Natural amino acids as chiral auxiliaries in asymmetric Diels–Alder reactions

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To test whether α -amino acids can be efficient chiral auxiliaries in asymmetric Diels–Alder reactions, the chiral dienophile *N*-acryloyl-L-phenylalanine methyl ester was made to react with cyclopentadiene. Diastereofacial selectivity is to a great extent dependent on the Lewis acid used to promote the reaction; whereas moderate excesses of the (1*R*, 2*R*)-cycloadduct were achieved with AlCl_3 , the reaction did not show diastereofacial selectivity when titanium catalysts were used. Moreover, with $\text{Ti}(\text{iPrO})_4$ a transesterification reaction, which leads to the isopropyl ester and competes with the Diels–Alder reaction, was observed. In spite of the structural similarity of this dienophile to the acrylate of (*S*)-ethyl lactate, it behaved very differently in the titanium-catalyzed reactions.

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Afin de déterminer si les acides α -aminés peuvent être des auxiliaires chiraux efficaces dans des réactions de Diels–Alder asymétriques, on a fait réagir le cyclopentadiène avec le diénophile chiral suivant: l'ester méthyle de la *N*-acryloyl-L-phénylalanine. La sélectivité diastéréofaciale dépend beaucoup de l'acide de Lewis utilisé pour promouvoir la réaction; alors que le AlCl_3 nous permet d'obtenir de légers excès du cycloadduit-(1*R*, 2*R*), on n'a pas détecté de sélectivité diastéréofaciale lorsqu'on a utilisé des catalyseurs de titane. De plus, avec le $\text{Ti}(\text{i-PrO})_4$, on a observé une réaction de transestérification qui entre en compétition avec la réaction de Diels–Alder et qui conduit à la formation de l'ester isopropylique. D'un point de vue structural, ce diénophile ressemble beaucoup à l'acrylate du (*S*)-lactate d'éthyle; malgré ces ressemblances, les deux se comportent très différemment au cours de réactions catalysées par le titane.

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High levels of diastereofacial selectivity have been achieved in asymmetric Diels–Alder additions of prochiral 1,3-dienes to dienophiles with a removable, chiral-directing auxiliary (1). However, it is interesting to test whether chiral reagents, both enantiomers of which are inexpensive and easily available, can be efficient chiral auxiliaries in this kind of reaction. In this context, reactions of acrylates (2) and fumarates (3) of several derivatives of chiral hydroxy acids with cyclopentadiene are reported to proceed with good selectivity, mainly when TiCl_4 is used to promote the reaction. The results obtained are explained by the formation of a dienophile– TiCl_4 chelate complex, which amplifies diastereofacial discrimination (4). Also several *N*-acryloyl and *N*-crotonyl compounds, such as the *N*-acyloxazolidones (5) and the *N*-acylsultams (6) derived from camphor, have been used as chiral dienophiles.

In spite of their availability, inexpensive natural α -amino acids, which have been used in a lot of asymmetric reactions (7), have not been tested as chiral auxiliaries in asymmetric Diels–Alder reactions. In view of that, we have studied the reaction between cyclopentadiene and *N*-acryloyl-L-phenylalanine methyl ester (1).

The chiral dienophile was easily obtained by reaction of L-phenylalanine with acryloyl chloride (8), followed by methylation with $\text{BF}_3\text{--MeOH}$ complex. *N*-acryloyl-L-phenylalanine methyl ester 1 was made to react with cyclopentadiene under several conditions, using a molar relationship dienophile: diene

= 1:6 (Scheme 1). The results of the reactions were determined by hplc and are shown in Table 1.

No significant solvent effect was found for the reaction of cyclopentadiene with dienophile *N*-acryloyl-L-phenylalanine methyl ester 1, the slight changes in *endo/exo* selectivity conforming to the pattern found by Berson *et al.* (9) for reactions of acrylates with cyclopentadiene.

As expected, the use of AlCl_3 as a catalyst caused a remarkable increase in both the reaction rate and *endo/exo* selectivity. When the reaction temperature was lowered the *endo/exo* ratio increased, but diastereofacial selectivity was not noticeably modified for reaction temperatures below 0°C.

Helmchen and co-workers have previously reported (2*a*) that the use of TiCl_4 to promote the reaction between cyclopentadiene and the acrylate of (*S*)-ethyl lactate causes a high diastereofacial differentiation, mainly with 0.75 equiv. of Lewis acid. In spite of the structural similarity between the dienophile used by these authors and *N*-acryloyl-L-phenylalanine methyl ester 1, in our case this catalyst gave low diastereofacial selectivity for all tested molar ratios of catalyst:dienophile.

To increase diastereofacial selectivity, a less effective titanium catalyst, $\text{Ti}(\text{iPrO})_4$, was tested. The relationship between the areas of the hplc peaks corresponding to the *endo* products 2*a*:2*b* followed an unexpected pattern, since it increased with increasing reaction temperatures. A careful analysis showed that the peak corresponding to 2*a* was contaminated by a new product, which was obtained by reaction of *N*-acryloyl-L-phenylalanine methyl ester with $\text{Ti}(\text{iPrO})_4$ and identified as

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SCHEME 1

N-acryloyl-L-phenylalanine isopropyl ester **4**. The proportion of this product increases with the reaction time and temperature (Scheme 2).

When the reaction was carried out at -25°C the formation of the isopropyl ester **4** was minimized, and the ratio of **2a**:**2b** approached that obtained with TiCl_4 . Neither the Diels-Alder reaction nor ester formation occurred at still lower reaction temperatures.

N-Acryloyl-L-phenylalanine isopropyl ester **4** was made to react, in CH_2Cl_2 at -40°C , with 6 equiv. of cyclopentadiene using 1.1 equiv. of AlCl_3 to promote the reaction. In comparison to the reaction between *N*-acryloyl-L-phenylalanine methyl

SCHEME 2

ester **1** and cyclopentadiene under the same conditions, a similar *endo*/*exo* ratio (35.4:1) but a lower diastereofacial selectivity (54:46) were obtained.

The low diastereofacial selectivities obtained with titanium catalysts suggest that the coordination of **1** with this kind of catalyst does not lead to a chelate complex, similar to that postulated by Helmchen *et al.* for the acrylate of (*S*)-ethyl lactate - TiCl_4 complex. However, the formation of *N*-acryloyl-

(a) SOCl_2 , followed by $\text{L-H}_2\text{NCH}(\text{CO}_2^-\text{CH}_2\text{Ph})$ and BF_3/MeOH
 (b) Column Chromatography on Silica gel using *n*-Hexane/ Et_2O (1/3) as eluting agent; (c) H_2 , Pd/C; (d) HCl 6N.

SCHEME 3

TABLE 1. Diels–Alder reactions of cyclopentadiene with *N*-acryloyl-L-phenylalanine methyl ester (2)

Lewis acid (equiv.)	Solvent ^a	T (°C)	Time (h)	Yield (%) ^b	endo/exo ratio of 2:3 ^b	Ratio of 2a:2b ^b
—	CH ₂ Cl ₂	25	70	63	2.8:1	52:48
—	Toluene	25	70	49	2.0:1	55:45
AlCl ₃ (1.1)	CH ₂ Cl ₂	25	5	99	7.3:1	60:40
AlCl ₃ (1.1)	Toluene	25	5	99	4.5:1	57:43
AlCl ₃ (1.1)	CH ₂ Cl ₂	0	20	80	15.9:1	70:30
AlCl ₃ (1.1)	CH ₂ Cl ₂	−25	25	95	29.0:1	68:32
AlCl ₃ (1.1)	CH ₂ Cl ₂	−40	50	93	31.3:1	71:29
AlCl ₃ (1.1)	CH ₂ Cl ₂	−60	55	76	42.8:1	65:35
TiCl ₄ (0.75)	CH ₂ Cl ₂	25	20	95	14.9:1	51:49
TiCl ₄ (0.75)	CH ₂ Cl ₂	−15	65	91	12.5:1	51:49
TiCl ₄ (1.1)	CH ₂ Cl ₂	−15	65	86	3.0:1	49:51
TiCl ₄ (1.7)	CH ₂ Cl ₂	−15	65	86	4.0:1	52:48
Ti(ⁱ PrO) ₄ (1.1)	CH ₂ Cl ₂	−25	65	40	5.1:1 ^c	58:42 ^c
Ti(ⁱ PrO) ₄ (1.1)	CH ₂ Cl ₂	−40	190	—	—	—

^aTwenty-five millilitres.^bDetermined by hplc. Column, 5 μm silica Hypersil®. Eluent, ethanol–hexane, gradient 1 to 5% of ethanol in 1 min. Flow rate, 2 mL/min. Detection, 215 nm, $\epsilon_1:\epsilon_{2a}:\epsilon_{2b}:\epsilon_{3a+3b} = 1.686:1.034:1.000:1.030$.^cThe peak corresponding to 2a is contaminated by a small amount of *N*-acryloyl-L-phenylalanine isopropyl ester 4.

L-phenylalanine isopropyl ester 4 indicates that, in spite of the greater basicity of the amide moiety, there may be some degree of coordination to the ester moiety.

To determine the absolute configuration of the major product, *endo*- and *exo*-5-norbornen-2-carboxylic acids, which were prepared by reaction of acrylic acid with cyclopentadiene followed by iodolactone separation, were used to prepare *endo* and *exo* cycloadducts 2 and 3. The *endo* mixture was separated into its components by means of column chromatography on silica gel, using *n*-C₆H₁₄/Et₂O (1:3) as eluting agent. By treatment of 2a or 2b with 20% aqueous NaOH only the ester moiety was hydrolysed and, after 2 h, partial epimerization was observed. Treatment of 2a and 2b with aqueous mineral acids led to a complex mixture of products, probably due to Wagner–Meerwein type rearrangements (10). In view of this, 2a and 2b were hydrogenated and converted without epimerization into both enantiomers of the *endo*-norbornan-2-carboxylic acid, 6a and 6b, by acid hydrolysis. The absolute configurations of these acids were determined by comparing their specific rotations with those given in the literature (11). Under these conditions 2a gave (1*S*, 2*R*, 4*R*) norbornan-2-carboxylic acid and 2b (1*R*, 2*S*, 4*S*) norbornan-2-carboxylic acid, with optical rotations $[\alpha]_D^{26}$ (EtOH) of +30° (*c* 1.2) and −30° (*c* 1.2) respectively (Scheme 3).

In all cases the Diels–Alder reaction led predominantly to the (1*R*, 2*R*)-*endo* diastereomer 2a, which comes from the attack of the cyclopentadiene on the Si face of the dienophile 1. This result can be explained on the basis of reactive conformer 1,

SCHEME 4

with antiplanar enoate conformation, which is similar to those postulated for complexes (7) of “classical” chiral acrylates with only one center capable of coordination (1a) (Scheme 4). The preferential attack on the Si face of the dienophile 1 suggests a possible electronic effect of the phenyl group (12).

Experimental

The ¹H nmr spectra were recorded at 80 MHz with a Bruker model WP 80 CW spectrometer and at 200 MHz with a Varian model XL 200 spectrometer in CDCl₃ with Me₄Si as internal standard. High pressure liquid chromatography was performed using a Hewlett–Packard model 1090 M chromatograph; specific rotations were measured with a Perkin–Elmer model 241-MC polarimeter. Melting points were determined on a Buchi 510 apparatus and are uncorrected.

The chiral dienophile 1 was easily obtained by reaction of L-phenylalanine with acryloyl chloride (8) followed by methylation with BF₃–MeOH complex.

A. Diels–Alder reactions

1. Without a catalyst

One millimole of 1 and 6 mmol of cyclopentadiene were stirred under nitrogen in 25 mL of the appropriate solvent and at the temperature specified (Table 1). After the corresponding time the solvent was removed under reduced pressure and the residue was dissolved in methanol. The solution was filtered and evaporated under reduced pressure to give a solid, which was analyzed by hplc.

2. With a catalyst

One millimole of 1 and the corresponding amount of the catalyst were stirred in 20 mL of dry CH₂Cl₂ under nitrogen at the appropriate temperature for 1 h. A solution of cyclopentadiene (6 mmol) in 5 mL of dry CH₂Cl₂ at the same temperature was then added. The mixture was stirred for the adequate time (Table 1) and treated with a cold 10% aqueous NaOH solution in the case of AlCl₃ or 15% aqueous NaOH solution in the case of titanium catalyst. The organic layer was dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to give a solid, which was analyzed by hplc.

B. Synthesis of *N*-acryloyl-L-phenylalanine isopropyl ester 4

One millimole of 1 and 1.1 mmol of Ti(ⁱPrO)₄ were stirred in 25 mL of dry CH₂Cl₂ under nitrogen at the appropriate temperature for the chosen time. The mixture was then treated with a 15% NaOH solution and the organic layer was dried with anhydrous sodium sulfate, filtered,

and evaporated under reduced pressure to give a solid, which was analyzed by hplc.

To obtain an analytically pure sample of **4**, the reaction was carried out with 2 mmol of $\text{Ti}(\text{PrO})_4$ at room temperature for 72 h, and the solid obtained after the treatment was recrystallized from diethyl ether/*n*-hexane; mp 81–83°C; nmr (CDCl_3) δ : 1.12 (d, 3H), 1.22 (d, 3H), 3.12 (dd, 2H), 4.9 (m, 2H), 5.5 (dd, 1H), 6.1 (m, 3H), 7.25 (m, 5H). *Anal.* calcd. for $\text{C}_{15}\text{H}_{19}\text{NO}_3$: C 68.94, H 7.33, N 5.36; found: C 69.29, H 7.07, N 5.43.

C. Alternative synthesis of methyl-N-(endo-bicyclo[2.2.1]hept-2-carbonyl)-L-phenylalaninates 2a and 2b

Ten millimoles of *endo*-bicyclo[2.2.1]hept-5-en-2-carboxylic acid and 15 mmol of thionyl chloride in dry chloroform were refluxed for 3 h. After this time the solution was evaporated under reduced pressure and the residue was distilled at 14 Torr (1 Torr = 133.3 Pa) to give 80% of the corresponding acyl chloride. This compound was dripped into a solution of 8 mmol of L-phenylalanine in 10 mL of 10% aqueous sodium hydroxide previously cooled in an ice bath (if a precipitate appeared, a little more water was added). After 3 h the stirred solution was acidified with 6 N hydrochloric acid; the precipitate was filtered and recrystallized from water to give a 65% yield of *N*-(endo-bicyclo[2.2.1]hept-5-en-2-carbonyl)-L-phenylalanine. Five millimoles of this compound were refluxed with BF_3 -MeOH complex for 2 h. The solution was washed with sodium acid carbonate solution and extracted several times with ether. The organic layer was separated and dried over anhydrous sodium sulfate. After removing the organic solvent a white oil appeared (yield 90%), which was passed through a chromatographic column of silica gel, using *n*-hexane/ Et_2O = 1:3 as eluting agent, to give both diastereoisomers. These were recrystallized from *n*-hexane to give analytically pure samples of methyl-*N*-(endo-bicyclo[2.2.1]hept-5-en-2-carbonyl)-L-phenylalaninate **2a** and **2b**. mp (**2a**) 114–116°C; nmr (**2a**) (CDCl_3) δ : 1.23–1.40 (m, 3H), 1.88 (m, 1H), 2.82–2.89 (m, 2H), 3.00–3.20 (m, 3H), 3.73 (s, 3H), 4.85 (m, 1H), 5.74 (m, 1H), 6.18 (m, 1H), 7.08–7.32 (m, 5H). *Anal.* calcd. for $\text{C}_{18}\text{H}_{21}\text{NO}_3$: C 72.22, H 7.07, N 4.68; found: C 71.96, H 7.20, N 4.93. For **2b**: mp 80–82°C; nmr (CDCl_3) δ : 1.24–1.45 (m, 3H), 1.92 (m, 1H), 2.81–2.90 (m, 2H), 3.00–3.20 (m, 3H), 3.73 (s, 3H), 4.83 (m, 1H), 5.85 (m, 1H), 6.18 (m, 1H), 7.06–7.38 (m, 5H). *Anal.* found: C 72.52, H 7.33, N 4.21.

Two millimoles each of **2a** and **2b** in 20 mL of methanol were hydrogenated at room temperature and atmospheric pressure using 10% Pd/C as catalyst until completion of the reaction (tlc). In 1 h the hydrogenation was completed, the catalyst filtered off, and the solvent removed under reduced pressure to give white solids, **5a** and **5b**, in quantitative yield. *Anal.* calcd. for $\text{C}_{18}\text{H}_{23}\text{NO}_3$: C 71.73, H 7.69, N 4.65; found for **5a**: C 71.54, H 7.99, N 4.15; found for **5b**: C 71.45, H 7.96, N 4.28.

To identify the major product in the Diels–Alder reaction, 1

millimole each of **5a** and **5b** in 5 mL of 6 N hydrochloric acid were refluxed for 24 h. After this time the solution was extracted with ether and the organic layer was dried over anhydrous sodium sulfate and evaporated to give both *endo* bicyclo[2.2.1]heptan-2-carboxylic acids **6a** and **6b** whose specific rotations were measured, $[\alpha]_D^{26}$ (**6a**) +30° (*c* 1.2, EtOH) and $[\alpha]_D^{26}$ (**6b**) –30° (*c* 1.2, EtOH), and compared with the literature value, $[\alpha]_D^{26}$ 30.6° (*c* 1.2, EtOH) (11).

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