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Camphorsulfonamide derivatives: a new class of chiral catalysts for the titanium alkoxide-promoted addition of dialkylzinc to aldehydes

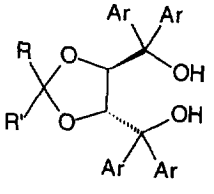
Diego J. Ramón and Miguel Yus *

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Alicante, Aptdo. 99, E-03080 Alicante, Spain

Abstract: The enantioselective addition of dialkylzinc to several aldehydes, using different chiral bidentate ligands (**3a–j**, **4a–h**) [derived from (+)-10-camphorsulfonyl chloride] and titanium alkoxide as catalysts, is studied. The influence of temperature, titanium alkoxide, stoichiometry, additive, aldehyde and ligand structure is also studied. © 1997 Elsevier Science Ltd

Introduction

Catalytic asymmetric synthesis[1] is a valuable method for preparing optically active substances. In contrast to stoichiometric methods, the chiral information of a ligand molecule is transferred to several product molecules, through a catalytic cycle; in addition, the reactivity of the active species bearing the chiral ligand is, in general, enhanced, compared to that of the non-chiral ligand, due to the so-called "ligand acceleration effect".[2] Among the enantioselective catalytic transformations, those involving carbon–carbon bond formation are probably the most attractive for synthesis, compared to functional group conversions on a given carbon skeleton.[3] Concerning this subject, the stereoselective addition of organometallics to one of the two heterotopic faces of a carbonyl group has been extensively studied, particularly, the addition of diethylzinc to benzaldehyde has become a prototype in the evaluation of new chiral catalysts.



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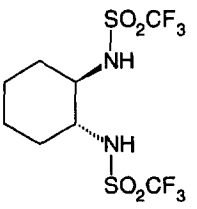

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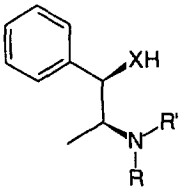
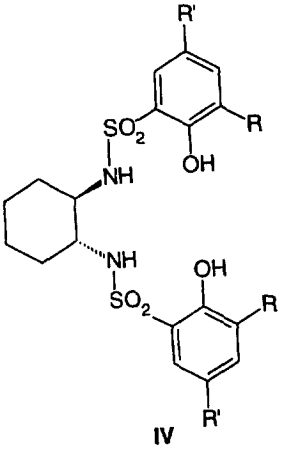


III (X = O, S)



IV

Originally,[4] dialkylzinc was activated to react with aldehydes by the addition of chiral 1,2-, 1,3- and 1,4-diols, aminoalcohols and diamines.[5] In these cases, several studies indicated that dimeric zinc complexes, containing the chiral ligands, act both as Lewis acid for carbonyl activation and as the origin from which the nucleophilic group was transferred.[5a,6] This fact introduced the idea of using a chiral Lewis acid for carbonyl activation, such as oxazaborolidines[7] and titanates.[8] In the case

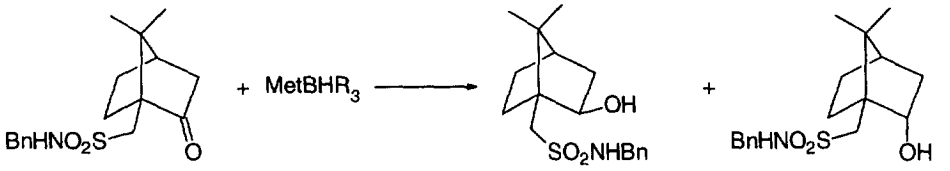
* Corresponding author. Fax: +34-6-5903549; Email: yus@ua.es

of titanium derivatives, chiral bidentate ligands, among them the diols[9] (TADDol **I**[10] being one of the most studied), ditriflamides **II**[11] and norephedrine derivatives **III**,[12] and tetradentate ligands **IV**[13] have been extensively and successfully used in the catalytic enantioselective addition of dialkylzinc to aldehydes.

Concerning a possible reaction pathway, the following features have been reported: (a) it is necessary to use one equivalent of titanium tetraalkoxide; (b) there is a ligand exchange between the diethylzinc and the titanium tetraalkoxide[11a,b] to form an ethyltitanium(IV) alkoxide derivative; (c) the catalytic species is a cationic titanium(IV)[10j] bearing the chiral ligand and the carbonyl compound; (d) the enantioselective differentation is due to the steric hindrance[10c,e,h,11l,13b,c] in the above mentioned intermediate; (e) the catalyst containing chiral ligand is a monomeric[10c,13] titanate; (f) the starting catalyst is renewed by exchange between titanium tetraalkoxide and the chiral titanium bearing the alkoxide, which came from the addition of the ethyltitanium derivative to the carbonyl system;[10e] (g) to decrease the catalytic activity of titanium tetraalkoxide *versus* chiral titanate, it is necessary to work at a low temperature.[9a,10,11a] In this paper we wish to report a procedure for the synthesis of a new class of bidentate ligands and the results of their use in the catalytic asymmetric alkylation of aldehydes.

Results and discussion

We have designed ligands based on the borneol structure with an alcohol ($pk_a \approx 16.5$) and a sulfonamide ($pk_a \approx 8$) group, which were prepared from the commercially available D-(+)-10-camphorsulfonyl chloride **1**. The reaction of chloride derivative **1** with benzylamine (2 equiv) catalysed by 4-dimethylaminopyridine (DMAP, 0.2 equiv) and isoquinoline (2 equiv) at 0°C gave after 3 h the expected camphorsulfonamide **2**,[14] which was reduced to the corresponding alcohol using different reducing agents (see Scheme 1 and Table 1).



2 **3a** **4a**

Scheme 1.

Table 1. Reduction of ketone **2**

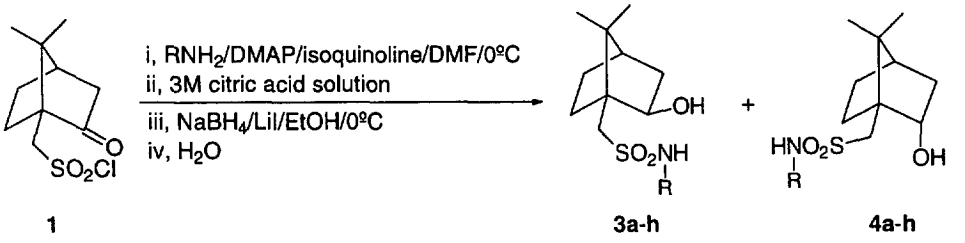
Entry	Met	R	Solvent	Additive	T (°C)	Yield (%)[a]		
						2	**3a**	**4a**
1	Na	H	EtOH	-	20	-	47	51
2	Na	H	EtOH	-	0	-	86	12
3	Na	H	EtOH	-	-78 to 20	-	65	32
4	Na	H	EtOH	LiI	0	-	88	10
5	Na	H	THF	LiI	0	-	75	22
6	Na	Bu[s]	THF	-	-78 to 20	46	48	3
7	Li	Bu[s]	THF	-	-78 to 20	26	70	1

[a] Yield of isolated product after flash chromatography based on starting ketone **2**.

The reduction of ketone **2** with sodium borohydride[15] (3 equiv) gave a mixture of the two possible epimers. The result of this reduction depends on temperature, giving a maximum *exo*/*endo* alcohol ratio at temperatures around 0°C, lower or higher temperatures giving a lower **3a**/**4a** compounds ratio (Table 1, entries 1–3). In the case of working at room temperature the *endo*-alcohol **4a** is even the major product (Table 1, entry 1). The presence of an additive[16] (lithium iodide, 2 equiv) in ethanol did not improve the *exo*/*endo* ratio (compare entries 2 and 4 in Table 1). The use of an aprotic solvent such as THF gave a worse **3a**/**4a** ratio (compare entries 4 and 5 in Table 1). When the reaction was carried out with more bulky reducing reagents, such as N- or L-selectride (3 equiv) the *exo*/*endo* ratio was improved, the corresponding lithium derivative being more selective. However, the reaction did not go to completion, some of the starting ketone (Table 1, entries 6 and 7) being recovered.

Due to the difficulty in isolating the ketone **2** from the mixture of *exo*/*endo* borneol derivatives, the easy separation of both alcohols **3a** and **4a** and our wish to test several related systems, we chose the conditions showed in Table 1, entry 4 for the reduction step in the preparation of several borneol derivatives.

The reaction of primary amines with (+)-10-camphorsulfonyl chloride **1** catalysed by isoquinoline and DMAP, followed by successive hydrolysis with a 3 M solution of citric acid, reduction with sodium borohydride (in the presence of lithium iodide) and final hydrolysis with water yielded the expected hydroxy sulfamides **3** and **4**, which were easily isolated by flash chromatography (Scheme 2 and Table 2). In all cases studied the *exo*-derivative **3** was the main product, *exo*/*endo* ratios being from 8.7/1 to 5.3/1 (Table 2, entries 7 and 8, respectively). More crowded ligands were obtained by addition of organometallic compounds to the ketone **2**, yielding in these cases only the *exo*-borneol derivative **3** (n.O.e experiments). Thus, the reaction of ketone **2** with methyl or phenyllithium (4 equiv) in THF at temperatures ranging between −78 and 20°C yielded a mixture of *exo*-borneol **3i** or **3j** and starting ketone **2** (Scheme 3 and Table 3 entries 1 and 3). The same reaction but adding dry $CeCl_3$ (2 equiv)[17] yielded almost exclusively the corresponding *exo*-borneol **3i** or **3j** (Table 3, entries 2 and 4).



1 **3a-h** **4a-h**

Scheme 2.

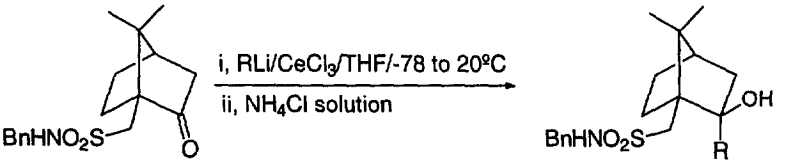
Once the ligands **3** had been prepared, we studied the influence of the temperature taking ligands **3a** and **3j** as standards for the reaction of diethylzinc and benzaldehyde using 20 mol% of ligand, 120 mol% of titanium isopropoxide and 180 mol% of the organometallic compound in toluene (Scheme 4). The obtained enantiomeric ratio (e.r. *R*:*S*) increased when the temperature was increased from −35 to 20°C (Table 4 entries 1–4), indicating that there is probably only one mechanism operating between those temperatures. This fact allows us to calculate with a correlation coefficient of 0.98 the entropy and enthalpy energy difference between the two diastereomeric transition states leading to enantiomeric product, using the Eyring's approach[18] (Figure 1). From the obtained values for $\Delta\Delta H^{\#}$ and $\Delta\Delta S^{\#}$ we conclude that with those differences the corresponding enantiomeric ratio can not be very high at those temperatutres. At higher temperatures the enantiomic ratio decreased, indicating that either a different pathway, or more than one mechanism occurs. Curiously, in the case of using the ligand **3j** the reaction at −35 and 20°C gave the opposite main enantiomer as product. This fact can be an indication of different active species acting at different temperatures (Table 4, entries 6 and 7).

Once the temperature influence had been studied, other parameters, such as stoichiometry, salt

Table 2. Preparation of ligands **3** and **4** by reduction of different ketones

Entry	R	no.	Yield (%)[a]	
			3	**4**
1	$PhCH_2$	**a**	73	9
2	$(CH_2)_2N(CH_3)_2$	**b**	20	3[b]
3	$(CH_2)_2N(CH_2)_2O(CH_2)_2$	**c**	40	5[b]
4	Bu^t	**d**	69	10
5	Ph	**e**	53	7
6	4-MeOPh	**f**	77	14
7	(*R*)-$PhCH(CH_3)$	**g**	79	9
8	(*S*)-$PhCH(CH_3)$	**h**	63	12

[a] Yield of isolated product after flash chromatography. [b] Detected and calculated from the crude mixture by ^1H NMR.



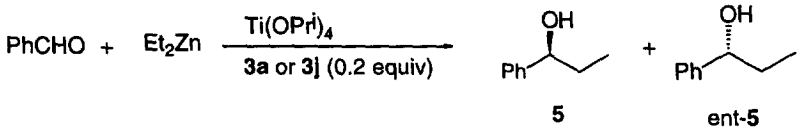
2 **3i**, R = Me; **3j**, R = Ph

Scheme 3.

Table 3. Preparation of ligands by addition of organometallics to ketone **2**

Entry	R	Additive	Recovered **2** (%)[a]	Product	
				no.	Yield (%)[a]
1	Me	-	38	**3i**	62
2	Me	$CeCl_3$	0	**3i**	91
3	Ph	-	8	**3j**	56
4	Ph	$CeCl_3$	3	**3j**	65

[a] Yield of isolated product after flash chromatography.



5 ent-**5**

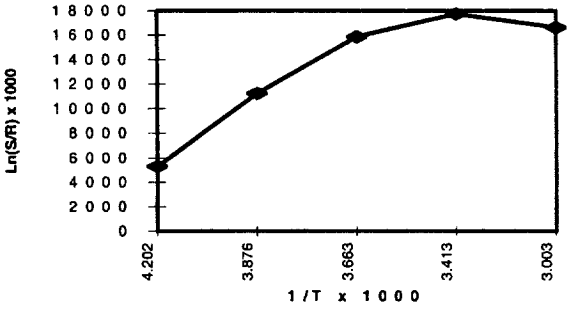
Scheme 4.

effect, bulkiness of titanium ligand and solvent were tested using the bidentate ligand **3a** as reference. Thus, the addition of diethylzinc (1.8 equiv) to benzaldehyde (1 equiv) in the presence of several amounts of ligand **3a**, and varying the titanium reagent and an additive in different solvents yielding the expected alcohol **5** and *ent*-**5** was studied (see Scheme 5 and Table 5). Thus, the reaction of

Table 4. Enantioselective addition of diethylzinc to benzaldehyde. Temperature effect

Entry	Ligand no.	Ligand R	T (°C)	t (h)	Product 5 Yield (%)[a]	Product 5 e.r.[b] *R* : *S*	Product 5 *e.e.*
1	**3a**	H	-35	5.5	54	37.0 : 63.0	26
2	**3a**	H	-15	5.5	>98[c]	24.5 : 75.5	51
3	**3a**	H	0	1	>98[c]	17.0 : 83.0	66
4	**3a**	H	20	0.5	>98[c]	14.5 : 85.5	71
5	**3a**	H	60	0.5	>98[c]	16.0 : 84.0	68
6	**3j**	Ph	-35	4	68	61.0 : 39.0	22
7	**3j**	Ph	20	1	>98[c]	29.0 : 71.0	42

[a] Yield of isolated product after bulb to bulb distillation. [b] Determined by GLC using β-CD column (see Experimental part). [c] Not other products were detected by GLC and ^{1}H NMR in the crude mixture.



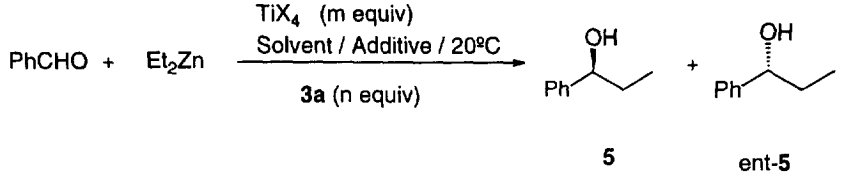
$$\text{Ln}\,(S/R) = -\,(\Delta\Delta H^{\#} / RT) + (\Delta\Delta S^{\#} / R)$$

$\Delta\Delta H^{\#} \approx 3.5$ kcal/mol; $\Delta\Delta S^{\#} \approx 1.6$ cal/mol K; r = 0.98

Figure 1. Eyring's diagram for ligand **3a**.

diethylzinc in toluene at 20°C with benzaldehyde was very slow when it was catalysed by one equiv of the spiro titanium derivative[10a] [generated *in situ* from 2 equiv of ligand **3a** and 1 equiv of tetrakis(diethylamino)titanium,[19] and final elimination of the generated diethylamine]: after 4 days the yield was only 30%, indicating that the ligand exchange to form the corresponding ethyltitanium derivative is too slow, probably due to steric hindrance in the spiro titanium compound. On the other hand, it is worth noting that the process works better using a substoichiometric amount of the ligand (20%; Table 4, entry 4) than under the former conditions (200%; Table 5, entry 1). When the reaction was carried out using 1 equiv of ligand the result was the same as when using only 0.2 equiv. However, when the amount of ligand was decreased down to 0.02 equiv, the enantiomeric ratio decreased, compared to previous reactions (Table 4, entry 4 and Table 5 entries 2 and 3). As it was pointed out in the substoichiometric version (it is necessary as a scavenger for the formed alkoxide compound[10e]), with this ligand the titanium species bearing the chiral bidentate ligand and the 1-phenyl-1-propoxide is less active in the reaction using substoichiometric amount of the ligand and in the corresponding enantioselective differentiation (Table 5, entry 4). The enantiomeric ratio decreased a little when the titanium isopropoxide was changed by titanium *tert*-butoxide[11] [generated by reaction of *tert*-butanol and tetrakis(diethylamino)titanium[19]] (Table 5, entry 5). The presence of a salt (calcium isopropoxide[12a] or lithium chloride[10d,g,20]) did not change the result, neither the yield nor the enantiomeric ratio (compare entry 4 in Table 4 and entries 6 and 7 in Table 5). When the reaction

was carried out in pentane, diethyl ether ot THF, the results were similar to the process carried out in toluene (entries 8–10 in Table 5 and entry 4 in Table 4). However, when the reaction was performed in methylene chloride the enantiomeric ratio decreased slightly (entry 11 in Table 5).



Scheme 5.

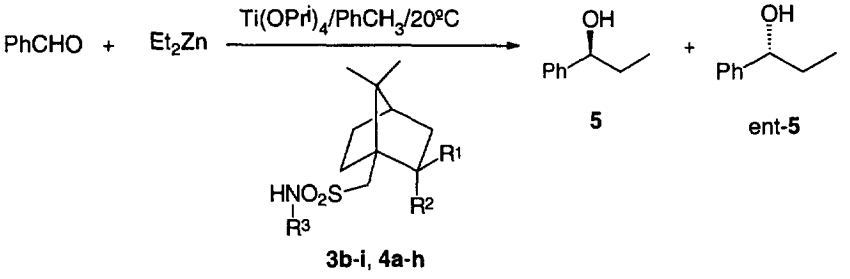
Once the reaction temperature and the stoichiometry had been studied, modified ligands were tested in order to find which one was the best for the enantioselective addition of diethylzinc to benzaldehyde. Thus, the reaction of diethylzinc (1.8 equiv), with benzaldehyde (1 equiv) in the presence of titanium isopropoxide (1.2 equiv) and the corresponding ligand (0.2 equiv) in toluene at 20°C yielded after 1 h the expected alcohol in more than 98% yield, and with variable enantiomeric ratios (Scheme 6 and Table 6). From the results included in Table 6, we concluded that the *exo*-ligands **3** always gave better enantiomeric ratio than the corresponding *endo*-ligands **4** (compare entries 3–7 in Table 6 and entry 1 in Table 4 to entries 9–14 in Table 6). The presence of a basic functionality in the ligand decreased the corresponding e.r. producing almost a racemic mixture (entries 1 and 2, Table 6). These facts can be explained if the basic part of the catalyst reacts with the metal acid center, masking the titanium atom for the catalysed reaction. When the reaction was carried out with the *tert*-butyl derivative **3d**, the e.r. decreased (compare entry 3, Table 6 and entry 4, Table 4) probably because the new system is more hindered. However, when the reaction was performed with the phenyl derivative **3e** the result was similar to that obtained with the benzyl derivative **3a** (Table 6 entry 3 and Table 4 entry 4). When the phenyl group had a methoxy group in the *ortho* position **3f**, the e.r. was similar, indicating that the electronic effect at the phenyl ring seems to be not too important (Table 6 entries 4 and 5). The reaction

Table 5. Enantioselective addition of diethylzinc to benzaldehyde. Stoichiometry and salt effect

	Reaction conditions						Product **5**		
Entry	Solvent	n	m	X	Additive /(equiv)	t (h)	Yield (%)[a]	e.r.[b] *R* : *S*	*e.e*
1	$PhCH_3$	2.20	1.10	NEt_2[c]	-	96	30	32.0 : 68.0	36
2	$PhCH_3$	1.05	1.05	OPr^i	-	1	>98[d]	14.0 : 86.0	72
3	$PhCH_3$	0.02	1.02	OPr^i	-	1	>98[d]	23.5 : 76.5	53
4	$PhCH_3$	0.20	0.20	OPr^i	-	168	50	52.0 : 48.0	4
5	$PhCH_3$	0.20	1.20	NEt_2[e]	Bu^tOH / (4.4)	2.5	>98[d]	17.0 : 83.0	66
6	$PhCH_3$	0.20	1.20	OPr^i	CaH_2[f] / (0.24)	1	>98[d]	14.0 : 86.0	72
7	$PhCH_3$	0.20	1.20	OPr^i	LiCl / (0.6)	1	>98[d]	15.0 : 85.0	70
8	n-C_5H_{12}	0.20	1.20	OPr^i	-	1	>98[d]	16.0 : 84.0	68
9	Et_2O	0.20	1.20	OPr^i	-	1	>98[d]	15.5 : 84.5	69
10	THF	0.20	1.20	OPr^i	-	1	>98[d]	14.5 : 85.5	71
11	CH_2Cl_2	0.20	1.20	OPr^i	-	1	>98[d]	18.0 : 82.0	64

[a] Yield of isolated product after bulb to bulb distillation. [b] Determined by GLC using a β-CD column (see Experimental part). [c] The spiro titanium derivative (see text) was formed *in situ*. [d] No other products were detected by GLC and ^1H NMR in the crude mixture. [e] $Ti(OBu^t)_4$ was generated *in situ*. [f] $Ca(OPr^i)_2$ was generated *in situ*.

with both (*R*)- and (*S*)-phenethyl derivatives (**3g** and **3h**, respectively) yielded poorer enantiomeric ratio than the corresponding benzylic derivative **3a**, justifying that steric hindrance at the α-position relative to the amido group decreased the e.r. Methyl groups in the last ligands did not behave in an equivalent manner, the methyl group in the (*R*)-derivative is closer to the titanium atom in the catalyst and makes the reaction more difficult; however, in the (*S*)-derivative, the methyl group is at sufficient distance to the metal, so that it does not disturb the reaction as much (entries 6 and 7 in Table 6). When the reaction was performed with *exo*-borneol derivatives with a tertiary alcohol functionality (ligands **3i** and **3j**), the enantiomeric ratio was rather similar (entry 8 in Table 6 and entry 7 in Table 4).



Scheme 6.

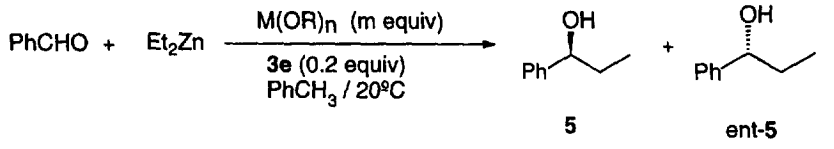
After verifying that the substitution on the nitrogen atom had some influence and that the relative *exo*/*endo* configuration of hydroxy group and the substitution at the alcoholic carbon atom had a bigger influence, the use of others metals[7] as catalysts was studied. Thus, the addition of diethylzinc to benzaldehyde was carried out with 20% of ligand **3e**, with different metals (with different stoichiometries) and also without any metal alkoxyde,[21] giving the expected alcohols **5** (Scheme 7 and

Table 6. Enantioselective addition of diethylzinc to benzaldehyde. Ligand effect

	Ligand				Product **5**[a]	
Entry	no.	R^1	R^2	R^3	e.r.[b] *R* : *S*	*e.e*
1	**3b**	OH	H	$(CH_2)_2N(CH_3)_2$	52.0 : 48.0	4
2	**3c**	OH	H	$(CH_2)_2N(CH_2)_2O(CH_2)_2$	43.5 : 56.5	13
3	**3d**	OH	H	Bu^t	18.0 : 82.0	64
4	**3e**	OH	H	Ph	15.0 : 85.0	70
5	**3f**	OH	H	2-MeOPh	17.0 : 83.0	66
6	**3g**	OH	H	(*R*)-PhCH(CH_3)	25.5 : 74.5	49
7	**3h**	OH	H	(*S*)-PhCH(CH_3)	17.0 : 83.0	66
8	**3i**	OH	CH_3	$PhCH_2$	30.0 : 70.0	40
9	**4a**	H	OH	$PhCH_2$	45.5 : 54.5	9
10	**4d**	H	OH	Bu^t	63.5 : 36.5	27
11	**4e**	H	OH	Ph	35.0 : 65.0	30
12	**4f**	H	OH	2-MeOPh	36.0 : 64.0	28
13	**4g**	H	OH	(*R*)-PhCH(CH_3)	40.0 : 60.0	20
14	**4h**	H	OH	(*S*)-PhCH(CH_3)	31.0 : 69.0	38

[a] All isolated yields were >98%. [b] Determined by GLC using a β-CD column (see Experimental part).

Table 7). In every case tested, the enantiomeric ratio was poor (*ca.* 1:1) and the process needed longer reaction times; other disadvantages are that benzyl alcohol was isolated from the reaction mixture, and the ligand was partially epimerised (probably, by a Oppenauer oxidation Meerwein–Pondorff–Verley-type reduction).



Scheme 7.

Finally, different aldehydes were tested as substrates in the enantioselective addition of dialkylzinc, using the *exo*-borneol derivative **3a** as ligand under the same conditions described in Table 4 entry 4 (see, Scheme 8 and Table 8), so the expected alcohols were isolated after one hour and final hydrolysis, yields being better than 95%. The enantiomeric ratio was similar for aromatic or aliphatic aldehydes in the addition of diethylzinc (Table 4 entry 4 and Table 8 entries 1 and 7). When the reaction was performed with dimethylzinc and benzaldehyde, the e.r. was almost similar. However, when the reaction was carried out with benzyl imine derivatives[22] and diethylzinc, the reaction time was longer (after 120 h the yield was 54%, after flash chromatography) and the product was isolated as a racemic mixture (Table 8, entry 3). Finally, the electronic effect[23] of *para*-substituted benzaldehydes was studied, finding that the variation of enantiomeric ratio was dependent on the basicity of the functional group present in the aldehyde aromatic ring and not on the electronic effect; the more basic is the functionality the less e.r. was found (see Table 8, entries 4–7). A similar decrease of the e.r. was found when the ligand had an amino group (Table 6, entries 1 and 2).

From the results described in this paper we conclude that hydroxysulfonamides derived from camphor are adequate ligands for the titanium-promoted enantioselective addition of dialkylzinc reagents to aldehydes. The enantioselectivity depends on different factors, such as temperature, ligand structure and titanium (or other metal) compound, the best result being obtained at room temperature, short reaction times and using ligand **3a** and titanium tetraisopropoxide as metallic salt.

Experimental section

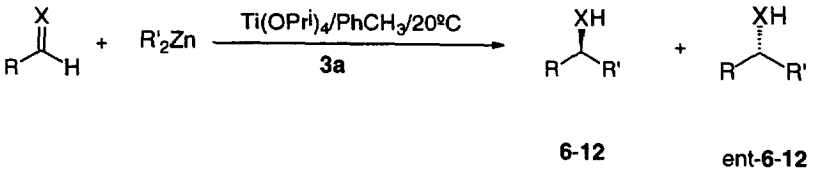
General

Melting points were obtained with a Reichert Thermovar apparatus. Distillation for purification of the products was performed in a Büchi GKR-51 bulb to bulb distillation apparatus, boiling points

Table 7. Enantioselective addition of diethylzinc to benzaldehyde. Metal effect

	Metal alkoxide					Yield (%)[a]				
Entry	m	M	R	n	t (h)	5 + *ent*-5	PhCHO	$PhCH_2OH$	e.r.[b] *R* : *S*	*e.e.*
1	-	-	-	-	24	80	15	5	44.0 : 56.0	12
2	0.2	B	Pr^i	3	24	90	-	10	45.0 : 55.0	10
3	1.2	B	Pr^i	3	120	62	34	4	44.0 : 56.0	12
4	0.2	Al	Pr^i	3	24	80	10	10	49.0 : 51.0	2
5	1.2	Al	Pr^i	3	16	80	10	10	45.0 : 55.0	10
6	1.2	Si	Pr^i	4	24	86	2	12	53.0 : 47.0	6
7	1.2	Zr	Et	4	120	41	5	54	46.5 : 53.5	7

[a] Yield based on the ^1H NMR crude mixture. [b] Determined by GLC using a β-CD column (see Experimental part).



Scheme 8.

Table 8. Enantioselective addition. Aldehyde effect

Entry	Product no.	R	X	R'	e.r.[a] *R* : *S*	*e.e.*
1	**6**	*n*-C_6H_{13}	O	Et	16.0 : 84.0	68
2	**7**	Ph	O	Me	17.5 : 82.5	65
3	**8**	Ph	$NP(O)Ph_2$	Et	50.0 : 50.0[b]	0
4	**9**	4-Me_2NPh	O	Et	43.0 : 57.0[c]	14
5	**10**	4-MeOPh	O	Et	23.0 : 77.0	54
6	**11**	4-NCPh	O	Et	22.0 : 78.0	56
7	**12**	4-ClPh	O	Et	16.0 : 84.0	68

[a] Determined by GLC using a β-CD column (see Experimental part). [b] Determined by optical rotation. [c] Determined using (*R*)-*O*-(4-chloro-2-methylphenyl)lactic acid as chiral solvating agent.[24]

correspond to the air bath temperature. $[\alpha]_D$ were recorded at room temperature (*ca.* 20°C) in a DIP-1000 JASCO polarimeter (*p.a.* solvents, Panreac). FT-IR spectra were obtained on a Nicolet Impact 400D spectrophotometer. NMR spectra were recorded on a Bruker AC-300 (300 MHz for ^1H and 75 MHz for ^{13}C) using $CDCl_3$ as solvent (unless otherwise stated) and TMS as internal standard; chemical shifts are given in δ (ppm) and coupling constants (*J*) in Hz. Mass spectra (EI) were obtained at 70 eV on a Shimazdu QP-5000 spectrometer, giving fragment ions in *m/z* with relative intensities (%) in parentheses. High resolution mass spectra were measured by the Mass Spectrometry Service at the University of Zaragoza. Elemental analyses were performed by the Microanalyses Service at the University of Alicante. The purity of volatile products and the chromatographic analyses (GLC) were determined with a Hewlett Packard HP-5890 instrument equipped with a flame ionization detector and a 12 m HP-1 capillary column (0.2 mm diam, 0.33 mm film thickness, OV-1 stationary phase), using nitrogen (2 ml/min) as carrier gas, $T_{injector}$=275°C, $T_{detector}$=300°C, T_{column}=60°C (3 min) and 60–270°C (15°C/min), P=40 kPa; t_r values are given in min under these conditions. The enantiomeric ratios (e.r.) were determined with the above GLC apparatus and a 50 m WCOT fused silica capillary column (0.25 mm diam, 0.25 mm film thickness, CP-cyclodextrin-β-2,3,6-M-19), using nitrogen as carrier gas, $T_{injector}$=250°C, $T_{detector}$=260°C: A conditions T_{column}=140°C (5 min) and 140–220°C (1°C/min), P=120 kPa; B conditions T_{column}=110°C (5 min) and 110–220°C (1°C/min), P=120 kPa; C conditions T_{column}=60°C (5 min) and 60–220°C (0.5°C/min), 100 kPa; $t_r(R)$ and $t_r(S)$ values are given in min under these three conditions. Thin layer chromatography (TLC) was carried out on Schleicher & Schuell F1400/LS 254 plates coated with a 0.2 mm layer of silica gel; detection by UV_{254} light, staining with phosphomolybdic acid (25 g phosphomolybdic acid, 10 g $Ce(SO_4)_2 \cdot 4H_2O$, 60 ml concentrated H_2SO_4 and 940 ml H_2O) or with I_2; R_f values are given under these conditions. Column chromatography was performed using silica gel 60 of 35–70 mesh. *N*-Benzylidenenediphenylphosphinamide[25] was prepared according to the literature procedure. Others reagents were commercially available (Acros, Aldrich) and were used as received. Solvents were dried by standard procedures.[26]

Preparation of (1S,4S)-N-benzyl-10-camphorsulfonamide 2

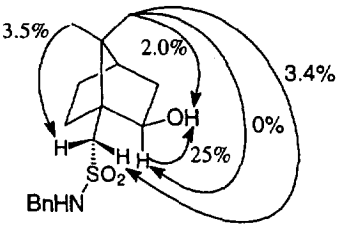
To a solution of benzylamine (21 mmol, 1.5 ml), isoquinoline (20 mmol, 2.35 ml) and DMAP (2 mmol, 0.235 g) in dry DMF (10 ml) at 0°C was slowly added (*ca.* 2 h) another solution of D-(+)-10-camphorsulfonyl chloride (**1**) (10 mmol) in dry DMF (10 ml). After one additional hour the mixture was poured into a 1 M citric acid solution (50 ml), and the obtained mixture was extracted with ethyl acetate (3×50 ml). The organic layer was washed successively with a 1 M citric acid solution (50 ml) and water (2×50 ml), and dried over Na_2SO_4. The solvents were removed under reduced pressure (15 Torr), obtaining the title compound **2**.[27] Yield 89%; t_r 19.04, R_f 0.28 (hexane/ethyl acetate: 7/3); $[\alpha]_D$ +6.68 [c=10 ($CHCl_3$)]; ν (film) 3302 (NH), 3064, 3027, 1455 (HC=C), 1743 (C=O), 1330, 1146 cm^{-1} (SO_2N); δ_H 0.73, 0.94 (3 and 3H, respectively, 2s, 2×CH_3), 1.30–1.45, 1.80–2.20, 2.30–2.40 [1, 5 and 1H, respectively, 3m, $(CH_2)_2CHCH_2$], 2.84, 3.17 (1 and 1H, respectively, 2d, *J*=15.1, CH_2S), 4.25–4.40 (2H, m, CH_2N), 5.86 (1H, t, *J*=6.4, NH), 7.20–7.40 (5H, m, Ph); δ_C 19.25, 19.6, 26.6, 26.85, 42.55, 42.75, 47.6, 48.55, 50.45, 59.1, 127.65, 128.2 (2C), 128.6 (2C), 136.9, 216.75; *m/z* 153 (M^+-168, 1%), 149 (11), 109 (31), 107 (24), 106 (100), 91 (29), 81 (26), 79 (14), 77 (12), 67 (19), 55 (14), 43 (16).

*Preparation of bidentate ligands by reduction. Isolation of compounds **3a–h** and **4a–h**. General procedure*

To a solution of corresponding amine (21 mmol) [in the case of (*R*)- and (*S*)-phenethylamine, 10 mmol of triethylamine and 10 mmol of the corresponding amine were placed], isoquinoline (20 mmol) and DMAP (2 mmol) in dry DMF (10 ml) at 0°C was slowly added (*ca.* 2 h) a solution of D-(+)-10-camphorsulfonyl chloride (**1**) (10 mmol). After one additional hour (18 h in the cases of aniline derivative, allowing temperature to rise to 20°C) the mixture was poured into a 1 M citric acid solution (50 ml) and the obtained mixture was extracted with ethyl acetate (3×50 ml). The organic layer was washed successively with 1 M citric acid solution (50 ml) and water (2×50 ml), and dried over Na_2SO_4. The solvents were removed under reduced presure (15 Torr). The residue was dissolved in ethanol (50 ml) at 0°C, and to this solution was added, with vigorous stirring, lithium iodide (22 mmol, 2.95 g) followed by sodium borohydride (35 mmol, 1.32 g). The resulting mixture was stirred for 2 h. The ethanol was removed (15 Torr), and the resulting residue was dissolved in water (50 ml) and extracted with ethyl acetate (3×50 ml). The organic layer was dried over Na_2SO_4 and the solvent was removed (15 Torr) yielding a residue which was then purified by flash chromatography (silica gel, hexane/ethyl acetate or ethyl acetate/methanol for compounds **3b** and **3c**) to afford the expected alcohols **3a–h** and **4a–h**. Yields are included in Table 2. Spectroscopic, physical and analytical data follow.

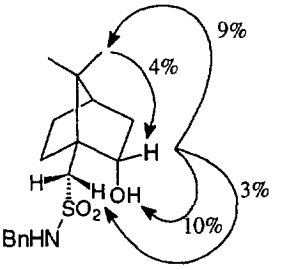
*(1S,2R,4S)-N-Benzyl-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide **3a***

t_r 18.73, R_f 0.37 (hexane/ethyl acetate: 7/3); mp 100–102°C (ethyl acetate/hexane); $[\alpha]_D$ −38.86 [c=0.8 ($CHCl_3$)]; ν (melted) 3521, 3283, 3227 (NH, OH), 3062, 3024, 1456 (HC=C), 1323, 1143 (SO_2N), 1073 cm^{-1} (CO); δ_H 0.70, 0.95 (3 and 3H, respectively, 2s, 2×CH_3), 1.05–1.15, 1.20–1.30, 1.35–1.80 [1, 1 and 5H, respectively, 3m, $(CH_2)_2CHCH_2$], 2.67, 3.26 (1 and 1H, respectively, 2d, *J*=13.7, CH_2S), 3.28 (1H, d, *J*=4.3, OH), 3.95–4.10 (1H, m, CHO), 4.25–4.35 (2H, m, CH_2N), 5.34 (1H, t, *J*=6.1, NH), 7.25–7.35 (5H, m, Ph); δ_C 19.65, 20.3, 27.2, 30.3, 38.9, 44.2, 47.15, 48.5, 50.25, 52.9, 76.25, 127.9, 128.0 (2C), 128.7 (2C), 136.75; *m/z* 241 (M^+-82, <1%), 109 (17), 108 (44), 107 (61), 106 (100), 93 (24), 91 (52), 79 (23), 77 (18), 67 (16), 55 (16), 44 (21), 43 (21) (Found: C, 63.04; H, 8.02; N, 4.48; S, 9.65. $C_{17}H_{25}NO_3S$ requires: C, 63.13; H, 7.79; N, 4.33; S, 9.91).



(1S,2S,4S)-N-*Benzyl-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide* ***4a***

t_r 19.08, R_f 0.23 (hexane/ethyl acetate: 7/3); mp 124–126°C (ethyl acetate/hexane); $[\alpha]_D$ +0.02 [c=0.4 ($CHCl_3$)]; ν (melted) 3415, 3133 (NH, OH), 3031, 1455 (HC=C), 1315, 1142 (SO_2N), 1051 cm^{-1} (CO); δ_H 0.77, 0.78 (3 and 3H, respectively, 2s, 2×CH_3), 1.00–1.10, 1.20–1.65, 1.70–1.85, 2.20–2.45 [1, 2, 2 and 2H, respectively, 4m, $(CH_2)_2CHCH_2$], 2.90, 2.95 (1 and 1H, respectively, 2d, *J*=14.3, CH_2S), 3.33 (1H, d, *J*=3.0, OH), 4.15–4.20 (1H, m, CHO), 4.25–4.40 (2H, m, CH_2N), 5.36 (1H, t, *J*=6.0, NH), 7.30–7.40 (5H, m, Ph); δ_C 18.7, 20.25, 23.65, 28.15, 38.4, 43.85, 47.45, 50.9, 51.4, 56.6, 75.05, 128.1 (2C), 128.2, 128.8 (2C), 136.75; *m/z* 207 (M^+−116, 2%), 107 (10), 106 (16), 91 (10), 44 (100), 43 (11) (Found: C, 63.04; H, 7.91; N, 4.36; S, 9.80. $C_{17}H_{25}NO_3S$ requires: C, 63.13; H, 7.79; N, 4.33; S, 9.91).



(1S,2R,4S)-N-*[2′-(N′,N′-Dimethylamino)ethyl]-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide* ***3b***

t_r 16.29, R_f 0.27 (ethyl acetate/methanol: 1/1); mp 155–157°C (methanol/hexane); $[\alpha]_D$ −23.82 [c=1.1 (CH_3COCH_3)]; ν (melted) 3504, 3293 (NH, OH), 1319, 1140 (SO_2N), 1026 cm^{-1} (CO); δ_H (CD_3COCD_3) 0.85, 1.07 (3 and 3H, respectively, 2s, 2×CH_3C), 1.40–1.50, 1.65–1.80, 2.00–2.15 [1, 5 and 3H, respectively, 3m, $(CH_2)_2CHCH_2$, OH, NH], 2.31 (6H, s, 2×CH_3N), 2.58 (2H, t, *J*=6.1, CH_2NCH_3), 3.07, 3.54 (1 and 1H, respectively, 2d, *J*=14.0, CH_2S), 3.29 (2H, td, *J*=6.1, 2.45, CH_2NH), 4.02 (1H, dd, *J*=7.95, 4.25 CHO); δ_C 19.5, 20.15, 26.85, 29.8, 39.0, 39.4, 43.85, 44.3 (2C), 48.3, 49.8, 51.35, 57.65, 75.45; *m/z* 211(M^+−93, 1%), 58 (100) (Found: C, 51.88; H, 9.68; N, 8.58; S, 9.77. $C_{14}H_{28}N_2O_3S \cdot H_2O$ requires: C, 51.98; H, 9.66; N, 8.66; S, 9.91).

(1S,2R,4S)-N-*[2′-(Morpholin-4-yl)ethyl]-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide* ***3c***[27]

t_r 19.09, R_f 0.73 (ethyl acetate/methanol: 1/1); $[\alpha]_D$ −33.18 [c=1.7 (CH_2Cl_2)]; ν (film) 3526, 3285 (NH, OH), 1318, 1141 (SO_2N), 1117 cm^{-1} (CO); δ_H 0.83, 1.07 (3 and 3H, respectively, 2s, 2xCH_3), 1.15–1.20, 1.40–1.60, 1.70–1.85, [1, 1 and 5H, respectively, 3m, $(CH_2)_2CHCH_2$], 2.45–2.60 [6H, m, $(CH_2)_3N$], 2.91, 3.47 (1 and 1H, respectively, 2d, *J*=14.0, CH_2S), 3.10–3.30 (2H, m, CH_2NH), 4.05–4.15 (2H, m, CHOH), 5.05 (1H, s, NH); δ_C 19.9, 20.55, 27.3, 30.4, 39.0, 39.25, 44.3, 48.65, 50.25, 52.15, 53.25 (2C), 57.4, 66.75 (2C), 76.2; *m/z* 253 (M^+−93, <1%), 100 (100), 44 (10).

(1S,2R,4S)-N-*(1,1-Dimethylethyl)-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide* ***3d***

t_r 14.95, R_f 0.60 (hexane/ethyl acetate: 7/3); mp 94–96°C (ethyl acetate/hexane); $[\alpha]_D$ −43.91 [c=2.5 (CH_2Cl_2)]; ν (melted) 3529, 3284 (NH, OH), 1313, 1134 (SO_2N), 995 cm^{-1} (CO); δ_H 0.83, 1.07 [3 and 3H, respectively, 2s, $(CH_3)_2C$], 1.39 [9H, s, $(CH_3)_3C$], 1.10–1.20, 1.45–1.85 [1, and 6H, respectively, 2m, $(CH_2)_2CHCH_2$], 2.92, 3.48 (1 and 1H, respectively, 2d, *J*=13.8, CH_2S), 3.51 (1H, d, *J*=4.0, OH), 4.00–4.15 (1H, m, CHO), 5.25 (1H, s, NH); δ_C 19.55, 20.2, 27.05, 30.0 (3C), 30.25, 38.6, 44.05, 48.2, 50.35, 54.25, 55.7, 76.0; *m/z* 274 (M^+−15, 1%), 135 (12), 109 (22), 108 (22), 107 (15), 102 (11), 93 (24), 79 (15), 74 (19), 69 (11), 67 (18), 59 (13), 58 (100), 57 (47), 55 (23), 46 (11), 43 (30), 42 (21) (Found: C, 58.12; H, 9.66; N, 4.94; S, 10.84. $C_{14}H_{27}NO_3S$ requires: C, 58.10; H, 9.40; N, 4.84; S, 11.08).

(1S,2S,4S)-N-*(1,1-Dimethylethyl)-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide* ***4d***

t_r 15.22, R_f 0.53 (hexane/ethyl acetate: 7/3); mp 110–112°C (ethyl acetate/hexane); $[\alpha]_D$ +12.68 [c=1.1 (CH_2Cl_2)]; ν (melted) 3474, 3199 (NH, OH), 1319, 1142 (SO_2N), 995 cm^{-1} (CO); δ_H 0.90, 0.91 [3 and 3H, respectively, 2s, $(CH_3)_2C$], 1.39 [9H, s, $(CH_3)_3C$], 1.05–1.15, 1.50–1.90, 2.15–2.50 [1, 4 and 2H, respectively, 3m, $(CH_2)_2CHCH_2$], 3.09, 3.17 (1 and 1H, respectively, 2d, *J*=14.2, CH_2S), 3.68 (1H, d, *J*=2.4, OH), 4.30–4.40 (1H, m, CHO), 5.00 (1H, s, NH); δ_C 18.7, 20.3, 23.65, 28.1, 30.2, 38.15, 43.8, 51.1, 51.35, 54.7, 59.65, 75.1; *m/z* 274 (M^+−15, 1%), 58 (100), 57 (20), 43 (13), 42 (11) (Found: C, 58.06; H, 9.71; N, 4.95; S, 10.68. $C_{14}H_{27}NO_3S$ requires: C, 58.10; H, 9.40; N, 4.84; S, 11.08).

(1S,2R,4S)-N-*Phenyl-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide* ***3e***

t_r 17.76, R_f 0.55 (hexane/ethyl acetate: 7/3); $[\alpha]_D$ −37.05 [c=3.3 (CH_2Cl_2)]; ν (film) 3540, 3262 (NH, OH), 3079, 3048, 1496 (HC=C), 1331, 1147 (SO_2N), 912 cm^{-1} (CO); δ_H 0.73, 1.01 (3 and 3H, respectively, 2s, 2×CH_3), 1.05–1.15, 1.50–1.90 [1, and 6H, respectively, 2m, $(CH_2)_2CHCH_2$], 3.00, 3.55 (1 and 1H, respectively, 2d, *J*=13.8, CH_2S), 3.44 (1H, d, *J*=3.7, OH), 4.10–4.20 (1H, m, CHO), 7.10–7.20, 7.25–7.40 (1 and 4H, respectively, 2m, Ph), 7.76 (1H, s, NH); δ_C 19.65, 20.25, 27.1, 30.25, 39.0, 44.15, 48.65, 50.20, 51.05, 76.25, 120.15 (2C), 124.8, 129.45 (2C), 136.9; *m/z* 309 (M^+, <1%), 94 (11), 93 (100), 92 (11), 67 (10), 65 (13), 55 (12), 44 (14), 43 (20) (Found: M^+, 309.1400. $C_{16}H_{23}NO_3S$ requires 309.1399).

(1S,2S,4S)-N-*Phenyl-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide* ***4e***

t_r 18.07, R_f 0.43 (hexane/ethyl acetate: 7/3); mp 88–90°C ($CHCl_3$); $[\alpha]_D$ +27.05 [c=1.1 (CH_2Cl_2)]; ν (melted) 3507, 3260 (NH, OH), 3085, 3054, 1496 (HC=C), 1337, 1149 (SO_2N), 917 cm^{-1} (CO); δ_H 0.81, 0.83 (3 and 3H, respectively, 2s, 2×CH_3), 1.00–1.15, 1.20–1.90, 2.20–2.55 [1, 4 and 2H, respectively, 3m, $(CH_2)_2CHCH_2$], 3.14, 3.21 (1 and 1H, respectively, 2d, *J*=14.3, CH_2S), 3.52 (1H, d, *J*=3.7, OH), 4.30–4.40 (1H, m, CHO), 7.10–7.40 (5H, m, Ph), 7.65 (1H, s, NH); δ_C 18.75, 20.25, 23.9, 28.2, 38.6, 43.9, 51.0, 51.5, 54.6, 75.3, 119.9 (2C), 124.8, 129.6 (2C), 137.2; *m/z* 309 (M^+, 1%), 94 (11), 93 (100), 92 (10), 65 (13), 55 (11), 44 (11), 43 (14) (Found: C, 62.40; H, 7.69; N, 4.63; S, 9.92. $C_{16}H_{23}NO_3S$ requires: C, 62.11; H, 7.49; N, 4.53; S, 10.36).

(1S,2R,4S)-N-*(2-Methoxyphenyl)-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide* ***3f***

t_r 18.95, R_f 0.36 (hexane/ethyl acetate: 7/3); mp 86–88°C (CH_2Cl_2); $[\alpha]_D$ −34.84 [c=2.8 (CH_2Cl_2)]; ν (melted) 3538, 3271 (NH, OH), 3071, 1501 (HC=C), 1333, 1149 (SO_2N), 1253, 1026 cm^{-1} (CO); δ_H 0.73, 1.00 [3 and 3H, respectively, 2s, $(CH_3)_2C$], 1.05–1.15, 1.45–1.85 [1, and 6H, respectively, 2m, $(CH_2)_2CHCH_2$], 2.96, 3.50 (1 and 1H, respectively, 2d, *J*=13.7, CH_2S), 3.33 (1H, d, *J*=4.0, OH), 3.86

(3H, s, CH_3O), 4.05–4.15 (1H, m, CHO), 6.90–6.95, 7.05–7.15, 7.45–7.55 (2, 1 and 1H, respectively, 3m, Ph), 7.21 (1H, s, NH); δ_C 19.5, 20.2, 27.0, 29.9, 38.8, 44.0, 48.4, 50.0, 50.9, 55.45, 76.0, 110.7, 120.25, 121.0, 125.1, 125.85, 149.2; *m/z* 340 (M^++1, 1%), 339 (M^+, 6), 124 (17), 123 (100), 122 (14), 108 (41), 107 (11), 94 (15), 93 (17), 92 (13), 79 (16), 77 (15), 67 (16), 65 (20), 55 (20), 53 (12), 52 (11), 43 (28) (Found: C, 60.55; H, 7.80; N, 3.91; S, 9.05. $C_{17}H_{25}NO_4S$ requires: C, 60.15; H, 7.42; N, 4.13; S, 9.44).

(1S,2S,4S)-N-*(2-Methoxyphenyl)-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide* ***4f***

t_r 19.35, R_f 0.31 (hexane/ethyl acetate: 7/3); mp 117–119°C (CH_2Cl_2); $[\alpha]_D$ +9.44 [c=1.0 (CH_2Cl_2)]; ν (melted) 3515, 3250 (NH, OH), 3081, 1500 (HC=C), 1332, 1151 (SO_2N), 1253, 1022 cm^{-1} (CO); δ_H 0.80, 0.84 [3 and 3H, respectively, 2s, $(CH_3)_2C$], 1.05–1.15, 1.30–1.50, 1.60–1.85 [1, 4 and 2H, respectively, 3m, $(CH_2)_2CHCH_2$], 3.14 (2H, s, CH_2S), 3.52 (1H, s, OH), 3.89 (3H, s, CH_3O), 4.30–4.40 (1H, m, CHO), 6.90–7.00, 7.05–7.15, 7.45–7.55 (2, 1 and 1H, respectively, 3m, Ph), 7.21 (1H, s, NH); δ_C 18.65, 20.2, 23.2, 27.95, 37.95, 43.75, 50.9, 51.4, 54.65, 55.6, 75.0, 110.8, 120.0, 121.1, 125.2, 126.0, 149.1; *m/z* 339 (M^+, 4%), 124 (15), 123 (100), 122 (10), 108 (30), 94 (11), 93 (12), 79 (11), 77 (10), 67 (13), 65 (15), 55 (15), 43 (20) (Found: C, 60.35; H, 7.69; N, 3.85; S, 9.25. $C_{17}H_{25}NO_4S$ requires: C, 60.15; H, 7.42; N, 4.13; S, 9.44).

(1S,2R,4S,1'R)-N-*(1'-Phenylethyl)-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide* ***3g***

t_r 18.46, R_f 0.49 (hexane/ethyl acetate: 7/3); mp 94–96°C (ethyl acetate/hexane); $[\alpha]_D$ −9.56 [c=1.1 (CH_2Cl_2)]; ν (melted) 3540, 3277 (NH, OH), 3092, 3073, 3035, 1455 (HC=C), 1316, 1146 (SO_2N), 1075 cm^{-1} (CO); δ_H 0.61, 0.79 [3 and 3H, respectively, 2s, $(CH_3)_2C$], 1.00–1.10, 1.30–1.75 [1, and 9H, respectively, 2m, CH_3CH, $(CH_2)_2CHCH_2$], 2.46, 2.90 (1 and 1H, respectively, 2d, *J*=13.7, CH_2S), 3.05 (1H, d, *J*=3.7, OH), 3.95–4.05 (1H, m, CHO), 4.65–4.75 (1H, m, CHN), 5.00 (1H, d, *J*=6.7, NH), 7.15–7.40 (5H, m, Ph); δ_C 19.5, 20.35, 23.65, 27.3, 30.35, 38.8, 44.2, 48.45, 50.25, 53.8, 54.0, 76.3, 126.4 (2C), 128.15, 128.95 (2C), 142.35; *m/z* 305 (M^+−32, <1%), 150 (16), 135 (14), 122 (29), 121 (42), 120 (70), 108 (43), 107 (43), 106 (100), 105 (84), 95 (11), 93 (37), 91 (19), 81 (14), 79 (40), 78 (10), 77 (30), 69 (17), 67 (28), 55 (33), 53 (15), 51 (12), 44 (28), 43 (44), 42 (27) (Found: C, 64.38; H, 8.30; N, 4.26; S, 9.22. $C_{18}H_{27}NO_3S$ requires: C, 64.06; H, 8.06; N, 4.15; S, 9.50).

(1S,2S,4S,1'R)-N-*(1'-Phenylethyl)-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide* ***4g***

t_r 18.82, R_f 0.46 (hexane/ethyl acetate: 7/3); mp 46–48°C ($CHCl_3$); $[\alpha]_D$ +30.95 [c=1.3 (CH_2Cl_2)]; ν (melted) 3504, 3287 (NH, OH), 3094, 3069, 3038, 1455 (HC=C), 1317, 1148 (SO_2N), 1020 cm^{-1} (CO); δ_H 0.62, 0.65 [3 and 3H, respectively, 2s, $(CH_3)_2C$], 1.00–1.10, 1.20–1.40, 1.50–1.75, 2.15–2.40 [1, 2, 5 and 2H, respectively, 4m, CH_3CH, $(CH_2)_2CHCH_2$], 2.56, 2.65 (1 and 1H, respectively, 2d, *J*=14.2, CH_2S), 3.67 (1H, s, OH), 4.05–4.20 (1H, m, CHO), 4.55–4.70 (1H, m, CHN), 5.59 (1H, d, *J*=7.0, NH), 7.25–7.40 (5H, m, Ph); δ_C 18.4, 20.15, 23.3, 23.35, 28.0, 38.0, 43.7, 50.8, 51.2, 53.95, 57.47, 75.15, 126.5 (2C), 127.9, 128.75 (2C), 142.3; *m/z* 322 (M^+−15, 1%), 122 (11), 121 (16), 120 (36), 109 (16), 108 (19), 107 (19), 106 (100), 105 (51), 93 (17), 79 (18), 77 (15), 67 (14), 55 (16), 43 (26), 42 (14) (Found: C, 64.12; H, 8.24; N, 4.20; S, 9.15. $C_{18}H_{27}NO_3S$ requires: C, 64.06; H, 8.06; N, 4.15; S, 9.50).

(1S,2R,4S,1'S)-N-*(1'-Phenylethyl)-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide* ***3h***

t_r 18.36, R_f 0.46 (hexane/ethyl acetate: 7/3); mp 109–111°C (ethyl acetate/hexane); $[\alpha]_D$ −82.64 [c=1.0 (CH_2Cl_2)]; ν (melted) 3565, 3275 (NH, OH), 3075, 3065, 1454 (HC=C), 1316, 1145 (SO_2N),

1076 cm^{-1} (CO); δ_H 0.52, 0.89 [3 and 3H, respectively, 2s, $(CH_3)_2C$], 1.00–1.10, 1.20–1.75 [1, and 9H, respectively, 2m, CH_3CH, $(CH_2)_2CHCH_2$], 2.20, 3.02 (1 and 1H, respectively, 2d, J=13.7, CH_2S), 3.36 (1H, d, J=3.7, OH), 3.95–4.05 (1H, m, CHO), 4.55–4.70 (1H, m, CHN), 5.25–5.35 (1H, m, NH), 7.25–7.40 (5H, m, Ph); δ_C 19.7, 20.15, 23.5, 27.2, 30.3, 38.9, 44.2, 48.4, 50.25, 53.7, 53.85, 76.35, 126.4 (2C), 128.0, 128.8 (2C), 142.45; *m/z* 305 (M^+-32, <1%), 122 (15), 121 (22), 120 (45), 109 (18), 108 (22), 107 (24), 106 (100), 105 (64), 104 (10), 93 (22), 91 (12), 79 (25), 77 (19), 69 (11), 67 (18), 55 (21), 44 (18), 43 (32), 42 (18) (Found: C, 64.34; H, 8.27; N, 4.28; S, 9.96. $C_{18}H_{27}NO_3S$ requires: C, 64.06; H, 8.06; N, 4.15; S, 9.50).

(1S,2S,4S,1'S)-N-(1'-Phenylethyl)-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide ***4h***

t_r 18.75, R_f 0.37 (hexane/ethyl acetate: 7/3); mp 125–127°C ($CHCl_3$); $[\alpha]_D$ −8.08 [c=1.0 (CH_2Cl_2)]; ν (melted) 3485, 3187 (NH, OH), 3064, 3027, 1459 (HC=C), 1317, 1147 (SO_2N), 1083 cm^{-1} (CO); δ_H 0.62 [6H, 2s, $(CH_3)_2C$], 0.95–1.05, 1.25–1.75, 2.10–2.40 [1, 7 and 2H, respectively, 3m, CH_3CH, $(CH_2)_2CHCH_2$], 2.47, 2.64 (1 and 1H, respectively, 2d, J=14.0, CH_2S), 3.58 (1H, d, J=3.0, OH), 4.00–4.10 (1H, m, CHO), 4.55–4.70 (1H, m, CHN), 6.07 (1H, d, J=7.9, NH), 7.25–7.45 (5H, m, Ph); δ_C 18.35, 19.85, 23.2, 23.35, 27.95, 37.9, 43.6, 50.6, 50.8, 53.85, 57.0, 74.75, 126.4 (2C), 127.75, 128.65 (2C), 142.4; *m/z* 304 (M^+-33, 2%), 122 (11), 121 (16), 120 (37), 109 (15), 108 (17), 107 (18), 106 (100), 105 (51), 93 (18), 79 (19), 77 (16), 67 (15), 55 (17), 44 (15), 43 (25), 42 (15) (Found: C, 64.11; H, 8.30; N, 4.27; S, 9.21. $C_{18}H_{27}NO_3S$ requires: C, 64.06; H, 8.06; N, 4.15; S, 9.50).

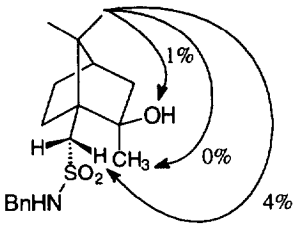
Preparation of bidentate ligands by addition of organometallics. Isolation of compounds ***3i,j****. General procedure*

Method A. To a solution of ketone **2** (5 mmol) in THF (30 ml) at −78°C was added the corresponding organolithium compound (20 mmol), allowing temperature to rise to 20°C overnight. The reaction mixture was hydrolysed with a saturated NH_4Cl solution (50 ml), and the resulting mixture was extracted with ethyl acetate (3×50 ml). The organic layer was dried over Na_2SO_4, and the solvents were removed under vacuum (15 Torr). The residue was then purified by flash chromatography (silica gel, hexane/ethyl acetate) to afford the expected *tert*-alcohols.

Method B. $CeCl_3 \cdot 7H_2O$ (20 mmol, 7.45 g) was dried at 100°C (0.1 Torr) during 1 h and at 140°C (0.1 Torr) during 3 h. Then, the residue was pured in THF (40 ml) under argon, and the resulting mixture was stirred overnight at 20°C. To the resulting milky suspention, a solution of ketone **2** (5 mmol) in THF (10 ml) was added at 0°C. After 2 h stirring the corresponding organolithium (20 mmol) was added, allowing temperature to rise to 20°C overnight. The reaction mixture was worked up as above to yield the expected alcohol, after flash chromatography. Yields are included in Table 3. Spectroscopic, physical and analytical data follow.

(1S,2R,4S)-N-Benzyl-2-hydroxy-2,7,7-trimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide ***3i***

t_r 19.26, R_f 0.36 (hexane/ethyl acetate: 7/3); mp 59–61°C ($CHCl_3$); $[\alpha]_D$ −29.76 [c=3.5 (CH_2Cl_2)]; ν (film) 3526, 3286 (NH, OH), 3093, 3060, 1456 (HC=C), 1319, 1142 (SO_2N), 1100, 1062 cm^{-1} (CO); δ_H 0.69, 1.01 [3 and 3H, respectively, 2s, $(CH_3)_2C$], 1.10–2.10 [10H, m, CH_3CO, $(CH_2)_2CHCH_2$], 2.60, 3.26 (1 and 1H, respectively, 2d, J=14.0, CH_2S), 2.75 (1H, s, OH), 4.28 (2H, d, J=6.0, CH_2N), 5.34 (1H, t, J=6.0, NH), 7.30–7.40 (5H, m, Ph); δ_C 20.9, 20.95, 26.75, 28.2, 28.65, 44.5, 47.1, 47.7, 52.05, 54.0, 54.15, 78.55, 127.95, 128.05 (2C), 128.75 (2C), 136.9; *m/z* 255 (M^+-82, 2%), 149 (31), 148 (45), 121 (13), 120 (10), 109 (20), 108 (48), 107 (65), 106 (69), 105 (66), 93 (52), 92 (22), 91 (99), 81 (13), 79 (41), 78 (12), 77 (41), 69 (18), 67 (16), 65 (17), 55 (25), 53 (16), 51 (16), 44 (13), 43 (100) (Found: C, 63.80; H, 8.12; N, 3.98; S, 9.31. $C_{18}H_{27}NO_3S$ requires: C, 64.06; H, 8.06; N, 4.15; S, 9.50).



(1S,2R,4S)-N-Benzyl-2-hydroxy-2-phenyl-7,7-trimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide 3j

t_r 29.28, R_f 0.33 (hexane/ethyl acetate: 7/3); mp 37–39°C (ethyl acetate/hexane); $[\alpha]_D$ +19.11 [c=1.6 (CH_2Cl_2)]; ν (melted) 3498, 3290 (NH, OH), 3064, 3026, 1456 (HC=C), 1325, 1143 (SO_2N), 1058 cm^{-1} (CO); δ_H 1.00–1.40, 1.75–1.85, 1.90–2.05, 2.15–2.20 [8, 2, 1 and 2H, respectively, 4m with 2s at 1.07 and 1.30, $(CH_3)_2C$, $(CH_2)_2CHCH_2$], 2.46 (1H, s, OH), 3.20, 3.29 (1 and 1H, respectively, 2d, J=15.4, CH_2S), 3.95, 4.07 (1 and 1H, respectively, 2dd, J=14.3, 6.2, CH_2N), 4.67 (1H, t, J=6.2, NH), 7.10–7.45 (10H, m, 2×Ph); δ_C 21.55, 22.1, 26.2, 27.0, 45.5, 46.35, 46.8, 51.3, 51.6, 54.7, 83.75, 126.8 (2C), 127.15, 127.6, 127.75 (2C), 128.5 (2C), 136.95, 144.85; *m/z* 212 (M^+−175, 3%), 211 (15), 105 (11), 91 (13), 57 (30), 56 (22) 44 (100), 43 (52), 42 (27) (Found: C, 68.80; H, 7.03; N, 3.12; S, 7.82. $C_{23}H_{29}NO_3S$ requires: C, 69.14; H, 7.32; N, 3.51; S, 8.02).

Enantioselective addition of dialkylzinc to aldehydes in the presence of (1S,4S)-N-substituted-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamides and metal alkoxide. General procedure

To a solution of the corresponding chiral bidentate ligand (**3** or **4**) (1 mmol) in toluene (5 ml) under argon was added the corresponding metal alkoxide (1 mmol) [in the case of spiro titanium derivative, only 0.5 mmol of $Ti(NEt_2)_4$ was added]. The resulting mixture was heated at 60–70°C during 0.5 h. After cooling to 20°C, toluene and the generated alcohol (or amine) was removed under vacuum (0.1 Torr) untill dryness. Then, the syrup (or solid) residue was dissolved in toluene (or other solvent, Table 5) (15 ml) under argon at 20°C (or other temperature, Table 4). Then, an excess of metal alkoxide (5.5 mmol) (for other stoichiometries, see Tables 5 and 7), dialkylzinc (*ca.* 2M, 4.5 ml, 9 mmol) and after 5 min the corresponding aldehyde (5 mmol) were successively added. The resulting mixture was stirred 1 h at 20°C (for other conditions, see Tables 4, 5, 7 and 8). Then, methanol (*ca.* 1 ml) and saturated NH_4Cl solution (*ca.* 20 ml) were successively added, the mixture was filtered through celite, extracted with ethyl acetate (3×50 ml) and the organic layer was dried over Na_2SO_4. The solvent was removed under vacuum (15 Torr) and the residue was destilled bulb to bulb to yield the expected alcohols. In the case of compound **9**, due to the partial decomposition, the destilled liquid was purified by flash chromatography (silica gel, hexane/ethyl acetate). Compound **8** was directly purified by flash chromatography (silica gel, hexane/ethyl acetate). Yields and enantiomeric ratios (e.r.) are included in Tables 4–8 and in the text. Spectroscopic, physical and analytical data follow.

1-Phenylpropan-1-ol 5[28]

t_r 7.24; t_r (*R*-**5**) 32.22, t_r (*S*-**5**) 32.71 (conditions B); R_f 0.47 (hexane/ethyl acetate: 6/1); bp 105–110°C (0.1 Torr); $[\alpha]_D$ −31.40 [c=6.95 ($CHCl_3$); e.r. (*R/S*) 16.0: 84.0]; ν (film) 3363 (OH), 3085, 3062, 3029 cm^{-1} (HC=C); δ_H 0.91 (3H, t, J=7.3, CH_3), 1.65–1.90 (2H, m, CH_2), 1.93 (1H, s, OH), 4.58 (1H, t, J=6.6, CHO), 7.25–7.35 (5H, m, Ph); δ_C 10.1, 31.85, 76.0, 125.95, 127.45 (2C), 128.35 (2C), 144.55; *m/z* 136 (M^+, 12%), 107 (100), 79 (90), 78 (11), 77 (49), 51 (29).

3-Nonanol 6[10f]

t_r 6.61; t_r (*R*-**6**) 87.45, t_r (*S*-**6**) 87.85 (conditions C); R_f 0.86 (hexane/ethyl acetate: 7/3); bp 100–105°C (0.1 Torr); $[\alpha]_D$ +6.58 [c=1.5 ($CHCl_3$); e.r. (*R/S*) 16.0: 84.0]; ν (film) 3353 cm^{-1} (OH);

δ_H 0.85–1.00 (6H, m, 2×CH_3), 1.25–1.50 (12H, m. 6×CH_2), 1.97 (1H, s, OH), 3.45–3.55 (1H, m, CHO); δ_C 9.77, 13.97, 22.55, 25.55, 29.3, 30.0, 31.8, 36.85, 73.15; *m/z* 126 (M^+−18, 5%), 115 (20), 97 (67), 69 (33), 59 (99), 58 (33), 57 (31), 56 (23), 55 (100), 44 (17), 43 (70), 42 (22).

1-Phenylethan-1-ol **7**[28]

t_r 6.44; t_r (*R*-**7**) 24.44, t_r (*S*-**7**) 25.20 (conditions B); R_f 0.37 (hexane/ethyl acetate: 7/3); bp 100–105°C (0.1 Torr); $[\alpha]_D$ −25.80 [c=6.3 (CH_3OH); e.r. (*R*/*S*) 17.5: 82.5]; ν (film) 3353 (OH), 3086, 3061, 3029, 1452 (HC=C), 1078 cm^{-1} (CO); δ_H 1.39 (3H, d, *J*=6.4, CH_3), 3.02 (1H, s, OH), 4.74 (1H, q, *J*=6.4, CHO), 7.20–7.35 (5H, m, Ph); δ_C 24.9, 69.9, 125.25 (2C), 127.05, 128.2 (2C), 145.7; *m/z* 122 (M^+, 24%), 107 (87), 105 (10), 79 (100), 78 (29), 77 (65), 53 (24), 52 (12), 51 (44), 50 (18), 43 (78).

N-*(1-Phenylpropyl)diphenylphosphinamide* **8**[22c]

t_r 19.18; R_f 0.55 (ethyl acetate); $[\alpha]_D$ −0.06 [c=2.1 (CH_2Cl_2)]; ν (film) 3191 (NH), 3058, 3025 (HC=C), 1190 cm^{-1} (P=O); δ_H 0.77 (3H, t, *J*=7.3, CH_3), 1.75–2.05 (2H, m. CH_2), 4.00–4.15 (2H, m, CHNH), 7.10–8.00 (15H, m, 3×Ph); δ_C 10.35, 32.15 (d, *J*=3.3), 56.8, 126.25 (2C), 126.6, 127.35, 127.75, 127.95, 128.05, 128.1, 128.2, 128.25, 131.44, 131.6, 132.25 (2C), 131.37, 133.95, 143.4 (d, *J*=6.0); *m/z* 308 (M^+−27, 3%), 307 (22), 306 (100), 202 (14), 201 (89), 134 (15).

*1-(4-*N,N*-Dimethylaminophenyl)propan-1-ol* **9**[23]

t_r 10.51; R_f 0.39 (hexane/ethyl acetate: 7/3); bp 185–190°C (0.1 Torr); $[\alpha]_D$ −45.85 [c=5.0 ($CHCl_3$); e.r. (*R*/*S*) 43.0: 57.0]; ν (film) 3389 (OH), 3101, 3089, 1613 cm^{-1} (HC=C); δ_H 0.85 (3H, t, *J*=7.5, CH_3C), 1.65–1.85 (2H, m, CH_2), 1.95 (1H, s, OH), 2.88 (6H, s, 2×CH_3N), 4.39 (1H, t, *J*=6.7, CHO), 6.64, 7.14 (2 and 2H, 2d, *J*=8.8, Ph); δ_H ($CDCl_3$ +2 ROAL)[24] 0.76 (*t*, *R*-**9**), 0.87 (*t*, *S*-**9**); δ_C 10.2, 31.35, 40.5 (2C), 75.5, 112.45 (2C), 121.15, 126.8 (2C), 149.9; *m/z* 162 (M^+−17, 13%), 161 (100), 160 (90), 145 (15), 144 (12), 134 (15), 118 (12), 117 (29), 116 (11), 115 (22), 91 (14), 80 (10), 79 (13), 77 (11), 51 (11), 44 (83), 43 (18), 42 (20).

1-(4-Methoxyphenyl)propan-1-ol **10**[28]

t_r 9.79; t_r (*R*-**10**) 32.63, t_r (*S*-**10**) 32.97 (conditions A); R_f 0.41 (hexane/ethyl acetate: 7/3); bp 150–155°C (0.1 Torr); $[\alpha]_D$ −11.71 [c=1.4 (C_6H_6); e.r. (*R*/*S*) 23.0: 77.0]; ν (film) 3438 (OH), 3119, 1609 (HC=C), 1037 cm^{-1}; δ_H 0.86 (3H, t, *J*=7.5, CH_3C), 1.75–1.90 (2H, m. CH_2), 2.34 (1H, s, OH), 3.74 (3H, s, CH_3O), 4.46 (1H, t, *J*=6.7, CHO), 6.80, 7.21 (2 and 2H, respectively, 2d, *J*=8.6, Ph); δ_C 10.05, 31.65, 55.0, 75.35, 113.55 (2C), 127.8 (2C), 130.2, 158.75; *m/z* 166 (M^+, 5%), 149 (11), 148 (100), 147 (60), 137 (51), 133 (25), 121 (22), 117 (38), 115 (23), 109 (18), 105 (29), 103 (21), 94 (15), 91 (33), 79 (30), 78 (22), 77 (65), 65 (20), 63 (20), 55 (20), 53 (12), 52 (13), 51 (37), 50 (19), 44 (45), 43 (16).

1-(4-Cyanophenyl)propan-1-ol **1**[23]

t_r 10.60; t_r (*R*-**11**) 56.20, t_r (*S*-**11**) 57.00 (conditions A); R_f 0.34 (hexane/ethyl acetate: 7/3); bp 175–180°C (0.1 Torr); $[\alpha]_D$ −27.03 [c=15.5 ($CHCl_3$); e.r. (*R*/*S*) 22.0: 78.0]; ν (film) 3439 (OH), 3106, 3088, 1609 (HC=C), 2229 (C≡N), 1047, 1017 cm^{-1}; δ_H 0.90 (3H, t, *J*=7.3, CH_3), 1.65–1.85 (2H, m, CH_2), 3.93 (1H, s, OH), 4.64 (1H, t, *J*=6.4, CHO), 7.44, 7.58 (2 and 2H, respectively, 2d, *J*=8.1, Ph); δ_C 9.55, 31.65, 74.45, 110.25, 118.65, 126.4 (2C), 131.8 (2C), 150.1; *m/z* 161 (M^+, 4%), 132 (82), 104 (46), 102 (10), 77 (26), 51 (17), 44 (100), 43 (28).

1-(4-Chlorophenyl)propan-1-ol **12**[28]

t_r 9.33; t_r (*R*-**12**) 31.65, t_r (*S*-**12**) 31.65 (conditions A); R_f 0.50 (hexane/ethyl acetate: 7/3); bp 135–140°C (0.1 Torr); $[\alpha]_D$ −20.46 [c=1.1 (C_6H_6); e.r. (*R*/*S*) 16.0: 84.0]; ν (film) 3371 (OH), 3052,

3021 cm^{-1} (HC=C); δ_H 0.85 (3H, t, *J*=7.5, CH_3), 1.55–1.80 (2H, m, CH_2), 2.70 (1H, s, OH), 4.46 (1H, t, *J*=6.4, CHO), 7.15–7.30 (4H, m, Ph); δ_C 9.85, 31.75, 75.05, 127.25 (2C), 128.3 (2C), 132.85, 142.9; *m/z* 172 (M^++2, 3%), 170 (M^+, 11), 152 (10), 143 (40), 142 (11), 140 (100), 117 (19), 115 (25), 112 (35), 78 (12), 77 (83), 75 (16), 57 (17), 51 (28), 49 (16).

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