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Synthesis of new C_2-symmetrical bis(hydroxycamphorsulfonamide) ligands and their application in the enantioselective addition of dialkylzinc reagents to aldehydes and ketones

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This paper is warmly dedicated to Professor Dr. Gerard van Koten on the occasion of his 60th birthday

Abstract—The preparation of several C_2-symmetric disulfonamides derived from chiral camphorsulfonyl chloride and different diamines (with or without stereogenic elements) is described. Their use in the titanium tetraisopropoxide-promoted enantioselective addition of dialkylzinc reagents to aldehydes has been tested, the best enantiomeric excess being up to 76%. Moreover, the unusual addition of dialkylzinc reagents to ketones can also be achieved with excellent enantioselectivity (up to 92% e.e.) using this type of ligand. When using *para*-substituted phenones as electrophiles, the enantiomeric excess of the resulting *tert*-alcohol is independent of the electronic properties of the group attached to the aromatic ring of the phenone. In the case of using more hindered ketones the enantioselectivity is lower, so indicating a steric influence in the reaction.

1. Intoduction

The invention and development of new methods for the synthesis of complex molecules of both natural and unnatural origin remains an enduring challenge in organic chemistry. Over the past decades one of the major efforts in this arena has been directed towards the controlled enantioselective construction of open chain systems with different stereogenic centers or elements.[1] Among methods for the generation of different stereogenic elements of a molecule, the synthesis of chiral building blocks containing a quaternary stereogenic carbon center[2] is a considerable challenge within organic synthesis, mainly as a result of steric factors. Biocatalytic approaches to the synthesis of such chiral building blocks are limited and, for example, the kinetic resolution of carboxylic esters containing fully substituted stereogenic carbon centers with proteases and carboxyl estereases is generally impeded by steric repulsion, being feasible only in special cases.[3] Heteroatom-substituted quaternary carbon stereocenters may be obtained by different methods such as enantioselective epoxidation,[4] dihydroxylation,[5] desymmetrization of *meso*-compounds,[6] bacterial hydrolysis,[7] as well as the use of α-functionalised configurationally stable[8] organolithium compounds.[9] The construction of quaternary stereogenic centers that allows the connection of two simple synthons by formation of one or more carbon–carbon bonds is strategically the most desirable option, since this generally maximises the overall efficiency of the reaction sequence required for the construction of the molecular framework. In addition, the enantioselective 1,2-addition of organometallic reagents to carbonylic derivatives is probably the most straightforward and useful method for achieving this goal.[10] Among non-stabilised organometallic compounds,[11,12] dialkylzinc reagents[13] are ideal alkyl nucleophile synthons as it is possible to prepare many different functionalised organometallic reagents due to their low reactivity. At the same time, this is also a drawback, since they do not react with simple carbonyl compounds. This has been turned into an advantage by the development of several promoters to allow different types of addition processes. Thus, a plethora of chiral

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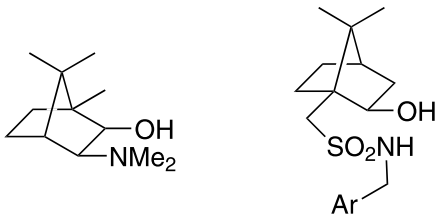


1 **2a**: Ar = Phenyl
2b: Ar = 1-Naphthyl

Figure 1. Chiral promoters for the addition of dialkylzinc reagents to ketones.

ligands has been introduced to carry out the enantioselective addition to aldehydes.[14] However, dialkylzinc reagents do not add to ketones, even at high temperatures, yielding only products arising from the reduction of ketones.[15] The lack of reactivity in the addition of dialkylzinc reagents to ketones has been used in the chemo- and enantioselective addition to keto-aldehyde derivatives promoted by α,β-amino alcohols.[16] Only very recently, the enantioselective addition of diphenylzinc to phenones using the amino alcohol **1** (Fig. 1) as a ligand has been reported.[17] In addition, simultaneously and independently we introduced hydroxycamphorsulfonamide derivatives **2**[18] as chiral ligands for the enantioselective addition of dialkylzinc reagents to ketones[19] in the presence of titanium tetraisopropoxide.[20] The enantioselective addition of diethylzinc to acetophenone under similar conditions using other common chiral ligands such as TADDol, binaphthol, 1,2-bistriflamidocyclohexane, as well as 1,2-hydroxysulfonamide derivatives failed.[19a] Therefore, the study of this type of addition using any structure derived from **2** is of great interest. In the particular case of the enantioselective addition of dialkylzinc reagents to aldehydes promoted by chiral amino alcohols, a general mechanism, involving a dimetallic aggregate as the catalytic species, has been widely accepted.[21] In the case of the related addition using titanium tetraalkoxides, neither the catalytic cycle nor the catalytic species is clearly defined. There are two possible structures for the catalyst, both being dimetallics (see Fig. 2): (a) An aggregate with two titanium atoms, one of them bearing the chiral ligand and the other bearing the alkyl group,[22] in this case the catalytic species seems to be a pentacoordinate positively charged titanium center and a octahedral hexacoordinate negatively charged titanium center;[23] and (b) an aggregate with a titanium atom bearing the chiral ligand and a zinc atom bearing

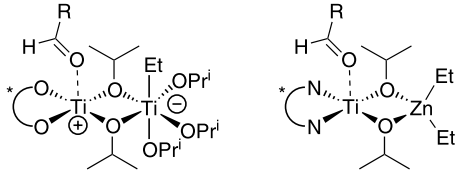


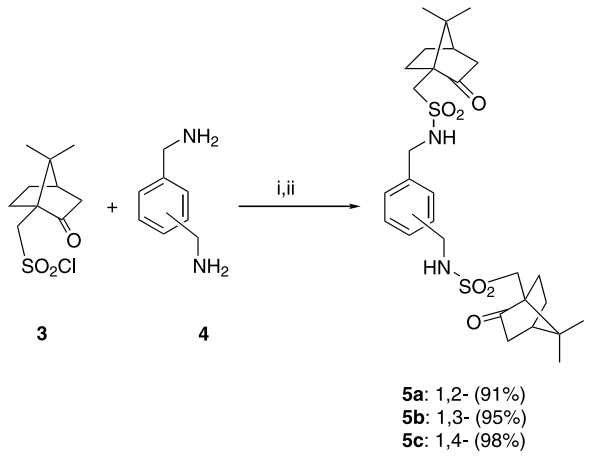
Figure 2. Postulated dimetallic catalytic species in the enantioselective addition of diethylzinc to aldehydes in the presence of titanium tetraisopropoxide.

two alkyl moieties.[24] In both cases, the two metal atoms are bonded by bridging-alkoxides. For ketones,[19a] we assumed a catalytic cycle and catalytic species similar to those reported for aldehydes (dititanium species). Since the non-linear effect was not observed when an excess of titanium isopropoxide was used, and the enantioselectivity was independent of chemical yield (no autoinduction effect was detected), as well as the fact that the enantioselectivity found when methyltitanium triisopropoxide was used as the source of the nucleophile was zero. This fact indicates that the uncatalysed reaction is very fast and the role of the dialkylzinc reagent is to transfer the alkyl moiety to the titanium center, thereby keeping its concentration very low.[19a] All these facts were previously outlined for the nucleophilic alkylation of aldehydes.[22] A similar synergistic effect occurring in the proximal metal centers has already been described for different reactions.[25] Usually, one metal center acts to activate the carbonyl derivative (acidic center) while the other metal center activates the nucleophile for attack.[26] However, the possibility of forming a double coordination complex between the carbonyl compound and both acidic metal centers cannot be ruled out.[25f,27] With these factors in mind, we report herein the synthesis of different C_2-symmetrical ligands[28] bearing two camphorsulfonamide[29] or hydroxycamphorsulfonamide moieties[30] connected by different diamines with or without stereogenic elements, and their use in the enantioselective addition of dialkylzinc reagents to aldehydes and, more interestingly and unusually, to ketones.[31] Where we hoped that the chiral ligand would force the binuclear metal complex into a more rigid and determinate form, with both metallic centers in closer proximity, thus improving the enantioselectivity of the reaction.

2. Results and discussion

2.1. Synthesis of chiral disulfonamide ligands

Disulfonamide ligands **5** were easily prepared from the corresponding commercially available (+)-10-camphorsulfonyl chloride **3** by reaction with the corresponding xylylenediamine (or xylylenediammonium dichloride[32]) **4** in the presence of triethylamine and a substoichiometric amount of 4-(dimethylamino)pyridine (DMPA) at 0°C giving, after basic work-up, the expected disulfonamides **5** in excellent yields (Scheme 1). In a similar manner (Fig. 3), the reaction of (+)-2,2′-diamino-1,1′-binaphthyl with the corresponding enantiomer of camphorsulfonyl chloride (**3** or *ent*-**3**) or methanesulfonyl chloride gave the corresponding disulfonamides **6**, **7** and **8**,[33] respectively, in low yield (25, 29 and 32%, respectively). The subsequent reduction of diketones **5**–**7** using an excess of diisobutylaluminium hydride gave the expected tetradentate hydroxycamphorsulfonamide ligands as a mixture of all possible *exo*/*endo* isomers. In all cases, the main product was the corresponding *exo*/*exo* diastereoisomer **9**–**11**, which was easily isolated by flash column chromatography (see Fig. 4 and Table 1). In some cases, the second most abundant diastereoisomer *exo*/*endo* could also be isolated (**12** and



Scheme 1. *Reagents and conditions*: i, DMAP (0.2 equiv.), MeCN, 0°C, 24 h. ii, NaOH (3 M); then 1 M HCl.

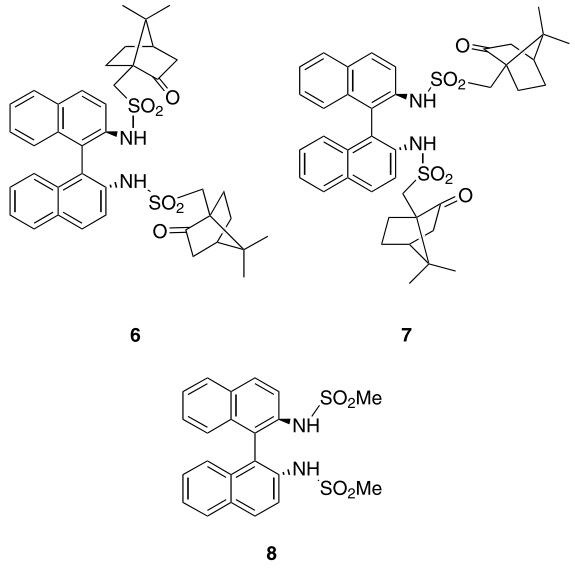


Figure 3. Chiral ligands derived from (+)-2,2′-diamino-1,1′-binaphthyl.

13). However, all attempts to purify the corresponding minor *endo*/*endo* diastereoisomer failed.

2.2. Enantioselective addition of diethylzinc to aldehydes

Once ligands **5** and **9**–**13** were prepared, they were tested in the standard enantioselective addition of diethylzinc to benzaldehyde, in the presence of titanium tetraisopropoxide and using 10 mol% of the corresponding chiral ligand (see Scheme 2 and Table 2, entries 1–15). The reaction using diketones **5** as chiral ligands gave in all cases modest enantioselectivity under the conditions assayed, irrespective of the relative position of the camphorsulfonyl moiety in the benzene ring (Table 2, entries 1–3). When the reaction was performed using the binaphthylamine derivative **6** the enantiomeric excess decreased, so near-racemic secondary alcohol **14a** was isolated (Table 2, entry 4). In order to establish whether this low enantiomeric excess was a consequence of a mismatched pair of chiral elements,[34] the same reaction was performed with the diastereomeric ketone **7**, again obtaining a racemic mixture of the secondary alcohol **14a** (Table 2, entry 5). Moreover, when the reaction was carried out using ligand **8**, where the only chiral element is due to the binaphthyl moiety, a racemic mixture was also obtained (Table 2, entry 6). These results may be interpreted considering that the steric hindrance in the catalytic specie is quite different using xylyl derivatives **5** or binaphthyl derivatives **6**–**8**. In the case of using bis(hydroxycamphorsulfonamide) ligands **9**, the obtained results depend on the relative position of the hydroxycamphorsulfonamide moieties: While the enantioselectivity for 1,3-[35] (**9b**) and 1,4- (**9c**) derivatives was the same, the enantiomeric ratio for the 1,2-isomer (**9a**) decreased. This may be attributed to steric interaction between both metals attached to each hydroxycamphorsulfonamide moiety (Table 2, entries 7–9). Surprisingly, when the reaction was performed using the chiral ligand **12**, which contains a hydroxy group in the *endo* position and the relative position of both hydroxycamphorsulfonamide moieties is *meta*, the enantiomeric

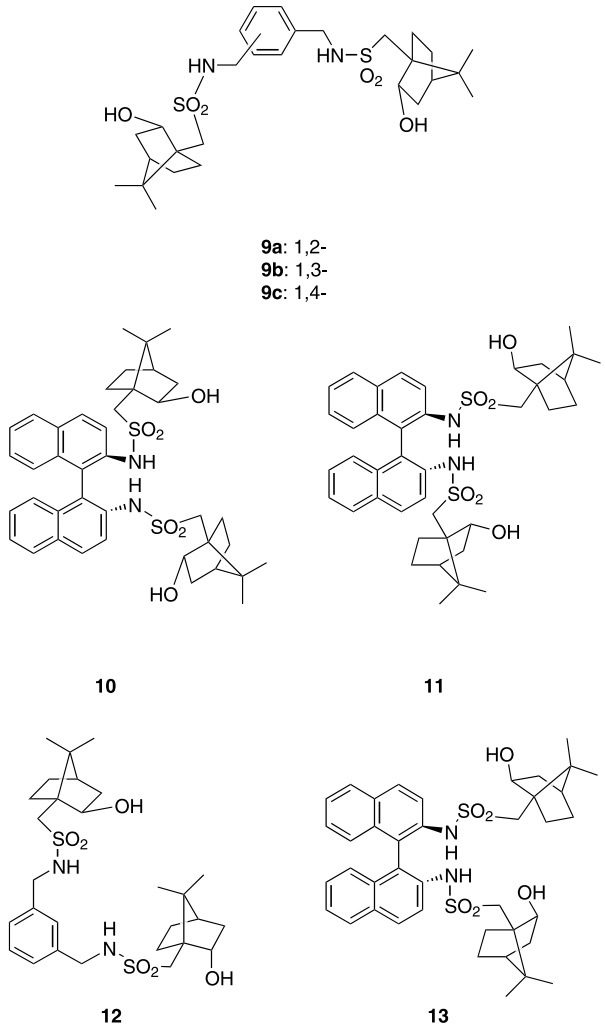
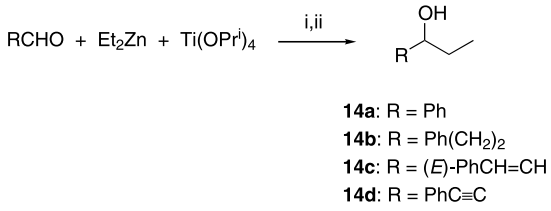


Figure 4. Chiral tetradentate ligands.

Table 1. Synthesis of tetradentate ligands **9**–**13** by reduction

Entry	Starting diketone	Diastereomeric ratio[a]			Ligand	
		exo/*exo*	*exo*/*endo*	*endo*/*endo*	No.	Yield (%)[b]
1	**5a**	90	7	3	**9a**	76[c]
2	**5b**	95	4	1	**9b**	72
3					**12**	5
4	**5c**	85	10	5	**9c**	58
5	**6**	85	10	5	**10**	50
6	**7**	95	4	1	**11**	56
7					**13**	4

[a] Determined by ^{1}H NMR (300 MHz) of the crude mixture.
[b] Isolated yield after flash column chromatography based on starting diketone.
[c] Isolated yield after recrystallization from $CHCl_3$.



Scheme 2. *Reagents and conditions*: i, chiral ligand **9**–**13** (10%), PhMe. ii, MeOH; then saturated NH_4Cl.

ratio obtained was the same as for ligand **9c** (both hydroxy groups are *exo*). Previously, we reported that the relative position of the hydroxy group is crucial in order to induce good enantioselectivity, the enantioselection with ligands of the type *endo*-**2** was nearly zero.[18] The enantiomeric excesses obtained using binaphthyl derivatives **10** and **11** as chiral ligands were lower than those obtained with the corresponding xylyl derivatives **9** (Table 2, entries 11–14), a change in the temperature having no effect on the enantioselectivity. When the reaction was performed using chiral ligand **13** (one of the hydroxy groups is placed in the *endo*-position), benzyl alcohol was the only reaction product isolated (94% yield). Finally, different aldehydes were submitted to the aforementioned enantioselective addition using the best chiral ligand **9b**. In all cases tested, the enantioselectivity was lower than for benzaldehyde (Table 2, compare entries 8 and 16–18).

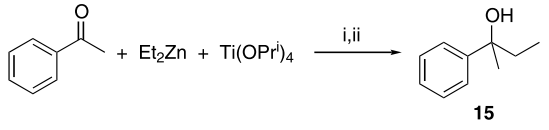
2.3. Enantioselective addition of dialkylzinc to ketones

The enantioselective addition of dialkylzinc reagents to ketones is a considerable challenge and only chiral ligands of the type **2** are known to promote this process. We anticipated that the use of dimetallic chelating ligands may lead to better enantioselectivity or improved reaction conditions, since the proximity and the spatial order around both metal centers could be controlled by the ligand. Therefore, we tested different chiral tetradentate C_2-symmetric ligands, as well as the corresponding related C_1-symmetric systems, in the enantioselective addition of diethylzinc to acetophenone to give the corresponding *tert*-alcohol **15**, using in all cases 10 mol% of the chiral ligand (Scheme 3 and Table 3). When the *ortho*-xylylenediamine derivative **9a** was used as promoter in the previously mentioned addition, the starting acetophenone was consumed after 3 days at room temperature. Although the enantiomeric excess obtained was promising (Table 3, entry 1), the yield of the expected alcohol **15** was modest[36] due to other side-reactions of the starting ketone but not to any process which involves decomposition of the formed *tert*-alcoholate. In fact, the *tert*-alcoholate is stable under the reaction conditions for 1 week. When the same reaction was performed using the corresponding *meta*-derivative **9b**, the yield increased in a shorter reaction time, as well as the enantiomeric excess (Table 3, entry 2). However, when the most remote *para*-derivative **9c** was used, both the chemical yield and enantioselectivity decreased again (Table 3, entry 5). In the case of the binaphthyl derivative **11**, the reaction was slower and after 10 days the chemical yield was miserable, the enantioselectivity being similar to that obtained with ligand **9b** (compare entries 1, 2, 5 and 6 in Table 3). These results show that ligand **9b** is the best promoter.[35] It must be pointed out that the absolute configuration of the *tert*-alcohol **15** can be correlated with the starting camphorsulfonyl chloride used. Thus, when the starting chloride is the D-(+)-10-camphorsulfonyl derivative, as in the cases of ligands **9** and **12**, the main enantiomer is *S*. Meanwhile, when the starting chloride is the opposite enantiomer, as for ligands **11** and *ent*-**2b**, the *tert*-alcohol **15** presents *R* configuration. In order to improve either the yield or the enantioselectivity, other reaction conditions, including temperature as well as the use of deprotonating bases,[37] were tested. However, in all cases the yield was lower but the enantiomeric excess of the alcohol **15** was similar (Table 3, entries 3 and 4). On the other hand, the reaction promoted by the tetradentate C_1-symmetric ligand **12** was slower than that promoted by the related C_2-system **9b**, giving both lower chemical yield and enantioselectivity (Table 3, compare entries 2 and 7). In ligand **12**, one of the hydroxy groups is placed at the *exo*-position (yielding high enantioselectivity) and the other hydroxy group is placed at the *endo*-position (low enantioselectivity), which could explain these poor results. To study a possible synergistic effect, the same reaction was carried out using a 1:1 mixture of *exo*:*endo* ligand *ent*-**2b** (Table 3, entry 8). As result, there is the same amount of chiral grouping in the

Table 2. Enantioselective addition of diethylzinc to aldehydes

Entry	R	Ligand	Temp. (°C)	Time (h)	*sec*-Alcohol		
					No.	Yield (%)[a]	e.e.[b,c]
1	Ph	**5a**	−20	16	**14a**	>95	40[d]
2	Ph	**5b**	−20	16	**14a**	>95	38[d]
3	Ph	**5c**	−20	16	**14a**	>95	36[d]
4	Ph	**6**	−20	16	**14a**	>95	6[d]
5	Ph	**7**	−20	16	**14a**	>95	2[d]
6	Ph	**8**	−20	16	**14a**	>95	2[d]
7	Ph	**9a**	25	3	**14a**	>95	50
8	Ph	**9b**	25	3	**14a**	>95	76
9	Ph	**9c**	25	3	**14a**	>95	74
10	Ph	**12**	25	3	**14a**	>95	74
11	Ph	**10**	0	3	**14a**	>95	30
12	Ph	**10**	25	3	**14a**	>95	26
13	Ph	**11**	−20	72	**14a**	60[e]	20[d]
14	Ph	**11**	25	3	**14a**	95	40[d]
15	Ph	**13**	25	48	**14a**	0[e]	–[f]
16	$Ph(CH_2)_2$	**9b**	25	16	**14b**	80[g]	50[h]
17	–[i]	**9b**	25	16	**14c**	65[j]	32[h,k]
18	PhC≡C	**9b**	25	16	**14d**	52[l]	26[h,k]

[a] Isolated yield after bulb-to-bulb distillation.
[b] Determined by GLC using a β-CD column.
[c] Absolute configuration: *S*.
[d] Absolute configuration: *R*.
[e] The starting aldehyde was recovered in 30% yield.
[f] The only product isolated was benzyl alcohol.
[g] The starting aldehyde was recovered in 15% yield.
[h] Determined as the corresponding trifluoroacetate by GLC using a γ-CD column (see Ref. 30).
[i] R = (*E*)-PhCH=CH.
[j] The starting aldehyde was recovered in 10% yield.
[k] Determined after being transformed into compound **14b** by hydrogenolysis under Pd/C catalysis (see Ref. 30).
[l] The starting aldehyde was recovered in 5% yield.



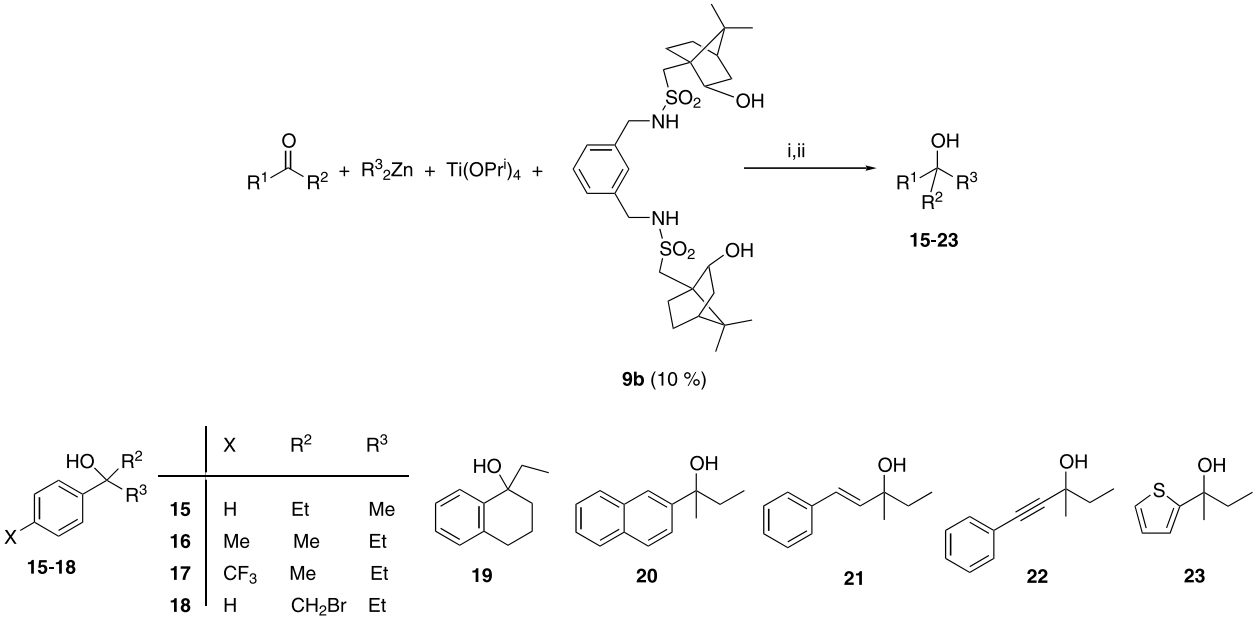
Scheme 3. *Reagents and conditions*: i, chiral ligand **9**, **11**, **12** or *ent*-**2b** (10%), PhMe. ii, MeOH; then saturated NH_4Cl.

reaction, but the chiral elements are not linked together covalently. For a better comparison of results for systems **12** and *ent*-**2b**, the reaction was quenched at the same chemical yield so as to get the same influence of the chiral *tert*-alcoholate product over the reaction.[19a] Although, the enantiomeric excess of the alcohol **15** was the same for both systems (compare entries 7 and 8 in Table 3), the reaction with ligand *ent*-**2b** was slower than that for system **12**. Apparently, there is only a slight synergistic effect using ligand **12**, accountable for the chemical yield. However, this effect is higher and is reflected in both the yield and the enantioselectivity when the results using ligand **9b** are compared with those previously reported for ligands of the type **2**.[19a] Once the enantioselective addition of diethylzinc to acetophenone was optimised, other ketones and dialkylzinc reagents were submitted to the same reaction using chiral ligand **9b** in order to obtain the expected *tertiary* alcohols (Scheme 4 and Table 4). The reaction took longer when dimethylzinc was used as the nucleophile source instead of diethylzinc, but the enantiomeric ratio was the same in both cases (Table 3, entry 2 and Table 4, entry 1). If we suppose a similar catalytic cycle is in operation for the enantioselective addition of dialkylzinc reagents to ketones[19a] as that reported for aldehydes,[22] the relationship between the product enantiomeric ratio and the electronic character of the group at the *para* position of the phenone ring could enlighten us about the rate-determining step. In the standard case of enantioselective addition of diethylzinc to different aromatic aldehydes, the plot of log(enantiomeric ratio) versus Hammett σ values[38] presents three types of tangents: (a) a positive tangent[39] (the greater the electron-withdrawing group character, the higher the enantiomeric ratio); (b) a negative tangent,[40] in both cases the rate-determining step is interpreted to be transfer of the alkyl group to the carbonylic moiety; and (c) the tangent is zero, so in this case the rate-determining step is believed to be the removal of the final alkoxide from the catalytic species.[24] Moreover, when there is a relationship between the enantiomeric ratio and the basic character of group at the *para* position[18] (instead of its electronic character), the rate-determining step seems to be the complexation between the titanium catalytic species and the carbonyl moiety, because the basic group attached to the aldehyde competes with the carbonyl group in the

Table 3. Enantioselective addition of diethylzinc to acetophenone promoted by titanium tetraisopropoxide

Entry	Ligand	Time (days)	Temp. (°C)	*tert*-Alcohol **15**	
				Yield (%)[a]	e.e. (*S*)[b]
1	**9a**	3	25	45	78
2	**9b**	2	25	75	86
3	**9b**	10	0	35[c]	81
4	**9b**[d]	10	0	5[e]	78
5	**9c**	2	25	60	76
6	**11**	10	25	15[c]	82[f]
7	**12**	3	25	45[g]	70
8	*ent*-**2b**[h]	4	25	45[i]	68[f]

[a] Isolated yield after bulb-to-bulb distillation.
[b] Determined by GLC using β-CD column.
[c] The starting ketone was recovered in 60% yield.
[d] CaH_2 was used as base to deprotonate the chiral ligand.
[e] The starting ketone was recovered in 90% yield.
[f] Absolute configuration: *R*.
[g] The starting ketone was recovered in 20% yield.
[h] A 1:1 mixture of *exo*:*endo* alcohol *ent*-**2b** was used as chiral ligand (20% total amount).
[i] The starting ketone was recovered in 10% yield.



Scheme 4. *Reagents and conditions*: i, PhMe, 25°C. ii, MeOH; then saturated NH_4Cl.

aforementioned complexation. In the case presented herein, the enantiomeric excess found for an electron-donating (methyl; Table 4, entry 2), neutral (hydrogen, Table 3, entry 2) and an electron-withdrawing group (trifluoromethyl; Table 4, entry 3) was the same within experimental error, which may be interpreted by considering that the rate-determining step is removal of the final *tert*-alkoxide from the catalytic titanium species. The presence of a bromine atom at the α-position to the carbonylic center in the ketone derivative changed neither the enantiomeric excess nor the yield (Table 4, entry 4). However, the use of a cyclic phenone, such as α-tetralone, led to decreased yield and enantiomeric ratio, giving nearly racemic product **19** (Table 4, entry 5). This unusually low yield may be attributed to the basicity of the organotitanium derivative formed in situ, which may deprotonate the starting ketone, thus preventing the addition process.[41] The reaction with a ketone containing a large aromatic moiety, such as 2-acetylnaphthalene, gave lower enantiomeric excess than that with simple phenyl ketones (Table 4, entry 6), indicating that the catalyst is sensitive to steric hindrance effects. The enantioselectivity found when the reaction was performed using an alkenylketone derivative gave similar results to the corresponding phenones (Table 4, entry 7). However, for a more conformationally restricted alkynylketone derivative, the enantiomeric excess was zero (Table 4, entry 8). It must be pointed out that when a heteroaromatic ketone derivative was used, such as 2-acetylthiophene, the enan-

Table 4. Enantioselective addition of dialkylzinc reagents to ketones promoted by titanium tetraisopropoxide

Entry	Ketone	R^3	Time (days)	*tert*-Alcohol		
				No.	Yield (%)[a]	e.e.[b]
1	PhCOEt	Me	3	**15**	>95	90[c]
2	4-MeC_6H_4COMe	Et	2	**16**	>95	92[d]
3	4-$CF_3C_6H_4COMe$	Et	2	**17**	>95	92[d]
4	$PhCOCH_2Br$	Et	2	**18**	95[e]	92[d,f]
5	α-Tetralone	Et	6	**19**	42[g]	16
6	2-Acetylnaphthalene	Et	2	**20**	85[h]	58
7	(*E*)-4-Phenyl-3-buten-2-one	Et	4	**21**	89[h]	86
8	4-Phenyl-3-butyn-2-one	Et	1	**22**	>95	2[d]
9	2-Acetylthiophene	Et	2	**23**	95[e]	40

[a] Isolated yield after bulb-to-bulb distillation.
[b] The e.e.s were determined by GLC using β-CD column and are given following the elution order.
[c] Absolute configuration: *R*.
[d] Determined by GLC using γ-CD column.
[e] The starting ketone was recovered in 5% yield.
[f] Absolute configuration: *S*.
[g] The starting ketone was recovered in 50% yield.
[h] The starting ketone was recovered in 10% yield.

tiomeric excess of the corresponding *tert*-alcohol decreased (Table 4, entry 9). Finally, when the reaction was performed using more electrophilic ketones, such as 2,2,2-trifluoroacetophenone or ethyl pyruvate, the only products isolated were the corresponding racemic 1-phenyl-2,2,2-trifluoroethanol (8 h) or isopropyl pyruvate (15 days), respectively. These products arise from a reduction process (typical reaction between ketones and dialkylzinc reagents) or a transesterification process (typically reaction between carboxylic esters and titanium alkoxides), respectively.

3. Conclusion

We have described new C_2-symmetric chiral disulfonamide ligands, which can be prepared easily from chiral camphorsulfonyl chloride and diamines (with or without stereogenic elements). These ligands have been successfully used in the enantioselective addition of dialkylzinc reagents to aldehydes and ketones in the presence of titanium isopropoxide. The relative position of both hydroxycamphorsulfonamide moieties in the chiral ligand has some effect on both the enantioselectivity and the yield of the reaction, as well as the reaction time, which may be interpreted in terms of some synergistic effects between both metal centers in the chiral ligand. There is no variation in the enantioselectivity of the reaction when *para*-substituted phenones bearing electron-donating or withdrawing groups are used. The ligands described show a higher enantioselectivity in the addition of dialkylzinc reagents to ketones than previously reported ligands, even using milder reaction conditions, which may indicate that the idea of covalently-linked groupings of chiral ligands could be useful for a further improvement in the enantioselectivity of this addition, as well as other reactions.

4. Experimental

4.1. General

Full general statements were described elsewhere.[30] All reactions using dialkylzinc or diisobutylaluminium hydride were carried out under an argon atmosphere. *o*-Xylylenediammonium dichloride was prepared in a two-step process according to the reported procedure,[32] starting from the corresponding dibrominated material, subsequent reaction with potassium phthalimide, hydrazine and final hydrolysis with hydrochloric acid gave the expected product in 45% overall yield. β-CD stands for 50 m WCOT fused silica capillary column (0.25 mm diam, 0.25 μm film thickness, CP-cyclodextrin-β-2,3,6-M-19). γ-CD stands for 50 m WCOT fused silica capillary column (0.25 mm diam, 0.25 μm film thickness, FS-Lipodex-E). MS samples were inserted in the modality of Direct Insertion Probed (DIP).

4.2. Preparation of disulfonamides 5–8

To a solution of the corresponding diamine **4** or (+)-2,2′-diamino-1,1′-binaphthalyl (12 mmol) in acetonitrile (25 mL) and 4-(dimethylamino)pyridine (DMPA, 0.66 g, 5.4 mmol) was added a solution of the corresponding sulfonyl chloride (25 mmol) in acetonitrile (25 mL) at 0°C. The resulting mixture was stirred during 24 h, allowing the temperature to rise to 25°C. Then, the reaction mixture was quenched with 3 M NaOH (25 mL) and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with 1 M HCl (25 mL), dried over $MgSO_4$ and evaporated (15 Torr) to afford the crude pure title product. Yields are included in Scheme 1 and text. Spectroscopic, physical and analytical data follow.

4.2.1. (1*S*,4*S*,1′*S*,4′*S*)-*N*-{2-(7′,7′-Dimethyl-2′-oxobicyclo[2.2.1]hept-1′-ylmethylsulfonamidomethyl)benzyl}-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-ylmethanesulfonamide, 5a. White solid, R_f 0.50 (hexane/ethyl acetate: 2/3); mp 50–52°C ($CHCl_3$); $[\alpha]_D^{25}=+24.4$ (*c* 1.6, EtOH); *v* (melted) 3289 (OH, NH), 3090 (C=CH), 1734 (C=O), 1329 cm^{-1} (SO_2); δ_H ($CDCl_3$) 0.78, 0.97 [6 and 6H, respectively, 2s, 2×$C(CH_3)_2$], 1.20–2.40 [14H, m, 2×$(CH_2)_2CHCH_2$], 2.86, 3.33 (2, 2H, respectively, 2d, $J=14.6$, 2×CH_2S), 4.45 (4H, d, $J=5.4$, CH_2N), 6.12 (2H, s, 2×NH), 7.25–7.30, 7.40–7.45 (2, and 2H, respectively, 2m, ArH); δ_C ($CDCl_3$) 19.0 (2C), 19.3 (2C), 25.7 (2C), 26.55 (2C), 42.2 (2C), 42.35 (2C), 44.2 (2C), 48.15 (2C), 49.35 (2C), 58.5 (2C), 127.85 (2C), 129.8 (2C), 135.15 (2C), 216.15 (2C); *m*/*z* (DIP) 564 (M^+, 1%), 349 (28), 333 (21), 332 (27), 119 (100), 118 (70), 109 (47), 95 (11). Anal. calcd for $C_{28}H_{40}N_2O_6S_2$: C, 59.55; H, 7.14; N, 4.96; S, 11.35. Found: C, 59.56; H, 7.21; N, 4.88; S, 11.33%.

4.2.2. (1*S*,4*S*,1′*S*,4′*S*)-*N*-{3-(7′,7′-Dimethyl-2′-oxobicyclo[2.2.1]hept-1′-ylmethylsulfonamidomethyl)benzyl}-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-ylmethanesulfonamide, 5b. White solid, R_f 0.52 (hexane/ethyl acetate: 2/3); mp 118–120°C (ethyl acetate/hexane); $[\alpha]_D^{25}=+9.05$ (*c* 1.7, $CHCl_3$); *v* (melted): 3229, 3264 (OH, NH), 3030 (C=CH), 1730 (C=O), 1331 cm^{-1} (SO_2); δ_H ($CDCl_3$) 0.77, 0.97 [6 and 6H, respectively, 2s, 2×$C(CH_3)_2$], 1.35–2.45 [14H, m, 2×$(CH_2)_2CHCH_2$], 2.86, 3.23 (2, 2H, respectively, 2d, $J=14.6$, 2×CH_2S), 3.25 (4H, d, $J=5.4$, 2×CH_2N), 5.85 (2H, s, 2×NH), 7.30–7.40, 7.40 (3, and 1H, respectively, m and s respectively, ArH); δ_C ($CDCl_3$) 19.3 (2C), 19.6 (2C), 26.3 (2C), 26.8 (2C), 42.55 (2C), 42.7 (2C), 47.3 (2C), 48.55 (2C), 50.1 (2C), 59.0 (2C), 127.55 (2C), 128.0, 128.95 (2C), 137.55, 216.85 (2C); *m*/*z* (DIP) 564 (M^+, <1%), 351 (43), 350 (48), 349 (100), 325 (44), 215 (32), 161 (32), 151 (29), 148 (32), 134 (24), 133 (23), 123 (31), 119 (42), 118 (57), 109 (85), 107 (35), 106 (29), 105 (41), 104 (29), 93 (28), 91 (27), 81 (59), 79 (48), 77 (41), 67 (42), 55 (42). Anal. calcd for $C_{28}H_{40}N_2O_6S_2$: C, 59.55; H, 7.14; N, 4.96; S, 11.35. Found: C, 59.57; H, 7. 14; N, 4.95; S, 11.32%.

4.2.3. (1*S*,4*S*,1′*S*,4′*S*)-*N*-{4-(7′,7′-Dimethyl-2′-oxobicyclo[2.2.1]hept-1′-ylmethylsulfonamidomethyl)benzyl}-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-ylmethanesulfonamide, 5c. White solid, R_f 0.42 (hexane/ethyl acetate: 2/3); mp 155–157°C (ethyl acetate/hexane); $[\alpha]_D^{25}=+6.3$ (*c* 1.2, $CHCl_3$); *v* (melted) 3300, 3273 (OH, NH), 3055 (C=CH), 1742 (C=O), 1323 cm^{-1} (SO_2); δ_H ($CDCl_3$) 0.78, 0.96 [6 and 6H, respectively, 2s, 2×$C(CH_3)_2$], 1.40–2.40 [14H, m, 2×$(CH_2)_2CHCH_2$], 2.86, 3.20 (2, 2H, respectively, 2d, $J=15.2$, 2×CH_2S), 4.31 (4H, d, $J=6.7$, 2×CH_2N), 5.82 (2H, t, $J=6.7$, 2×NH), 7.30–7.40 (4H, m, ArH); δ_C ($CDCl_3$) 19.25 (2C), 19.65 (2C), 26.6 (2C), 26.85 (2C), 42.55 (2C), 43.7 (2C), 47.15 (2C), 48.6 (2C), 50.25 (2C), 59.1 (2C), 128.5 (4C), 136.6 (2C), 216.9 (2C); *m*/*z* (DIP) 564 (M^+, <1%), 351 (48), 349 (100), 325 (29), 215 (52), 161 (90), 152 (25), 151 (45), 135 (61), 134 (65), 133 (89), 132 (20), 123 (34), 119 (35), 118 (71), 109 (75), 108 (32), 105 (78), 95 (30), 93 (41), 91 (30), 81 (48), 79 (27), 67 (71), 55 (43). Anal. calcd for $C_{28}H_{40}N_2O_6S_2$: C, 59.55; H, 7.14; N, 4.96; S, 11.35. Found: C, 59.51; H, 7.12; N, 4.88; S, 11.23%.

4.2.4. (*M*,1*S*,4*S*,1′*S*,4′*S*)-*N*-{1-[2-(7′,7′-Dimethyl-2′-oxobicyclo[2.2.1]hept-1′-ylmethylsulfonamido)-1-naphthyl]-2-naphthyl} - 7,7 - dimethyl - 2 - oxobicyclo[2.2.1]hept - 1 - ylmethanesulfonamide, 6. Pale yellow solid, R_f 0.26 (hexane/ethyl acetate: 3/2); mp 119–121°C (ethyl acetate/hexane); $[\alpha]_D^{25}=+19.6$ (*c* 2.5, $CHCl_3$); *v* (melted) 3331, 3268 (OH, NH), 3050, 1610 (C=CH), 1740 (C=O), 1156 cm^{-1} (SO_2); δ_H ($CDCl_3$) 0.55, 0.91 [6 and 6H, respectively, 2s, 2×$C(CH_3)_2$], 1.20–2.20 [14H, m, 2×$(CH_2)_2CHCH_2$], 2.95, 3.38 (2, 2H, respectively, 2d, $J=14.7$, 2×CH_2S), 7.01 (2H, s, 2×NH), 6.97, 7.20-7.30, 7.35–7.45, 7.90, 8.19 (2, 2, 2, 2, 2 and 2H, respectively, d, m, m, d, d and d, respectively, $J=7.9$, 8.5, 9.1, 9.1, ArH); δ_C ($CDCl_3$) 19.35 (2C), 19.4 (2C), 25.6 (2C), 26.8 (2C), 42.35 (2C), 42.55 (2C), 48.2 (2C), 51.25 (2C), 58.6 (2C), 118.65 (2C), 119.25 (2C), 125.0 (2C), 125.35 (2C), 127.5 (2C), 128.3 (2C), 130.75 (2C), 130.95 (2C), 132.9 (2C), 134.9 (2C), 214.8 (2C); *m*/*z* (DIP) 712 (M^+, <1%), 124 (22), 122 (26), 121 (39), 110 (27), 109 (60), 108 (47), 107 (77), 95 (46), 94 (16), 93 (82), 91 (70), 82 (21), 81 (45), 79 (100), 77 (65), 69 (57), 67 (85), 66 (28), 65 (29), 55 (78), 53 (45). Anal. calcd for $C_{40}H_{44}N_2O_6S_2$: C, 67.39; H, 6.22; N, 3.93. Found: C, 67.42; H, 6.15; N, 3.86%.

4.2.5. (*M*,1*R*,4*R*,1′*R*,4′*R*)-*N*-{1-[2-(7′,7′-Dimethyl-2′-oxobicyclo[2.2.1]hept - 1′ - ylmethylsulfonamido) - 1 - naphthyl]-2-naphthyl}-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-ylmethanesulfonamide, 7. Brown solid, R_f 0.54 (hexane/ethyl acetate: 1/1); mp 84–86°C (ethyl acetate/hexane); $[\alpha]_D^{25}=+23.9$ (*c* 1.48, $CHCl_3$); *v* (melted): 3340, 3251 (OH, NH), 3050, 1619 (C=CH), 1740 (C=O), 1153 cm^{-1} (SO_2); δ_H ($CDCl_3$) 0.71, 0.91 [6 and 6H, respectively, 2s, 2×$C(CH_3)_2$], 1.20–2.30 [14H, m, 2×$(CH_2)_2CHCH_2$], 2.79, 3.52 (2, 2H, respectively, 2d, $J=14.9$, 2×CH_2S), 6.91 (2H, s, 2×NH), 7.04, 7.25–7.30, 7.40–7.45, 7.91, 8.06, 8.18 (2,2,2,2,2, and 2H, respectively, d, m, m, d, d, d, $J=8.5$, 7.9, 9.1, 9.1, ArH); δ_C ($CDCl_3$) 19.35 (2C), 19.5 (2C), 25.15 (2C), 27.0 (2C), 42.15 (2C), 42.4 (2C), 48.1 (2C), 50.65 (2C), 58.4 (2C), 118.25 (2C), 118.9 (2C), 124.7 (2C), 125.35 (2C), 127.5, (2C), 128.3 (2C), 130.75 (2C), 130.9 (2C), 132.5 (2C), 135.0 (2C), 215.15 (2C); *m*/*z* (DIP) 712 (M^+, 100%), 81 (10), 69 (12). Anal. calcd for $C_{40}H_{44}N_2O_6S_2$: C, 67.39; H, 6.22; N, 3.93. Found: C, 67.31; H, 6.17; N, 3.87%.

4.2.6. (*M*)-*N*-{1-[(2-Methylsulfonamido)-1-naphthyl]-2-naphthyl}methanesulfonamide, 8.[33] Pale yellow solid, R_f 0.64 (hexane/ethyl acetate: 2/3); mp 100–102°C (ethyl acetate/hexane); $[\alpha]_D=+92.65$ (*c* 1.6, $CHCl_3$); *v* (melted) 3331, 3268 (OH, NH), 3050 (C=CH), 1356 cm^{-1} (SO_2); δ_H ($CDCl_3$) 2.86 (6H, s, 2×CH_3), 6.18 (2H, s, 2×NH), 6.96, 7.25–7.30, 7.40–7.50, 7.90–8.10 (2, 2, 2 and 6H, respectively, d, m, m and m, respectively $J=8.5$, ArH); δ_C ($CDCl_3$) 40.70 (2C), 118.35 (2C), 118.65 (2C), 124.45 (2C), 125.85 (2C), 127.9

(2C), 128.55 (2C), 131.0 (2C), 131.25 (2C), 132.5 (2C), 134.3 (2C); m/z (GC) 440 (M^+, 38%), 283 (24), 282 (100), 281 (31), 280 (15), 279 (19), 267 (30), 266 (13), 265 (17), 264 (15), 207 (10), 141 (11), 140 (28).

4.3. Preparation of bis(hydroxycamphorsulfonamides) ligands 9–13

To a solution of the corresponding diketone **5**–**7** (10 mmol) in THF (50 mL) was added a solution of diisobutylaluminium hydride (1 M in hexane 25 mL, 25 mmol) at −78°C under an argon atmosphere. The resulting mixture was stirred during 24 h, allowing the temperature to rise to 25°C. Then, the reaction mixture was quenched with 2 M HCl (25 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and evaporated (15 Torr) yielding a residue, which was purified by flash chromatography (silica gel, hexane/ethyl acetate) to afford the expected title alcohols. Yields are included in Table 1. Spectroscopic, physical and analytical data follow.

4.3.1. (1*S*,2*R*,4*S*,1′*S*,2′*R*,4′*S*)-*N*-{2-(2′-Hydroxy-7′,7′-dimethylbicyclo[2.2.1]hept - 1′ - ylmethylsulfonamidomethyl)benzyl}-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide, 9a. White solid, R_f 0.69 (hexane/ethyl acetate: 3/2); mp 79–81°C (ethyl acetate/hexane); $[\alpha]_D^{25}=-46.2$ (c 2.0, $CHCl_3$); ν (melted) 3522, 3247 (OH, NH), 3092 (C=CH), 1320 (SO_2), 1144 cm^{-1} (CO); δ_H ($CDCl_3$) 0.78, 1.01 [6 and 6H, respectively, 2s, 2×C$(CH_3)_2$], 1.05–1.85 [14H, m, 2×$(CH_2)_2CHCH_2$], 2.82, 3.41 (2, 2H, respectively, 2d, $J=13.4$, 2×CH_2S), 3.13 (2H, s, 2×OH), 4.00–4.10 (2H, m, 2×CHO), 4.43 (4H, d, $J=6.1$, 2×CHN), 5.06 (2H, s, 2×NH), 7.30–7.45 (4H, m, ArH); δ_C ($CDCl_3$) 19.75 (2C), 20.35 (2C), 27.25 (2C), 30.25 (2C), 40.0 (2C), 44.25 (2C), 44.55 (2C), 48.65 (2C), 50.25 (2C), 52.2 (2C), 76.2 (2C), 128.7 (2C), 130.45 (2C), 135.1 (2C); m/z (DIP) 568 (M^+, <1%), 334 (50), 33 (64), 316 (100), 135 (81), 133 (32), 117 (59), 108 (49), 95 (36), 93 (36), 79 (51), 77 (32), 67 (40). Anal. calcd for $C_{28}H_{44}N_2O_6S_2$: C, 59.13; H, 7.80; N, 4.93; S, 11.27. Found: C, 59.14; H, 7.85; N, 4.87; S, 11.33%.

4.3.2. (1*S*,2*R*,4*S*,1′*S*,2′*R*,4′*S*)-*N*-{3-(2′-Hydroxy-7′,7′-dimethylbicyclo[2.2.1]hept - 1′ - ylmethylsulfonamidomethyl)benzyl}-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide, 9b. White solid, R_f 0.61 (hexane/ethyl acetate: 2/3); mp 66–68°C (ethyl acetate/hexane); $[\alpha]_D^{25}=-46.2$ (c 1.8, EtOH); ν (melted) 3530, 3286 (OH, NH), 3085, 1316 (C=CH), 1138 cm^{-1} (CO); δ_H ($CDCl_3$) 0.75, 0.96 [6 and 6H, respectively, 2s, 2×C$(CH_3)_2$], 1.05–1.75 [14H, m, 2×$(CH_2)_2CHCH_2$], 2.15 (2H, s, 2×OH), 2.75, 3.24 (2, 2H, respectively, 2d, $J=14.0$, 2×CH_2S), 4.00–4.05 (2H, m, 2×CHO), 4.26 (4H, d, $J=5.5$ 2×CHN), 5.56 (2H, t, $J=5.7$, 2×NH), 7.25–7.35, 7.36 (3 and 1H, respectively, m and s, respectively, ArH); δ_C ($CDCl_3$) 19.75 (2C), 20.45 (2C), 27.25 (2C), 30.35 (2C), 39.0 (2C), 44.25 (2C), 47.0 (2C), 48.65 (2C), 50.3 (2C), 52.75 (2C), 76.35 (2C), 127.85 (2C), 129.3 (2C), 137.6 (2C); m/z (DIP) 568 (M^+, <1%), 353 (43), 351 (45), 335 (63), 333 (38), 166 (70), 137 (60), 136 (80), 135 (100), 134 (91), 121 (34), 120 (46), 119 (80), 118 (69), 109 (34), 108 (78), 107 (35), 106 (37), 105 (37), 93 (46), 91 (34), 81 (39), 79 (57), 67 (43). Anal. calcd for $C_{28}H_{44}N_2O_6S_2$: C, 59.13; H, 7.80; N, 4.93; S, 11.27. Found: C, 59.19; H, 7.75; N, 4.97; S, 11.31%.

4.3.3. (1*S*,2*R*,4*S*,1′*S*,2′*R*,4′*S*)-*N*-{4-(2′-Hydroxy-7′,7′-dimethylbicyclo[2.2.1]hept - 1′ - ylmethylsulfonamidomethyl)benzyl}-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide, 9c. White solid, R_f 0.63 (hexane/ethyl acetate: 2/3); mp 147–149°C (ethyl acetate/hexane); $[\alpha]_D^{25}=-1.4$ (c 1.5, $CHCl_3$); ν (melted) 3430, 3302 (OH, NH), 3042 (C=CH), 1322 (SO_2), 1142 cm^{-1} (CO); δ_H ($CDCl_3$) 0.76, 1.00 [6 and 6H, respectively, 2s, 2×C$(CH_3)_2$], 1.05–2.15 [14H, m, 2×$(CH_2)_2CHCH_2$], 2.79, 3.35 (2, 2H, respectively, 2d, $J=13.4$, 2×CH_2S), 3.14 (2H, s, 2×OH), 4.05–4.10 (2H, m, 2×CHO), 4.30 (4H, d, $J=6.1$, 2×CHN), 4.97 (2H, t, $J=5.5$, 2×NH), 7.30–7.40 (4H, m, ArH); δ_C ($CDCl_3$) 19.8 (2C), 20.5 (2C), 27.3 (2C), 30.45 (2C), 39.0 (2C), 44.3 (2C), 46.95 (2C), 48.7 (2C), 50.35 (2C), 52.9 (2C), 76.35 (2C), 128.55 (4C), 136.75 (2C); m/z (DIP) 568 (M^+, <1%), 335 (55), 334 (49), 333 (90), 136 (39), 135 (85), 134 (54), 133 (95), 121 (45), 120 (62), 119 (43), 118 (52), 109 (38), 108 (51), 107 (73), 106 (72), 105 (46), 93 (57), 91 (52), 81 (30), 79 (100), 77 (33). Anal. calcd for $C_{28}H_{44}N_2O_6S_2$: C, 59.13; H, 7.80; N, 4.93; S, 11.27. Found: C, 59.09; H, 7.71; N, 4.84; S, 11.16%.

4.3.4. (*M*,1*S*,2*R*,4*S*,1′*S*,2′*R*,4′*S*)-*N*-{1-[2-(2′-Hydroxy-7′,7′-dimethylbicyclo[2.2.1]hept-1′-ylmethylsulfonamido)-1-naphthyl]-2-naphthyl}-2-hydroxy-7,7-dimethylbicyclo-[2.2.1]hept-1-ylmethanesulfonamide, 10. Pale brown solid, R_f 0.52 (hexane/ethyl acetate: 3/2); mp 133–135°C (ethyl acetate/hexane); $[\alpha]_D^{25}=+24.05$ (c 1.7, $CHCl_3$); ν (melted) 3521, 3402 (OH, NH), 3062, 1610 (C=CH), 1152 cm^{-1} (CO); δ_H ($CDCl_3$) 0.73, 0.89 [6 and 6H, respectively, 2s, 2×C$(CH_3)_2$], 1.00–1.75 [14H, m, 2×$(CH_2)_2CHCH_2$], 2.74 (2H, s, 2×OH),2.86, 3.24, (2, 2H, respectively, 2d, $J=13.7$, 2×CH_2S), 3.90–3.95 (2H, m, 2×CHO), 6.31 (2H, s, 2×NH), 7.04, 7.30–7.40, 7.45–7.55, 7.95–8.05, 8.01 (2, 2, 2, 4 and 2H, respectively, d, m, m and d, respectively, $J=8.5$, 9.1, respectively, ArH); δ_C ($CDCl_3$) 18.6 (2C), 19.6 (2C), 27.25 (2C), 28.05 (2C), 38.35 (2C), 43.85 (2C), 48.85 (2C), 50.5 (2C), 53.65 (2C), 74.8 (2C), 119.15 (2C), 119.5 (2C), 125.0 (2C), 125.95 (2C), 127.95 (2C), 128.05 (2C), 128.65 (2C), 131.15 (2C), 132.75 (2C), 134.5 (2C); m/z (DIP) 716 (M^+, 56%), 499 (20), 482 (100), 284 (81), 283 (99), 282 (22), 281 (63), 268 (35), 267 (69), 266 (75), 265 (54), 135 (29), 107 (20), 79 (22), 67 (22). Anal. calcd for $C_{40}H_{48}N_2O_6S_2$: C, 67.01; H, 6.75; N, 3.91. Found: C, 67.07; H, 6.76; N, 3.88%.

4.3.5. (*M*,1*R*,2*S*,4*R*,1′*R*,2′*S*,4′*R*)-*N*-{1-[2-(2′-Hydroxy-7′,7′-dimethylbicyclo[2.2.1]hept-1′-ylmethylsulfonamido)-1-naphthyl]-2-naphthyl}-2-hydroxy-7,7-dimethylbicyclo-[2.2.1]hept-1-ylmethanesulfonamide, 11. Pale brown solid, R_f 0.62 (hexane/ethyl acetate: 3/2); mp 111–113°C (ethyl acetate/hexane); $[\alpha]_D^{25}=+25.5$ (c 1.3, $CHCl_3$); ν

(melted) 3545, 3346 (OH, NH), 3040, 1598 (C=CH), 1145 cm^{-1} (CO); δ_H ($CDCl_3$) 0.65, 0.97 [6 and 6H, respectively, 2s, 2×$C(CH_3)_2$], 1.25–1.85 [14H, m, 2×$(CH_2)_2CHCH_2$], 2.66, 3.48 (2, 2H, respectively, 2d, J= 13.4, 2×CH_2S), 3.74 (2H, s, 2×OH), 3.95–4.00 (2H, m, 2×CHO), 6.21 (2H, s, 2×NH), 7.01, 7.25–7.35, 7.35–7.50, 7.50–8.05, 8.10 (2, 2, 2, 4 and 2 H, respectively, d, 3m and d, respectively, J=8.5, 9.1, ArH); δ_C ($CDCl_3$) 19.35 (2C), 19.85 (2C), 26.75 (2C), 29.8 (2C), 38.75 (2C), 43.85 (2C), 48.4 (2C), 50.0 (2C), 53.05 (2C), 75.65 (2C), 118.55 (2C), 118.95 (2C), 124.4 (2C), 125.5 (2C), 127.65 (2C), 128.3 (2C), 130.75 (2C), 131.05 (2C), 132.15 (2C), 133.95 (2C); m/z (DIP) 716 (M^+, 100%), 501 (16), 500 (47), 482 (15), 285 (15), 284 (19), 283 (44), 282 (51), 281 (34), 268 (11), 267 (45), 93 (15). Anal. calcd for $C_{40}H_{48}N_2O_6S_2$: C, 67.01; H, 6.75; N, 3.91. Found: C, 67.01; H, 6.69; N, 3.86%.

4.3.6. (1*S*,2*R*,4*S*,1′*S*,2′*S*,4′*S*)-*N*-{3-(2′-Hydroxy-7′,7′-dimethylbicyclo[2.2.1]hept-1′-ylmethylsulfonamidomethyl)benzyl}-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide, 12. White solid, R_f 0.71 (hexane/ethyl acetate: 2/3); mp 57–59°C (ethyl acetate/hexane); $[\alpha]_D^{25}=-9.6$ (c 1.9, EtOH); ν (melted) 3532, 3285 (OH, NH), 3045 (C=CH), 1317 (SO_2), 1141 cm^{-1} (CO); δ_H ($CDCl_3$) 0.74, 0.95, 0.82 [3, 3 and 3H, respectively, 3s, 2×$C(CH_3)_2$], 1.00–2.40 [14H, m, 2×$(CH_2)_2CHCH_2$], 2.75, 2.96, 3.02, 3.24 (1, 1, 1 and 1H, respectively, 2d and 2d, respectively, J=13.7, 14.3, 2×CH_2S), 3.28, 3.61 (1 and 1H, respectively, 2s, 2×OH), 4.00–4.05, 4.15–4.20 (1 and 1H, respectively, 2m, 2×CHO), 4.24, 4.27 (2, 2H, respectively, 2d, J=6.1, 2×CHN), 5.63, 5.97 (1, 1H, respectively, 2t, J=6.1, 2×NH), 7.25–7.40 (4H, m, ArH); δ_C ($CDCl_3$) 18.7, 19.7, 20.25, 20.4, 23.6, 27.2, 28.1, 30.35, 38.4, 38.9, 43.85, 44.2, 46.9, 47.0, 48.6, 50.25, 50.8, 51.35, 52.8, 56.0, 75.05, 76.3, 127.6, 127.65, 127.7, 129.15, 137.6, 137.7; m/z (DIP) 566 (M^+−2, <1%), 353 (43), 352 (17), 351 (24), 335 (30), 333 (39), 166 (32), 137 (33), 136 (86), 135 (82), 134 (34), 133 (19), 120 (46), 119 (100), 109 (17), 108 (31), 107 (21), 106 (10), 93 (25), 91 (21). Anal. calcd for $C_{28}H_{44}N_2O_6S_2$: C, 59.13; H, 7.80; N, 4.93; S, 11.27. Found: C, 59.17; H, 7.84; N, 4.91; S, 11.27%.

4.3.7. (*M*,1*R*,2*S*,4*R*,1′*R*,2′*R*,4′*R*)-*N*-{1-[2-(2′-Hydroxy-7′,7′-dimethylbicyclo[2.2.1]hept-1′-ylmethylsulfonamido)-1-naphthyl]-2-naphthyl}-2-hydroxy-7,7-dimethylbicyclo-[2.2.1]hept-1-ylmethanesulfonamide, 13. White solid, R_f 0.69 (hexane/ethyl acetate: 1/1); mp 58–60°C (ethyl acetate/hexane); $[\alpha]_D^{25}=+8.3$ (c 1.05, $CHCl_3$); ν (melted) 3450, 3364 (OH, NH), 3034, 1624 (C=CH), 1159 cm^{-1} (CO); δ_H ($CDCl_3$) 0.63, 0.72, 0.78 and 0.96 [3, 3, 3 and 3H, respectively, 4s, 2×$C(CH_3)_2$], 1.15–2.60 [14H, m, 2×$(CH_2)_2CHCH_2$], 2.67, 2.86, 3.02, 3.50 (1, 1, 1 and 1H, respectively, 2d and 2d, respectively, J=13.4, 13.7, 2×CH_2S), 3.90–3.95, 4.05–4.10 (1 and 1H, respectively, 2m, 2×CHO), 6.21, 6.49 (1 and 1H, respectively, 2s, 2×NH), 7.00–7.05, 7.25–7.35, 7.45–7.50, 7.95–8.15 (2, 2,2 and 6H, respectively, 4m, ArH); δ_C ($CDCl_3$) 18.25, 19.3, 19.7, 18.8, 23.15, 26.75, 27.55, 29.75, 37.75, 38.8, 43.45, 43.8, 48.35, 50.65, 51.15, 52.45, 53.05, 56.75, 74.45, 75.55, 118.4, 118.9, 119.05, 119.1, 119.25, 124.25, 124.35, 124.4, 124.65, 125.5, 127.5, 128.25, 130.75, 130.8, 130.85, 130.95, 132.15, 132.2, 133.8, 134.05; m/z (DIP) 716 (M^+, <1%), 351 (59), 349 (37), 136 (47), 135 (100), 134 (43), 133 (33), 118 (50), 109 (32), 107 (38), 106 (31), 104 (33), 91 (38), 81 (52), 79 (46), 67 (30). Anal. calcd for $C_{40}H_{48}N_2O_6S_2$: C, 67.01; H, 6.75; N, 3.91. Found: C, 67.10; H, 6.70; N, 3.97%.

4.4. Enantioselective addition of dialkylzinc to aldehydes or ketones in the presence of titanium isopropoxide

To a solution of corresponding ligand **5**–**13** (0.5 mmol) in toluene (5 mL) was added a ca. 2 M solution in toluene of the corresponding dialkylzinc reagent (9 mmol, 4.5 mL) at temperatures ranging from −20°C to rt (see Tables 2–4) under an argon atmosphere (see Schemes 2–4). After 10 min stirring, titanium tetraisopropoxide (6.5 mmol, 2 mL) was added to the resulting solution and, after 10 additional min, the corresponding aldehyde or ketone (5 mmol) was added. The resulting mixture was stirred at the same temperature during several hours to days (see Tables 2–4). Then, methanol (1 mL) and a saturated NH_4Cl solution (20 mL) were successively added, the mixture was filtered through celite, extracted with ethyl acetate (3× 50 mL) and the organic layer dried over $MgSO_4$. The solvents were removed under reduced pressure (15 Torr) and the residue was distillate bulb-to-bulb to yield the expected alcohols. Yields and enantiomeric excess (e.e.) are included in Tables 2–4. Compounds **14a**,[18] **14b**–**d**,[30] as well as **15**, **18**–**21** and **23**,[19a] were already described by us and were characterised by comparison of their physical and spectroscopic data with those reported in the literature. Spectroscopic and physical data, as well as literature references follow.

4.4.1. 2-(4-Methylphenyl)-2-butanol, 16.[42] Colourless oil, bp 150–155°C (0.1 Torr); R_f 0.65 (hexane/ethyl acetate: 7/3); $[\alpha]_D=-2.89$ (c 1.9, EtOH; e.e. 92%); ν (film) 3428 (OH), 3024, 1649 (C=CH), 1127 cm^{-1} (CO); δ_H ($CDCl_3$) 0.78 (3H, t, J=7.4, CH_2CH_3), 1.51 (3H, s, CH_3), 1.81 (2H, q, J=7.4, CH_2CH_3), 1.87 (1H, s OH), 2.32 (3H, s $ArCH_3$), 7.13, 7.29 (2, 2H, respectively, 2d, J=8.0, ArH); δ_C ($CDCl_3$) 8.3, 20.85, 29.5, 36.55, 74.75, 124.75 (2C), 128.7 (2C), 135.9, 144.8; m/z (GC) 164 (M^+, 2%), 135 (100), 131 (13), 91 (21), 57 (12).

4.4.2. 2-(4-Trifluoromethylphenyl)-2-butanol, 17.[42] Colourless oil, bp 150–155°C (0.1 Torr); R_f 0.60 (hexane/ethyl acetate: 7/3); $[\alpha]_D=-10.6$ (c 2.5, EtOH; e.e. 92%); ν (film): 3406 (OH), 3060, 1618 (C=CH), 1327 (CF), 1125 cm^{-1} (CO); δ_H ($CDCl_3$) 0.79 (3H, t, J=7.4, CH_2CH_3), 1.55 (3H, s, CH_3), 1.84 (2H, q, J=7.4, CH_2CH_3), 1.89 (1H, s, OH), 7.53, 7.58 (2, 2H, respectively, 2d, J=8.6, ArH); δ_C ($CDCl_3$) 8.05, 29.6, 36.6, 74.85, 120.7 (q, $^2J_{CF}$=271.1), 125.0 (q, $^3J_{CF}$=10.95), 125.35 (2C), 127.85 (q, $^1J_{CF}$=815.0), 151.5; m/z (GC) 218 (M^+, <1%), 189 (100), 145 (10).

4.4.3. 3-Methyl-1-phenyl-1-pentyn-3-ol, 22.[43] Colourless oil, bp 155–160°C (0.1 Torr); R_f 0.85 (hexane/ethyl acetate: 7/3); $[\alpha]_D=+3.2$ (c 2.1, EtOH; e.e. 2%); ν (film) 3404 (OH), 3049, 1636 (C=CH), 2196 (C≡C), 1118 cm^{-1}

(CO); δ_H ($CDCl_3$) 1.10 (3H, t, $J=7.4$, CH_2CH_3), 1.56 (3H, s, CH_3), 1.78 (2H, q, $J=7.4$, CH_2CH_3), 2.10 (1H, s, OH), 7.25–7.30, 7.40–7.45 (3, 2H, respectively, 2m, ArH); δ_C ($CDCl_3$) 9.05, 29.25, 36.6, 69.05, 83.3, 92.7, 122.8, 128.15, 128.2 (2C), 131.6 (2C); m/z (GC) 174 (M^+, 5%), 146 (10), 145 (100), 129 (10), 115 (10).

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