Remarkable dependence of the regioselectivity of free radical additions to 3-cinnamoyloxazolidin-2-ones on the stability of the intermediate adduct-radical, electrophilicity of the adding radicals and the conditions for their generation

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Electrophilic (CCl_3) and nucleophilic radicals (Pr^i) are found to add at 80 °C to the C=C bond of 3-(*E*)-cinnamoyl-4-phenyloxazolidin-2-one 1a and 3-(*E*)-cinnamoyl-4-benzyloxazolidin-2-one 1b predominantly at the α-position of the bond. While for the CCl_3 radical no product of β-addition has been found, for the Pr^i radical such a path constitutes up to 40% of the whole process at 80 °C. An interplay between the stability of the intermediate adduct radicals and the electrophilicity or nucleophilicity of the radicals undergoing addition are invoked to rationalize the observation. At a low temperature (−23 °C) β-addition of the Pr^i radical becomes the dominant process (up to 75%).

Introduction

In recent years there has been tremendous progress in the stereoselective synthesis of organic compounds *via* radical addition to the olefinic bond. It has been documented that steric models (Felkin, chelate *etc.*), developed earlier for heterolytic reactions, work well in the cases of homolytic reactions also.[1] Much less explored and still a somewhat obscure process is the regioselectivity of radical addition to RC=CR bonds.[2] Generally, such factors as stability of the intermediate reactive adducts, so important in the carbanion chemistry with its late transition state situation, seem to be of minor importance in exothermic, earlier transition state radical addition chemistry.[2]

We have now studied the addition of both electrophilic (CCl_3) and nucleophilic (Pr^i) radicals to the C=C bond of 3-(*E*)-cinnamoyl-4-phenyloxazolidin-2-one **1a** and 3-(*E*)-cinnamoyl-4-benzyloxazolidin-2-one **1b** (see Schemes 1 and 2), to find out if the stability of the intermediate radical adducts **A** and **B**, or the relative electrophilicity of the attacking radicals, was responsible for the regioselectivity of the attack. Although as expected, we found that the regioselectivity of the radical addition was influenced by the relative electrophilicity of the attacking radicals, it was also necessary to take into account the stability of the intermediate adduct-radical as being a more important factor in rationalizing the radical addition pattern at high temperatures. Unexpectedly, we discovered that the α-/β-regioselectivity of the addition of the nucleophilic radical was reversed by changing the conditions under which the radical was generated.

Results and discussion

Compounds **1a** [both racemic and of the (*R*)-configuration] and (*R*)-**1b** were synthesized, as described in the Experimental section. The addition of $BrCCl_3$ to (*R*)-**1a** was initiated either by benzoyl peroxide (BP) or $Fe(CO)_5$ at 80 °C. Out of eight possible isomers which might be formed only **2** and **3** (see Scheme 1) were recovered from the reaction mixture and separated by TLC (SiO_2). The structure of these and their ratio (close to 1 : 1, see Table 1, runs 1 and 2) were unaffected by the use of peroxide or redox initiation. The structures of the compounds were established by single crystal X-ray analysis.[3] Isomer **2**, having a greater R_f value on SiO_2, was found to have an α*S*,β*R*,4*R*-configuration † whilst isomer **3** had an α*R*,β*S*,4*R*-configuration. The compounds arose from primary attack of the CCl_3 radical at the α-position of the C=C bond of **1a**. The next stage of C–Br formation in the chain transfer reaction proceeded with very high diastereoselection to give the products of *anti*-configuration (see Scheme 1 and Fig. 1). The A-strain model[1d] can be invoked to rationalize the observed stereoselectivity of the bromine atom transfer in both peroxide and $Fe(CO)_5$ promoted reactions (see Fig. 1). Preliminary results of $BrCCl_3$ addition to (*R*)-**1b** indicated that here too only two isomers were formed.

The first conclusion derived from the results is that chelation control effects were absent for both C-CCl_3 and C-Br formation stages with initiation by $Fe(CO)_5$ [or other $Fe(CO)_5$-derived Fe-containing particles].[4] If this were not so, the stereoselectivities of the peroxide or the metal-redox processes would have been different since oxazolidinone substrates of similar structure are known to be greatly influenced when undergoing diastereoselective nucleophilic radical addition by the complexation with metal ions and stabilization of the *syn*-(s)-conformation of the substrate in which the α- and β-positions of the C=C bond are shielded by the 4-substituent of the heterocycle.[5]

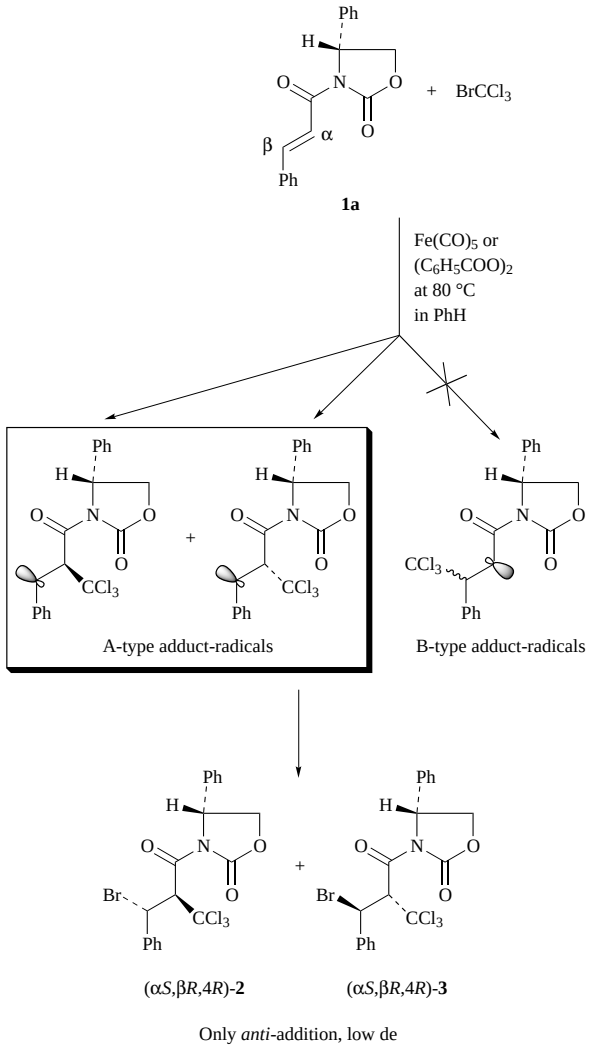
Another salient feature of the reaction is the primary attack of the CCl_3 radical at the α-position of the C=C bond. Two explanations may account for this: (a) A positive charge localized at the β-position of the C=C bond of **1a** influences the electrophilic CCl_3 radical to attack preferentially the α-position of the cinnamoyl moiety and thus avoid electrostatic repulsion at the β-position. (b) The primary α-attack is directed by the relative stability of the intermediate adduct-radical **A**, as compared to radical **B**. The stability of the benzyl-type radical **A** is greater than that of **B** (at least 7 kcal mol^{-1}, as assessed by the corresponding energies of C–H bond dissociation of toluene[6]

† For convenience, the terms α and β have been used for the two positions of the cinnamoyl double bond (see formula **1a**). However, in the Experimental section, where the products prepared have been named, these positions, the double bond having been reduced, are referred to as 2′ and 3′.

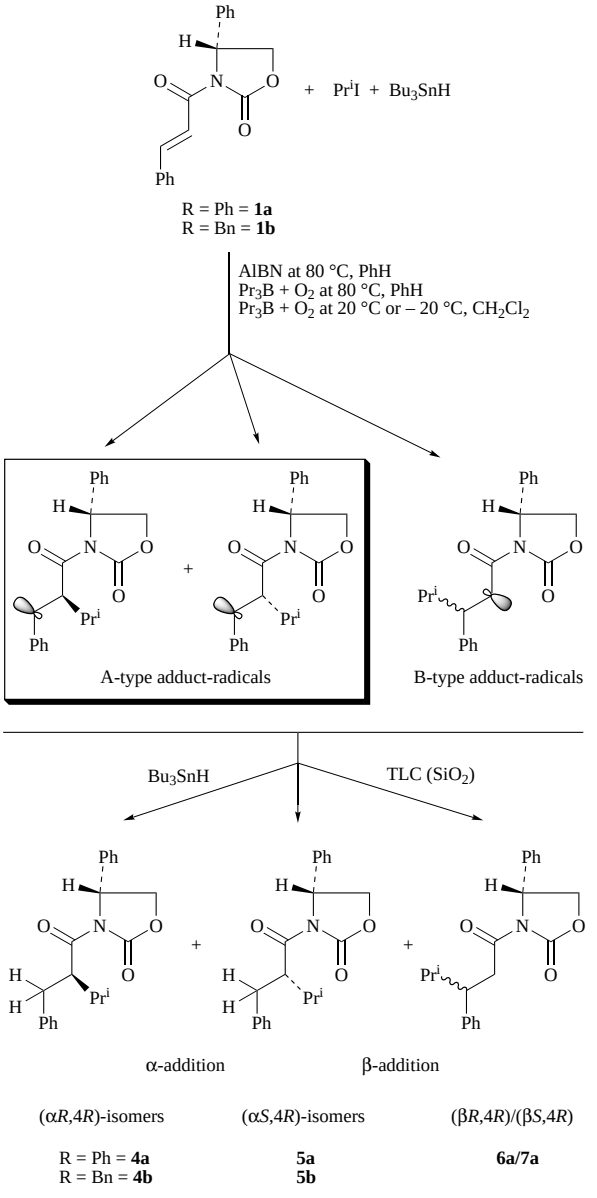
Table 1 Regio- and diastereo-selectivity of the addition of CCl_3 and Pr^i radicals to (*R*)-3-(*E*)-cinnamoyl-4-benzyloxazolidin-2-one (*R*)-**1b** and *rac*- or (*R*)-3-(*E*)-cinnamoyl-4-phenyloxazolidin-2-one *rac*-**1a**, or (*R*)-**1a** *

Run	RHal	Substr.	Initiator	*T*/°C	*t*/h	α : β [a]	Ratio of α-isomers [a]	Ratio of β-isomers [a]	c.y. [b]
1	CCl_3Br	(*R*)-**1a**	$Fe(CO)_5$ [c]	80	0.3	α only	1.3 (**3**) : 1(**2**) [d]	–	58
2	CCl_3Br	(*R*)-**1a**	PB [c]	80	30	α only	1.2 (**3**) : 1(**2**) [d]	–	28
3	Pr^iI	*rac*-**1a**	Pr_3B [c]	80	2.5	2.3 : 1	4.1 (**5a**) : 1(**4a**)	2.7 (**7a**) : 1(**6a**)	83
4	Pr^iI	*rac*-**1a**	AIBN [c]	80	17	1.6 : 1	1.8 (**5a**) : 1(**4a**)	1.2 (**7a**) : 1(**6a**)	65
5	Pr^iI	(*R*)-**1b**	AIBN [c]	80	15	3 : 1	1.5 (**5b**) : 1(**4b**)	*e*	74
6	Pr^iI	*rac*-**1a**	Pr_3B [f]	20	2.5	1 : 3	1.4 (**5a**) : 1(**4a**)	1.6 (**7a**) : 1(**6a**)	51
7	Pr^iI	*rac*-**1a**	Pr_3B [f]	−23	3	1 : 2.4	1.3 (**5a**) : 1(**4a**)	1.4 (**7a**) : 1(**6a**)	20

* Runs 3–7 were performed with Bu_3SnH. [a] The ratios of diastereoisomers and α/β ratios were established from the ^1H NMR spectra of the mixtures or by weighing the fractions. [b] Isolated yield of diastereoisomeric mixture of products. [c] In PhH. [d] Only *anti*-product. [e] Not determined. [f] In CH_2Cl_2.



Scheme 1



Scheme 2

and ethyl acetate[7]) and, as a result, no β-primary attack occurred in the system.

The data available from the literature indicated that for similar types of substrate, nucleophilic Pr^i radicals added intermolecularly at the β-position of the C=C bond of their cinnamoyl moieties at a low temperature (−78 °C).[8,9] Thus, it seemed that the main reason for the greater degree of α-attack with the CCl_3 radical was a result of its electrophilicity [hypothesis (a)]. Unfortunately, the conditions under which the experiments were conducted [−78 °C and Bu_3SnH in case of refs. 8 and 9 and 80 °C, $(PhCO_2)_2$ in our case] were insufficiently close to make this kind of reasoning convincing. It was therefore necessary to obtain experimental results on the regioselectivity of Pr^i radical addition to our substrates at 80 °C.

The additions of Pr^iI (see Scheme 2) in the presence of Bu_3SnH (AIBN or $Pr_3B + O_2$ as initiators) to *rac*-**1a** and (*R*)-**1b** were conducted in PhH at 80 °C. Unexpectedly, the reaction mixture was found to consist of, at least, four isomeric products of Pr^i- and H-addition to the C=C bonds of both **1a** and **1b** (see Scheme 2, products **4**–**7**). The reaction mixtures were purified on SiO_2 (hexane) to remove all the Sn-containing products and the isomers were separated by preparative TLC. One of the isomers, derived from *rac*-**1a** (second in its R_f values), formed good quality crystals and its structure, as determined by the X-ray single crystal analysis, was found to be that of *rac*-(α*R**,4*R**)-3-α-isopropylhydrocinnamoyl-4-phenyloxazolidin-2-one **4a**. In other words, at least one of the isomers resulted

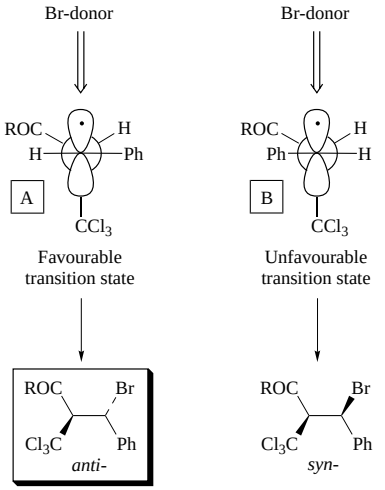
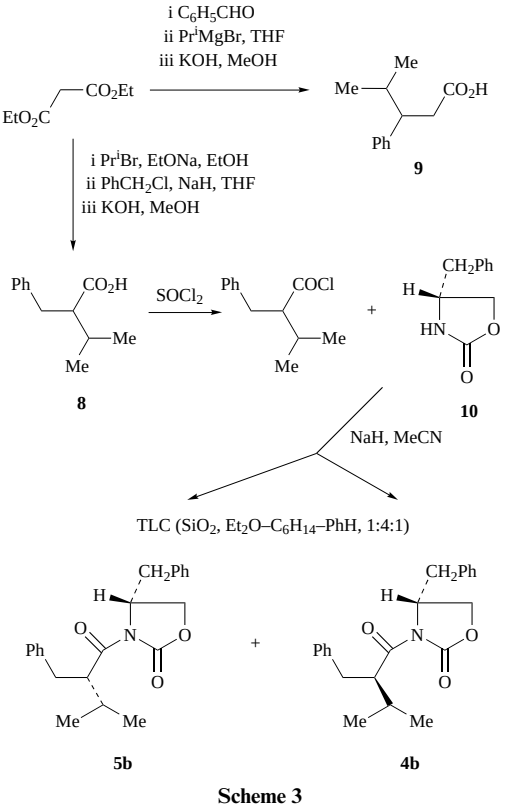


Fig. 1



Scheme 3

from the α-addition which was clearly observed at 80 °C even in the case of nucleophilic radical addition to the C=C bond of the cinnamoyl moiety. Still the question remained as how much of α- and β-addition was really occurring.

In order to answer this, model compounds were synthesized, starting with the malonic ester (see Scheme 3). A mixture of racemic α-isopropylhydrocinnamic acid **8** and β-isopropylhydrocinnamic acid **9**, synthesized in this way, were found to be easily separated and analyzed by GLC as their methyl esters.

Thus, we were able to establish which isomer, recovered from the reaction mixtures, had come from α- or β-addition by simply hydrolyzing it and analyzing the corresponding isopropylhydrocinnamic acid. For the isomers derived from both **1a** and **1b**, the first two diastereoisomers, having greater R_f values (Scheme 2, products **4** and **5**), were found to come from the α-addition and other two isomers having smaller R_f values (Scheme 2, products **6** and **7**) came from the β-addition.

The absolute configurations of the diastereoisomers were established in the following way. The condensation of acid **8** with (*R*)-4-benzyloxazolidin-2-one **10** (see Scheme 3) gave a mixture of two diastereoisomers which were separated by TLC. The structure of one of these isomers (that with the greater R_f value) was established (X-ray) as (α*S*,4*R*)-*N*-α-isopropylhydrocinnamoyl-4-benzyloxazolidin-2-one **5b**. Thus, the assignment of configuration of the α-products from **1b** was made by comparing the ^{1}H NMR spectra of the two diastereoisomers with those of the model isomer. The configuration of the diastereoisomers originating from α-addition to **1a** was established by X-ray analysis, as indicated above whilst the configurations of the β-products **6a** and **7a**, were established by comparing their ^{1}H NMR spectra with those described in the literature.[10]

Finally, we established the ratio of α to β addition of the Pr^i radical to either **1a** or **1b** at 80 °C and the diastereoisomeric ratio of the α-addition simply by analyzing the ^{1}H NMR spectra of the reaction mixtures or by weighing the fractions containing the corresponding isomers. The results, summarized in Table 1 (runs 3–5), indicated unequivocally that it was the α-attack of the nucleophilic Pr^i radicals which prevailed at 80 °C for both **1a** and **1b**. As can be seen from the data, the simple picture of electrostatic effects being mainly responsible for the direction of α- *versus* β-attack, was insufficient to account for the experimental observations. On the contrary, it is the greater stability of the intermediate radical adducts **A** *versus* **B** which seemed to govern the process [hypothesis (b)]. It seemed that the electrophilicity of the radicals also played a part because a significant portion of the addition product (30–40%) came from the β-addition path. No such products were found in the electrophilic CCl_3 radical addition to either **1a** or **1b**.

Still unexplained however was the 100% β-regioselectivity of the Pr^i radical addition to the cinnamoyl moiety of other 3-cinnamoyloxazolidin-2-ones at low temperatures.[8,9] To resolve this apparent contradiction we studied the addition of the Pr^i radical to **1a** and **1b** at 20 and −20 °C, using a $Pr_3B + O_2$ initiation system. The results are summarized in Table 1 (runs 6,7). Since, as can be seen from the data, it was the β-addition which clearly prevailed at the low temperatures, it is tempting to suggest that there were some complexes derived from Pr_3B (or other boron-derived compounds in the reaction mixture) and the substrates that had much more electrophilic C=C bonds than those in the initial **1a** or **1b**. Thus, the electrophilicity of the bond in the complexes might be increased concomitantly with the rate of the nucleophilic radical attack at the β-position relative to the α-attack. But the comparison of runs 3 and 4 of Table 1 indicated that both AIBN and Pr_3B initiations gave similar α : β ratio patterns at 80 °C.

Another Lewis acid, Bu_3SnI, formed in the reaction mixture, might be the next candidate for the role of the chelating agent, and increasing the relative proportion of the β-isomer in the reaction mixture. In a recent publication by Sibi and co-workers this Sn-derivative was shown to affect (as postulated by the authors *via* chelation) the relative rates of reduction *versus* intramolecular cyclization, and favouring the latter in enoyloxazolidinones, bearing a bromo (or iodo)methyl group at 4-position of the heterocycle.[5] We believe that kind of influence highly unlikely on the following grounds: (a) according to ref. 5, the effect should be observed (or most pronounced) at 80 °C. In fact, we observed a predominance of α-attack of the Pr^i radical at the temperature, (b) The diastereoselectivities of the Bu_3SnH initiated β-additions were low at all the temperatures studied. Had the chelation been responsible for the increased proportion of the β-addition products at low temperatures, the de of the addition would have been much higher.[5,8,9]

A further hypothetical mechanism for the reaction is possible, based on the assumption that the reactions of alkyl halides initiated by Bu_3SnH proceed by two different mechanisms, one of which, being typically radical, predominates at high temperatures and gives the α-addition products and the other, ionic or metal-organic, playing an important role at the

range of low temperatures and giving rise to the β-addition products.

The extension of these studies and investigation of the addition of electrophilic radicals to the C=C bond of **1a** and **1b** at low temperatures and similar substrates are underway.

Experimental

General

All reactions requiring anhydrous conditions were performed in oven-dried glassware under argon. All transfers of solutions and solvents were performed by syringe techniques. Chemicals and solvents were purified by standard procedures. Melting points are uncorrected. Kieselgel 60 (Merck) was used for column chromatography and silica gel 60 F_{254} pre-coated plates (Merck) were used for TLC. Preparative TLC was carried out with glass plates on silica gel (Chemapol) LSL_{254} 5/40. ^{1}H NMR spectra were recorded on Bruker 200 and 400 MHz instruments. The optical rotations were measured with a Perkin-Elmer M241 polarimeter and were recorded as 10^{-1} deg cm^2 g^{-1}. The chemical shifts are given in δ (ppm) relative to $SiMe_4$ as an internal standard. The analyses of α-isopropylhydrocinnamic acid and β-isopropylhydrocinnamic acid, were conducted by CGLC of their methyl esters on a model 3700-00 gas chromatograph equipped with a flame ionisation detector, and SE-54 fused silica capillary column 25 m × 0.20 mm i.d., 0.20 μm film; col. temp. 140 °C; carrier gas He at 1.5 bar.

Preparation of starting compounds

(*R*)-2-Amino-3-phenylpropan-2-ol. This compound was prepared by a modified literature procedure.[11] To a stirred solution of (*R*)-phenylalanine (2.2 g, 13 mmol) in THF (20 cm^3) was added $LiBH_4$ (0.88 g, 39 mmol) followed by a solution of H_2SO_4 (99.5%; 1.04 cm^3, 19.5 mmol) in THF (1 cm^3), added dropwise. The mixture was stirred at the ambient temperature for 24 h after which it was treated with MeOH (15 cm^3) with continued stirring until a clear solution was formed. Aq. NaOH (4 M; 20 cm^3) was then added dropwise to it. The resulting precipitate was filtered off and the filtrate evaporated *in vacuo*. The residue was extracted with PhMe (10 cm^3 × 3). The combined extracts were evaporated *in vacuo* to give the amino alcohol which was vacuum dried: yield 1.73 g (88%); mp 86–88 °C, $[a]_D^{25}$ +22.1 (*c* 1.5 EtOH) {lit.,[12] mp 88–90 °C, $[a]_D^{25}$ +22.0 (*c* 1.5 EtOH}.

(*R*)-2-Amino-2-phenylethanol. This compound was obtained from L-phenylglycine in the same manner and was used further without purification.

***rac*-2-Amino-2-phenylethanol.** This compound was obtained from D,L-phenylglycine in the same manner (87%), mp 75–77 °C (lit.,[13] mp 76–77 °C).

(*R*)-4-Benzyloxazolidin-2-one 10. Methyl chloroformate (1.92 g, 20 mmol, 1.6 cm^3) in toluene (10 cm^3) was added dropwise to a mixture of a solution of (*R*)-2-amino-3-phenylpropan-1-ol (1.6 g, 10 mmol) in toluene (20 cm^3) and aq. KOH [1.12 g, 20 mmol in water (7.8 cm^3)]. Vigorous stirring was continued for 1 h after which the organic layer was separated and the aqueous layer was extracted with PhMe (10 cm^3 × 2). The combined extracts were dried ($MgSO_4$) and refluxed over K_2CO_3 (0.1 g) for 3 h, the reaction being monitored by TLC (PhH–C_6H_{14}–Et_2O, 2:1:1). Finally, the mixture was evaporated *in vacuo* and the residue allowed slowly to crystallize. Subsequent recrystallisation from hexane–ether (8:1) gave the product **10** (1.57 g, 84%), mp 86–88 °C, $[a]_D^{20}$ −4.58 (*c* 1.1 EtOH) [lit.,[14a] mp 87–88.5 °C, for (*S*)-isomer $[a]_D^{25}$ +4.9 (*c* 1.1 EtOH)] (Found: C, 66.77; H, 6.26; N, 7.90. $C_{10}H_{11}NO_2$ requires C, 66.22; H, 6.56; N, 7.82%); δ_H[$(CD_3)_2CO$] 7.20 (m, 5 H), 5.64 (1 H, br d), 3.88 (1 H, m), 3.45 (2 H, m), 3.00 (1 H, br d) and 2.85 (1 H, t, *J* 7.2).

(*R*)-4-Phenyl-2-oxazolidinone. This compound, obtained by a literature procedure,[14b] had mp 130–131 °C, $[a]_D^{25}$ −55 (*c* 1, $CHCl_3$) [lit.,[14c] for the (*S*)-isomer, mp 128–130 °C, $[a]_D^{25}$ +58 (*c* 1, $CHCl_3$)].

***rac*-4-Phenyloxazolidin-2-one.** This compound, obtained in the same manner (85%), had mp 137–138 °C (EtOH) (lit.,[13] mp 137–138 °C) (Found: C, 66.18; H, 5.56; N, 8.50. $C_9H_9NO_2$ requires C, 66.24; H, 5.56; N, 8.58%); δ_H($CDCl_3$) 7.30 (5 H, m), 6.51 (1 H, br d), 4.73–5.04 (1 H, m), 4.73–4.54 (1 H, m) and 4.30–4.02 (1 H, m).

(*R*)-3-(*E*)-Cinnamoyl-4-benzyloxazolidin-2-one (*R*)-1b. NaH (60% suspension in oil; 0.28 g, 7.11 mmol) was added to **10** (0.9 g, 5.08 mmol) in MeCN (15 cm^3) with stirring and cooling to 0 °C. When the evolution of H_2 stopped, a solution of cinnamoyl chloride (1.18 g, 7.11 mmol) in MeCN (5 cm^3) was added dropwise to the mixture. Stirring was continued for a further 1 h, after which the reaction mixture was acidified (to pH < 7) with 10% aq. AcOH. The mixture was then extracted with PhMe–ether (3:1; 8 cm^3 × 3), and the combined extracts were dried (K_2CO_3) and evaporated *in vacuo*. The residue was recrystallised from EtOH to give the product (1.42 g, 91%), mp 129–130 °C; $[a]_D^{25}$ −57.83 (*c* 1, $CHCl_3$) (Found: C, 74.23; H, 5.52; N, 4.35. $C_{19}H_{17}NO_3$ requires C, 74.24; H, 5.57; N, 4.56%); δ_H($CDCl_3$) 7.58 (2 H, m), 7.37–7.30 (10 H, m), 4.75–4.71 (1 H, m), 4.20–4.13 (2 H, m), 3.32 (1 H, dd, *J* 3.0 and 13.4) and 2.80 (1 H, dd, *J* 9.5 and 13.3).

(*R*)-3-(*E*)-Cinnamoyl-4-phenyloxazolidin-2-one (*R*)-1a. This compound, synthesized in the same manner (70%), had mp 170–171 °C, $[a]_D^{25}$ −4.1 (*c* 1, $CHCl_3$) [lit.,[14c] for the (*S*)-isomer, mp 169–171 °C, $[a]_D^{25}$ +3.4].

***rac*-3-(*E*)-Cinnamoyl-4-phenyloxazolidin-2-one *rac*-1a.** This compound, prepared analogously, had mp 179–181 °C (Found: C, 73.76; H, 5.22; N, 4.94. $C_{18}H_{17}NO_3$ requires C, 73.70; H, 5.16; N, 4.78%); δ_H($CDCl_3$) 7.94 (1 H, d, *J* 15.7), 7.76 (1 H, d, *J* 15.7), 7.52–7.60 (2 H, m), 7.25–7.45 (8 H, m), 5.53 (1 H, dd, *J* 3.8 and 8.6), 4.69 (1 H, t, *J* 8.6) and 4.27 (1 H, dd, *J* 3.8 and 8.6).

Preparation of model compounds

***rac*-2-Benzyl-3-methylbutanoic acid 8.** This compound was obtained by a double alkylation of ethyl malonate. The first alkylation of the ester with Pr^{i}Br was carried out in EtOH in the presence of EtONa, as described in the literature.[15a] The product (without prior purification) was alkylated further with $PhCH_2Cl$ in THF in the presence of NaH under reflux (3 h). The corresponding benzyl(isopropyl)malonic ester (60% yield) was obtained after distillation *in vacuo* 122 °C/0.7 mmHg, n_D^{20} 1.4893 (lit.,[15b] 109–112 °C/0.5 mmHg, n_D^{20} 1.4890). The target compound **8** was obtained by hydrolysis and decarboxylation of the initial diester, as described in the literature[15b] (Found: C, 74.68; H, 8.43. $C_{12}H_{16}O_2$ requires C, 74.96; H, 8.39%); δ_H($CDCl_3$) 7.28–7.10 (5 H, m), 2.80 (2 H, br d, *J* 6.5), 2.56–2.48 (1 H, m), 2.04–1.83 (1 H, m) and 1.09–1.03 (6 H, m).

***rac*-4-Methyl-3-phenylpentanoic acid 9.** This compound was synthesized, starting with the malonic ester condensation with benzaldehyde to give a benzylidene-malonic ester, according to a literature procedure.[16a] The purified (by distillation) intermediate was then added to an isopropylmagnesium bromide solution in THF, as described in the literature for phenylmagnesium bromide addition[16b] (no cuprous salts were added). The target acid **9**, obtained after the hydrolysis and decarboxylation at 140–180 °C in an oil-bath of the intermediate substituted malonic acid as indicated above, was distilled *in vacuo* and had bp 133 °C/0.7 mmHg (Found: C, 74.23; H, 7.88. $C_{12}H_{16}O_2$ requires C, 74.96; H, 8.39%); δ_H($CDCl_3$) 7.26–7.11 (5 H, m), 2.93–2.62 (3 H, m), 1.93–1.84 (1 H, m), 0.92 (3 H, d, *J* 6.7) and 0.74 (3 H, d, *J* 6.7).

(2′*R*,4*R*)-4b and (2′*S*,4*R*)-3-(2′-Isopropyl-3′-phenylpropionyl)-4-benzyloxazolidin-2-one 5b. A mixture of **4b** and **5b** was prepared by the condensation of **8** (as its acyl chloride) with **10** in the same manner, as described for the synthesis of **1b**. Pure **5b** was isolated by preparative TLC (SiO_2, C_6H_{14}–PhH–Et_2O, 4:1:1) as a fraction, having the highest R_f value. The crystals

of the isomer for the X-ray single-crystal analysis were grown from an ethanol solution and had mp 100–101 °C; $[\alpha]_D^{25}$ −100.19 (*c*, 1.04, $CHCl_3$) (Found: C, 75.03; H, 7.22; N, 3.95. $C_{22}H_{25}NO_3$ requires C, 75.18; H, 7.17; N, 3.98%); $\delta_H(CDCl_3)$ 7.45–7.05 (10 H, m), 4.23 (1 H, m), 4.04 (1 H, m), 3.95 (1 H, dd, *J* 2.1 and 8.9), 3.59 (1 H, t, *J* 8.9), 3.27 (1 H, dd, *J* 3.3 and 13.3), 3.04 (1 H, dd, *J* 4.8 and 13.0), 2.85 (1 H, t, *J* 13.0), 2.65 (1 H, t, *J* 13.3), 2.09–2.06 (1 H, m) and 0.98–1.05 (6 H, m).

Compound **4b**, recovered as the second fraction (lowest R_f value), had mp 126–127 °C; $[\alpha]_D^{25}$ −19.47 (*c*, 0.99 in $CHCl_3$) (Found: C, 75.05; H, 7.21; N, 3.95. $C_{22}H_{25}NO_3$ requires C, 75.18; H, 7.17; N, 3.98%); $\delta_H(CDCl_3)$ 7.27–7.16 (8 H, m), 6.92–6.88 (2 H, m), 4.61–4.56 (1 H, m), 4.29–4.24 (1 H, m), 4.04 (1 H, t, *J* 8.8), 3.95 (1 H, dd, *J* 5.8 and 8.8), 3.00 (1 H, dd, *J* 4.9 and 13.3), 2.94 (1 H, t, *J* 13.3, 1 H), 2.77 (1 H, dd, *J* 3.3 and 13.6, 1 H), 2.12 (1 H, dd, *J* 9.4 and 13.6), 2.07–1.99 (1 H, m) and 1.09–1.04 (6 H, m).

Addition of $BrCCl_3$ to (*R*)-1a

Benzoyl peroxide (BP) initiation. A solution of (*R*)-**1a** (1.37 g, 4.7 mmol), $BrCCl_3$ (1.86 g, 9.4 mmol) and BP (0.03 g, 0.12 mmol) in anhydrous benzene (6.5 cm^3) was refluxed for 15 h with, every 3 h, a fresh portion of BP (0.02 g, 0.085 mmol) being introduced. After the addition of 4 portions of BP the solution was refluxed for a further 15 h. The reaction was monitored by TLC (SiO_2, C_6H_{14}–PhH–Et_2O, 4:1:1). The reaction mixture was cooled, and the precipitate was filtered off and washed with benzene to afford the starting material (*R*)-**1a** (0.47 g, 20.3%). The filtrate was evaporated to dryness to give a mixture of initial (*R*)-**1a** (1.3 g) and diastereoisomeric products (2.3 g, 28%). The ratio of αR,βS,4R:αS,βR,4R was estimated to be 1.2:1 (^{1}H NMR spectra of initial mixture). Isomers were separated by preparative TLC (SiO_2, C_6H_{14}–PhH–Et_2O, 4:1:1). Samples of the diastereoisomers were additionally purified by recrystallization from a benzene–hexane mixture. The absolute configuration of the isomers were assigned by a single-crystal X-ray analysis.[3]

(2′*R*,3′*S*,4*R*)-3-(3′-Bromo-2′-trichloromethyl-3′-phenylpropionyl)-4-phenyloxazolidin-2-one **2**. Highest R_f; mp 154–155 °C; $[\alpha]_D^{25}$ −122.4 (*c*, 1.9, PhH) (Found: C, 46.47; H, 3.04; N, 2.65. $C_{19}H_{15}BrCl_3NO_3$ requires C, 46.42; H, 3.08; N, 2.84%); $\delta_H(CDCl_3)$ 7.48–7.62 (2 H, m), 7.21–7.41 (8 H, m), 6.52 (1 H, d, *J* 10.6), 5.57 (1 H, d, *J* 10.6), 5.54 (1 H, dd, *J* 3.6 and 8.7), 4.76 (1 H, t, *J* 8.7) and 4.38 (1 H, dd, *J* 3.6 and 8.7).

(2′*S*,3′*R*,4*R*)-3-(3′-Bromo-2′-trichloromethyl-3′-phenylpropionyl)-4-phenyloxazolidin-2-one **3**. Lowest R_f; mp 120–124 °C; $\delta_H(CDCl_3)$ 7.1–8.7 (10 H, m), 6.51 (1 H, d, *J* 10.6), 5.52 (1 H, dd, *J* 3.7 and 8.7), 5.47 (1 H, d, *J* 10.6), 4.73 (1 H, t, *J* 8.7) and 4.38 (1 H, dd, *J* 3.7 and 8.7).

$Fe(CO)_5$ initiation. A glass tube was charged with (*R*)-**1a** (0.13 g, 0.44 mmol), $Fe(CO)_5$ (8.6 mg, 0.044 mmol), $BrCCl_3$ (1.78 g, 9.0 mmol) and anhydrous benzene (1 cm^3). The mixture was cooled to −78 °C, evacuated *in vacuo*, and filled with Ar. The procedure was repeated twice and finally the tube was sealed and placed in a thermostat (80 °C) for 4 h. After this, the reaction mixture was separated by preparative TLC to afford a mixture of diastereoisomers **2** and **3** (0.7 g, 32%) in 1:1 ratio, as estimated from the ^{1}H NMR spectra of the mixture.

The addition of Pr^iI to *rac*-1a and (*R*)-1b in the presence of Bu_3SnH

(a) AIBN initiation. To a solution of *rac*-**1a** (0.15 g, 0.5 mmol) and Pr^iI (0.1 cm^3, 1.0 mmol) in PhH (10 cm^3) was added a solution of Bu_3SnH (0.22 cm^3, 0.75 mmol) and AIBN (0.03 g, 0.15 mmol) by syringe within a period of 17 h at 80 °C. The reaction was stopped when the starting material had been consumed (TLC control). The reaction mixture was evaporated and then flash chromatographed on SiO_2, first with hexane, to separate the Sn derivatives, and then with PhH. The benzene fraction was evaporated to give the mixture of the isomers (1 g, 65%) which were separated by preparative TLC (SiO_2, EtOAc–Cl_3CH–C_6H_{14}, 1:8:15). The two isomers with the highest R_f values, **4a** and **5a**, were each decomposed (see below) to give the acid **8** (GLC) which indicated that they were α-diastereoisomers. One of the α-isomers with the lower R_f value, **4a**, produced good quality crystals (EtOH) suitable for X-ray crystal analysis. The determined configuration was *rac*-(α*R**,4*R**) which indicated that the other isomer (of higher R_f) **5a** had a *rac*-(α*S**,4*R**) configuration.

rac-(2′*S**,4*R**)-3-(2′-Isopropyl-3′-phenylpropionyl)-4-phenyloxazolidin-2-one **4a** (highest R_f). Mp 106.5–107.5 °C (Found: C, 74.61; H, 6.90; N, 4.14. $C_{21}H_{23}NO_3$ requires C, 74.75; H, 6.87; N, 4.15%); $\delta_H(CDCl_3)$ 7.45–7.12 (10 H, m), 5.08 (1 H, dd, *J* 3.2 and 8.2), 4.19–4.01 (3 H, m), 2.85 (1 H, dd, *J* 4.6 and 11.1), 2.76 (1 H, t, *J* 11.1), 2.05–1.95 (1 H, m) and 0.95 (6 H, dd, *J* 6.7 and 12.6).

rac-(2′*R**,4*R**)-3-(2′-Isopropyl-3′-phenylpropionyl)-4-phenyloxazolidin-2-one **5a** (lowest R_f). Mp 96.5–97.5 °C (Found: C, 75.01; H, 6.75; N, 4.18. $C_{21}H_{23}NO_3$ requires C, 74.75; H, 6.87; N, 4.15%); $\delta_H(CDCl_3)$ 7.25–7.00 (8 H, m), 6.75–6.72 (2 H, m), 5.32 (1 H, dd, *J* 4.3 and 8.6), 4.52 (1 H, t, *J* 8.6), 4.26 (1 H, m), 4.04 (1 H, dd, *J* 4.2 and 8.5), 2.83 (2 H, m), 2.03–1.97 (1 H, m) and 1.05 (6 H, br d, *J* 6.8).

The other two diastereoisomers (with lower R_f values) **6a** and **7a** were also decomposed (see below) and found to contain the acid **9** (GLC); thus, their structures could be assigned as those of the β-isomers. The absolute configuration of the β-isomers could also be easily established by comparing their ^{1}H NMR spectra with those reported in the literature (ref. 10) for the compounds whose structures were determined by X-ray analysis.

rac-(3′*R**,4*R**)-3-(3′-Isopropyl-3′-phenylpropionyl)-4-phenyloxazolidin-2-one **6a** (lower R_f) $\delta_H(CDCl_3)$ 7.25–7.10 (8 H, m), 6.75 (2 H, m), 5.28 (1 H, dd, *J* 4.1 and 8.7), 4.55 (1 H, t, *J* 8.7), 4.07 (1 H, dd, *J* 4.1 and 8.7), 3.73 (1 H, dd, *J* 9.9 and 15.8), 3.13 (1 H, t, *J* 15.8), 2.95 (1 H, m), 1.88 (1 H, m), 0.96 (3 H, d, *J* 6.7) and 0.74 (3 H, d, *J* 6.7).

rac-(3′*S**,4*R**)-3-(3′-Isopropyl-3′-phenylpropionyl)-4-phenyloxazolidin-2-one **7a** (Higher R_f of the two β-isomers) $\delta_H(CDCl_3)$ 7.32–7.12 (10 H, m), 5.16 (1 H, dd, *J* 3.5 and 8.7), 4.43 (1 H, t, *J* 8.7), 4.17 (1 H, dd, *J* 3.5 and 8.7), 3.58 (1 H, dd, *J* 10.4 and 16.6), 3.16 (1 H, dd, *J* 16.6 and 4.3), 2.95 (1 H, m), 1.83 (1 H, m), 0.93 (3 H, d, *J* 6.7) and 0.73 (3 H, d, *J* 6.7).

The reaction with (*R*)-**1b** was performed in the same way to give a mixture of four diastereoisomers (0.13 g, 74%) which were separated by preparative TLC (C_6H_{14}–PhH–Et_2O, 4:1:1). The decomposition of each isomer established that the first two isomers (higher R_f) were α-isomers and other two (lower R_f) were β-isomers. The absolute configuration of the α-isomers were assigned by comparing their parameters (^{1}H NMR and mp) with those of the model compounds (see above). The first fraction (higher R_f) contained **5b** and the next fraction (lower R_f) contained **4b**.

(b) Pr_3B + O_2 initiation at 80 °C. To a refluxing solution of *rac*-**1a** (0.23 g, 0.78 mmol) and Pr^iI (0.78 cm^3, 7.8 mmol) in PhH (9 cm^3), were added simultaneously, by two syringes, Bu_3SnH (1.71 cm^3, 2.9 mmol) and Pr_3B (1.05 cm^3, 5.85 mmol). Dry air (5 cm^3) was bubbled through the reaction mixture. After 1.5 h further portions of Bu_3SnH (0.6 cm^3) and Pr_3B (0.3 cm^3) were added to the reaction mixture; then further air (5 cm^3) was passed through it. The solution was refluxed for a further 1 h, the reaction being monitored by TLC (see above). Work-up of the reaction mixture and separation of the isomers were conducted as described above. The ratios of the isomers (0.21 g, 83% total) were determined from ^{1}H NMR spectral measurements of the reaction mixture and comparison of the integral intensities of the proton resonances at 5.08 ppm (for α*S*,4*R*-**5a**), 5.32 ppm (α*R*,4*R*-**4a**), 5.16 ppm (β*S*,4*R*-**7a**) and 5.28 ppm (β*R*,4*R*-**6a**).

(c) Pr_3B + O_2 initiation at low temperatures. To a solution of

rac-**1a** (0.15 g, 0.5 mmol) and Pr^iI (0.5 cm^3, 5.0 mmol) in CH_2Cl_2 (4 cm^3), were added Bu_3SnH (0.5 cm^3, 1.7 mmol) and Pr_3B (0.5 cm^3, 2.77 mmol) at −23 °C (CCl_4–solid CO_2); dry air (5 cm^3) was then bubbled through the mixture *via* a syringe for 2 h with stirring. Further portions of Bu_3SnH (0.23 cm^3, 0.8 mmol) and Pr_3B (0.4 cm^3, 2.23 mmol) were added to the mixture and stirring was continued for a further 1 h at −23 °C. The reaction mixture was then cooled to −75 °C and put on a SiO_2 column (jacketted at −78 °C); washing of the column with cooled hexane removed all the Sn- and boron-derivatives. The column was then warmed to ambient temperature and washed with PhH. Evaporation of the benzene solution afforded a residue consisting of a mixture of isomers (0.03 g, 20%) which were separated by preparative TLC (EtOAc–$CHCl_3$–C_6H_{14}, 1 : 8 : 15). A reaction at ambient temperature was conducted in a similar manner (0.08 g, 51%), the only difference being that cooling of the column was unnecessary.

Hydrolysis of the diastereoisomeric 3-(2′-isopropyl-3′-phenylpropionyl)-4-benzyl(or phenyl)oxazolidin-2-ones and recovery of 4 methyl-3-phenylpentanoic acids

To a solution of an isomer (0.11 g, 0.33 mmol), in a mixture of THF (5 cm^3) and water (5 cm^3) was added aq. H_2O_2 (30%; 0.08 cm^3, 2.64 mmol) and LiOH (0.03 g, 1.32 mmol). The reaction mixture was stirred at 20 °C for 3 h. After completion of the reaction (TLC), most of the THF was removed by evaporation to leave an aqueous solution (pH 12) which was extracted with CH_2Cl_2 (3 × 10 cm^3); work-up of the extracts gave recovery of 4-benzyl-(or phenyl)oxazolidin-2-ones. The aqueous solution was acidified with aq. HCl (3 M) to pH 1 and then again extracted with CH_2Cl_2 (4 × 15 cm^3). The combined extracts were dried ($MgSO_4$) and concentrated to yield a 4-methyl-3-phenylpentanoic acid. The acid was esterified by MeOH (with $SOCl_2$) and the ester was used for the analysis by GLC method.

X-Ray diffraction analysis

Crystal data for (3′*R**,4*R**)-3-(2′-isopropyl-3′-phenylpropionyl)-4-phenyloxazolidin-2-one: $C_{21}H_{23}NO_3$, $M = 337.40$, monoclinic, space group $C2/c$, at 20 °C: $a = 28.216(7)$, $b = 6.284(2)$, $c = 21.509(6)$ Å, $\beta = 102.08(2)°$, $V = 3729(2)$ Å^3, $Z = 8$, $D_c = 1.202$ g cm^{-3}. Unit cell parameters and 3247 reflections were measured with an automated 4-circle Siemens P3/PC diffractometer [293 K, λ(Mo-Kα), graphite monochromator, $\theta/2\theta$-scan, $\theta_{max} = 25°$]. The structure was solved by direct methods and refined by the full-matrix least-squares technique in anisotropic approximation for non-hydrogen atoms. Hydrogen atoms in the geometrically calculated positions were included in refinement with fixed positional and isotropic thermal ('riding' model) parameters. The final discrepancy factors are $R_1 = 0.066$ for 1493 unique reflections with $I > 2\sigma(I)$ and $wR_2 = 0.152$ for 3121 unique reflections.

Crystal data for (2′*S*,4*R*)-3-(2′-isopropyl-3′-phenylpropionyl)-4-benzyloxazolidin-2-one: $C_{22}H_{25}NO_3$, $M = 351.43$, orthorhombic, space group $P2_12_12_1$, at 20 °C: $a = 6.350(2)$, $b = 9.420(2)$, $c = 32.806(8)$ Å, $V = 1962.3(8)$ Å^3, $Z = 4$, $D_c = 1.190$ g cm^{-3}. Unit cells parameters and 1944 reflections for the sample were measured analogously. The final discrepancy factors are $R_1 = 0.058$ for 1237 unique reflections with $I > 2\sigma(I)$ and $wR_2 = 0.107$ for all 1901 unique reflections. A small contribution for anomalous scatterers (three oxygen atoms with Mo radiation) did not allow us to determine the absolute configuration merely on the basis of X-ray experiment. Nevertheless, the presence of the chiral centre at C(4) with the authentic known configuration—(*R*) made it possible to assign unambiguously the configuration of the newly formed chiral centre at the C(7) atom that was of *S*-configuration.

All calculations were carried out with SHELXTL PLUS and SHELXL-93 programs. Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre [see Notice to Authors, (1997), *J. Chem. Soc.*, *Perkin Trans 1*, 1997, Issue 1]. Any requests for this material should be accompanied by a full bibliographic citation for this work together with the reference number 207/134.

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