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REVIEW

Asymmetric Diels–Alder Reactions of Cyclopentadiene in the Synthesis of Chiral Norbornene Derivatives

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Abstract—The review discusses available data on asymmetric Diels–Alder reactions of cyclopentadiene, which were published in the past decade. Both noncatalytic and catalytic (in the presence of achiral and chiral catalysts) versions of these reactions are considered. Effects of various factors on the chemical and optical yields, stereoselectivity, and optical purity of the Diels–Alder adducts are analyzed. Prospects in the development of this field of organic chemistry are examined.

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1. INTRODUCTION

Nowadays increasing number of medicines, fragrance substances, and agricultural chemicals are produced in their optically active forms. The use of optically active compounds in practical pharmaceutical chemistry has become more and more important. The application of an optically active but not enantiomerically pure substance involves some limitations related to the therapeutic effect of the other enantio-

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Fields of scientific interest: functionally substituted alicyclic compounds, asymmetric syntheses, Diels–Alder reactions, physiologically active compounds.

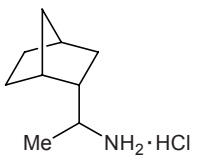
Klabunovskii Evgenii Ivanovich was born in 1923 in Putivl' (Ukrainian SSR). In 1944 he graduated from the Faculty of Chemistry, Moscow State Universitety. E.I. Klabunovskii is Doctor of chemical sciences, Professor, Honored Scientific Worker of the Russian Federation, Senior Research Worker at the Laboratory of Asymmetric Catalysis, Zelinskii Institute of Organic Chemistry, Russian Academy of Sciences.

Fields of scientific interest: homogeneous and heterogeneous asymmetric catalysis, natural origin of homochirality.

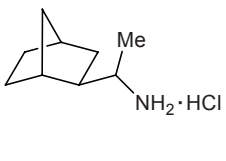
mer. According to Pfeiffer's rule, the efficiency of an optically active substance is characterized by the *enantiomer ratio* (*ER*) which is defined as the ratio of the therapeutic efficiencies of its enantiomers [1–9]. For example, (*S*)-Propranolol has an *ER* value of 130. Some preparations must contain only one enantiomer if the other exhibits adverse properties. 3,4-Dihydroxyphenylalanine (DOFA) is an anti-Parkinson drug which is used as only L-DOFA, whereas D-enantiomer induces side effects. (*S*)-Penicillamine [7] is an antiarrhythmic drug, while its (*R*)-isomer is a mutagen; (*S*,*S*)-Ethambutol is an antituberculous drug with *ER* 200, while its (*R*,*R*)-enantiomer induces blindness. Different enantiomers may exert positive but different therapeutic effects; for example, (2*R*,3*S*)-Darvon is an analgesic, while (2*S*,3*R*)-Novrad is an antitussive drug. Finally, the (*R*)-enantiomer of Thalidomide is an analgesic, whereas (*S*)-Thalidomide exhibits a strong mutagenic effect [10]. If the other enantiomer has no adverse affect, it is not necessary to use optically pure substance in practice.

Advantages of optically active drugs are now completely recognized. For example, since 1994 till 1999 sales volume of optically active drugs has grown by a factor of 3 and reached 115 billion dollars in 1999 [2, 3, 10].

Various methods for the preparation of optically active compounds are known; these include kinetic resolution, enzymatic and microbiological reactions, asymmetric synthesis, and asymmetric catalysis [11]; the latter seems to be the most promising. Bicyclo[2.2.1]heptane (or norbornane) skeleton constitutes a structural base of numerous biologically important natural compounds, such as borneol, camphor, etc. Many amines used as drugs are derivatives of norbornene, norbornane, and adamantane [12]. Cage-like amines having a norbornene fragment typically display antiviral activity. 2-(1-Aminoethyl)bicyclo[2.2.1]heptane hydrochloride known as viral inhibitor is readily obtained from norbornane as a mixture of two stereoisomers, *endo*-**1a** and *exo*-**1b** [13].



Ia



Ib

Interest in norbornene derivatives is determined by their increased accessibility due to improvement of procedures for the Diels–Alder reactions. In most cases, Diels–Alder reactions are highly selective; therefore, it becomes possible to reveal factors responsible for the reaction rate, reaction direction, and equilibrium in the absence and in the presence of catalysts. Asymmetric Diels–Alder reactions involving cyclopentadiene underlie one of the most promising and convenient methods for the synthesis of optically active norbornene derivatives. Norbornene is used as a model for studying mechanisms of some organic reactions [14, 15]. Advances in the field of asymmetric Diels–Alder reactions of cyclopentadiene have been discussed in part in monographs [16–19] and review articles [20–23], as well as in [24].

The present review summarizes recently published results of studies on asymmetric Diels–Alder reactions of cyclopentadiene with various activated dienophiles. Two versions of asymmetric Diels–Alder reactions are known; the first of these involves introduction of an auxiliary chiral fragment into the diene or dienophile molecule, while the other is based on the use of chiral catalysts.

2. ASYMMETRIC DIELS–ALDER REACTIONS WITH CHIRAL ADDENDS

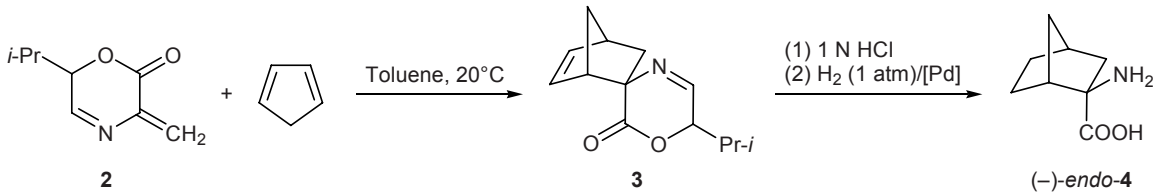
2.1. Noncatalytic Asymmetric Diels–Alder Reactions

Asymmetric Diels–Alder reaction was described for the first time in 1948 by Korolev and Mur [25] who studied reactions of substituted 1,3-butadienes with di-(–)-menthyl fumarate or maleic anhydride. Auxiliary chiral substituent was introduced into both dienophile and diene molecule. The noncatalytic reactions were carried out in xylene at 140°C; after removal of the chiral fragment, the products were isolated with an optical yield (*enantiomeric excess*, *ee*) of 0.6–6.8%.

The asymmetric Diels–Alder reaction of di-(–)-menthyl fumarate with buta-1,3-diene was found to be strongly affected by ultrahigh pressure. The reaction at 70°C under atmospheric pressure takes 24 h and gives 98% of optically inactive product, while increased pressure favored formation of the positively rotating enantiomer. At 2500 MPa, the *ee* value was 2.9%, and at 5000 MPa, 4.7% [26].

First studies in the series of uncatalyzed asymmetric Diels–Alder reactions showed relatively low stereo- and enantioselectivity. Therefore, asymmetric Diels–Alder reactions at fairly high temperatures without a catalyst have attracted little interest. During the past decade, only a few publications were concerned

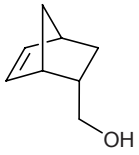
Scheme 1.



2 **3** (–)-*endo*-**4**

with uncatalyzed asymmetric Diels–Alder reactions. 2-Aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acid (**4**) was synthesized by reaction of cyclopentadiene with chiral dienophiles in toluene at room temperature [27]. After hydrolysis and hydrogenation of **3**, the *endo* isomer of bicyclic amino acid **4** was isolated in 55% yield with *ee* 51% (Scheme 1).

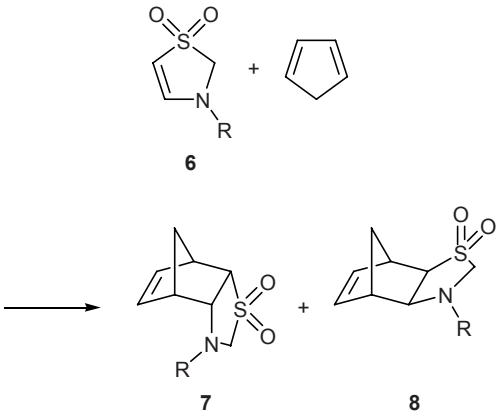
Asymmetric Diels–Alder reaction of α-sulfinylacrylate with cyclopentadiene at 0°C gave the corresponding adduct in a high chemical yield (81–94%) but with low stereoselectivity and poor optical yield [28]. Nagatsuka et al. [29] studied asymmetric Diels–Alder reactions of cyclopentadiene with chiral acrylates using natural carbohydrates, 6-deoxyglucopyranosides, as chiral reagents. After removal of the chiral fragment, (*S*)-enantiomer **5** was obtained with a low stereoselectivity (*endo*:*exo* = 79:21, *ee* = 13%).



(2*S*)-(–)-**5**

Noncatalytic asymmetric Diels–Alder reactions of cyclopentadiene with α,β-unsaturated sultams **6** were studied by Ho et al. [30] (Scheme 2). The reactions were carried out at 110°C (4 days), and the effect of the substituent R on the enantio- and stereoselectivity was examined; adducts **7** and **8** were formed in 80% yield (*ee* = 25%, *endo*-**7**:*exo*-**8** = 7:3).

Scheme 2.



Optically active polybrominated norbornene derivatives were synthesized for the first time by uncatalyzed Diels–Alder reaction of polybromocyclopentadienes with (–)-menthyl acrylate in organic solvents (chlorobenzene, benzyl chloride, toluene) at 100–160°C (reaction time 6–10 h) [31]. Stereospecific cycloaddition reactions gave the corresponding adducts in up to 84% yield, *ee* being 17%. The same authors also described the synthesis of enantiomerically pure polybrominated norbornenecarboxylic acids and their derivatives by optical resolution of the racemic mixtures through diastereoisomeric salts with *l*-ephedrine.

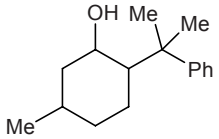
Thus analysis of published data shows that uncatalyzed asymmetric Diels–Alder reactions do not ensure high asymmetric induction and stereoselectivity.

2.2. Asymmetric Diels–Alder Reactions in the Presence of Achiral Catalysts

The first example of catalytic asymmetric Diels–Alder reaction, the reaction of buta-1,3-diene with di-(–)-menthyl fumarate [32], showed that its enantioselectivity increases in the presence of Lewis acids. The best results were obtained in toluene in the presence of $TiCl_4$: the corresponding (*R*,*R*)-stereoisomer was formed with an *ee* value of 78%. The reaction occurred at an appreciable rate at room temperature and even at –70°C.

In the past decade, asymmetric Diels–Alder reactions of cyclopentadiene in the presence of achiral catalysts have attracted researcher's attention, and chiral compounds have been synthesized with a high optical purity. Cycloaddition of chiral acrylates to cyclopentadiene has become a common model for studying asymmetric induction in Diels–Alder reactions, though incomplete *endo*-selectivity hinders analysis of the results. The stereoselectivity is usually estimated by analyzing mixtures of alcohols obtained after removal of auxiliary chiral fragment via reduction with $LiAlH_4$. A high enantioselectivity (*ee* = 80%) was

attained with the use of 3,3-dimethylbutan-2-ol as chiral alcohol [33]. (–)-8-Phenylmenthol (**9**) ensured even higher efficiency (*ee* = 99%) [34, 35].



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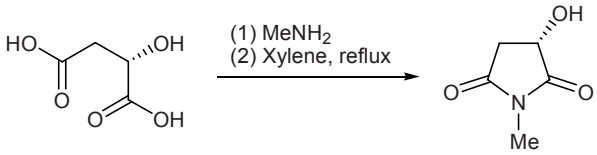
N-Substituted hydroxysuccinimide **10** obtained from (*S*)-(–)-malic acid (Scheme 3) was used as chiral reagent to synthesize a series of chiral dienophiles **10a**–**10c**. Compounds **10a**–**10c** reacted with cyclopentadiene at –78 to 0°C in the presence of $TiCl_4$ to give adducts **11a**–**11d**, and hydrolysis of the latter afforded carboxylic acids **12a**–**12d** in 70–86% yield (*ee* = 98%) [36] (Scheme 4).

Scheme 3.



(*S*)-Malic acid **10**

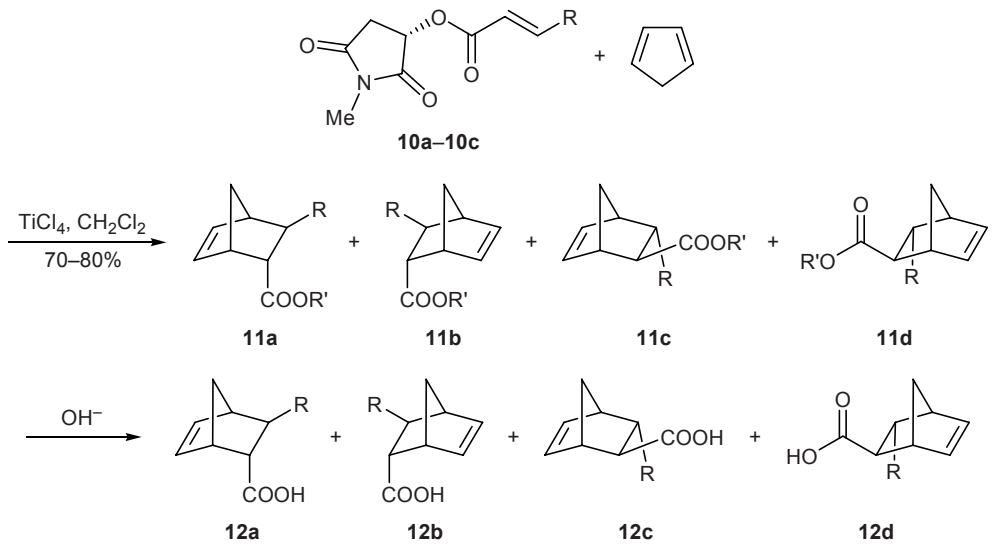
Chiral dienophiles, (*E*)-2-cyano-3-phenylprop-2-enoic acid esters **18**, were synthesized from chiral alcohols **13**–**17**, and the subsequent [4+2]-cycloaddition to cyclopentadiene in the presence of $TiCl_4$, $AlCl_3$, or $AlCl_2OEt$ at –78 to 20°C gave adducts **19** with an optical yield of up to 89% [37] (Scheme 5).

Nieman and Keay [38] synthesized new chiral auxiliaries for asymmetric Diels–Alder reactions, *cis*,*cis*-spiro[4.4]nonane-1,6-diol (**20**) and chiral acrylates **21**; their reactions with cyclopentadiene gave adducts **22** (*ee* = 97%; diastereoselectivity 98–99% with respect to the *endo* isomer; Scheme 6). Achiral Lewis acids, such as $BF_3 \cdot OEt_2$, $TiCl_4$, $SnCl_4$, $SbCl_5$, $MeAlCl_2$, and BCl_3, were used as catalysts. Esters **21** derived from spiro diol **20** were shown to be effective chiral reagents in catalytic asymmetric Diels–Alder reactions.

Nouguier et al. [39] reported on the effective synthesis of (2*S*)-bicyclo[2.2.1]hept-5-en-2-ylmethanol (**5**) in the presence of Lewis acids using fructose derivatives as chiral auxiliaries. Chiral alcohol **23** derived from D-fructose was converted into acrylate **24**, and asymmetric Diels–Alder reaction of the latter with cyclopentadiene in the presence of Lewis acid ($SnCl_4$, $EtAlCl_2$) gave adduct **25** which was reduced to norbornene **5** with (*S*) configuration of the chiral center (C^2) (Scheme 7). Table 1 contains the reaction conditions (catalyst, temperature, reaction time), product compositions, and optical yields.

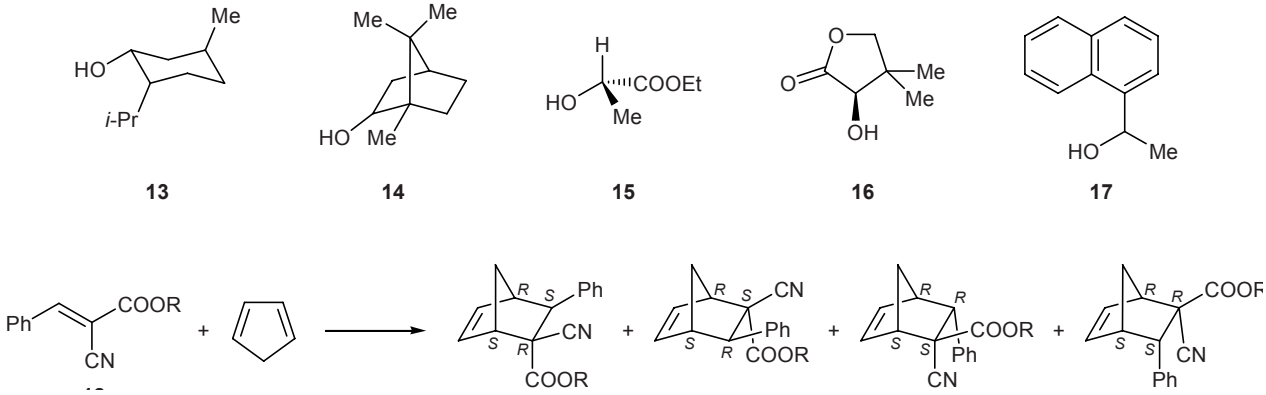
Asymmetric Diels–Alder reaction of benzyl (*S*)-2-(*p*-tolylsulfinyl)acrylates with cyclopentadiene in the presence of Lewis acids [$TiCl_4$, $ZnCl_2$, $ZnBr_2$, ZnI_2, $Eu(fod)_3$] at –70 to 20°C was studied in [40]. It was found that the asymmetric induction was relatively poor. In the presence of $Eu(fod)_3$ at –20°C, the optical yield of the corresponding norbornene derivative was 32%, while in the other cases it did not exceed 0.04–6.7%.

Scheme 4.



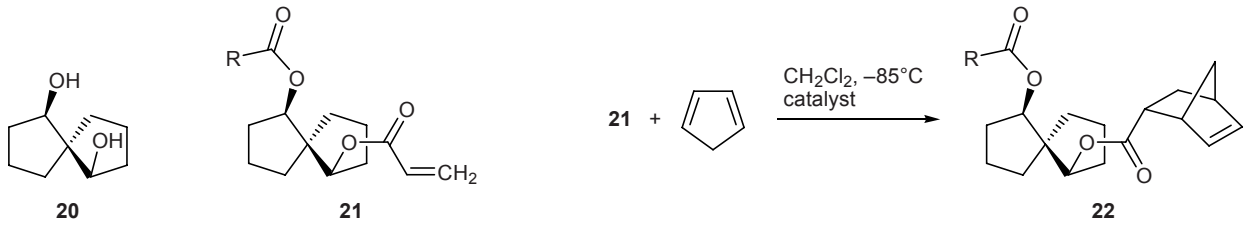
R = H, Me, Br; R′ = 1-methyl-2,5-dioxopyrrolidin-3-yl.

Scheme 5.



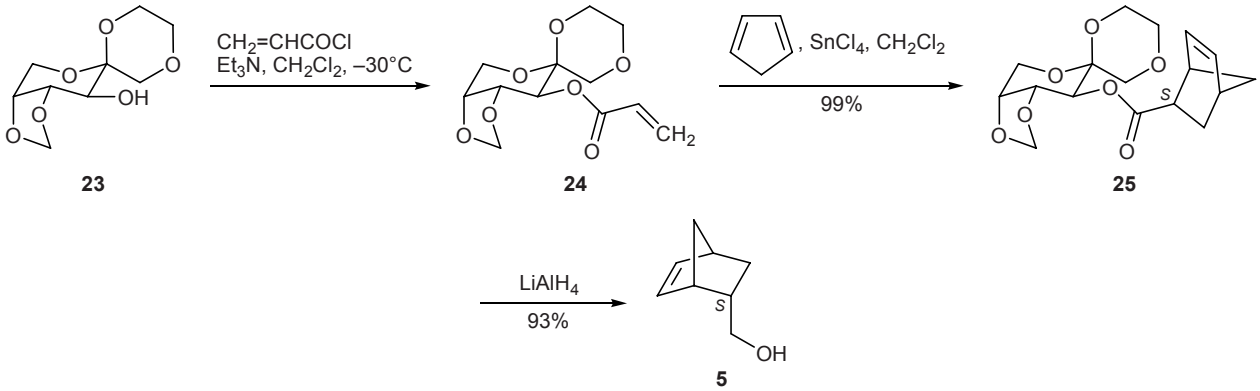
R = (**13**–**17**) – OH.

Scheme 6.

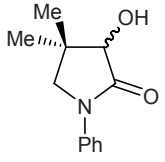


R = *t*-Bu, Ph, 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$.

Scheme 7.



Camps et al. [41] were the first to use (*R*)- and (*S*)-3-hydroxy-4,4-dimethyl-1-phenylpyrrolidin-2-ones **26** as highly efficient chiral auxiliaries. Chiral esters obtained from alcohol **26** and acrylic, methacrylic, *trans*-crotonic, and *trans*-cinnamic acids reacted with cyclopentadiene in different organic solvents in the presence of $TiCl_4$. In some cases, the asymmetric induction reached 96–97%. For example, (1*R*,2*R*,4*R*)-acid **11** was obtained with an optical yield of 97%

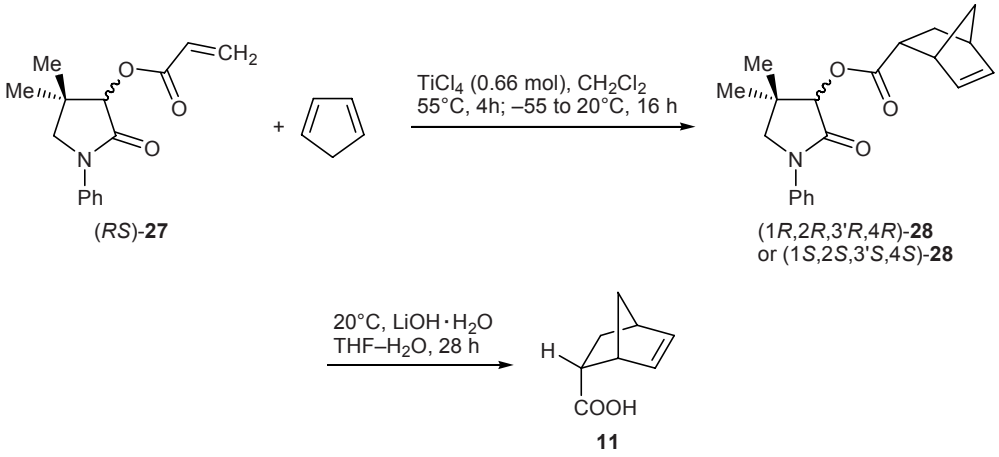


(*RS*)-**26**

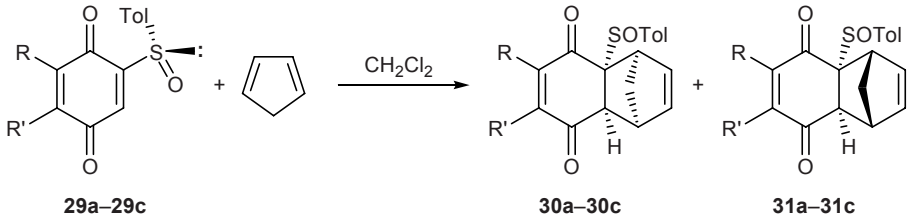
Table 1. Diels–Alder reaction of cyclopentadiene with acrylate **24**

Lewis acid	Time, min	Temperature, °C	Isomer composition, %			Yield, %
			(2*S*)-*endo*	(2*R*)-*endo*	(2*R*+2*S*)-*exo*	
Zn_2Cl_4	40	0	>99	<1	2	>99
$EtAlCl_2$	40	0	75	25	5	>99
$EtAlCl_2$	360	–78	90	10	1	96

Scheme 8.



Scheme 9.



R = H, R′ = Me (**a**), *i*-Pr (**b**); R = MeO, R′ = *i*-Pr (**c**).

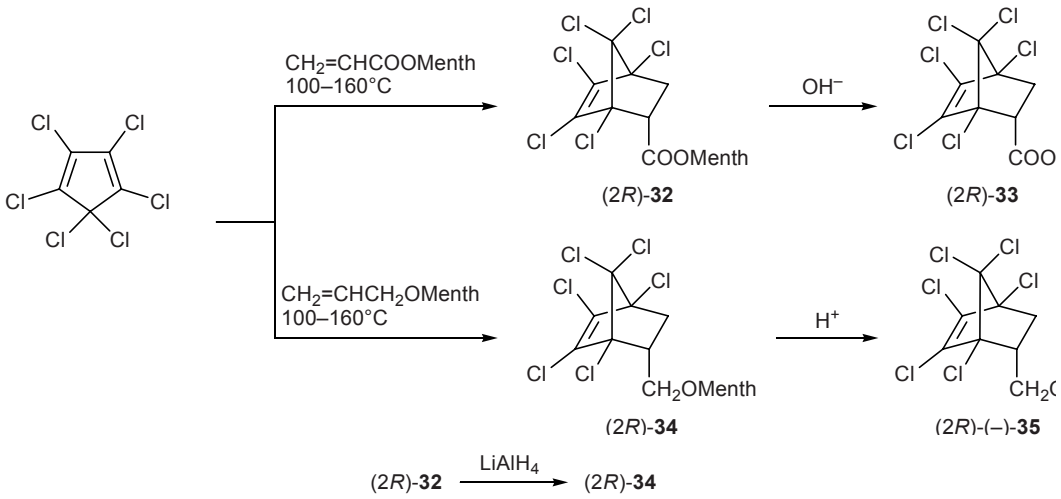
using chiral (*R*)-acrylate **27** as dienophile, while the (*S*)-enantiomer of **27** gave rise to (1*S*,2*S*,4*S*)-acid **11** with an optical yield of 95% (Scheme 8).

Carreno et al. [42] studied asymmetric Diels–Alder reactions of cyclopentadiene with 5- and 5,6-substituted (*S*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinones **29a**–**29c** in the presence of $ZnBr_2$ and $BF_3 \cdot OEt_2$ in methylene chloride (Scheme 9). The data in Table 2 show that the stereo- and enantioselectivity of the cycloaddition depend on the temperature and nature of substit-

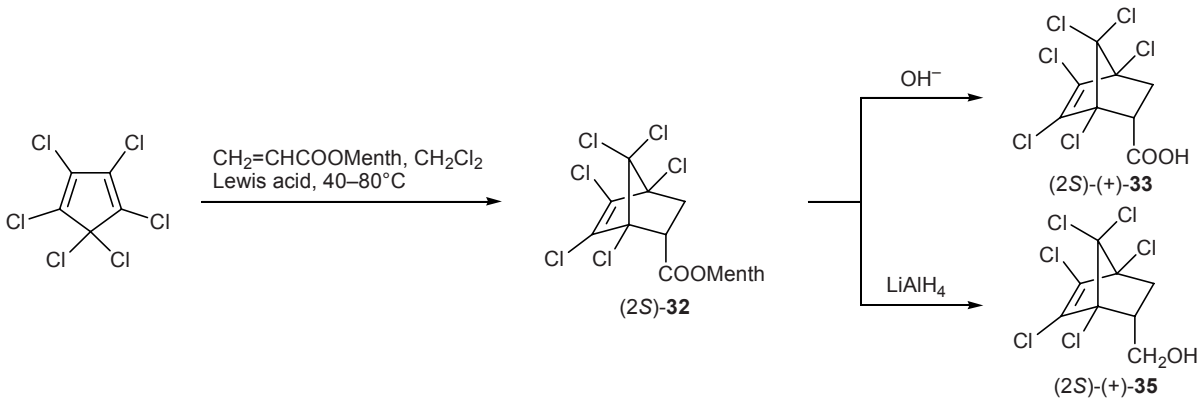
Table 2. Asymmetric Diels–Alder reaction of *p*-tolylsulfinyl-substituted benzoquinones **29a**–**29c** with cyclopentadiene in methylene chloride

Quinone	Temperature, °C	Lewis acid	Time, h	Yield, %	Product ratio **30**:**31**	*ee*, %
29a	–20	–	48	63	>97:<3	>94
29a	–78	–	168	69	96:4	92
29a	–20	$BF_3 \cdot OEt_2$	0.5	53	96:4	92
29a	–20	$ZnBr_2$	0.3	80	9:91	82
29a	–20	$ZnBr_2$	0.3	–	4:96	92
29b	–20	–	15	53	96:4	92
29b	–78	–	45	72	>95:<5	>90
29b	–78	$BF_3 \cdot OEt_2$	0.75	76	98:2	96
29b	–78	$ZnBr_2$	1	70	<3:>97	>94
29c	–20	–	22	73	89:11	78
29c	–78	–	72	65	89:11	78
29c	–20	$BF_3 \cdot OEt_2$	1	50	31:69	38
29c	–20	$ZnBr_2$	1	86	10:90	80
29c	–20	$ZnBr_2$	1	72	<3/>97	>97

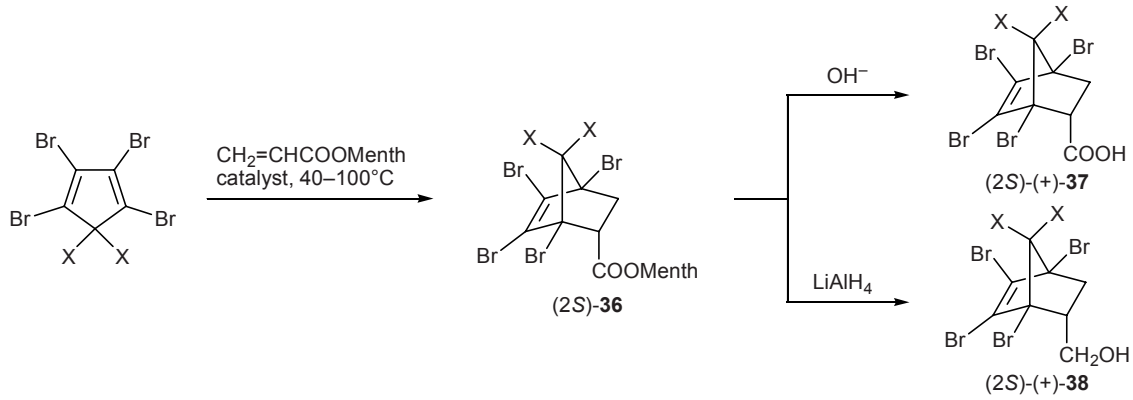
Scheme 10.



Scheme 11.



Scheme 12.



X = Br, MeO.

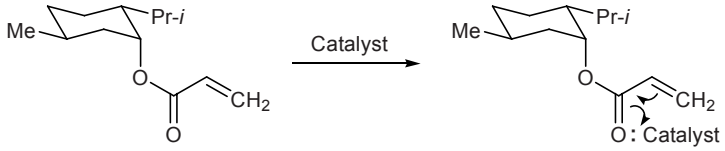
uent in the dienophile. Asymmetric Diels–Alder reactions of cyclopentadiene with (*S*,*S*)-2-(2-methoxynaphthalen-1-ylsulfinyl)-1,4-benzoquinone, 2-(*p*-methoxyphenylsulfinyl)-1,4-benzoquinone, and 2-(*p*-nitrophenyl)-1,4-benzoquinone in the presence of $Eu(fod)_3$, $BF_3 \cdot OEt_2$, and $ZnBr_2$ in CH_2Cl_2 were reported in [43]. Thermal Diels–Alder reactions of (–)-menthyl acrylate and allyl (–)-menthyl ether with perchlorocyclopentadiene at 100–160°C resulted in the formation of norbornene derivatives (*R*)-(–)-**33** and (*R*)-(–)-**35**, respec-

tively (*ee* = 15%) [44] (Scheme 10). The use of achiral Lewis acids ($Et_2O \cdot BF_3$, $AlCl_3$, BBr_3, $SnCl_4$) as catalysts ensured increase in the optical yield by a factor of 2.8 (Scheme 11), the stereoselectivity of the process remaining unchanged: (*S*)-*endo* isomers **33** and **35** were formed exclusively (the structures of **33** and **35** shown in Schemes 10 and 11 do not reflect differences between enantiomers).

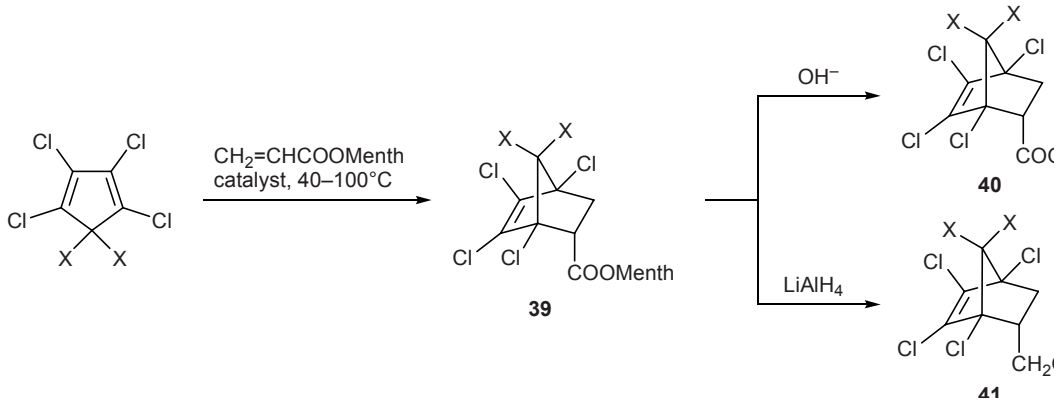
Likewise, asymmetric cycloaddition of polybromocyclopentadienes to (–)-menthyl acrylate in the presence of achiral Lewis acids ($AlCl_3 \cdot OEt_2$, $BF_3 \cdot OEt_2$, BBr_3, and $SnCl_4$) gave chiral polybromonorbornenes [45] (Scheme 12). The effects of various factors on the enantiomeric purity, isomeric composition, and yield of the products were studied. Unlike uncatalyzed reaction [31], the catalytic process at 40–100°C provides exclusively (2*R*)-*endo*-(+)-polybromonorbornene derivatives. The maximal optical yield (38–45%) was obtained at 40°C. The catalytic action of Lewis acids is rationalized in terms of formation of a complex with dienophile (Scheme 13).

The synthesis of optically active tetrachloronorbornenes by [4+2]-cycloaddition of tetrachlorocyclopentadiene to chiral dienophile, (–)-menthyl acrylate in the presence of achiral Lewis acids ($AlCl_3$, $AlCl_3 \cdot OEt_2$, $TiCl_4$, BBr_3, $SnCl_4$, $BBr_3 \cdot OEt_2$) in various organic solvents (CH_2Cl_2, C_6H_6, $C_6H_5CH_3$, C_6H_5Cl) at 40–100°C was studied in [46] (Scheme 14). Effects of

Scheme 13.

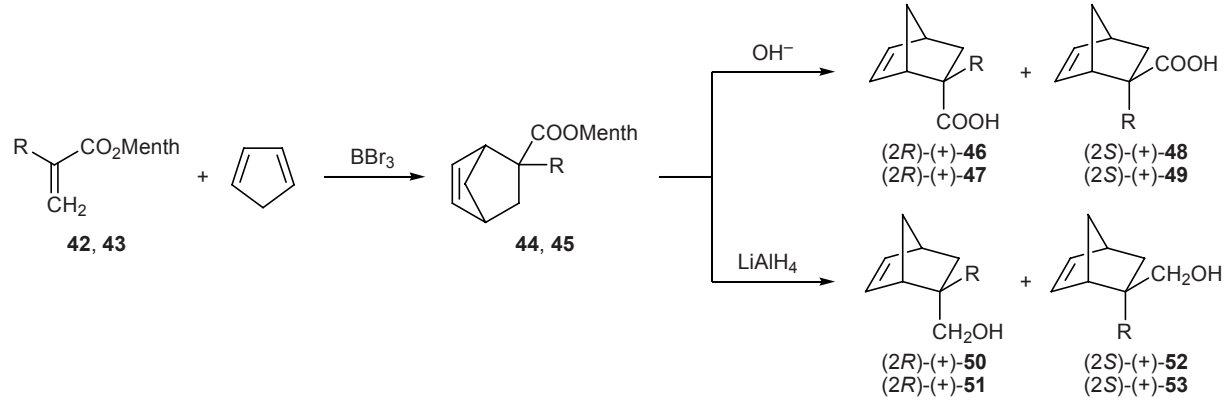


Scheme 14.



X = H, MeO.

Scheme 15.



R = H, Me.

Table 3. Cycloaddition of menthyl acrylate and menthyl methacrylate to cyclopentadiene in the presence of BBr_3

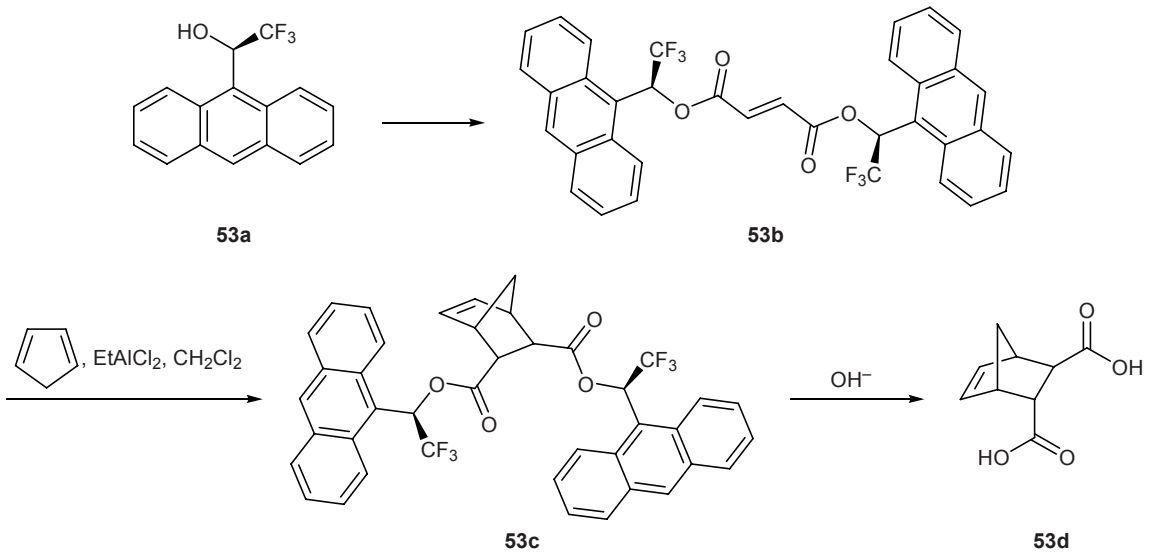
Dienophile	*T*, °C	Solvent	Molar ratio BBr_3–**42** (**43**)	Yield of **44**/**45**, %	*endo*/*exo*-Isomer ratio **44** (**45**), %	*ee*, %				$[\alpha]_D^{20}$ (EtOH)			
						46, **47**	**48**, **49**	**50**, **51**	**52**, **53**	**46**, **47**	**48**, **49**	**50**, **51**	**52**, **53**
42	20	CH_2Cl_2	0.25	90	86.4:13.6	21	20	30	24	+30.28	+29.42	+22.98	+22.45
42	–10	CH_2Cl_2	0.25	81	91.7:8.3	32	30	49	–	+46.14	+45.13	+37.5	–
42	–40	CH_2Cl_2	0.25	73	98.7:5.3	40	31	53	–	+57.68	+55.3	+40.6	–
42	–70	CH_2Cl_2	0.25	62	96.5:3.5	69	–	80	–	+99.5	–	+88.31	–
42	–78	CH_2Cl_2	0.25	60	98.4:1.6	74	–	84	–	+104.470	–	+94.36	–
42	20	C_6H_6	0.25	91	87.3:12.7	19	19	28	27	+27.4	+24.25	+22.20	+20.45
42	20	C_6H_6	0.5	94	89.2:10.8	21	19	27	25	+27.10	+22.25	+22.19	+19.28
42	20	C_6H_6	0.75	96	80.3:9.7	27	–	29	–	+30.28	–	+22.93	–
42	20	C_6H_5Cl	0.25	91	87.2:13.8	20	21	30	31	+29.25	+28.76	+21.97	+20.17
43	20	CH_2Cl_2	0.25	82	10:90	19	18	28	27	+20.12	+19.13	+19.33	+12.63
43	–10	CH_2Cl_2	0.25	63	11:89	28	27	47	45	+42.63	+41.09	+21.61	+20.59
43	–40	CH_2Cl_2	0.25	59	16:84	37	36	51	50	+49.16	+43.45	+23.45	+22.99
43	–70	CH_2Cl_2	0.25	54	13:87	57	56	66	65	+60.33	+56.61	+30.35	+34.19
43	–78	CH_2Cl_2	0.25	52	15:85	65	64	70	67	+68.87	+61.54	+32.19	+30.55

various factors on the chemical and optical yields of compounds **39**–**41**, as well as on the reaction stereoselectivity, were examined; the (+)-adducts were found to have (2*R*) configuration. The reaction at 40°C in methylene chloride in the presence of BBr_3 gave the corresponding adducts in 39% chemical yield and 40% optical yield.

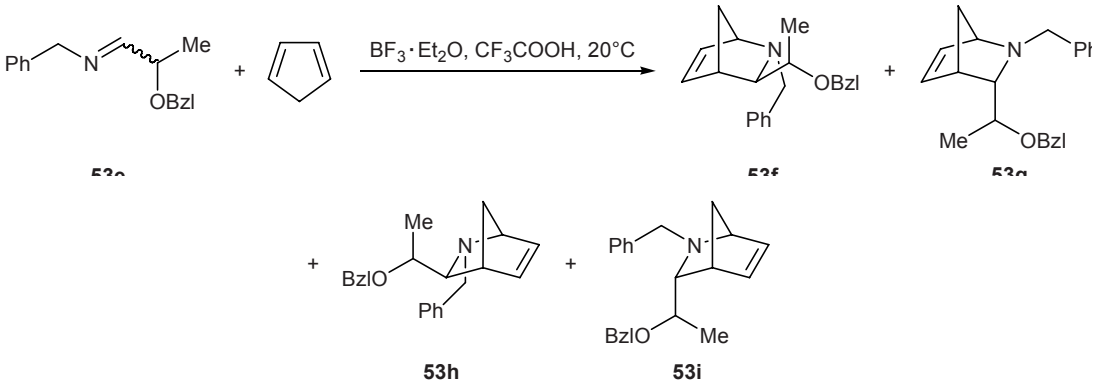
Asymmetric synthesis of bicyclo[2.2.1]hept-5-ene derivatives **46**–**53** by cycloaddition of (–)-menthyl acrylate and (–)-menthyl methacrylate to cyclopentadiene in the presence of BBr_3 was described in [47] (Scheme 15). The data on isomeric composition, yields, and enantiomeric purity of the products are collected in Table 3. The stereo- and enantioselectivity depend on the temperature and substituent R in the dienophile. The reaction in methylene chloride at –78°C was characterized by 98.4% stereoselectivity, and the adducts had an optical purity of 84%.

Asymmetric synthesis of chiral norbornenes from di-(–)-menthyl fumarate and cyclopentadiene in the

Scheme 16.

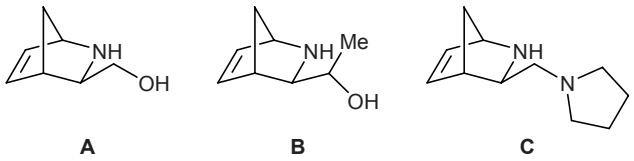


Scheme 17.



53h **53i**

presence of BBr_3 and $BBr_3 \cdot OEt_2$ was studied in [48–50]. Optically active norbornenes were thus obtained with high chemical (95%) and optical yields (91%). A new chiral reagent, 2,2,2-trifluoro-1-(anthracen-9-yl)ethanol (**53a**), was synthesized [50], and the corresponding fumaric acid diester **53b** was used as dienophile in the Diels–Alder reaction with cyclopentadiene at –78°C in the presence of $EtAlCl_2$ to obtain dicarboxylic acid **53d** in 99% yield with an *ee* value of 82%. Diels–Alder reactions of cyclopentadiene provide a promising method for stereoselective synthesis of nitrogen-containing bicyclic compounds **A**–**C** which can be used as ligands in chiral metal complex catalysts for asymmetric hydrogenation of prochiral ketones [50].



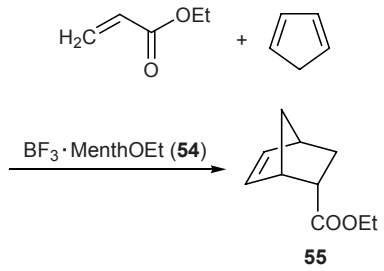
A **B** **C**

The reaction of cyclopentadiene with Schiff base **53e**, catalyzed by $BF_3 \cdot Et_2O/CF_3COOH$, leads to the formation of four diastereoisomeric adducts **53f**–**53i** which can be readily separated by chromatography on silica gel [50] (Scheme 17). The yield of **53f**–**53i** is 70%, and the *endo*/*exo* stereoselectivity is 55–45%; the optical yield reaches 60%.

3. ASYMMETRIC DIELS–ALDER REACTIONS IN THE PRESENCE OF CHIRAL CATALYSTS

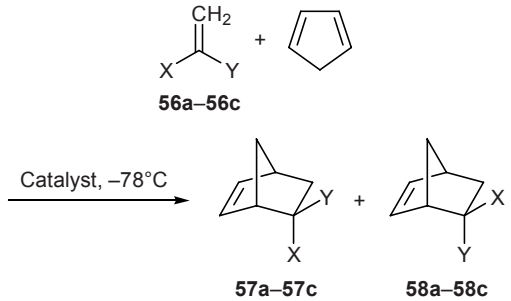
The first example of asymmetric Diels–Alder reaction with the use of a chiral catalyst [0.01 mol of $BF_3 \cdot$MenthOEt (**54**)] was reported in 1976 [51]: the reaction of cyclopentadiene with ethyl acrylate was performed in methylene chloride at 30°C (reaction time 2 h) (Scheme 18). Although its enantioselectivity was poor (*ee* = 3.3%), this new approach was successfully developed [52, 53]. Chiral metal complex catalysts (Lewis acids) were synthesized by reaction of $EtAlCl_2$ with optically active alcohols, such as (–)-menthol and (+)-borneol, and reactions of cyclopentadiene with dienophiles **56a**–**56c** in the presence of these catalysts gave the corresponding adducts **57a**–**57c** and **58a**–**58c** with a chemical yield of up to 84% and *ee* of up to 72%.

Scheme 18.



55

Scheme 19.



56a–56c **57a–57c** **58a–58c**

X = MeOCO, Y = H (**a**); X = OCH, Y = H (**b**); X = Me, Y = OCH (**c**).

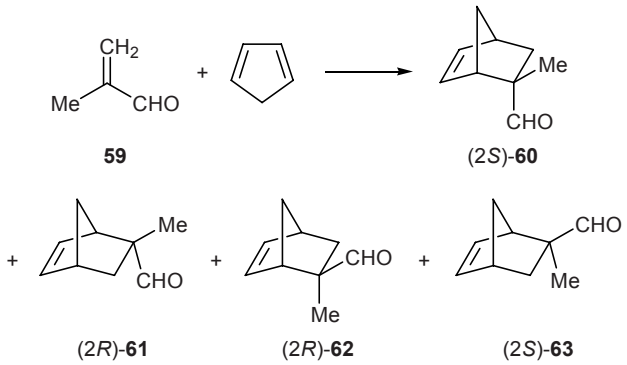
The main requirement imposed on chiral catalysts for asymmetric Diels–Alder reactions is that they should contain fragments of optically active natural

compounds, such as menthol, derivatives of camphor, amino acids, and various diols and polyols capable of forming complexes with various metals [54].

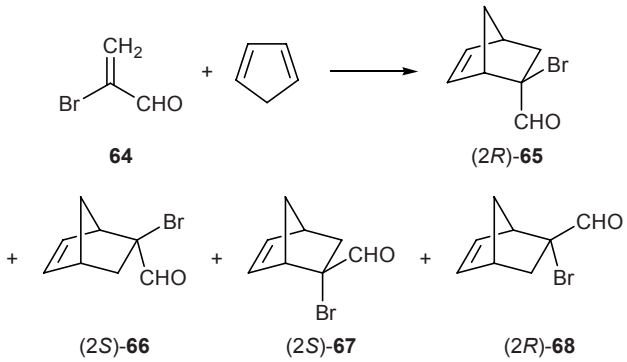
3.1. Chiral Aluminum-Containing Catalysts

Hashimoto et al. [52, 53] were the first to use aluminum-containing chiral catalysts in asymmetric Diels–Alder reactions on the basis of cyclopentadiene. A number of norbornene derivatives were synthesized in high chemical and optical yields. Asymmetric Diels–Alder reactions of cyclopentadiene with methacrolein (**59**) and 2-bromoacrolein (**64**) in the presence of Al-containing chiral catalysts were studied in [55] (Schemes 20, 21).

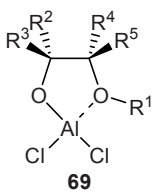
Scheme 20.



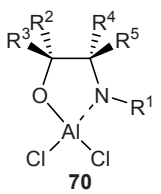
Scheme 21.



The catalysts were synthesized by treatment of (*S*)-tyrosine, (*S*)-proline, or (–)-menthol applied onto silica gel with a solution of $EtAlCl_2$. The formation of complexes **69** and **70** was assumed. The effect of the reaction conditions on the chemical and optical yields and isomeric composition of compounds **60**–**63** and **65**–**68** was studied. The optical yield reached 31% in the presence of silica gel-supported (–)-menthol–Al–Lewis acid.



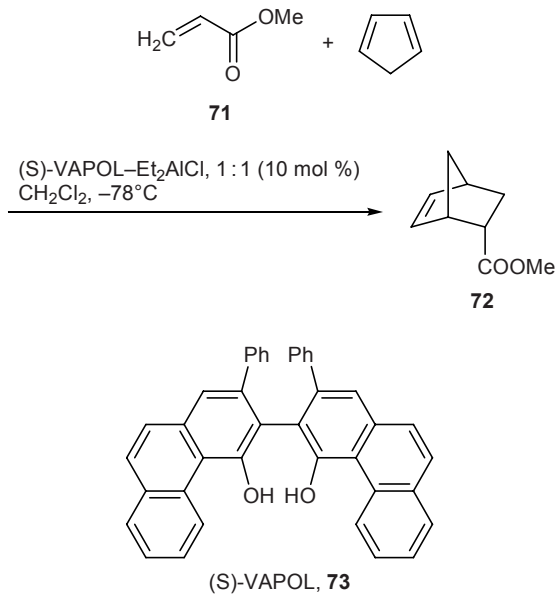
69



70

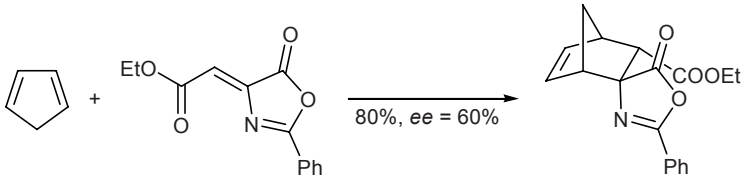
Naraku et al. [56] synthesized a new chiral catalyst from (–)-menthol derivative **9** and $EtAlCl_2$ and used it in the cycloaddition of cyclopentadiene to 3-crotonoyl-1,3-oxazolidin-2-one in various solvents (methylene chloride, 1,2-dichloroethane, toluene, diethyl ether, dioxane) to obtain the corresponding adduct with an *exo*/*endo* stereoselectivity of 96:4 and *ee* value of up to 66%. Heller et al. [57] described asymmetric cycloaddition of cyclopentadiene to methyl acrylate (**71**) in the presence of a chiral aluminum complex based on (*S*)-VAPOL (**73**) and Et_2AlCl (Scheme 22). The reaction in methylene chloride at –78°C gave adduct **72** in 60% yield with 99% *endo*-selectivity and 98.5% optical yield.

Scheme 22.

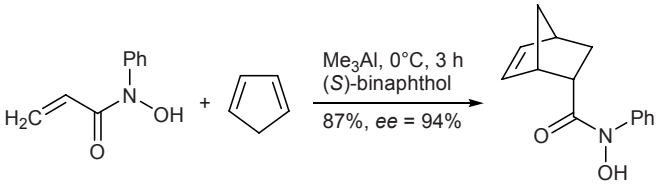


Clerici et al. [58] reported on the cycloaddition of ethyl (5-oxo-2-phenyl-4,5-dihydro-1,3-oxazol-4-ylidene)acetate (**74**) to cyclopentadiene in the presence of aluminum complex with (*R*)-(–)-1,1′-binaphthalene-2,2′-diol in methylene chloride at –20 to 40°C (2–5 h), which resulted in the formation of a mixture of *endo* and *exo* isomers **75** at a ratio of 70:30 (Scheme 23). Enantioselective cycloaddition of cyclopentadiene to *N*-hydroxy-*N*-phenylacrylamide (**76**) in the presence of (*S*)-binaphthol and Me_3Al was studied in [59]

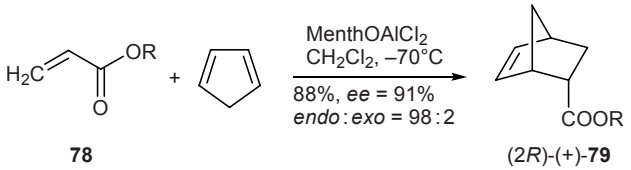
Scheme 23.



Scheme 24.



Scheme 25.

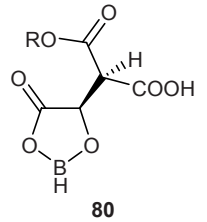


R = Pr, Bu, *i*-Bu.

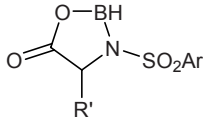
(Scheme 24). Asymmetric Diels–Alder reactions of cyclopentadiene with alkyl acrylates **78** in the presence of $MenthOAlCl_2$ were described in [60] (Scheme 25).

3.2. Chiral Boron-Containing Catalysts

As noted in the preceding section, the first asymmetric Diels–Alder reaction in the presence of a chiral catalyst [51] was performed using boron-containing compound. Later on, numerous studies were concerned with asymmetric Diels–Alder reactions catalyzed by chiral boron compounds. Various boron-containing catalysts with chiral ligands were successfully used in the recent years. It was found that the catalytic efficiency depends on the structure and electronic properties of the ligands. New boron compounds **80** and **81** [61] were used to catalyze asymmetric Diels–Alder reactions of cyclopentadiene with acrolein to obtain unsaturated aldehydes **82a** and **82b** (Scheme 26).

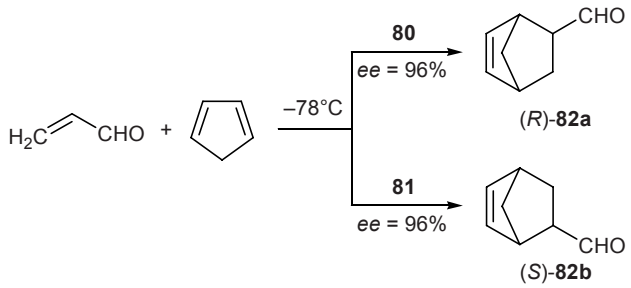


80



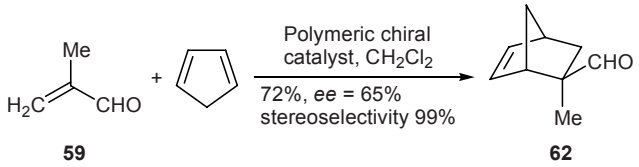
81

Scheme 26.



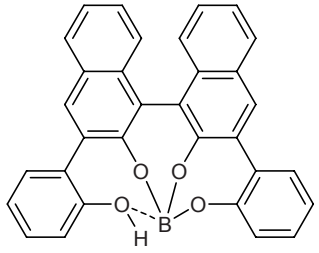
Polymeric materials obtained by copolymerization of chiral monomers containing amino alcohol, diol, and *N*-sulfonyl amino acid fragments were treated with BH_3 and BH_2Br and used as catalysts in the reaction of cyclopentadiene with methacrolein [62] (Scheme 27). Asymmetric Diels–Alder reactions of methacrolein with cyclopentadiene in the presence of boron-containing chiral catalysts based on prolinol, quinidine, and cinchonidine were studied in [63, 64]. The yield of adducts attained 90%, the stereoselectivity was 99%, and the optical yield ranged from 69 to 97%.

Scheme 27.

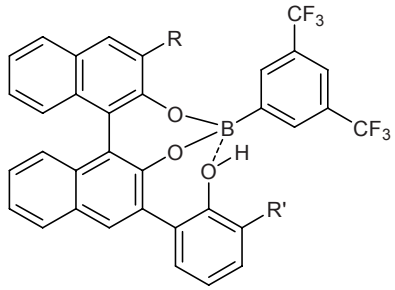


59 **62**

Ishihara et al. [65] proposed chiral boron-containing catalysts **83a**–**83e** for asymmetric Diels–Alder reactions; these compounds constitute a new class of catalysts that are a combination of Brønsted and Lewis acids.



83a

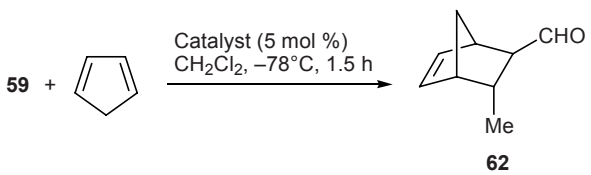


83b–83e

R = H, R′ = Ph (**b**), Me (**c**), H (**d**); R = Ph, R′ = H (**e**).

Catalysts **83a**–**83e** were used in a model Diels–Alder reaction of cyclopentadiene with methacrolein; they ensured synthesis of adduct **62** with a chemical yield of 97% and an optical yield of 99% [(2*S*)-configuration; Scheme 28].

Scheme 28.

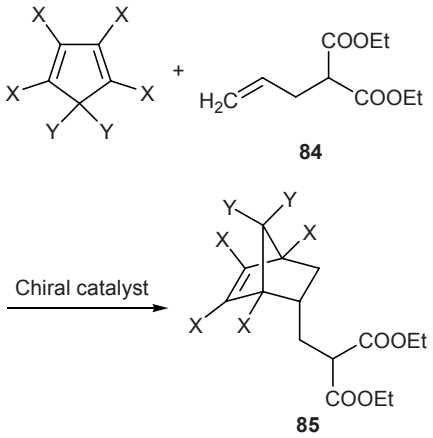


62

New chiral catalysts were synthesized from biarenediols and bromoborane–dimethyl sulfide complex ($BH_2Br \cdot Me_2S$) and were used in asymmetric Diels–Alder reaction of methacrolein with cyclopentadiene [66]. The synthesis of new boron-containing Brønsted acid-assisted chiral Lewis acid (BLA) catalysts (optically active 2-dichloroboryl-1,1′-binaphtholes) for enantioselective [4+2]-cycloaddition of α-unsubstituted and α-substituted α,β-unsaturated aldehydes to cyclopentadiene was described in [67, 68].

Asymmetric induction in the [4+2]-cycloaddition of diethyl 2-allylmalonate to substituted cyclopentadiene in the temperature range from 60 to 160°C in the presence of chiral boron-containing Lewis acids ($BBr_3 \cdot$MenthOEt, $BF_3 \cdot$MenthOEt, BBr_2OMenth) was studied in [69]. The use of chiral catalysts ensured preparation of optically active diethyl 2-(bicyclo[2.2.1]-hept-5-en-2-ylmethyl)malonates **85** (Scheme 29).

Scheme 29.



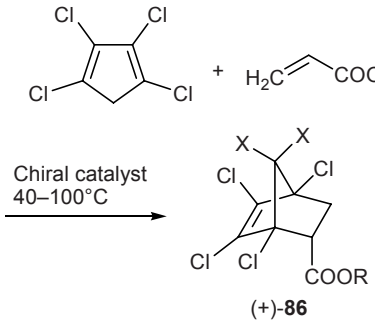
84 **85**

X = H, Cl; Y = H, Cl, MeO.

The effect of the reaction conditions on the yield, isomeric composition, and specific optical rotation $[\alpha]_D^{20}$ of adducts **85** was examined [70, 71]. Insofar as specific rotations of the pure enantiomers of **85** were unknown, the enantioselectivity of the reaction was judged by the specific rotation of the enantiomer mixture. Rise in the temperature resulted in increased overall yield, while the optical rotation decreased. The best results were obtained with the use of $BBr_3 \cdot$MenthOEt as catalyst. Asymmetric synthesis of polychloronorbornenes **86** from chlorinated cyclopentadienes was performed in the presence of chiral catalysts (BBr_2OMenth, $BBr_3 \cdot$MenthOEt, $BF_3 \cdot$MenthOEt) in toluene and methylene chloride at 40–100°C [70] (Scheme 30). The optical yields of compounds **86** depended on the temperature and reached 64–65% at 40°C, the chemical yield being 43–49%. Optically active brominated bicyclo[2.2.1]hept-5-ene-2-carboxylic acid derivatives were synthesized under analogous

conditions [71], and the results were consistent with those obtained in [70]. The use of chiral catalysts in Diels–Alder reactions with polybromocyclopentadienes makes it possible to reduce the reaction temperature from 160 to 100°C and raise the optical yield of the (+)-adduct from 15 to 68%, as compared to the uncatalyzed asymmetric synthesis [47].

Scheme 30.



(+)-**86**

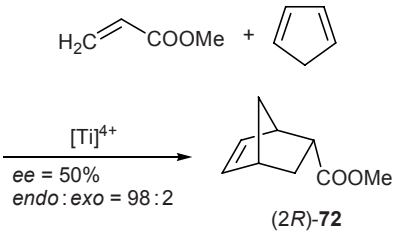
X = Cl, H, MeO; R = H, Me.

Asymmetric Diels–Alder reactions of alkyl norbornenecarboxylates with cyclopentadiene in the presence of chiral boron-containing catalysts [$BBr_3 \cdot$MenthOEt, BBr_2OMenth, $BBr(OMenth)_2$] were characterized by high stereo- and enantioselectivity [60, 72]. The reactions were carried out in the temperature range from 20 to –70°C using various organic solvents (methylene chloride, benzene, toluene, chlorobenzene). At –70°C in the presence of BBr_2OMenth the optical yield reached 91%, the overall yield was 89%, and the *endo*/*exo*-isomer ratio was 99:1. Asymmetric Diels–Alder reactions leading to chiral norbornenecarboxylic and norbornenedicarboxylic acid esters were studied in detail in [73–75] using boron-containing complexes with (–)-menthol as catalysts. A number of aliphatic and alicyclic mono- and diesters of the bicyclo[2.2.1]-heptene series were synthesized from cyclopentadiene and unsaturated aliphatic carboxylic acid esters, and the effect of the reaction conditions on the chemical and optical yields and stereoselectivity of the process was studied.

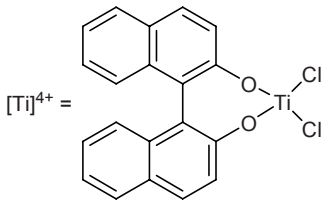
3.3. Chiral Titanium-Containing Catalyst

Titanium complexes as chiral catalysts for asymmetric Diels–Alder reaction were prepared for the first time on the basis of optically active diols [23]. Later on, a number of titanium-containing coordination compounds were synthesized from various optically active compounds and were used to catalyze asymmetric [4+2]-cycloadditions. For example, Carpius and Jureza [76] studied the addition of cyclopentadiene to acrylamide and crotonamide in the presence of a chiral catalyst prepared from optically active 1,1′-binaphthalene-2,2′-diol and $TiCl_4$. Asymmetric Diels–Alder reaction of cyclopentadiene with methyl acrylate in the presence of chiral titanium complex **87** gave adduct **72** with a high stereoselectivity (*endo*/*exo*-isomer ratio 98:2; *ee* = 50%) [77] (Scheme 31).

Scheme 31.



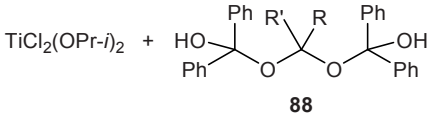
(2*R*)-**72**



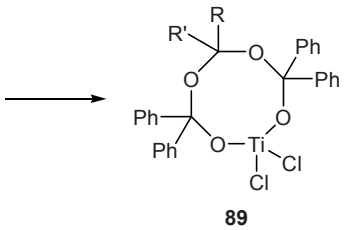
87

Narasaka et al. [78] synthesized chiral complexes **89** from diols **88** and dichlorodiisopropoxytitanium (Scheme 32) and used them in asymmetric Diels–Alder reactions. The yield of adducts **91a** and **91b** at –15°C was 93%, the *endo*/*exo*-isomer ratio (**91a**:**91b**) being 90:10 (*ee* = 92%; Scheme 33). Asymmetric Diels–Alder reaction of dimethyl fumarate (**92**) with cyclopentadiene, catalyzed by chiral titanium complex **93**, was reported in [79] (Scheme 34).

Scheme 32.



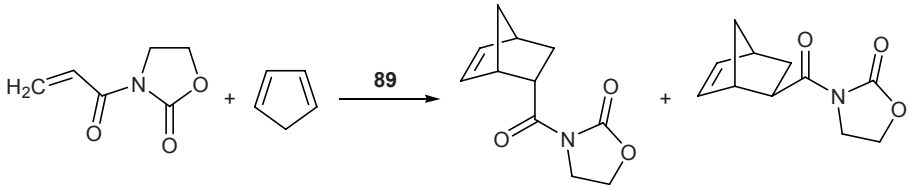
88



89

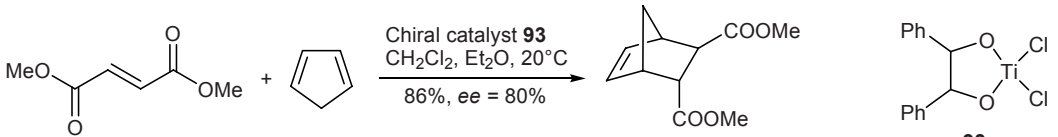
R = Me, Bu; R′ = Me, Bu, Ph.

Scheme 33.



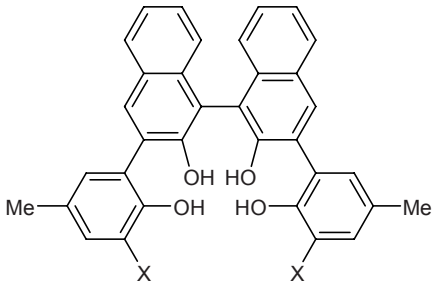
90 *endo*-**91a** *exo*-**91b**

Scheme 34.



92 **94** **93**

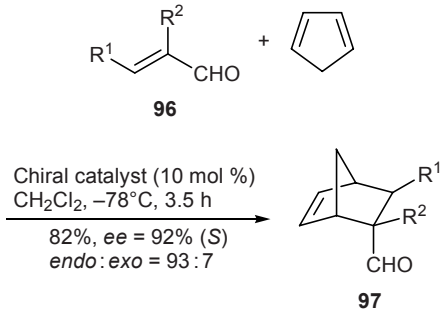
Titanium-containing catalysts for asymmetric Diels–Alder reactions were prepared from substituted 1,1′-binaphthalene-2,2′-diols **95** and $TiCl_4$ [80]; these complexes catalyzed the synthesis of new chiral bicyclic aldehydes **97** having (*S*) configuration with a high optical yield (Scheme 35).



(*R*)-**95**

R = Ph, Ph_3Si, $(i\text{-}Pr)_3Si$.

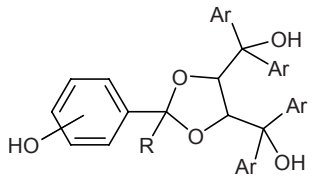
Scheme 35.



96 **97**

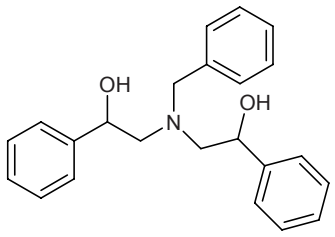
R^1, R^2 = H, Me.

Other titanium complexes were obtained from chiral 4,5-bis[diaryl(hydroxy)methyl]-1,3-dioxolan-2-ylphenols **98** and $Ti(OCHMe_2)_2Cl_2$ [81]. The complexes were applied to polymeric materials in different ways and used as heterogeneous catalysts in the asymmetric Diels–Alder reaction of 3-acryloyl-1,3-oxazolidin-2-one (**90**) with cyclopentadiene (see Scheme 33).



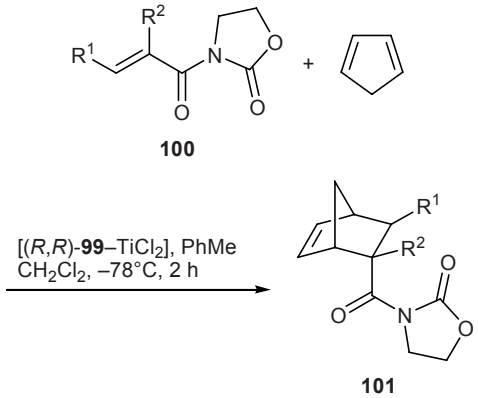
98

R = H, Me; Ar = Ph, 3,5-$Me_2C_6H_3$, 2-naphthyl, 4-$MeOC_6H_4$.



(1*R*,5*R*)-**99**

Scheme 36.



100 **101**

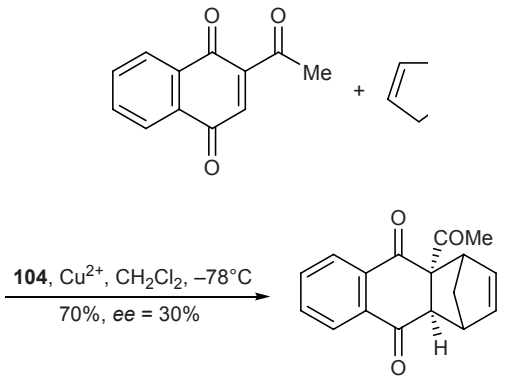
R^1 = Ph, Me, H; R^2 = H, Me, $HOCOCH_2$.

The optical yield of diastereoisomeric adducts **91a** and **91b** was 25%. Manickam and Sundararajan [82] synthesized a new chiral Ti(IV) complex with (1*R*,5*R*)-3-aza-3-benzyl-1,5-diphenylpentane-1,5-diol [(1*R*,5*R*)-**99**] which effectively catalyzed the cycloaddition of cyclopentadiene to oxazolidinones **100** to obtain adducts **101** (Scheme 36). The yield of compounds **101** attained 92%, the *endo*/*exo* stereoselectivity was 90:10, and the optical yield reached 65%.

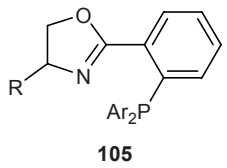
3.4. Chiral Copper(II)-Containing Complexes

Chiral copper(II) complexes have been used in asymmetric Diels–Alder reactions relatively recently. Ghosh et al. [83] studied reactions of substituted aliphatic esters derived from glyoxylic acid in the presence of chiral Cu(II) complexes with bis(dihydrooxazoles). The yield of the adducts was 76% (*ee* = 70%). Brimble and McEwan [84] reported on the asymmetric Diels–Alder reactions of substituted 1,4-naphthoquinones **102** with cyclopentadiene in the presence of chiral Cu(II) complexes based on compound **104** (Scheme 37).

Scheme 37.



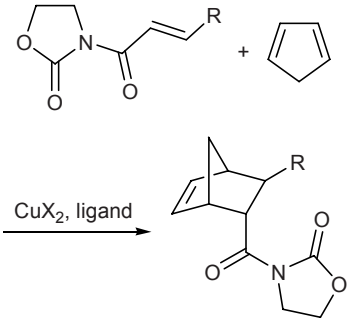
Chiral copper(II) complexes were also synthesized using 2-(2-diarylphosphinophenyl)-4,5-dihydrooxazoles **105** as ligands [85]. The reactions were carried out by adding dienophile and diene to a solution of the catalyst. The best results were obtained in CH_2Cl_2 or $EtNO_2$ at –78 to –20°C [yield of adducts **106** 84–95%, optical yield 87–97% (2*S*), *endo*/*exo*-isomer ratio 96:4; Scheme 38].



105

R = Me, *i*-Pr, *t*-Bu, Ph; Ar = 2,4,6-$Me_3C_6H_2$, naphthyl, anthryl.

Scheme 38.

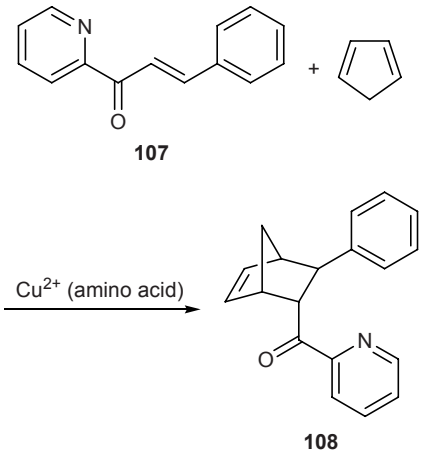


(*S*)-**106**

R = H, Me, Ph, EtOCO.

In the recent time, much attention is given to organic reactions occurring in aqueous medium. The first examples of asymmetric Diels–Alder reactions in the presence of chiral Cu(II) complexes in aqueous medium were described in [86, 87]. Here, copper(II) complexes were prepared using natural amino acids as chiral ligands [L-valine, L-leucine, L-phenylalanine, L-tyrosine, L-tryptophane, and N^{α}-methyl-L-tryptophane (L-abrine)]. The complexes were found to be effective catalysts in the reaction of 3-phenyl-1-(pyridin-2-yl)prop-2-en-1-one (**107**) with cyclopentadiene (Scheme 39). The best results were obtained using aromatic amino acids as ligands in the chiral copper(II)

Scheme 39.

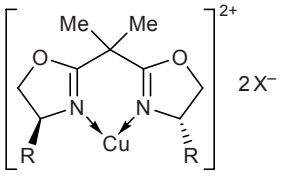


107

108

complexes. Adduct **108** with *ee* = 74% was isolated in the reaction performed in the presence of 10% of the catalyst at room temperature (48 h). The effect of the solvent on the optical yield was studied (Table 4).

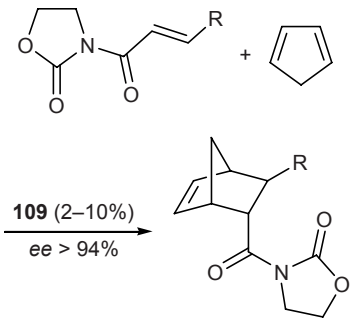
New chiral bis(dihydrooxazole) copper(II) complexes **109** successfully catalyzed the asymmetric Diels–Alder reactions of cyclopentadiene with 1-(oxazolidin-3-yl)prop-2-en-1-ones to give adducts **106b** with high stereo- and enantioselectivity [88–90] (Scheme 40).



109

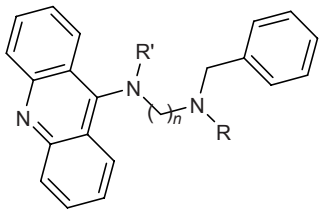
X = OTf, SbF_6.

Scheme 40.



106

Sibi et al. [91] obtained new data on enhancement of enantioselectivity by studying the mechanism of chirality transfer in the Diels–Alder reaction between unsaturated ketones and cyclopentadiene in the presence of 15 mol % of $Cu(OTf)_2$ and a ligand. High chemical yield (90%) and *endo*-selectivity (97%) were achieved, the enantiomeric excess being 86%. Roelfes and Feringa [92] reported on the Cu(II)-catalyzed reaction of cyclopentadiene with aza chalcone in the presence of DNA and nitrogen-containing ligands **110**



110

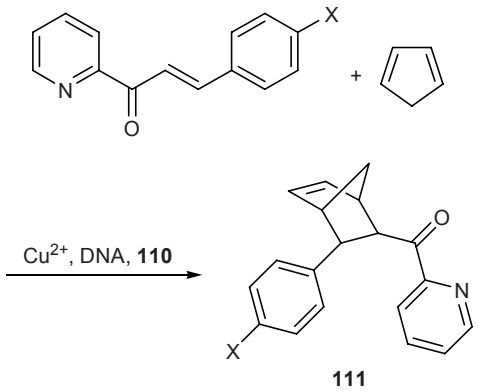
n = 2–5.

Table 4. Asymmetric Diels–Alder reaction of 3-phenyl-1-(pyridin-2-yl)prop-2-en-1-one (**107**) with cyclopentadiene in the presence of copper(II) complex with *N*-methyl-L-tryptophane at 0°C

Solvent	*ee*, %
Acetonitrile	17
THF	24
Ethanol	39
Chloroform	44
Water	74

(Scheme 41). The reaction was carried out at room temperature (reaction time 3 days), and adduct **111** was formed with a high stereoselectivity (*endo*:*exo* = 98:2). The *ee* value for the *endo* isomer attained 49%, and for the *exo* isomer, 90%. It was presumed that the enantioselectivity of this reaction is determined by chirality of the DNA double helix.

Scheme 41.

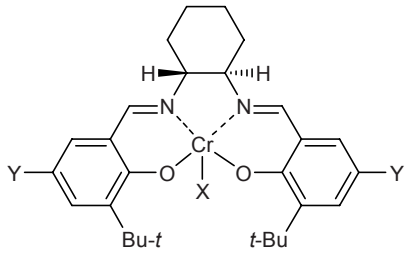


111

X = H, O_2N, MeO.

3.5. Chiral Chromium(III), Iron(III), and Lanthanide-Containing Complexes

In the recent years, various chiral complexes used previously in other asymmetric syntheses were tried as catalysts in asymmetric Diels–Alder reactions. Among these, chromium(III), iron(III), and lanthanide-containing complexes with chiral ligands occupy a specific place. Schaus et al. [93] described the synthesis of Cr(III) complexes **112** with Salen ligand, which were used as chiral catalysts in asymmetric [4+2]-cycloadditions involving cyclopentadiene. It was found that the reaction at –20°C in the presence of 0.2% of the catalyst gives 94% of the corresponding adduct with an optical yield of 84%.

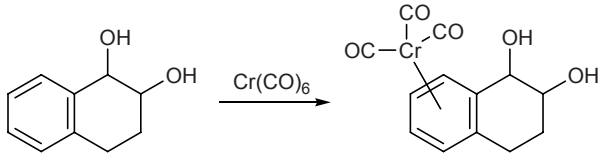


(*R*,*R*)-**112**

X = Cl, F, BF_4; Y = *t*-Bu, MeO.

Chromium(III) complex **113** was synthesized from $Cr(CO)_6$ and (1*R*,2*S*)-1,2,3,4-tetrahydronaphthalene-1,2-diol [94] (Scheme 42).

Scheme 42.



113

New chiral catalysts were obtained on the basis of complex **113** and such Lewis acids as $BH_3 \cdot THF$, $EtAlCl_2$, and Et_2AlCl; these catalysts ensured high optical yield in the [4+2]-cycloaddition of cyclopentadiene to methacrolein (Scheme 43).

Scheme 43.

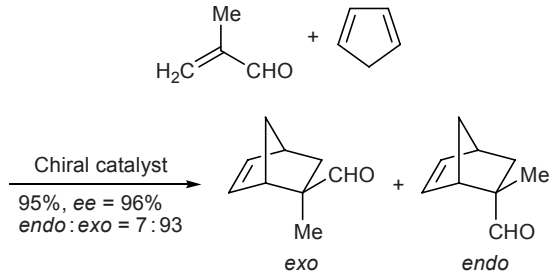
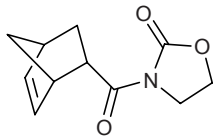


Table 5. Asymmetric Diels–Alder reaction of methacrolein with cyclopentadiene in the presence of rhodium complexes

Catalyst RhL, mol %, L = **114a–114c**	*T*, °C	Time, h	Yield, %	Isomer composition (*exo*/*endo*)	*ee*, %
114a (5)	20	24	62	94:6	29
114b (5)	20	48	10	90:10	2
114c (1)	20	24	45	94:6	52
114c (2)	20	24	57	94:6	53
114c (2)	0	72	81	95:5	68

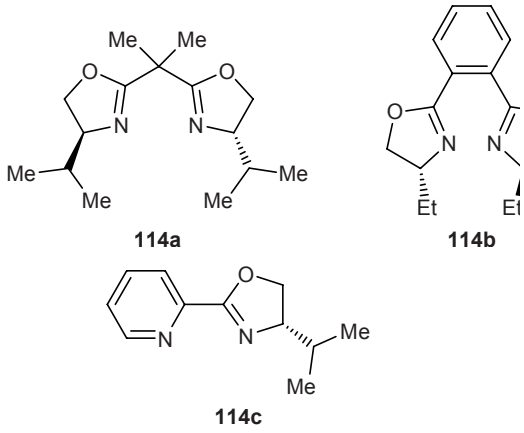
Iron(III) complexes with chiral bis(dihydrooxazoles) were used as catalysts in the Diels–Alder reaction of cyclopentadiene with 3-acryloyl-1,3-oxazolidin-2-one [95]. Adduct **106a** was thus obtained in 95% yield.



106a, *ee* = 82.2%
endo:*exo* = 94:4

New chiral iron(III) Lewis acids were studied as catalysts in the reactions of cyclopentadiene with 3-alkenoyloxazolidin-2-ones [96, 97].

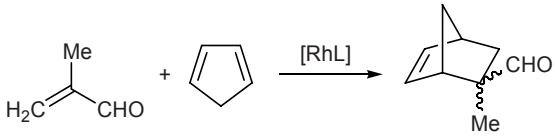
The synthesis of chiral *half-sandwich* rhodium dihydrooxazole complexes and their application in asymmetric Diels–Alder reactions were described in [98]. The complexes $[(\eta\text{-}C_5Me_5)RhClL]X$ (X = PF_6, SbF_6; L = ligand) were obtained in a good yield from bidentate ligands **114a–114c** and rhodium salts $[(\eta\text{-}C_5Me_5)RhCl_2]_2$, and their structure was determined by X-ray analysis. Table 5 contains the results of using these complexes as catalysts in the cycloaddition of methacrolein to cyclopentadiene (Scheme 44).



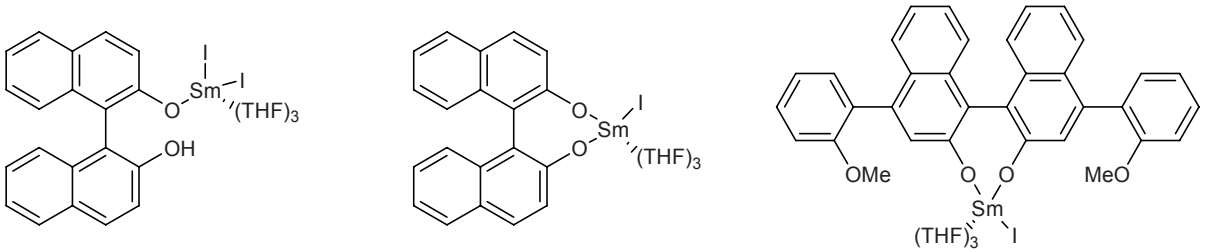
114a **114b**

114c

Scheme 44.

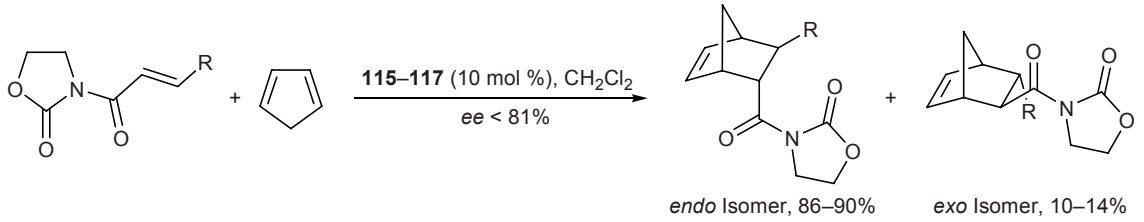


Giuseppone et al. [99] synthesized samarium(III) binaphthol complexes **115–117** which showed a fairly high efficiency in the cycloaddition of cyclopentadiene to unsaturated 3-acyloxazolidin-2-ones (Scheme 45). Asymmetric Diels–Alder reaction of acryloyloxazoli-



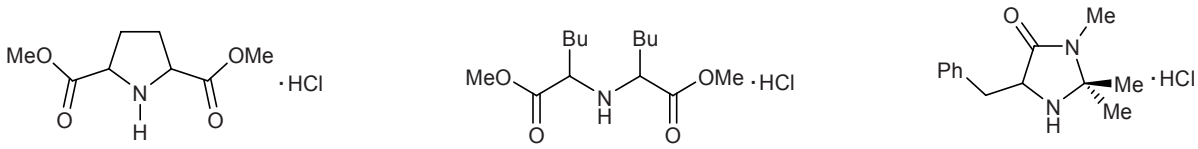
115 **116** **117**

Scheme 45.



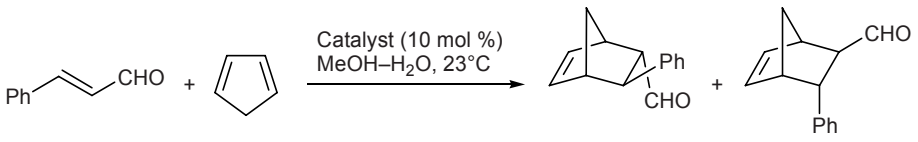
endo Isomer, 86–90% *exo* Isomer, 10–14%

R = H, Me.



118 **119** **120**

Scheme 46.



121 *endo*-**122a** *exo*-**122a**

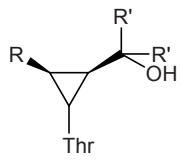
dine with cyclopentadiene in the presence of 10 mol % of a chiral lanthanum complex and molecular sieves in methylene chloride at –50 to 80°C showed a high enantioselectivity [100, 101]: the adducts were isolated in an optical yield of 92%. New chiral 2,2′-binaphthyldiimine Ni(II) complexes were used in asymmetric Diels–Alder reactions with cyclopentadiene to obtain the corresponding norbornene derivatives in 78% yield with *ee* 89% [102]. In the recent years, chiral natural organic compounds were used as catalysts in asymmetric Diels–Alder reactions [103]. For example, compounds **118–120** catalyzed [4+2]-cycloaddition of cyclopentadiene to various dienophiles. Table 6 contains the results of the reaction of cinnamaldehyde (**121**) with cyclopentadiene in the presence of amino acid catalysts **118–120** (Scheme 46).

Enantiomerically pure 2-aziridinylmethanols **123** prepared from aziridine-2-carboxylic acid esters were used as catalysts in asymmetric Diels–Alder reaction of cyclopentadiene with unsaturated aldehydes [104] (Scheme 47). Adducts **122b** and **122c** were thus obtained in up to 88% yield; the optical yield of the *exo* isomer was 60%, and of the *endo* isomer, 57%.

Table 6. Asymmetric Diels–Alder reaction of cinnamaldehyde (**121**) with cyclopentadiene in the presence of organic catalysts

Catalyst	Time, h	Yield, %	*exo*/*endo*-**122a**	*ee* (%) for *exo* isomer
(*S*)-ProOMe·HCl	27	81	2.7:1	48 (2*R*)
(*S*)-AbrOMe·HCl[a]	10	80	2.3:1	59 (2*S*)
118	23	92	2.6:1	57 (2*R*)
119	84	82	3.6:1	74 (2*R*)
120	8	99	1.3:1	93 (2*S*)

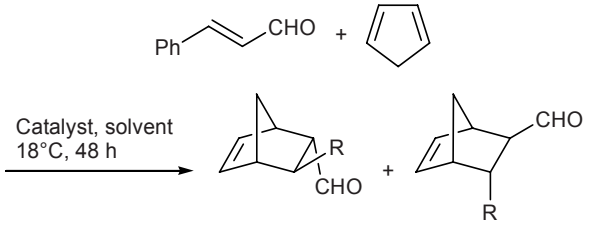
[a] Abr stands for *N*-methyltryptophane.



123

R = H, Me; R′ = Ph, 4-$CF_3C_6H_4$, *i*-Pr, Me, 2-naphthyl; ThrH = L-threonine.

Scheme 47.



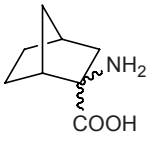
endo-**122b** *exo*-**122c**

R = H, Me.

4. BIOLOGICAL ACTIVITY

A specific feature of living matter is that almost all its chemical components having one or more asymmetric carbon atoms exist exclusively in a single stereochemical configuration possessing optical activity. Biochemical processes occurring in human organism are also stereospecific. As noted above, enantiomers having identical chemical properties often exhibit strongly different physiological activities.

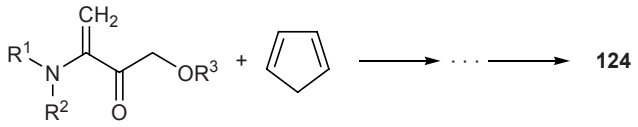
Substituted bicyclo[2.2.1]heptenes are convenient synthons for the preparation of various physiologically active compounds, and they can be readily obtained as enantiomerically pure substances via asymmetric Diels–Alder reactions of cyclopentadiene, which are the subject of the present review. Amino derivatives of bicyclo[2.2.1]heptene system are good starting materials for the synthesis of effective biologically active compounds [105]. As early as 1972, Tager and Christensen [106] noted that aminonorbornanecarboxylic acid **124** is a physiologically active substance and that it could exhibit antiviral activity.



124

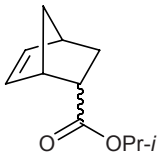
Methods of synthesis of amino acids of the norbornene series were reviewed in detail in [107]. A widely used procedure is based on the Diels–Alder reaction of cyclopentadiene with derivatives of α,β-unsaturated α-amino acids [108–113] (Scheme 48). β-Substituted dienophiles can also be involved in this reaction. Diastereoselective and enantioselective versions have also been tested. Another approach utilizes the classical Strecker reaction [114, 115], the initial norbornan-2-one being synthesized according to Diels–Alder.

Scheme 48.

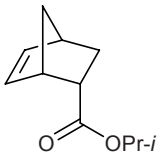


Biological activity of unsubstituted 2-aminonorbornane-2-carboxylic acid (**124**) was studied in many aspects. It was shown that acid **124** is selectively transported by sodium-independent systems destined to transport hydrophobic amino acids to almost all cells. The transport system is selective for one diastereoisomer of **124** (*endo* or *exo*). Another kind of activity (glutaminase-activating) was revealed by incubation of 2-aminonorbornane-2-carboxylic acid **124** with a sample of rat mitochondria [116].

Several norbornenecarboxylic and norbornenedicarboxylic acid esters as different diastereoisomers and enantiomers were tested for antimicrobial activity against various species [24, 60, 74, 75, 117–123], and their biological activity was compared with that of known antiseptics used in medical practice (ethanol, phenol, chloramine, rivanol, furacilin). These studies have shown that the *endo* isomers of norbornenecarboxylic acid are stronger antimicrobial agents than their *exo* isomers. Enantiomerically pure ester (2*S*)-(–)-**126** is a more effective antimicrobial agent than racemate **125**.



rac-**125**



(2*S*)-**126**

5. CONCLUSION

We can conclude that studies in the field of asymmetric Diels–Alder reactions with large-scale chemical products [124] with the goal of extending the series of available optically active norbornene and norbornane derivatives as synthons and biologically active substances are now rapidly developing. On the other hand,

analysis of published data indicates that asymmetric [4+2]-cycloadditions of cyclopentadiene have not been explored in sufficient detail and that the available data are not systematic. No detailed studies on the mechanism of asymmetric Diels–Alder reaction have been performed, though such studies would be useful for prediction of the results of reactions with a view to obtain new biologically active compounds.

Factors responsible for high regio-, stereo-, and enantioselectivity of asymmetric Diels–Alder reactions and their relative contributions under different reaction conditions attract much interest from both theoretical and practical viewpoints; therefore studies in this field seems to be very important.

Recent advances in performing selective asymmetric Diels–Alder reactions could give rise to development of large-scale processes for manufacture of optically active medical agents. In this respect, a specific place should be occupied by studies on Diels–Alder reactions in the presence of chiral catalysts. Diversity of action of chiral complexes with various metals in asymmetric catalysis has been demonstrated using Diels–Alder reaction as an example. In the future, extension of the series of available methods for the synthesis of new complexes from readily accessible ligands and transition metals should be expected.

Further extension of the diene and dienophile series via inclusion of new complex structures, as well as the use of highly effective chiral catalysts in asymmetric Diels–Alder reactions, should open new prospects in synthesizing previously inaccessible or difficultly accessible biologically active compounds belonging to various structural types. One of the most urgent problems of organic synthesis is preparation of useful compounds by practically reasonable methods [125].

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