

DIASTEREOFACE-DISCRIMINATIVE METAL COORDINATION IN ASYMMETRIC SYNTHESIS: D-PANTOLACTONE AS PRACTICAL CHIRAL AUXILIARY FOR LEWIS ACID CATALYZED DIELS-ALDER REACTIONS¹

Thomas Poll, Andrzej Sobczak, Horst Hartmann and Günter Helmchen*

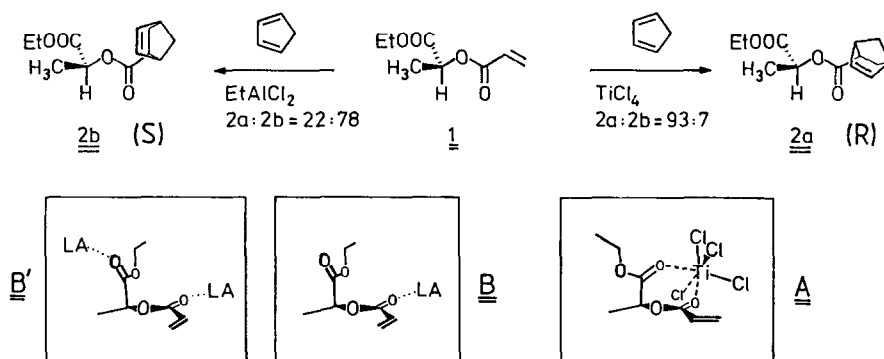
Institut für Organische Chemie der Universität Würzburg, Am Hubland, D-8700 Würzburg, FRG

Abstract: TiCl₄-catalyzed Diels-Alder additions of the acrylate of commercial D-pantolactone to cyclopentadiene, isoprene and butadiene proceed with very high diastereofacial selectivity. Practical and mechanistic aspects of these reactions are discussed.

Metal coordination is known to be important for a variety of useful asymmetric syntheses. Chelate formation, in particular, can amplify inherently weak diastereoface-discrimination to the extent that high levels of stereoselection may be achieved with very simple chiral auxiliaries. Following this general guideline, we have uncovered that acrylic esters of lactates are very effective dienophiles in Lewis acid promoted Diels-Alder reactions². In an effort to clarify puzzling effects of Lewis acids associated with these reagents we have recently succeeded in growing single crystals of a 1:1 acrylate-TiCl₄ complex³. The structure of this complex has provided a basis for rationalization of our observations and, moreover, has given an essential hint for identifying the title compound to be a most useful chiral auxiliary.

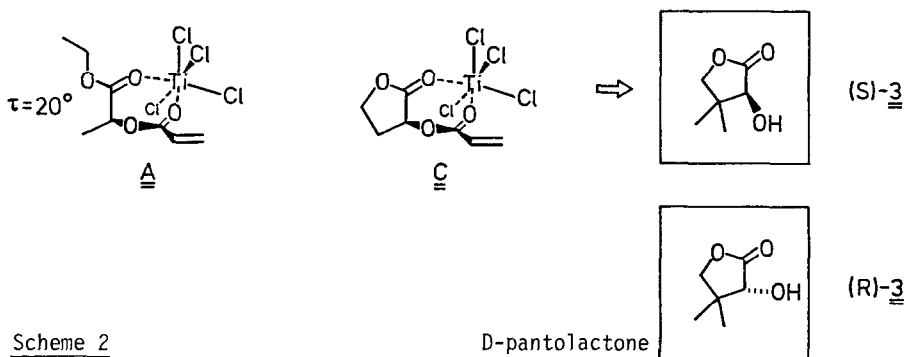
The facts which have induced the work presented here are comprised in Scheme 1 which is representative of a number of similar reactions. The reaction of acrylate 1 with cyclopentadiene preferentially yields endo adduct 2a with TiCl₄ as catalyst. This result can be understood by assuming that a single species of structure A, corresponding to the crystal structure of the 1-TiCl₄ complex, reacts and that A is attacked at the less shielded face (2Si) of its enoate group. However, this simple rationale does not explain the response of diastereoselectivity to variations of reaction conditions (Fig. 1). In particular, steep decrease of diastereoselectivity is found with more than ca. 1 equivalent of TiCl₄. This indicates that besides A other reactive species are present. According to the modified Walborsky model⁴, likely such species are the non-chelate

Scheme 1 (LA Lewis acid)



complexes \underline{B} and \underline{B}' . This proposal is supported by the fact (Scheme 1) that Lewis acids disposed to four-coordination, EtAlCl_2 and BF_3 , induce preferential addition to the acrylate 2Re-face as is to be expected for \underline{B} and \underline{B}' .

From the scheme outlined above an interesting conclusion can be drawn: stabilization of complexes of type \underline{A} relative to those of types $\underline{B}/\underline{B}'$ should raise the level of diastereoselectivity and decrease dependence of diastereoselectivity on reaction conditions. The essential hint to realize this expectation came from the crystal structure of \underline{A}^2 in that this displays a torsion angle of only 20° for the lactate backbone $\text{O}-(\text{CO})-\text{C}-\text{CH}_3$. Consequently, a cyclic structure \underline{C} (cf. Scheme 2) should possess a coordination geometry similar to that of \underline{A} ; but the entropy balance with respect to competing monodentate complexes should be more favourable for \underline{C} than for \underline{A} . These considerations prompted the selection of the readily available D-pantolactone as reagent. With regard to configurational relationships D-pantolactone is equivalent to (R)-lactates which are produced but are not yet available from suppliers of fine organic chemicals.



Results obtained with D-pantolactone [(R)- $\underline{3}$] as chiral auxiliary are summarized on the opposite page. The requisite acrylate $\underline{4}$ was prepared⁵ in 88 % yield from (R)- $\underline{3}$ and propenoyl chloride. In order to compare this new dienophile with acrylate $\underline{1}$ and acrylates of other chiral auxiliaries the TiCl_4 promoted reaction of $\underline{4}$ with cyclopentadiene was studied in detail. The products of this reaction ($\underline{5a}, \underline{b}$ and corresponding exo isomers) can be easily separated by liquid chromatography; therefore, determination of diastereoselectivity was carried out by HPLC⁶. The following general features are apparent from this study: 1. Depending on reaction conditions, endo-exo selectivity in the range 45:1 to 20:1 was found which is typical for acrylates. 2. For the endo isomers $\underline{5a}, \underline{b}$ a very high level of diastereoselection is achieved (maximum: $\underline{5a}:\underline{5b} = 97.5:2.5$). 3. The ratio of $\underline{5a}:\underline{5b}$ is almost invariant to variations of temperature (Fig. 1B) and total concentration (Fig. 1C). 4. In contrast to most other chiral dienophiles⁷, $\underline{4}$ yields a high level of stereoselection even with 0.1 equiv. of the Lewis acid. This indicates that $\underline{4}$ forms an unusually stable chelate complex and, furthermore, that exchange of the catalyst between products $\underline{5}$ and starting material $\underline{4}$ is fast. In summary, all these observations are fully consistent with our expectation that, towards TiCl_4 , $\underline{4}$ would be a better chelate ligand than $\underline{1}$.

In order to demonstrate applications of the new reagent, preparations of enantiomerically pure (-)(1S,2S)-5-norbornene-2-carboxylic acid ($\underline{6}$) (cf. experimental procedure⁸), (-)(S)-3-cyclohexenecarboxylic acid ($\underline{10}$) and (-)(S)-4-methyl-3-cyclohexenecarboxylic acid ($\underline{9}$) are described on the opposite page. These compounds are useful starting materials for natural product syntheses⁷.

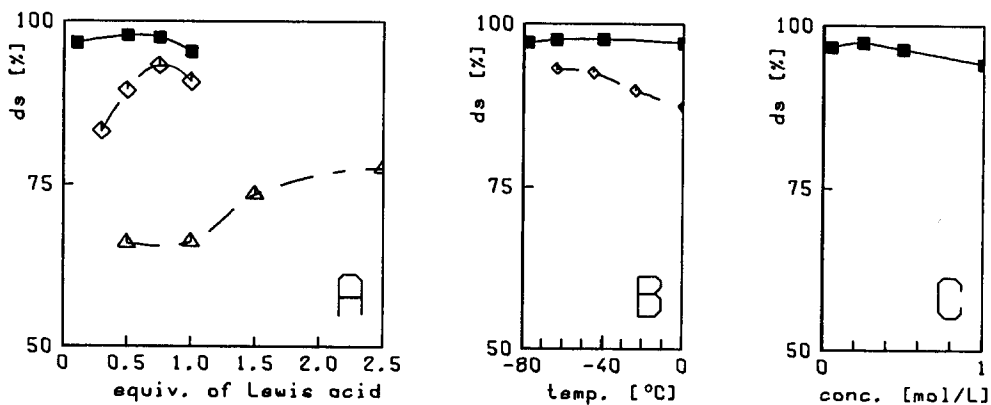
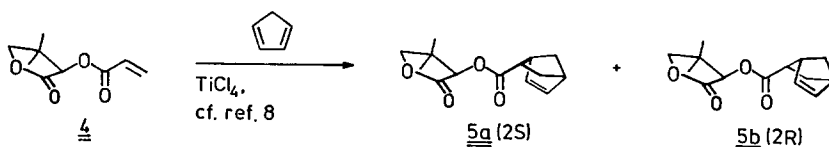
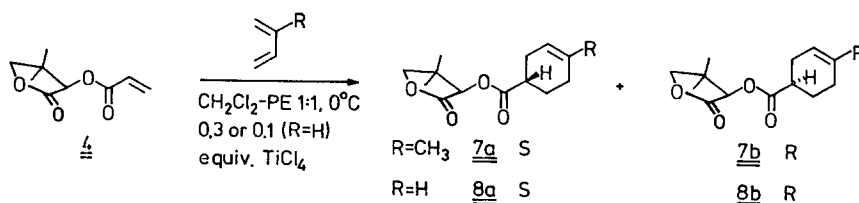


Fig. 1. Dependence of diastereoselectivity (ds^9) of Lewis acid catalyzed Diels-Alder reactions of cyclopentadiene with 1 (cf. Scheme 1) or 4 (cf. Scheme 3) on reaction conditions.

- A \blacksquare 4, $n\text{-C}_6\text{H}_{14}/\text{CH}_2\text{Cl}_2$ 1:1, TiCl_4 ; \diamond 1, $n\text{-C}_6\text{H}_{14}/\text{CH}_2\text{Cl}_2$ 1:1, TiCl_4 ; \triangle 1, CH_2Cl_2 , EtAlCl_2 ; temp. -63°C ; conc. (of 1 or 4) 0.05 mol/L.
- B \blacksquare 4; \diamond 1; $n\text{-C}_6\text{H}_{14}/\text{CH}_2\text{Cl}_2$ 1:1; 0.75 equiv. TiCl_4 ; conc. (of 1 or 4) 0.05 mol/L.
- C \blacksquare 4; temp. -40°C ; CH_2Cl_2 ; 0.1 equiv. TiCl_4 .



diastereoselectivity	<u>5a</u> : <u>5b</u> = 97 : 3	
recrystallized material (2 cryst.)	<u>5a</u> : <u>5b</u> \geq 99.9 : 0.1	Y.: 81 %
	mp (<u>5a</u>) = 117 $^\circ\text{C}$	
\downarrow LiOH/THF, H_2O		
	(2S)- <u>6</u>	ep \geq 99.9 % Y.: 97 % $[\alpha]_D^{20}$ -147 (c 3, 95 % EtOH)



diastereoselectivity	<u>7a</u> : <u>7b</u> = 97 : 3 <u>8a</u> : <u>8b</u> = 93 : 7	
recrystallized material (3 cryst.)	<u>7a</u> : <u>7b</u> > 99.5 : 0.5 <u>8a</u> : <u>8b</u> > 99.5 : 0.5	Y.: 76 % Y.: 73 %
	mp(<u>7a</u>) = 56 $^\circ\text{C}$, mp(<u>8a</u>) = 38 $^\circ\text{C}$	
\downarrow LiOH/THF, H_2O		
	(S)- <u>9</u> R = CH ₃	ep \geq 99.7 % $[\alpha]_D^{20}$ -107 (c 4, 95 % EtOH) Y.: 97 %
	(S)- <u>10</u> R = H	ep \geq 99.5 % $[\alpha]_D^{22}$ -95 (c 7, CH ₃ OH) Y.: 97 %

With respect to practicality, the following observations are significant: 1. Preparatively convenient reaction conditions may be employed (temperature: near 0 °C, concentration: ca. 0.3 M, ca. 0.1 equiv. of Lewis acid). 2. With TiCl_4 as catalyst no polymerization is observed. 3. All Diels-Alder adducts of enoates of D-pantolactone obtained so far are crystalline, and preferred diastereoisomers were obtained pure by recrystallization. 4. Saponification of 5a, 7a and 8a can be carried out with LiOH in THF/water (cf. experimental procedure⁸). According to careful HPLC analyses, neither epimerization nor racemization, respectively, occurs during this process¹⁰. 5. Auxiliary cleavage gives D-pantoic acid as water-soluble by-product which can be removed by extraction. From the aqueous phase, D-pantolactone can be recovered¹¹.

In view of the results presented above, there can be no doubt that D-pantolactone is the most efficient chiral auxiliary yet probed in asymmetric Diels-Alder reactions with acrylic esters. Other asymmetric syntheses with complexes of types A and C, in particular β -addition reactions, are currently explored.

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

1. Part of this work was presented (G.H.) at "4. Vortragsveranstaltung der Arbeitsgemeinschaft Organische Chemie (Gesellschaft Deutscher Chemiker)", Bad Nauheim (FRG), October 5, 1984.
2. T.Poll, G.Helmchen, B.Bauer, *Tetrahedron Lett.* 1984, 2191.
3. T.Poll, J.O.Metter, G.Helmchen, *Angew.Chem.* 97, 116 (1985).
4. G.Helmchen, R.Schmierer, *Angew.Chem.* 93, 208 (1981); *Angew.Chem., Int. Ed. Engl.* 20, 205 (1981); R.Schmierer, Dissertation, Stuttgart 1980.
5. **Preparation of acrylate 4:** Under nitrogen, propenoyl chloride (113 g) was added over 1 h to a stirred cold (-24 °C) solution of D-pantolactone (130 g) and NET_3 (152 g) in dry CH_2Cl_2 (1.25 L). Stirring at -24 °C for 4.5 h, extraction with 1 N HCl (0.7 L), sat. aq. NaHCO_3 and water, evaporation and distillation ($\text{Cu}/\text{Cu}_2\text{Cl}_2$ as polym. inhibitor) gave 4 in 88 % yield; bp 84 °C (0.1 mm Hg), mp 7.5 °C, $[\alpha]_D^{20} +6.5$ (c 17, CH_2Cl_2).
6. HPLC: Merck LiChrosorb Si 60, 5 μm , 20 cm, petroleum ether/ethyl acetate 9:1, RI detection; ds values (Fig. 1) are based on ratios of peak areas.
7. Reviews: Y.Mori, *J.Synth.Org.Chem.Jpn.* 40, 321 (1982); P.Welzel, *Nachr.Chem.Techn.Lab.* 1983, 979; L.A.Paquette in J.D.Morrison, *Asymmetric Synthesis* 3B, 455 (1984); H.Wurzinger, *Kontakte* (Merck, Darmstadt) Nr. 2, p. 3 (1984); W.Oppolzer, *Angew.Chem.* 96, 840 (1984); *Angew.Chem., Int. Ed. Engl.* 23, 876 (1984).
8. **Diels-Alder reaction:** Under nitrogen, 1 M TiCl_4 in petroleum ether (8.7 mL) was added to a stirred cold (-10 °C) solution of 4 (16.0 g) in dry CH_2Cl_2 /petroleum ether 7:1 (160 mL). After 30 min, cyclopentadiene (7.2 g) was added. After stirring for 1 h at -10 °C, the reaction was quenched by addition of finely pulverized $\text{Na}_2\text{CO}_3 \cdot 10 \text{H}_2\text{O}$ (10 g). On warming to r.t. and stirring pellets formed. Filtration and evaporation followed by two recrystallizations, n-hexane/AcOEt (ca. 5:3), gave 17.0 g (81 %) of pure (HPLC) 5a, mp 116.5-117 °C. **Saponification:** A mixture of 5a (6.2 g), $\text{LiOH} \cdot \text{H}_2\text{O}$ (4.4 g) and THF/water 5:4 (125 mL) was vigorously stirred at r.t. for 26 h. THF was then evaporated in vacuo, the aqueous solution acidified and extracted with n-pentane/ CH_2Cl_2 98:2. Drying (Na_2SO_4) and evaporation of the organic phase gave 3.33 g (97 %) of 6, $[\alpha]_D^{20} -146.9$ (c 3.0, 95 % EtOH).
9. Here, we define the ds value as the percent content of the predominating diastereomer in the mixture of the endo addition products 5a/5b.
10. Epimerization: Determination as described in Ref. 17 of the above Ref. 2. Racemization: Enantiomeric purity was determined via HPLC analysis of diastereomeric amides [phenylglycinol, 1-(1-naphthyl)-ethylamine], obtained from (-)-9 and (-)-10 via their imidazolides (cf. G.Helmchen, H.Völter, W.Schühle, *Tetrahedron Lett.* 1977, 1477).
11. E.T.Stiller, J.C.Keresztesy, J.Finkelstein, *J.Am.Chem.Soc.* 62, 1779 (1940).

(Received in Germany 10 April 1985)