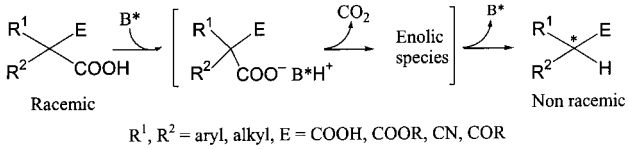
Catalysed Asymmetric Protonation of Simple Linear Keto-Enolic Species − A Route to Chiral α-Arylpropionic Acids

Olivier Roy,[a] Abdelkhalek Riahi,[a] Françoise Hénin,*[a] and Jacques Muzart[a]

Keywords: Alkaloids / Asymmetric catalysis / Cleavage reactions / Decarboxylation / Protonation

The reaction cascade consisting of deprotection/decarboxylation/asymmetric protonation of enolic species, starting from open-chain benzyl β-oxo esters, has been studied. When carried out in the presence of catalytic amounts of cinchonine, the reaction gave optically active α-aryl ketones with up to 75% *ee*. Enantio-enriched (*S*)-3-phenyl-2-butanone can be converted into 2-phenylpropionic acid without racemisation.

The enantioselective protonation of prostereogenic enol derivatives is conceptually simple, but the development of catalytic methods remains a challenge, especially in terms of rational design.[1] The methodologies currently in use are largely empirical and numerous parameters need to be considered. One general approach involves the generation of an enolate, which is protonated by a catalytic chiral protic source, which is in turn regenerated by an achiral stoichiometric proton donor. The generation of ketone enolates mainly makes use either of cleavage of enol ether derivatives by organometallic compounds,[2] or of nucleophilic addition to ketenes.[3] Under these conditions, high enantioselectivities can be achieved by the use of a great variety of chiral proton donors in association with achiral sources of moderate acidity.[4] The creation of two contiguous chiral centres by a sequence of asymmetric conjugated addition/protonation reactions between enones and thiols, catalysed by a chiral lithium complex, has recently been reported.[5] Another catalytic strategy utilises a transition metal with a chiral ligand for the formation of the enolic species, which can be protonated[6] or arylated[7] enantioselectively. We have used different methodologies (a photochemical activation[8,9] and a palladium-induced cascade reaction[10,11]) to produce enolic species. The common feature of our procedures is the presence of a chiral amino alcohol in the key step, which interacts with the enolic species and promotes its enantioselective protonation. Thanks to the enol itself, the amino alcohol is regenerated, allowing its use in catalytic amounts, without any other proton source. Our preparation of optically active ketones, which starts from racemic β-oxo acids protected as benzyl β-oxo esters, corresponds to a cascade reaction involving deprotection, decarboxylation and final asymmetric protonation of the resulting enolic species.[10,11] The key step under these conditions is probably analogous to that observed with malonic acid derivative starting materials (Scheme 1). Advances in the field of asymmetric decarboxylation since the pioneering work of Marckwald[12] have been reviewed by Brunner.[13] The reaction is generally assisted by an alkaloid base (B*), allowing the formation of an ammonium carboxylate, which on decarboxylation affords an enolate, which is protonated by the ammonium group.[12−14] Naproxen derivatives can thus be prepared with *ee*s up to 72% by use of a catalytic amount of an amide synthesised from cinchonine.[13,15]



Scheme 1. Asymmetric decarboxylation of malonic derivatives

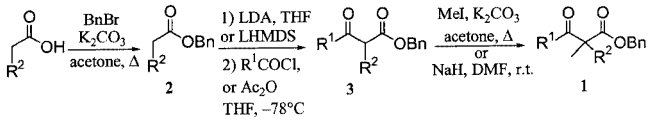
When E is a carbonyl group,[16] however, different problems occur. 2-Methyl-1-oxotetralin-2-carboxylic acid and 2-methyl-1-oxoindan-2-carboxylic acid can be prepared by saponification of the corresponding oxo esters, but dilute solutions of these oxo acids are not stable at room temperature, due to spontaneous decarboxylation. Consequently, reproducible results are difficult to obtain. Furthermore, our attempts to prepare linear analogues either in the same way[16] or by direct acylation of the substituted acid were unsuccessful.[17] In situ preparation of oxo acids by reductive cleavage of their corresponding benzyl esters, however, has allowed us to circumvent these obstacles.[10,11] This paper describes our studies on the asymmetric transformations of racemic open-chain benzyl β-oxo esters; part of this

[a] Unité Mixte de Recherche "Réactions Sélectives et Applications", CNRS − Université de Reims Champagne-Ardenne,
B. P. 1039, 51687 Reims Cedex 2, France
E-mail: francoise.henin@univ-reims.fr

work has already been presented in a preliminary communication.[11]

Synthesis of Starting Substrates

The synthesis of β-oxo esters **1** starts with benzyl esters **2** of suitable acids, which are acylated under classical conditions,[18] to afford monosubstituted oxo esters **3**, which are further methylated in basic media (Scheme 2 and Table 1).



1–3	a	b	c	d	e	f	g
R^1	Ph	Ph	Ph	Ph	Ph	Ph	Me
R^2	Bn	Ph	*p*-$MeOC_6H_4$	*p*-MeC_6H_4	*p*-PhC_6H_4	*p*-FC_6H_4	Ph

Scheme 2. Route to racemic oxo esters

Table 1. Synthesis of **1**

Product	Yield [%]	Product	Yield [%][a][b]	Product	Yield [%][a][c]
2a	85	**3a**	43[d]	**1a**	61[e]
2b	99	**3b**	87	**1b**	75
2c	99	**3c**	71	**1c**	52
2d	99	**3d**	65	**1d**	50
2e	99	**3e/P'**	87	**1e**	23
2f	99	**3f**	58	**1f**	62
		3g	49[f]	**1g**	75

[a] Isolated yields of purified products. [b] LDA used as a base, unless otherwise noted. [c] K_2CO_3 used as a base, unless otherwise noted. [d] Also isolated: 33% of starting material. [e] The alkylation was carried out with NaH in DMF. [f] For acylation, LHMDS and Ac_2O were used in place of LDA and R^1COCl.

Enantioselective Deprotection/Decarboxylation

The cascade reaction has already been studied with cyclic substrates, particularly with substituted indanones. In these cases the products were isolated with elevated enantioselectivities.[10] When the same method was applied to linear substrates, a substitution pattern of **1a** with an aryl and homobenzylic carbonyl group, analogous to that in indanones, was chosen as the starting point for investigation. This oxo ester was subjected to heterogeneous hydrogenation conditions (Pd/C, 0.025 equiv., H_2, bubbling or gas bag, solvent, room temp.) in the presence of catalytic amounts of A*H. Amino alcohols **6**–**9** (Figure 1) were chosen as chiral protic sources for different reasons: (–)-ephedrine (**6**) was a reference catalyst in our experiments of asymmetric tautomerisation[9,19] while camphor derivatives based on structure **7** produced the best results[10,20] and cinchona alkaloids **8**, **9** gave the best selectivities from malonic substrates.[13–15]

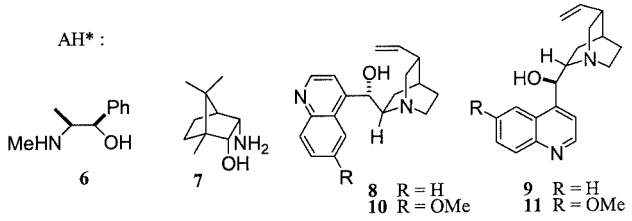


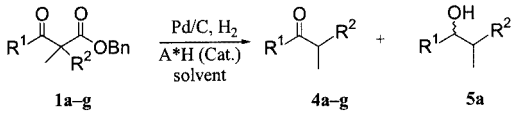
Figure 1. Amino alcohols used as chiral protic sources

The results were disappointing (Table 2, Scheme 3). The expected ketone **4a** was obtained in reasonable yields, but was accompanied by alcohol **5a**, arising from over-reduction.[21] Furthermore, the *ee* of **4a** did not exceed 16%, even when the reaction temperature, the nature of the supported catalyst[22,23] or the solvent (THF and toluene instead of acetonitrile) were changed.

Table 2. Enantioselective hydrogenolysis/decarboxylation/tautomerization of **1a** in acetonitrile

Entry	AH*[a]	*T* [°C]	Time [h][a]	**4a** Yield [%][b]	**4a** *ee* [%][c] (configuration)[d]	**5a** Yield [%][b]
1	**6**	22	0.25	79	2 (*S*)	17
2	**6**	22	1	71	4 (*S*)	22
3	**6**	50	0.25	58	6 (*S*)	11
4	**6**	80	0.25	65	6 (*S*)	10
5	**6**	80	1	22	6 (*S*)	61
6	**7**	22	0.5	83	6 (*S*)	trace
7	**7**	50	0.25	60	10 (*S*)	n.d.[e]
8	**7**	80	0.17	62	10 (*S*)	n.d.[e]
9	**8**	22	1.1	82	5 (*R*)	n.d.[e]
10	**9**	0	7[f]	19	16 (*S*)	n.d.[e]
11	**9**	22	1	89	10 (*S*)	trace
12	**9**	50	0.37	81	9 (*S*)	n.d.[e]

[a] Pd/C (0.025 equiv.), H_2 (gas bag), A*H, 0.3 equiv.; the reaction time shows the period required to reach full conversion of the substrate, as indicated by TLC. [b] Isolated yields of purified products. [c] Enantiomeric excess determined by HPLC. [d] The configuration was attributed by comparison of the optical rotation with literature values.[24] [e] Not determined. [f] Also isolated: 65% of starting material.



Scheme 3. Decarboxylative reduction/tautomerization of **1**

A change from **1a** to **1b** (R^2 = Ph instead of CH_2Ph) as substrate produced improved results (Table 3). The reaction became more chemoselective and gave **4b** without any detectable amounts of alcohol **5b**. Nevertheless, in MeCN, the use of **6** (Entry 13) or **7** (Entry 14) as chiral protic sources gave no or little enantioselectivity. Fortunately, cinchona amino alcohols afforded enhanced *ee*s: 49% with cinchonidine (**9**, Entry 15), giving **4b** of (*R*) configuration, and 56% with cinchonine (**8**, Entry 16), this pseudo-enantiomer of **9** producing **4b** of opposite configuration. When the amount of cinchonine, which is insoluble in acetonitrile, was reduced, the reaction became slightly more enantioselective (Entry 18 compared to Entries 16 and 17). When **8** was preadsorbed on the supported palladium, better enantioselectivity was obtained (Entry 19). Of the other solvents used (Entries 20−26), ethyl acetate gave the best results (Entry 21). In this solvent, a decrease in the amount of amino alcohol to 0.05 equiv. was not detrimental to the *ee* (Entries 21−23). Preadsorption of the chiral catalyst as above in ethyl acetate did not improve the *ee* (Entry 24), while a slight modification of the cinchona structure strongly reduced the *ee* in both solvents (Entries 25, 26).

In order to evaluate the importance of electronic effects on the selectivity, the reaction was further studied by varying the substituent pattern on the aryl group R^2 (Table 4). Under the same conditions, the *ee*s of **4** varied from 66 to

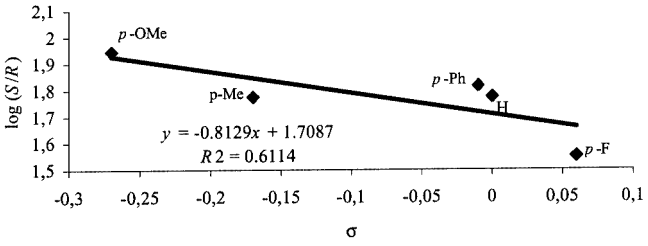


Figure 2. Plot (22 °C) of log [selectivity] values for each substrate versus the corresponding Hammett constant σ

Table 3. Enantioselective hydrogenolysis/decarboxylation/tautomerization of **1b**

Entry	Solvent	AH* (equiv.)	Time [h][a]	**4b** Yield [%][b]	*ee* [%][c] (configuration)[d]
13	MeCN	**6** (0.3)	1	97	0
14	MeCN	**7** (0.3)	0.5	85	16 (*R*)
15	MeCN	**9** (0.3)	0.5	70	49 (*R*)
16	MeCN	**8** (0.3)	1	94	56 (*S*)
17	MeCN	**8** (0.5)	1	100	56 (*S*)
18	MeCN	**8** (0.1)	1	100	61 (*S*)
19	MeCN	adsorbed[e]			
		8 (0.3)	7	95	64 (*S*)
20	THF	**8** (0.3)	17	85	52 (*S*)
21	EtOAc	**8** (0.3)	1	100	71 (*S*)
22	EtOAc	**8** (0.1)	2	56[f]	70 (*S*)
23	EtOAc	**8** (0.05)	2	100	68 (*S*)
24	EtOAc	adsorbed[e]			
		8 (0.3)	8	49[g]	70 (*S*)
25	EtOAc	**10** (0.3)	1	100	35 (*S*)
26	MeCN	**11** (0.3)	1	100	33 (*R*)

[a] Pd/C (0.025 equiv.), H_2 (gas bag), A*H, 0.3 equiv.; the reaction time shows the period required to reach full conversion of the substrate, as indicated by TLC. [b] Isolated yields of purified products. [c] Enantiomeric excess determined by HPLC. [d] The configuration was attributed by comparison of the optical rotation with literature values.[24,25] [e] The suspension was prepared as follows: palladium on charcoal was added to a solution of **8** in chloroform and the solvent was then evaporated under reduced pressure and replaced by a solution of the substrate in MeCN or EtOAc. [f] Undistilled solvent. [g] Also isolated: 51% of **1b**.

Table 4. Enantioselective hydrogenolysis/decarboxylation/tautomerization of **1c−1f** in the presence of cinchonine

Entry	Substrate[a]	Time [h]	Product	Yield [%][b]	*ee* [%][c] (configuration)[d]
27	**1c**	1.5	**4c**	92	75 (*S*)
28	**1d**	2	**4d**	99	71 (*S*)
29	**1e**	2	**4e**	95	72 (*S*)
30	**1f**	1.8	**4f**	99	66 (*S*)

[a] Substrate **1**; Pd/C, 0.025 equiv.; H_2; **8** (0.3 equiv.); EtOAc; room temp. [b] Isolated yields of purified products. [c] Enantiomeric excess determined by HPLC. [d] Configurations determined by comparison of Cotton effects of compounds **4c−f** with those of **4b** (see Exp. Sect.).

Table 5. Enantioselective hydrogenolysis/decarboxylation/tautomerization of **1g**

Entry	Solvent	AH* (equiv.)	Time [h][a]	**4g** Yield [%][b]	**4g** *ee* [%][c] (configuration)[d]
31	MeCN	**8** (0.3)	1	41	55 (*S*)
32	EtOAc	**8** (0.3)	1	99	67 (*S*)
33	EtOAc	**8** (0.1)	1	81	62 (*S*)
34	EtOAc	**8** (0.05)	1	80	48 (*S*)
35	EtOAc	**9** (0.3)	1	96	67 (*R*)
36	EtOAc	**7** (0.3)	1.25	94	17 (*R*)
37	EtOAc	**9** (0.3)	1.25	97	30 (*S*)
38	EtOAc	**8**, HCl[e] (0.3)	1.5	96	5 (*S*)

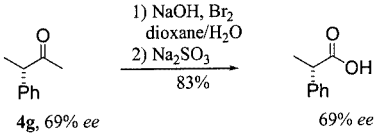
[a] Pd/C (0.025 equiv.) H_2 (gas bag), A*H, 0.3 equiv.; the reaction time shows the period required to reach full conversion of the substrate, as indicated by TLC. [b] Isolated yields of purified products. [c] Enantiomeric excess determined by HPLC. [d] Configuration attributed by comparison of the optical rotation with literature values.[26] [e] Cinchonium hydrochloride.

75%. However, the Hammett correlation did not correspond to a straight line (Figure 2, see below).

It appears (Table 2 versus Tables 3 and 4), that the nature of the R^2 group plays an important role in both the chemo- and the enantioselectivity of **4**. Obviously, the influence of the R^1 group also has to be considered, and so we studied the reaction starting from **1g** (R^1 = Me instead of Ph). This did not affect the chemoselectivity of the transformation into ketone **4g** (Table 5); when ethyl acetate was used as solvent, the *ee*s of **4g** were also higher (Entries 31 and 32). Cinchonine and cinchonidine produced the same *ee* but with opposite configurations of **4g** (Entries 32 and 35). These compounds are more effective chiral protic sources than aminoborneol, quinidine and cinchonium hydrochloride (Entries 36−38). The optimum amount of chiral catalyst seems to be about 0.3 equiv., since lower values gave reductions in *ee* (Entries 32−34).

Access to Phenylpropionic Acid

Optically active arylpropionic acids belong to a class of nonsteroidal antiinflammatory agents of which the (*S*) form is generally more effective;[27] it is therefore still of interest to develop new methods for their production.[28] Ru^{3+}/sodium periodate[29] failed to convert the phenyl ketone **4b** into the expected acid. However, the haloform reaction, which has already been used for the preparation of (*S*)-naproxen from the corresponding methyl ketone,[30] proved to be a convenient method[31] for the transformation of **4g** (69% *ee*) into 2-phenylpropanoic acid without racemisation (83% yield, 69% *ee*) (Scheme 4).



Scheme 4. Haloform reaction of **4g**

Origin of the Enantioselectivity

The *nature of the enolic species* has to be considered first if we assume that its asymmetric protonation is the discriminating step. However, since a multistep process is involved, several species can be envisaged as able to influence the reaction course[10] (Figure 3). Hydrogenolysis of **1** gives an oxo acid **KA-H** or a palladium oxo carboxylate **KA-Pd**. The decarboxylation of **KA-H** may occur spontaneously, producing an enol **E-H**, or it may be assisted by the basic amino group of the chiral inductor (as **KA-N***), producing an ammonium enolate **E-N***. Asymmetric protonation of **E-N*** may be mediated by the ammonium group and that of **E-H** after interaction with the amino group of **A*H**, through the above enolate or a nonionic tight association. From **E-N*** or **E-H** the proton could be delivered through a nine-membered cyclic transition state, by the ammonium group of **EN***,[32] by the hydroxy group of **EN*** or by the amino alcohol **A*H**.[19] The enol itself may also act as a protic source giving rise to the formation of racemic **4**. It is also

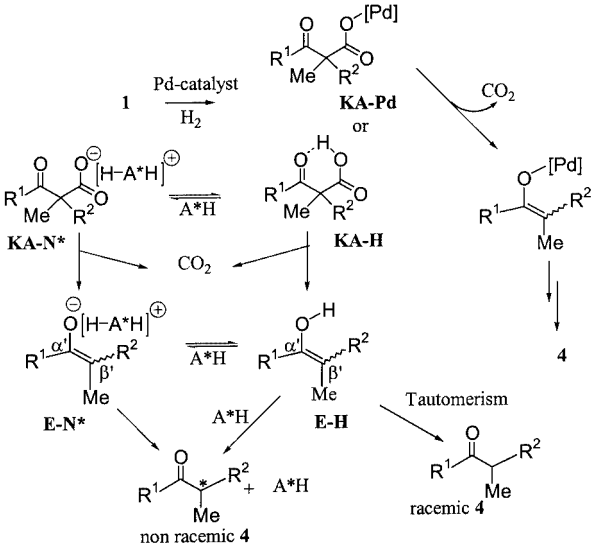


Figure 3. Possible routes for the formation of **4**

possible that palladium intermediates are involved in the reaction (starting from **KA-Pd**).

In the pathways shown in Figure 3, the chiral amino alcohol is used in catalytic amounts and its turnover is assured by the final protonation step (directly, with the ammonium group as the protic source,[32] or stepwise with the OH group[19]). As no methods to suppress the competitive racemic process are available, the amino alcohol as a base may also play a role in accelerating the nonracemic reaction. It seems likely that the slow generation of the oxo acid and (or) the enolic species in the medium maintains an appropriate base/substrate ratio and so higher *ee*s have been observed when starting from **1** rather than **KA-H** as the initial substrate.[16] The presence of palladium in the medium could also influence one determining enantioselective step and explain these higher *ee* values.

In view of the complexity of the process, no simple interpretation is possible. However, additional data are available, through consideration of the influence of the *stereochemistry of the enollenolate double bond*. Both (*Z*) and (*E*) configurations of the enolic species would be expected from decarboxylation of the linear oxo acid, the facial discrimination being determined mainly by the enol-bound groups[33] (Figure 4). Both isomers are capable of providing the same enantiomer if the asymmetric protonation step takes place under control of the β′-substituents (latent C-α′), unlike the case of control governed by the α′-substituents (latent C-β′) (Figure 4). In our case, we have observed: i) reasonably high enantioselectivities (up to 75%), ii) the importance of the β′-substituents, since much higher *ee*s are obtained in the presence of an aryl group (Tables 3−5) than with a benzyl moiety (Table 2), and iii) only a minor effect of the α′-substituents, since switching from **1b−f** to **1g**, in which an α-aryl group is replaced by a methyl group, has almost no effect on the *ee* of **4** (Table 5). All these facts seem to be compatible with control by the β′-substituents during the key step of asymmetric protonation of the enolic species; a similar interpretation has also been proposed for the asymmetric protonation of ammonium dienolates.[32]

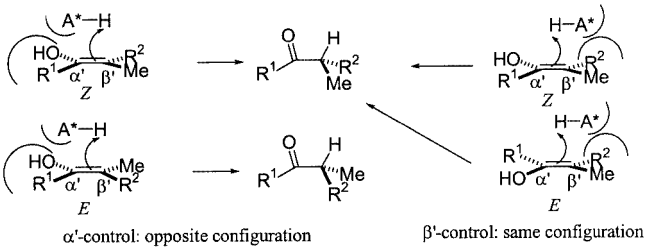


Figure 4. Comparison of α′- and β′-control of the protonation step

Generally, selective reactions are also influenced by *electronic factors*. We have approached this aspect by modifying the nature of the aryl group of **1** (R^2), which corresponds to a change on the β′-position of the enolic species (Table 4). In Figure 2, in which the observed selectivities {log[(*S*)]/[(*R*)]} are plotted against the Hammett constant σ,[34] the correlation is moderate, due probably to the existence of different rates of protonation of the (*Z*)- and (*E*)-enolic species. Although no straight line appears, a trend is perceptible, with electron-donating substituents (*p*-meO, *p*-me, *p*-Ph) giving enhanced enantioselectivities.[35] The term ln[(*S*)]/[(*R*)] is proportional to $-\Delta\Delta G^{\ddagger}$ (i.e., to the difference in free energies between the two diastereomeric transition states giving rise to the enantiomers).[36] Such a correlation does not allow us to predict whether or not the rate of formation of the (*R*) enantiomer is changed more than that of the (*S*) enantiomer. It is reasonable to assume that the faster reaction is also the more selective, as in the cases of i) Halpern's well-known asymmetric hydrogenation,[37] ii) several examples of heterogeneous hydrogenation reactions,[38] and iii) diethylzinc addition to aldehydes.[39] If this is the case, our results are consistent with protonation of the enolic species as the key step, since it corresponds (according to the Hammett equation) to the development of a positive charge in the transition state, namely the approach of a proton to the enolic species.

In conclusion, we have shown that open-chain keto-enolic species can be enantioselectively protonated with *ee*s of up to 75%, this being due to β′-control of the selectivity. under the conditions used, the enol α′-carbon atom remains a "latent trigonal centre". In the linear series, cinchonine is the best catalytic protic chiral source; this differs from our previous observations in the cyclic series[10] but is closer to results found with malonic substrates.[13]

Experimental Section

General Remarks: NMR spectra: Bruker AC 250 (^{1}H: 250 MHz; ^{13}C: 62 MHz) or Bruker AC 500 (^{1}H: 500 MHz; ^{13}C: 124 MHz); internal TMS. Infrared spectra: FTIR Spectrafile IR plus midac. EI mass spectra: JEOL D-300 (70 eV), recorded at the Faculty of pharmacy of Reims. Optical rotations: Perkin−Elmer 241 (0.5-dm cell). Microanalyses: Perkin−Elmer CHN 2400. HPLC: Shimadzu LC10AS, UV SPD 10A detector (254 nm). Circular dichroism: Jasco 810. Chromatography: TLC: Alufolien Merck 5554 silica gel PF_{254}; flash chromatography: silica gel Merck 9385, 0.04−0.063 mm. Purification of the solvents: diethyl ether and THF distilled from Na/benzophenone; dichloromethane, chloroform, ethyl acetate and toluene distilled from CaH_2; DMF distilled from $MgSO_4$; acetonitrile distilled from P_2O_5 and then CaH_2.

General Procedure for the Preparation of Starting Esters 2a−f: A mixture of the carboxylic acid, benzyl bromide (1.1 equiv.) and potassium carbonate (1 equiv.) was heated at reflux in acetone (15 mL/g of carboxylic acid) overnight, and then cooled, filtered and concentrated under vacuum. The residue was dissolved in diethyl ether, washed with water and saturated brine and dried with $MgSO_4$. After elimination of the solvent, the product was used for the next step.

Benzyl 2-Phenylpropanoate (2a): Colourless oil (13.6 g, 85%). IR (KBr): $\tilde{\nu}$ = 3030, 1736, 1497, 1454, 1159 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 2.71 (t, *J* = 7.6 Hz, 2 H), 2.99 (t, *J* = 7.6 Hz, 2 H), 5.14 (s, 2 H), 7.15−7.4 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 30.9, 35.8, 66.2, 126.2, 128.1, 128.2, 128.5, 135.8, 140.3, 172.6 ppm.

Benzyl 2-Phenylethanoate (2b): Colourless oil (41.6 g, 99%). IR (KBr): $\tilde{\nu}$ = 3030, 1736, 1497, 1454, 1159 cm^{-1}. ^{1}H NMR ($CDCl_3$):

δ = 3.70 (s, 2 H), 5.16 (s, 2 H), 7.28−7.29 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 41.3, 66.6, 127.1, 128.1, 128.2, 128.5, 128.6, 129.2, 133.8, 135.8, 171.4 ppm.

Benzyl 2-(4-Methoxyphenyl)ethanoate (2c): Colourless oil (15.3 g, 99%). IR (KBr): ṽ = 2956, 1737, 1612, 1585, 1513, 1456, 1249 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 3.64 (s, 2 H), 3.80 (s, 3 H); 5.15 (s, 2 H), 6.88 (m, 2 H), 7.23 (m, 2 H), 7.29−7.41 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 40.3, 55.2, 66.5, 113.9, 125.9, 128, 128.1, 128.5, 130.3, 135.8, 158.6, 171.7 ppm.

Benzyl 2-(4-Methylphenyl)ethanoate (2d): Colourless oil (15.6 g, 99%). IR (KBr): ṽ = 3032, 1737, 1515, 1498, 1455, 1256, 1147 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 2.37 (s, 3 H), 3.67 (s, 2 H), 5.16 (s, 2 H), 7.16 (d, *J* = 8.0 Hz, 2 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 7.32−7.42 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.0, 40.8, 66.5, 128.0, 128.1, 128.5, 129.1, 129.2, 130.8, 135.8, 136.7, 171.6 ppm.

Benzyl 1,1′-Biphenyl-4-ylethanoate (2e): Yellow solid (11.1 g, 99%); m.p. 67 °C. IR (KBr): ṽ = 3030, 1730, 1487, 1454, 1409, 1378, 1227, 1160 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 3.75 (s, 2 H), 5.20 (s, 2 H), 7.38−7.50 (m, 10 H), 7.61 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 40.9, 66.6, 127.0, 127.2, 127.3, 128.1, 128.2, 128.5, 128.7, 129.7, 132.8, 135.7, 140.0, 140.7, 171.4 ppm.

Benzyl 2-(4-Fluorophenyl)ethanoate (2f): White solid (7.9 g, 99%); m.p. 55 °C. IR (KBr): ṽ = 3045, 2953, 1733, 1606, 1510, 1456, 1422, 1384, 1339, 1225 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 3.67 (s, 2 H), 5.47 (s, 2 H), 7.25−7.37 (m, 7 H) 7.50 (m, 2 H), ppm. ^{13}C NMR ($CDCl_3$): δ = 40.3, 66.6, 115.3 (d, *J* = 21 Hz, 2 CH), 128.1, 128.2, 128.5, 129.5 (d, *J* = 3 Hz), 130.8 (d, *J* = 8 Hz, 2 CH), 135.6, 161.5 (d, *J* = 244 Hz), 171.2 ppm.

General Procedure for the Benzoylation of 2a−f: A solution of lithium diisopropylamide (1.1 equiv.) was prepared by addition of *n*BuLi (1.6 M in hexane) to diisopropylamine under argon at −78 °C in THF (10 mL). After 45 min of stirring, a THF solution (1 mL/mmol) of the ester **2** (1 equiv.) was added dropwise. The mixture was allowed to warm to room temp., stirred for 2 h and then cooled to −78 °C, before addition of benzoyl chloride (1.2 equiv.). After 1 h, the contents of the flask were poured into ice-cold 1 M HCl. The aqueous phase was extracted three times with diethyl ether. The combined organic phases were washed with brine and dried with $MgSO_4$. After removal of the solvents, the residue was purified by flash chromatography to afford **3a−f**.

Benzyl 2-Benzoyl-3-phenylpropanoate (3a): Colourless oil (1.63 g, 43%). IR (KBr): ṽ = 2978, 1734, 1631, 1448, 1338 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 3.37 (d, *J* = 7.4 Hz, 2 H), 4.70 (t, *J* = 7.4 Hz, 1 H), 5.09 (s, 2 H), 7.10−7.60 (m, 13 H), 7.95 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.9, 42.1, 56.1, 67.2, 127.0, 127.6, 127.9, 128.1, 128.2, 128.3, 128.5, 129.6, 132.5, 135.1, 135.5, 139.6, 172.1, 196.9 ppm. $C_{23}H_{20}O_3$ (344.41): calcd. C 80.21; H 5.85; found C 80.02, H 5.78.

benzyl 2-Benzoyl-2-phenylethanoate (3b): White solid (12.2 g, 87%); m.p. 63−64 °C. IR (KBr): ṽ = 3062, 1725, 1691, 1293, 1143 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 5.24 (s, 2 H), 5.68 (s, 0.5 H), 7.24−7.51 (m, 13 H), 7.95 (m, 2 H), 10.43 (s, 0.5 H, enol)] ppm. ^{13}C NMR ($CDCl_3$): δ = 60.5, 67.4, 128.2, 128.3, 128.5, 128.7, 128.8, 128.9, 129.6, 132.8, 133.5, 135.4, 135.5, 168.9, 198.0 ppm. $C_{22}H_{18}O_3$ (330.12): calcd. C 79.98, H 5.49; found C 79.92; H 5.62.

Benzyl 2-Benzoyl-2-(4-methoxyphenyl)ethanoate (3c): White solid (15.01 g, 71%); m.p. 73−74 °C. IR (KBr): ṽ = 2953, 1726, 1692, 1513, 1449, 1284, 1141 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 3.76 (s, 3 H), 5.19 (s, 2 H), 5.60 (s, 1 H), 6.87 (m, 2 H), 7.29−7.50 (m, 10 H), 7.92 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 55.2, 59.7, 67.3, 114.3, 124.8, 128.2, 128.3, 128.5, 128.7, 129.8, 130.7, 133.5, 135.4, 135.5, 159.4, 169.0, 193.3 ppm. $C_{23}H_{20}O_4$ (360.13): calcd. C 76.65, H 5.59; found C 76.51; H 5.68.

Benzyl 2-Benzoyl-2-(4-methylphenyl)ethanoate (3d): White solid (14.0 g, 65%); m.p. 88−89 °C. IR (KBr): ṽ = 3031, 1749, 1675, 1595, 1450, 1262 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 2.35 (s, 3 H), 5.25 (s, 2 H), 5.69 (s, 1 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 7.34−7.54 (m, 10 H), 8.00 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.0, 60.1, 67.2, 128.1, 128.4, 128.6, 128.8, 129.3, 129.5, 129.7, 133.3, 135.4, 135.5, 137.9, 168.8, 193.2 ppm. $C_{23}H_{20}O_3$ (344.41): calcd. C 80.21, H 5.85; found C 80.07, H 6.08.

Benzyl 2-Benzoyl-2-(1,1′-biphenyl-4-yl)ethanoate (3e): White solid (11.7 g, 87%); m.p. 148−149 °C. IR (KBr): ṽ = 3063, 1726, 1692, 1597, 1488, 1449, 1284, 1141 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 5.21 (s, 2 H), 5.69 (s, 1 H), 7.30−7.58 (m, 16 H), 7.95 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 60.2, 67.5, 127.1, 127.5, 127.6, 128.2, 128.3, 128.5, 128.7, 128.9, 130.0, 131.7, 133.6, 140.4, 141.0, 168.7, 193.0 ppm. $C_{28}H_{22}O_3$ (406.15): calcd. C 82.74, H 5.46; found C 82.60, H 5.45.

Benzyl 2-Benzoyl-2-(4-fluorophenyl)ethanoate (3f): White solid (6.01 g, 58%); m.p. 62 °C. IR (KBr): ṽ = 3064, 2958, 1727, 1691, 1600, 1510, 1449, 1278 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 5.21 (s, 2 H), 5.66 (s, 1 H), 7.07 (m, 2 H), 7.26−7.49 (m, 9 H), 7.56 (m, 1 H), 7.95 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 59.5, 67.5, 115.8, 128.2, 128.3, 128.5, 128.7, 128.8, 131.3, 133.6, 135.2, 135.4, 162.5, 168.5, 192.9 ppm. $C_{22}H_{17}FO_3$ (348.37): calcd. C 75.85, H 4.92; found C 75.52, H 4.81.

Acetylation of 2g: A solution of lithium hexamethyldisilazane (53.1 mmol) was prepared by addition of *n*BuLi (1.6 M in hexane, 33.2 mL) to hexamethyldisilazane (11.2 mL, 53.1 mmol) under argon at −78 °C in THF (50 mL). After 45 min of stirring, a THF solution (50 mL) of benzyl phenylethanoate (**2g**, 10 g, 44.25 mmol) was added dropwise. The mixture was allowed to warm to room temp., stirred for 2 h and then cooled to −78 °C, before addition of acetic anhydride (5 mL, 53.1 mmol). After 1 h, the contents of the flask were poured into ice-cold 1 M HCl. The aqueous phase was extracted three times with diethyl ether (20 mL). The combined organic phases were washed with brine and dried with $MgSO_4$. After removal of the solvents, the residue was purified by flash chromatography (petroleum ether/ethyl acetate, 95:5) to afford a white solid (3.27 g, 49%); m.p. 63−64 °C. IR (KBr): ṽ = 3064, 1735, 1715, 1145 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 2.17 (s, 3 H), 4.78 (s, 1 H), 5.22 (s, 2 H), 7.37 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.7, 65.5, 67.2, 128.2, 128.25, 128.3, 128.5, 128.8, 129.3, 132.4, 135.2, 168.3, 201.3 ppm. $C_{17}H_{16}O_3$ (268.31): calcd. C 76.10, H 6.01; found C 76.45; H 5.89.

Benzyl 2-Benzoyl-2-methyl-3-phenylpropanoate (1a): A solution of benzyl 2-benzoyl-3-phenylpropanoate (5.13 g, 14.9 mmol) in DMF (100 mL) was added dropwise under argon to a suspension of sodium hydride (17.7 mmol) in DMF (30 mL). After 45 min, iodomethane (1.85 mL, 29.6 mmol) was added and the mixture was stirred for a further 4 h and then hydrolysed. The aqueous phase was extracted with diethyl ether (3 × 30 mL) and the organic layer was washed with brine, dried with $MgSO_4$ and concentrated. the residue was purified by flash chromatography (petroleum ether/ethyl acetate, 95:5) to afford a colourless oil (3.26 g, 61%). IR (KBr): ṽ = 2999, 1722, 1672, 1454, 1178 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.50 (s, 3 H), 3.35 (d, *J* = 13.7 Hz, 1 H), 3.44 (d, *J* = 13.7 Hz, 1 H), 5.09 (s, 2 H), 6.9−7.4 (m, 13 H), 7.75 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.9, 42.1, 58.1, 67.2, 127.0, 127.6, 127.9, 128.1,

128.2, 128.3, 128.5, 129.6, 132.5, 135.1, 135.5, 139.6, 172.1, 196.9 ppm. $C_{24}H_{22}O_3$ (358.15): calcd. C 80.42, H 6.19; found C 80.28, H 6.57.

Methylation of Compounds 3b−g: A suspension of benzyl oxo ester (10 mmol), potassium carbonate (6.9 g, 50 mmol) and iodomethane (1.25 mL, 20 mmol) in acetone (67 mL) was heated at reflux overnight whilst stirring. The mixture was filtered. After concentration of the filtrate, the residue was dissolved in diethyl ether, washed with brine and dried with $MgSO_4$. Concentration and purification by flash chromatography afforded compounds **1b−g**.

Benzyl 2-Benzoyl-2-phenylpropanoate (1b): White solid (8.56 g, 75%); m.p. 60−61 °C. IR (KBr): $\tilde{\nu}$ = 3330, 1732, 1675, 1452, 1253, 1213 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.92 (s, 3 H), 5.08 (d, J = 12.5 Hz, 1 H), 5.09 (d, J = 12.5 Hz, 1 H), 7.03 (m, 2 H), 7.17−7.48 (m, 11 H), 7.63 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.3, 62.3, 67.1, 127.4, 127.6, 127.9, 128.0, 128.1, 128.3, 128.4, 129.5, 132.4, 135.0, 135.3, 139.5, 172.0, 196.8 ppm. $C_{23}H_{20}O_3$ (344.14): calcd. C 80.21, H 5.85; found C 79.88, H 6.07.

Benzyl 2-Benzoyl-2-(4-methoxyphenyl)propanoate (1c): White solid (2.92 g, 52%); m.p. 60−61 °C. IR (KBr): $\tilde{\nu}$ = 2976, 1718, 1688, 1608, 1515, 1450, 1258, 1239, 1184 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.90 (s, 3 H), 3.78 (s, 3 H), 5.09 (s, 2 H), 6.85 (m, 2 H), 7.06 (m, 2 H), 7.23 (m, 5 H), 7.39 (m, 3 H), 7.65 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.2, 55.1, 61.7, 67.1, 113.8, 127.9, 128.0, 128.1, 128.3, 128.8, 129.5, 131.3, 132.4, 135.1, 135.4, 158.7, 172.3, 197.0 ppm. $C_{24}H_{22}O_4$ (374.15): calcd. C 76.99, H 5.92; found C 76.76, H 5.72.

Benzyl 2-Benzoyl-2-(4-methylphenyl)propanoate (1d): Yellow oil (2.92 g, 50%). IR (KBr): $\tilde{\nu}$ = 3002, 1726, 1668, 1461, 1181 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.94 (s, 3 H), 2.34 (s, 3 H), 5.12 (s, 2 H), 7.08 (m, 2 H), 7.12 (d, J = 8.0 Hz, 2 H), 7.25 (m, 5 H), 7.38 (m, 3 H), 7.67 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.9, 25.3, 62.0, 67.1, 127.4, 127.9, 128.0, 128.1, 128.3, 129.1, 129.5, 132.4, 135.1, 135.4, 136.4, 137.1, 172.2, 197.0 ppm. $C_{24}H_{22}O_3$ (358.15): calcd. C 80.42, H 6.19; found C 80.39, H 6.40.

Benzyl 2-Benzoyl-2-(1,1′-biphenyl-4-yl)propanoate (1e): White solid (1.43 g, 23%); m.p. 59−60 °C. IR (KBr): $\tilde{\nu}$ = 3031, 1729, 1674, 1257, 1214 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.96 (s, 3 H), 5.12 (d, J = 7.8 Hz, 1 H), 5.13 (d, J = 7.8 Hz, 1 H), 7.08 (m, 2 H), 7.19−7.54 (m,15 H), 7.68 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.3, 62.4, 67.2, 127.4, 127.6, 127.9, 128.0, 128.1, 128.3, 128.5, 129.5, 132.4, 135.1, 135.4, 139.5, 172.1, 196.8 ppm.

Benzyl 2-Benzoyl-2-(4-fluorophenyl)propanoate (1f): Yellow oil (1.30 g, 62%). IR (KBr): $\tilde{\nu}$ = 3032, 1739, 1688, 1598, 1377, 1262 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.94 (s, 3 H), 5.09 (d, J = 12.2 Hz, 1 H), 5.15 (d, J = 12.2 Hz, 1 H), 7.06 (m, 4 H), 7.25 (m, 4 H), 7.46 (m, 4 H), 7.65 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.4, 61.6, 67.3, 115.3, 128.0, 128.1, 128.2, 128.3, 129.4, 132.6, 134.9, 135.2, 161.9, 172.0, 196.5 ppm. $C_{23}H_{19}FO_3$ (362.13): calcd. C 76.23, H 5.28; found C 75.97, H 5.59.

Benzyl 2-Acetyl-2-phenylpropanoate (1g): Colourless oil (2.10 g, 75%). IR (KBr): $\tilde{\nu}$ = 3062; 1713; 1497; 1246 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.80 (s, 3 H), 2.08 (s; 3H; H7), 5.24 (s, 2 H), 7.25−7.36 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.2, 27.2, 64.7, 67.2, 127.3, 127.7, 128.1, 128.3, 128.5, 128.6, 135.3, 138.3, 171.7, 204.8 ppm. $C_{18}H_{18}O_3$ (282.12): calcd. C 76.57, H 6.43; found C 76.54, H 6.44.

General Procedure for the Decarboxylation: The amino alcohol and palladium on charcoal (0.025 equiv.) were successively added to a solution of **1** (100 mg) in the corresponding solvent (20 mL, Tables 2−5) in a round-bottomed flask. Gaseous hydrogen was supplied from a "gas bag" or bubbled continuously through the solution until complete disappearance of the starting material, as indicated by TLC (Tables 2−5). The crude mixture was filtered through a pad of silica and purified by chromatography. Yields are reported in Tables 2−5. The spectroscopic data of the resulting ketones are in agreement with the literature: **4a**,[24] **4b**,[24,25] **4c**,[40] **4d**,[39] **4e**,[41] **4g**.[26] HPLC analyses of **4a** and **4b** with chiral columns were carried out as previously reported.[11] For other ketones: **4c**: $[\alpha]_D$= +94.5 (c = 0.88, $CHCl_3$) [(*S*) 75% *ee*]; Chiracel OD, 2-propanol/hexane (1:99); flow rate: 0.6 mL/min; retention time: (*S*) 8.2 min, (*R*) 9.3 min; α = 1.06. **4d**: $[\alpha]_D$ = +108 (c = 1.0, $CHCl_3$) [(*S*) 71% *ee*]; Chiracel OD, 2-propanol/hexane (1:99); flow rate: 0.6 mL/min; retention time: (*S*) 7.4 min, (*R*) 8.5 min; α = 2.4. **4e**: $[\alpha]_D$ = +107 (c = 1.06, $CHCl_3$) [(*S*) 72% *ee*]; Chiracel OD, 2-propanol/ hexane (1:99); flow rate: 0.6 mL/min; retention time: (*S*) 10.9 min, (*R*) 13.0 min; α = 1.5. **4g**: $[\alpha]_D$ = −234 (c = 1.0, $CHCl_3$) [(*R*) 67% *ee*]; Chiracel OD, 2-propanol/hexane (1:99); flow rate: 0.6 mL/min; retention time: (*S*) 17.25 min, (*R*) 18.0 min; α = 1.1.

2-(4-Fluorophenyl)-1-phenylpropan-1-one (4f): Yellow oil (62 mg, 99%) (petroleum ether/ethyl acetate, 95:5). $[\alpha]_D$ = +60.4 (c = 1.02, $CHCl_3$) [(*S*) 61% *ee*]. IR (KBr): $\tilde{\nu}$ = 2977, 2932, 1683, 1504 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.53 (d, J = 6.9 Hz, 3 H), 4.70 (q, J = 6.9 Hz, 1 H), 6.99 (m, 2 H), 7.26 (m, 2 H), 7.44 (m, 3 H), 7.97 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.5, 46.8, 115.7 (d, J = 21 Hz),

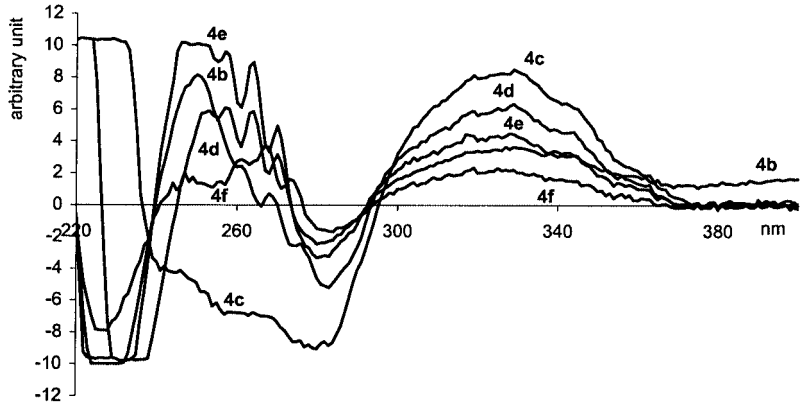


Figure 5. CD spectra of **4b−f** recorded in acetonitrile solutions for samples having the *ee* in theTable 3: (*S*)-**4b**: [1.14 × 10^{-5}] M; **4c**: [1.17 × 10^{-5}] M; **4d**: [9.82 × 10^{-6}] M; **4e**: [9.44 × 10^{-6}] M; **4f**: [1.14 × 10^{-5}] M

128.5, 128.6, 129.2 (d, J = 8 Hz), 132.9, 136.2, 137.1, 161.7 (d, J = 245 Hz), 200.1 ppm. $C_{15}H_{13}FO$ (228.09): calcd. C 78.93, H 5.74; found C 78.60, H 5.40. HPLC analysis: Chiracel OD, 2-propanol/hexane (1:99); flow rate: 0.6 mL/min; retention time: (*S*) 8.7 min, (*R*) 10.7 min; α = 1.95.

The configurations of **4c**−**f** were attributed by comparison of their CD spectra (Figure 5) with that of **4b**, the configuration of which is known.[24,25]

Haloform Reaction.[30] **2-Phenylpropionic Acid:** A solution of sodium hypobromite was prepared by dropwise addition of bromine (1 g, 6.6 mmol) to a cooled solution (−5 °C) of sodium hydroxide in water (9 mL) and diluted with dioxane (6 mL). The mixture was then added dropwise at 10 °C to a solution of **4g** (298 mg, 2.01 mmol, *ee* = 69%) in dioxane (26 mL) and water (8 mL). After 3 h of stirring, the mixture was diluted with sodium sulfite (250 mg/2.5 mL of water) and acidified with 2 M HCl, extracted with dichloromethane (30 mL × 3), dried with $MgSO_4$ and concentrated to afford 2-phenylacetic acid as white crystals (250 mg, 83%, *ee* = 69%). The ^{1}H NMR spectroscopic data of this compound are identical to those described in ref.,[42] . HPLC analysis: Regis (*S*,*S*) Whelk-O1 column; hexane/2-propanol/AcOH (93:7:0.5), 1 mL/min; retention time: (*S*) 8.2 min, (*R*) 8.9 min; α = 1.43.

Acknowledgments

Part of this work was carried out in the framework of the COST D12/0028/99 program. Thanks to Prof. J. Conolly (Glasgow University) for a fruitful discussion, and to Prof. A. Alix and to G. Moroy (Reims University) for the facilities and help in recording CD spectra. We are grateful to the "Ministère de la Recherche et de la Technologie" for a PhD studentship to O. R. and to Engelhard Company for a gift of Pd catalysts.

[1] Reviews: [1a] L. Duhamel, P. Duhamel, J.-C. Launay, J.-C. Plaquevent, *Bull. Soc. Chim. Fr.* **1984**, *II*, 421−430. [1b] C. Fehr, *Chimia* **1991**, *45*, 253−261. [1c] S. Hünig, *Methoden Org. Chem. (Houben-Weyl)* **1996**, vol. VII, p. 3887−3911.[1d]C. Fehr, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2566−2587. [1e] A. Yanagisawa, K. Ishihara, H. Yamamoto, *Synlett* **1997**, 411−420. [1f] J. Eames, N. Weerasooriya, *Tetrahedron: Asymmetry* **2000**, *12*, 1−24.

[2] Alkyllithium cleavage of silyl enol ethers or enol acetates and chiral protic sources: [2a] A. Yanagisawa, T. Watanabe, T. Kikuchi, H. Yamamoto, *J. Org. Chem.* **2000**, *65*, 2979−2983. [2b] G. Asensio, J. Gil, P. Alemán, M. Medio-Simón, *Tetrahedron: Asymmetry* **2001**, *12*, 1359−1362. Alkyllithium cleavage of silyl enol ethers or enol acetates and chiral ligands: [2c] Y. Yamashita, Y. Emura, K. Odashima, K. Koga, *Tetrahedron Lett.* **2000**, *41*, 209−213. Lewis acid assisted cleavage of silyl enol ethers and chiral protic sources: [2d] S. Nakamura, M. Kaneeda, K. Ishihara, H. Yamamoto, *J. Am. Chem. Soc.* **2000**, *122*, 8120−8130.

[3] [3a] C. Fehr, J. Galindo, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1888−1889. [3b] Y. Nakamura, S. Takeuchi, A. Ohira, Y. Ohgo, *Tetrahedron Lett.* **1996**, *37*, 2805−2808. [3c] S. Takeuchi, Y. Nakamura, Y. Ohgo, D. P. Curran, *Tetrahedron Lett.* **1998**, *39*, 8691−8694.

[4] For a discussion of acidity effects in asymmetric protonation, see: E. Vedejs, A. W. Kruger, E. Suna, *J. Org. Chem.* **1999**, *64*, 7863−7870.

[5] [5a] T. Ishikawa, Y. Oku, T. Tanaka, T. Kumamoto, *Tetrahedron Lett.* **1999**, *40*, 3777−3780. [5b] K. Nishimura, K. Tomioka, *J. Org. Chem.* **2002**, *67*, 431−434.

[6] [6a] S. H. Bergens, B. Bosnich, *J. Am. Chem. Soc.* **1991**, *113*, 958−967. [6b] M. Sujiura, T. Nakai, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2366−2368. [6c] Review: P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2001**, *40*, 3726−3748.

[7] [7a] J. Åhman, J. P. Wolfe, M. V. Troutman, M. Palucki, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 1918−1919. [7b] B. M. Trost, G. M. Schroeder, *J. Am. Chem. Soc.* **1999**, *120*, 6759−6760. [7c] S.-H. You, X.-L. Hou, L.-X Dai, X-Z. Zhu, *Org. Lett.* **2001**, *3*, 149−151. [7d] A. Chieffi, K. Kamikawa, J. Åhman, J. M. Fox, S. L. Buchwald, *Org. Lett.* **2001**, *3*, 1897−1900. [7e] T. Hamada, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 999−1001.

[8] F. Hénin, J. Muzart, J.-P. Pète, O. Piva, *New J. Chem.* **1991**, *15*, 611−613.

[9] [9a] F. Hénin, J. Muzart, J.-P. Pète, A. M′Boungou M′Passi, H. Rau, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 416−418. [9b] F. Hénin, A. M'Boungou-M'Passi, J. Muzart, J.-P. Pète, *Tetrahedron* **1994**, *50*, 2849−2864.

[10] J. Muzart, F. Hénin, S. Jamal Aboulhoda, *Tetrahedron: Asymmetry* **1997**, *8*, 381−389.

[11] O. Roy, M. Diekmann, A. Riahi, F. Hénin, J. Muzart, *Chem. Commun.* **2001**, 533−534 and p. 1418.

[12] W. Marckwald, *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 349−354.

[13] H. Brunner, P. Schmidt, *Eur. J. Org. Chem.* **2000**, 2119−2133.

[14] H. Brunner, J. Müller, J. Spitzer, *Monatsh. Chem.* **1996**, *127*, 845−858.

[15] [15a] H. Brunner, P. Schmidt, *Z. Naturforsch., Teil B* **2000**, *55*, 369−372. [15b] H. Brunner, P. Schmidt, M. Prommesberger, *Tetrahedron: Asymmetry* **2000**, *11*, 1501−1512.

[16] F. Hénin, J. Muzart, M. Nedjma, H. Rau, *Monatsh. Chem.* **1997**, *128*, 1181−1188.

[17] In both cases we only observed degradation of the starting material, probably due to retro-Claisen-type reactions.

[18] N. Petragnani, M. Yonashiro, *Synthesis* **1982**, 521−578.

[19] O. Piva, R. Mortezaei, F. Hénin, J. Muzart, J.-P. Pète, *J. Am. Chem. Soc.* **1990**, *112*, 9263−9272.

[20] O. Piva, J.-P. Pète, *Tetrahedron Lett.* **1990**, *31*, 5157−5160.

[21] A *syn* relative configuration has been determined for the diastereomer in slight excess (ca. 55 ± 3%) which can be compared with analogous values observed for **5a** resulting from the hydride reduction of **4a**: C. Alvarez Ibarra, F. Fernandez Gonzalez, M. L. Quiroga Feijoo, J. Santoro, *An. Quim.* **1978**, *74*, 449−454; C. lvarez Ibarra, R. Pérez-Ossorio, M. L. Quiroga, M. S. Arias Pérez, M. J. Fernandez Dominguez, *J. Chem. Soc., Perkin Trans. 2* **1988**, 101−105.

[22] The selectivities are greatly influenced by the nature of the support, as observed in some of our previous experiments[23] and as discussed in, for example: R. L. Augustine, *Heterogeneous Catalysis for the Synthetic Chemist*, M. Dekker, New York, **1996**, chapters 2, 3, 9.

[23] S. Jamal Aboulhoda, S. Létinois, J. Wilken, I. Reiners, F. Hénin, J. Martens, J. Muzart, *Tetrahedron: Asymmetry* **1995**, *6*, 1865−1868.

[24] [24a] W. Oppolzer, C. Darcel, P. Rochet, S. Rosset, J. De Brabander, *Helv. Chim. Acta* **1997**, *80*, 1319−1337. [24b] T. Izawa, Y. Terao, K. Suzuki, *Tetrahedron: Asymmetry* **1997**, *8*, 2645−2648.

[25] A. I. Meyers, D. R. Williams, S. White, G. W. Erickson, *J. Am. Chem. Soc.* **1981**, *103*, 3088−3093.

[26] C. Fuganti, P. Grasselli, F. Spreafico, C. Zirotti, *J. Org. Chem.* **1984**, *49*, 543−546.

[27] G. P. Stahly, M. R. Starrett, *Chirality in Industry II*, (Eds.: A. N. Collins, G. N. Sheldrake, G. Crosby), Wiley, Chichester, **1997**, p. 19−40.

[28] H. R. Sonawane, N. S. Bellur, J. R. Ahuja, D. G. Kulkarni, *Tetrahedron: Asymmetry* **1992**, *3*, 163−192.

[29] M. Asaoka, M. Tanaka, T. Houkawa, T. Ueda, S. Sakami, H. Takei, *Tetrahedron* **1998**, *54*, 471−486.

[30] J. D. Brown, *Tetrahedron: Asymmetry* **1992**, *3*, 1551−1552.
[31] J. Staunton, E. Eisenbraun, *Org. Synth., Coll. Vol.* **1973**, *5*, 8−11.
[32] S. Létinois, F. Hénin, J. Muzart, *Tetrahedron: Asymmetry* **2000**, *11*, 2037−2044.
[33] This concept of the control of an electrophilic attack of an enolic species by the enol-bound groups was developed by Duhamel, and here we have adopted an "α′ and β′" nomenclature for the enol definition (Figures 3 and 4) to avoid confusion with α- and β-positions of the carbonyl group: [33a] L. Duhamel, P. Duhamel, *C. R. Acad. Sci. Paris, Série II* **1995**, *320*, 689−694. [33b] P. Duhamel, *Bull. Soc. Chim. Fr.* **1996**, *133*, 457−459.
[34] C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165−195.
[35] Such a correlation has already been observed during the asymmetric protonation of enolates derived from Schiff bases: L. Duhamel, J.-C. Plaquevent, *Bull. Soc. Chim. Fr.* **1982**, *II*, 75−83.
[36] Eyring equation: $\ln k_S/k_R = -\Delta\Delta G^{\ddagger}/RT$, where k_S and k_R correspond to the rate of formation of the enantiomers, assumed to be proportional to their respective concentrations.
[37] C. Landis, J. Halpern, *J. Am. Chem. Soc.* **1987**, *109*, 1746−1754.
[38] [38a] K. Balázsik, K. Szöri, K. Felföldi, B. Török, M. Bartók, *Chem. Commun.* **2000**, 555−556. [38b] M. Von Arx, T. Mallat, A. Baiker, *Tetrahedron: Asymmetry* **2001**, *12*, 3089−3094.
[39] [39a] H. Zhang, F. Xue, T. C. W. Mak, K. S. Chan, *J. Org. Chem.* **1996**, *61*, 8002−8003. [39b] M. Kitamura, H. Oka, R. Noyori, *Tetrahedron* **1999**, *55*, 3605−3614.
[40] M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.* **1999**, *121*, 1473−1478.
[41] M. A. Garcia-Garibay, S. Shin, C. N. Sanrame, *Tetrahedron* **2000**, *56*, 6729−6737.
[42] C.-F. Yao, K.-H. Kao, J.-T. Liu, C.-M. Chu, Y. Wang, W.-C. Chen, Y.-M. Lin, W.-W. Lin, M.-C. Yan, J.-Y. Liu, M.-C. Chuang, J.-L. Shiue, *Tetrahedron* **1998**, *54*, 791−822.

Received July 8, 2002
[O02369]