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A REINVESTIGATION OF ASYMMETRIC INDUCTION IN *DIELS-ALDER* REACTIONS TO CHIRAL ACRYLATES.

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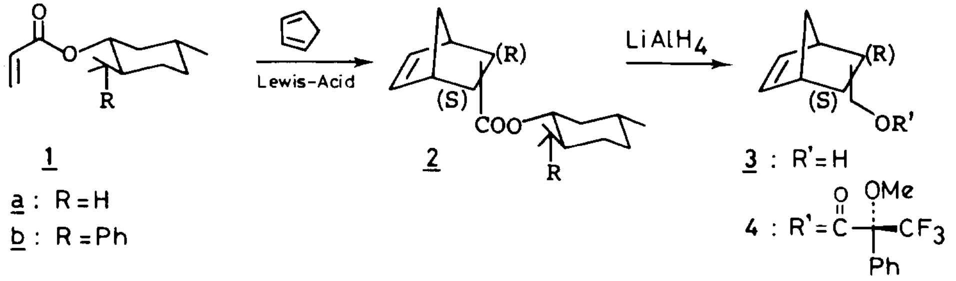
Abstract. The chiral induction in the *Diels-Alder* addition 1 → 2, assessed reliably by ^{19}F-NMR-spectroscopy of the *endo*-esters 4, varied between 47 - 93% in favor of the 2-(R)-adducts 2 depending on the auxiliary chiral group and the *Lewis*-acid catalyst.

The achievement of high asymmetric induction in *Diels-Alder* reactions requires further studies despite encouraging work using either chiral dienophiles[1,2] or dienes[3,4] or *Lewis*-acid catalysts[5]. Thus, the *Lewis*-acid promoted additions 1 → 2 of cyclopentadiene to acrylates derived from (-)-menthol[1b,c] or (-)-8-phenylmenthol[2a] have been reported to take place with good stereoselectivity and permit the recovery of the chiral auxiliary unit by the reduction 2 → 3. However, the degree of asymmetric induction in the reaction 1 → 2 was assessed entirely by chiroptic measurements of the alcohols 3.

Scheme 1



As a part of a program directed towards the rational design of new chiral acrylates disposed to undergo highly enantioselective *Diels-Alder*, ene-, and other addition reactions, we report here a reinvestigation of the reaction 1 → 2 and the development of a reliable method to determine the enantiomeric purity of the alcohol 3.

This latter problem was solved by subjecting the *Mosher*[6] derivatives 4 of the *endo*-alcohols 3 to ^{19}F-NMR-analysis in the presence of Eu(FOD)$_3$; the derivative (4) of the (+)-(R)-alcohol showed a ^{19}F-singlet 0.15 ppm upfield from that of the (S)-alcohol derivative. Similarly, the enantiomeric purity of the auxiliary alcohols (-)-menthol and (-)-8-phenylmenthol was established to be 95% and 100%, respectively by ^{19}F-NMR-analysis of their esters derived from (+)- as well as from (-)-α-methoxy-α-trifluoromethylphenylacetic acid.[7]

Having thus set up and calibrated our diagnostic tool we then studied systematically the influence of solvent, temperature and *Lewis*-acid on the chemical and optical yields of the reactions 1 → 2 : Table[8]

TABLE

Entry	Acrylate	Lewis Acid	Solvent	Temp. (°C)	Time (h)	Yield	2/1	endo/exo	% e.e. of 2-(R)-3
1	1a	1 eq. $SnCl_4$	toluene	0	0.5	-	-	-	51
2	1b	0.7eq. $SnCl_4$	toluene	0	1	-	-	86:14	84
3	1b	0.7eq. $SnCl_4$	toluene	0	1	-	-	-	86
4	1b	1.5eq. $SnCl_4$	toluene	0	3.5	95	100:0	84:16	89
5	1b	1.5eq. $SnCl_4$	CH_2Cl_2	-20	3.5	54	61:39	88:12	91
6	1a	0.7eq. $AlCl_3$	CH_2Cl_2	-55	2	-	-	-	48
7	1b	0.7eq. $AlCl_3$	CH_2Cl_2	-55	2	72	88:12	93:7	70
8	1b	0.7eq. $AlCl_3$	CH_2Cl_2	-20	3.5	89	100:0	91:9	65
9	1b	0.7eq. $AlCl_3$	toluene	-20	3.5	96	100:0	92:8	52
10	1a	1.5eq. Me_2AlCl	CH_2Cl_2	0	3.5	73	100:0	92:8	47
11	1b	1.5eq. Me_2AlCl	CH_2Cl_2	0	3.5	95	100:0	89:11	64
12	1b	1.5eq. Me_2AlCl	toluene	0	3.5	81	100:0	88:12	55
13	1a	1.5eq. $TiCl_4$	CH_2Cl_2	-20	3.5	65	83:17	92:8	62
14	1a	1.5eq. $TiCl_4$	CH_2Cl_2	-55	3.5	No Reaction		-	-
15	1b	1.5eq. $TiCl_4$	CH_2Cl_2	-20	3.5	83	100:0	89:11	90
16	1b	1.5eq. $TiCl_4$	CH_2Cl_2	-55	3.5	No Reaction		-	-
17	1b	1.5eq. $TiCl_4$	toluene	-20	3.5	86	86:14	88:12	93
18	1b	0.7eq. $BF_3.Et_2O$	CH_2Cl_2	-20	3.5	59	68:32	92:8	92
19	1b	1.5eq. $BF_3.Et_2O$	toluene	0	3.5	44	53:47	90:10	93

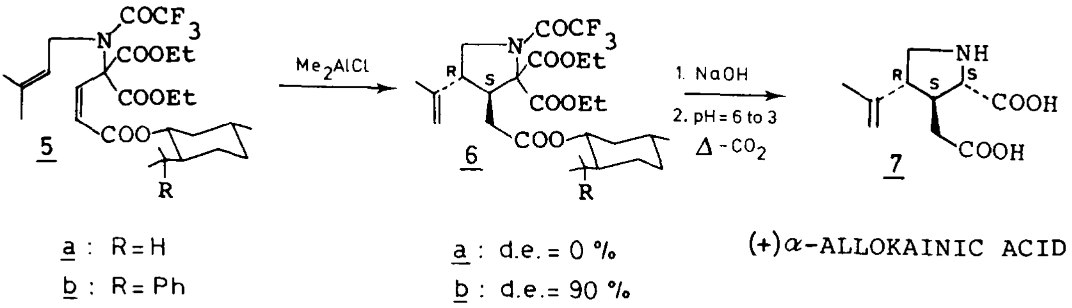
The rate and chiral induction of the reaction 1 → 2 proved to be most significantly dependent on the nature of the *Lewis*-acid. Thus, only partial or no reaction was observed with $BF_3.Et_2O$ at 0°C, with $SnCl_4$ or Me_2AlCl at -20°C or with $TiCl_4$ at -55°C. Asymmetric induction near 90% was observed for the reaction 1b → 2b using either $SnCl_4$ or $BF_3.Et_2O$. For example, entries 2, 3 and 4 show optical yields between 84 to 89% under reaction conditions similar to those previously reported to yield (R)-3 from 1b in 99% enantiomeric excess.[2a] Me_2AlCl and $AlCl_3$ induce asymmetry in 2b to only a modest extent in both CH_2Cl_2 (65% d.e.) and the more strongly coordinating solvent toluene (52 - 54% d.e.). Lowering the reaction temperature from -20°C to -55°C (entries 7 and 8) improved slightly the chiral induction and *endo*-selectivity.

The *endo*-alcohol 3, obtained using the reaction conditions mentioned in entry 7 of the Table, displayed an optical rotation $[\alpha]_D^{25°} = +67.7°$ (c = 0.718, EtOH) indicating the 2-(R)-enantiomer of 3 to be the predominant product in each entry.[9]

In terms of practical synthetic utility the conditions outlined in entries 4 and 15, which lead to (R)-3 with 89 and 90% e.e., demonstrate the advantageous use of $SnCl_4$ or $TiCl_4$[10]. Without exception the phenylmenthyl-group induces chirality in the *Diels-Alder* reaction 1 → 2 more efficiently than the menthyl moiety.[11]

However, it is noteworthy that this difference is far less dramatic than in the ene-type reaction 5 → 6. Thus, we have obtained the pyrrolidine 6b with 90% chiral induction (based on NMR-evidence) by the Me_2AlCl-induced intramolecular ene-type reaction 5b → 6b, which served as the key step for our highly enantioselective synthesis of (+)-α-allokainic acid (7). By contrast, we observed no induction in the analogous cyclization of the menthyl-acrylate 5a.[12]

Scheme 2



Work is in progress to rationalize these findings and to use them as a starting point for the development of more versatile and effective chiral auxiliary groups.

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[7] The same ^{19}F-NMR measurements of the esters, prepared from (-)-8-phenylmenthol and the (+)- as well as the (-)-α-methoxy-α-trifluoromethylphenylacetic acid, showed both acids to be 100% enantiomerically pure.

[8] The acrylates 1 were added to freshly prepared cyclopentadiene (2.5 eq.) under the reaction conditions mentioned in the Table. Quenching of the mixture with water at the corresponding reaction temperature, successive extraction (CH_2Cl_2), evaporation of the dried (Na_2SO_4) organic phase and filtration through SiO_2 (hexane/ether 450:1) gave a mixture which on H-NMR-analysis (360 MHz) revealed the amount of conversion of 1 to 2. Reduction of crude 2 with $LiAlH_4$ in Et_2O furnished 3 together with some of its *exo*-isomer as shown by GC-analysis (5% Carbowax on Chromosorb W, 140°). Removal of the *exo*-isomer by preparative GC (10% OV 225 on Chromosorb W 80/100 mesh, 120°C) gave 3 as a mixture of enantiomers which on esterification with (+)-α-methoxy-α-trifluoromethylphenylacetic acid [1.1 eq., dicyclohexylcarbodiimide (1.1 eq.), dimethylaminopyridine (0.05 eq.), CH_2Cl_2] followed by preparative TLC (SiO_2, hexane/ethylacetate 19:1) gave an inseparable mixture of the diastereoisomers 4.

[9] For the assignment of the absolute configuration of (+)-3 see: J.A. Berson, J.S. Walia, A. Remanick, S. Suzuki, P. Reynolds-Warnhoff and D. Willner, *J. Am. Chem. Soc.* 83, 3986 (1961).

[10] For the *Lewis*-acid catalyzed addition of butadiene to acrylate 1b, $TiCl_4$ was reported to be superior to $AlCl_3$ and $SnCl_4$ in terms of chemical and optical yields: Ref. [2b], footnote 18.

[11] The depicted e.e. values of 3, derived from the menthylacrylate 1a account for 95% enantiomerically pure (-)-menthol used for the preparation of 1a.

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