Chiral 2-Cyanocinnamates in Conjugate Addition Asymmetric Enolate Trapping Reactions

Carlos CATIVIELA,* Maria Dolores DIAZ-DE-VILLEGAS, and José Antonio GALVEZ
Instituto de Ciencia de Materiales de Aragón, Departamento de Química Orgánica,
Universidad de Zaragoza-C.S.I.C., 50009 Zaragoza, Spain
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Chiral 2-cyanocinnamates react with L-selectride® to give an intermediate enolate which can be stereoselectively trapped with different halides to afford α-substituted phenylalanine precursors with excellent chemical yields and good diastereomeric excess.

The significance of non-proteinogenic amino acids has recently been recognized in connection with the design and synthesis of enzyme inhibitors as potential pharmaceutical drugs and also for the study of enzymatic reaction mechanisms.[1] In particular α-alkyl α-amino acids have attracted medicinal and biological interest. α-Alkyl α-amino acids also provide a challenging synthetic problem for chemists since the α-alkyl α-amino acids have chiral quaternary carbons, and thus conventional enzymatic optical resolution technology cannot be applied effectively.

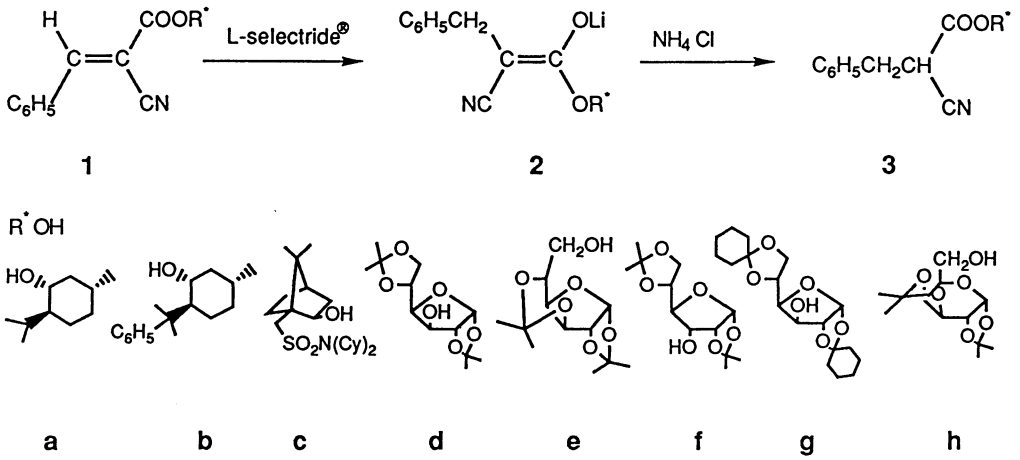
Although numerous new and useful approaches to the asymmetric synthesis of α-amino acids have appeared in recent years,[2] the most usual ones involving the asymmetric hydrogenation of prochiral dehydroamino acid derivatives[3] or the highly stereoselective hydrogenation of chiral, nonracemic dehydroamino acid derivatives[4] suffer from the range of substitutions accessible on the α-R group, so the most recent advances in this field have concentrated on the development of chiral, optically pure amino acid enolate equivalents[5] and amino acid cation equivalents.[6] The attraction of these asymmetric amino acid equivalents is the inherent versatility in preparing a diverse array of amino acids from a few common precursors with the appropriate C–C bond-forming technology. We now wish to develop a new methodology for the synthesis of α-alkyl α-amino acids based on the use of α,β-didehydro compounds as Michael acceptors to afford α-amino acid precursors and in particular we have studied the preparation of α-alkylphenylalanines.

Although 2-acetamidoacrylates[7] can act as acceptors in Michael type reactions, the corresponding 2-acetamidocinnamates are useless as α-amino acid precursors by 1,4-addition as the competitive 1,2-addition is the major reaction, so we had to choose other α-amino acid precursor which could act as a good acceptor in conjugate additions.

Due to their structure, 2-cyanocinnamic esters acted as acceptors in Michael-type reactions[8] with metallic hydrides to afford, after quenching with an electrophile, 2-substituted 2-cyanocinnamic esters which can easily be transformed to the corresponding α-amino acids.[9] Thus chiral 2-cyanocinnamic esters would be potential new and versatile chiral anionic α-alkyl α-amino acid equivalents and we have focused our attention on the study of their behavior as Michael acceptors.

Results and Discussion

In a preliminary study to select the best chiral auxiliary some chiral 2-cyanocinnamic esters were obtained[10] and their reduction with L-selectride® was performed to obtain in all cases the corresponding 3-phenyl-2-



Scheme 1.

cyanopropanoate in nearly quantitative yields. The observed diastereoselectivities, always lower than 15% diastereomeric excess, showed that commercially available (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoyl isoborneol[11] acts as a best chiral auxiliary and so it was chosen to test the conjugate addition-asymmetric enolate trapping reaction. In general this chiral auxiliary confers good to excellent π-face topological differentiations to reactions of their enoyl as well as enolate derivatives.[12]

Treatment of (*E*)-2-cyanocinnamate (**1**) with L-selectride® and subsequent protonation using an ammonium chloride saturated aqueous solution of the resulting enolate provides the saturated cyano ester with high chemical yield but poor diastereomeric excess (14%). Better diastereoface differentiation was observed on palladium-catalyzed hydrogenation of (*E*)-cyanocinnamate (**1**) to give the same saturated cyano ester in nearly quantitative yield and a diastereomeric excess of 55% but, as mentioned before, this synthetic procedure could not be generalized in order to obtain α-alkyl derivatives.

In order to obtain α-alkyl α-amino acid precursors we first tested the electrophilic trapping of the enolate **2** with methyl iodide which afforded the corresponding α-methyl derivative with a high chemical yield but a moderate diastereomeric excess (48%), and therefore we tried to improve the α-stereodifferentiation using two different strategies.

As all factors that make the transition state more compact should enhance the diastereoface selection with respect to the electrophilic attack on the enolate intermediate the exchange of lithium for metals with shorter metal–oxygen bonds should lead to a higher degree of diastereomeric excess, we substituted lithium for diethylaluminium, trimethylsilicon, and tris(diethylamino)-titanium.[13]

Both the aluminium and silicon compounds were unreactive towards the methyl iodide and after quenching we only obtained the corresponding protonated compounds in about 20% diastereomeric excess but the intermediate titanium enolate upon alkylation with methyl iodide afforded the α-methyl derivative **4** with excellent yield and a diastereoselectivity of 64%.

In some cases the presence of additives dramatically changes the reaction course[14] and in his work McGarvey[15] demonstrated that the inclusion of hexamethylphosphoric triamide (HMPA) can change a chelated enolate to an extended one, presumably due to the fact that HMPA occupies the coordination sites on the lithium atom, we therefore have examined the effect of the addition of this external lithium complexing agent together with the electrophile on diastereoselectivity, and observed an increase in diastereoselectivity when one and a half equivalents of HMPA and methyl iodide were simultaneously added. A 64% diastereomeric excess was obtained.

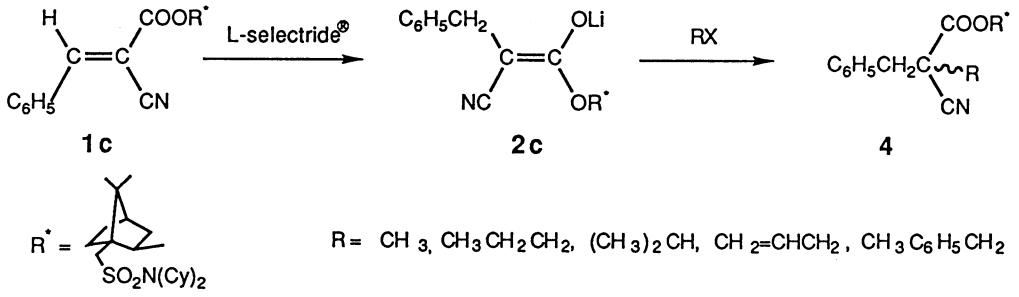
In order to explore the stereoselectivity further, alkylation of the enolate **2** in the presence of HMPA with a range of alkylating agents that differ in reactivity and steric requirements was studied.

The stereochemical composition of the product from each reaction was determined in the crude reaction spectra by integration of the NMR absorptions of the methine proton of the ester in the 300 MHz ^{1}H NMR spectrum (each diastereomer gave a doublet of doublets at about 5 ppm) and by integration of the two signals for the same carbon. In the case of **4e** the stereochemical composition of the product was determined by the integration of the two signals for each aromatic carbon.

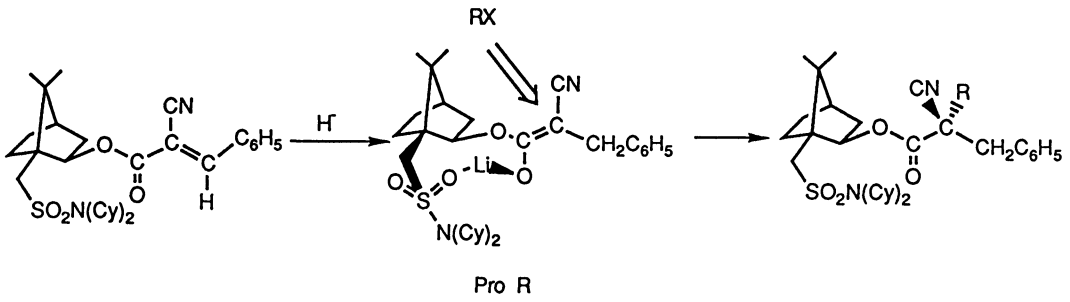
In the case of **4a**, hydrolysis of the cyano ester was performed and the absolute configuration of the major product (R) was determined by comparison of the sign of the specific rotation with the reported value.[9] In all cases the absolute stereochemistry of the product present in the larger diastereomeric excess was assumed to be R. Supporting this assumption is the fact that in all cases the methine proton appearing at a lower field

Table 1. Diastereoselective Enolate Trapping

Run	Electrophile	Product	Yield/%	d.e./%
1	H^+	**3c**	97	14
2	ICH_3	**4a**	96	48 (R)
3	ICH_3/$ClTi[N(CH_2CH_3)_2]_3$	**4a**	83	64 (R)
4	ICH_3/HMPA	**4a**	96	64 (R)
4	$ICH_2CH_2CH_3$/HMPA	**4b**	76	50
5	$ICH_2(CH_3)_2$/HMPA	**4c**	40	65
6	$BrCH_2CH{=}CH_2$/HMPA	**4d**	84	64
7	$ClCH_2C_6H_4CH_3$/HMPA	**4e**	60	60
8	$BrCH_2C_6H_4CH_3$/HMPA	**4e**	87	72



Scheme 2.



Scheme 3.

corresponds to the major diastereomer.

The diastereoface differentiations observed throughout this work are consistent with the model proposed by Oppolzer[16] in the case of 1,4-addition to C(α) substituted enoylsultams. We can assume, as in Oppolzer's case, a chelation by lithium (C=O/SO_2 synperiplanar) and the operation of a cyclic transition state which enforces the C=O/C(α),C(β) *s-cis* conformation regardless of the C(α)-cyano/bornane repulsion. This reactive *s-cis* conformation would entail the stereoselective formation of the enolate when the nucleophile undergoes 1,4-additions to (*E*)-2-cyanocinnamates. Subsequently, the electrophile predominantly approaches opposite to the auxiliary-shielded *re*-face which accounts for the absolute configuration of the major diastereomer. The presence of HMPA with lithium leads to an effective coordination which imposes larger steric requirements on the *re*-face and enhances the diastereoface differentiation.

Experimental

General: All reactions were carried out under Ar with magnetic stirring. Solvents were dried prior to use. Chiral 2-cyanocinnamates (**1**) were prepared according to the previously described procedure.[10] L-Selectride® 1.0 M solution (1 M=1 mol dm^{-3}) in tetrahydrofuran (THF) was purchased from Aldrich. 'Workup' denotes extraction with ether, washing of the organic phase with water, drying with $MgSO_4$, and evaporation (rotatory evaporator). Thin-layer chromatography was performed on Merck precoated silica-gel plates. TLC plates were visualized using UV light and anisaldehyde-sulfuric acid ethanolic solution. Gravity column chromatography was performed using 70—230 mesh (Merck) silica-gel. Melting points were determined on a Büchi 510 capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 1600 FT-IR infrared spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Unity 300 MHz spectrometer. Optical rotations were measured on a Perkin-Elmer 241-C polarimeter. Microanalyses were carried out using a Perkin-Elmer 240-C element analyzer.

Conjugate Addition of L-Selectride® to (*E*)-2-Cyanocinnamates and Subsequent Diastereoselective 'Enolate' Protonation. (1*S*,2*R*,4*R*)-10-Dicyclohexylsulfamoylisobornyl 3-Phenyl-2-cyanopropanoate (3c). To a dry ether solution (25 ml) of (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisobornyl (*E*)-2-cyanocinnamate (**1c**) (0.551 g, 1 mmol) under argon at −78 °C was added a 1.0 M solution of L-selectride® in THF (1.2 ml). After 1 h the low-temperature bath was replaced by an ice bath and stirring was continued for 1 h. After recooling to −78 °C the mixture was quenched with saturated aqueous NH_4Cl solution (5 ml). The cold bath was removed after 5 min and the mixture allowed to warm to room temperature. 'Workup' afforded a mixture of diastereomers (d.e. 14%) as a crude oil which was chromatographed on a silica-gel column (230—400 mesh) eluting with ether–hexane (1 : 1). ^{1}H NMR of the major diastereomer δ=0.78 (3H, s), 0.81 (3H, s), 1.01—2.00 (27H, m), 2.59 (1H, d), 3.10—3.50 (5H, m), 3.77 (1H, dd), 5.00 (1H, dd), 7.27—7.29 (5H, m); ^{13}C NMR of the major diastereomer δ=19.5, 20.1, 25.1, 26.1, 26.3, 26,8, 30.4, 32.3, 33.0, 35.2, 38.7, 39.3, 44.3, 49.1, 49.7, 53.8, 57.4, 80.4, 116.3, 127.5, 128.0, 128.6, 129.1, 135.1, 164.0. Anal. ($C_{32}H_{46}N_2O_4S$) C, H, N.

Conjugate Addition of L-Selectride® to (*E*)-2-Cyanocinnamates and Subsequent Diastereoselective 'Enolate' Methylation. (1*S*,2*R*,4*R*)-10-Dicyclohexylsulfamoylisobornyl 3-Phenyl-2-methyl-2-cyanopropanoate (4a).

Method A: To a dry ether solution (25 ml) of (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisobornyl (*E*)-2-cyanocinnamate (**1c**) (0.551 g, 1 mmol) under argon at −78 °C was added a 1.0 M solution of L-selectride® in THF (1.2 ml). After 1 h the low-temperature bath was replaced by an ice bath and stirring was continued for 1 h. The reaction mixture was allowed to reach room temperature and a solution of CH_3I (1.42 g, 10 mmol) in dry ether (5 ml) was added by syringe. Stirring was kept for 1 day and 'workup' afforded a mixture of diastereomers (d.e. 48%) as a crude oil which was chromatographed on a silica-gel column (230—400 mesh) eluting with ether–hexane (1 : 3).

Method B: To a dry ether solution (25 ml) of (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisobornyl (*E*)-2-cyanocinnamate (**1c**) (0.551 g, 1 mmol) under argon at −78 °C was added a 1.0 M solution of L-selectride® in THF (1.2 ml). After 1 h the low-temperature bath was replaced by an ice bath and stirring was continued for 1 h. After recooling to −78 °C, a solution of chlorotris(diethylamino)titanium (1.2 mmol) in hexane (1.2 ml) was slowly injected, stirring at −78 °C was continued for 45 min. The mixture was allowed to warm to room temperature and a solution of CH_3I (1.42 g, 10 mmol) in dry ether (5 ml) was added by syringe. The solution was stirred for 1 day and 'workup' afforded a mixture of diastereomers (d.e. 64%) as a crude oil which was chromatographed on a silica-gel column (230—400 mesh) eluting with ether–hexane (1 : 3).

Conjugate Addition of L-Selectride® to (*E*)-2-Cyanocinnamates and Subsequent 'Diastereoselective Enolate' Alkylation. To a dry ether solution (25 ml) of (1*S*,2*R*,4*R*)-10-dicyclo-

hexylsulfamoylisobornyl (*E*)-2-cyanocinnamate (**1c**) (0.551 g, 1 mmol) under argon at −78 °C was added a 1.0 M solution of L-selectride® in THF (1.2 ml). After 1 h the low-temperature bath was replaced by an ice bath and stirring was continued for 1 h. The reaction mixture was allowed to reach room temperature and a solution of the corresponding alkyl halide (10 mmol), HMPA (0.27 g, 1.5 mmol) in dry ether (5 ml) was added by syringe.

(1*S*,2*R*,4R)-10-Dicyclohexylsulfamoylisobornyl 3-Phenyl-2-methyl-2-cyanopropanoate (4a). The mixture was stirred for 1 d at room temperature and 'workup' afforded a mixture of diastereomers (d.e. 64%) as a crude oil which was chromatographed on a silica-gel column (230—400 mesh) eluting with ether–hexane (1 : 3). ^{1}H NMR of the major diastereomer δ=0.89 (3H, s), 1.08 (3H, s), 1.43 (3H, s), 1.00—2.20 (27H, m), 2.66 (1H, d), 3.09 (1H, d), 3.22—3.36 (2H, m), 3.37 (1H, d), 3.44 (1H, d), 5.06 (1H, dd), 7.26—7.32 (5H, m); ^{13}C NMR of the major diastereomer δ=20.0, 20.3, 21.9, 25.1, 26.2, 26.4, 26.9, 30.8, 32.1, 33.3, 39.3, 42.1, 44.0, 44.3, 49.3, 49.8, 53.9, 57.4, 80.5, 119.9, 127.6, 128.4, 130.3, 134.0, 167.9. Anal. ($C_{33}H_{48}N_2O_4S$) C, H, N.

(1*S*,2*R*,4R)-10-Dicyclohexylsulfamoylisobornyl 3-Phenyl-2-propyl-2-cyanopropanoate (4b). The mixture was strirred for 3 d at 35 °C and 'workup' afforded a mixture of diastereomers (d.e. 50%) as a crude oil which was chromatographed on a silica-gel column (230—400 mesh) eluting with ether–hexane (1 : 3). ^{1}H NMR of the major diastereomer δ=0.86 (3H, t), 0.89 (3H, s), 0.98 (2H, t), 1.08 (3H, s), 1.08—2.10 (29H, m), 2.65 (1H, d), 3.11 (1H, d), 3.22—3.30 (2H, m), 3.38 (1H, d), 3.49 (1H, d), 5.01 (1H, dd), 7.26—7.32 (5H, m); ^{13}C NMR of the major diastereomer δ=13.8, 18.7, 20.0, 20.3, 25.2, 26.4, 27.0, 31.0, 32.2, 33.4, 37.8, 39.5, 41.9, 44.5, 49.4, 49.9, 54.0, 57.5, 80.7, 119.4, 127.5, 128.3, 130.5, 134.1, 167.9. Anal ($C_{35}H_{52}N_2O_4S$) C, H, N.

(1*S*,2*R*,4R)-10-Dicyclohexylsulfamoylisobornyl 3-Phenyl-2-isopropyl-2-cyanopropanoate (4c). The mixture was stirred for 5 d at 35 °C and 'workup' afforded a mixture of diastereomers (d.e. 65%) as a crude oil which was chromatographed on a silica-gel column (230—400 mesh) eluting with ether–hexane (1 : 3). ^{1}H NMR of the major diastereomer δ=0.89 (3H, s), 1.09 (3H, s), 1.18 (6H, d), 1.06—2.20 (28H, m), 2.63 (1H, d), 3.20—3.35 (4H, m), 3.43 (1H, d), 4.95 (1H, dd), 7.26—7.32 (5H, m); ^{13}C NMR of the major diastereomer δ=18.3, 18.4, 20.3, 20.5, 25.1, 26.1, 26.9, 30.8, 32.0, 33.4, 38.7, 39.4, 44.4, 48.4, 49.2, 49.8, 54.4, 57.3, 80.7, 118.9, 127.3, 128.2, 130.3, 134.2, 166.3. Anal. ($C_{35}H_{52}N_2O_4S$) C, H, N.

(1*S*,2*R*,4R)-10-Dicyclonexylsulfamoylisobornyl 3-Phenyl-2-allyl-2-cyanopropanoate (4d). The mixture was stirred for 3 d at room temperature and 'workup' afforded a mixture of diastereomers (d.e. 64%) as a crude oil which was chromatographed on a silica-gel column (230—400 mesh) eluting with ether–hexane (1 : 3). ^{1}H NMR of the major diastereomer δ=0.87 (3H, s), 1.06 (3H, s), 1.05—2.05 (27H, m), 2.29 (1H, dd), 2.53 (1H, dd), 2.63 (1H, d), 3.13 (1H, d), 3.20—3.35 (2H, m), 3.39 (1H, d), 3.47 (1H, d), 5.00 (1H, dd), 5.10—5.20 (2H, m), 5.66—5.82 (1H, m), 7.31—7.33 (5H, m); ^{13}C NMR of the major diastereomer δ=19.9, 20.3, 25.1, 26.1, 26.3, 27.0, 30.8, 32.1, 33.3, 39.3, 39.9, 41.3, 44.4, 49.0, 49.3, 49.7, 53.9, 57.4, 80.7, 118.7, 120.7, 127.5, 128.3, 130.4, 130.6, 133.8, 167.2. Anal. ($C_{35}H_{50}N_2O_4S$) C, H, N.

(1*S*,2*R*,4R)-10-Dicyclohexylsulfamoylisobornyl 3-Phenyl-2-(4-methylbenzyl)-2-cyanopropanoate (4e). The mixture was stirred for 3 d at room temperature and 'workup' afforded a mixture of diastereomers (d.e. 72%) as a crude oil which was chromatographed on a silica-gel column (230—400 mesh) eluting with ether–hexane (1 : 3). ^{1}H NMR of the major diastereomer δ=0.40 (3H, s), 0.74 (3H, s), 0.80—2.20 (27H, m), 2.26 (3H, s), 2.52 (1H, d), 2.74 (1H, d), 3.01 (1H, d), 3.25 (1H, d), 3.36 (1H, d), 3.46 (1H, d), 3.25—3.35(2H, m), 4.85 (1H, dd), 7.00—7.50 (9H, m); ^{13}C NMR of the major diastereomer δ=19.0, 19.9, 20.8, 25.1, 26.0, 26.2, 26.8, 30.7, 31.8, 33.3, 38.3, 41.1, 42.0, 48.9, 49.5, 51.4, 52.0, 53.8, 57.1, 80.1, 119.1, 127.4, 128.3, 128.7, 129.7, 130.5, 131.0, 133.9, 137.0, 167.2. Anal. ($C_{40}H_{54}N_2O_4S$) C, H, N.

Hydrolysis to 3-Phenyl-2-methyl-2-cyanopropanoic Acid. To a solution of KOH 2 M in methanol (20 ml) was added a 64% diastereomeric excess mixture of (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisobornyl 3-phenyl-2-methyl-2-cyanopropanoate (**4a**) (0.5 g) and the reaction mixture was refluxed for 3 h. The resulting solution was cooled and the solvent evaporated. The residue was diluted in water (15 ml) and washed with ether. The aqueous layer was then acidified and extracted with ether. After extraction, the organic layer was dried over Na_2SO_4 and evaporated under vacuum to afford the corresponding acid (yield 93%) as a pale yellow solid. Mp 86 °C [lit,[9] 88—89 °C], $[\alpha]_D$=−17°, *c*=2.5 in chloroform [lit,[9] for the *S* enantiomer $[\alpha]_D$=+27.4°, *c*=2.556 in chloroform].

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