Tetrahedron Letters,Vol.25,No.21,pp 2191-2194,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

INFLUENCE OF POLAR GROUPS IN THERMAL AND LEWIS ACID PROMOTED ASYMMETRIC DIELS-ALDER ADDITIONS: LACTIC ACID DERIVATIVES AS PRACTICAL HIGHLY SELECTIVE AND CONFIGURATIONALLY DICHOTOMIC REAGENTS

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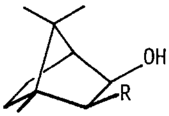
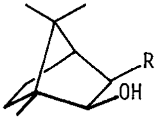
Summary: Diels-Alder reactions of the acrylate of (S)-ethyl lactate with cyclopentadiene proceed with diastereoface-selectivity of up to 85:15 (non-catalyzed) and 93:7 ($TiCl_4$-promoted). Depending on the Lewis acid, products of inverse configuration are obtained. In conjunction with facile product analysis by LC, effective means for suppression of polymerization of the diene, and virtually epimerization-free ester hydrolysis these findings constitute a method for large scale practical applications of the asymmetric Diels-Alder reaction.

High levels of stereoselection have been achieved in a variety of asymmetric Diels-Alder reactions[1]. However, efficacious reagents of which both enantiomers are inexpensive and readily available have so far been elusive. We wish to report findings which demonstrate that simple derivatives of lactic acid and presumably other hydroxy acids can fill this void. Furthermore, we have found that a novel type of acrylate enantioface-discrimination is operative with these reagents.

This work developed from earlier studies[2] which included, as model reactions, $AlCl_3$-promoted additions of anthracene to 3-methoxycarbonyl-acrylates of 1a-c and 2c. Stereoselection of up to > 99:1 was achieved. As expected on the basis of previous investigations of acrylates[1a], no significant diastereoselection was obtained in non-catalyzed reactions of the acrylates of 1a and 1b. However, acrylates of 1c and 2c were found to be exceptional in that they gave diastereoselection of up to 80:20[3]. This suggested[2a] that the carbamoyl group exerts an electronic (as distinct from steric) face-differentiating effect on the acrylate moiety.

1



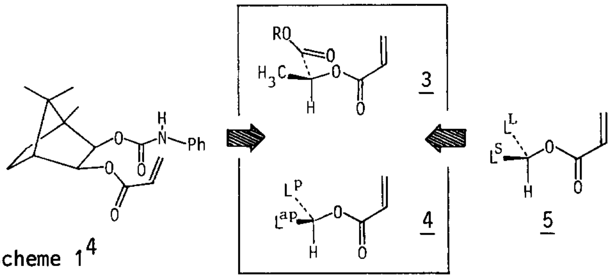


2

	R
a	OCH_2Ph
b	$OCHPh_2$
c	OCONHPh

Pursuing the lead given by the results mentioned above, acrylates of lactic acid esters (3) were selected as dienophiles with acrylate-face-differentiating groups, CH_3 and COOR, of approximately equivalent steric bulk but distinctly differing electronic type. Furthermore, we hoped that acrylates 3 would show interesting effects in Lewis acid catalyzed reactions. In contrast to "classical" acrylates 5 (example: menthyl acrylate), compounds with apolar groups L and one donor center (the acrylate oxygen), acrylates 3 provide two donor centers and are thus adapted to formation of chelate complexes with Lewis acids.

In order to test these ideas reactions of the acrylate of (S)-ethyl lactate (6)[5] and other simple lactates with cyclopentadiene were investigated (Scheme 2). As first pleasant surprise it was found that the four diastereoisomeric reaction products 7a-d are remarkably easily separable by



Scheme 1[4]

L^S small
L^L large apolar group

L^{ap} apolar group

L^P polar, electron donating group

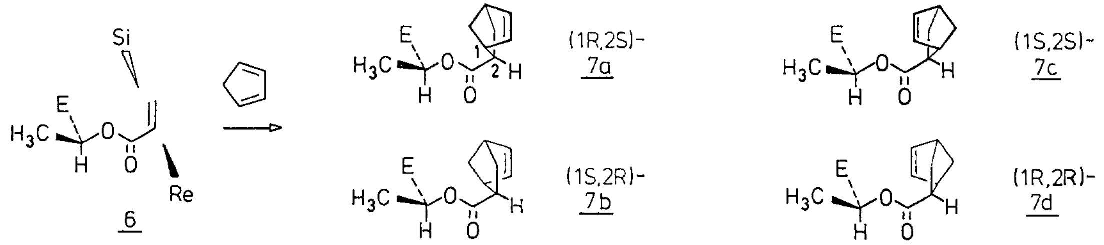
liquid chromatography (Fig. 1). This allowed convenient product analysis by HPLC and in consequence coverage of a wide variety of reaction variables. Furthermore, preparative isolation of the products 7a-d[6] on a gram scale was easily accomplished by MPLC or, in the case of 7d, even by flash chromatography in conjunction with TLC monitoring. Chromatography was not necessary, however, for preparation of optically pure endo 5-norbornene-2-carboxylic acid (see below).

Selectivity data obtained for non-catalyzed reactions of 6 with cyclopentadiene are displayed numerically and graphically in Table 1[7]. Compared to previous results obtained with type 5 acrylates (cf.[1a]) an extreme degree of diastereoface selectivity (ratios of 7a:7b and 7c:7d) is found which demonstrates a fundamentally new type of acrylate diastereoface differentiation[3]. As anticipated, the effect has an electronic (polar) origin. This view is supported by four observations: 1. Diastereoface selectivity is strongly dependent on solvent polarity, expressed by E_T values[8]. 2. Diastereoface selectivity decreases with increasing solvent polarity. This is rationalized by assuming that solvation of both acrylate faces by polar molecules levels off the effect of the lactate COOR group. 3. Results almost identical with those shown in Table 1 have been obtained with acrylates of methyl and isopropyl lactate. This indicates that steric effects are not important. 4. No significant solvent effect was found for the reaction of cyclopentadiene with menthyl acrylate (type 5)[9a,b]. On the other hand, for this compound[9b] as well as for acrylate 6 variation of endo-exo selectivity, ratio of (7c+7d):(7a+7b), conforms to the pattern found by Berson[10] to be characteristic for reactions of simple achiral acrylates with cyclopentadiene.

Investigation of Lewis acid catalyzed reactions of 6 with cyclopentadiene yielded further exciting results which are summerized in Table 2. Entries 1a-f pertain to experiments not optimized with regard to stereoselectivity. The following data were collected for optimisation of the $TiCl_4$-promoted reaction and for a rather detailed evaluation of the systems response to variation of important reaction variables[11]. The following general features are apparent: 1. As was to be expected on the basis of previous results[1], compared to the non-catalyzed reaction all the Lewis acids cause steep increase in endo-exo selectivity and reaction rate. 2. However, the acrylate 6 is unique in that the configuration of the prevailing adduct[12] is a function of the Lewis acid: in non-catalyzed reactions and with $BF_3 \cdot Et_2O$, aluminum halides, and $ZrCl_4$(!) 7c is formed in excess; but with $TiCl_4$ and $SnCl_4$ mainly 7d is obtained[12]. This indicates that at least two types of acrylate/Lewis acid complexes can be formed. 3. With $TiCl_4$, the ratio of 7d:7c varies considerably with temperature (entr. 2) and molar ratio of $TiCl_4$:6 (entr. 3). Both functions show a maximum; therefore, even one and the same Lewis acid probably forms more than one reacting species.

Three problems had to be solved in order to arrive at a preparatively useful and broadly applicable method. 1. As is usually found, polymerization of the diene was a serious impediment for the Lewis acid promoted reaction, particularly with $TiCl_4$ as the catalyst[13]. 2. Being extremely reactive cyclopentadiene is not a representative diene. Reaction temperatures considerably higher than -60° are usually required (f.i. with butadiene). Pronounced decrease of selectivity with increasing temperature is thus an undesirable feature (Table 2, entr. 2). 3. Esters $R_2CHCOOR^*$, as they result from asymmetric Diels-Alder additions, commonly yield partially epimerized or racemized carboxylic acids upon saponification because drastic reaction conditions are required. This problem can be circumvented by reductive ester cleavage which creates, however, the new problem of separating two alcohols[14].

The first two problems were solved simultaneously. Considering that polymerization of dienes is most likely induced by free $TiCl_4$ rather than associated species, we used CH_2Cl_2/n-hexane mixtures as solvents. Surprisingly, even a content of ca. 50 % (v/v) of n-hexane[15] suppresses polymerization to a level beyond detection. Furthermore, the reaction is more selective and stereoselectivity is less dependent on temperature in this mixture than in CH_2Cl_2 (cf. entries 2 and 4



Scheme 2   E = $COOC_2H_5$

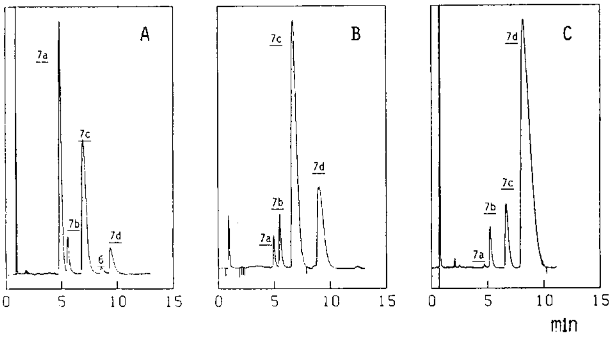


Fig. 1. Analytical HPLC separations of raw mixtures from reactions of 6 with cyclopentadiene.

A Non-catalyzed (n-hexane) (table 1)
B $AlEtCl_2$-promoted (table 2, e. 1f)
C $TiCl_4$-promoted (table 2, e. 4a)

Column: 20×0.46 cm, 5 µ silica Hypersil®, eluent: petroleum ether (l.b.)-t-butyl-methyl-ether 99:1, flow: 3 ml min^{-1}, detection: UV at 220 nm, ratio of extinction coefficients at 220 nm: $\varepsilon_{\underline{7a}}:\varepsilon_{\underline{7b}}:\varepsilon_{\underline{7c}}:\varepsilon_{\underline{7d}}$ = 1.50:1.06:0.95:0.75.

Table 1. Non-catalyzed asymmetric Diels-Alder additions of acrylate 6 to cyclopentadiene; conditions: 0° C, 186 h, c(cyclopentadiene) = 1.0 M, c(6) = 0.05 M, c(hydroquinone) = 0.005 M.

Graphical representation:
A r = 7a:7b, B r = 7c:7d, C r = (7c+7d):(7a+7b)

solvent	E_T	product ratio of 7a:7b	 7c:7d	 (7c+7d):(7a+7b)
n-hexane	30.9	85:15	80:20	1.68
CCl_4	32.5	82:18	77:23	1.78
toluene	33.9	80:20	73:27	1.94
CH_2Cl_2	41.1	68:32	58:42	3.22

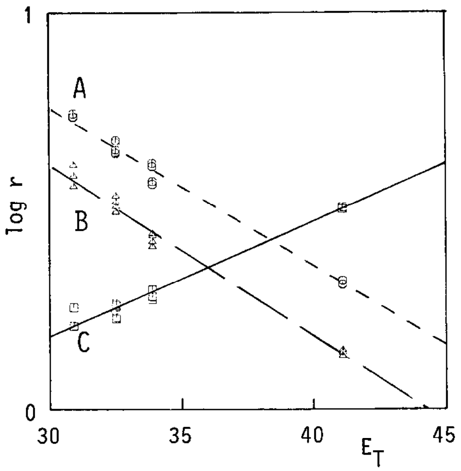


Table 2. Lewis acid promoted Diels-Alder reactions of acrylate 6 with cyclopentadiene; concentrations: as given in Table 1.

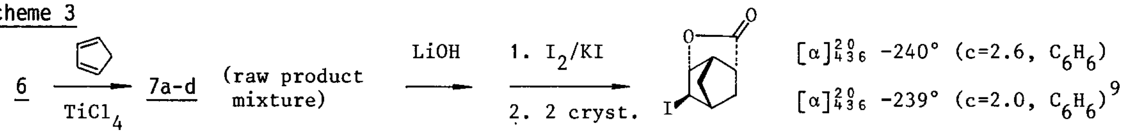
entry	Lewis acid	equiv. of Lewis acid	temp. [°C]	solvent	ratio of 7d:7c	endo-exo ratio of (7c+7d):(7a+7b)
1a	$TiCl_4$	1.1	-45	CH_2Cl_2	85:15	16:1
1b	$SnCl_4$	1.1	-45	CH_2Cl_2	84:16	18:1
1c	$ZrCl_4$	1.1	-45	CH_2Cl_2	48:52	17:1
1d	$BF_3\cdot Et_2O$	1.1	-45	CH_2Cl_2	34:66	12:1
1e	$AlCl_3$	1.1	-45	CH_2Cl_2	36:64	13:1
1f	$AlEtCl_2$	1.1	-63.5	CH_2Cl_2	33:67	16:1
2a	$TiCl_4$	1.1	-75	CH_2Cl_2	90:10	21:1
2b	$TiCl_4$	1.1	-63.5	CH_2Cl_2	90:10	22:1
2c=1a	$TiCl_4$	1.1	-45	CH_2Cl_2	85:15	16:1
2d	$TiCl_4$	1.1	0	CH_2Cl_2	78:22	7:1
3a	$TiCl_4$	0.3	-63.5	CH_2Cl_2	91: 9	31:1
3b	$TiCl_4$	0.5	-63.5	CH_2Cl_2	92: 8	28:1
3c	$TiCl_4$	0.75	-63.5	CH_2Cl_2	93: 7	32:1
3d=2b	$TiCl_4$	1.1	-63.5	CH_2Cl_2	90:10	22:1
4a	$TiCl_4$	0.75	-63.5	CH_2Cl_2/n-hexane [a]	93: 7	39:1
4b	$TiCl_4$	0.75	-45	CH_2Cl_2/n-hexane [a]	92: 8	29:1
4c	$TiCl_4$	0.75	-24	CH_2Cl_2/n-hexane [a]	90:10	17:1
4d	$TiCl_4$	0.75	0	CH_2Cl_2/n-hexane [a]	87:13	12:1

[a] ratio of 4.5:5.5 (v/v), c(6) = 0.046 M.

of Table 2)[16]. Thus, replacing n-hexane by petroleum ether (l.b.) and otherwise using conditions as stated by entry 4a of Table 2, preparative experiments showed complete consumption of 6 (6 h) with only 1.25 eq of cyclopentadiene. On a 10 g scale, pure 7d was obtained in 88 or ca. 50 % yield after product purification by MPLC or flash chromatography, respectively.

Finally, saponification of adducts 7a-d without epimerization was found to be possible with LiOH in THF/water at room temperature[17]. This finding enabled the preparation of optically pure (+)-(1R,2R)-5-norbornene-2-carboxylic acid according to Scheme 3. Avoiding chromatography, this method combines the procedures described above with a purification protocol based on iodolactonization/elimination developed by Sauer and Kredel[9] (enantiomeric purity of 8: 99±1 %[9c]).

Scheme 3



8 (71 %, from 6)

The work reported here opens a possibility to obtain many important Diels-Alder adducts enantiomerically pure or highly enriched at a very low price. We are currently exploring scope and mechanistic aspects in conjunction with obvious structural variations of the chiral auxiliary.

Acknowledgements: This work was supported by the Fonds der Chemischen Industrie.

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[3] Even higher stereoselection has recently been achieved with a ketol-type dienophile: W.Choy, L.A. Reed, S.Masamune, J.Org.Chem. 48, 1137 (1983).

[4] The enantiomer of the acrylate of 1c is presented for better illustration of the relationship of 1c to 3. 1c-acrylate with cyclopentadiene yields crystalline LC-separable adducts in Lewis acid promoted Diels-Alder reactions with selectivity of 98:2 (endo-exo ratio of 97:3): T.Poll, Diplomarbeit, Universität Würzburg 1982, and further unpublished work.

[5] This acrylate was prepared (yield: 83 %) from commercial (S)-ethyl lactate (FLUKA) using the esterification procedure of A.R.Banks, R.F.Fibinger, T.Jones, J.Org.Chem. 42, 3965 (1977). This and the other new compounds described here were fully characterized by elemental analysis and appropriate spectral data. Diastereomers were isolated pure and were individually characterized.

[6] Assignment of relative configuration (endo or exo) is based on NMR; absolute config.: ref. 17.

[7] Reactions were run on a mmol scale (> 95 % completion) and analyzed by HPLC; the extinction coefficients at 220 nm of the diastereomers 7a-d differ considerably (Fig.1). A preparative run (0.05 mol, CH_2Cl_2, 0 °C, 62 h) followed by MPLC separation and Kugelrohr distillation gave 7a, 7b, 7c, and 7d in 15.4, 7.4, 42.8, and 29 % yield, respectively.

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[10] J.A.Berson, Z.Hamlet, W.A.Mueller, J.Am.Chem.Soc. 84, 297 (1962).

[11] Compounds were mixed isothermally; cyclopentadiene was added to the solution of acrylate-Lewis acid complex. All reaction mixtures were homogeneous.

[12] In contrast, for all Lewis acids, 7b was the prevailing exo adduct.

[13] Polymerization has been avoided with $TiCl_2(OiPr)_2$ as catalyst: W.Oppolzer, C.Chapuis, G.M.Dao, D.Reichlin, T.Godel, Tetrahedron Lett. 1982, 4781. In our hands, this catalyst gave low acrylate face selectivity for the addition of cyclopentadiene to an acrylate 3 with R = iPr.

[14] For the present case no difficulty arises because the resultant 1,2-propanediol can be removed by extraction with water and there is no need to recover the low-priced chiral auxiliary.

[15] A higher content causes a heterogeneous system (-63 °C) and lowering of selectivity.

[16] The acrylate of isopropyllactate, 3 R=iPr, under conditions corresponding to entries 4a-d of Table 2 gave adducts with stereoselectivity of 93:7, 93:7, 92:8, and 90:10, respectively.

[17] Using these conditions, 7a and 7d gave (1R,2S)- and (1R,2R)-5-norbornene-2-carboxylic acids, respectively, with optical rotations $[\alpha]^{20}_{D}$ (95 % EtOH) of +14.3° (c=3.7) and +144° (c=2.4), respectively; absol. configurations: J.A.Berson et al. J.Am.Chem.Soc. 83, 3986 (1961). Diastereomeric purities (exo/endo content) of these acids was found to be ≥99 % according to HPLC analysis of their methyl esters (reaction with diazomethane, HPLC conditions as given in Fig. 1).

(Received in Germany 1 February 1984)