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ON THE ENHANCEMENT OF STEREOSELECTION BY COOPERATION BETWEEN CHIRAL AUXILIARIES. ASYMMETRIC DIELS-ALDER REACTIONS WITH FUMARIC ACID BIS ((*S*)-PROLINE BENZYL ESTER) AMIDE

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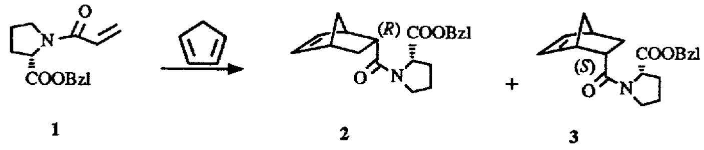
Abstract: Fumaric acid bis ((*S*)-proline benzyl ester) amide reacts with cyclopentadiene in thermal and Lewis acid catalyzed Diels-Alder reactions to give the cycloadducts with high yields and diastereomeric ratios up to 100:1.

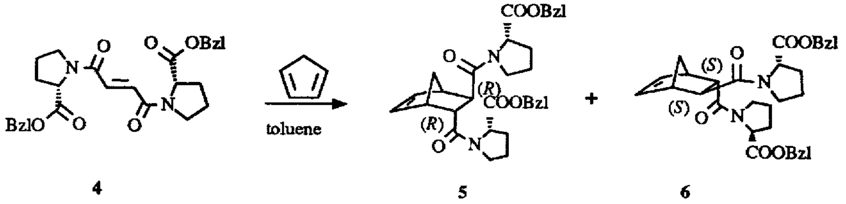
The asymmetric Diels-Alder cycloaddition represents one of the most powerful tools available from modern synthetic methodology.[1)] In this process exceptionally high stereoselectivities may be obtained if the dienophiles used contain not only one but two chiral auxiliaries with synergistic stereodirecting influences. This prediction by Tolbert and Ali[2)] has been addressed and exploited[3)] and the most impressive results were obtained by Helmchen et al. by applying O-ethyl lactate as stereodifferentiating moiety.[3a)] In the course of investigations directed towards the use of the easily accessible amino acid esters as chiral auxiliaries in asymmetric syntheses[4)] we introduced (S)-proline benzyl ester as efficient auxiliary group for asymmetric Diels-Alder reactions.[4c)] For instance, it reacts with cyclopentadiene at 0°C and in the presence of 1 equiv. $TiCl_4$ to give the cycloadducts **2** and **3** in a ratio of 96.5:3.5. Considering the above-mentioned prediction by Tolbert and Ali, we investigated whether the proline ester might also display cooperative properties and, thus, allow for a further enhancement of the stereoselectivity in analogous Diels-Alder reactions.

N-Acryloyl-(*S*)-proline benzyl ester reacts with cyclopentadiene in the absence of a Lewis acid to give the bicyclo[2.2.1]heptenes **2** and **3** in a ratio of 19:81 (ca 1:4). However, if the fumaric acid bis-amide **4** is employed under the same conditions as the dienophile, the observed diastereomeric ratio is 93.5:6.5 (ca. 16:1; ratios of diastereomers were determined by HPLC-analysis of the crude reaction mixtures; diode array detection). These values are in good agreement with Tolbert and Ali's theory and indicate that the two chiral auxiliaries in the fumaric acid derivative **4** are capable of cooperating in these cycloadditions. The predominating (*2R,3R*)-isomer **5** can easily be obtained in enantiomerically pure form by a single



CH_2Cl_2, 1eq. $TiCl_4$: **2** : **3** = 96.5 : 3.5, yield 85%

toluene: **2** : **3** = 19 : 81, yield 27%



0°C: **5** : **6** = 93.5 : 6.5, yield 100%

-30°C: **5** : **6** = 96 : 4, yield 65%

recrystallization from ether/petroleum ether in 80-85% yield. Its absolute configuration was unambiguously determined by X-ray analysis (see Fig. 1.).[5)]

In the analogous $TiCl_4$-mediated Diels-Alder reactions, the observed stereoselectivity depends on the amount of Lewis acid added. Whereas at -40°C in the presence of 0.5-1 equiv. $TiCl_4$ the ratio of **5** to **6** reaches values of up to 100:1, the sense of the asymmetric induction begins to reverse if more Lewis acid is added and with 2 equiv. $TiCl_4$ the (*2S,3S*)-isomer predominates with a ratio of 5:6 = 9:91 (see Fig. 2.). Thus the two possible diastereomers can selectively be obtained by this process by simply varying the concentration of $TiCl_4$. Contrary to the behaviour of N-acryloyl-(*S*)-proline benzyl ester, however, here a change from $TiCl_4$ to $EtAlCl_2$ (1 equiv.) does not induce a reversal in the sense of the diastereomer ratio.

Fig. 1.: X-ray structure of the Diels-Alder adduct **5**.

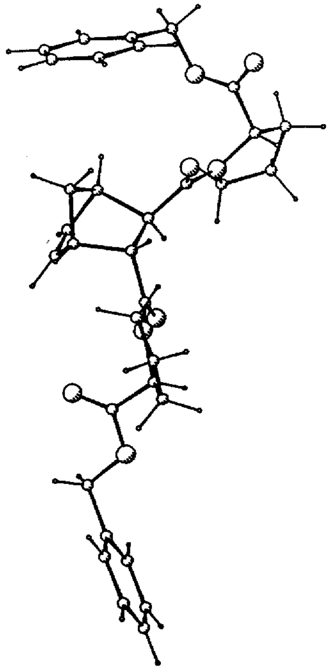
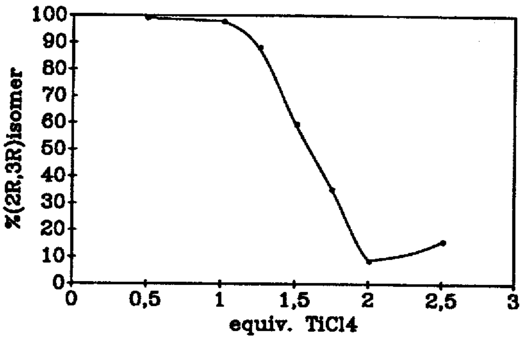


Fig. 2.: Dependence of the asymmetric induction on the amount of Lewis acid added in the $TiCl_4$-catalyzed Diels-Alder reactions of the fumaric acid bis amide **4** with cyclopentadiene.

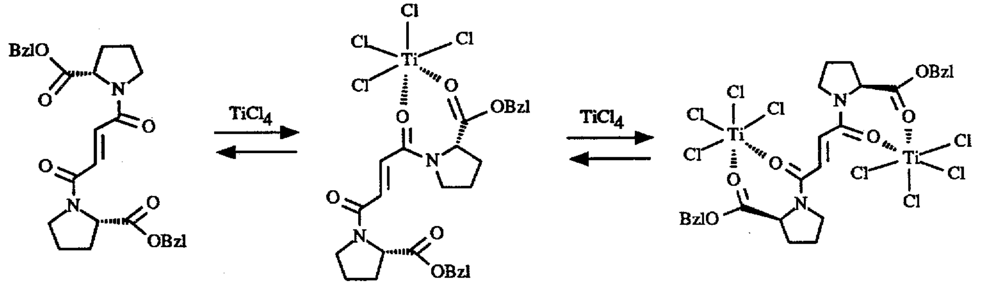


0.5-1.0 equiv. $TiCl_4$: **5**:**6** = 100:1-98:2; yield 85-90%

2.0 equiv. $TiCl_4$: **5**:**6** = 9:91; yield 97%

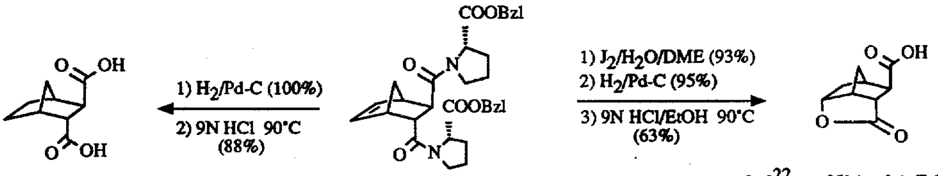
1.0 equiv. $EtAlCl_2$: **5**:**6** = 93.5:6.5; yield 97%

As a mechanistic rationale for this behaviour, which stands in contrast to the observations obtained for fumaroyl(O-ethyl)lactate,[3a)] we propose that the fumaric acid bis-amide in the absence of a Lewis acid preferably adopts the C_2-symmetric conformation **7** with both α,ß-unsaturated amides syn-configured. This assumption is supported by MMX-calculations which clearly favour this conformation.[6)] In addition, a weak NOE-effect between the α-CH of the proline residues and the olefinic protons of the fumaric acid part can be observed and both, the ^{1}H- and the ^{13}C-spectra of **4**, show only one set of signals for the prolines and the fumaric acid part, respectively.[7)] The diene should preferably approach **7** from the less hindered *Re*-side and, as is observed, the (*2R,3R*)-isomer **5** should predominate. In the presence of 1 equiv. of $TiCl_4$ a monochelate **8** may be formed in which for steric reasons one syn- and one anti-configured α,ß-unsaturated amide conformation are preferred. With 2 equiv. $TiCl_4$ present, the bis-chelate **9**, displaying again two syn-conformations, should be predominating. Here, the attack on the double bond from the *Si*-side is favoured and the (*2S,3S*)-isomer is formed in excess.



7 **8** **9**

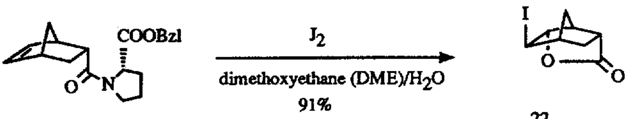
For further synthetic exploitation of the cycloadducts **5** and **6**, a chemical differentiation between the two carboxylic acid derivatives during the removal of the chiral auxiliaries is desirable. This can easily be achieved by an iodolactonization reaction and subsequent removal of the second proline by acidic hydrolysis. This method also allows for an efficient cleavage of the amino acid ester from the acrylamide-derived bicyclo[2.2.1]heptenes and complements the process which is based on the O-alkylation of the amide group with oxonium salts.[4c)] In addition, in **5** the amides can be cleaved by hydrolysis after simultaneous hydrogenolysis of the benzyl ester and the double bond.



5

$[\alpha]^{22}_D$= -85° (c= 2.1, EtOH), m.p. = 140°C

Ref[8)] : $[\alpha]^{22}_D$= -89° (c= 2.2, EtOH), m.p. = 142-143°C



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$[\alpha]^{22}_D$= -115° (c= 2.2, C_6H_6), m.p. = 73°C

Ref[8,9)] : $[\alpha]^{22}_D$= -116° (c= 2.0, C_6H_6), m.p. = 71-72°C

In conclusion, the proline ester presented in this paper proves to be an efficient chiral auxiliary which displays cooperative properties in Diels-Alder reactions in the sense of the prediction given by Tolbert and Ali. As this prediction may also be valid for other transformations, the auxiliary group should also be of great value in other asymmetric processes.

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References:

1) For recent reviews on asymmetric Diels-Alder reactions, see: a) G. Helmchen, P. Karge and J. Weetmann in *"Modern Synthetic Methods"*, R. Scheffold, Ed.; Springer, Berlin 1986; p. 261. b) W. Oppolzer, *Angew. Chem.* **96** (1984) 840; *Angew. Chem. Int. Ed. Engl.* **23** (1984) 876.

2) L. M. Tolbert and M. B. Ali, *J. Am. Chem. Soc.* **106** (1984) 3806.

3) a) H. Hartmann, A. F. A. Hady, K. Sator, J. Weetmann and G. Helmchen, *Angew. Chem.* **99** (1987) 1188; *Angew. Chem. Int. Ed. Engl.* **26** (1987) 1143. b) K. Furuta, K. Iwanaga and H. Yamamoto, *Tetrahedron Lett* **27** (1986) 4507.; K. Furuta, S. Hayashi, Y. Miwa and H. Yamamoto, *Tetrahedron Lett.* **28** (1987) 5841. c) E. J. Corey and W. Su, *Tetrahedron Lett* **29** (1988) 3423.

4) a) H. Waldmann, *Angew. Chem.* **100** (1988) 307; *Angew. Chem. Int. Ed. Engl.* **27** (1988) 275. b) H. Waldmann, *Liebigs Ann. Chem.* **1989** 231. c) H. Waldmann, *J. Org. Chem.* **53** (1988) 6133. In a recent communication M. E. Jung et al. also recognized the potential of pyrrolidines as chiral auxiliaries for asymmetric Diels-Alder reactions: M. E. Jung, W. D. Vaccaro and K. R. Buszek, *Tetrahedron Lett.* **30** (1989) 1893. In a parallel and independent investigation C.Cativiela et al. applied phenylalanine methyl ester as chiral auxiliary in Lewis acid catalyzed Diels-Alder reactions of the corresponding acrylamide with cyclopentadiene. However, with this amino acid derivative the stereoselectivities are not satisfying: M. P. Bueno, Ç. Cativiela, J. A. Mayoral, A. Avenoca, P. Charro, M. A. Roy and J. M. Andrés, *Can. J. Chem.* **66** (1989) 2826.

5) Crystal structure analysis of **5**: monoclinic $P2_1$ (no. 4), a = 9.141(1), b = 6.550(1), c = 24.821(3) Å, ß = 90.35(1)°, V = 1486(1) Å^3, Z = 2, F(000) = 952, d_{calc} = 1.244, d_{obs} = 1.28(2) g/cm^3. Data collection on a E.N. CAD4 diffractometer (Mo-Kα): 4656 independent Friedel pairs (θ_{max} = 30°), 2326 Friedel pairs with $I>2\sigma(I)$. Solution by direct methods (shelx-86), refinement with perfect phenyl groups and calculated hydrogen atoms (290 variables), absolute configuration by fixing the two known (S)-proline centers: R = 0.0957. Atomic parameters and observed vs. calculated structure factors were deposited at the Fachinformationszentrum Energie, Physik, Mathemathik GmbH, D-7514 Eggenstein-Leopoldshafen 2.

6) MMX-calculations were carried out using the program PCMODEL, distributed by Serena Software, Bloomington, Indiana, USA.

7) Further evidence, that α,ß-unsaturated amides prefer the syn- over the anti-conformation comes from n.m.r.-spectroscopic investigations and from X-ray data: a) G. Montaudo, V. Librando, S. Caccanese and P. Maravigna, *J. Am. Chem. Soc* **95** (1973) 6365. b) W. Oppolzer, G. Poli, C. Starkemann and G. Bernardinelli, *Tetrahedron Lett.* **29** (1988) 3559. c) W. Oppolzer, J. Rodriguez, J. Blagg and G. Bernardinelli, *Helv. Chim. Acta* **72** (1989) 123.

8) J. Kredel, Dissertation, Univ. of Munich, 1967.

9) a) J. Sauer and J. Kredel, *Tetrahedron Lett.* **1966** 6359. b) T. Poll, G. Helmchen and B. Bauer, *Tetrahedron Lett.* **25** (1984) 2191.

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