Enantioselective addition of nitromethane to α-keto esters catalyzed by copper(II)–iminopyridine complexes

Gonzalo Blay,* Victor Hernández-Olmos and José R. Pedro*

Received 25th October 2007, Accepted 23rd November 2007
First published as an Advance Article on the web 12th December 2007
DOI: 10.1039/b716446g

The copper complex of a chiral iminopyridine easily prepared from (*R*)-(−)-fenchone and picolylamine catalyzes the enantioselective Henry (nitroaldol) reaction between nitromethane and α-keto esters. Good yields and modest to good enantioselectivities are obtained for a wide range of α-keto esters, bearing aromatic, alkyl or alkenyl groups attached to the ketone carbonyl group.

Introduction

The Henry or nitroaldol reaction represents an important procedure for C–C bond formation, providing easy access to nitroalkanols by coupling of readily available nitroalkanes and carbonyl compounds.[1] Because of the chemical versatility of the nitro group, the β-nitroalkanols obtained can be further transformed into valuable polyfunctional molecular frameworks, such as 1,2-amino alcohols, hydroxy acids, *etc.*[2] Due to its significance in organic synthesis, considerable effort has been dedicated to the development of the catalytic enantioselective version of this reaction.[3] As a consequence, a substantial advance has been achieved for the enantioselective nitroaldol reaction with aldehydes, for which several metal-catalyzed[4] or organocatalytic[5] procedures have been developed.

In contrast, the development of the nitroaldol reaction with ketones has met with limited success. In fact a catalytic enantioselective procedure for the nitroaldol reaction with simple ketones still has to be developed, although Shibasaki has described a resolution of racemic nitroalkanols proceeding from ketones.[6] α-Keto esters, with an intermediate reactivity between simple ketones and aldehydes, are more prone to react with nitroalkanes to give the corresponding β-nitro-α-hydroxy esters with the formation of a quaternary stereogenic center.[7] However, to date, only three catalytic systems have been identified to afford synthetically useful enantioselectivity for the addition of nitromethane to α-keto esters. The first example, reported by Jørgensen, relied on the combined use of the C_2-symmetric Cu–bis(oxazoline) (BOX) complex and triethylamine.[8] The system afforded good yields and enantioselectivities with α-keto esters bearing aliphatic substituents, or aromatic rings with electron-withdrawing groups, and more modest results with keto esters bearing aromatic rings with electron-releasing groups. The same authors have reported a related aza-Henry reaction employing tertiary nitro compounds as nucleophiles and α-imino esters as electrophiles.[9] Xu *et al.* have developed a series of C_2-symmetric tridentate bis(oxazoline) and bis(thiazoline) ligands which catalyze the enantioselective Henry reaction with α-keto esters in the presence of Zn(II) or Cu(II) Lewis acids. Enantiomeric excesses up to 84% are obtained in the reaction promoted by Et_2Zn with some α-keto esters bearing aliphatic substituents. Low ee is obtained, however, with ethyl phenyloxoacetate. The copper complexes of these ligands afford products with reversed enantioselectivity.[10] Recently, Deng *et al.* have reported a highly enantioselective nitroaldol reaction of α-keto esters catalyzed by derivatized *Cinchona* alkaloids.[11] The reaction proceeds with good yields and enantioselectivities with a range of aromatic and aliphatic α-keto esters. The β-nitro-α-hydroxy esters that result from these reactions can be used as building blocks for the preparation of β-lactams, aziridines and other synthetic intermediates for the preparation of natural products and biologically active molecules.[11] Despite the relative success attained with some of these catalytic systems, some drawbacks are still to be solved such as improved enantioselectivities, substrate scope, reaction conditions or catalyst preparation. Therefore there is still room for the development of new catalytic systems that catalyze the Henry reaction with this particular kind of substrates. As a part of our current research, we have developed a new group of C_1-symmetric *N*,*N*-ligands with iminopyridine structures which are easily prepared in a modular way from readily available monoterpene ketones and pyridylalkylamines (Fig. 1).[12] Although the presence of C_2-symmetry in the catalyst is considered advantageous since it reduces the number of possible transition states,[13] recent examples have shown the potential of C_1-symmetric catalysts which, in some cases, can be more efficient than related C_2-systems.[14]

We have shown that some of these ligands in combination with copper(II) acetate catalyze the Henry reaction between nitromethane and aldehydes with high yields and good enantiomeric excesses.[12] In particular ligands **1** and **5** in combination with $Cu(OAc)_2$ and diisopropylethylamine (DIPEA) afforded the best results in EtOH or $CHCl_3$, respectively, yielding products with reversed enantioselectivity (Scheme 1). In this article, we describe the development of a new enantioselective Henry reaction between nitromethane and α-keto esters by using this kind of ligands.

Results and discussion

Synthesis of ligand 8

Ligand **8** was prepared in a similar way to ligands **1–7**,[12] by condensation of commercially available (*R*)-(−)-fenchone and picolylamine in the presence of a catalytic amount of $BF_3{\cdot}Et_2O$

Departament de Química Orgànica, Facultat de Química, Universitat de València, Dr. Moliner 50, E-46100-Burjassot, València, Spain. E-mail: gonzalo.blay@uv.es, jose.r.pedro@uv.es; Fax: +34 963544328; Tel: +34 963544336

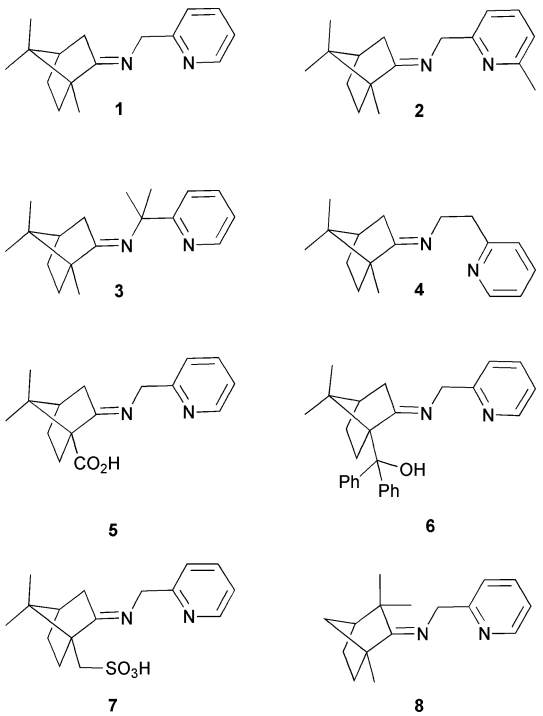
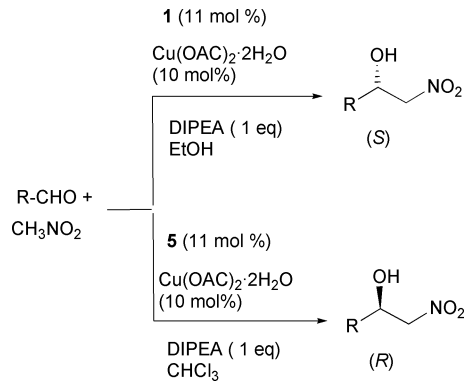


Fig. 1 Structures of ligands **1**–**8**.



Scheme 1 Henry reaction with aldehydes catalyzed with ligands **1** and **5**.

with azeotropic removal of toluene–water (Scheme 2). Ligand **8** was obtained preferentially with the *Z*-geometry at the C–N double bond as was confirmed by the observation of NOE between the methylene group of the pyridylmethyl moiety (δ 4.75) and the two methyl groups at C3 of the fenchone framework (δ 1.24 and 1.19) in NOE and NOESY experiments carried out in DMSO-d_6 solution (Fig. 2)

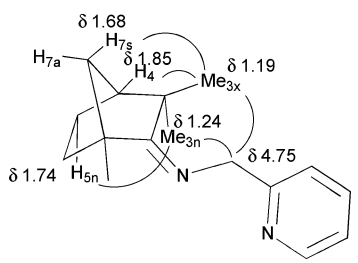
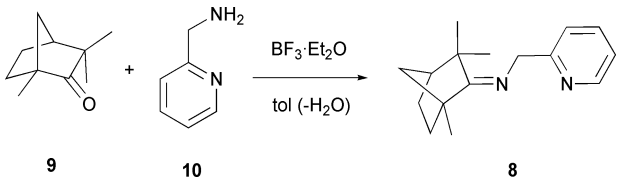


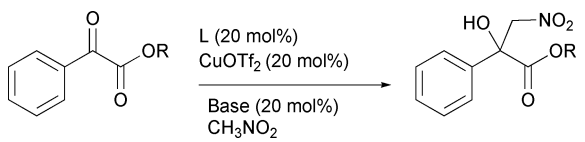
Fig. 2 Some representative NOEs in compound **8**.



Scheme 2 Synthesis of ligand **8**.

Optimization of the reaction conditions

We first focused on the addition of nitromethane to ethyl phenyloxoacetate (Scheme 3, R = Et). The reaction was first attempted under the conditions previously developed for the addition of nitromethane to aldehydes, using the complexes **1**–$Cu(OAc)_2$ and **5**–$Cu(OAc)_2$.[12] However, in both cases the expected nitroalkanol was obtained in racemic form. This result caused us to change the initial reaction conditions drastically. Thus, following reaction conditions similar to those described by Jørgensen, the reaction with ethyl phenyloxoacetate was carried out using $Cu(OTf)_2$ as Lewis acid in nitromethane as solvent and in the presence of Et_3N (20 mol%). We were very pleased to observe that ligand **1** catalyzed the reaction under these conditions giving the expected product with 80% conversion and 54% ee in a short reaction time (Table 1, entry 1). A screening of the different ligands was carried out under these conditions (Table 1). Iminopyridine **8**, derived from (*R*)-(−)-fenchone, was the most efficient ligand in terms of conversion and enantioselectivity giving the expected product in full conversion and 70% ee (entry 8). Ligands **5** and **7** which bear an acidic function required a larger amount of base for the reaction and afforded the expected product with no or low enantioselectivity, respectively (entries 5, 7). It should also be noticed that ligands **6** and **7** yielded products with the opposite stereochemistry to those obtained with ligands **1**–**4** and **8**. The use of $Zn(OTf)_2$ or $Mg(OTf)_2$ instead of $Cu(OTf)_2$ gave the nitroalkanol products in racemic form.



Scheme 3 Addition of nitromethane to phenyloxoacetate esters.

Table 1 Copper(II)-catalyzed enantioselective addition of nitromethane to ethyl phenyloxoacetate (R = Et) according to scheme 3. Ligand screening[a]

Entry	L	Time/h	Yield[b] (%)	Ee[b](%)	Config.[c]
1	**1**	3	80	54	*R*
2	**2**	24	46	29	*R*
3	**3**	4	91	48	*R*
4	**4**	3	98	50	*R*
5	**5**[d]	24	97	0	—
6	**6**	24	29	22	*S*
7	**7**[e]	20	78	13	*S*
8	**8**	3	97	70	*R*

[a] $Cu(OTf)_2$ (20 mol%), **L** (20 mol%), Et_3N (20 mol%), keto ester (0.25 mmol) in 1 mL CH_3NO_2, rt. [b] Conversion and ee determined by HPLC using a Chiralcel OD-H column. [c] Configuration assigned by comparison of the optical rotation sign with literature data (ref. 8). [d] 40 mol% Et_3N was used. [e] 30 mol% Et_3N was used.

Table 2 Copper(II)-catalyzed enantioselective addition of nitromethane to ethyl phenyloxoacetate (R = Et) according to Scheme 3. Effect of the base[a]

Entry	Base	T/°C	Time/h	Yield[b] (%)	Ee[b] (%)
1	Et_3N	rt	3	97	70
2	Bu_3N	rt	3	91	70
3	DIPEA	rt	3	90	62
4	Proton sponge	50	24	87	53
5	Dicyclohexylamine	rt	5	95	68
6	i-Pr_2NH	rt	3.5	95	66
7	K_2CO_3	50	20	54	44
8	Cs_2CO_3	rt	23	77	62
9	Et_3N[c]	rt	51	50	57
10	Et_3N[d]	rt	3	96	16

[a] $Cu(OTf)_2$ (20 mol%), **8** (20 mol%), base (20 mol%), keto ester (0.25 mmol) in 1 mL CH_3NO_2, rt. [b] Conversion and ee determined by HPLC using a Chiralcel OD–H column; (*R*)-configuration. [c] 10 mol% Et_3N was used. [d] 40 mol% Et_3N was used.

The effect of different bases was tested next (Table 2). A number of primary, secondary and tertiary amines, as well as some inorganic bases, were tested. All of them led to reduced enantioselectivities compared to Et_3N, with the exception of Bu_3N which gave similar results (entry 2). The chiral Lewis acid : Brønsted base ratio was crucial to the outcome of the reaction. A lower concentration of Brønsted base relative to Lewis acid led to a significant drop in enantioselectivity and yield (entry 9), whereas a higher concentration of Brønsted base gave a high yield of the Henry product with low ee (entry 10), in a similar way to that which has previously been described with the Cu(II)–BOX catalyst.[8]

The anion of the copper salt was also important to the outcome of the reaction (Table 3). Thus, from all the copper salts tested, only $Cu(ClO_4)_2$ was able to induce some enantioselectivity in the reaction although the product was obtained in lower ee than with $Cu(OTf)_2$. On the other hand, the use of $CuCl_2$ or $Cu(OAc)_2{\cdot}H_2O$ gave racemic products (entries 3–4).

Substrate scope

The influence of the ester group in the substrate was tested next (Table 4). A number of phenyloxoacetate esters were used as substrates. The best results in terms of conversion and enantioselectivity were obtained with ethyl (entry 1) and methyl (entry 2) esters, which gave almost identical results. A further improvement of the enantioselectivity with the ethyl ester was obtained by lowering the temperature. Thus, the reaction with ethyl phenyloxoacetate could be carried out at −20 °C to attain the expected product in 80% yield and 81% ee (entry 8).

Table 3 Copper(II)-catalyzed enantioselective addition of nitromethane to ethyl phenyloxoacetate (R = Et) according to Scheme 3. Effect of the copper(II) salt[a]

Entry	Copper(II) salt	Time/h	Yield[b] (%)	Ee[b] (%)
1	$Cu(OTf)_2$	3	97	70
2	$Cu(ClO_4)_2$	3	95	35
3	$CuCl_2$	4	90	0
4	$Cu(OAc)_2{\cdot}H_2O$	3	99	0

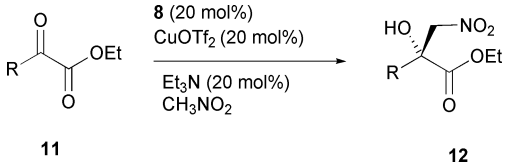
[a] CuX_2 (20 mol%), **8** (20 mol%), Et_3N (20 mol%), keto ester (0.25 mmol) in 1 mL CH_3NO_2, rt. [b] Conversion and ee determined by HPLC using a Chiralcel OD–H column; (*R*)-configuration.

Table 4 Copper(II)-catalyzed enantioselective addition of nitromethane to phenyloxoacetate esters according to Scheme 3. Effect of the ester group R[a]

Entry	R	T/°C	Time/h	Yield (%)[b]	Ee (%)[b]
1	Et	rt	3	97	70
2	Me	rt	3.5	96	70
3	i-Pr	rt	4	95	62
4	t-Bu	rt	4	84	69
5	CCl_3CH_2	rt	3.5	90	64
6	$PhCH_2$	rt	3.5	90	59
7	Et	0	24	94[c]	78
8	Et	−20	46	80[c]	81

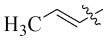
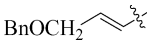
[a] $Cu(OTf)_2$ (20 mol%), **8** (20 mol%), Et_3N (20 mol%), keto ester (0.25 mmol) in 1 mL CH_3NO_2. [b] Conversion and ee determined by HPLC using a Chiralcel OD–H column. [c] Yield of isolated product.

Also substrate generality was studied with a number of ethyl keto esters having different substituents on the ketone carbonyl group (Scheme 4). The results are gathered in Table 5. Unlike the catalytic system formed by tridentate bis-oxazolines and diethylzinc,[10] which failed with aromatic keto esters, good yields and enantiomeric excesses were obtained with our catalyst with a number of aromatic (entries 1–11) and aliphatic (entries 12–16) keto esters. Yields above 80% and enantiomeric excesses between 71–81% were obtained for most of the aromatic keto esters. The presence of the electron-releasing methoxy group of ethyl (*p*-methoxyphenyl)oxoacetate (**11e**) caused a decrease in the ee of the Henry product (entry 5). A similar effect was observed with 2-oxo-2-(2-thienyl)acetate (**11k**), which is substituted with an electron-rich thiophene heterocycle. The low yield and ee obtained with compound **11i** is most probably due to the bulkiness of the two trifluoromethyl groups (entry 9). With alkyl-substituted keto esters (entries 12–16) we obtained similar results with either linear (entries 12–14) or branched groups (entries 15–16), which afforded the expected products with good yields and enantiomeric excesses in the range of 80%. These results are similar to those reported by Xu with alkyl-substituted α-keto esters,[10] although the enantioselectivities are lower than those reported with the Cu(II)–BOX system,[8] with the exception of compound **11n** (entry 14), for which the Cu(II)–BOX catalyst afforded the expected product with 77% ee but only 47% yield. Finally, the more challenging β,γ-unsaturated α-keto esters were screened as substrates for the Henry reaction (entries 17, 18). With these substrates the 1,4-addition reaction to the double bond can compete with the 1,2-addition to the carbonyl group. Furthermore, low enantioselectivities with these substrates are obtained with the Cu(II)–BOX system.[8] Under our reaction conditions, the reaction took place with excellent chemoselectivity and yields giving the 1,2-addition products **12q** and **12r**, exclusively, with good enantiomeric excesses in both cases (entries 17, 18).



Scheme 4 Addition of nitromethane to ethyl α-keto esters. Substrate scope.

Table 5 Copper(II)-catalyzed enantioselective addition of nitromethane to α-keto esters according to Scheme 4[a]

Entry	**11** (R)		*T*/°C	Time/h	Yield (%)[b]	Ee (%)[c]
1	Ph-	**a**	−20	46	80	81
2	4-Me-C_6H_4-	**b**	0	28	86	74
3	4-Cl-C_6H_4-	**c**	−20	22	80	76
4	4-Br-C_6H_4-	**d**	−20	16	93	74
5	4-MeO-C_6H_4-	**e**	rt	25	73	48
6	4-NO_2–C_6H_4-	**f**	−20	22	92	71
7	4-CN-C_6H_4-	**g**	−20	28	91	63
8	3,5-F_2–C_6H_3-	**h**	−20	46	90	76
9	3,5-$(CF_3)_2$–C_6H_3-	**i**	−20	70	73	52
10	2-Naphthyl-	**j**	−20	94	83	75
11	2-Thienyl-	**k**	rt	3	75	56
12	CH_3-	**l**	−20	4	99	78
13	$CH_3(CH_2)_9$-	**m**	−20	23	85	78
14		**n**	−20	40	81	82
15	$(CH_3)_2CH$-	**o**	−20	4	99	80
16		**p**	−20	4	94	78
17		**q**	−20	22	94	73
18		**r**	−20	24	86	80

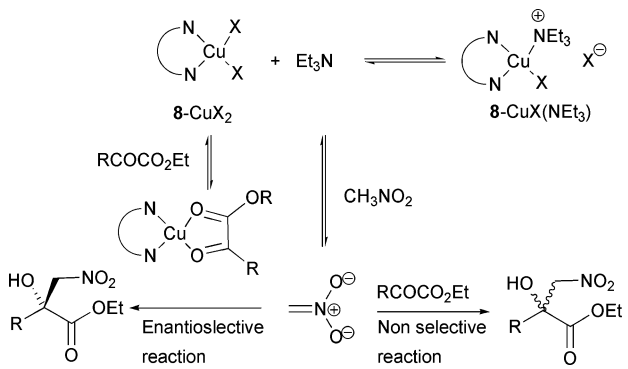
[a] $Cu(OTf)_2$ (20 mol%), **8** (20 mol%), Et_3N (20 mol%), **11** (0.25 mmol) in 1 mL CH_3NO_2. [b] Yields refer to isolated product **12** after column chromatography. [c] Ee determined by chiral HPLC. (*R*)-configuration assigned by comparison of the optical rotation signs and HPLC retention times with data reported in the literature for known compounds, and by analogy for all new compounds.

Mechanistic and stereochemical considerations

The results obtained in the catalytic Henry reaction with different amounts of base (Table 2, entries 1, 9 and 10) and with different copper salts (Table 3) can be rationalized (Scheme 5) in terms very similar to those described by Jørgensen for the Cu(II)–BOX catalyzed reaction. The enantioselective catalytic pathway requires the coordination of the α-keto ester to the copper atom of the **8**–Cu complex and the presence of a deprotonated molecule of nitromethane (a nitronate). A competitive equilibrium between triethylamine and the initial **8**–CuX_2 with an inactive **8**–$CuX(Et_3N)$ is established. The Henry reaction requires the presence in the solution of enough base to deprotonate the nitromethane. If the base is in excess with respect to the Lewis acid, the equilibrium is shifted toward the inactive complex, hence trapping the chiral Lewis acid. The remaining base induces a non-enantioselective pathway between the nitronate and uncoordinated keto ester. If the Lewis acid is in excess with respect to the base, then the low concentration of free amine brings about a slow reaction with low conversion and poor enantioselectivity.

On the other hand, coordination of the keto ester to the metal complex **8**–CuX_2 requires a shift of the X groups (the copper salt counter ion) by the dicarbonyl substrate, and this is only effective if X is a poorly coordinating anion such as triflate or, to a lesser extent, perchlorate, while more coordinating anions such as acetate or chloride lead to non-selective catalysts.

The reaction catalyzed by the **8**–$Cu(OTf)_2$ complex yields the Henry products with the *R* configuration at the stereogenic center. Based on previously reported steric and electronic considerations,[4c] we propose two transition state models that account for the observed stereochemistry, which may be both operative (Fig. 3). The active species simultaneously binds the two reaction partners to the metal center. In the first model[8] (a) the keto functionality of the α-keto ester is coordinated to one of the more Lewis acidic equatorial positions, away from the fenchone skeleton, for maximum electrophilic activation and minimization



Scheme 5 Mechanistic pathways for the enantioselective Henry reaction.

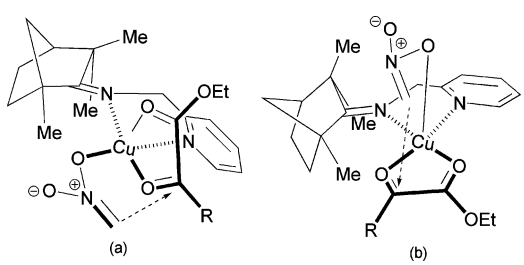


Fig. 3 Proposed transition states for the addition of nitromethane to α-keto esters catalyzed by **8**–Cu(II).

of steric interactions. The ester carbonyl group would coordinate to the copper ion from the upper apical position in order to minimize steric interactions of the OR group with the C1- or the axial C_{3n}-methyl groups of the monoterpene. Thus the nitronate would bind to the vacant equatorial position facing the *Re* face of the ketone carbonyl group. In the second model (b) the α-keto ester would coordinate to the copper atom by the two equatorial positions of the complex plane.[10] The nitronate would occupy the upper, less hindered, apical position from which it would be transferred to the *Re* face of the ketone carbonyl group. In this model (b), both the electrophile and nucleophile would reach the maximum activation, although it is probable that coordination of the keto ester in this way would be hampered by steric interactions with the pyridine ring and the 1-Me group of the fenchone.

Conclusion

We have described a new catalytic enantioselective Henry reaction with α-keto esters, using a copper(II)–iminopyridine complex in combination with triethylamine. The ligands are easily prepared in a one-step procedure from economical monoterpene ketones and pyridylalkylamines, their modular design allows structural variety and they can be prepared in both enantiomeric forms starting from the appropriate ketone enantiomer. The Henry reaction works with a wide range of substrates including, aromatic, aliphatic and β,γ-unsaturated α-keto esters. The corresponding products are obtained with high yields and modest to good enantiomeric excesses. Compared with the two previously described metal-based procedures, our catalytic system shows broader scope than the combination of Zn with tridentate bis-oxazolines, which is limited to aliphatic keto esters, and it gives higher enantioselectivities with unsaturated keto esters than the Cu(II)–BOX system. The results reported here show the usefulness of this kind of iminopyridines, recently introduced by us, as ligands for metal-catalyzed enantioselective reactions.

Experimental

General

Commercial reagents were used as purchased. Glassware was oven-dried overnight at 120 °C. Reactions were monitored by TLC analysis using Merck Silica Gel 60 F-254 thin layer plates. Flash column chromatography was performed on Merck silica gel 60, 0.040–0.063 mm. Specific optical rotations were recorded on a Perkin-Elmer 241 polarimeter using sodium light (D line 589 nm). NMR spectra were recorded on Bruker Advance spectrometers in the deuterated solvents as stated, using residual non-deuterated solvent as internal standard and $CFCl_3$ as internal standard for ^{19}F NMR. *J* values are given in Hz. The carbon type was determined by DEPT experiments. Mass spectra were recorded on a Fisons Instruments VG Autospec GC 8000 series. Mass spectra (EI) were run at 70 eV. Mass spectra (FAB) were carried out at 30 kV in a MNBA matrix. Chiral HPLC analyses were performed in a Hitachi Elite Lachrom instrument equipped with a Hitachi UV diode-array L-4500 detector using chiral stationary columns from Daicel. Retention times are given in min. *tert*-Butyl[15] and benzyl phenyloxoacetate[16] were prepared according to the literature. Keto esters **11a–c**, **11e–h**, **11k–l** and **11n–o** were obtained from commercial sources, keto esters **11d**, **11i–j**, and **11m–p** were prepared by addition of Grignard reagents to ethyl oxalate,[17] keto esters **11q–r** were prepared by Wittig reaction.[18]

Synthesis of ligand 8

A solution of (*R*)-(−)-fenchone (**9**, 5.0 g, 32.2 mmol), picolylamine (**10**, 3.53 mL, 33.8 mmol) and $BF_3{\cdot}Et_2O$ (0.18 mL) in toluene (75 mL) in a round bottomed flask provided with a Dean–Stark system was refluxed for 7 d under nitrogen. The reaction mixture was diluted with EtOAc (50 mL), washed with saturated aqueous $NaHCO_3$ (15 mL) and dried over $MgSO_4$. Solvent removal was followed by column chromatography eluting with hexane–dichloromethane to give 3.22 g (64%) of unreacted fenchone and 1.64 g (21%) of ligand **8**: $[a]_D^{25}$ −70.9 (*c* 0.38 in $CHCl_3$); *m*/*z* (EI) 242 (M^+, 62%), 241 (100), 93 (65); 242.1780 (M^+), $C_{16}H_{22}N_2$ requires 242.1783; δ_H (300 MHz, $CDCl_3$) 8.50 (1H, d, *J* 5.4), 7.67 (1H, t, *J* 7.5, pyr-H), 7.52 (1H, d, *J* 7.5, pyr-H), 7.13 (1H, d, *J* 5.4, pyr-H), 4.93 (1H, d, *J* 16.8, CH_2-N), 4.86 (1H, d, *J* 16.8, CH_2-N), 1.87–1.39 (7H, m), 1.29 (3H, s, Me), 1.28 (3H, s, Me), 1.22 (3H, s, Me); δ_C (300 MHz, $CDCl_3$) 186.5 (s), 161.3 (s), 148.7 (d), 136.5 (d), 121.4 (d), 121.1 (d), 55.8 (t), 52.9 (s), 49.8 (d), 44.4 (s), 42.2 (t), 33.9 (t), 25.2 (t), 24.2 (q), 23.6 (q), 17.7 (q); δ_H (400 MHz, DMSO-d_6) 8.48 (1H, ddd, *J* 4.8, 2.0, 0.8, pyr-H), 7.76 (1H, td, *J* 8.0, 2.0, pyr-H), 7.41 (1H, d, *J* 8.0, pyr-H), 7.24 (1H, ddd, *J* 8.0, 4.8, 0.8, pyr-H), 4.75 (2H, AB system, CH_2-N), 1.85 (1H, m, 4-H), 1.74 (1H, tt, *J* 12.0, 2.5, 5n-H), 1.68 (1H, dq, *J* 10.0, 2.5, 7s-H), 1.58 (1H, m, 5x-H), 1.52 (1H, td, *J* 12.0, 3.2, 6x-H), 1.38 (1H, dd, *J* 10.0, 1.6, 7a-H), 1.31 (1H, m, 6n-H), 1.24 (3H, s, 3n-Me), 1.90 (3H, s, 3x-Me), 1.15 (3H, s, 1-Me); δ_c (300 MHz, DMSO-d_6) 184.5 (s), 160.7 (s), 148.5 (d), 136.5 (d), 121.6 (d), 121.1 (d), 55.4 (t), 52.4 (q), 49.1 (d), 43.7 (s), 41.5 (t), 33.4 (t), 24.8 (t), 23.9 (q), 23.3 (q), 17.7 (q).

Synthesis of 2′,2′,2′-trichloroethyl 2-oxo-2-phenylacetate

Oxalyl chloride (0.43 mL, 5.0 mmol) was added to a solution of phenylglyoxylic acid (0.5 g, 3.33 mmol) and DMF (1 drop) in dichloromethane (10 mL) at 0 °C. The reaction mixture was stirred at rt for 4 h and concentrated under reduced pressure. The resulting oil was dissolved in dichloromethane (10 mL), a catalytic amount of 4-DMAP was added and a solution of trichloroethanol (323 μL, 3.33 mmol) and Et_3N (1.33 mL) in dichloromethane (10 mL) was added dropwise. After 24 h, the reaction mixture was diluted with dichloromethane (10 mL), washed with water (2 × 10 mL), 10% aqueous NaOH (10 mL) and brine (10 mL), and dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by column chromatography eluting with hexane–dichloromethane (2 : 8) gave 623 mg (67%) of the title compound: *m*/*z* (EI) 280 (M^+, 0.1%), 105 (100), 77 (43); 279.9470 (M^+), $C_{10}H_7Cl_3O_3$ requires 279.9461; δ_H (300 MHz, $CDCl_3$) 8.07–8.04 (2H, m, Ph), 7.70 (1H, tt, *J* 6.6, 1.2, Ph), 7.57–7.52 (2H, m, Ph), 5.03 (2H, s, CCl_3–CH_2–O); δ_C (75.5 MHz, $CDCl_3$) 184.6 (s), 161.9 (s), 135.4 (d), 132.0 (s), 130.1 (d), 129.0 (d), 93.9 (d), 74.5 (t).

General procedure for the enantioselective nitroaldol reaction

Copper(II) triflate (18.0 mg, 0.05 mmol) contained in a Schlenk tube was dried under vacuum for 30 min. After this time, the tube was filled in with nitrogen and a solution of ligand **8**

(13.0 mg, 0.05 mmol) in nitromethane (1 mL) was added. After 1 h, triethylamine (7 μL, 0.05 mmol) was added (the solution changed from blue to dark green). The reaction mixture was introduced in a bath at the reaction temperature and the keto ester **11** (0. 25 mmol) was added. Stirring was continued until the reaction was complete (TLC). The β-nitro-α-hydroxy esters **12** were obtained by column chromatography. Yields and ee are shown in Tables 4 and 5.

(−)-Methyl 2-hydroxy-3-nitro-2-phenylpropanoate (Table 4, entry 2)

Purified by column chromatography eluting with hexane–EtOAc (92 : 8). Enantiomeric excess (70%) determined by HPLC (Chiralcel OD-H), hexane–*i*-PrOH 90 : 10, 1 mL min^{-1}, major enantiomer (−) t_R 15.9, minor enantiomer (+) t_R 13.1; $[\alpha]_D^{25}$ −15.6 (*c* 0.54 in CH_2Cl_2, ee 70%); *m*/*z* (EI) 225 (M^+, 0.7%), 166 (25), 105 (100), 77 (28); 225.0639 (M^+), $C_{10}H_{11}NO_5$ requires 225.0637; δ_H (300 MHz, $CDCl_3$) 7.61–7.58 (2H, m, Ph), 7.41–7.26 (3H, m, Ph), 5.26 (1H, d, *J* 14.1, CH_2NO_2), 4.69 (1H, d, *J* 14.1, CH_2NO_2), 4.29 (1H, br s, OH), 3.90 (3H, s, MeO); δ_C (75 MHz, $CDCl_3$) 172.2 (s), 136.2 (s), 129.1 (d), 128.9 (d), 125.2 (d), 80.7 (t), 76.1 (s), 54.0 (q).

(−)-Isopropyl 2-hydroxy-3-nitro-2-phenylpropanoate (Table 4, entry 3)

Purified by column chromatography eluting with hexane–EtOAc (92 : 8). Enantiomeric excess (62%) determined by HPLC (Chiralpak AD-H), hexane-*i*-PrOH 95 : 5, 1 mL min^{-1}, major enantiomer (−) t_R 17.2, minor enantiomer (+) t_R 15.5; $[\alpha]_D^{25}$ −2.3 (*c* 1.07 in CH_2Cl_2, ee 62%); *m*/*z* (EI) 253 (M^+, 0.1%), 166 (15), 105 (100), 77 (26); 253.0945 (M^+), $C_{12}H_{15}NO_5$ requires 253.0950; δ_H (300 MHz, $CDCl_3$) 7.63–7.60 (2H, m, Ph), 7.44–7.37 (3H, m, Ph), 5.24 (1H, d, *J* 13.8, CH_2NO_2), 5.19 (1H, m, *J* 6.3, $OCHMe_2$), 4.67 (1H, d, *J* 13.8, CH_2NO_2), 4.24 (1H, br s, OH), 1.35 (3H, d, *J* 6.3, $OCHMe_2$), 1.29 (3H, d, *J* 6.3, $OCHMe_2$); δ_C (75 MHz, $CDCl_3$) 171.1 (s), 136.6 (s), 129.0 (d), 128.8 (d), 125.2 (d), 80.7 (t), 75.9 (s), 71.9 (d), 21.5 (q), 21.4 (q).

(+)-*tert*-Butyl 2-hydroxy-3-nitro-2-phenylpropanoate (Table 4, entry 4)

Purified by column chromatography eluting with hexane–EtOAc (92 : 8). Enantiomeric excess (69%) determined by HPLC (Chiralcel OD-H), hexane–*i*-PrOH 90 : 10, 1 mL min^{-1}, major enantiomer (+) t_R 8.9, minor enantiomer (−) t_R 7.4; $[\alpha]_D^{25}$ +4.9 (*c* 0.59 in CH_2Cl_2, ee 69%); *m*/*z* (EI) 267 (M^+, 0.1%), 166 (31), 120 (36), 105 (100), 77 (23), 57 (72); 267.1113 (M^+), $C_{13}H_{17}NO_5$ requires 267.1107; δ_H (300 MHz, $CDCl_3$) 7.55–7.51 (2H, m, Ph), 7.36–7.28 (3H, m, Ph), 5.13 (1H, d, *J* 14.1, CH_2NO_2), 4.58 (1H, d, *J* 14.1, CH_2NO_2), 4.17 (1H, br s, OH), 1.44 (9H, s, Me_3C); δ_C (75 MHz, $CDCl_3$) 170.5 (s), 137.0 (s), 129.9 (d), 128.9 (d), 125.2 (d), 85.0 (s), 80.8 (t), 75.9 (s), 27.7 (q).

(−)-Trichloroethyl 2-hydroxy-3-nitro-2-phenylpropanoate (Table 4, entry 5)

Purified by column chromatography eluting with hexane–EtOAc (92 : 8). Enantiomeric excess (64%) determined by HPLC (Chiralcel OD-H), hexane–*i*-PrOH 90 : 10, 1 mL min^{-1}, major enantiomer (−) t_R 17.0, minor enantiomer (+) t_R 10.9; $[\alpha]_D^{25}$ −9.4 (*c* 0.96 in CH_2Cl_2, ee 64%); *m*/*z* (EI) 341 (M^+, 0.2%), 166 (75), 123 (66), 105 (100), 91 (46), 77 (60); 340.9639 (M^+), $C_{11}H_{10}Cl_3NO_5$ requires 340.9625; δ_H (300 MHz, $CDCl_3$) 7.68–7.65 (2H, m, Ph), 7.43–7.10 (3H, m, Ph), 5.38 (1H, d, *J* 14.4, CH_2NO_2), 4.97 (1H, d, *J* 12.0, CCl_3CH_2O), 4.80 (1H, d, *J* 12.0, CCl_3CH_2O), 4.75 (1H, d, *J* 14.4, CH_2NO_2), 4.20 (1H, br s, OH); δ_C (75 MHz, $CDCl_3$) 170.4 (s), 135.2 (s), 129.6 (d), 129.1 (d), 125.4 (d), 93.7 (s), 80.6 (t), 76.2 (s), 75.9 (q).

(−)-Benzyl 2-hydroxy-3-nitro-2-phenylpropanoate (Table 4, entry 6)

Purified by column chromatography eluting with hexane–EtOAc (92 : 8). Enantiomeric excess (59%) determined by HPLC (Chiralcel OD-H), hexane–*i*-PrOH 90 : 10, 1 mL min^{-1}, major enantiomer (−) t_R 20.5, minor enantiomer (+) t_R 15.3; $[\alpha]_D^{25}$ −26.5 (*c* 0.91 in CH_2Cl_2, ee 59%); *m*/*z* (EI) 302 ($M^+ + 1$, 0.2%), 166 (54), 123 (31), 105 (100), 91 (97), 77 (15); 302.1031 ($M^+ + 1$), $C_{16}H_{16}NO_5$ requires 302.1028; δ_H (300 MHz, $CDCl_3$) 7.58–7.55 (2H, m, Ph), 7.39–7.33 (6H, m, Ph), 7.31–7.25 (2H, m, Ph), 5.29 (2H, s, $PhCH_2$), 5.25 (1H, d, *J* 14.1, CH_2NO_2), 4.67 (1H, d, *J* 14.1, CH_2NO_2), 4.25 (1H, br s, OH); δ_C (75 MHz, $CDCl_3$) 171.6 (s), 136.2 (s), 134.2 (s), 129.2 (d), 128.9 (d), 128.8 (d), 128.7 (d), 128.5 (d), 125.2 (d), 80.7 (t), 76.1 (s), 69.2 (t).

(*R*)-(−)-Ethyl 2-hydroxy-3-nitro-2-phenylpropanoate (12a)[8,11]

Purified by column chromatography eluting with hexane–EtOAc (92 : 8). Enantiomeric excess (81%) determined by HPLC (Chiralcel OD-H), hexane–*i*-PrOH 90 : 10, 1 mL min^{-1}, major enantiomer (*R*) t_R 12.9, minor enantiomer (*S*) t_R 10.2; $[\alpha]_D^{25}$ −15.7 (*c* 1.06 in CH_2Cl_2, ee 81%); δ_H (300 MHz, $CDCl_3$) 7.62–7.59 (2H, m), 7.44–7.35 (3H, m, Ph), 5.26 (1H, d, *J* 14.1, CH_2NO_2), 4.68 (1H, d, *J* 14.1, CH_2NO_2), 4.46–4.29 (2H, CH_3CH_2O), 4.24 (1H, br s, OH), 1.34 (3H, t, *J* 7.2, CH_3CH_2O); δ_C (75 MHz, $CDCl_3$) 171.7 (s), 136.4 (s), 129.1 (d), 128.9 (d), 125.2 (d), 80.8 (t), 76.0 (s), 63.6 (t), 13.9 (q).

(*R*)-(−)-Ethyl 2-hydroxy-3-nitro-2-*p*-tolylpropanoate (12b)

Purified by column chromatography eluting with hexane–EtOAc (92 : 8). Enantiomeric excess (74%) determined by HPLC (Chiralcel OD-H), hexane–*i*-PrOH 90 : 10, 1 mL min^{-1}, major enantiomer (*R*) t_R 13.0, minor enantiomer (*S*) t_R 9.3; $[\alpha]_D^{25}$ −16.6 (*c* 1.06 in CH_2Cl_2, ee 74%); *m*/*z* (EI) 253 (M^+, 0.6%), 119 (100), 91 (28); 253.0954 (M^+), $C_{12}H_{15}NO_5$ requires 253.0950; δ_H (300 MHz, $CDCl_3$) 7.50–7.46 (2H, m, Ar), 7.21 (2H, d, *J* 8.1, Ar), 5.24 (1H, d, *J* 14.1, CH_2NO_2), 4.66 (1H, d, *J* 14.1, CH_2NO_2), 4.48–4.27 (2H, m, CH_3CH_2O), 4.20 (1H, br s, OH), 2.35 (3H, s, Me-Ar), 1.33 (3H, t, *J* 7.2, CH_3CH_2O); δ_C 75 MHz, $CDCl_3$) 171.8 (s), 139.1 (s), 133.5 (s), 129.5 (d), 125.1 (d), 80.8 (t), 75.9 (s), 63.5 (t), 21.0 (q) 13.9 (q).

(*R*)-(−)-Ethyl 2-(4-chlorophenyl)-2-hydroxy-3-nitropropanoate (12c)[8,11]

Purified by column chromatography eluting with hexane–EtOAc (92 : 8). Enantiomeric excess (76%) determined by HPLC (Chiralcel OD-H), hexane–*i*-PrOH 90 : 10, 1 mL min^{-1}, major enantiomer (*R*) t_R 12.8, minor enantiomer (*S*) t_R 10.5; $[\alpha]_D^{25}$ −25.4 (*c* 0.83 in CH_2Cl_2, ee 76%); δ_H (300 MHz, $CDCl_3$) 7.56 (2H, d, *J* 8.7, Ar),

7.40–7.36 (2H, m, Ar), 5.22 (1H, d, *J* 14.1, CH_2NO_2), 4.64 (1H, d, *J* 14.1, CH_2NO_2), 4.44–4.31 (2H, m, CH_3CH_2O), 4.25 (1H, br s, OH), 1.34 (3H, t, *J* 7.2, CH_3CH_2O); δ_C (75 MHz, $CDCl_3$) 171.3 (s), 135.3 (s), 134.9 (s), 129.1 (d), 126.8 (d), 80.6 (t), 75.7 (s), 63.8 (t), 13.9 (q).

(*R*)-(−)-Ethyl 2-(4-bromophenyl)-2-hydroxy-3-nitropropanoate (12d)

Purified by column chromatography eluting with hexane–EtOAc (92 : 8). Enantiomeric excess (74%) determined by HPLC (Chiralcel OD-H), hexane–*i*-PrOH 90 : 10, 1 mL min^{-1}, major enantiomer (*R*) t_R 15.5, minor enantiomer (*S*) t_R 11.3; $[\alpha]_D^{25}$ −16.3 (*c* 1.02 in CH_2Cl_2, ee 74%); *m*/*z* (EI) 319 (2.1%), 317 (M^+, 2.1%), 246 (21), 244 (21), 185 (98), 183 (100), 157 (16), 155 (18); 316.9896 (M^+), $C_{11}H_{12}BrNO_5$ requires 316.9899; δ_H (300 MHz, $CDCl_3$) 7.55–7.47 (4H, m, Ar), 5.22 (1H, d, *J* 14.1, CH_2NO_2), 4.64 (1H, d, *J* 14.1, CH_2NO_2), 4.45–4.29 (2H, m, CH_3CH_2O), 4.25 (1H, br s, OH), 1.34 (3H, t, *J* 7.2, CH_3CH_2O); δ_C (75 MHz, $CDCl_3$) 171.2 (s), 135.4 (s), 132.0 (d), 127.1 (d), 123.6 (s), 80.5 (t), 75.7 (s), 63.9 (t), 13.9 (q).

(*R*)-(−)-Ethyl 2-hydroxy-2-(4-methoxyphenyl)-3-nitropropanoate (12e)[8,11]

Purified by column chromatography eluting with hexane–EtOAc (92 : 8). Enantiomeric excess (48%) determined by HPLC (Chiralcel OD-H), hexane–*i*-PrOH 90 : 10, 1 mL min^{-1}, major enantiomer (*R*) t_R 15.7, minor enantiomer (*S*) t_R 14.8; $[\alpha]_D^{25}$ −10.5 (*c* 0.83 in CH_2Cl_2, ee 48%); δ_H (300 MHz, $CDCl_3$) 7.51 (2H, d, *J* 9.0, Ar), 6.91 (2H, d, *J* 9.0, Ar), 5.22 (1H, d, *J* 14.1, CH_2NO_2), 4.65 (1H, d, *J* 14.1, CH_2NO_2), 4.44–4.27 (2H, m, CH_3CH_2O), 4.21 (1H, br s), 3.81 (3H, s, MeO), 1.33 (3H, t, *J* 7.2, CH_3CH_2O); δ_C (75 MHz, $CDCl_3$) 171.8 (s), 160.1 (s), 128.3 (s), 126.5 (d), 114.2 (d), 80.8 (t), 75.7 (s), 63.4 (t), 55.3 (q), 13.9 (q).

(*R*)-(−)-Ethyl 2-hydroxy-3-nitro-2-(4-nitrophenyl)propanoate (12f)[8]

Purified by column chromatography eluting with hexane–EtOAc (85 : 15). Enantiomeric excess (71%) determined by HPLC (Chiralcel OD-H), hexane–*i*-PrOH 90 : 10, 1 mL min^{-1}, major enantiomer (*R*) t_R 26.6, minor enantiomer (*S*) t_R 24.5; $[\alpha]_D^{25}$ −12.1 (*c* 1.07 in CH_2Cl_2, ee 71%); δ_H (300 MHz, $CDCl_3$) 8.25 (2H, d, *J* 9.0, Ar), 7.85 (2H, d, *J* 9.0, Ar), 5.28 (1H, d, *J* 14.1, CH_2NO_2), 4.68 (1H, d, *J* 14.1, CH_2NO_2), 4.48–4.31 (2H, m, CH_3CH_2O), 4.42 (1H, br s, OH), 1.35 (3H, t, *J* 7.2, CH_3CH_2O); δ_C (75 MHz, $CDCl_3$) 170.5 (s), 148.3 (s), 143.1 (s), 126.7 (d), 123.9 (d), 80.3 (t), 75.9 (s), 64.3 (t), 13.9 (q).

(*R*)-(−)-Ethyl 2-(4-cyanophenyl)-2-hydroxy-3-nitropropanoate (12g)[11]

Purified by column chromatography eluting with hexane–EtOAc (90 : 10). Enantiomeric excess (63%) determined by HPLC (Chiralcel OD-H), hexane–*i*-PrOH 90 : 10, 1 mL min^{-1}, major enantiomer (*R*) t_R 23.8, minor enantiomer (*S*) t_R 22.3; $[\alpha]_D^{25}$ −18.2 (*c* 1.07 in $CHCl_3$, ee 63%); δ_H (300 MHz, $CDCl_3$) 7.78 (2H, d, *J* 8.7, Ar), 7.72–7.69 (2H, m, Ar), 5.24 (1H, d, *J* 14.1, CH_2NO_2), 4.65 (1H, d, *J* 14.1, CH_2NO_2), 4.65 (1H, br s, OH), 4.47–4.30 (2H, m, CH_3CH_2O), 1.34 (3H, t, *J* 7.2, CH_3CH_2O); δ_C (75 MHz, $CDCl_3$) 170.6 (s), 141.3 (s), 132.6 (d), 126.3 (d), 118.0 (s), 113.3 (s), 80.3 (t), 75.8 (s), 64.2 (t), 13.9 (q).

(*R*)-(−)-Ethyl 2-(3,5-difluorophenyl)-2-hydroxy-3-nitropropanoate (12h)

Purified by column chromatography eluting with hexane–EtOAc (92 : 8). Enantiomeric excess (76%) determined by HPLC (Chiralcel OD-H), hexane–*i*-PrOH 90 : 10, 0.5 mL min^{-1}, major enantiomer (*R*) t_R 17.9, minor enantiomer (*S*) t_R 16.9; $[\alpha]_D^{25}$ −11.8 (*c* 1.01 in CH_2Cl_2, ee 76%); *m*/*z* (EI) 275 (M^+, 0.4%), 141 (100), 113 (26); 275.0604 (M^+), $C_{11}H_{11}F_2NO_5$ requires 275.0605; δ_H (300 MHz, $CDCl_3$) 7.23–7.14 (2H, m, Ar), 6.83 (1H, tt, *J* 8.7, 2.4, Ar), 5.17 (1H, d, *J* 14.1, CH_2NO_2), 4.63 (1H, d, *J* 14.1, CH_2NO_2), 4.49–4.31 (2H, m, CH_3CH_2O), 4.31 (1H, br s, OH), 1.36 (3H, t, *J* 7.2, CH_3CH_2O); δ_C (75 MHz, $CDCl_3$) 170.7 (C), 163.2 (d, $J_{C\text{-}F}$ 249.9, CF), 163.0 (d, $J_{C\text{-}F}$ 249.9, CF), 140.2 (t, $J_{C\text{-}F}$ 9.0, C), 109.1–108.7 (m, 2 × CH), 104.7 (t, $J_{C\text{-}F}$ 25.5, CH), 80.3 (CH_2), 75.5 (C), 64.2 (CH_2), 13.9 (CH_3); δ_F (282 MHz, $CDCl_3$) −107.8.

(*R*)-(−)-Ethyl 2-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxy-3-nitropropanoate (12i)

Purified by column chromatography eluting with hexane–diethyl ether (90 : 10). Enantiomeric excess (52%) determined by HPLC (Chiralpak AD-H), hexane–*i*-PrOH 99 : 1, 0.5 mL min^{-1}, major enantiomer (*R*) t_R 20.6, minor enantiomer (*S*) t_R 16.9; $[\alpha]_D^{25}$ −6.2 (*c* 1.11 in CH_2Cl_2, ee 52%); *m*/*z* (EI) 375 (M^+, 0.1%), 356 (21), 259 (46), 256 (38), 241 (100), 227 (28), 213 (34); 375.0560 (M^+), $C_{13}H_{11}F_6NO_5$ requires 375.0541; δ_H (300 MHz, $CDCl_3$) 8.15 (2H, s, Ar), 7.92 (1H, s, Ar), 5.26 (1H, d, *J* 14.1, CH_2NO_2), 4.68 (1H, d, *J* 14.1, CH_2NO_2), 4.54–4.36 (2H, m, CH_3CH_2O), 4.47 (1H, br s, OH), 1.37 (3H, t, *J* 7.2, CH_3CH_2O); δ_C (75 MHz, $CDCl_3$) 170.3 (C), 139.1 (C), 132.4 (q, $J_{C\text{-}F}$ 33.9, C), 126.0 (q, $J_{C\text{-}F}$ 3.0, CH), 123.3 (m, $J_{C\text{-}F}$ 3.8, CH), 122.9 (q, $J_{C\text{-}F}$ 273.3, CF_3), 80.4 (CH_2), 64.5 (CH_2), 13.8 (CH_3); δ_F (282 MHz, $CDCl_3$) −63.4.

(*R*)-(−)-Ethyl 2-hydroxy-2-(2-naphthyl)-3-nitropropanoate (12j)

Purified by column chromatography eluting with hexane–EtOAc (92 : 8). Enantiomeric excess (75%) determined by HPLC (Chiralcel OD-H), hexane–*i*-PrOH 80 : 20, 1 mL min^{-1}, major enantiomer (*R*) t_R 34.6, minor enantiomer (*S*) t_R 12.3; $[\alpha]_D^{25}$ −37.7 (*c* 1.01 in $CHCl_3$, ee 75%); δ_H (300 MHz, $CDCl_3$) 8.13 (d, *J* 1.5, 1H, Ar), 7.89–7.83 (3H, m, Ar), 7.67 (1H, dd, *J* 9.0, 2.1, Ar), 7.56–7.51 (2H, m, Ar), 5.40 (1H, d, *J* 14.1, CH_2NO_2), 4.77 (1H, d, *J* 14.1, CH_2NO_2), 4.48–4.31 (2H, m, CH_3CH_2O), 4.39 (1H, br s), 1.36 (3H, t, *J* 7.2, CH_3CH_2O); δ_C (75 MHz, $CDCl_3$) 171.6 (s), 133.6 (s), 133.2 (s), 133.0 (s), 128.8 (d), 128.4 (d), 127.6 (d), 127.0 (d), 126.7 (d), 125.1 (d), 122.3 (d), 80.7 (t), 76.2 (s), 63.7 (t), 14.0 (q).

(*R*)-(−)-Ethyl 2-hydroxy-3-nitro-2-(2-thienyl)propanoate (12k)

Purified by column chromatography eluting with hexane–EtOAc (92 : 8). Enantiomeric excess (56%) determined by HPLC (Chiralcel OD-H), hexane–*i*-PrOH 95 : 5, 1 mL min^{-1}, major enantiomer (*R*) t_R 15.6, minor enantiomer (*S*) t_R 14.8; $[\alpha]_D^{25}$ −17.0 (*c* 0.45 in CH_2Cl_2, ee 56%); *m*/*z* (EI) 245 (M^+, 1.3%), 172 (15), 126 (17), 111 (100); 245.0350 (M^+), $C_9H_{11}NO_5S$ requires 245.0358; δ_H (300 MHz,

$CDCl_3$) 7.33 (1H, dd, *J* 4.8, 0.8, Het), 7.14 (1H, dd, *J* 3.6, 0.8, Het), 7.02 (1H, dd, *J* 4.8, 3.6, Het), 5.18 (1H, d, *J* 14.1, CH_2NO_2), 4.76 (1H, d, *J* 14.1, CH_2NO_2), 4.49–4.33 (2H, m, CH_3CH_2O), 4.46 (1H, br s, OH), 1.37 (3H, t, *J* 7.2, CH_3CH_2O); δ_C (75 MHz, $CDCl_3$) 170.6 (s), 140.4 (s), 127.5 (d), 126.8 (d), 125.1 (d), 80.6 (t), 74.8 (s), 63.9 (t), 13.9 (q).

(*R*)-(+)-Ethyl 2-hydroxy-2-methyl-3-nitropropanoate (12l)[8,10,11]

Purified by column chromatography eluting with hexane–EtOAc (80 : 20). Enantiomeric excess (78%) determined by HPLC (Chiralpak AD-H), hexane–*i*-PrOH 90 : 10, 0.5 mL min^{-1}, major enantiomer (*R*) t_R 20.6, minor enantiomer (*S*) t_R 19.4; $[\alpha]_D^{25}$ +15.3 (*c* 0.54 in CH_2Cl_2, ee 78%); δ_H (300 MHz, $CDCl_3$) 4.84 (1H, d, *J* 13.8, CH_2NO_2), 4.55 (1H, d, *J* 13.8, CH_2NO_2), 4.41–4.25 (2H, m, CH_3CH_2O), 3.76 (1H, br s, OH), 1.45 (3H, s, MeCO), 1.34 (3H, t, *J* 7.2, CH_3CH_2O); δ_C (75 MHz, $CDCl_3$) δ 173.4 (s), 80.9 (t), 72.4 (s), 63.1 (t), 23.8 (q), 14.0 (q).

(*R*)-(+)-Ethyl 2-hydroxy-2-(nitromethyl)dodecanoate (12m)

Purified by column chromatography eluting with hexane–EtOAc (95 : 5). Enantiomeric excess (78%) determined by HPLC (Chiralcel OD-H), hexane–*i*-PrOH 98 : 2, 0.5 mL min^{-1}, major enantiomer (*R*) t_R 14.7, minor enantiomer (*S*) t_R 15.8; $[\alpha]_D^{25}$ +8.4 (*c* 0.50 in CH_2Cl_2, ee 78%); *m*/*z* (FAB) 304 (M^+ + 1, 100%), 289 (12), 154 (95); 304.2112 (M^+ + 1), $C_{15}H_{30}NO_5$ requires 304.2124; δ_H (300 MHz, $CDCl_3$) 4.81 (1H, d, *J* 13.5, CH_2NO_2), 4.55 (1H, d, *J* 13.5, CH_2NO_2), 4.42–4.26 (2H, m, CH_3CH_2O), 3.70 (1H, br s, OH), 1.73–1.55 (2H, m), 1.54–1.39 (1H, m), 1.33 (3H, t, *J* 7.2, CH_3CH_2O), 1.24 (14H, m), 1.14–1.03 (1H, m), 0.87 (3H, t, *J* 6.6, Me); δ_C (75 MHz, $CDCl_3$) 172.9 (s), 80.9 (t), 75.2 (s), 63.0 (t), 36.5 (t), 31.8 (t), 29.5 (t), 29.4 (t), 29.3 (t), 29.3 (t), 29.3 (t), 22.6 (t), 22.6 (t), 14.1 (q), 14.1 (q).

(*R*)-(+)-Ethyl 2-hydroxy-2-(nitromethyl)-4-phenylbutanoate (12n)[8,10,11]

Purified by column chromatography eluting with hexane–EtOAc (90 : 10). Enantiomeric excess (82%) determined by HPLC (Chiralpak AD-H), hexane–*i*-PrOH 90 : 10, 1 mL min^{-1}, major enantiomer (*R*) t_R 14.4, minor enantiomer (*S*) t_R 11.7; $[\alpha]_D^{25}$ +23.8 (*c* 1.08 in CH_2Cl_2, ee 82%); δ_H (300 MHz, $CDCl_3$) 7.32–7.14 (5H, m, Ph), 4.84 (1H, d, *J* 13.8, CH_2NO_2), 4.59 (1H, d, *J* 13.8, CH_2NO_2), 4.41–4.24 (2H, m, CH_3CH_2O), 3.87 (1H, br s, OH), 2.88–2.78 (1H, m, CH_2CO), 2.54–2.44 (1H, m, CH_2CO), 2.08–1.91 (2H, m, CH_2Ph), 1.34 (3H, t, *J* 7.2, CH_3CH_2O); δ_C (75 MHz, $CDCl_3$) 172.6 (s), 140.2 (s), 128.5 (d), 128.3 (d), 126.3 (d), 80.8 (t), 75.0 (s), 63.2 (t), 38.2 (t), 29.0 (t), 14.0 (q).

(*R*)-(+)-Ethyl 2-hydroxy-3-methyl-2-(nitromethyl)butanoate (12o)

Purified by column chromatography eluting with hexane–EtOAc (80 : 20). Enantiomeric excess (80%) determined by HPLC (2 × Chiralpak AD-H), hexane–*i*-PrOH 99 : 1, 1 mL min^{-1}, major enantiomer (*R*) t_R 104.9, minor enantiomer (*S*) t_R 110.4; $[\alpha]_D^{25}$ +17.9 (*c* 0.37 in CH_2Cl_2, ee 80%); *m*/*z* (EI) 206 (M^+ + 1, 0.2%), 132 (22), 89 (60), 85 (22), 71 (100); 206.1020 (M^+ + 1), $C_8H_{15}NO_5$ requires 206.0950; δ_H (300 MHz, $CDCl_3$) 4.82 (1H, d, *J* 13.5, CH_2NO_2), 4.66 (1H, d, *J* 13.5, CH_2NO_2), 4.35 (2H, qd, *J* 7.2, 1.5, CH_3CH_2O), 3.57 (1H, br s, OH), 1.97 (1H, m, *J* 6.9, Me_2CH), 1.33 (3H, t, *J* 7.2, CH_3CH_2O), 0.98 (3H, d, *J* 6.9, Me_2CH), 0.89 (3H, d, *J* 6.9, Me_2CH); δ_C (75 MHz, $CDCl_3$) 173.0 (s), 80.1 (t), 77.5 (s), 62.9 (t), 34.0 (d), 16.8 (q), 16.2 (q), 14.0 (q).

(*R*)-(+)-Ethyl 2-cyclohexyl-2-hydroxy-3-nitropropanoate (12p)

Purified by column chromatography eluting with hexane–EtOAc (80 :20). Enantiomeric excess (78%) determined by HPLC (Chiralcel OD-H), hexane–*i*-PrOH 90 : 10, 0.5 mL min^{-1}, major enantiomer (*R*) t_R 11.6, minor enantiomer (*S*) t_R 12.3; $[\alpha]_D^{25}$ +17.3 (*c* 1.05 in CH_2Cl_2, ee 78%); *m*/*z* (EI) 246 (M^+ + 1, 7%), 172 (46), 129 (57), 117 (30), 111 (41), 83 (100), 55 (43); 246.1344 (M^+ + 1), $C_{11}H_{19}NO_5$ requires 246.1263; δ_H (300 MHz, $CDCl_3$) 4.81 (1H, d, *J* 13.5, CH_2NO_2), 4.68 (1H, d, *J* 13.5, CH_2NO_2), 4.39–4.28 (2H, m, CH_3CH_2O), 3.58 (1H, br s, OH), 1.79–1.59 (5H, m), 1.40–1.01 (6H, m), 1.33 (3H, t, *J* 7.2, CH_3CH_2O); δ_C (75 MHz, $CDCl_3$) 172.9 (s), 79.9 (t), 77.6 (s), 62.9 (t), 43.7 (d), 26.7 (t), 26.2 (t), 26.0 (t), 25.9 (t), 25.8 (t), 14.0 (q).

(*R, E*)-(−)-Ethyl 2-hydroxy-2-(nitromethyl)pent-3-enoate (12q)[8,11]

Purified by column chromatography eluting with hexane–EtOAc (90 : 10). Enantiomeric excess (73%) determined by HPLC (Chiralpak AD-H), hexane–*i*-PrOH 90 : 10, 0.8 mL min^{-1}, major enantiomer (*R*) t_R 10.7, minor enantiomer (*S*) t_R 9.8; $[\alpha]_D^{25}$ −46.7 (*c* 1.11 in $CHCl_3$, ee 73%); δ_H (300 MHz, $CDCl_3$) 6.18 (1H, m, olefinic), 5.44 (1H, d, *J* 15.3, olefinic), 4.86 (1H, d, *J* 14.1, CH_2NO_2), 4.47 (1H, d, *J* 14.1, CH_2NO_2), 4.45–4.25 (2H, m, CH_3CH_2O), 3.79 (1H, br s, OH), 1.74 (3H, dt, *J* 6.6, 1.5, *Me*-olefinic), 1.33 (3H, t, *J* 7.2, CH_3CH_2O); δ_C (75 MHz, $CDCl_3$) 171.8 (s), 130.7 (d), 125.7 (d), 79.9 (t), 75.1 (s), 63.2 (t), 17.6 (q), 14.0 (q).

(*R, E*)-(−)-Ethyl 5-(benzyloxy)-2-hydroxy-2-(nitromethyl)pent-3-enoate (12r)[11]

Purified by column chromatography eluting with hexane–EtOAc (90 : 10). Enantiomeric excess (80%) determined by HPLC (Chiralpak AD-H), hexane–*i*-PrOH 90 : 10, 0.8 mL min^{-1}, major enantiomer (*R*) t_R 20.7, minor enantiomer (*S*) t_R 19.1; $[\alpha]_D^{25}$ −27.1 (*c* 1.05 in $CHCl_3$, ee 80%); δ_H (300 MHz, $CDCl_3$) 7.39–7.30 (5H, m, Ph), 6.25 (1H, dt, *J* 15.3, 4.8, olefinic), 5.76 (1H, dt, *J* 15.3, 1.8, olefinic), 4.89 (1H, d, *J* 13.8, CH_2NO_2), 4.53 (2H, s, CH_2O), 4.49 (1H, d, *J* 13.8, CH_2NO_2), 4.42–4.26 (2H, m, CH_3CH_2O), 3.89 (1H, br s, OH), 1.34 (3H, t, *J* 7.2, CH_3CH_2O); δ_C (75 MHz, $CDCl_3$) 171.4 (s), 137.7 (s), 131.6 (d), 128.4 (d), 127.8 (d), 127.7 (d), 125.7 (d), 79.8 (t), 75.1 (s), 72.7 (t), 69.0 (t), 63.4 (t), 13.9 (q).

Acknowledgements

Financial support from the Ministerio de Educación y Ciencia (CTQ 2006–14199) and the Generalitat Valenciana (GV 05/10) is gratefully acknowledged. V.H.-O. thanks the Universitat de València by a pre-doctoral grant (V Segles program).

Notes and references

1 (*a*) G. Rosini, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, New York, 1991, vol. 2, pp. 321–340; (*b*) F. A. Luzzio, *Tetrahedron*, 2001, **57**, 915–945.

2 N. Ono, *The Nitro Group in Organic Synthesis*, Wiley-VCH, New York, 2001.

3 For reviews see: C. Palomo, M. Oiarbide and A. Mielgo, *Angew. Chem., Int. Ed.*, 2004, **43**, 5442–5444; J. Boruwa, N. Gogoi, P. P. Saikia and N. C. Barua, *Tetrahedron: Asymmetry*, 2006, **17**, 3315–3326; C. Palomo, M. Oiarbide and A. Laso, *Eur. J. Org. Chem.*, 2007, 2561–2574.

4 H. Sasai, T. Suzuki, S. Arai, T. Arai and M. Shibasaki, *J. Am. Chem. Soc.*, 1992, **114**, 4418–4420; T. Arai, Y. M. A. Yamada, N. Yamamoto, H. Sasai and M. Shibasaki, *Chem.–Eur. J.*, 1996, **2**, 1368–1372; B. M. Trost and V. S. C. Yeh, *Angew. Chem., Int. Ed.*, 2002, **41**, 861–863; D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw and C. W. Downey, *J. Am. Chem. Soc.*, 2003, **125**, 12692–12693; C. Palomo, M. Oiarbide and A. Laso, *Angew. Chem., Int. Ed.*, 2005, **44**, 3881–3884; H. Maheswaran, K. L. Prasant, G. G. Krishna, K. Ravikumar, B. Sridhar and M. L. Kantam, *Chem. Commun.*, 2006, 4066–4068; K. Ma and J. You, *Chem.–Eur. J.*, 2007, **13**, 1863–1871; T. Arai, M. Watanabe and A. Yanagisawa, *Org. Lett.*, 2007, **9**, 3595–3597; Y. Xiong, F. Wang, X. Huang, Y. Wen and X. Feng, *Chem.–Eur. J.*, 2007, **13**, 829–833.

5 Guanidine catalysis: Y. Sohtome, Y. Hashimoto and K. Nagasawa, *Adv. Synth. Catal.*, 2005, **347**, 1643–1648; Y. Sohtome, Y. Hashimoto and K. Nagasawa, *Eur. J. Org. Chem.*, 2006, 2894–2897; *Cinchona* alkaloids: M. Marcelli, R. N. S. van der Haas, J. van Maarseveen and H. Hiemstra, *Angew. Chem., Int. Ed.*, 2006, **45**, 929–931; H. Li, B. Wang and L. Deng, *J. Am. Chem. Soc.*, 2006, **128**, 732–733; phase transfer conditions: E. J. Corey and F.-Y. Zhang, *Angew. Chem., Int. Ed.*, 1999, **38**, 1931–1934; T. Ooi, K. Doda and K. Maruoka, *J. Am. Chem. Soc.*, 2003, **125**, 2054–2055; D. Uraguchi, S. Sakaki and T. Ooi, *J. Am. Chem. Soc.*, 2007, **129**, 12392–12393; biocatalytic: T. Purkarthofer, K. Gruber, M. Gruber-Khadjawi, K. Waich, W. Skrank, D. Mink and H. Griengl, *Angew. Chem., Int. Ed.*, 2006, **45**, 3454–3456.

6 S. Tosaki, K. Hara, V. Gnanadesikan, H. Morimoto, S. Harada, M. Sugita, N. Yamagiwa, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2006, **128**, 11776–11777.

7 For reviews on the stereoselective preparation of quaternary stereocenters see: *Quaternary Stereocenters. Challenges and Solutions in Organic Synthesis*, ed. J. Christoffers and A. Baro, Wiley, Weinheim, 2006; O. Riant and J. Hannedouche, *Org. Biomol. Chem.*, 2007, **5**, 873–888.

8 C. Christensen, K. Juhl and K. A. Jørgensen, *Chem. Commun.*, 2001, 2222–2223; C. Christensen, K. Juhl, R. G. Hazell and K. A. Jørgensen, *J. Org. Chem.*, 2002, **67**, 4875–4881.

9 K. R. Knudsen and K. A. Jørgensen, *Org. Biomol. Chem.*, 2005, **3**, 1362–1364.

10 S. F. Lu, D. M. Du, S. W. Zhang and J. Xu, *Tetrahedron: Asymmetry*, 2004, **15**, 3433–3441; D. M. Du, S. F. Lu, T. Fang and J. Xu, *J. Org. Chem.*, 2005, **70**, 3712–3715.

11 H. Li, B. Wang and L. Deng, *J. Am. Chem. Soc.*, 2006, **128**, 732–733.

12 G. Blay, E. Climent, I. Fernández, V. Hernández-Olmos and J. R. Pedro, *Tetrahedron: Asymmetry*, 2006, **17**, 2046–2049; G. Blay, E. Climent, I. Fernández, V. Hernández-Olmos and J. R. Pedro, *Tetrahedron: Asymmetry*, 2007, **18**, 1603–1612.

13 J. Whitesell, *Chem. Rev.*, 1989, **89**, 1581–1590; C. Halm and M. J. Kurth, *Angew. Chem., Int. Ed.*, 1998, **37**, 510–512.

14 For some examples of successful C_1 symmetric catalysts: M. Shi and W. S. Sui, *Tetrahedron: Asymmetry*, 2000, **11**, 835–841; A. V. Malkov, P. Spoor, V. Vinader and P. Kocovsky, *Tetrahedron Lett.*, 2001, **42**, 509–512; M. P. Sibi, L. Venkatraman, M. Liu and C. P. Jasperse, *J. Am. Chem. Soc.*, 2001, **123**, 8444–8445; W. A. Nugent, *Org. Lett.*, 2002, **4**, 2133–2136; A. J. A. Cohn and C. M. Marson, *Tetrahedron: Asymmetry*, 2001, **12**, 1547–1550; P. Wipf and X. Wang, *Org. Lett.*, 2002, **4**, 1197–1200; J. Priego, O. G. Mancheno, S. Cabrera and J. C. Carretero, *J. Org. Chem.*, 2002, **67**, 1346–1353; K. Nordstrom, E. Macedo and C. Moberg, *J. Org. Chem.*, 1997, **62**, 1604–1609; G. Chelucci, M. G. Sanna and S. Gladiali, *Tetrahedron*, 2000, **56**, 2889–2893; H. Brunner, H. Kagan and G. Kreutzer, *Tetrahedron: Asymmetry*, 2003, **14**, 2177–2187; X.-Y. Wu, H.-D. Xu, F.-Y. Tang and Q.-L. Zhou, *Tetrahedron: Asymmetry*, 2001, **12**, 2565–2569; A. J. Davenport, D. L. Davies, J. Fawcett, S. A. Garratt and D. R. Russell, *J. Chem. Soc., Dalton Trans.*, 2000, **23**, 4432–4441; Y. Himeda, N. Onozawa-Komatsuzaki, H. Sugihara, H. Arakawa and K. Kasuga, *J. Mol. Catal. A: Chem.*, 2003, **195**, 95–100; C. A. Luchaco-Cullis, H. Mizutani, K. E. Murphy and A. H. Hoveyda, *Angew. Chem., Int. Ed.*, 2001, **40**, 1456–1460. For a discussion on C_1 symmetric ligands see also:; A. C. Humphries and A. Pfaltz, in *Stimulating Concepts in Chemistry, Vögtle*, ed. J. F. Stoddart and M. Shibasaki, Wiley-VCH, Weinheim, 2000, pp. 89–103.

15 H. Koch, H. D. Scharf, J. Runsink and H. Leismann, *Chem. Ber.*, 1985, **118**, 1485–503.

16 E. F. DiMauro and M. C. Kozlowski, *J. Am. Chem. Soc.*, 2002, **124**, 12668–12669.

17 X. Creary, *J. Org. Chem.*, 1987, **52**, 5026–5030.

18 K. B. Jensen, J. Thorhauge, R. G. Hazell and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2001, **40**, 160–163.

