Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 1629–1644

TETRAHEDRON: *ASYMMETRY*

Camphordisulfonamides: good chiral ligands for the addition of dialkylzinc to aliphatic aldehydes

Oscar Prieto, Diego J. Ramón and Miguel Yus*

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

Received 29 February 2000; accepted 13 March 2000

Abstract

The preparation of several disulfonamides derived from camphor and their use in the titanium tetraisopropoxide-promoted enantioselective addition of dialkylzinc to aldehydes is described. The enantiomeric ratio is up to 98:2, the best results being obtained for aliphatic aldehydes.

1. Introduction

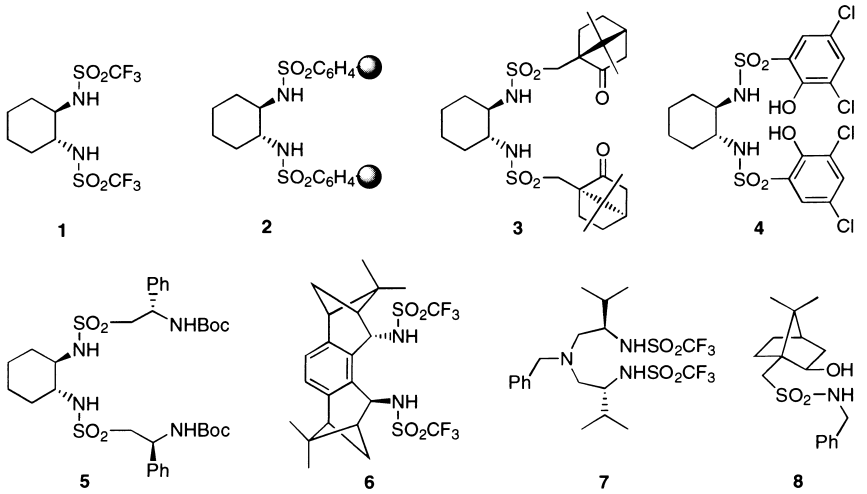
The difference in biological activity between two enantiomers, the necessity of homochiral compounds for the total synthesis of natural products, and the questions of regulatory agencies about data of fate and effects of both enantiomers of a chiral pharmaceutical compound in the course of registration, focuses interest on enantioselective reactions.[1] Among them, the nucleophilic addition to carbonyl compounds is of paramount importance in synthetic organic chemistry, as a useful tool for enantioselective carbon–carbon bond formation. Concerning this subject, the addition of diethylzinc to benzaldehyde has become a prototype for the evaluation of any new chiral ligand.

The use of titanium[2] tetraalkoxide as a Lewis acid in the promotion of the aforementioned reaction has been quite popular although the use of diols, such as TADDOL[3] and BINOL[4] and their corresponding polymeric[5,6] and dendritic[7,8] derivatives, as chiral ligands is constantly increasing. One of the most expansive classes of chiral ligands are disulfonamide derivatives **1**–**7**. Originally,[9] ligand **1** has been used in the addition of functionalised dialkylzinc reagents[10] to aldehydes in the presence of titanium tetraisopropoxide and it has been, probably, the most studied.[11] A similar ligand has been used as co-monomer in the preparation of the corresponding polymer **2**,[12] the enantioselection being quite similar to that found in the homogeneous phase. Instead of using chiral *trans*-1,2-cyclohexyldiamine as starting material, it is possible to use the

* Corresponding author. Tel: +34-965 903548; fax: +34-965 903549; URL: www.ua.es/dept.quimorg. E-mail: yus@ua.es

0957-4166/00/$ - see front matter
PII: S0957-4166(00)00100-2

racemic mixture: its reaction with chiral camphorsulfonyl chloride, followed by separation of both diastereomers, yielded the chiral ligand **3**, which shows a lower enantioselection compared to ligand **1**.[13] The corresponding tetradentate ligands **4**[14] and **5**[15] have also been developed, which show a different level of enantioselection depending on the nature of the aldehyde. Other ligands with 1,4- and 1,5-disulfonamide moieties (structures **6**[16] and **7**[17]) have been used as alternative chiral ligands for the aforementioned reaction. A general characteristic behaviour of this reaction is that the enantioselection is better for aromatic aldehydes than for aliphatic ones.[2] On the other hand, the ample amount of chiral disulfonamides used successfully as ligands for the above mentioned enantioselective addition, together with the unusual properties of hydroxysulfonamide **8**, which is the only ligand able to promote the enantioselective addition of dialkylzinc reagents to aldehydes[18] and ketones,[19] in the presence of titanium tetraisopropoxide, prompted us to prepare chiral disulfonamide ligands with the structure of camphor[20] and to study their use as chiral ligands in the enantioselective alkylation of aldehydes.



2. Results and discussion

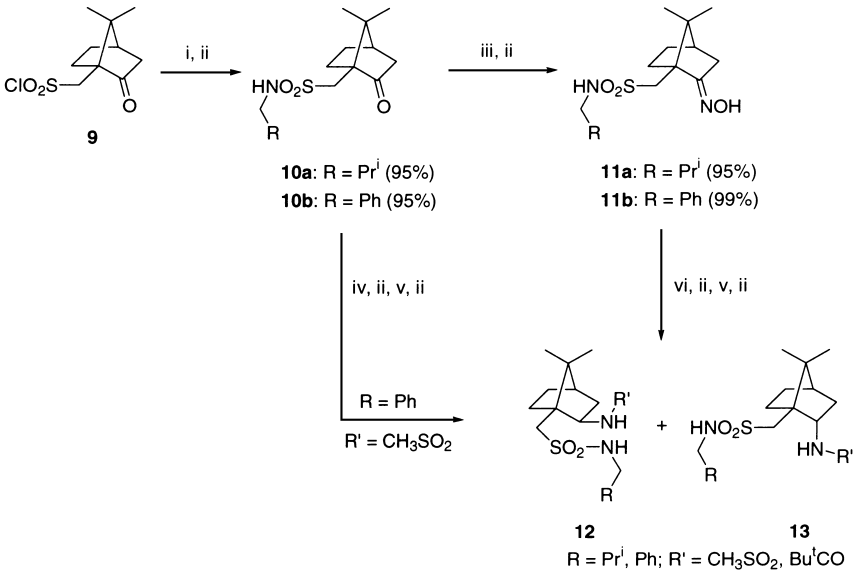
2.1. Preparation of chiral disulfonamide ligands

Disulfonamide ligands **12** and **13** were first prepared from the commercially available D-(+)-10-camphorsulfonyl chloride **9**. Its reaction with isobutylamine or benzylamine (2 equiv.), catalysed by 4-dimethylaminopyridine (DMAP, 0.2 equiv.), at 0°C gave after 3 h the expected camphorsulfonamides **10** with good yields. The corresponding reaction of these ketones with an excess of hydroxylammonium chloride (2.5 equiv.) and triethylamine (2 equiv.) in refluxing ethanol[21] gave the expected oximes **11** with good yields and as a single diastereoisomer. The final step was the reduction of oximes **11** to the corresponding amines and, for that purpose, several methods were tested (Table 1). However, due to the problems in their isolation, the crude mixture of amines were directly transformed into the corresponding mesylated derivatives **12** and **13** or the pivaloylamide derivative **12c** by reaction with methanesulfonyl chloride[22] or pivaloyl chloride, respectively, in the presence of triethylamine (Scheme 1). In this way, the isolation of *exo*-**12** and *endo*-**13** epimers was easily achieved.

Table 1
Reduction of oximes **11** and preparation of bidentate ligands

	oxime			Ligands				
entry	no.	R	reduction method	R'	no.	yield (%)[a]	no.	yield (%)[a]
1	**11a**	Pr^i	$NaBH_3CN/TiCl_3$	CH_3SO_2	**12a**	39	**13a**	5
2	**11b**	Ph	$LiAlH_4$	CH_3SO_2	**12b**	22	**13b**	10
3	**11b**	Ph	BH_3	CH_3SO_2	**12b**	15	**13b**	26
4	**11b**	Ph	$NaBH_4/NiCl_2 \cdot 6H_2O$	CH_3SO_2	**12b**	7	**13b**	17
5	**11b**	Ph	$NaBH_3CN/(PhS)_2/PBu^n_3$	CH_3SO_2	**12b**	2	**13b**	3
6	**11b**	Ph	$NaBH_4/TiCl_4$	CH_3SO_2	**12b**	17	**13b**	29
7	**11b**	Ph	$NaBH_3CN/TiCl_3/NaOAc$	CH_3SO_2	**12b**	16	**13b**	20
8	**11b**	Ph	$NaBH_3CN/TiCl_3$	CH_3SO_2	**12b**	41	**13b**	17
9	**11b**	Ph	$NaBH_3CN/TiCl_3$	Bu^tCO	**12c**	17[b]	**13c**	-[c]

[a] Yield of isolated product after flash chromatography based on starting oxime **11**.
[b] Yield of isolated product by recrystallisation Hex/AcOEt based on starting oxime **11b**.
[c] Not determined.



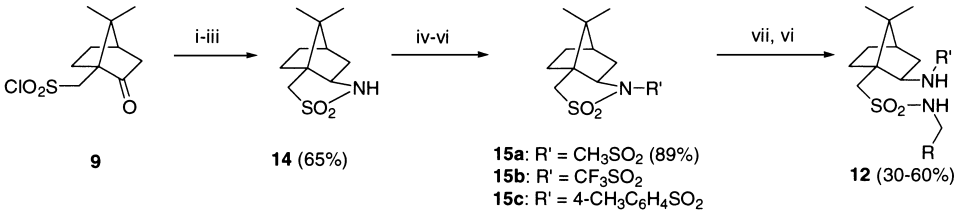
Scheme 1. Reagents and conditions: i, RCH_2NH_2, DMAP, CH_3CN, 0°C; ii, H_2O; iii, $NH_2OH{\cdot}HCl$, Et_3N, EtOH, 80°C; iv, $CH_3CO_2NH_4$, $NaBH_3CN$, MeOH, 70°C; v, R′Cl, Et_3N, CH_3CN, 0 to 25°C; vi, $CH_3CO_2NH_4$, $NaBH_3CN$, $TiCl_3$, MeOH, 0 to 25°C

The different strong reduction methods used for oximes **11**, such as lithium aluminium hydride[23] or borane[24] both in refluxing THF, gave, after mesylation, a low yield of the corresponding mesylamide, the diastereomeric ratio also being poor (Table 1, entries 2 and 3). Other mild reduction methods, such as sodium borohydride in the presence of nickel(II) chloride,[25] sodium cyanoborohydride in the presence of diphenyldisulfide and triethylphosphine,[26] sodium borohydride in the presence of titanium(IV) chloride,[27] or sodium borohydride in the presence of titanium(III) chloride and sodium acetate,[28] gave very poor yields or diastereomeric ratios of nearly 1:1 (Table 1, entries 4–7). However, the reduction using sodium borohydride in the presence of titanium(III) chloride and ammonium acetate[29] yielded the expected amines with a reasonable

yield and diastereomeric ratio, independently either of the starting camphorsulfonamide (entries 1 and 8) or of the isolation procedure (chromatography or recrystallisation; compare entries 8 and 9 in Table 1). Nevertheless, the results of this former procedure were inconsistent in the scaling-up process.

On the other hand, the corresponding reductive amination of camphorsulfonamide **10b**, using ammonium acetate and sodium cyanoborohydride in the presence of 4 Å molecular sieves in refluxing methanol,[30] gave the expected amines. Their transformation into the corresponding mesylamide derivatives, as has been mentioned previously, gave an isolable mixture of both epimers **12b** and **13b** with a 10% yield for both epimers.

The aforementioned problems made us turn to another way to prepare these ligands. The starting material was 10,2-camphorsultam **14**, which was easily prepared from the corresponding camphorsulfonyl chloride **9** by a two step process:[31] monodeprotonation of sultam **14** at low temperature, followed by a reaction with various sulfonyl chloride derivatives, gave the corresponding sultams **15** in good yields. The nucleophilic opening[32] of heterocycles **15** using various lithium amides yielded the expected ligands **12** (Scheme 2 and Table 2).



Scheme 2. Reagents and conditions: i, NH_4OH, 1,4-dioxane, 25 to 110°C; ii, $NaBH_4$, $MeOH/H_2O$, 0 to 25°C; iii, H_2SO_4 (4 M); iv, Bu″Li, THF, –78°C; v, R′Cl, –78 to 25°C; vi, H_2O; vii, RCH_2NH_2/Bu″Li, THF, –78 to 25°C.

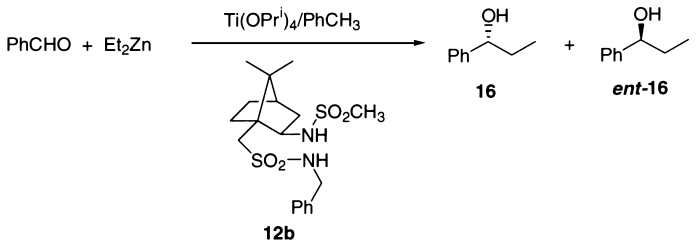
Table 2
Preparation of ligands **12** by nucleophilic opening

	heterocycle		ligand		
entry	no.	R'	no.	R	yield (%)[a]
1	**15a**	CH_3SO_2	**12b**	Ph	37
2	**15b**	CF_3SO_2	**12d**	Ph	30
3	**15c**	4-$MeC_6H_4SO_2$	**12e**	Ph	32
4	**15a**	CH_3SO_2	**12f**	4-$MeOC_6H_4$	60
5	**15a**	CH_3SO_2	**12g**	$PhCH_2$	44
6	**15a**	CH_3SO_2	**12h**	1-naphthyl	35

[a] Yield of isolated product after flash chromatography based on starting sultam **14**.

2.2. Asymmetric addition of dialkylzinc to aldehydes

Once the ligands **12** had been prepared, we studied first the influence of the temperature taking the ligand **12b** as standard 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 3 and Fig. 1). The maximum enantiomeric ratio was found at –20°C, and in all cases, the yield was higher than 95% after 4 h at the selected temperature, except in the case of



Scheme 3.

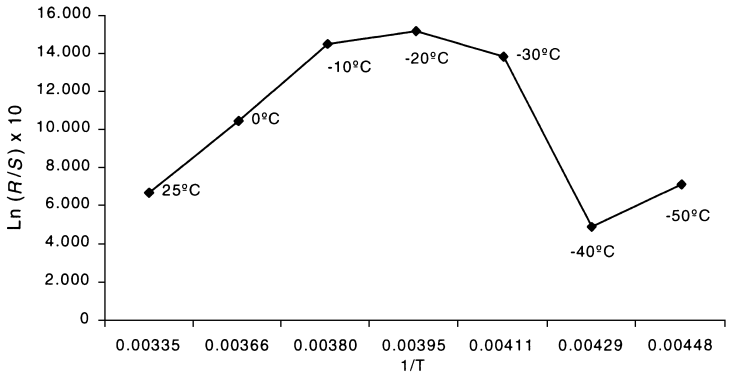


Figure 1. Eyring's diagram for ligand **12b**

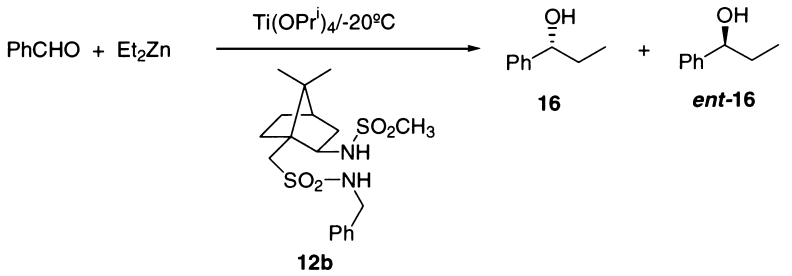
performing the reaction at –50°C after 120 h, in which only 70% yield was obtained. The Eyring diagram[33] shown in Fig. 1 probably indicates the existence of several reaction mechanisms in competition.

Once the optimal temperature had been found, other parameters such as solvent and bulkiness of titanium alkoxide were tested. Thus, the addition of diethylzinc (1.8 equiv.) to benzaldehyde (1 equiv.) in different solvents was studied using the chiral ligand **12b**, finding that the enantioselectivity of the reaction dropped down to nearly zero giving a racemic mixture when THF or dichloromethane were used (Table 3, entries 1 and 2). However, when toluene was used as solvent the enantiomeric ratio was 82:18 (Table 3, entry 3). This important influence of the solvent in the enantioselection was not present in the related ligand **8** (see above).[18]

The ligand **12g** was used as standard for studying the influence of the nature of titanium alkoxide. In the case of using the corresponding titanium ethoxide or propoxide derivatives, the enantiomeric ratio was lower than in the case of using titanium tetraisopropoxide (Table 4, compare entries 1–3). However, when the reaction was performed under similar conditions but using a more crowded derivative, such as titanium tetra-*tert*-butoxide, the reaction time was longer and the enantioselection was similar to those obtained using the less crowded titanium derivatives (Table 4, entry 4).

After verifying that toluene and titanium tetraisopropoxide were the best options for the conditions tested, we tried to find the best ligand for the aforementioned enantioselective reaction. Firstly we studied the influence of substitution of a 10-sulfonamide moiety (R^3), finding that the presence of an aromatic ring improved the enantioselection (Table 5, entries 1, 3 and 4). However, in the case of using a more crowded aromatic ring derivative, such as naphthyl, the enantiomeric ratio dropped. In the case of ligand **12a**, the influence of the temperature was also tested, and, as

Table 3



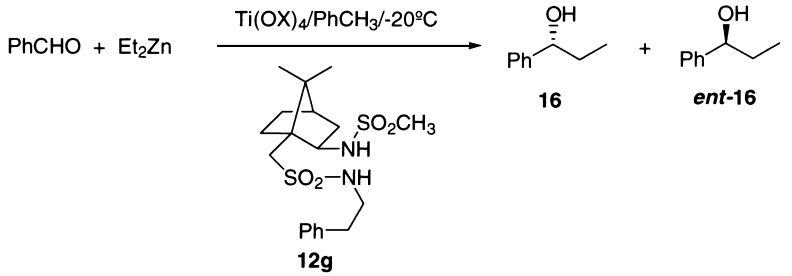
12b

			alcohol **16**		
entry	solvent	t(h)	yield (%)[a]	e.r.[b] *R*:*S*	e.e.
1	THF	2	>95	56.0:44.0	12
2	CH_2Cl_2	2	>95	58.0:42.0	16
3	$PhCH_3$	2	>95	82.0:18.0	64

[a] Isolated yield after bulb to bulb distillation.

[b] Determined by GLC using a β-CD column (see Experimental part).

Table 4



12g

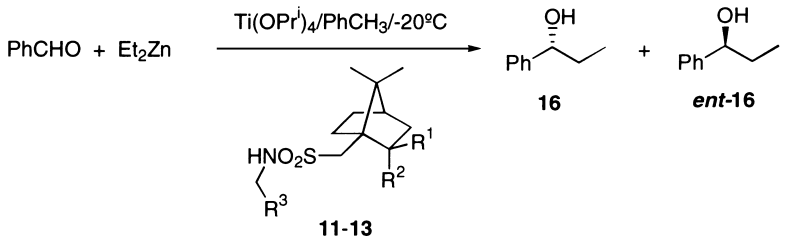
			alcohol **16**		
entry	X	t(h)	yield (%)[a]	e.r.[b] *R*:*S*	e.e.
1	Et	2	>95	63.0:37.0	26
2	Pr^n	2	>95	66.0:34.0	32
3	Pr^i	2	>95	82.0:18.0	64
4	Bu^t	96	>95	66.0:34.0	32

[a] Isolated yield after bulb to bulb distillation.

[b] Determined by GLC using a β-CD column (see Experimental part).

in the previous case, the best temperature seemed to be –20°C, the enantiomeric ratio being worse; even the main enantiomer was different performing the reaction at –30°C (Table 5, entry 2). The influence of substitution of a 2-sulfonamide moiety (R^1) and its nature was studied: mesylamide derivative gave the best results (Table 5, entry 3), better than the more acidic triflamide derivative (Table 5, entry 6) or the more hindered tosylamide derivative (Table 5, entry 7). When the reaction was performed using the corresponding pivaloylamide (Table 5, entry 8) a nearly racemic mixture of alcohol **16** was obtained. The relative position of mesylamide is also very important, since the modification from *exo*-position to *endo*-position (see compounds **12b** and **13b**; Table 5, entries 3 and 9) changed the enantioselection down to lead to a racemic mixture; a similar behaviour was found with the corresponding hydroxysulfonamide derivatives **9**.[18] Finally,

Table 5



	chiral ligand					alcohol **16**		
entry	no.	R^1	R^2	R^3	t(h)	yield (%)[a]	e.r.[b] *R*:*S*	e.e.
1	**12a**	CH_3SO_2NH	H	Pr^i	2	>95	70.0:30.0	40
2	**12a**	CH_3SO_2NH	H	Pr^i	3[c]	>95	47.5:52.5	5
3	**12b**	CH_3SO_2NH	H	Ph	2	>95	82.0:18.0	64
4	**12g**	CH_3SO_2NH	H	$PhCH_2$	2	>95	82.0:18.0	64
5	**12h**	CH_3SO_2NH	H	1-naphthyl	2	>95	54.0:46.0	8
6	**12d**	CF_3SO_2NH	H	Ph	2	>95	57.0:43.0	14
7	**12e**	4-$CH_3C_6H_4SO_2NH$	H	Ph	2	>95	60.0:40.0	20
8	**12c**	Bu^tCO	H	Ph	2	>95	44.0:56.0	12
9	**13b**	H	CH_3SO_2NH	Ph	2	>95	44.0:56.0	12
10	**11a**	-N(OH)-		Pr^i	2	>95	47.5:52.5	5

[a] Isolated yield after bulb to bulb distillation.

[b] Determined by GLC using a β-CD column (see Experimental part).

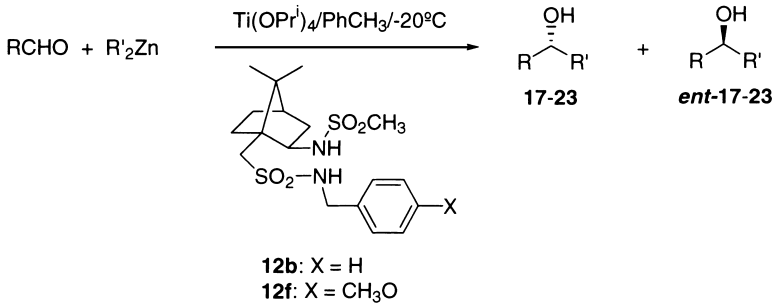
[c] The reaction was performed at –30ºC.

no enantioselection was found when the reaction was carried out using the oxime **11a** as chiral ligand (Table 5, entry 10).

Once the best ligand **12b** had been found for the enantioselective addition of diethylzinc to benzaldehyde, we tested the influence of dialkylzinc reagents and aldehydes, these results being included in Table 6. In all cases, the reactions were finished after 2 h and yields were greater than 95%. As was pointed out previously, for other disulfonamide ligands,[11i,34] the reaction with dimethylzinc gave a lower enantiomeric ratio than the corresponding diethylzinc reagent (Table 6, entry 1). The enantioselective addition carried out using benzadehyde derivatives gave a worse result in comparison with benzaldehyde (Table 5, entry 3 and Table 6, entries 2 and 3); the more basic the functionality present on the benzaldehyde derivative is, the lower the enantiomeric ratio, even the main enantiomer being changed. Surprisingly, the best enantioselection was found when the reaction was carried out using aliphatic aldehydes, independently of their steric hindrance (Table 6, entries 4, 6 and 7). Also in these cases of high enantioselection, the presence of an extra basic atom in the ligand **12** decreased the e.r. as in the previous case of benzaldehyde derivatives (Table 6, entries 4 and 5). Finally, the enantiomeric ratio was very low when the reaction was performed using alkenyl- or alkynylaldehydes (Table 6, entries 8–10). These results emphasize the special properties of this ligand in which the influence of the electronic aspects of the aldehyde is the major contribution in the enantioselectivity, giving the best results for the less reactive aliphatic aldehydes.

The main enantiomer obtained with the here described disulfonamide derivatives is usually *R*. However, in the case of using the corresponding hydroxysulfonamide **9**, the main enantiomer had *S* configuration,[18] in both cases the absolute configuration of the ligand being the same, which indicates that small changes in the structure of the chiral auxiliary may produce major consequences in the enantioselection.

Table 6



		Alcohol				
entry	X	no.	R	R'	e.r.[a] *R*:*S*	e.e.
1	H	**17**	Ph	CH_3	52.0:47.0	5
2	H	**18**	4-ClC_6H_4	CH_3CH_2	72.0:28.0	44
3	H	**19**	4-$CH_3OC_6H_4$	CH_3CH_2	40.0:60.0	20
4	H	**20**	*n*-C_6H_{13}	CH_3CH_2	98.0:2.0[b]	96
5	CH_3O	**20**	*n*-C_6H_{13}	CH_3CH_2	87.0:14.0[b]	73
6	H	**21**	$Ph(CH_2)_2$	CH_3CH_2	97.0:3.0[b]	94
7	H	**22**	*c*-C_6H_{11}	CH_3CH_2	96.0:4.0[b]	92
8	H	**23**	(*E*)-CH_3CH=CH	CH_3CH_2	56.0:44.0	12
9	H	**24**	(*E*)-PhCH=CH	CH_3CH_2	57.0:43.0[b,d]	14
10	H	**25**	PhC≡C	CH_3CH_2	69.0:31.0[b,d]	38

[a] Determined by GLC using a β-CD column (see Experimental part).

[b] Determined as trifluoroacetate derivative.

[c] Determined by GLC using a γ-CD column (see Experimental part).

[d] Determined by GLC using a γ-CD column after being transformed into compund **21** by hydrogenolysis using Pd/C (see Experimental part).

3. Conclusion

In conclusion, we have described here new disulfonamide ligands, which can be easily prepared from chiral camphorsulfonyl chloride and can be successfully used in the enantioselective addition of dialkyzinc reagents to aldehydes. It is worthy of note that the enantioselection is higher for aliphatic aldehydes than for aromatic derivatives, this behaviour being unusual for this type of reaction.

4. Experimental

4.1. General

Melting points were obtained with a Reichert Thermovar apparatus. Distillation for purification of the alcohol products was performed in a Büchi GKR-51 bulb to bulb distillation apparatus; boiling points correspond to the air bath temperature. $[\alpha]_D$ values were recorded at room temperature (ca. 25°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. NOESY and NOE experiments for assignation of relative configuration in ligands **12** and **13** were performed in a Bruker Avance DRX-500 (500 MHz for ^{1}H and 125 MHz for ^{13}C). Mass spectra (EI) were obtained at 70 eV on a Shimadzu QP-5000 spectrometer, giving fragment ions in m/z with relative intensities (%) in parentheses. High resolution mass spectra and elemental analyses were performed by the corresponding Mass Spectrometry and Microanalysis 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 ionisation detector and 12 m HP-1 capillary column (0.2 mm diameter, 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 aforementioned apparatus and a 50 m WCOT fused silica capillary column (0.25 mm diameter, 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: $T_{column} = 60°C$ (10 min) and 220°C (0.3°C/min), P = 130 kPa; B conditions: $T_{column} = 80°C$ (20 min) and 220°C (0.6°C/min), P = 120 kPa; C conditions: $T_{column} = 80°C$ (5 min) and 220°C (0.5°C/min), P = 120 kPa; or with a WCOT fused silica capillary column (0.25 mm diameter, 0.25 μm film thickness, FS-Lipodex-E) γ-CD, $T_{injector} = 250°C$, $T_{detector} = 260°C$; D conditions: $T_{column} = 75°C$ (20 min) and 210°C (0.1°C/min), P = 120 kPa; $t_R(R)$ and $t_R(S)$ values are given in min under these four conditions. In the cases of alcohols **20**, **21** and **22**, for achieving a good resolution in the GLC-analyses it was necessary to transform them in their trifluoroacetate derivatives (TFA) by reaction of the corresponding alcohol (5 mg) in CH_2Cl_2 (0.5 ml) at 25°C with trifluoroacetic anhydride (ca. 0.25 ml); after 30 min of stirring, nitrogen gas was passed through for several minutes and the obtained sample was used directly.[35] In the case of alcohols **24** and **25**, previously to the GLC-analyses, they were hydrogenated in methanol by hydrogen (1 atm) using palladium on activated carbon under standard conditions, [22] to give alcohol **21**. Thin layer chromatography (TLC) was carried out on Schleicher and 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. 10,2-Camphorsultam **14** was prepared from D-(+)-camphorsulfonyl chloride by a two step process with a 65% overall yield;[31] other reagents were commercially available (Acros, Aldrich, Strem) and were used as received. Solvents were dried by standard procedures.[36]

4.2. Preparation of ligands

4.2.1. Preparation of camphorsulfonamides *10*. General procedure

To a solution of the corresponding alkylamine (21 mmol) and dimethylaminopyridine (2.0 mmol, 0.235 g) in acetonitrile (20 ml) at 0°C was slowly added (ca. 1 h) a solution of D-(+)-10-camphorsulfonyl chloride **9** (10 mmol) in acetonitrile (20 ml). After one additional hour the mixture was hydrolysed with water (10 ml) and the obtained mixture was extracted with ethyl acetate (3×25 ml) and the organic layer was dried over Na_2SO_4.The solvents were removed under reduced pressure (15 torr), obtaining the pure title compound **10** in yields indicated in Scheme 1. Compound **10b** was already described by us and was characterised by comparison of its physical and spectroscopic data with those reported in the literature.[18] Spectroscopic, physical and analytical data follow.

4.2.1.1. (1S,4S)-N-*2-Methylpropyl-10-camphorsulfonamide* ***10a***. White solid, t_R 17.1, R_f 0.12 (hexane/ethyl acetate: 1/1); mp 78–79°C (ethyl acetate/hexane); $[\alpha]_D$ +1.85 [c = 1.4 (Me_2CO)]; ν (melted) 3397, 2950 (NH), 1723 (CO), 1394 cm^{-1} (SO_2); δ_H 0.92, 1.03 [3 and 3H, respectively, 2s, $C(CH_3)_2$], 1.4–2.45 [8H, m, $(CH_2)_2CHCH_2CO$, $CH(CH_3)_2$], 2.91, 3.39 (2H, 2d, J = 15.2, CH_2S), 2.95–3.15 (2H, m, CH_2N), 5.30 (1H, t, J = 5.4, NH); δ_C 19.4, 19.8, 19.9, 26.5 (2C), 27.0, 42.7, 42.8 (2C), 48.7, 49.1, 50.9, 59.15, 216.9; m/z 288 (M^++1, < 1%), 244 (14), 215 (61), 151 (26), 123 (31), 115 (23), 109 (64), 108 (14), 107 (27), 95 (12), 93 (26), 91 (13), 81 (66), 79 (24), 77 (12), 72 (37), 69 (13), 67 (49), 60 (29), 57 (20), 55 (34), 53 (22), 43 (49), 41 (100), 40 (13) (found: C, 58.45; H, 8.82; N, 4.90. $C_{14}H_{25}NO_3S$ requires: C, 58.50; H, 8.77; N, 4.87%).

4.2.2. Preparation of camphoroximes ***11***. *General procedure*[21]

To a solution of corresponding camphorsulfonamide **10** (8.4 mmol) in ethanol (50 ml) were added hydroxylammonium chloride (50.5 mmol, 3.5 g) and triethylamine (38.5 mmol, 4.7 ml). The resulting mixture was refluxed over 24 h. Then the solvent was removed under reduced pressure (15 torr) and the residue was suspended in water (10 ml). The aforementioned suspension was extracted with ethyl acetate (3×25 ml) and the organic layer was dried over Na_2SO_4. The solvents were removed under reduced pressure (15 torr) yielding a residue which was then purified by flash chromatography (silica gel, hexane/ethyl acetate) to afford the expected oxime as a single isomer. Yields are indicated in Scheme 1. Spectroscopic, physical and analytical data follow.

4.2.2.1. (1S,4S)-N-*(2-Methylpropyl)-2-hydroxyimino-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide* ***11a***. White solid, t_R (decompose), R_f 0.60 (hexane/ethyl acetate: 1/1); mp 113–115°C (ethyl acetate/hexane); $[\alpha]_D$ +7.25 [c = 1.50 (Me_2CO)]; ν (melted) 3423 (OH), 3311 (NH), 1609 (C=N), 1311 cm^{-1} (SO_2); δ_H 0.86, 0.97 [3 and 3H, respectively, 2s, $C(CH_3)_2$], 0.95 [6H, t, J = 4.2, $CH(CH_3)_2$], 1.25–2.65 [8H, m, $(CH_2)_2CHCH_2C{=}N$, $CH(CH_3)_2$], 2.80–2.95 (2H, m, $NHCH_2$), 3.01, 3.41 (1 and 1H, respectively, 2d, J = 15.2, CH_2S), 5.80 (1H, dd, J = 5.5, 2, NH); δ_C 14.1, 19.5, 20.0, 27.3, 28.75 (2C), 29.55 (2C), 30.05, 43.0, 50.9, 51.1, 52.8, 168.55; m/z 306 (M^++4, 1%), 134 (20), 109 (42), 108 (82), 107 (12), 94 (15), 93 (100), 91 (30), 82 (35), 81 (17) (found: C, 55.65; H, 8.40; N, 9.16; S, 10.47. $C_{14}H_{26}N_2O_3S$ requires: C, 55.60; H, 8.34; N, 9.26; S, 10.60%).

4.2.2.2. (1S,4S)-N-*Benzyl-2-hydroxyimino-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide* ***11b***. White solid, t_R (decompose), R_f 0.58 (hexane/ethyl acetate: 1/1); mp 129–131°C (ethyl acetate/hexane); $[\alpha]_D$ –7.25 [c = 1.37 ($CHCl_3$)]; ν (melted) 3424 (OH), 2947 (NH), 1609 (C=N), 1327 cm^{-1} (SO_2); δ_H 0.70, 0.89 (3 and 3H, respectively, 2s, 2×CH_3), 1.20–2.60 [7H, m, $(CH_2)_2CHCH_2C{=}N$], 2.95, 3.21 (1 and 1H, respectively, 2d, J = 15.0, CH_2S), 4.22, 4.34 (1 and 1H, respectively, 2d, J = 14.0, CH_2N), 6.4, 7.11 (1 and 1H, respectively, 2s, NH, OH), 7.10–7.40 (5H, m, Ph); δ_c 18.8, 19.45, 27.3, 29.85, 32.95, 42.95, 47.85, 50.7, 53.0, 53.9, 127.75, 128.35 (2C), 128.7 (2C), 138.1, 168.35; m/z 304 (M^+–NOH, < 1%), 153 (28), 149 (12), 135 (32), 134 (13), 127 (20), 109 (34), 108 (42), 106 (32), 105 (15), 93 (46), 91 (61), 83 (16), 82 (12), 79 (41), 78 (12), 77 (13), 67 (34), 65 (36), 55 (20), 53 (16), 51 (20), 48 (20), 44 (100), 42 (13), 41 (46) (found: C, 60.78; H, 7.14; N, 8.29; S, 9.48. $C_{17}H_{24}N_2O_3S$ requires: C, 60.69; H, 7.19; N, 8.33; S, 9.53%).

4.2.3. Preparation and isolation of ligands ***12*** *and* ***13***. *General procedure*

To a solution of corresponding camphoroxime **11** (4.5 mmol) in methanol (45 ml) at 0°C were added ammonium acetate (58.0 mmol, 4.5 g) and sodium cyanoborohydride (18.0 mmol, 1.15 g). Then, a solution of titanium trichloride (13.5 mmol, 12 ml, 15%) was slowly added (*ca.* 1 h) to the

above mixture and the resulting dark brown mixture was stirred overnight allowing the temperature to rise to 25°C.[29] Then, the resulting mixture was quenched by addition of a saturated $NaHCO_3$ solution (25 ml) and filtered through Celite. The colourless solution was extracted with ethyl acetate (3×25 ml) and the organic layer was dried over Na_2SO_4. The solvents were removed under reduced pressure (15 torr) yielding a residue which was dissolved in acetonitrile (40 ml). To the resulting mixture at 0°C was added triethylamine (18 mmol, 2.5 ml) and then the corresponding sulfonyl[22] or alkanoyl chloride (9 mmol) was slowly added during 1 h. After one additional hour a solution of saturated NH_4Cl solution (10 ml) was added and the resulting mixture was extracted with ethyl acetate (3×25 ml) and the organic layer was dried over Na_2SO_4. The solvents were removed under reduced pressure (15 torr), yielding a residue which was then purified by flash chromatography (silica gel, hexane/ethyl acetate) to afford the expected ligands **12a**,**b** and **13b**. The ligand **12c** was purified by crystallisation from a mixture of ethyl acetate and hexane. Yields are included in Table 1. Spectroscopic, physical and analytical data follow.

*4.2.3.1. (1*S*,2*R*,4*S*)*-N-*(2-Methylpropyl)-2-methylsulfonylamino-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide* ***12a***. Pale yellow syrup, t_R 22.2, R_f 0.30 (hexane/ethyl acetate: 1/1); $[\alpha]_D$ –17.1 [c = 1.60 ($CHCl_3$)]; ν (film) 3299, 2942 (NH), 1320 cm^{-1} (SO_2); δ_H 0.94, 0.97 [3 and 3H, respectively, 2s, $C(CH_3)$], 0.96, 0.98 [3 and 3H, respectively, 2s, $CH(CH_3)_2$], 1.25–2.15 [7H, m, $(CH_2)_2CHCH_2$], 2.30–2.45 (1H, m, $CHCH_3$), 2.90–2.95 (2H, m, $NHCH_2$), 3.00 (3H, s, SO_2CH_3), 3.13, 3.17 (2H, d, J = 3.6, CH_2S), 3.80–3.85 (1H, m, CHN), 4.86 (1H, t, J = 6.4, $NHCH_2$), 5.78 (1H, d, J = 4.2, CHN*H*); δ_C 18.95, 19.8, 19.9, 25.2, 28.0, 29.0, 38.2, 40.65, 43.1, 44.2, 50.4, 50.7, 54.85, 57.65, 68.1; m/z 325 (M^+–41, < 1%), 230 (65), 223 (22), 136 (16), 135 (100), 94 (11), 93 (38), 91 (16), 81 (12), 79 (41), 74 (12), 67 (27), 57 (12), 55 (19), 44 (12), 43 (33), 41 (47) (found: C, 47.54; H, 8.29; N, 7.34; S, 17.40. $C_{15}H_{30}N_2O_4S_2 \cdot 2/3H_2O$ requires: C, 47.59; H, 8.34; N, 7.40; S, 16.94%).

*4.2.3.2. (1*S*,2*R*,4*S*)*-N-*Benzyl-2-methylsulfonylamino-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide* ***12b***. Pale yellow syrup, t_R 26.1, R_f 0.38 (hexane/ethyl acetate: 1/1); $[\alpha]_D$ –34.3 [c = 2.02 ($CHCl_3$)]; ν (film) 3297, 2957 (NH), 3031 (CH=C), 1328 cm^{-1} (SO_2); δ_H 0.74, 0.92 [3 and 3H, respectively, 2s, $C(CH_3)_2$], 1.10–2.20 [7H, m, $(CH_2)_2CHCH_2$], 2.70, 3.22 (1 and 1H, respectively, 2d, J = 14.6, CH_2S), 2.96 (3H, s, SO_2CH_3), 3.55–3.65 (1H, m, CHN), 4.32 (2H, d, J = 6.1, CH_2N), 4.99 (1H, d, J = 4.9, CHN*H*), 5.19 (1H, t, J = 6.1, $NHCH_2$), 7.25–7.55 (5H, m, Ph); δ_C 20.15, 20.4, 27.05, 32.65, 39.25, 39.3, 44.6, 46.15, 47.25, 50.1, 52.5, 59.2, 128.05, 128.25 (2C), 128.9 (2C), 136.9; m/z 281 (M^+–119, < 1%), 139 (12), 111 (31), 101 (14), 95 (14) (found: C, 52.28; H, 6.93; N, 6.76; S, 14.99. $C_{18}H_{28}N_2O_4S_2 \cdot 1/3H_2O$ requires: C, 53.18; H, 7.11; N, 6.89; S, 15.77%).

*4.2.3.3. (1*S*,2*R*,4*S*)*-N-*Benzyl-2-pivaloylamino-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide* ***12c***. White solid, t_R 23.7, R_f 0.5 (hexane/ethyl acetate: 1/1); mp 143–146°C (ethyl acetate/hexane); $[\alpha]_D$ –32.8 [c = 1.13 ($CHCl_3$)]; ν (melted) 3433, 2966 (NH), 2656, 2333, 1659 (C=O), 1322 cm^{-1} (SO_2); δ_H 0.86, 0.92 [3 and 3H, respectively, 2s, $C(CH_3)_2$], 1.16 [9H, s, $C(CH_3)_3$], 1.20–2.10 [7H, m, $(CH_2)_2CHCH_2$], 2.94, 3.16 (1 and 1H, respectively, 2d, J = 14.3, CH_2S), 4.00–4.20 (1H, m, CHN), 4.30–4.35 (2H, m, CH_2N), 5.65 (1H, t, J = 5.8, $NHCH_2$), 5.78 (1H, d, J = 7.9, CHN*H*), 7.10–7.40 (5H, m, Ph); δ_C 20.15, 20.6, 27.0, 27.5(3C), 31.5, 38.7, 39.7, 43.3, 46.6, 49.25, 49.5, 52.95, 55.05, 127.65, 127.85 (2C), 128.6 (2C), 137.6, 178.1; m/z 343 (M^+–63, < 1%), 237 (12), 236 (26), 157 (72), 156 (59), 141 (16), 135 (38), 109 (13), 108 (10), 107 (18), 106 (32), 102 (37), 93 (18), 91 (24), 79 (20), 67 (12), 57 (100) (found: C, 63.23; H, 8.42; N, 6.77; S, 7.42. $C_{22}H_{34}N_2O_3S \cdot 2/3H_2O$ requires: C, 63.13; H, 8.51; N, 6.70; S, 7.66%.

*4.2.3.4. (1*S*,2*S*,4*S*)*-N-*Benzyl-2-methylsulfonylamino-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide* ***13a***. Pale yellow syrup, t_R 21.8, R_f 0.31 (hexane/ethyl acetate: 1/1); $[\alpha]_D$ +26.2 [c = 1.61 ($CHCl_3$)]; ν (film) 3297, 2957 (NH), 3031 (CH=C), 1328 cm^{-1} (SO_2); δ_H 0.81, 0.82 [3 and 3H, respectively, $C(CH_3)_2$], 0.75–2.4 [7H, m, $(CH_2)_2CHCH_2$], 2.92 (2H, s, CH_2S), 2.97 (3H, s, SO_2CH_3), 3.70–3.75 (1H, m, CHN), 4.30 (2H, s, CH_2N), 5.40–5.45 (1H, m, N*H*CH_2), 5.77 (1H, d, *J* = 4.3, CHN*H*), 7.25–7.45 (5H, m, Ph); δ_C 18.7, 19.7, 25.1, 28.1, 38.15, 40.65, 44.0, 47.2, 50.35 (2C), 56.25, 57.45, 128.0, 128.3 (2C), 128.8 (2C), 136.85; *m/z* 305 (M^+–95, <1%), 91 (100), 79 (13), 77 (10), 65 (14), 64 (12), 44 (69), 43 (22), 42 (11), 41 (21) (found: C, 52.61; H, 6.95; N, 6.51; S, 15.41. $C_{18}H_{28}N_2O_4S_2 \cdot 3/5H_2O$ requires: C, 52.56; H, 7.15; N, 6.81; S, 15.59%).

4.2.4. Preparation and isolation of ligands ***12***. *General procedure*

To a solution of (1*S*,2*R*,4*S*)-methylsulfonyl-10,2-camphorsultam **14** (20 mmol, 4.23 g) in THF at –78°C was added butyllithium (25.6 mmol, 16 ml, 1.6 M), allowing the temperature to rise to 0°C during 30 min. Then, the resulting solution was cooled down to –78°C and the corresponding sulfonyl chloride (26 mmol) was slowly added (ca. 10 min), allowing the temperature to rise to 25°C overnight. The resulting mixture was hydrolysed by successive addition of methanol (2 ml) and saturated NH_4Cl solution (20 ml), extracted with ethyl acetate (3×50 ml) and the organic layer was dried over Na_2SO_4. The solvents were removed under reduced pressure (15 torr) yielding a residue. In the case of compound **15a**, it was purified by crystallisation from a mixture of chloroform and hexane. Yield is included in Scheme 2. Spectroscopic, physical and analytical data follow for (1*S*,2*R*,4*S*)-*N*-methylsulfonyl-10,2-camphorsultam **15a**: white solid, t_R (descompose), R_f 0.30 (hexane/ethyl acetate: 1/1); mp 162–164°C (chloroform/hexane); $[\alpha]_D$ –74.45 [c = 1.6 ($CHCl_3$)]; ν (melted) 1328 cm^{-1} (SO_2); δ_H 0.97, 1.23 (3 and 3H, respectively, 2s, CH_3), 1.30–2.00 [7H, m, $(CH_2)_2CHCH_2$], 3.19 (3H, s, SO_2CH_3), 3.39, 3.46 (1 and 1H, respectively, 2d, *J* = 13.7, CH_2S), 3.65–3.70 (1H, m, CHN); δ_C 19.8, 20.4, 26.5, 32.8, 37.45, 39.1, 44.65, 48.0, 49.5, 52.45, 66.5; *m/z* 292 (M^+–1, <1%), 158 (12), 157 (100), 154 (11), 141 (22), 135 (21), 134 (19), 109 (31), 108 (51), 107 (17), 93 (26), 67 (19), 55 (16), 43 (15), 41 (34) (found: C, 43.67; H, 6.41; N, 4.66; S, 21.00. $C_{11}H_{19}NO_4S_2 \cdot 1/2H_2O$ requires: C, 43.69; H, 6.67; N, 4.63; S, 21.20%). The aforementioned residue was dissolved in THF and to the resulting solution at –78°C was added a THF solution (60 ml) which contained the corresponding lithium alkylamide prepared from alkylamine (120 mmol) and butyllithium (80 mmol, 50 ml, 1.6 M) at –78°C. The resulting mixture was stirred overnight, allowing temperature to rise to 25°C. The reaction was hydrolysed with water (40 ml) and the resulting mixture was extracted with ethyl acetate (3×50 ml) and the organic layer was dried over Na_2SO_4. The solvents were removed under reduced pressure (15 torr) yielding a residue which was then purified by flash chromatography (silica gel, hexane/ethyl acetate) to afford the expected ligands **12b**,**d**–**h**. Ligand **12b** has been described above. Yields are included in Table 2. Spectroscopic, physical and analytical data follow.

*4.2.4.1. (1*S*,2*R*,4*S*)*-N-*Benzyl-2-trifluoromethylsulfonylamino-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide* ***12d***. Yellow syrup, t_R 20.4, R_f 0.70 (hexane/ethyl acetate: 1/1); $[\alpha]_D$ –25.6 [c = 1.04 ($CHCl_3$)]; ν (film) 3342, 2949 (NH), 1384 (SO_2), 1187 cm^{-1} (CF); δ_H 0.68, 0.83 (3 and 3H, respectively, 2s, 2×CH_3), 1.20–2.10 [7H, m, $(CH_2)_2CHCH_2$], 2.51, 2.56 (1 and, 1H, respectively, 2d, *J* = 6.7, CH_2S), 3.85–3.95 (1H, m, CHN), 4.37 (2H, s, CH_2N), 5.68 (2H, s, 2×NH), 7.25–7.40 (5H, m, Ph); δ_C 19.55, 20.0, 26.85, 32.75, 38.15, 44.3, 47.05, 49.45, 50.3, 52.95, 60.05, 121.45, 127.9 (2C), 128.25 (2C), 128.85, 137.2; *m/z* 390 (M^+–64, <1%), 135 (16), 108 (22), 107

(48), 106 (100), 93 (18), 91 (39), 79 (15), 67 (10), 43 (12), 41 (16) (found: C, 47.45; H, 5.42; N, 6.99; S, 13.81. $C_{18}H_{25}F_3N_2O_4S_2$ requires: C, 47.56; H, 5.54; N, 6.16; S, 14.11%).

*4.2.4.2. (1*S*,2*R*,4*S*)*-N-*Benzyl-2-[(4-methylphenyl)sulfonylamino]-7,7-dimethylbicyclo[2.2.1]-hept-1-ylmethanesulfonamide* ***12e***. Yellow solid, t_R 27.9, R_f 0.65 (hexane/ethyl acetate: 1/1); mp 64–66°C (ethyl acetate/hexane); $[\alpha]_D$ –30.1 [c = 1.29 ($CHCl_3$)]; ν (melted) 3288, 2952 (NH), 1328 cm^{-1} (SO_2); δ_H 0.68, 0.92 [3 and 3H, respectively, 2s, $CC(CH_3)_2$], 1.00–2.20 [7H, m, $(CH_2)_2CHCH_2$], 2.39 (3H, s, CH_3CCH), 2.65, 3.24 (1 and 1H, respectively, 2d, J = 14.6, CH_2S), 2.69–3.20 (1H, m, CHN), 2.96, 4.28 (2H, d, J = 6.1, CH_2N), 5.50–5.70 (2H, m, 2×NH), 7.29, 7.74 (2 and 2H, respectively, 2d, J = 7.9, SC_6H_4), 7.25–7.40 (5H, m, Ph); δ_C 19.85, 20.4, 21.45, 26.9, 32.3, 36.0, 44.4, 47.05, 49.45, 50.2, 52.55, 59.1, 127.55 (2C), 127.75, 128.2 (2C), 128.65 (2C), 129.6 (2C), 135.75, 137.0, 143.55; *m/z* 452 (M^+–23, < 1%), 126 (15), 113 (75), 98 (14), 85 (19), 84 (14), 71 (24), 70 (42), 56 (22), 55 (43), 44 (95), 43 (100), 42 (20), 41 (43), 40 (83) (found: C, 57.84; H, 6.74; N, 5.99; S, 13.75. $C_{24}H_{32}N_2O_4S_2 \cdot 1/3H_2O$ requires: C, 57.87; H, 6.77; N, 6.13; S, 14.04%).

*4.2.4.3. (1*S*,2*R*,4*S*)*-N-*(4-Methoxyphenyl)methyl-2-methylsulfonylamino-7,7-dimethylbicyclo[2.2.1]-hept-1-ylmethanesulfonamide* ***12f***. White solid, t_R 23.3, R_f 0.30 (hexane/ethyl acetate: 1/1); mp 156–158°C (ethyl acetate/hexane); $[\alpha]_D$ –32.7 [c = 1.33 ($CHCl_3$)]; ν (melted) 3294, 2950 (NH), 1321 (SO_2), 1149 cm^{-1} (CO); δ_H 0.74, 0.92 [3 and 3H, respectively, s, $C(CH_3)_2$], 1.10–2.20 [7H, m, $(CH_2)_2CHCH_2$], 2.67, 3.15 (1 and 1H, respectively, 2d, J = 14.5, CH_2S), 2.95 (3H, s, SO_2CH_3), 3.55–3.60 (1H, m, CHN), 3.79 (3H, s, OCH_3) 4.24 (2H, d, J = 3.7, CH_2N), 5.11, 5.33 (1 and 1H, respectively, 2×NH), 6.89, 7.29 (2 and 2H, respectively, 2d, J = 8.4, OC_6H_4); δ_C 20.1, 20.35, 27.05, 32.6, 39.1, 39.15, 44.55, 46.7, 49.45, 50.05, 52.35, 55.25, 59.1, 114.15 (2C), 128.9, 129.65 (2C), 159.35; *m/z* 430 (M^+, < 1%), 157 (31), 156 (25), 137 (47), 136 (100), 135 (32), 121 (32), 109 (18), 108 (14), 107 (14), 106 (14), 93 (16), 79 (17), 67 (14), 43 (12), 41 (17) (found: C, 53.12; H, 7.07; N, 6.06; S, 14.09. $C_{19}H_{30}N_2O_5S_2 \cdot 1/3AcOEt$ requires: C, 53.10; H, 7.16; N, 6.09; S, 13.99%).

4.2.4.4. (1S,2R,4S)-N-*(2-Phenylethyl)-2-methylsulfonylamino-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide* ***12g***. Pale yellow syrup, t_R 29.0, R_f 0.31 (hexane/ethyl acetate: 1/1); $[\alpha]_D$ –30.4 [c = 1.43 ($CHCl_3$)]; ν (film) 3298, 2949 (NH), 1320 cm^{-1} (SO_2); δ_H 0.80, 0.97 [3 and 3H, respectively, 2s, $C(CH_3)_2$], 1.55–2.40 [7H, m, $(CH_2)_2CHCH_2$], 2.73, 3.23 (1 and 1H, respectively, 2d, J = 14.6, CH_2S), 2.86 (2H, t, J = 17.3, CH_2Ph), 2.90 (3H, s, SO_2CH_3), 3.30–3.45 (2H, m, NCH_2), 3.50–3.60 (1H, m, CHN), 5.02 (1H, t, J = 6.1, $NHCH_2$), 5.19 (1H, d, J = 4.9, CHN*H*), 7.15–7.35 (5H, m, Ph); δ_C 20.25, 20.5, 27.05, 32.55, 36.55, 39.25, 39.45, 44.45, 44.55, 44.65, 49.55, 51.55, 59.2, 128.8 (2C), 128.85, 128.95 (2C), 137.95; *m/z* 326 (M^+–88, < 1%), 323 (22), 259 (43), 230 (66), 136 (15), 135 (100), 119 (13), 109 (49), 108 (23), 107 (33), 230 (60), 136 (15), 135 (100), 105 (18), 93 (40), 91 (50), 81 (14), 79 (42), 77(14), 67 (29), 65 (16), 55 (19), 44 (23), 43 (27), 41 (40) (found: C, 53.88; H, 6.93; N, 6.66; S, 15.99. $C_{18}H_{28}N_2O_4S_2$ requires: C, 53.97; H, 7.05; N, 6.99; S, 16.01%).

*4.2.4.5. (1*S*,2*R*,4*S*)*-N-*(Naphth-1-ylmethyl)-2-methylsulfonylamino-7,7-dimethylbicyclo[2.2.1]-hept-1-ylmethanesulfonamide* ***12h***. Yellow solid, t_R 15.7, R_f 0.42 (hexane/ethyl acetate: 1/1); mp 117–119°C (ethyl acetate/hexane); $[\alpha]_D$ –15.3 [c = 1.35 ($CHCl_3$)]; ν (melted) 3299 (NH), 3046 (CH=C), 1318 cm^{-1} (SO_2); δ_H 0.60, 0.84 [3 and 3H, respectively, 2s, $C(CH_3)_2$], 1.60–1.90 [7H, m, $(CH_2)_2CHCH_2$], 2.64, 3.11 (1 and 1H, respectively, 2d, J = 14.6, CH_2S), 2.95 (3H, s, SO_2CH_3), 3.45–3.60 (1H, m, CHN), 4.78 (2H, d, J = 2.4, CH_2Ph), 4.83, 5.02 (1 and 1H, respectively, 2s, 2×NH), 7.40–7.65 (7H, m, ArH); δ_C 21.1, 20.3, 27.05, 32.65, 39.25, 40.75, 44.6, 45.2, 49.45, 50.05,

52.25, 59.2, 125.35, 125.45, 126.15, 126.2, 126.85, 127.35, 128.85, 128.9, 129.1, 129.15; *m/z* 321 (M^+–129, <1%), 235 (22), 156 (16), 155 (59), 154 (100), 141 (20), 135 (14), 129 (22), 128 (19), 127 (23), 115 (12), 109 (11), 108 (13), 107 (32), 106 (52), 93 (11), 91 (18), 79 (16), 77 (17), 44 (26), 41 (13) (found: C, 58.69; H, 6.62; N, 5.34; S, 14.44. $C_{22}H_{30}N_2O_4S_2$ requires: C, 58.64; H, 6.71; N, 6.22; S, 14.23%).

*4.3. Enantioselective addition of dialkylzinc to aldehydes in the presence of ligands **12** or **13** and titanium tetraisopropoxide. General procedure*

To a solution of corresponding ligand **12** or **13** (1 mmol) in toluene (5 ml) under nitrogen atmosphere was added the corresponding solution of dialkylzinc reagent (9 mmol, 4.5 ml, ca. 2 M) at –20°C. After 10 min, titanium tetraisopropoxide (6.5 mmol, 2 ml) was added to the above solution and after an additional 10 min the corresponding aldehyde (5 mmol) was successively added. The resulting mixture was stirred at the same temperature for 2 h. 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 solvents were removed under reduced pressure (15 torr) and the residue was distilled bulb to bulb to yield the expected alcohols. Yields and enantiomeric ratios (e.r.) are included in Tables 3–6. Compounds **16**–**20** were already described by us and were characterised by comparison of their physical and spectroscopic data with those reported in the literature.[18] Spectroscopic and physical data, as well as literature references, follow.

*4.3.1. 3-Nonanol **20**[18]*

t_R (*S*-TFA-**20**) 54.44, t_R (*R*-TFA-**20**) 54.88 (A conditions); $[\alpha]_D$ = +9.2 [c = 7.06, $CHCl_3$; e.r. (*R*/*S*) 98.0:2.0].

*4.3.2. 1-Phenylpentan-3-ol **21**[37]*

Colourless oil, bp 140–145°C (0.1 torr), t_R 7.8; t_R (*R*–TFA-**21**) 117.92, t_R (*S*-TFA-**21**) 119.61 (D conditions); R_f 0.75 (hexane/ethyl acetate: 1/1); $[\alpha]_D$ –21.2 [c = 7.72 (EtOH), e.r. (*R*/*S*) 97.0:3.0]; ν (film) 3404 (OH), 1629 (CH=C) cm^{-1}; δ_H 0.93 (3H, q, J = 5.8, CH_3), 1.40–1.60 (2H, m, CH_2CH_3), 1.65–1.89 (2H, m, CH_2CH_2Ph), 2.60–2.75 (2H, m, CH_2Ph), 2.75–2.80 (1H, m, CHO), 3.53 (1H, s, OH), 7.15–7.30 (5H, m, Ph); δ_C 9.75, 30.15, 32.0, 34.15, 72.5, 125.65 (2C), 128.3 (3C), 142.15; *m/z* 165 (M^++1, <1%), 164 (M^+, 3), 146 (29), 117 (54), 104 (27), 92 (34), 91 (100), 78 (16), 65 (16), 59 (17), 44 (22), 43 (15), 41 (12).

*4.3.3. 1-Cyclohexy-1-propanol **22**[37]*

Colourless oil, bp 105–110°C (0.1 torr), t_R 5.1; t_R (*S*-TFA-**22**) 37.20, t_R (*R*-TFA-**22**) 37.50 (B conditions); R_f 090 (hexane/ethyl acetate: 1/1); $[\alpha]_D$ +7.7 [c = 1.63 ($CHCl_3$); e.r. (*R*/*S*) 96.0:4.0]; ν (film) 3369 cm^{-1} (OH); δ_H 0.95 (3H, t, J = 7.3, CH_3), 1.00–1.85 (13H, m, 6×CH_2, OH), 3.20–3.35 (1H, m, CHO); δ_C 10.15, 26.15, 26.35, 26.5, 26.75, 27.7, 29.25, 43.1, 77.55; *m/z* 141 (M^+–1, <1%), 113 (37), 95 (85), 83 (11), 82 (26), 81 (14), 69 (11), 67 (43), 59 (100), 58 (47), 57 (15), 56 (13), 55 (51), 54 (11), 43 (25), 41 (66).

*4.3.4. (E)-4-Hexen-3-ol **23**[37]*

Colourless oil, bp 30°C (760 torr), t_R 2.0; t_R (*R*-**23**) 12.82, t_R (*S*-**23**) 13.13 (C conditions); R_f 0.59 (hexane/ethyl acetate: 1/1); $[\alpha]_D$ +0.15 [c = 0.45 ($CHCl_3$); e.r. (*R*/*S*) 57.0:43.0]; ν (film) 3403

(OH), 3034, 1663, 1638 cm^{-1} (HC=C); δ_H 0.83 (3H, t, $J=7.3$ CH_2CH_3), 1.35–1.55 (2H, m, CH_2CH_3), 1.60–1.65 (3H, m, CH_3CH), 3.85–3.95 (1H, m, $CHCH_2$), 5.35–5.55 (1H, m, CHCHCH), 5.55–5.65 (1H, m, $CHCH_3$); δ_C 9.75, 17.65, 25.55, 30.1, 126.9, 134.0; *m/z* 100 (M^+, <1%), 92 (45), 91 (79), 71 (26), 65 (12), 45 (21), 44 (45), 43 (100), 41 (19).

*4.3.5. (*E*)-1-Phenyl-1-penten-3-ol* ***24***[37]

Colourless oil, bp 140–145°C (0.1 torr), t_R 8.49; t_R (*R*-H_2-TFA-**24**≅*R*-TFA-**21**) 117.92, t_R (*S*-H_2-TFA-**24**≅*S*-TFA-**21**) 119.61 (D conditions); R_f 0.73 (hexane/ethyl acetate: 1/1); $[\alpha]_D$ +0.75 [c=2.14 ($CHCl_3$); e.r. (*R*/*S*) 56.0/44.0]; ν (film) 3381 (OH), 3090, 1590 cm^{-1} (CH=C); δ_H 0.94 (3H, t, $J=7.4$, CH_3), 1.60–1.70 (2H, m, CH_2), 2.28 (1H, s, OH), 4.15–4.30 (1H, m, CH_2O), 6.15–6.25 (1H, m, C*H*Ph), 6.25–6.55 (1H, m, C*H*CHO), 7.20–7.40 (5H, m, Ph); δ_C 9.65, 30.1, 74.25, 126.35 (2C), 127.45, 128.45 (2C), 130.25, 132.15, 136.65; *m/z* 163 (M^++1, 2%), 162 (M^+, 21), 144 (39), 143 (12), 134 (13), 133 (81), 131 (14), 129 (100), 128 (56), 127 (16), 115 (59), 92 (16), 91 (58), 79 (20), 78 (25), 77 (50), 71 (15), 65 (20).

4.3.6. 1-Phenyl-1-pentin-3-ol ***25***[37]

Colourless oil, bp 145–150°C (0.1 torr), t_R 8.28; t_R (*R*-H_2-TFA-**25**≅*R*-TFA-**21**) 117.92, t_R (*S*-H_2-TFA-**25**≅*S*-TFA-**21**) 119.61 (D conditions); R_f 0.69 (hexane/ethyl acetate: 1/1); $[\alpha]_D$ +7.8 [c=2.12 (Et_2O); e.r. (*R*/*S*) 69.0:31.0]; ν (film) 3374 (OH), 2192 (C≡C), 1595 cm^{-1} (Ph); δ_H 1.05 (3H, t, $J=7.3$, CH_3), 1.70–1.90 (2H, m, CH_2), 2.73 (1H, s, OH), 4.54 (1H, t, $J=6.4$, CHO), 7.25–7.45 (5H, m, Ph); δ_C 9.4, 30.85, 64.0, 84.75, 89.95, 128.15 (2C), 128.2, 131.55 (3C); *m/z* 161 (M^++1, <1%), 132 (16), 131 (100), 103 (33), 102 (14), 77 (34), 51 (20), 44 (33), 43 (14).

Acknowledgements

This work was financially supported by the DGICYT (Project PB97-0133) from the Spanish Ministerio de Educación y Cultura and Generalitat Valenciana (Project GVDOC99-2-4).

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