51. Asymmetric *Diels-Alder* Reactions of Cyclopentadiene with *N*-Crotonoyl- and *N*-Acryloyl-4,4-dimethyl-1,3-oxazolidin-2-one, Mediated by Chiral *Lewis* Acids

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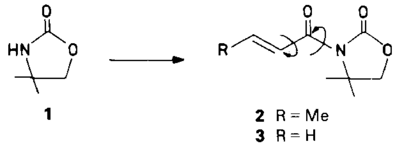
(29.XII.86)

One-pot *Diels-Alder* reactions of cyclopentadiene with 3-crotonoyl- (**2**) and 3-acryloyl-4,4-dimethyl-1,3-oxazolidin-2-one (**3**), mediated by chiral *Lewis* acids, are described. $AlCl_3$, $EtAlCl_2$, Et_2AlCl, $TiCl_4$, $ZrCl_4$, $SnCl_4$, $SiCl_4$, and BBr_3, modified with derivatives of D-mannitol, L-tartaric acid, and (*R*)-binaphthol, were applied as chiral promotors. The reaction with dienophile **2**, carried out in CH_2Cl_2 at –78° with high yield, was characterized by excellent π-face selectivity. In case of the reaction with dienophile **3**, the efficiency of the chirality transfer was much lower.

Almost complete π-face stereodifferentiation in *Lewis*-acid-catalyzed *Diels-Alder* reactions has recently been achieved applying either chiral diene or chiral dienophile [1]. In contrast to this approach, the use of chiral catalysts offers a unique possibility of inducing chirality to a principally unlimited amount of cycloadduct by a small quantity of catalyst. So far, this exciting field has remained practically unexplored [2]. We resolved to study the influence of chiral *Lewis* acids on the stereochemical course of the *Diels-Alder* reaction of cyclopentadiene with two bidentate dienophiles: 3-crotonoyl- (**2**) and 3-acryloyl-4,4-dimethyl-1,3-oxazolidin-2-one (**3**), readily available from compound **1** (*Scheme 1*). Very recently, similar investigations have been undertaken by Japanese authors [3].

Scheme 1



Compound **2** (m.p. 54–55°) was obtained in quantitative yield from **1** [4] by treatment with BuLi, followed by acylation with crotonoyl chloride [1e]. Likewise, compound **3** (m.p. 61–62°) was obtained in 78% yield from **1** by deprotonation using MeMgBr, followed by acylation with acryloyl chloride [1e].

Dienophiles **2** and **3** were selected because of their potential conformational rigidity. This rigidity was assumed to result from prevention of rotation around the C(O)–N bond, caused by chelation with a *Lewis* acid. Moreover, the C=C bond should be forced

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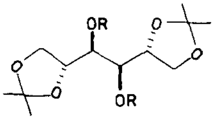
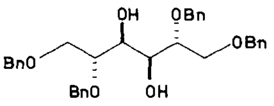
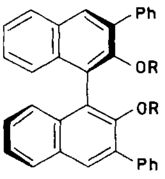


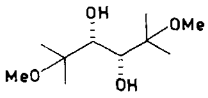
4 R = H
5 R = Me_3Si



6 (Bn = $PhCH_2$)



7 R = H
8 R = Me_3Si



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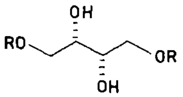
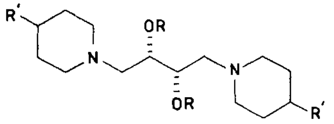
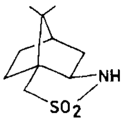


10 R = $PhCH_2$
11 R = Ts



12 R = H, R' = H
13 R = Me_3Si, R' = H
14 R = H, R' = Me
15 R = Me_3Si, R' = Me



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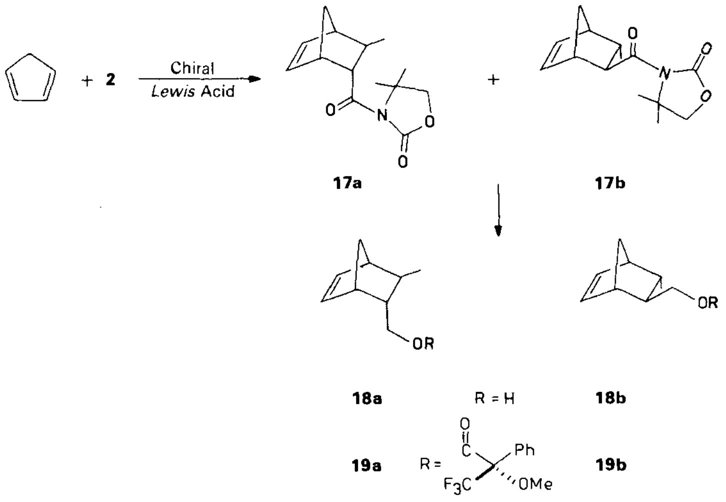
by the geminal Me groups to adopt *syn*-planar conformation with respect to the chelated carbonyl groups.

Chiral *Lewis* acids were generated *in situ* by addition of $EtAlCl_2$ or Et_2AlCl to chiral ligands containing the diol functionality. Alternatively, in case of application of perhalogenated *Lewis* acids, chiral diols protected by Me_3Si groups were used [5].

Scheme 2



Cycloaddition of cyclopentadiene to dienophile **2** was chosen as model reaction for comparison of the effects of various chiral ligands **4–16** on the π-face selectivity (*Scheme 2*).

A crude, crystalline mixture of the resulting cycloadducts **17a/17b** (m.p. 72–74°), separated from chiral ligand by filtration through a short silica-gel column or by simple extraction in case of ligands **12–14**, was reduced with $LiAlH_4$ to afford a mixture of alcohols **18a/18b**. The *endo/exo* ratio was determined at this stage using GC. Esterification of a mixture **18a/18b** with (–)-(*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid ((–)-MTPA) gave a mixture **19a/19b**, applied for the determination of the diastereomeric excess by ^{19}F-NMR [6]. The results are presented in *Table 1*.

Table 1. *Asymmetric Induction in the Reaction of Cyclopentadiene with Dienophile* **2** *in the Presence of Chiral* Lewis *Acids*[a])

Entry	*Lewis* acid	Ligand	Dienophile/*Lewis* acid/Ligand	Yield [%]	*endo/exo*[b]) Ratio	d.e.[c]) [%]
a	$EtAlCl_2$	**4**	1:2:1	89	75:25	94
b	$AlCl_3$	**5**	1:1:1	55	88:12	92
c	$TiCl_4$	**5**	1:1:1	86	93:7	96
d	Et_2AlCl	**6**	1:1:1	5	77:23	87
e	$EtAlCl_2$	**6**	1:2:1	73	73:27	92
f	Et_2AlCl	**7**	1:1:1	92	68:32	88
g	$EtAlCl_2$	**7**	1:2:1	92	76:24	95
h	$TiCl_4$	**8**	1:1:1	99	94:6	> 98
i	$EtAlCl_2$	**9**	1:2:1	90	70:30	93
j	$EtAlCl_2$	**10**	1:2:1	71	73:27	91
k	$EtAlCl_2$	**11**	1:2:1	82	71:29	97
l	$EtAlCl_2$[d])	**11**	1:2:1	15	81:19	> 98
m	$EtAlCl_2$	**12**	1:2:1	21	91:9	89
n	$EtAlCl_2$	**12**	1:1:0.5	71	84:16	94
o	$EtAlCl_2$	**16**	1:1:1	75	81:19	> 98

[a]) Reactions were carried out in CH_2Cl_2 at –78°.

[b]) *endo/exo* Ratios were determined by GC with a *Hewlett-Packard 5890* unit (*Carbowax 20M*, 530 μ), and were confirmed by the ^1H-NMR spectra (500 MHz) recorded with a *Bruker AM-500* spectrometer.

[c]) Diastereomeric excess (d.e.) was determined for (–)-MTPA esters using ^{19}F-NMR spectrometry. The ^{19}F-NMR spectra (376.3 MHz) were recorded with a *Varian XL-400* spectrometer. The direction of asymmetric induction was determined by polarimetric measurements of the mixtures **18a/18b**, using a *Perkin-Elmer 141* automatic polarimeter [1d]. In all cases, (*R*)-configuration was induced.

[d]) This reaction was carried out at –100°.

Several aspects of the present findings are noteworthy. A comparison of *Entries b* and *c*, or *f* and *h* showed that chiral titanium catalysts exhibited higher *endo/exo* selectivity as well as π-face selectivity than their aluminium analogues. The very low yield obtained with ligand **6** [7] (*Entry d*) possibly reflects intramolecular chelation by the free-rotating benzyloxy groups. This self-chelation was not observed in the case of ligand **4**, owing to the rigid isopropylidene protection. Therefore, we decided to use 2 equiv. of $EtAlCl_2$ (*Entry e*) to avoid this self-chelation. On the other hand, it was interesting to compare the results obtained for derivatives of D-mannitol with those to be found for a conformationally rigid ligand. For this purpose, we selected (*R*)-2,2′-dihydroxy-3,3′-diphenyl-1,1′-

binaphthyl (**7**) [8] for application in the model reaction. When $EtAlCl_2$ was used as *Lewis* acid, the results obtained for simple derivatives of D-mannitol **4** and **6** were fully comparable with those obtained for **7** (*Entries a* and *e vs. g*). *Entry h* represents the best chiral efficiency with regard to the *endo/exo* ratio.

L- or D-tartaric acids are cheap chiral starting materials, allowing different kinds of functionalization by simple chemical transformations. Ligand **9** [9] readily available from L-tartaric acid was as competitive as the highly elaborated binaphthyl derivative **7** (*Entries g vs. i*) in terms of the yield, *endo/exo* and π-face selectivity. Even more simple ligands, like (*S,S*)-1,4-dibenzyloxy-2,3-butanediol (**10**) [10] and commercially available ditosylate **11**, exhibited very high chiral efficiency (*Entries j* and *k*, respectively). Upon lowering of temperature, the *endo/exo* ratio as well as the π-face selectivity were increased (*Entry l*).

(*S,S*)-1,4-Dipiperidino-2,3-butanediol (**12**) [11], being advantageous from the practical point of view, since it can be fully recovered by simple extraction without losing optical purity, gave with $EtAlCl_2$ (2 mol-equiv.) the cycloadduct in low yield (*Entry m*). This drawback was overcome by the use of 1 mol-equiv. of *Lewis* acid (*Entry n*). It is evident that, upon use of 2 equiv. of *Lewis* acid for 1 equiv. of a chiral ligand, in the resulting complex, C_2 symmetry was changed. To prove that preservation of C_2 symmetry is unnecessary for effective asymmetric induction, the non-symmetric compact ligand **16** [1d] was applied. In this case, the chiral complex with $EtAlCl_2$ afforded in the reaction between cyclopentadiene and dienophile **2** asymmetric induction exceeding 98% (*Entry o*).

Scheme 3

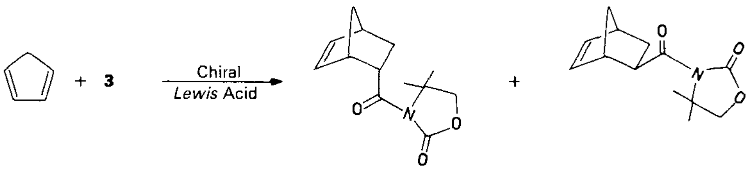


Table 2. *Asymmetric Induction in the Reaction of Cyclopentadiene with Dienophile* **3** *in the Presence of Chiral* Lewis *Acids*[a])[b])

Entry	*Lewis* acid	Ligand	Dienophile/*Lewis* acid/Ligand	Yield [%]	*endo/exo*[b]) Ratio	d.e. [%]
a	$EtAlCl_2$	**12**	1:2:1	29	77:23	36
b	$EtAlCl_2$	**12**	1:1:0.5	80	83:17	21
c	$EtAlCl_2$	**12**	1:0.5:0.25	96	81:19	17
d	$SiCl_4$	**13**	1:1:0.5	95	89:11	21
e	BBr_3	**13**	1:1:0.5	35	86:14	19
f	$EtAlCl_2$	**14**	1:1:0.5	84	90:10	19
g	$TiCl_4$	**15**	1:1:0.5	48	97:3	29
h	$ZrCl_4$	**15**	1:1:0.5	84	91:9	26
i	$SnCl_4$	**15**	1:1:0.5	82	99:1	23

[a]) The reactions were carried out in CH_2Cl_2 at −78°.

[b]) The *endo/exo* ratio and diastereomeric excess were determined similarly as indicated in *Table 1*. In all cases, (*R*)-configuration was induced.

The results obtained in the reaction of cyclopentadiene with dienophile **3** in the presence of chiral *Lewis* acids, leading to a mixture of cycloadducts **20a/20b**[2]) *(Scheme 3)*, are recorded in *Table 2*.

Comparison of *Entry n* in *Table 1* with *Entry b* in *Table 2* showed that, under the same experimental conditions, the π-face selectivity was much lower in case of dienophile **3** than **2**. Reduction of the amount of chiral *Lewis* acid relative to that of the dienophile resulted in a drop in the efficiency of chirality transfer (*Entries a–c*). $SiCl_4$ and BBr_3 (*Entries d* and *e*, respectively) also promoted asymmetric *Diels-Alder* reactions with π-face selectivity comparable to that obtained for Al-containing complexes. An increase in steric hindrance by introduction of Me groups into the chiral ligand **14**[3]) did not substantially influence asymmetric induction (*Entries b* and *f*). Ti as compared with Zr, Sn, and Al (*Entries f–i*) showed the highest ability of effective chelation.

The present results open a convenient and efficient route to optically pure cycloadducts which may be used in the synthesis of various natural products. Applications of the present findings in ene reactions and [4+2] cycloadditions with heterodienophiles, which we have taken up and will soon report, seem to be an interesting extension of this field.

The authors wish to thank Dr. *Kjell Ankner* (*AB Hässle*, Mölndal, Sweden) for recording NMR spectra, Dr. *Tomasz Kościelski* (Institute of Physical Chemistry, Polish Academy of Sciences) for GC measurements, and Dr. *Tomasz Bauer* for preparation of compound **6**. This work was supported by the *Swiss National Science Foundation* and by the *Polish Academy of Sciences* (grant CPBP 01.13).

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[2]) A crude, crystalline mixture **20a/20b** (m.p. 102–103°) was treated in analogous manner as that obtained from the reaction of cyclopentadiene with dienophile **2**.

[3]) 1,4-Di-*O*-tosyl-2,3-*O*-isopropylidene-L-threitol in γ-pipecoline was refluxed for 3 h, and then the resulting product was hydrolyzed to afford **14** (m.p. 69–70° from hexane, $[\alpha]_D^{25} = -19.7°$ ($c = 1.0$, CCl_4)) in 83% yield.