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Steric and Electronic Requirements of Amide and Ester Groups in Benzylidenemalonates

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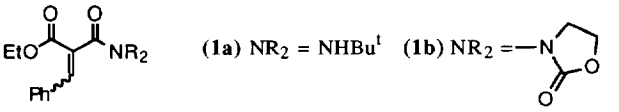
Abstract : Stereoisomeric benzylidinemalonates have been synthesised. In the case of N-(2-ethoxycarbonyl-3-phenylpropenoyl)-2-oxazolidinone, both E- and Z-isomers could be obtained, but the Z-isomer isomerised (>95%) to the E-isomer in the presence of catalytic amounts of Rh(I) complex catalysts. For ethyl tert-butylamidobenzalmalonate, the Z-isomer initially predominates under Knoevenagel conditions, but is very readily converted into the more stable E-isomer, which is here isolated stereoisomerically pure and is the only product of other synthetic routes. The configuration of benzylidinemalonates was established in two cases by X-ray crystallography, and the relative stability of the isomeric forms correctly simulated by MM2 calculations. In both the amide and oxazolidinone series, asymmetric hydrogenation catalysed by cationic Rh complexes gave a configurationally stable product cleanly but in low e.e..

Asymmetric homogeneous hydrogenation of carbon-carbon double bonds catalysed by rhodium or ruthenium diphosphine complexes is one of the most widely utilised enantioselective transformations. Only a limited range of reactants have proved suitable in rhodium catalysis, the two most commonly encountered types being dehydroamino acids or esters and structurally related αβ-unsaturated acids or esters with a further functionality at the α'-position (e.g. itaconates). They succeed because they contain a carbonyl group β-to the olefin in place for binding to the metal centre, and an electron-withdrawing group adjacent to the olefin making the double bond electron-deficient and hence more susceptible to metal binding.[1]

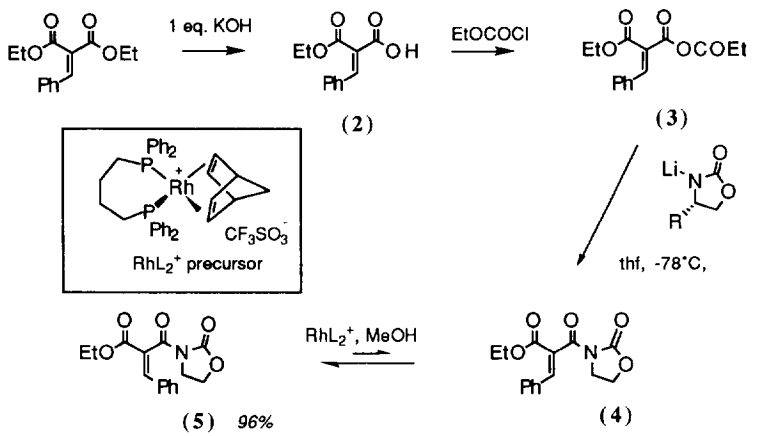
It would be desirable to extend the range of reactants to which rhodium-catalysed asymmetric hydrogenation can be applied and for this reason β-keto amides of type **1** were examined. They possess the prerequisite electron-deficient prochiral olefin but a carbonyl group with the potential for coordination is α- to the olefin in **1a** and α- or γ- to the olefin in **1b**. Whilst it might appear that the integrity of the newly formed asymmetric centre in these β-dicarbonyl adducts might easily be lost *via* enolisation, this was not the case in related systems.[2] For example, acylation of the enolates derived from chiral propionamides afforded diastereomerically pure β-ketoimides in which the β-keto methine proton exhibited strikingly low acidity. In ruthenium asymmetric hydrogenation of the ketone carbonyl group of β-ketoesters it was observed that some can

be hydrogenated with dynamic kinetic resolution; that is to say, both enantiomers of racemic reactant give rise to a single enantiomer of product because their interconversion is faster than reduction. The effectiveness varies widely with the substituents at the stereogenic centre of the reactant, and with the solvent. Thus acyclic β-keto esters are unresponsive to Ru-complex catalysed dynamic kinetic resolution as the rates of epimerisation are low relative to the rates of ketone hydrogenation.

An alternative reductive approach to the synthesis of enantiomerically enriched β-dicarbonyl compounds is via hydrogenation of the alkene in prochiral alkylidenemalonates. Hence the synthesis of compounds of type **1** was carried out.

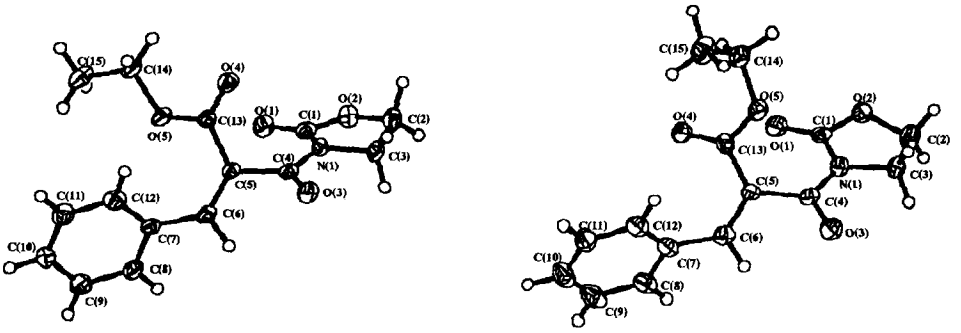


Synthesis of Reactants : Initial routes to an amidoester in this class relied on literature precedent for synthesis of a precursor[3].Thus selective hydrolysis of commercially available diethyl benzalmalonate with one equivalent of potassium hydroxide yielded *Z*-ethyl hydrogenbenzalmalonate (**2**) in 64% yield, with none of the *E*-isomer detected (Scheme 1). Conversion of the acid to the mixed acid anhydride (**3**) followed by reaction with N-lithiated 2-oxazolidinone, prepared in situ, afforded N-(2-ethoxycarbonyl-3-phenylpropenoyl)-2-oxazolidinone (**4**) which crystallised out of the reaction mixture in 27% yield (competing side-reactions at the ethoxycarbonyl group), and was shown to be a single diastereomer, ν_{max} 1699, 1680 cm^{-1}, ^1H NMR revealing the benzylidene-H at 7.53 ppm, downfield of the arene envelope. The stereochemistry about the double bond was assumed to be Z (phenyl trans to amide carbonyl) by analogy with Stammer's early work,which involved Curtius rearrangement of his product to a dehydroamino acid of known configuration.[3] In order to verify this, a sample of X-ray quality was prepared by recrystallisation from EtOH. The stereoisomer (**5**) was prepared adventitiously. During the course of preliminary hydrogenation work (vide infra) it was noted that rapid E-Z interconversion occurred, and that the E-isomer strongly predominated at equilibrium. By conducting the Rh-catalysed isomerisation in the absence of hydrogen, compound (**5**) was isolated in 96% yield.



Scheme 1

The mechanism of the E-Z interconversion probably involves coordination of both of the flanking carbonyl groups to the rhodium cation, followed by reversible attack of a nucleophile (e.g. solvent MeOH) on the now-activated double bond. Consistent with this, it was found that proton acids could effect the interconversion. Data collection for the X-ray structural analysis of (4) was carried out at ambient, but more satisfactorily at 150K; reported parameters relate to the latter refinement. There are two independent molecules in the unit cell which correspond to the s-cis or s-trans conformation about the αβ-unsaturated ester moiety (Figure 1).



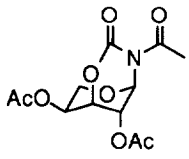
Molecule A **Molecule B**

Figure 1. Structures of the two molecules of (4) both viewed on the $C_6C_5C_{13}$ plane, showing the atom labelling used and the difference in conformation about the C(5)-C(6) bond. The small circles represent H atoms.

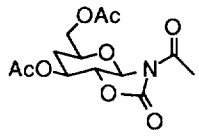
Table 1: Bond Lengths (Å) and Bond Angles (°) for Compound (4), 150K.

	Molecule (A)	Molecule (B)		Molecule (A)	Molecule (B)
Bond lengths					
C(1)-O(1)	1.200(4)	1.206(4)	C(4)-N(1)-C(1)	126.0(3)	127.0(3)
C(1)-O(2)	1.343(4)	1.331(4)	C(4)-N(1)-C(3)	120.1(3)	121.2(3)
C(2)-O(2)	1.457(4)	1.455(4)	O(2)-C(1)-O(1)	123.4(3)	122.9(3)
C(4)-O(3)	1.218(4)	1.213(3)	N(1)-C(1)-O(1)	128.0(3)	127.4(3)
C(13)-O(4)	1.210(4)	1.207(4)	N(1)-C(1)-O(2)	108.6(3)	109.7(3)
C(13)-O(5)	1.331(4)	1.343(4)	C(3)-C(2)-O(2)	105.3(3)	105.6(3)
C(14)-O(5)	1.459(4)	1.465(4)	C(2)-C(3)-N(1)	100.7(3)	101.4(3)
C(1)-N(1)	1.391(4)	1.385(4)	N(1)-C(4)-O(3)	118.6(3)	119.0(3)
C(3)-N(1)	1.467(4)	1.464(4)	C(5)-C(4)-O(3)	121.4(3)	121.4(3)
C(4)-N(1)	1.379(4)	1.383(4)	C(5)-C(4)-N(1)	120.0(3)	119.6(3)
C(3)-C(2)	1.514(5)	1.518(5)	C(6)-C(5)-C(4)	116.9(3)	115.3(3)
C(5)-C(4)	1.503(5)	1.501(5)	C(13)-C(5)-C(4)	114.5(3)	120.6(3)
C(6)-C(5)	1.342(4)	1.341(4)	C(13)-C(5)-C(6)	128.0(3)	124.1(3)
C(13)-C(5)	1.486(4)	1.491(4)	C(7)-C(6)-C(5)	130.3(2)	130.4(2)
C(7)-C(6)	1.473(4)	1.472(4)	C(8)-C(7)-C(6)	123.6(3)	118.6(3)
C(8)-C(7)	1.398(4)	1.393(4)	C(12)-C(7)-C(6)	118.4(3)	122.6(3)
C(12)-C(7)	1.389(4)	1.390(4)	C(12)-C(7)-C(8)	117.8(3)	118.6(3)
C(9)-C(8)	1.376(4)	1.385(5)	C(9)-C(8)-C(7)	120.5(3)	120.8(4)
C(10)-C(9)	1.383(5)	1.372(5)	C(10)-C(9)-C(8)	121.2(3)	119.8(4)
C(11)-C(12)	1.375(4)	1.385(5)	C(11)-C(10)-C(9)	119.0(3)	120.5(4)
C(12)-C(11)	1.391(4)	1.390(4)	C(12)-C(11)-C(10)	120.2(3)	119.6(4)
C(15)-C(14)	1.496(5)	1.494(5)	C(11)-C(12)-C(7)	121.2(3)	120.5(3)
Bond angles			O(5)-C(13)-O(4)	124.4(3)	124.2(3)
C(2)-O(2)-C(1)	110.3(3)	110.0(3)	C(5)-C(13)-O(4)	122.3(3)	125.3(3)
C(14)-O(5)-C(13)	116.4(3)	116.5(3)	C(5)-C(13)-O(5)	113.3(3)	110.5(3)
C(3)-N(1)-C(1)	111.4(3)	111.3(3)	C(15)-C(14)-O(5)	106.6(3)	110.8(3)

The main difference is in the αβ-unsaturated ester group, transoid in **A** and cisoid in **B**. Examination of the relevant X-ray literature indicates that both rotamers are accessible in the solid-state structures of unsaturated esters, although the s-cis form is much more common.[4] Detailed comparision of the molecular geometry (Table 1) shows that all the corresponding bond lengths and most of the angles are very similar in the two molecules, but some angles around the benzylidene double bond are significantly different. In particular, the variations in the angles C(13)-C(5)-C(4) [114.5(3)° (**A**), 120.6(3)° (**B**)] and C(13)-C(5)C(6) [128.0(3)° (**A**), 124.1(3)° (**B**)] are much larger than the rest. It is impossible to orientate the two conjugated carbonyl groups and the alkylidene double bond in the same plane because of the ensuing hard non-bonded interactions. For both molecules **A** and **B**, it is the amide rather than the ester which rotates more out of the plane of conjugation. This leads to local distinctions between the two structures compensated by the differences noted, explicable in terms of the intramolecular short contacts O(1)···O(5) = 2.915(3)Å in **A** and O(5)···C(8) = 2.901(3)Å in **B**, arising from the particular orientations of the -CO-OCH_2CH_3 groups. As is general in oxazolidinones,[5] the endo- and exocyclic carbonyl groups are distal, with torsion angle O(3)C(4)-N(1)C(1) being close to 180°. This constrained geometry is a key factor in understanding their success as chiral auxiliaries.[6] A CSSR search of all of the X-ray crystal structures containing this functionality reveals a characteristic torsion angle of 164° to 180° for the same bond, with two exceptions to this generalisation being found in the rigid systems (**6**) and (**7**), where the specified torsion angles are 143° and 144° respectively.[6]



(**6**)



(**7**)

When a similar synthetic approach was applied to the corresponding t-butyl amide (see Scheme 2), a single diastereomeric product was again observed, ν_{max} 1771, 1634 cm^{-1}. Recrystallisation from hexane \ CH_2Cl_2 yielded X-ray quality crystals whose structure is shown in Figure 2. Strikingly, it is in the E- rather than the Z-sterochemical family.

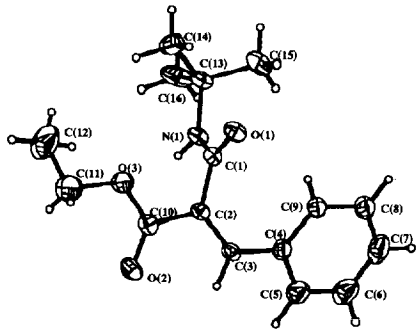


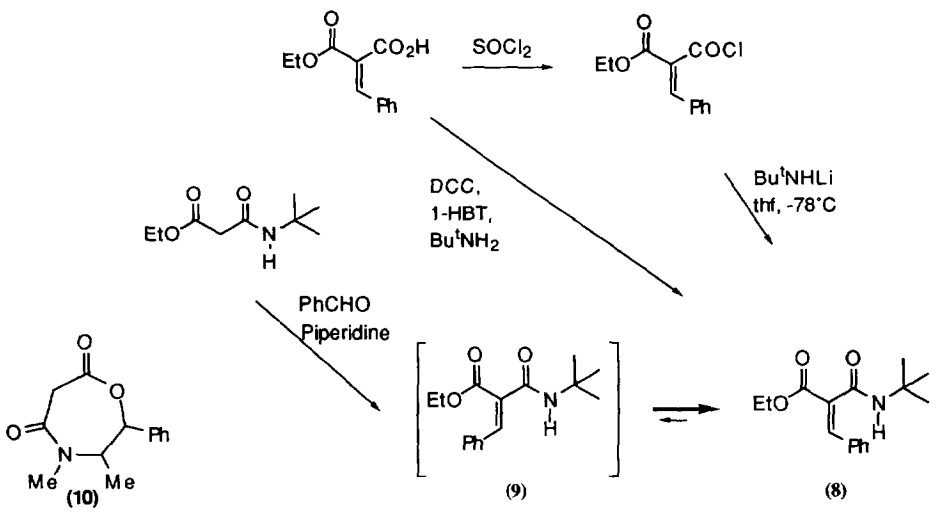
Figure 2. Structure of (8) showing the atom labelling used. The small circles represent the H atoms.

Table 2: Bond Lengths (Å) and Bond Angles (°) for (8)

Bond lengths			
C(1)-O(1)	1.229(4)	C(10)-O(2)	1.204(4)
C(10)-O(3)	1.330(4)	C(11)-O(3)	1.462(5)
C(1)-N(1)	1.334(4)	C(13)-N(1)	1.485(4)
C(2)-C(l)	1.505(6)	C(3)-C(2)	1.328(5)
C(10)-C(2)	1.490(5)	C(4)-C(3)	1.469(5)
C(5)-C(4)	1.391(5)	C(11)-C(4)	1.388(5)
C(6)-C(5)	1.378(6)	C(7)-C(6)	1.361(7)
C(8)-C(7)	1.362(7)	C(11)-C(8)	1.388(6)
C(12)-C(11)	1.328(7)	C(14)-C(13)	1.514(6)
C(15)-C(13)	1.525(6)	C(16)-C(13)	1.523(6)
Bond angles			
C(11)-O(3)-C(10)	116.5(4)	C(13)-N(1)-C(1)	125.7(3)
N(1)-C(1)-O(1)	125.1(4)	C(2)-C(1)-O(1)	120.7(3)
C(2)-C(1)-N(1)	114.2(3)	C(3)-C(2)-C(1)	125.2(4)
C(10)-C(2)-C(1)	116.4(4)	C(10)-C(2)-C(3)	118.3(4)
C(4)-C(3)-C(2)	129.0(4)	C(5)-C(4)-C(3)	118.8(4)
C(9)-C(4)-C(3)	123.3(4)	C(9)-C(4)-C(5)	117.9(4)
C(6)-C(5)-C(4)	121.1(5)	C(7)-C(6)-C(5)	120.2(6)
C(8)-C(7)-C(6)	119.8(5)	C(9)-C(8)-C(7)	121.1(5)
C(8)-C(9)-C(4)	119.9(5)	O(3)-C(10)-O(2)	123.9(4)
C(2)-C(10)-O(2)	126.2(4)	C(2)-C(10)-O(3)	109.9(4)
C(12)-C(11)-O(3)	111.1(5)	C(14)-C(13)-N(1)	109.8(4)
C(15)-C(13)-N(1)	109.0(4)	C(15)-C(13)-C(14)	110.7(4)
C(16)-C(13)-N(1)	106.2(3)	C(16)-C(13)-C(14)	110.6(4)
C(16)-C(13)-C(15)	110.3(4)		

This structure clearly establishes the E-stereochemistry, with molecular dimensions (Table 2) as expected, but some important dihedral angles are quite different from the corresponding values in (**4**). Thus in amide (**8**), the carbonyl groups linked to the s-cis ester and amide fragments are respectively planar with and perpendicular to the alkene, with torsion angles O(2)-C(10)-C(2)-C(3) = 0.9(3)° and O(l)-C(l)-C(2)-C(3) = 89.7(3)°. This situation is in sharp contrast with the oxazolidinone (**4**) where the equivalent torsion angles are : *ester* O(4)-C(13)-C(5)-C(6) = 32.2(3)° (**A**), 24.0(3)° (**B**) and *imide* : O(3)-C(4)-C(5)-C(6) = 53.7(3)° (**A**), 44.7(3) ° (**B**). Part of the distortion of the ester group in compound (**4**) is due to the alleviation of its non-bonded interactions with the Ph group, but it is still closer to coplanarity with the double bond than is the unconstrained oxazolidinone ring. In (**8**) the NH proton is involved in an intermolecular hydrogen bond to the O-alkyl group of the ester.

Knoevenagel condensation of benzaldehyde with ethyl-*t*-butylamido acetate, itself formed from a Ritter reaction on ethyl cyanoacetate, led initially to a mixture of geometrical isomers (Z:E (**8**) : (**11**) = 4:1 from ^{1}H nmr analysis). On standing the mixture was converted into the E-isomer, which was the only species isolated on workup, although GC/MS analysis of the initial reaction mixture confirmed the presence of two separate species both with m/z 275. We were unsuccessful in isolating the pure Z-isomer and it appears to be considerably more labile than the corresponding Z-oxazolidinone (**4**). In this context it is interesting that the corresponding condensation of the cyclic malonate derivative (**10**) with benzaldehyde led to the isolation only of the Z-isomer and in that case E = Z isomerisation was not reported[7]. An alternative preparation, via DCC coupling, gave exclusively the E-isomer. (Scheme 2)



Scheme 2

Molecular Modelling :

In view of the greater thermodynamic stability of the E-isomer compared to the Z-isomer in both pairs of benzylidenemalonates, it proved of interest to determine whether molecular mechanics gave agreement with the experimental observations. MM2 calculations were carried out using Macromodel version version 3.5a.[8] For the oxazolidinone series , the E-isomer is predicted to be 6 kJ/mol more stable than the Z-isomer. The difference in energy is not due to any one contributing factor but is dispersed between torsional, bending and van der Waal's energies (*ca.* 2kJ/mol each). As an X-ray crystal structure of the metastable Z-isomer had been obtained, a useful comparison of the more important torsion angles can be carried out. Using an identical numbering scheme, the torsion angle O(1)-C(2)-N(1)-C(4) was virtually identical to that arrived at crystallographically (167.2° vs. 167.9°). The most significant difference was that the ethoxycarbonyl group was more out of the plane of the ethylenic fragment in the MM2 structure than in the X-ray, O(4)-C(13)-C(5)-C(6) = 47° from MM2 vs 32° and 24° for the two independent X-ray molecules. For the more stable E-isomer (**5**), the MM2-derived torsion angle between the imide oxygen carbonyls, O(3)-C(4)-N(1)-C(1) is 169^0. Significantly, the ethoxycarbonyl group is now close to planarity with the C-C double bond, the torsion angle O(4)-C(13)-C(5)-C(6) being 8.6°.

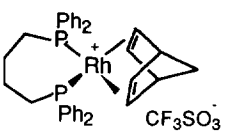
In the t-butyl imide series, MM2 calculations again suggest that the the E-isomer is favoured by 4kJ / mol. The calculated structure of the E-isomer compares reasonably with that obtained crystallographically. The carbon-carbon double bond is coplanar with the ethoxycarbonyl group but describes a torsion angle of 146.7° with the amide carbonyl group; whilst in the X-ray structure of compound (**8**) it is orthogonal. By MM2 calculations, the less favoured Z-isomer has the C-C bond at an angle of 13.3° to the ethoxycarbonyl group and 163° to the amide carbonyl group, i.e O(2)-C(10)-C(2)-C(3) = 13.3^0 and O(1)-C(1)-C(2)-C(10) = 163°.

The main conclusion to be drawn from these studies is that the ester carbonyl group is more strongly conjugated with the double bond than is either the amide or oxazolidinone carbonyl group, irrespective of whether the E- or Z-series is considered. This ensures that the distortion which occurs to reduce in-plane non-bonded interactions involves preferential rotation of the amide out of the π–atom plane. In simple αβ-unsaturated amides lacking this constraint the carbonyl group is coplanar with the double bond, with the carbonyl group in s-cis

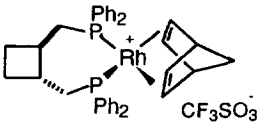
conformation.[9]. When there is a bulky β-substituent on a Z-double bond, the amide carbonyl group can be close to orthogonal to that bond, exactly as observed here.[10]

Preliminary Hydrogenation Studies :

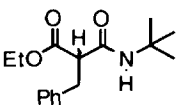
Reductions were carried out according to the protocol of Table 3. Compared to the reduction of dehydroamino esters, turnover was quite slow, and complete reduction was achieved at ambient pressure in MeOH only with Rh complexes *I* and *II*; the corresponding BINAP complex was inactive. The hydrogenation products (**11**) and (**12**) both contain a methine proton at the newly created chiral centre. ^{1}H nmr spectroscopy showed that the chemical shifts of these protons were quite different. In the amide derivative (**11**) the signal appears at 3.3 ppm. In contrast, the corresponding proton in the oxazolidinone derivative (**12**) resonated at 4.9 ppm, consistent with a deshielding interaction between the endocyclic carbonyl group and that proton.



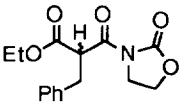
(I)



(II)



(11)



(12)

Table 3. Hydrogenation of benzylidenemalonates

Substrate	Catalyst(mol %)	Time	Product (%)	e.e (%)
4	BUTAPHOS (20)	48 h	**12** (100)	-
8	BUTAPHOS (20)	48 h	**11** (100)	-
4*	(-)-TBCP (4)	3000 s	**12** (100)	15
5*	(-)-TBCP (4)	1200 s	**11** (100)	8
8	(-)-TBCP (4)	15000 s	**11** (100)	18

* 1.6 atm of H_2 .

The optical activity of the reduced products was measured by ^{1}H nmr spectroscopy using the chiral shift reagent *tris*-[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium (III) in d_8-toluene at ambient temperature. The enantioselectivities observed were low (8-18%) but the value did not diminish with time, indicating that the asymmetric centre was not compromised by enolisation in either case under ambient conditions. Further work will be carried out with a broader range of Rh and Ru catalysts.

Experimental

General methods: Elemental Microanalysis were carried out by Mrs V. Lamburn in the Dyson Perrins Laboratory, using a Carlo Erba 1106 elemental analyser. N.m.r. Spectra: ^{1}H n.m.r. spectra were recorded on Varian Gemini 200 (200 MHz), Bruker WH 300 (300 MHz) and Bruker AM 500 (500 MHz) spectrometers; ^{13}C n.m.r. spectra were recorded on Bruker AM 250 (62.9 MHz) and Varian Gemini 200 (50.3 MHz) spectrometers. Chemical shifts for ^{1}H and ^{13}C spectra are quoted as parts per million (p.p.m.) downfield of tetramethylsilane. ^{1}H n.m.r. chiral shift experiments were carried out in C_7D_8 adding portions of the europium shift reagent as a 0.2M solution in C_7D_8 by microsyringe, and recording the ^{1}H spectrum to the point of optimum separation. IR Spectra were recorded on a Perkin Elmer 1750 Fourier Transform spectrometer. Mass spectra were recorded on V.G. Micromass and V.G. Masslab 20-250 spectrometers. Values are followed by the intensity in parentheses as a percentage of the base peak. Melting points were recorded on a Reichert-Koffler block and are uncorrected. All manipulations of oxygen and water sensitive materials were carried out under an argon atmosphere using standard vacuum line and Schlenk techniques.

Flash Chromotography refers to column chromotography using head pressure by means of compressed air, using Kiesegel 60 PF_{254}. Preparative thin layer chromotography (prep. tlc) was performed using Kiesegel HF_{254}. Solvents were purchased from Rhone-Poulenc and were dried prior to use according to the procedures described by Perrin and Armarego. Deuterated solvents and reagents were purchased from the Aldrich Chemical company. Hydrogenations were carried out in a constant-volume apparatus[11] with an initial pressure of 1.6 bar and a controlled temperature of 25°C. Rhodium catalysts were prepared as previously described.[12]

Z-N-(2-Ethoxycarbonyl-3-phenylpropenoyl)-oxazolidinone **(4)**

To a solution of Z-ethyl hydrogen benzalmalonate, prepared by the method of Stammer,[3] (5.00 g, 22.7 mmol) in dry tetrahydrofuran (30 ml), under an atmosphere of argon, was added di-isopropylethylamine (4.35 ml, 25 mmol). The solution was chilled to -5°C (salt/ice-bath), and a solution of ethyl chloroformate (2.40 ml, 25 mmol) in dry tetrahydrofuran (10 ml) was added dropwise, while maintaining the temperature at -5°C. After 1 h, a solution of lithium 2-oxazolidinone (25 mmol) in dry tetrahydrofuran (20 ml), prepared *in situ* by the reaction of n-butyllithium (12.5 ml, 25 mmol) with 2-oxazolidinone (2.175 g, 25 mmol), was added at -78°C and the reaction mixture was stirred for 12 h and then allowed to warm up to 0°C. An ammonium chloride solution (25 mmol) was then added and the resulting mixture extracted with diethyl ether (3 x 25 ml). The ethereal extracts were then combined and dried ($MgSO_4$). Solvents were removed *in vacuo* giving a viscous orange liquid. Crystallisation occurred after 3 h and was complete after 24 h to afford (**4**) as white *crystals*, (1.69 g, 27%), m.p. 101-103°C, δ_H (300 MHz, $CDCl_3$) 7.53 (1H, *s*, C<u>H</u>=), 7.52-7.35 (5H, *m*, Ph), 4.49 (2H, *t*, J=7.7, N-C<u>H</u>$_2$), 4.16 (2H, *q*, J=7.1, C<u>H</u>$_2$CH$_3$), 4.14 (2H, *t*, J=7.7, CH$_2$C<u>H</u>$_2$O), and 1.15 (3H, *t*, J=7.1, CH$_2$C<u>H</u>$_3$). δ_C (50.3 MHz, $CDCl_3$) 166.5 (<u>C</u>O$_2$Et), 163.8 (=C<u>C</u>O-N), 153.6 (N-<u>C</u>O$_2$), 146.2 (Ph<u>C</u>H), 133.7 (*ipso* C), 130.3 (*meta* C), 130.1 (*para* C), 128.8 (=<u>C</u>CO-N), 128.0 (*ortho* C), 62.7 (NCH$_2$<u>C</u>H$_2$), 61.0 (N-CH$_2$), 42.7 (<u>C</u>H$_2$CH$_3$), and 13.5 (CH$_2$<u>C</u>H$_3$). υ_{max} (KBr) 2995, 2928, 1780, 1699, 1680 (NC=OOCH$_2$), 1624 (C=OOEt), 760, and 695 cm^{-1}; *m/z* 307 (M+NH$_4^+$, 45%), 244 (15), 220 (20), 203 (21), 88 (90), and 77 (5); (Found: C, 62.26; H, 5.30; N, 4.78. $C_{15}H_{15}NO_5$ requires C, 62.27; H, 5.22; N 4.86%).

E-N-(2-Ethoxycarbonyl-3-phenylpropenoyl)-oxazolidinone **(5)**

1,4-*Bis*(diphenylphosphino)butane norborna-2,5-diene rhodium trifluoromethanesulphonate (0.004 g, 3%) was dissolved in degassed methanol (1 ml) in a Schlenk tube. The solution was degassed by using freeze-pump-thaw techniques (6 times). Hydrogen was then added and the solution vigerously stirred. After 5 mins stirring, the hydrogen was removed by the freeze-pump-thaw method and replaced with argon. Z-N-(2-Ethoxycarbonyl-3-phenylpropenoyl)-2-oxazolidinone (0.05 g, 0.16 mmol) was added to the solution, which was degassed a further 3 times with argon. After 48 h, the product was obtained and purified by preparative tlc (ethyl acetate / hexane = 1/1) to afford (**5**) (0.49 g, 98%) as white *crystals*. m.p. 96-98°C. δ_H (500 MHz, $CDCl_3$) 7.81 (1H, *s*, C<u>H</u>=), 7.42-7.35 (5H, *m*, ArH), 4.44 (2H, *br t*, O<u>C</u>H_2CH_2N), 4.31 (2H, *q*, J=7.0, O<u>C</u>H_2CH_3), 4.16 (2H, *br t*, N<u>C</u>H_2CH_2), and 1.32 (3H, *t*, J=7.0, CH_3CH_2); δ_C (50.3 MHz, $CDCl_3$) 166.2 (C=O), 163.9 (C=O), 153.6 (N-<u>C</u>O_2), 146.2 (Ph<u>C</u>H), 133.0 (*ipso* C), 130.6 (PhC), 129.6 (PhC), 129.0 (PhC), 127.1 (CO<u>C</u>CO)), 62.3 (NCH_2<u>C</u>H_2), 61.6 (N-CH_2), 42.1 (<u>C</u>H_2CH_3), and 14.1 (CH_3). υ_{max} (KBr) 3436, 2980, 1771, 1697, 1633, 1479, 1450, 1387 and 687 cm^{-1}. *m/z* 307($M+NH_4^+$, 17%),), 290(40), 244(55), 220(50), 203(100), 105(40), and 88(90).

E-Ethyl tert-butylamidobenzalmalonate **(8)**

Thionyl chloride (0.725 ml, 10 mmol) was added to a stirred solution of Z-ethyl hydrogen benzalmalonate (1.10 g, 5 mmol) in dry dichloromethane (10 ml). Pyridine (0.5 ml) was slowly added to the mixture as a catalyst. After 8 h under reflux, the acid chloride formed was transferred to dry tetrahydrofuran (10 ml) and cooled to -78°C. Lithiated *tert*-butylamine, formed by the reaction of *tert*-butylamine (0.525 ml, 0.366 g, 5 mmol) with n-butyl lithium (2.5 ml, 2M solution in tetrahydrofuran), was added at -78C°. After stirring for 3 h, the mixture was filtered (to remove LiCl) and the solvents removed *in vacuo* . Crystallisation occurred after 3 days to afford (**8**) as white *crystals* (0.57 g, 41%), m. p. 86-88°C, δ_H (500 MHz, $CDCl_3$) 7.61-7.59 (3H, *m*, 1 vinyl H, 2 PhH), 7.37-7.36 (3H, *m*, PhH), 5.49 (1H, *br s*, NH), 4.28 (2H, *q*, J=7.0, CH_2CH_3), 1.38 (9H, *s*, $C(CH_3)_3$), and 1.33 (3H, *t*, J=7.0 Hz, CH_3CH_2). δ_C (50.3 MHz, $CDCl_3$) 165.5 (C=O), 140.9 (<u>C</u>HPh), 133.2 (*ipso* C), 130.5 (PhC), 130.0 (PhC), 128.8 (PhC), 128.8 (PhCH=<u>C</u>), 61.4 (CH_2O), 51.7 (<u>C</u>$(CH_3)_3$), 28.2 (C(<u>C</u>$H_3)_3$), and 13.9 (CH_2CH_3).υ_{max} (KBr) 3064, 2961, 1771, 1634, 1556, 1498, 1478, 1455, 875, 789, 766, and 699. *m/z* 278(60%), 276(100), 248, 220, 218, 188, 177, 106, 74, and 58. (Found: C, 69.59; H, 7.56; N, 4.94. $C_{16}H_{21}NO_3$ requires C, 69.82; H, 7.69; N 5.11%). The same stereoisomer was formed from a Ritter reaction on E-ethyl 2-cyano-3-phenylpropenoate[13] (isobutene, conc. H_2SO_4, AcOH, 20°C, 6h.) in 45% purified yield or by DCC coupling of Z-ethyl hydrogen benzalmalonate[3] with t-butylamine. A second compound which readily isomerised to the E-amide (**8**), and assumed to be the Z-isomer, was formed in the Knoevenagel condensation of ethyl t-butylamidoacetate[14] and excess benzaldehyde (piperidine, 20°C).

N-(2-Ethoxycarbonyl-3-phenylpropionyl)-2-oxazolidinone **(12)**

1,4-*Bis*(diphenylphosphino)butane norborna-2,5-diene rhodium trifluoromethanesulphonate (0.004 g, 3%) was dissolved in degassed methanol (1 ml) in a Schlenk tube. The solution was degassed by using freeze-pump-thaw techniques (6 times). Z-N-(2-Ethoxycarbonyl-3-phenylpropenoyl)-2-oxazolidinone (0.05 g, 0.16 mmol) was added to the solution, which was degassed a further 3 times with argon. Hydrogen was then added and the

solution vigorously stirred. After 72 h, the product was obtained and purified by preparative tlc (ethyl acetate / hexane = 1/1) to afford (**12**) (0.48 g, 96%) as white *crystals*. m.p. 141-143°C. δ_H (500 MHz, $CDCl_3$) 7.27-7.18 (5H, *m*, ArH), 4.97 (1H, *dd*, J=6.1, J=8.9, $PhCH_2C\underline{H}$), 4.37 (1H, *ddd*, J=6.4, J=9.3, J=15.4, $OC\underline{H}HCH_2N$), 4.28 (1H, *ddd*, J=7.2, J=9.3, J=16.5, $OCH\underline{H}CH_2N$), 4.17 (2H, *q*, J=7.1, $CH_3C\underline{H}_2$), 4.04 (1H, *ddd*, J=7.2, J=9.3, J=16.5, $OCH_2C\underline{H}HN$), 3.91 (1H, *ddd*, J=6.4, J=9.3, J=15.5, $OCH_2CH\underline{H}N$), 3.28 (2H, dd, J=8.9, J=5.9, $PhC\underline{H}H$), and 1.23 (3H, *t*, J= 7.1, CH_3CH_2); δ_C (50.3 MHz, $CDCl_3$) 166.5 (C=O), 163.8 (C=O), 153.6 (N-$\underline{C}O_2$), 146.2 (Ph$\underline{C}$H) 133.7 (PhCH=$\underline{C}$), 130.3 (meta C), 130.1 (para C), 128.8 (ispo C), 128.1 (*ortho* C), 62.8 ($NCH_2\underline{C}H_2$), 61.0 (N-CH_2), 42.7 ($\underline{C}H_2CH_3$), and 13.5 (CH_3). υ_{max} (KBr) 3024, 2995, 1780, 1731, 1699, 1680, 1624, 1493, 1396, 1334, 1246, and 987cm^{-1}.*m/z* 309(60), 292(75), 237(25), 221(100), 205(10), 196(25),and 177(20).

Ethyl tert-butylamidobenzylmalonate **(11)**

In a similar method to above, (**11**) (0.49 g, 98%) was obtained as white *crystals*., m.p. 71-73°C, δ_H(500 MHz, $CDCl_3$) 7.27-7.24(2H, *br m, meta* H),7.21-7.15 (3H, *m, ortho and para* H), 6.14 (1H,*br s*, NH), 4.10 (2H, *q*, J=7.1, CH_2CH_3), 3.33 (1H, *dd*, J=6.8, J=8.2, CH_2CH), 3.22 (1H, *dd*, J=6.8, J=13.8, $PhC\underline{H}H$), 3.13 (1H, *dd*, J=8.2, J=13.8, $PhCH\underline{H}$), 1.28 (9H, *s*, $C(CH_3)_3$), and 1.15 (3H, *t*, J=7.1, CH_2CH_3). δ_C (50.3 MHz, $CDCl_3$) 171.6(C=O), 166.9(C=O), 138.3(*ipso* C), 129.1(ortho C), 128.6(para C), 126.9(*meta* C), 61.3($CH_3\underline{C}H_2$), 55.6(CH), 51.3($\underline{C}(CH_3)_3$), 36.2($Ph\underline{C}H_2$), 28.3($C(\underline{C}H_3)_3$), and 13.8 ($\underline{C}H_3CH_2$).m/z 279(15) 278(100), 204(20), 148(20), 131(25), 91(30) and 58(25). (Found:C, 69.07; H, 8.65; N 4.83. $C_{16}H_{23}NO_3$ requires C, 69.32; H, 8.36; N, 5.07 %).

X-Ray Structure Determinations of Compounds (4) and (8). The intensity data were collected on a Delft Instruments FAST area detector diffractometer positioned at the window of a rotating anode generator using Mo-Kα radiation (λ = 0.71069A) by following procedures described elsewhere.[15]

The structure of (**4**) containing two symmetry independent molecules was determined by direct methods,[16] at first using data collected at room temperature (298K) but the crystal was very weak and the quality of data rather poor. Full-matrix least-squares refinement[17] on F gave a final R-value of 0.071 (R_ω = 0.071) for 2255 data [Fo>2σ(Fo)] and 354 parameters (non-H atoms anisotropic, H atoms riding on the parents in calculated positions with C-H distance fixed at 0.96Å and a common Uiso refined for all); it also indicated orientational disorder of the -OCH_2CH_3 group in one molecule (B). An improved data set was then collected at low temperature (150K) from a better quality crystal; use of this data in the refinement gave finally an R-value of 0.031 (R_ω = 0.033) for 3142 reflections [Fo>3σ(Fo)] and 499 parameters (non-H atoms anisotropic, H atoms isotropic), and also removed the orientational disorder of the -OCH_2CH_3 group observed in the RT structure. The structure of (**8**) was also determined by direct methods[15] and refined by full-matrix least squares,[16] which gave a final R-value of 0.045 (R_ω = 0.043) for 1485 reflections [Fo>3σ(Fo)] and 203 parameters (non-H atoms anisotropic, H atoms isotropic, those on N(l) and C(l) free, others riding on the parents in calculated positions with C-H distance fixed at 0.96Å). Important bond lengths and angles for (**4**) and (**8**) are presented in Tables 1 and 2. Full details of data

collection and refinement, atomic coordinates and thermal parameters for both compounds have been deposited at Cambridge Crystallographic Data Centre.

Table 4 Crystallographic Data for **4** and **8**

	4	**8**
Formula	$C_{15}H_{15}NO_5$	$C_{16}H_{21}NO_3$
Molecular Weight	289.288	275.348
Data collection T (K)	150	300
Crystal system	Triclinic	Monoclinic
Space group	P-1	$P2_1/n$
a (Å)	9.218(2)	11.035(2)
b (Å)	10.195(3)	9.195(1)
c (Å)	15.305(1)	16.421(3)
α (deg)	90.09(2)	90
β (deg)	103.32(1)	96.28(1)
γ (deg)	95.95(1)	90
V ($Å^3$)	1391.61	1656.28
Z	4	4
ρ calcd (g/cm^3)	1.381	1.104
F(000)	608	592
Crystal size (mm)	0.25 x 0.15 x 0.12	0.45 x 0.25 x 0.10
Minimum and maximum absorption correction factors	0.896, 1.061	0.856, 1.126
θ range for data collection (deg)	2.2 to 29.9	2.21 to 28.70
Index ranges	-12 <= h <= 12	-12 <= h <= 12
	-10 < =k <= 13	-11 < =k <= 7
	-11 <= l <= 20	-11 <= l <= 21
Reflections collected	9529	4708
Independent reflections	6173 [R(int) = 0.0485]	1770 [R(int) = 0.0354]
R indices (all data)	R = 0.0306, ωR = 0.0328	R = 0.0450, ωR = 0.0431

a) $R = \Sigma(\Delta F)/\Sigma(F_O)$ and $\omega R = [\Sigma\{\omega(DF)^2\} / \Sigma[\omega(F_O)^2\}]^{1/2}$

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References

1. Ojima, I., Ed. *Catalytic Asymmetric Synthesis*, VCH, New York, **1993**; Noyori, R., *Asymmetric Catalysis in Organic Synthesis*, John Wiley and Sons, New York, **1994.**
2. Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.*, **1993**, *115*, 144-152, and earlier papers. Genet, J. P.; Pfister, X.; Ratovelomananavidal, V.; Pinel, C.; Laffitte, J. A. *Tetrahedron Lett.*, **1994**, *35*, 4559-4562.
3. Nitz, T. J.; Holt, E. M.; Stammer, C. H. *J. Org. Chem.*, **1981**, *46*, 2667.
4. For s-cis structures : Krohn, K.; Franke, C.; Jones, P. G.; Aust, H. J.; Draeger, S.; Schulz, B. *Ann.Chem.*, **1992**, 789-798; Hagihara, M.; Anthony, N. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.*, **1992**, *114*, 6568-6570.Horne, S.; Taylor, N.; Collins, S.; Rodrigo, R. *J.Chem Soc. Perkin Trans. 1* , **1991**, 3047-3051; .Rohrer, D. C.; Kihara, M.; Deffo, T.; Rathore, H.; Ahmed, K.; From, A.; Fullerton, D. S. *J. Am. Chem. Soc.*, **1984**, *106*, 8269-8276; Mara, A. M.; Singh, O.; Thomas, E. J.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1*, **1982**, 2169-2173; Begley, M. J.; Crombie, L.; Crombie, W.; Gatuma, A. K.; Maradufu, A. *J. Chem. Soc., Perkin Trans. 1*, **1981**, *1981*, 2702-2709. For an example of an s-trans conformer see : Vela, M. A.; Fronczek, F. R.; Horn, G. W.; McLaughlin, M. L., *J. Org. Chem.*, **1990**, *55*, 2913.
5. There are around 20 such structures in the CSSR file. For recent examples see :Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.*, **1989**, *111*, 5340-5345; Bonner, M. P.; Thornton, E. R., *J. Am. Chem. Soc.*, **1991**, *113*, 1299-1308; Walton, D. M.; Thurmes, W. N.; Haltiwanger, R. C.; *J. Org. Chem.*, **1988**, *53*, 1046
6. Cano, F. H.; Foces-Foces, C.; Jimenez-Barbero, J.; Alemany, A.; Bernabe, M.; Martinlomas, M. *J. Org. Chem.* ,**1987**, *52*, 3367-3372.
7. Tietze, L. F.; Brand, S.; Pfeiffer, T.; Antel, J.; Harms, K.; Sheldrick, G. M. *J. Am. Chem. Soc.* **1987**, *109*, 921-923. ; see also Mukaiyama, T.; Takeda, T.; Osaki, M. *Chemistry Lett.* **1977**, 1165.
8. Mohamadi, F.; Richards, N.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J.Computational Chemistry* ,**1990**, *11*, 440-467.
9. Rodriguez, J. G.; Canoira, L.; Calderon, C. E.; Martinezripoll, M.; Blanco, S. G. *J. Chem. Soc., Perkin Trans. 2* ,**1986**, 199-203;.Yamana, T; Achida, T.; Hashimoto, K.; Sumimoto, H., *Bull. Chem. Soc. Japan*, **1992**, *65*, 1138; Banerjee, T.; Chaudhuri, S.; *Can. J. Chem.*, **1986**, *64*, 876; Oppolzer, W.; Chapuis, C.; Bernardinelli, G.; *Helv. Chim. Acta.*, **1984**, *67*, 1397; Shimizu, S.; Kekka, S.; Kashino, S.; Haisa, M., *Bull. Chem. Soc. Japan*, **1974**, *47*, 1627; Leiserowitz, L.; Rabinovich, D., *J. Chem. Soc. A*, **1969**, 2367, Filippakis, S. E.; Leiserowitz, L.; Schmidt, G. M. J., *J. Chem. Soc. B*, **1967**, 297
10. Lewis, F. D.; Stern, C. L.; Yoon, B. A., *J. Am. Chem. Soc.*, **1992**, *114*, 3131; Mahato, S. B.; Sahu, N. P.; Muller, E.; Luger, P, *J. Chem. Soc. Perkin Trans 2*, **1985**, 193.
11. Conn, A.,. D. Phil thesis, Oxford 1991; Price, D. W., D. Phil thesis, Oxford 1992.
12. Brown, J. M., Evans, P. L; James, A. P., Org. Syn **1989**, 68, 64
13. Cabello, J. A.; Campelo, J. M.; Garcia, A.; Luna, D.; Marinas, J. M. *J. Org. Chem.* ,**1984**, *49*, 5195-5197.
14. Takei, H; Fukuda, Y; Sugaya, K; Taguchi, T; Kawara, T, *Chem. Lett.* **1980**,1307-10
15. Drake,S.R.; Hursthouse, M.B.; Malik K.M.A.; Miller,S.A.S.; *Inorg. Chem.*, **1993**, *32*, 4653-4657
16. Sheldrick, G.M.; SHELX-S Program, *Acta Cryst*, **1990**, *A46*, 467.
17. Sheldrick, G.M.; SHELX-80 Program, Univ. of Gottingen, Germany, **1980**

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