCl_2$			5:95	20	90	22
3	0.10	**18**/$EtAlCl_2$			2:98	73	90	22
4	1.0	**19**/$EtAlCl_2$[a]			73:27	92	73	23
5	1.0	**20**/Et_2AlCl			68:32	88	92	23
6	1.0	**20**/$EtAlCl_2$[a]			76:24	95	92	23
7	0.05	**21**/Et_2AlCl			7:93	23	78	24
8	0.10	**22**/Et_2AlCl			8:92	17	85	24
9	0.05	**23**/Et_2AlCl[b]			3:97	98	100	24
10	1.0	**24**/$EtAlCl_2$			81:19	>98	75	23
11	0.10	**25**/$AlMe_3$			98:2	91	92	25
12	0.50	**25**/DIBAH	 [c]		*endo*	97	85	25
13	2.0	**16**/$EtAlCl_2$			7:93	54:38[d]	-	21
14	1.0	**16**/$EtAlCl_2$			11:89	28:48[d]	-	21

a) 2 equivalents of Lewis acid to ligand was utilized. b) slow addition of dienophile. c) R* = l-menthyl. d) ee of corresponding endo- and exo-isomers.

Aluminum-based Lewis acids modified by chiral sulfonamides **24** and **25** gave high enantioselectivities as well as high *endo*-selectivities (entries 10 and 11). Double asymmetric induction was utilized with sulfonamide **25** and *l*-menthyl acrylate to obtain 97% ee (entry 12). An aluminum catalyst

derived from **25** was utilized in the generation of prostaglandin precursor **28** in 95% ee (Eq. 4).



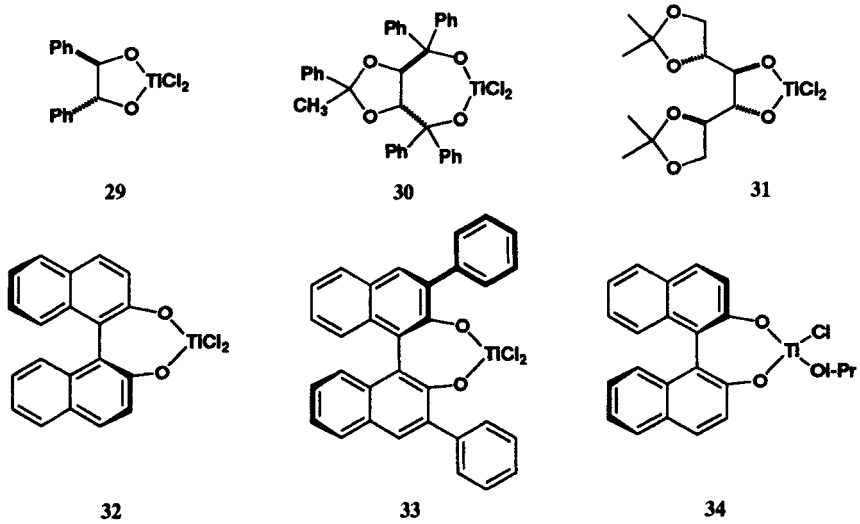
26 **27**

28, 95% ee, 94% yield

The exocyclic dienophiles, α-methylene tetralone and α-methylene cyclohexanone derivative, undergo cycloaddition with cyclopentadiene catalyzed by *l*-menthoxyaluminum dichloride (entries 13 and 14); the reactions were highly *endo*-selective and moderately enantioselective.

3. Titanium-based Lewis Acids

Titanium Lewis acids generally have been modified by chiral diols (Fig. 5). Aromatic and aliphatic diols were equally effective. The dienophile range includes carboxylic esters, diesters, and oxazolidinone groups (Table 3). The reactions were highly *endo*-selective and good yields were obtained.



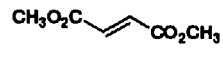
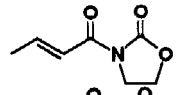
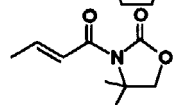
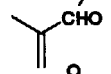
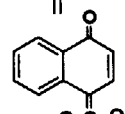
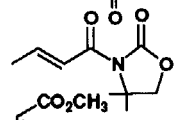
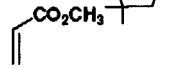
29 **30** **31**

32 **33** **34**

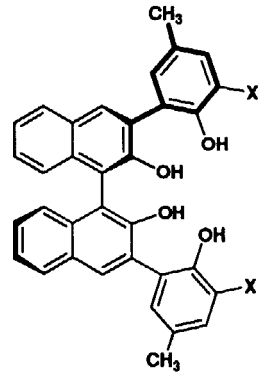
FIG. 5

The aliphatic diol-modified Lewis acids **29**[26], **30**[27], and **31**[23] gave high enantioselectivities with oxazolidinone and diester dienophiles (Table 3, entries 1,2, and 3). Generally, one equivalent of Lewis acid was required, but catalyst **30** and **32** were effective in catalytic quantities in the presence of 4Å molecular sieves (MS) (entries 2, 4, and 5).[27d,e] Of the binaphthol-modified Lewis acids **32**[28,29], **33**[23], and **34**[30], only **32** and **33** gave high enantioselectivity (entries 4, 5, and 6).

TABLE 3. Asymmetric Diels-Alder Reactions: Titanium-Based Lewis Acids

Entry	Lewis Acid	Dienophile	Diene	*endo*:*exo*	ee	Yield	Ref.
1	1.0 eq. **29**			*endo*	92	79	26
2	0.10 eq. **30**/ 4 Å MS			92 : 8	91	87	27d
3	1.0 eq. **31**			93 : 7	96	86	23
4	0.10 eq. **32**/ 4 Å MS			99:1	85	67	29
5	0.10 eq. **32**/ 4 Å MS			*endo*	85	76	29
6	1.0 eq. **33**			94 : 6	98	99	23
7	1.0 eq. **34**			98 : 2	50	77	30

The unusual ligands **35-39** with four hydroxyl groups were designed to wrap around a single titanium metal (Fig. 6)[31]. The catalyst was prepared by treatment of the ligand with Ti(O-*i*-Pr)$_4$ and azeotropic removal of 2-propanol. Catalyst derived from ligands **36**, **37**, and **38** gave highest enantioselectivity with aldehyde dienophiles. Representative results obtained with catalyst derived from **38** are presented in Table 4. While the catalyst structure is uncertain, cryoscopic studies of catalyst modified with **35** suggests that it is a monomer. ^{1}H NMR spectra of these titanium reagents derived from **36**-**38** indicate that 0.5-1.0 equivalent of 2-propanol was present.



35, X = Ph
36, X = $SiPh_3$
37, X = $SiBu^tPh_2$
38, X = Si (*o*-Tolyl)$_3$
39, X = $SiPr^i_3$

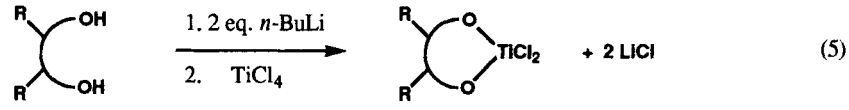
FIG. 6

TABLE 4. Asymmetric Diels-Alder Reactions: Titanium Based Lewis Acids Derived from **38** with cyclopentadiene and conjugated aldehydes[31]

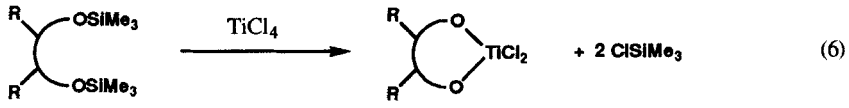
Entry	Dienophile[a]	*endo:exo*	ee	Yield
1	CH_2=CHCHO	85:15	96	70
2	CH_2=C(CH_3)CHO	1:99	94	75
3	CH_3CH=CHCHO	70:30	95	76

a) 0.10 eq. of catalyst

With titanium-based Lewis acids, the generation of the catalysts deserve some comment. Three general methods have been developed (Eqs. 5-7). Generation of dilithiodialkoxide followed by addition of $TiCl_4$ results in generation of the titanium catalyst with LiCl as a by-product (Eq. 5). A second method is the exchange of the trimethylsilyl group with $TiCl_4$, resulting in $ClSiMe_3$ as the by-product (Eq. 6). The third method is exchange of the diol ligand with two isopropoxide ligands of (*i*-PrO)$_2$TiCl$_2$ (Eq. 7). While the equilibrium in the latter favors the diol-titanium complex, there is about 15% of (*i*-PrO)$_2$TiCl$_2$ in the solution. This equilibrium can be shifted further to the right by the azeotropic removal of the isopropanol; there is also evidence that 4Å molecular sieves shifts the equilibrium in the same direction.[32] While all three methods have been effective, the method of catalyst generation can influence the outcome of the Diels-Alder reaction. This will be further discussed in section IV-2.



(5)



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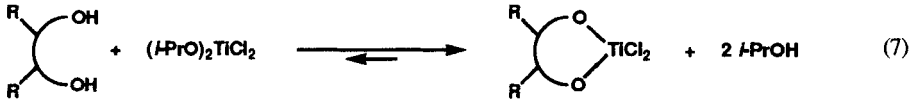
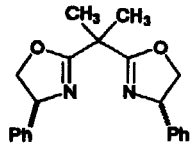


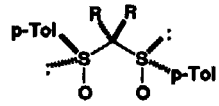
(7)

4. Iron-based Lewis Acid

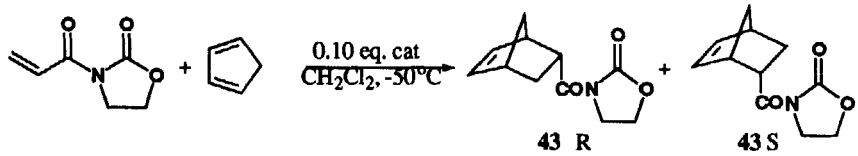
There has been two examples of modified iron Lewis acid. Chiral iron Lewis acids were generated from bis(oxazoline) **40**,[33,34] bis-sulfoxides (**41** and **42**) (Eqs. 8 and 9).[35] Compound **40** was treated with $FeCl_2$ in the presence of iodine to obtain the presumed catalytic complex **40**•$FeCl_2I$. This complex catalyzed cycloaddition between acroyloxazolidinone and cyclopentadiene to give the adduct in 85% ee (Eq. 10). Catalysts generated from bis-sulfoxides gave lower selectivities (Eq. 10).



40



41, R = H
42, R = CH_3



26

40·$FeCl_2I$, 43 R, 80 % ee, 85 % yield
41·FeI_3, 43 S, 36% ee, 74 %
42·FeI_3, 43 S, 56% ee, 78 %

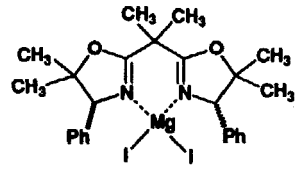
(8)

(9)

(10)

5. Magnesium-based Lewis Acid

There has been one example of modified magnesium Lewis acid using bis(oxazoline) ligand.[34] Bis(oxazoline) modified magnesium Lewis acid **44** (O.1 eq, Fig. 7), was used to catalyzed cycloaddition of oxazolidone **26** and cyclopentadiene to obtain **43** in 91% ee (82% yield; 93:7, *endo*:*exo*).



44

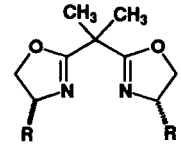
FIG. 7

6. Copper-based Lewis Acid

Chiral bis(oxazoline)copper complexes have been developed as catalyst for enantioselective olefin cyclopropanation[36] and aziridination.[37] In addition, they have been shown to catalyze Diels-Alder reactions.[38] The bis(oxazoline) ligands **40**, **45** or **46** were stirred with one equivalent of $Cu(OTf)_2$ and utilized in 5-10 mol% to catalyze the cycloaddition (Fig. 8). bis(Oxazoline) **46** with bulky *t*-butyl group gave the highest ee. High selectivities were observed with N-acyloxazoline and thiazolidine-2-thione analog dienophiles (Eq. 11 and 12).

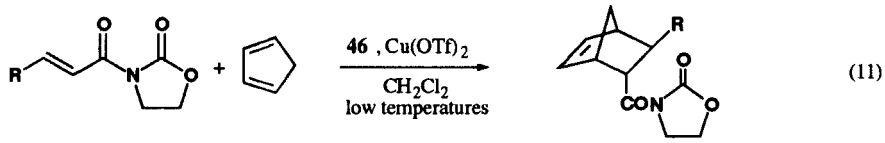
Double stereodifferentiating experiments were carried out with chiral dienophiles **51** and **54**. In the stereochemically matched case, high selectivity and yield were obtained (Eq. 13). In the

mismatched case, the selectivity was low and the rate of reaction was significantly slower (Eq. 14). Its important to note that, in the mismatched case, the major product was that of *catalyst-controlled* process and not the *substrate-controlled* process.



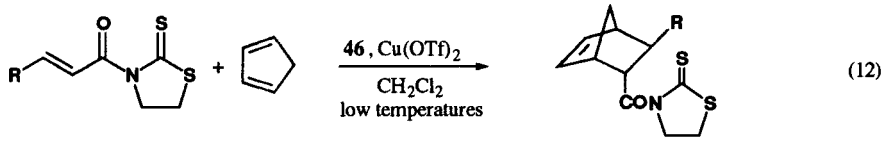
40, R = Ph
45, R = *i*-Pr
46, R = *t*-Bu

FIG. 8



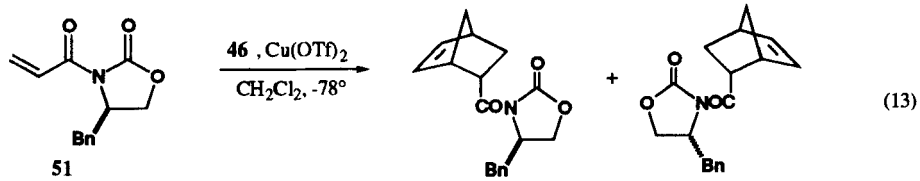
47 **48**, R = H, CH_3, Ph, CO_2Me
90-97% ee, 85-92%

(11)



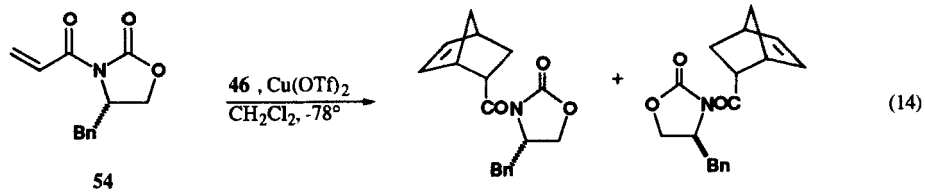
49 **50**, R = CH_3, Ph, CO_2Me
90-97% ee, 82-88%

(12)



51 **52:53**, ≥ 99:1, 87%

(13)



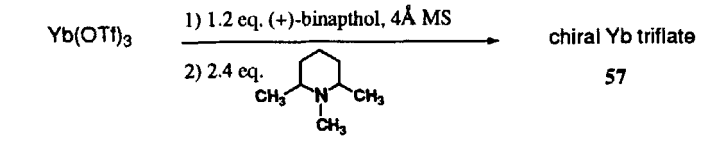
54 **55:56**, 68:31, 10%

(14)

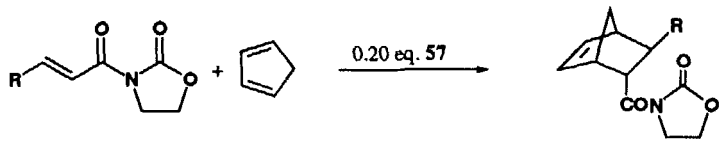
7. Ytterbium-based Lewis Acid

Ytterbium triflate modified with (R)-(+)-binaphthol has been used as chiral Lewis acid.[39] The chiral catalyst was prepared from $Yb(OTf)_3$, (+)-binaphthol, 4Å MS and an amine base (Eq. 15). High enantioselectivities were obtained with N-acyloxazolidone dienophiles (Eq. 16). Of the variety of amines surveyed, sterically hindered amines gave the highest selectivities. Cycloaddition with

methacrolein dienophile resulted in lower yield and selectivity (54%, 44% ee).



(15)



47

(16)

58, R = CH_3, 90% ee, 91%
59, R = *n*-Pr, 83% ee, 81%
60, R = Ph, 83% ee, 40%

II. HETERO DIELS-ALDER REACTIONS

Hetero Diels-Alder reactions involving carbonyl and imine dienophiles have been developed to practical levels. This has been achieved through activation of the dienophile with Lewis acids[40] or by the use of high pressure reaction conditions.[41] Even with these activation methods, reactive dienes are still necessary. Development of asymmetric hetero Diels-Alder reactions have led to chirally modified aluminum,[42,43] boron,[44] ruthenium,[45] eruropium[43,46-48] vanadium[49,50] and titanium[51] Lewis acid-catalyzed reactions.

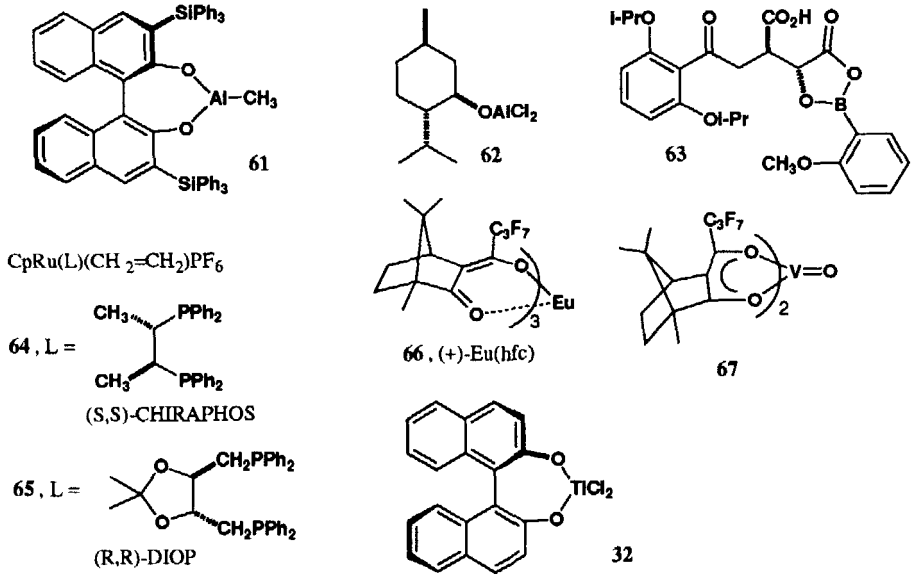
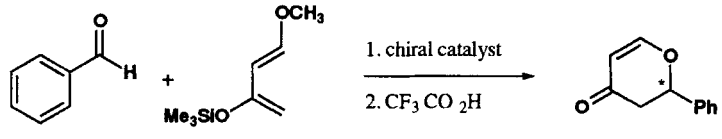


FIG. 9

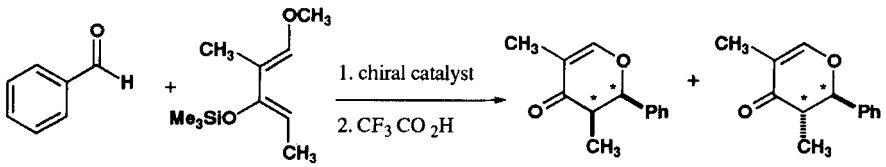
1. Aldehyde Dienophiles

The modified Lewis acids which have been examined with carbonyl dienophiles are illustrated in Fig. 9. In a typical Diels-Alder reaction involving a carbonyl dienophile and Danishefsky's diene, the initial cycloadduct was converted to the pyrone by trifluoroacetic acid (Eq. 17). With highly

substituted dienes, diastereomeric products are also possible (Eq. 18). A summary of the Diels-Alder reactions are presented in Table 5. Comparison of the reaction between benzaldehyde and Danishefsky's diene indicates that the modified aluminum, boron and vanadium Lewis acids, **61**, **63** and **67** are the most promising reagents (entries 1-5). The highest reported enantioselectivity to date, 79% ee, was achieved by catalyst **63**. High enantioselectivities were observed with representative



68 **69** (17)



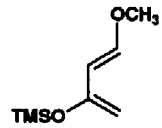
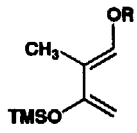
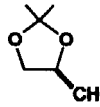
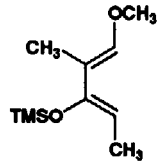
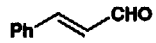
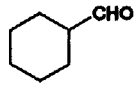
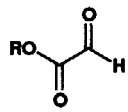
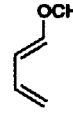
70 **71**, *cis* **72**, *trans* (18)

dienophiles, such as benzaldehyde and cinnamaldehyde, as well as other conjugated aldehydes (entries 13-15, and 18). Both alicyclic and acyclic dienophiles gave good enantioselectivities (entries 16 and 17). The enantioselectivities seem to be diene dependent. For example, a more substituted diene (entries 12 and 13) gave significantly higher ee's than the less substituted Danishefsky's diene (entries 2 and 3). When the methoxy group of the diene (entry 7) was replaced by a *t*-butoxy group (entry 8), the enantioselectivity increased from 15% to 39% ee. This result led Danishefsky to investigate double asymmetric induction. When the R group was replaced with *l*-menthyl and the reaction was catalyzed by (+)-Eu(hfc)$_3$, the two chiral auxiliaries reinforced each other to give 84% ee (entry 9). Replacing the *l*-menthyl with a *d*-menthyl group dropped the selectivity to 18% (entry 10). It should be noted that it was the mismatching, L-selective (+)-Eu(hfc)$_3$ and D-selective diene (R = *l*-menthyl) that gave the highest ee (84%) while matching, L-selective diene (R = *d*-menthyl) gave the lower enantioselectivity (18% ee). And also noteworthy is the fact that the product of the mismatching pair was L-selective, *i. e.*, the product that the chiral catalyst favors and opposite that of the chiral diene.

Double asymmetric induction with a chiral dienophile and chiral vanadium Lewis acid was also investigated. The Diels-Alder reaction between matching (2R)-2,3-O-isopropylideneglyceraldehyde, promoted by **67**, gave 89% ee and a 97:3 *cis-trans* ratio (entry 11). The mismatching conditions gave high *cis-trans* ratio, but no enantioselectivity was observed.

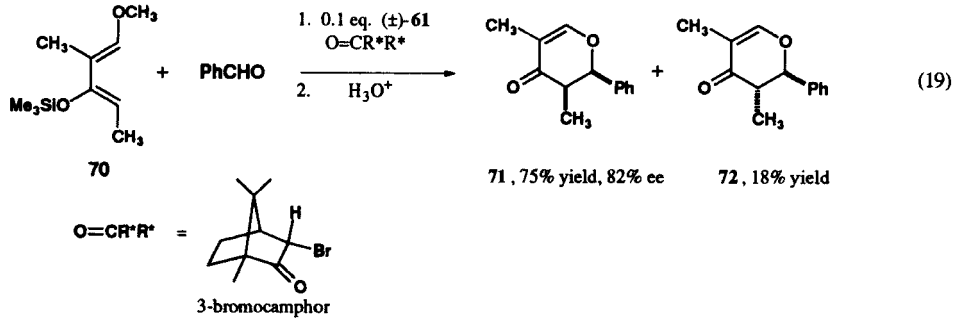
Modified aluminum and ruthenium catalysts **62**, **64**, and **65** gave low enantioselectivities (entries 5 and 6). The (+)-Eu(hfc)$_3$-catalyzed Diels-Alder reaction of *n*-butyl glyoxalate gave moderate selectivity (entry 19). The titanium reagent **32**, on the other hand gave high enantioselectivity (entry 20). The cycloadditions were generally *cis*-selective, however, there was one case (entry 19) where the *trans*-compound was proposed as the major isomer.

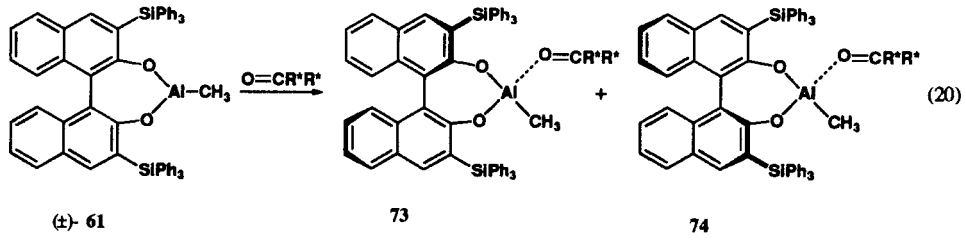
TABLE 5. Asymmetric Diels-Alder Reactions: Carbonyl Dienophiles

Entry	Lewis Acid	Dienophile	Diene	*cis*:*trans*	ee/de	Yield	Ref.
1	0.01 eq. **66**	PhCHO		-	18	-	47
2	0.20 eq. **63**	PhCHO		-	79	80	44
3	0.10 eq. **61**	PhCHO		-	56	-	42
4	0.05 eq. **67**	PhCHO		-	68	82	49
5	0.05 eq. **64**	PhCHO		-	25	60	46
6	0.05 eq. **65**	PhCHO		-	16	60	46
7[a]	0.01 eq. **66**	PhCHO		-	15	-	47
8[b]	0.01 eq. **66**	PhCHO		-	39	-	47
9[c]	0.01 eq. **66**	PhCHO		-	84	-	48
10[d]	0.01 eq. **66**	PhCHO		-	18	-	48
11	0.05 eq. **67**			97:3	89	49	49
12	0.10 eq. **61**	PhCHO		77:7	95	84	42
13	0.10 eq. **63**	PhCHO		95:5	97	100	44
14	0.10 eq. **61**			89:10	90	99	42
15	0.10 eq. **63**			86:6	97	92	44
16	0.10 eq. **61**			100:0	91	65	44
17	0.10 eq. **61**	$CH_3(CH_2)_3CHO$		62:18	86	80	42
18	0.10 eq. **63**	$CH_3CH{=}CHCHO$		79:1	92	80	44
19[e]	0.05 eq. **66**			19:79	64;39	98	43
20[f]	0.10 eq. **32**			78:22	94;90	77	51

a) R = CH_3, b) R = *t*-Bu, c) R = *l*-menthyl, d) R = *d*-menthyl, e) R = $CH_2CH_2CH_2CH_3$, f) R = CH_3

Yamamoto has developed a method to discriminate between two carbonyl groups by complexing the less hindered carbonyl selectively with bulky aluminum Lewis acids.[52] With this concept, he has devised a novel approach in *reagent-controlled* Diels-Alder reactions.[53] Cycloaddition of benzaldehyde and a reactive diene, catalyzed by a mixture of racemic aluminum Lewis acid **61** and optically pure *l*-3-bromocamphor, resulted in 82% ee for the *cis*- isomer (Eq. 19). It was proposed that racemic **61** and *l*-3-bromocamphor form diastereomeric complexes **73** and **74** (Eq. 20). Complex **73** selectively decomplexes to form a new complex between (+)-**61** and benzaldehyde which then undergoes cycloaddition. Of the variety of ketones that were examined, 3-bromocamphor gave the highest enantioselectivity (82% ee). The usefulness of this asymmetric hetero Diels-Alder methodology with carbonyl dienophiles has been demonstrated by Danishefsky through the synthesis of unnatural L-glycolipids and L-glucose.[48]





2. Imine Dienophiles

Reagent-controlled asymmetric Diels-Alder reactions of imine dienophiles have not been developed to the extent of that of carbonyl dienophiles. There are only few examples of intermolecular cycloaddition with imine dienophiles.[54] Cycloaddition of aldimine **76** and Danishefsky's diene was promoted by a modified boron Lewis acid, **75** (Fig 10) in the presence of 4Å molecular sieves, gave 75% of the cycloadduct with 82% ee (Eq. 21). Several aldimines were examined. The yields were in the range of 31% to 83% with enantioselectivities of 72% to 90% ee. This method was applied in the synthesis of (-)-anabasine, an alkaloid derived from nicotinic acid (Fig. 11).

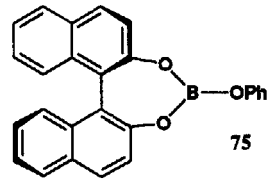


FIG. 10

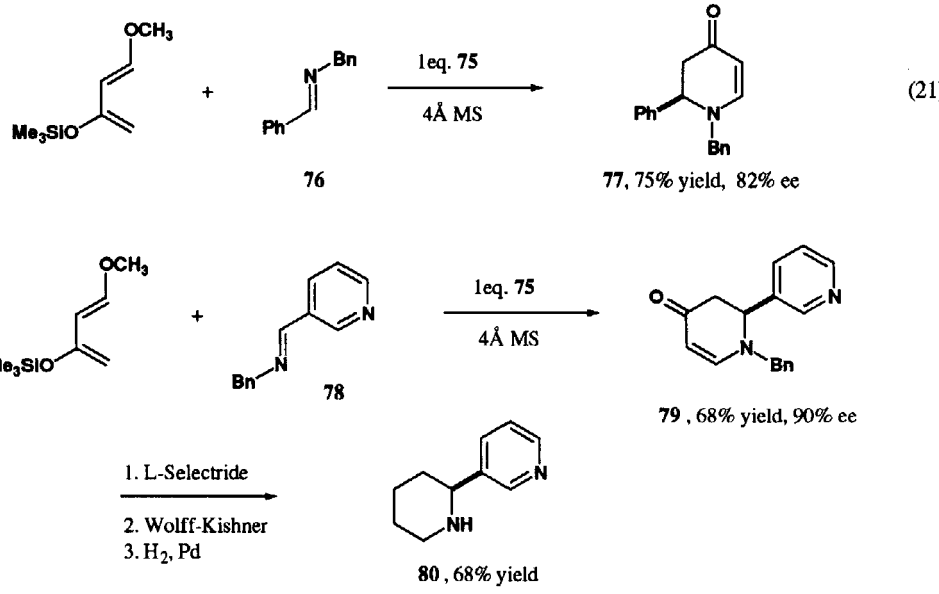
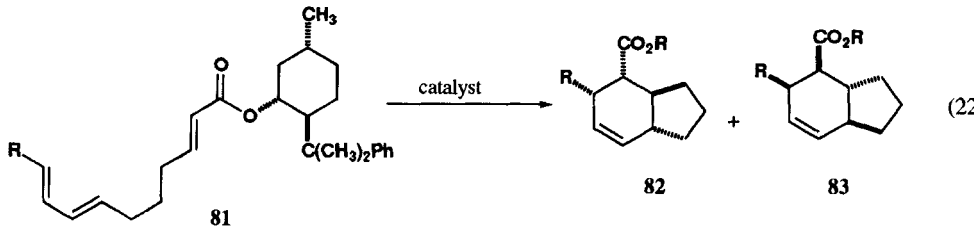


FIG. 11

III. INTRAMOLECULAR DIELS-ALDER REACTIONS

There are several examples of reagent-controlled intramolecular asymmetric Diels-Alder reactions. One of the first examples were carried out by Roush in 1980.[55] Under substrate-controlled conditions with (-)-phenylmenthol as the chiral auxiliary, only 16% diastereomeric excess (de) was obtained for cycloadduct **82** (Eq. 22, Table 6, entry 1). When the reaction was catalyzed by a racemic mixture of ((±)-menthyloxy)$AlCl_2$, 36% de was obtained (entry 2). The diastereoselectivity did not increase when optically pure Lewis acids were employed. When the reaction of the corresponding methyl ester of **81** (R = *i*-Pr) was catalyzed by (*l*-menthyloxy)$AlCl_2$ or (*l*-bornyl)$AlCl_2$, no enantioselectivity was observed. These results indicate that there was some interaction between the bulky phenylmenthol on the substrate and the bulky chiral Lewis acid. Whether optically pure or racemic Lewis acids were employed, similar enantioselectivities were observed (entries 2 and 3). This may be the result of selective interaction of one of the chiral Lewis acids with the substrate. The diastereoselectivities were substrate dependent. For substrate **81** (R = H), a higher diastereoselectivity of 64% de was achieved with chiral Lewis acids (entries 5 and 6).



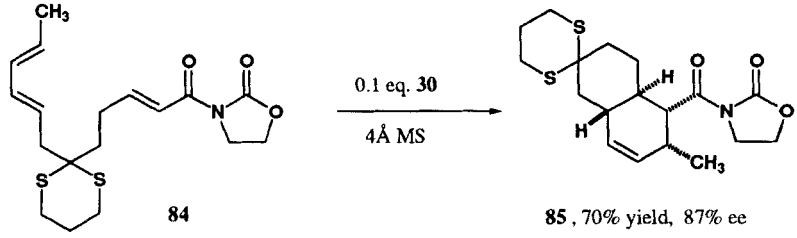
(22)

TABLE 6. Intramolecular Asymmetric Diels-Alder Reactions[55]

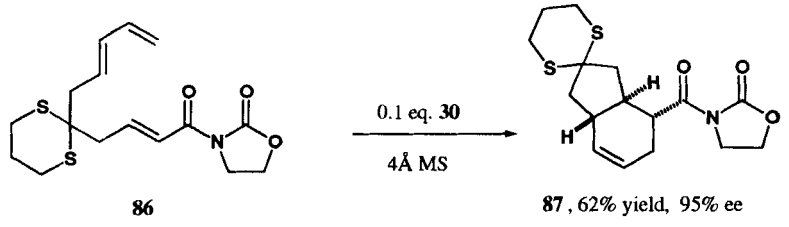
Entry	R	Lewis Acid	82:83	de (82)[a]
1	*i*-Pr	0.9 eq. $EtAlCl_2$	58:42	16
2	*i*-Pr	1.9 eq. ((±)-menthyloxy)$AlCl_2$	68:32	36
3	*i*-Pr	1.6 eq. (*l*-menthyloxy)$AlCl_2$	65:35	30
4	*i*-Pr	1.8 eq. (*l*-bornyloxy)$AlCl_2$	67:33	34
5	H	1.8 eq. ((±)-menthyloxy)$AlCl_2$	75:25	50
6	H	1.6 eq. (*l*-bornyloxy)$AlCl_2$	82:18	64

a) diastereomeric excess of compound **82**

Modified titanium Lewis acids developed by Narasaka proved just as effective in the intramolecular version (eqs. 23 and 24).[56] In the presence of 0.10 equivalent **30** (Fig. 3) and 4Å molecular sieves, **84** and **86** undergo cycloaddition in 87% and 95% ee respectively. The presence of 1,3-dithiane moiety was found to accelerate the reaction and enhance the diastereo- and enantioselectivity. It was proposed that the geminal dialkyl effect improved the outcome of the cycloaddition. This method was successfully applied in the synthesis of the hydronaphthalene moiety of mevinic acids.[57]

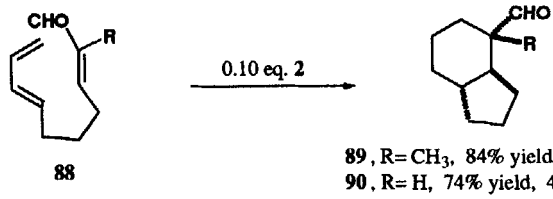


(23)



(24)

Chiral acyloxyborane was also effective in an intramolecular case.[58] Substrate **88** undergoes Diels-Alder cycloaddition in the presence of 0.10 equivalent of catalyst **2** to give **89** and **90** in 92% and 74% ee respectively (Eq. 25).

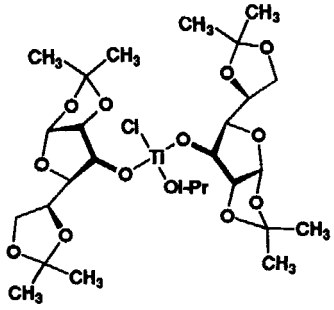


88

89, R= CH_3, 84% yield, 92% ee
90, R= H, 74% yield, 46% ee

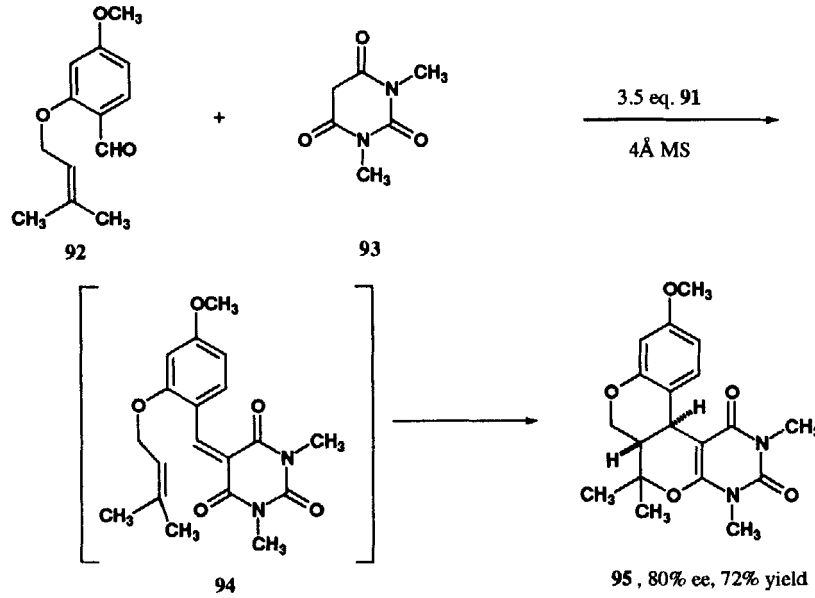
(25)

The modified titanium Lewis acid **91** has been shown to be an effective catalyst for the intramolecular hetero Diels-Alder reaction (Fig. 12).[59] The substrate **94** was obtained *in situ* by a Knoevenagel condensation of aldehyde **92** and barbituric acid **93**, which subsequently undergoes *aza* Diels-Alder reaction to the cycloadduct **95** in 72% yield with 80% ee (Fig. 13).



91

FIG. 12



92 93

94

95, 80% ee, 72% yield

FIG. 13

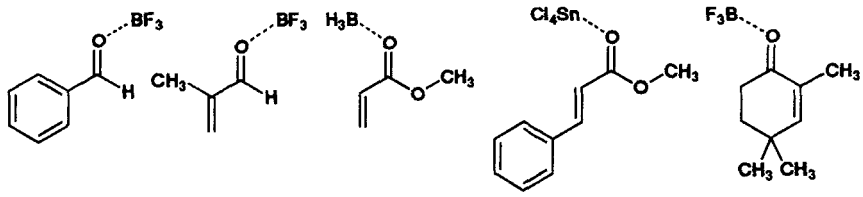
IV. MECHANISTIC CONSIDERATIONS

It is well documented that enone dienophiles are activated by Lewis acids.[60] Lewis acid-mediated Diels-Alder reactions are known to proceed with improved regio- and stereoselectivity relative to uncatalyzed reactions. In the area of chiral Lewis acids, the origins of the enantioselectivity is not well understood. To better understand the mechanism of asymmetric induction, the conformational relationship between the chiral auxiliary and the reaction site as well as the solution structure of the Lewis acid-carbonyl complexes must be elucidated. Theoretical, NMR, and X-ray crystallographic studies have provided some insight into the structures of the Lewis acid-carbonyl complexes.[61] A thorough discussion of the mechanistic implications are beyond the scope of this review. However, some highlights into the mechanistic aspects should aid in the application of this technology.

1. Lewis Acid-Carbonyl Complexes

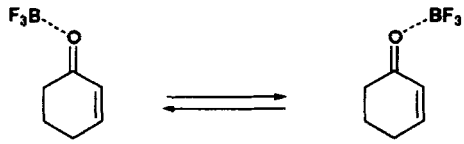
X-ray structure determination of benzaldehyde-BF_3 complex **96**[62] and 2-methylacrolein-BF_3 complex **97**[63] give excellent insight into the structural features of the Lewis acid-aldehyde complex (Fig. 14). In each case, the boron atom lies in the plane of the molecule and BF_3 is coordinated *anti* to the *ene*-moiety. MNDO calculations indicate that *anti*-coordination in **96** is 1.8 Kcal/mol lower in energy than *syn*-coordination. The enal in **97** is in the s-*trans* geometry. These structural features persist in solution as indicated by NMR investigations.

X-ray crystallography[64] and theoretical[65] investigations of Lewis acid-carboxylic ester complexes indicate the Lewis acids prefer *syn*-coordination (structures **98** and **99**). The s-*trans* of the enal moiety is the more stable conformation. In 6-methylcyclohex-2-en-1-one derivative **100**,



96 **97** **98** **99** **100**

FIG. 14



101 **102** (26)

solution NMR indicates that BF_3 is chelated *anti* to the double bond (Fig. 14).[66,67] In general, the *syn-anti* complexation seems to be sterically driven. For aldehydes and carboxylic esters, the sterically favored position is readily identified; for ketones, this is not always as clear and where the steric bias is minimal, mixtures of the *syn*- and *anti*-complexes are present (Eq. 26).[66]

The *syn* and *anti* preference can be altered by a second coordination site. In the N-acryloyl oxazolidinone system, it is accepted that titanium, tin, and aluminum Lewis acids chelate to both carbonyl groups (Fig. 15).[68,4a] In the acrylate of alkyl lactate, the titanium Lewis acid chelates to both carbonyl groups (structure **105**) while the aluminum Lewis acid chelates only to one of the carbonyl group (structure **106**).[69]

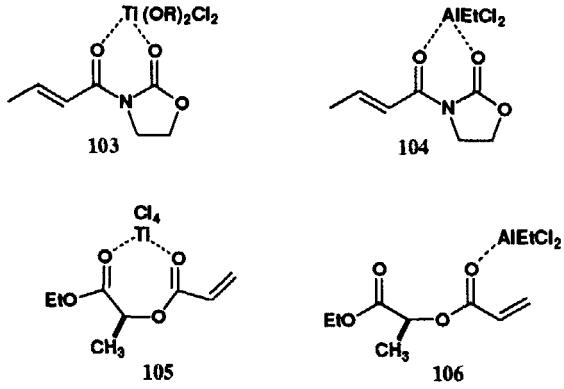


FIG. 15

The structure of catalyst 9-methyl crotonate complex **107** was determined by X-ray crystallography (Fig. 16).[15] The enone is in the *s-trans* conformation and the carbonyl group is nearly parallel to the naphthalene moiety, indicating π-π interaction. In this conformation, the naphthalene moiety blocks one face of the dienophile. This ground state argument is consistent with the absolute configuration of the products.

Boron Lewis acids **3**[11] and **4**[12] derived from amino acids gave enantioselectivity opposite to that of **5**[14] which contain an indole moiety (Fig. 1). The intermediate **108** has been proposed for Lewis acids derived from **3** and **4** (Fig. 16).[70] This model takes recent *ab initio* calculations into account which show that BH_3 coordinated acrolein prefers *s-cis* conformation in the transition state.[71] This model leads to *si*-attack by the diene. In the presence of indole moiety transition state

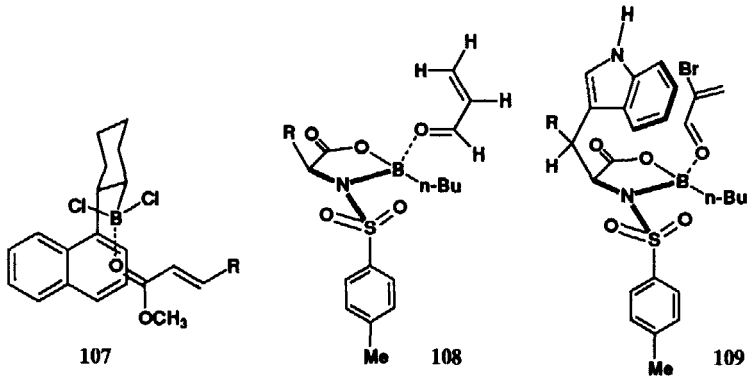
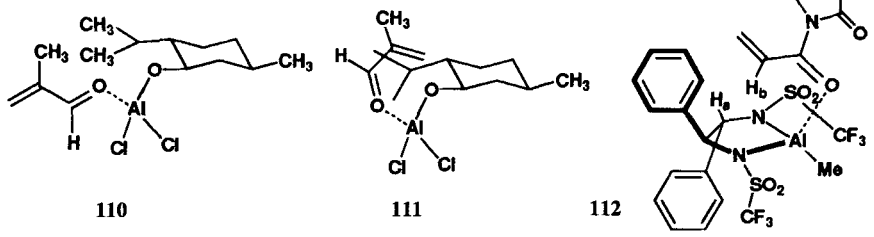


FIG. 16

109 was proposed. The position of the enal optimizes the π-π interaction between the enal and the indole moiety.[72]

Two intermediates **110**[73] and **111**[74] have been proposed for the menthoxyaluminum dichloride catalyst (Fig. 17). The intermediate **110** incorporates s-*trans* conformation of the enal and aluminum coordinated *syn* to the formyl group. The intermediate **111**, on the other hand, incorporates s-*cis* conformation and aluminum coordinated *anti* to the formyl group.

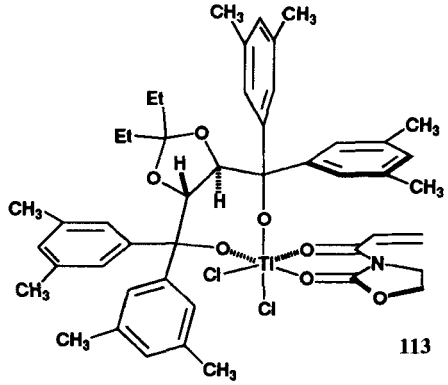
The proposed intermediate for diazaaluminolidine catalyzed reaction is illustrated by **112** (Fig. 17).[75] The dienophile position is consistent with the 5% NOE between H_a of the chiral ligand and H_b of the dienophile.



110 **111** **112**

FIG. 17

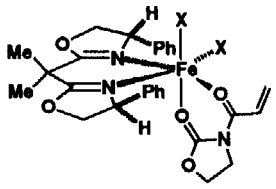
When titanium chiral ligand **30** was modified with more electron rich aromatic moiety, the enantioselectivities of the cycloaddition were improved. This led to the proposal of intermediate **113** for the modified titanium Lewis acid and an oxazolidinone dienophile (Fig. 18).[76,77] The dienophile is complexed to the metal in the s-*trans* geometry such that the α,β-unsaturated carbonyl moiety and the proximate aromatic ring are in parallel planes. This allows for optimum π-donor-acceptor interaction.



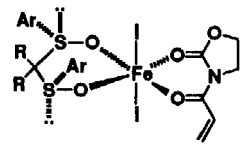
113

FIG. 18

Diels-Alder reactions catalyzed by bis(oxazoline) **40**,[33] modified iron Lewis acids gave opposite facial selectivity than the reaction catalyzed by bis-sulfoxide **41** and **42** modified Lewis acid.[35] The mechanism proposed for the two system differ in the position of the coordination site around the octahedral iron atom (Fig. 19).



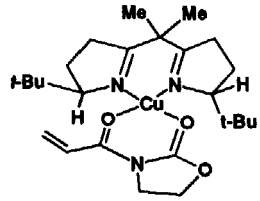
114, X = Cl or I



115

FIG. 19

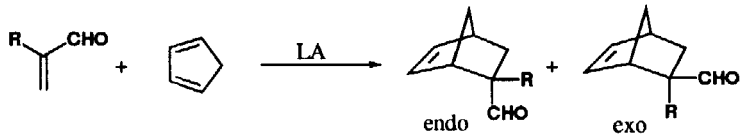
In the case of modified copper Lewis acid, the mechanism was rationalized based of the square-planar intermediate **116** as opposed to a tetrahedral complex (Fig. 20).[38,78]



116

FIG. 20

Generally, the enhanced *endo* selectivities have been accepted for Lewis acid catalyzed Diels-Alder reactions. However, there is some evidence that the steric bulk of the Lewis acid can influence the extent of the *endo-exo* stereoselectivity. In the reaction of acrolein and methacrolein, the sterically bulky methylaluminum bis(2,6-di-*t*-butyl-4-methylphenoxide (MAD) enhances *exo* selectivity relative to trimethylaluminum (Eq. 27, Table 7).[79] It has been suggested that the increased steric bulk of the MAD group destabilizes the *endo* approach of the dienophile and the diene.



(27)

TABLE 7. Steric Effects of Lewis Acid on Diastereoselectivity[79]

Entry	R	Lewis Acid	*endo* : *exo*	% Yield
1	H	Me_3Al	24 : 1	57
2	H	MAD	12 : 1	56
3	CH_3	Me_3Al	1 : 15	64
4	CH_3	MAD	1 : 49	76

MAD = methylaluminum bis(2,6-di-*t*-butyl-4-methylphenoxide)

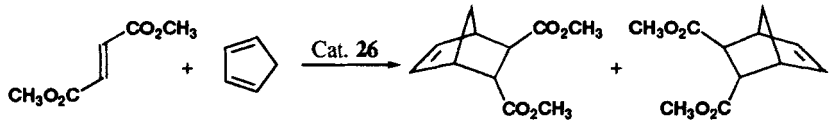
2. Additives and Preparation of Chiral Lewis Acids

In many of the aforementioned reactions, a number of the procedures call for 4Å molecular sieves (Entries 2, 4 and 5, Table 3; Eqs. 21, 23 and 24; Fig. 13). It is clear that 4Å MS enhanced the enantioselectivity significantly in many but not all cases. It is not clear by what mechanism molecular

sieves participate in the reaction. Scavenging trace amounts of water may be partially responsible.

Kagan has investigated various experimental parameters with chiral aluminum Lewis acids, such as temperature, solvent, and aging of the catalyst.[22] With some chiral ligands, the structure of the chiral aluminum Lewis acids seems to change over a period of time.

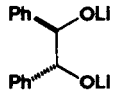
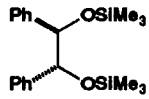
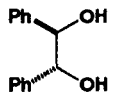
A systematic study of catalyst preparation versus the enantioselectivity for a chiral titanium Lewis acid catalyzed cycloaddition (Eq. 28), has shown that various methods of preparation can indeed influence the enantioselectivity of the Diels-Alder reaction (Table 8).[80] The preparation that resulted in high enantioselectivity had LiCl as a by-product. Alternate preparations of this catalyst with LiCl and related additives clearly show that chloride ion plays a role in this system (Table 9).



(28)

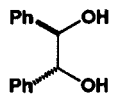
113 2-80% ee **114**

TABLE 8. Effect of Catalyst Preparation on Enantioselectivity[80]

Entry	Catalyst Preparation	Yield(%)	% ee
1	 $TiCl_4/LiCl$	86	80
2	 $TiCl_4$	91	6
3	 $(i\text{-PrO})_2TiCl_2$	88	10
4	$(i\text{-PrO})_2TiCl_2$[a]	80	14
5	$(i\text{-PrO})_2TiCl_2$/4Å MS	90	2

a) Isopropanol was removed by azeotropic distillation with toluene.

TABLE 9. Effect of Additives on Enantioselectivity[80]

Entry	Catalyst Preparation	Yield(%)	% ee
1	 $(i\text{-PrO})_2TiCl_2/LiCl$	75	26
2	$(i\text{-PrO})_2TiCl_2/Me_4NCl$	82	26
3	$(i\text{-PrO})_2TiCl_2/NH_4Cl$	88	24
4	$(i\text{-PrO})_2TiCl_2/Me_4NBr$	78	8
5	$(i\text{-PrO})_2TiCl_2/Bu_4NI$	50	8
6	$(i\text{-PrO})_2TiCl_2/LiBr$	84	10

V. CONCLUSION

Reagent-controlled asymmetric Diels-Alder reactions have developed rapidly in recent years. Synthetic application is now possible with simple dienophiles. This approach works well for enone, carbonyl and imino dienophiles, leading to carbocycles as well as oxygen and nitrogen heterocyclic compounds.

The mechanistic details, such as the organizational role of the Lewis acid and the conformational relationship between the chiral auxiliary and the reaction site, need further documentation. The role of additives (molecular sieves, LiCl) are not well understood. The dependence on various experimental conditions (aging of catalyst, temperature, solvent, additives, etc.) are now just coming to light.

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