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trans-1-Sulfonylamino-2-isoborneolsulfonylaminocyclohexane Derivatives: Excellent Chiral Ligands for the Catalytic Enantioselective Addition of Organozinc Reagents to Ketones

Vicente J. Forrat, Oscar Prieto, Diego J. Ramón,* and Miguel Yus*[a]

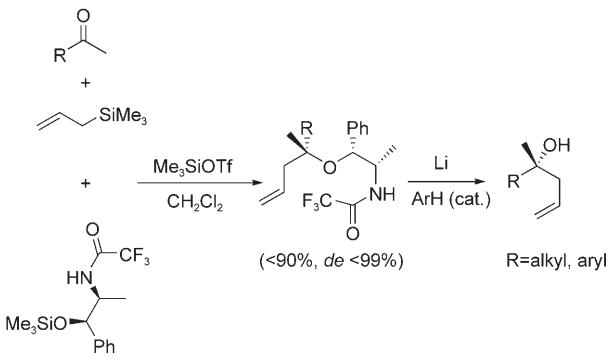
Abstract: The catalytic enantioselective addition of different organozinc reagents (such as alkyl and aryl derivatives or in situ generated aryl, allyl alkenyl, and alkynyl derivatives obtained through different transmetallation processes) to simple ketones has been accomplished by using titanium tetraisopropoxide and chiral ligands derived from substituted *trans*-1-sulfonylamino-2-isoborneolsulfonylaminocyclohexane, producing the corresponding tertiary alcohols with enantiomeric excesses (*ee*) up to >99%. A simple and efficient procedure for the synthesis of the chiral ligands used in these reactions is described.

Keywords: alcohols · asymmetric catalysis · C–C coupling · enantioselectivity · titanium

Introduction

The preparation of chiral molecules bearing a quaternary stereocenter is still a very important challenge in synthetic organic chemistry, with the diastereoselective approach being the most commonly used.[1] However, the enantioselective version of these reactions have, in general, some advantages over the diastereoselective ones, such as for the repeated preparation of a compound, the need for the attachment and deattachment of a chiral auxiliary at the beginning and end of the synthetic process is avoided. Nevertheless, there are some elegant diastereoselective approaches which do not need the first step. Thus, the asymmetric multicomponent Sakurai reaction,[2] which utilizes aliphatic methyl ketones, allyl silanes, and chiral norpseudoephedrine derivatives, yielded the expected benzyl ether with excellent diastereoselectivity;[3] the final reductive deprotection with lithium and substoichiometric amounts of an arene[4] liberates the corresponding homoallylic tertiary alcohol (Scheme 1).

Among the different enantioselective approaches to the synthesis of this kind of molecule,[5] those which imply the formation of a carbon–carbon bond are more powerful than those that use simple functionalization. In this case the simplest approach for the preparation of chiral tertiary alcohols is the enantioselective 1,2-addition of organometallics[6] to the corresponding carbonyl compounds.[7] Although there are several examples of addition of organolithium or Grignard reagents to ketones, at least one equivalent of an often expensive and difficult to prepare chiral ligand is compulsory in all cases. To reduce the amount of the chiral ligand required, an organometallic reagent with lower nucleophilic character is usually considered. However, under these new conditions, and to guarantee the success of the reaction, the chiral system must determine not only the topol-



Scheme 1. Diastereoselective approach to the synthesis of tertiary alcohols. OTf = trifluoromethanesulfonate; *de* = diastereomeric excess.

[a] V. J. Forrat, Dr. O. Prieto, Dr. D. J. Ramón, Prof. Dr. M. Yus
Instituto de Síntesis Orgánica (ISO) and Departamento de Química Orgánica. Facultad de Ciencias
Universidad de Alicante, Apdo. 99, 03080 Alicante (Spain)
Fax: (+34) 965-90-35.49
E-mail: djramon@ua.es
yus@ua.es

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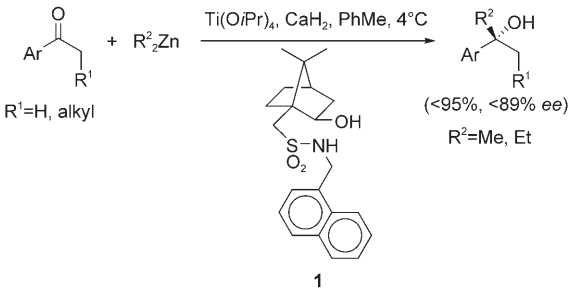
ogy of the reaction, but also the chemical reaction itself. This new role of the catalyst may be achieved by either activating the organometallic reagent or, in the most classical sense, by activating the carbonyl compound. Some catalysts are able to activate both the nucleophile and the carbonyl compound at the same time.[8]

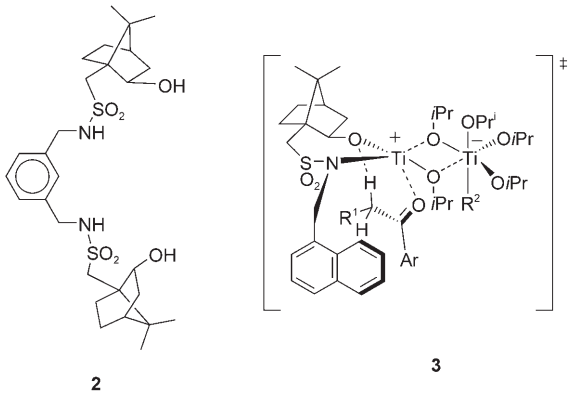
Organozinc reagents are the ideal candidates for this type of addition as their nucleophilicity is very low. In fact, it is well known that they do not add to aldehydes in noncoordinating solvents or to ketones.[9] Only recently, and in the framework of our ongoing project for the development of new chiral sulfonamides and their use in enantioselective catalytic synthesis,[10] the introduction of the isoborneolsulfonamide ligand **1**[11] permitted the first enantioselective catalytic addition of commercially available dialkylzinc reagents to simple ketones[12] in the presence of titanium alkoxides[13] (Scheme 2). The role of the titanium alkoxide is not only to



Scheme 2. First enantioselective catalytic addition of dialkylzinc reagents to simple ketones.

form the active chiral catalytic species, but also the removal of the tertiary alcohol generated during the catalytic cycle.

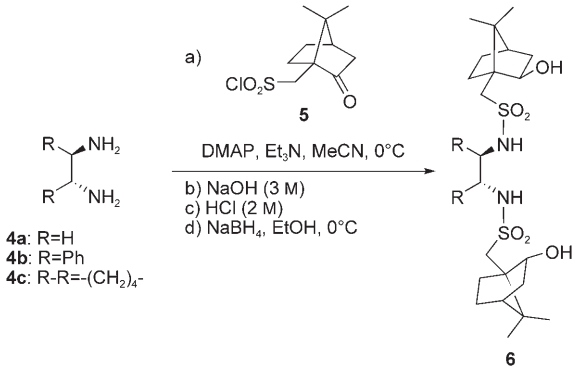
In a further effort to improve the enantioselectivity, ligands derived from aryl or benzyl diamines containing two isoborneolsulfonamide moieties were prepared. Among the tested systems, ligand **2** was the best, improving the enantioselectivity and the reaction conditions.[14] The design of this type of ligand was governed by the hypothetical existence of the bimetallic catalytic species **3**,[11b] which is similar to that described for the enantioselective addition of dialkylzinc reagents to aldehydes in the presence of titanium tetraisopropoxide.[15] In this proposal, it is assumed that the bimetallic species[16] has both a highly electrophilic, pentacoordinated, positively charged titanium center and a highly nucleophilic, hexacoordinated, negatively charged titanium center.[17] The idea was to remove the flexible alkoxide bridge ligands generating a more rigid structure in which, playing with the diamine used, the length and angles between both guest titanium centers could be clearly controlled and therefore the synergistic effect of both metallic centers and the enantioselectivity could be improved.



Results and Discussion

In this paper, we present our results on the development of new chiral isoborneolsulfonamide ligands and their uses as chiral promoters for the catalytic enantioselective addition of different organozinc reagents to simple ketones to give tertiary alcohols, the driving force of the design being that closer 1,2-etylendiamine linkers might favor the aforementioned synergistic effect of the two guest titanium metals.

Synthesis of the isoborneolsulfonamide ligands: The symmetrical chiral bis(isoborneolsulfonamide) ligands **6a–c** (Scheme 3) were prepared by reaction of the corresponding



Scheme 3. Synthesis of chiral tetradentate ligands **6a–c**. DMAP = 4(dimethylamino)pyridine.

ethylendiamine **4** with two equivalents of commercially available (1*S*)-(+)-10-camphorsulfonyl chloride (**5**) to give, after successive basic and acidic treatment, the corresponding ketones with yields $\geq 90\,\%$.[18] These crude ketone products were directly reduced with sodium borohydride to yield a mixture of all possible diastereomeric alcohols (Table 1), with the *exo–exo* diastereoisomer as the main product, easily isolated in all cases by flash chromatography. Alternatively, the final reduction can be performed by using an excess of diisobutylaluminium hydride at low temperature, rendering after hydrolysis the expected diols with similar chemical yields and diastereomeric ratios. The crystal structure of the *exo*-diol **6c** (HOCSAC), derived from the corre-

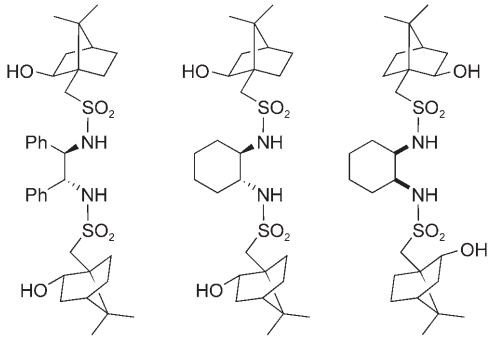
Table 1. Synthesis of tetradentate ligands **6a–c**.

Entry	Diastereomeric ratio[a]				Yield [%][b]
	exo–exo	*exo–endo*	*endo–endo*		
1	90	7	3	**6a**	53
2	98	1	1	**6b**	45
3	97	2	1	**6c**	66

[a] Determined by ^{1}H NMR spectroscopy (300 MHz) from the crude mixture. [b] Yield of the main diastereoisomer after flash chromatography.

sponding *trans*-1,2-bis(camphorsulfonylamido)cyclohexane was obtained by recrystallization of the pure ligand (see below).

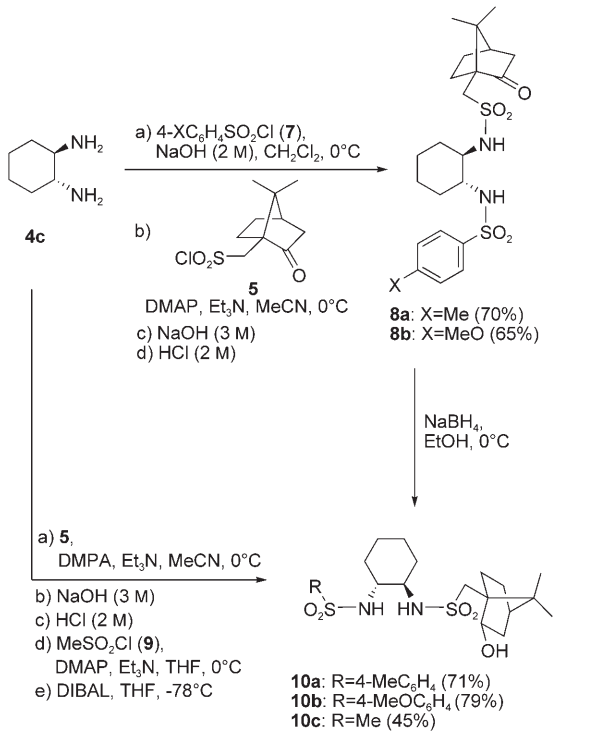
In a similar way, the diastereomeric partners **6d**,**e** were prepared with moderate chemical yields for the overall process; this was achieved by substituting the starting chiral



sulfonyl chloride with its enantiomer (1*R*)-(−)-10-camphorsulfonyl chloride (*ent*-**5**). The use of the achiral 1,2-*cis*-diaminocyclohexane as the starting amine led to the preparation of the ligand **6f**.

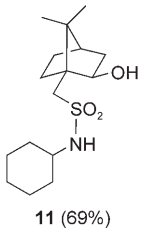
In addition to the symmetrical bis(isoborneol)sulfonamides (**6**), the unsymmetrical compounds **10** were prepared. In this case two different reaction pathways should be followed depending on the substituents (Scheme 4). In the case of aryl-substituted compounds **10a**,**b**, the only way to obtain them was by reaction of equivalent amounts of the chiral amine **4** and the corresponding arylsulfonyl chloride derivative **7** in a biphasic media of aqueous NaOH and methylene chloride. Then, subsequent reaction with the chiral (1*S*)-(+)-10-camphorsulfonyl chloride (**5**) and final basic and acidic treatment gave the expected ketones **8**.[19] Reduction with sodium borohydride under standard conditions produced a mixture of two possible diastereomeric alcohols, the major *exo*-derivatives **10a**,**b** were easily isolated after flash chromatography. However, the best procedure to obtain the mesylamide **10c** was firstly to introduce the camphorsulfonyl moiety and then the mesyl group, the final reduction producing the ligand **10c** in 45% overall yield.

Finally, the isoborneolsulfonamide **11** was prepared by the reaction of the commercially available chiral (1*S*)-(+)-10-camphorsulfonyl chloride (**5**) with cyclohexylamine under



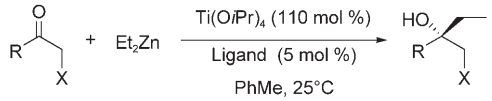
Scheme 4. Synthesis of chiral ligands **10a–c**. DIBAL = diisobutylaluminum hydride.

standard conditions, followed by reduction of the in situ generated ketone to the corresponding *exo*-derivative **11** with 69% overall yield. This bidentate ligand was the reference for the rest of the tri- and tetradentate ligands **6** and **10** to check our ligand design hypothesis.



Catalytic enantioselective addition of zinc reagents to simple ketones: Once the ethylenic ligands were prepared, they were first tested in the enantioselective addition of commercially available diethylzinc (**13a**) to ketones **12**,[20] in the presence of a slight excess of titanium tetraisopropoxide (Table 2). As a reference (entry 1), the ethylation of acetophenone with 10 mol% of ligand **11** gave the expected alcohol **14a** in a practically quantitative yield after 8 h, the *ee* determined as only 66% with *S* configuration. To our delight, the same reaction with the simple ethylene derivative **6a** rendered the alcohol **14a** with a notable 92% *ee* (entry 2). It should be pointed out that the amount of ligand was reduced to keep the total amount of isoborneolsulfonamide unit constant and, despite this decrease, the result was significantly higher for the ligand able to bind to two titanium atoms compared to the one (used in a double amount) able to bind only one titanium atom, indirectly confirming our initial hypothesis of the presence of bimetallic species.

Table 2. Ligand optimization for the catalytic enantioselective ethylation of ketones.



12 13a 14

Entry	Ligand	*t* [h]	Product	R	X	Yield [%][a]	*ee* [%][b]
1	**11**[c]	8	**14a**	Ph	H	>95	66 (*S*)
2	**6a**	96	**14a**	Ph	H	60	92 (*S*)
3	**6b**	48	**14a**	Ph	H	15	23 (*S*)
4	**6c**	8	**14a**	Ph	H	80	98 (*S*)
5	**6c**[d]	72	**14a**	Ph	H	20	97 (*S*)
6	**6c**[e]	3	**14a**	Ph	H	90	90 (*S*)
7	**6c**[f]	216	**14a**	Ph	H	90	90 (*S*)
8	**6c**[g]	15	**14a**	Ph	H	90	96 (*S*)
9	**6d**	120	*ent*-**14a**	Ph	H	25	33 (*R*)
10	**6e**	120	*ent*-**14a**	Ph	H	20	36 (*R*)
11	**6f**	72	*ent*-**14a**	Ph	H	16	24 (*R*)
12	**10a**	120	**14a**	Ph	H	55	>99[h] (*S*)
13	**10b**	120	**14a**	Ph	H	65	>99[h] (*S*)
14	**10c**	8	**14a**	Ph	H	83	96 (*S*)
15	**6a**	22	**14b**	Ph	Br	79	49 (*R*)
16	**6c**	0.2	**14b**	Ph	Br	70	50 (*R*)
17	**6a**	17	**14c**	(*E*)-PhCH=CH	H	80	16 (−)
18	**6c**	8	**14c**	(*E*)-PhCH=CH	H	90	>99[h] (−)

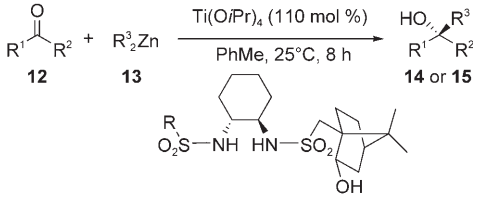
[a] Isolated yields after bulb-to-bulb distillation. [b] Determined by using GLC with a cyclodextrin column, the absolute configuration or the sign of the predominant enantiomer is indicated in parentheses. [c] 10 mol % of ligand used. [d] The addition was performed at 0 °C. [e] The addition was performed at 60 °C. [f] Only 10 mol % of titanium tetraisopropoxide was used. [g] Only 40 mol % of titanium tetraisopropoxide was used. [h] Only one enantiomer was detected.

However, it is also worth noting that the reaction with the tetradentate ligand **6a** was slower than for the bidentate ligand **11**. This result encouraged us to try the ligand **6b**, as in our previous experience *N*-benzyl isoborneolsulfonamides yielded the best results.[11,14] However, the enantioselectivity for the ethylation of acetophenone with **6b** was very modest (entry 3), thus we reasoned that the phenyl substituents on the ligand **6b** make it more difficult to achieve the appropriate arrangement in the catalyst. To ensure the favorable synergistic effect of both metallic centers we turned our attention to the *exo*-diol derived from *trans*-1,2-bis(camphorsulfonylamido)cyclohexane (**6c**, HOCSAC) in which the rotation around the carbon–carbon bond of the 1,2-diamine subunit was restricted. After only 8 h, the starting acetophenone was consumed producing the expected alcohol with excellent results (entry 4). The effect of temperature on the ethylation of acetophenone (**12a**) was studied by using the HOCSAC ligand (**6c**) as model. From this study, we found that despite the enantioselectivity remaining practically unchanged when the temperature was decreased to 0 °C, the chemical yield decreased and the reaction time was longer. When the same ethylation was performed at 60 °C, the enantioselectivity decreased to some extent (entry 6). The fact that the amount of titanium tetraisopropoxide played an important role in these results was demonstrated by the long reaction time and lower enantioselectivity observed for the addition of diethylzinc to acetophenone by using 5 mol % of **6c** and only 10 mol % of the titanium alkoxide. However, an increase in the amount of titanium complex up to 40 mol % yielded very close results to those obtained by using a stoichiometric amount (compare entries 4, 7, and 8). It should be pointed out that when the reaction was performed with triethylaluminium instead of standard diethylzinc, the alcohol **14a** was isolated as a racemic mixture. The diastereomeric ligands **6d**,**e** were tested to determine if both chiral starting materials (diamines and sulfonyl chloride) produced the matched or mismatched couples. The results indicated that both the ligands **6d**,**e** were the mismatched diastereoisomers as the reaction took a very long time, producing very modest enantioselectivities. From these results, and comparing with those of entries 3 and 4, the outcome of the reaction seems to be controlled by the isoborneol motif and not by the amine. However, when the reaction was conducted by using ligand **6f** (entry 11) (prepared from the achiral *cis*-1,2-diaminoyclohexane and the chiral (1*S*)-(+)-10-camphorsulfonyl chloride (**5**)), the absolute configuration of the alcohol *ent*-**1a** produced was *R* instead of *S* as expected when using ligands of the series derived from **5**. All these results point out the inherent difficulties involved in proposing any transition-step model. Once we ascertained that ligands with two isoborneol moieties gave better results than the ligand with only one group (compare entries 1 and 4), we wondered if the second isoborneol group was actually necessary or whether it could be replaced by another achiral group. Thus, the enantioselective addition of diethylzinc to acetophenone in the presence of titanium tetraisopropoxide was carried out by using ligands **10**. Surprisingly, the enantioselectivity was unbeatable for the arylsulfonyl derivatives **10a**,**b**, with only one enantiomer of alcohol **14a** detected by CG analysis, although the reaction time was sensibly increased (entries 12 and 13). The reaction with the less hindered ligand **10c** derived from mesyl gave a slightly worse result compared to previous ligands, but it was practically the same as for the HOCSAC ligand (compare entries 14 and 4). If the reaction time is included in the comparison, the HOCSAC ligand (**6c**) gave the best results, this tendency was also observed for other ketones, such as bromoacetophenone and benzylidenacetone, for the last case the alcohol **14c** was detected as only one enantiomer (entry 18).

Once ligands **6c** and **10a**,**b** were determined as the best promoters for the ethylation of simple ketones, we studied the scope of the reaction by changing starting ketones **12**

and organozinc reagents **13** (Table 3). The reaction worked nicely when dimethylzinc (**13b**) was used as the source of nucleophile, giving excellent results for the reaction promoted by HOCSAC (**6c**) and only one enantiomer for ligands **10a**,**b**; however, the reaction times and the chemical yields were accountably more inferior for ligands **10** than for **6c** (compare entries 1–3). The presence of either electron-donating or -withdrawing groups at the 4-position of the aromatic ring of the ketone did not have any impact on the results (compare entries 4 and 5 in Table 3 and entry 4 in Table 2). However, the size of both the aromatic group and the corresponding alkyl substituent of the ketones had an important impact on the results. Thus, the increase in size of the aryl substituent from phenyl to naphthyl (entries 4 and 6 in Tables 2 and 3, respectively) or the alkyl substituent from methyl to *n*-butyl (entries 18 and 7 in Tables 2 and 3, respectively) decreased the enantioselectivity from 98, >99% to 86, 85%, respectively. The ethylation process also worked nicely for α,β-unsaturated ketones, independent of the multiple bonds, with only one enantiomer detected. These excellent results with HOCSAC as the promoter ligand have been applied to the synthesis of (−)-frontatlin through the catalytic enantioselective addition of dimethylzinc to a functionalized α,β-unsaturated ketone,[21] and to other tertiary alcohols.[22] It is worth noting that the enantioselective addition of dimethylzinc (**13b**) to cyclohexyl butyl ketone took place, for the first time, with a meritorious 65% *ee* (entry 9, Table 3), the same addition giving the racemic alcohol **14i** when the simple ligand **1** was used.[11b] This example is illustrative of the scope of the reaction as the promoter differentiates between two rather similar alkyl substituents on the ketone, this ketone being less reactive than the related aryl alkyl ketones. Finally, it should be pointed out that the reaction can be performed by using commercially available diphenylzinc[23] to yield the corresponding diarylalkanol derivatives[24] **15** with good enantioselectivities.[25] The arylation process was insensitive to the presence of either electron-donating or -withdrawing groups at the 4-position on the aromatic ring of ketone,[26] while the enantioselectivity decreased when the bulkiness of alkyl group was increased (entries 10–13), as was previously found when using diethylzinc.

Table 3. Catalytic enantioselective addition of zinc reagents to ketones.



6c: R=10-isobornyl (HOCSAC)
10a: R=4-MeC$_6$H$_4$
10b: R=4-MeOC$_6$H$_4$

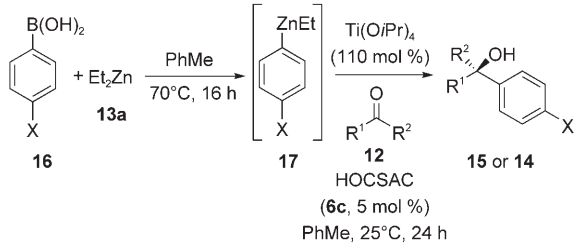
(5 mol %)

Entry	Ligand	R^1	R^2	R^3	Product	Yield [%][a]	*ee* [%][b]
1	**6c**	Ph	Et	Me	*ent*-**14a**	>95	98 (*R*)
2	**10a**	Ph	Et	Me	*ent*-**14a**	25[c]	>99[d] (*R*)
3	**10b**	Ph	Et	Me	*ent*-**14a**	29[c]	>99[d] (*R*)
4	**6c**	4-MeC$_6$H$_4$	Me	Et	**14d**	90	95 (−)
5	**6c**	4-F$_3$CC$_6$H$_4$	Me	Et	**14e**	90	93 (−)
6	**6c**	2-naphthyl	Me	Et	**14f**	>95	86 (−)
7	**6c**	(*E*)-PhCH=CH	*n*Bu	Et	**14g**	80	85 (+)
8	**6c**	PhC≡C	Me	Et	**14h**	>95	>99[d] (+)
9	**6c**	*c*C$_6$H$_{11}$	*n*Bu	Me	**14i**	70[e]	65 (−)
10	**6c**	4-MeC$_6$H$_4$	Me	Ph	**15a**	>95[f]	92[g] (−)
11	**6c**	4-BrC$_6$H$_4$	Me	Ph	**15b**	>95[f]	96[g] (+)
12	**6c**	4-F$_3$CC$_6$H$_4$	Me	Ph	**15c**	>95[f]	91[g] (+)
13	**6c**	4-BrC$_6$H$_4$	Et	Ph	**15d**	>95[f]	80[g] (+)

[a] Isolated yields after bulb-to-bulb distillation or column chromatography. [b] Determined by using GLC with a cyclodextrin column, the absolute configuration or the sign of the predominant enantiomer is indicated in parentheses. [c] Yield after 120 h. [d] Only one enantiomer was detected. [e] Yield after 240 h. [f] Yield after 24 h. [g] Determined by using HPLC with Chiracel AD column.

Despite the potential high interest of the above mentioned type of chiral diarylalkanols **15** with electronically and sterically similar aryl rings, the use of very expensive diphenylzinc (**13c**) makes this approach less attractive for their enantioselective syntheses. To avoid this inconvenience, other alternative preparations of organozinc reagents were evaluated.[27] Our first choice was the use of arylboronic acids as a viable phenyl source,[28] as they avoid the use of the aryllithium or the related magnesium derivative and overcomes the intrinsic problem of the presence of achiral lithium or magnesium salts, which could compete with the chiral catalysts in the addition step.[29] Thus, the reaction of different boronic acids **16** with an excess of diethylzinc at 70°C gave the corresponding arylzinc derivatives **17**, which were in situ trapped by reaction with different ketones **12** to yield the expected diarylalkanols **15** or the related alcohols **14** after hydrolysis (Table 4). In fact, the reaction of phenyl boronic acid and 4-bromoacetophenone produced the expected alcohol **15b** with a slightly worse result than when pure diphenylzinc was used (compare entries 11 and 1 in Tables 3 and 4, respectively), with byproducts resulting from the ethylation of the ketone and the auto-aldol condensation process detected. To minimize the formation of these byproducts, several reaction condition parameters were changed, such as the addition temperature, amount of titanium tetraisopropoxide, and solvent, and in all cases the chemical yields were significantly inferior and the enantioselectivity similar. We then studied the influence of the nature of the ketone on the enantio-

Table 4. Catalytic enantioselective arylation of ketones by using boronic acids as source of nucleophile.



Entry	X	R^1	R^2	Product	Yield [%][a]	*ee* [%][b]
1	H	4-BrC_6H_4	Me	**15b**	79	81 (+)
2	H	4-BrC_6H_4	Me	**15b**[c]	45[d]	73 (+)
3	H	4-BrC_6H_4	Me	**15b**[e]	2	n.d.[f]
4	H	4-BrC_6H_4	Me	**15b**[g]	40	72 (+)
5	H	4-BrC_6H_4	Me	**15b**[h]	35	75 (+)
6	H	Et	Me	*ent*-**14a**	25	6[i] (*R*)
7	H	*n*Bu	Me	*ent*-**14j**	65	30[i] (*R*)
8	Me	Ph	Me	*ent*-**15a**	58	84 (+)
9	Br	Ph	Me	*ent*-**15b**	65	93 (−)
10	CF_3	Ph	Me	*ent*-**15c**	31[j] (52)[k]	64[l] (−)
11	H	Ph	Et	**15d**	41[j] (91)[k]	68 (+)

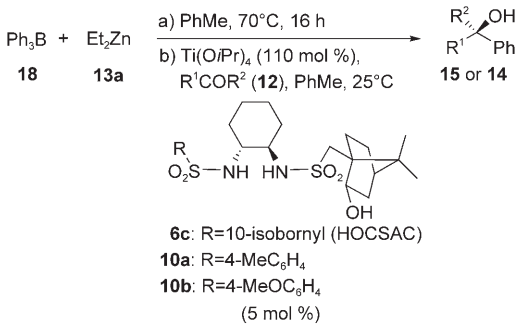
[a] Isolated yields after column chromatography. [b] Determined by HPLC using a Chiracel columns, the absolute configuration or the sign of the predominant enantiomer is indicated in parentheses. [c] The temperature for the addition step was 0°C. [d] Isolated yield after 10 d. [e] The temperature for the addition step was 60°C. [f] n.d. = not detected. [g] Only 10 mol% of $Ti(OiPr)_4$ was used. [h] CH_2Cl_2 was used as the solvent. [i] Determined by using GLC with a cyclodextrin column. [j] Isolated yield after 3 d. [k] Yield based on the amount of starting ketone consumed. [l] Isolated yield after 3 d.

selectivity, finding that the results for simple small dialkyl ketones were very low, increasing as the difference between both alkyl groups increased (entries 6 and 7, Table 4). For aryl alkyl ketones the results were good, decreasing as the alkyl group became more hindered (compare entries 1 and 11). The effect of the substitutents on the arylboronic acid was also checked, and the enantioselectivity obtained for systems bearing either a weak electron-donating group or a slightly electron-withdrawing group gave results in the range of those obtained by using pure diphenylzinc (entries 8 and 9), which could lead one to believe that the electronic character of arylboronic acid did not have any influence on the results. However, when the reaction was performed with 4-trifluoromethylphenylboronic acid as a nucleophilic aryl source, the enantioselectivity substantially dropped (entry 10) and the reaction time was increased to three days producing chemical yield of only 31% (40% of starting ketone was recovered).

The reaction performed by using 3-pyridylboronic acid or diethyl(3-pyridyl)borane merits a separate comment, as in both cases the expected tertiary alcohol could not be detected, the starting acetophenone being consumed in reduction, auto-aldol, and ethylation processes.

One of the drawbacks of the aforementioned protocol was the use of a large excess of diethylzinc due to the presence of two acidic protons from the boronic acid, which are partially removed[30] prior to the exchange to form the hypothetical species **17**. The difficulty in adjusting this excess meant that one of the byproducts was the corresponding ethylated tertiary alcohol, the amount of which was always lower than 10%. To overcome this problem, we turned our attention to triarylborane as an initial source of nucleophile, as three aryl moieties of borane compound are exchangeable in principle.[31] Thus, the overnight reaction of triphenylborane (**18**) and diethylzinc (**13a**) at 70°C under an argon atmosphere, hypothetically, produced the corresponding ethyl phenyl zinc intermediated of type **17**, which was in situ trapped by standard catalytic enantioselective addition to 4-bromoacetophenone, by using HOCSAC (**6c**) as chiral promoter, to yield the expected diaryl alkanol **15b** with excellent results after a 16 h reaction (Table 5, entry 1). The enantioselectivity obtained for this reaction was similar to that obtained when using either the pure diphenylzinc or the boronic/zinc exchange strategy. The previous transmetallation step could be avoided and the alcohol **15b** obtained by simply mixing all reagents at the same time, which implies that the transmetallation step is faster than the further

Table 5. Catalytic enantioselective phenylation of ketones by using triphenylborane as source of nucleophile.



Entry	Ligand	*t* [h]	R^1	R^2	Product	Yield [%][a]	*ee* [%][b]
1	**6c**	16	4-BrC_6H_4	Me	**15b**	96	90 (+)
2	**6c**	60[c]	4-BrC_6H_4	Me	**15b**	81	82 (+)
3	**10a**	120	4-BrC_6H_4	Me	**15b**	90	>99[d] (+)
4	**10b**	24	4-BrC_6H_4	Me	**15b**	96	>99[d] (+)
5	**6c**	16	4-MeC_6H_4	Me	**15a**	98	93 (−)
6	**6c**	16	4-$F_3CC_6H_4$	Me	**15c**	83	78 (+)
7	**6c**	40	4-BrC_6H_4	Et	**15d**	63	79 (+)
8	**6c**	70	*n*Bu	Me	*ent*-**14j**	50	25[e] (*R*)

[a] Isolated yields after column chromatography. [b] Determined by using HPLC with a Chiracel column, the absolute configuration or the sign of the predominant enantiomer is indicated in parentheses. [c] The previous transmetallation process was not performed. [d] Only one enantiomer was detected. [e] Determined by using GLC with a cyclodextrin column.

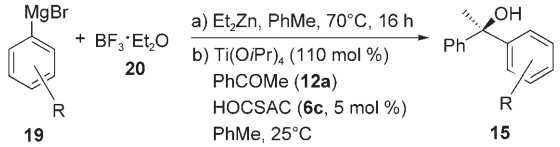
catalytic enantioselective one (entry 2). However, in this case, the enantioselectivity and chemical yield were slightly lower, while the reaction time was greatly increased. Surprisingly, when the reaction was performed with the tridentate chiral systems **10a**,**b**, only one enantiomer of product could be detected, although the reaction time suffered an important increase. The presence of a weak electron-donating group on the aryl moiety of the ketone had a beneficial effect as far as the enantioselectivity was concerned; however, the presence of electron-withdrawing groups on the aryl moiety or the presence of a more hindered alkyl moiety in the ketone decreased these results (entries 5–7). The use of 2-pentanone gave the expected alcohol *ent*-**14j** with similar results to those obtained when phenylboronic acid was used as a nuleophilic source (compare entries 7 and 8 in Tables 4 and 5, respectively) and significantly lower than those obtained for aryl alkyl ketones.

Surprisingly, the reaction failed when other commercially available triarylborane derivatives were used as a source of nucleophile. We rationalized these results by proposing that amine derivatives present in the reaction mixture were acting as stabilizating agents for the borane, which could interfere in either the transmetallation or the addition step. In fact, very recently, the kinetics of the transmetallation reactions between different phenylborane complexes and diethylzinc has been studied, showing that the presence of amines retarded this equilibrium and that even the phenylzinc reagent generated from ammonia complex was significantly less reactive.[30g] To prove this hypothesis, we prepared the corresponding substituted triarylborane by direct reaction of the corresponding arylmagnesium bromide **19** with trifluoro boron ether complex,[32] followed by precipitation of magnesium salts to avoid the possible competition of this Lewis acid with the chiral titanium one. The salt-free triarylborane was then transmetallated with diethylzinc and the arylzinc reagent of type **17** was trapped in the catalytic enantioselective addition to acetophenone (**12a**) in the presence of chiral promoter HOCSAC (**6c**) to yield, after hydrolysis, the expected diarylalkanols **15** (Table 6). The results were excellent for 4-methylphenylmagnesium bromide (entry 1) and practically independent of the electronic character of substituents (compare entries 2 and 4). It should be pointed out that in the cases where chloro- and methoxyphenylmagnesium bromide derivatives were used (entries 3 and 5), the typical elimination of magnesium salts failed. These results point out the great importance of the presence of any hypothetical "inert" salt additives to obtain good results.

After the great success in the arylation of ketones after the boron/zinc-transmetallation process, we focused on the use of alternative zinc reagents obtained by transmetallation in the catalytic enantioselective addition, the first trial being an allylation process.[33] The idea was to employ allyl esters as a source of nucleophile through π-allyl palladium umpolung processes. It is well known that their reaction with palladium(0) renders the corresponding allyl palladium complex, which in turn can be transmetallated with diethylzinc to generate in situ allylzinc derivatives.[34] The final catalytic enantioselective reaction with ketones would give the corresponding chiral tertiary homoallylic alcohol. Thus, when the reaction was performed by using diallyl carbonate (**21a**) with acetophenone (**12a**) as the electrophilic partner and HOCSAC (**6c**) as the chiral promoter, the expected alcohol **22a** was obtained with an excellent chemical yield, but with a very low enantioselectivity (Scheme 5), the absolute configuration of alcohol being *S*,[35] as was expected for this ligand. The same reaction with cinnamyl acetate (**21b**) gave an equimolecular mixture of the two diastereoisomers *syn*- and *anti*-**22b**, the enantioselectivity depending on the chiral promoter used. When the promoter HOCSAC (**6c**) was used, the diastereoisomer *syn*-**22b** showed the highest *ee* of the series (Scheme 5). Independently of the promoter used (**6c**, **10a**, or **10c**), the diastereoisomer *syn*-**22b** produced higher *ee* than the related *anti*-**22b**, the value for the former isomer being double that of the previous one. The results are indeed not very good, so the transmetallation strategy is not a good one to use for the allylation processes.

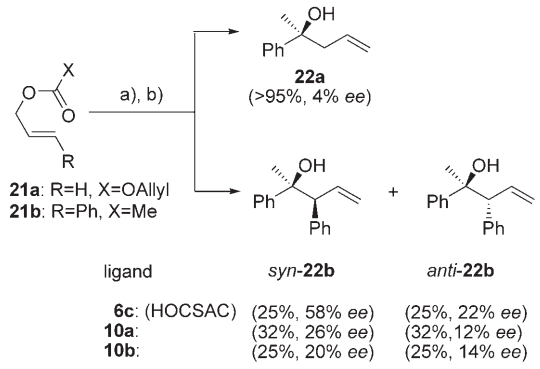
The next process studied was the alkynylation process,[36] performed by deprotonation of phenylacetylene (**23a**) with diethylzinc to yield the corresponding alkynyl zinc re-

Table 6. Catalytic enantioselective arylation of ketones by using Grignard reagents as source of nucleophile.



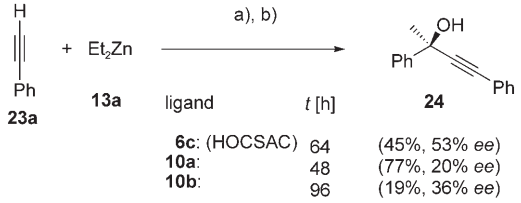
Entry	*t* [h]	R	Product	Yield [%][a]	*ee* [%][b]
1	5	4-Me	*ent*-**15a**	95	96 (+)
2	23	3-Me	**15e**	30	86 (−)
3	97	4-Cl	**15f**	15	12 (−)
4	23	4-F	**15g**	70	84 (−)
5	100	4-MeO	**15h**	0	–

[a] Isolated yields after column chromatography. [b] Determined by using HPLC with a Chiracel column, the sign of the predominant enantiomer is indicated in parentheses.



Scheme 5. Allylation of acetophenone (**12a**): a) $[Pd(PPh_3)_4]$ (1 mol %), Et_2Zn (900 mol %), PhMe, 70 °C, 16 h; b) $Ti(OiPr)_4$ (110 mol %), ligand (5 mol %), PhCOMe (**12a**, 100 mol %), 25 °C.

agent,[37] which was trapped by subsequent reaction with acetophenone (**12a**) in the presence of substoichiometric amounts of a chiral ligand and titanium tetraisopropoxide (Scheme 6). The results when HOCSAC (**6c**) was used



Scheme 6. Alkynylation of acetophenone (**12a**): a) PhMe, 25 °C, 3 h; b) Ti(O*i*Pr)$_4$ (10 mol %), ligand (5 mol %), PhCOMe (**12a**, 100 mol %), 25 °C.

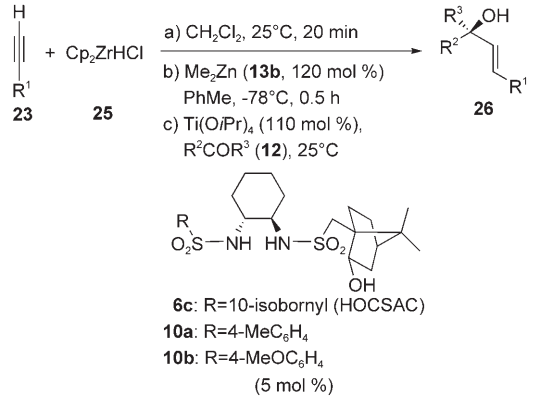
(53 % *ee*) were better than those obtained when tridentate ligands **10a**,**b** were used (20 and 36 % *ee*, respectively). This level of enantioselectivity could not be improved by either the addition of 2.5 mol % of the polyethyleneglicol derivative[38] (DiMPEG: polyethylene glycol dimethyl ether M_n 2000, after 62 h: 24 %, 32 % *ee*) or by performing the previous preparation of phenylethynyltitanium triisopropoxide[39] and final addition to acetophenone (after 48 h: 60 %, 8 % *ee*), protocols which have been successfully applied for other enantioselective additions to carbonyl compounds.

Finally, we studied the catalytic enantioselective alkenylation of ketones through a hydrozirconation process of terminal alkynes,[40] followed by a transmetallation with dimethylzinc (**13b**) and addition to ketones, which was far more successful (Table 7). Firstly, we studied the influence of the chiral promoter on the enantioselectivity, finding that ligand **6c** gave slightly lower enantioselection than ligand **10b** in the alkenylation of acetophenone by using trimethylsilyl-substituted alkynes to yield alcohol **26a** (compare entries 1 and 2); this functionalized tertiary alcohol had extra value due to its possible utilization as starting material in further coupling reactions.[41] As in previous addition processes, the alkenylation by using phenylacetylene (**23a**) gave practically the same results for ligands **10a**,**b** (entries 3 and 4). Concerning the scope of the reaction, the best results were obtained by using aliphatic alkynes (with or without functionalization). The nature of the ketone was more important than the bulkiness of the substitutents, thus the α,β-unsaturated ketones produced a worse result (entry 6).

Spectroscopic studies on the possible catalyst: Once we found that the ligands reported in this study (tri- and tetradentate isoborneolsulfonamide derivatives) produced better enantioselectivity than the related bidentate isoborneolsulfonamide derivatives (indirect proof of our hypothesis that the catalytic species was a bimetallic titanium complex), we then tried to confirm it spectroscopically. We initiated the study with the crystal structure of chiral ligand HOCSAC (**6c**, Figure 1), which showed a typical C_2 symmetry, in concordance with the ^{1}H NMR spectrum obtained. However, all our attempts to obtain suitable crystals of the related HOCSAC–titanium complexes failed, producing powdered materials.

After this failure, we turned our attention to the possibility of detecting the bimetallic HOCSAC-titanium complex by other spectroscopic techniques. Thus, ^{1}H NMR spectra of mixtures of different ratios of ligand HOCSAC (**6c**) and titanium tetraisopropoxide were recorded at room temperature (Figure 2). Previously, we applied this strategy with the simple ligand **1**, obtaining complicated spectra in which the structure of the main complex depended strongly on the initial amount of titanium tetraisopropoxide added.[11b] In the case studied here, when a equimolecular amount of HOCSAC was mixed with titanium tetraisopropoxide in toluene at room temperature, after removing all volatiles, the spectrum showed mainly two compounds: the starting unchanged ligand and another complex. Surprisingly, when the reagents ratio increased from 1:1 to 1:2, only one complex appeared, the same compound detected in the previous spectrum. This complex was also the main product of the mixture obtained by using a large excess of titanium tetraisopropoxide, which indi-

Table 7. Catalytic enantioselective alkenylation of ketones.



Entry	Ligand	R^1	R^2	R^3	*t* [h]	Product	Yield [%][a]	*ee* [%][b]
1	**6c**	$SiMe_3$	Ph	Me	108	**26a**	55	85 (–)
2	**10b**	$SiMe_3$	Ph	Me	60	**26a**	75	94 (–)
3	**10a**	Ph	Ph	Me	72	**26b**	85	76 (*S*)
4	**10b**	Ph	Ph	Me	72	**26b**	77	78 (*S*)
5	**10b**	*n*Bu	Ph	Me	60	**26c**	57	94 (*S*)
6	**10b**	*n*Bu	PhC≡C	Me	16	**26d**	98	74 (–)
7	**10b**	*n*Bu	Ph	Et	132	**26e**	45	90 (*S*)

[a] Isolated yields after column chromatography. [b] Determined by using HPLC with a Chiracel column, the absolute configuration or the sign of the predominant enantiomer is indicated in parentheses.

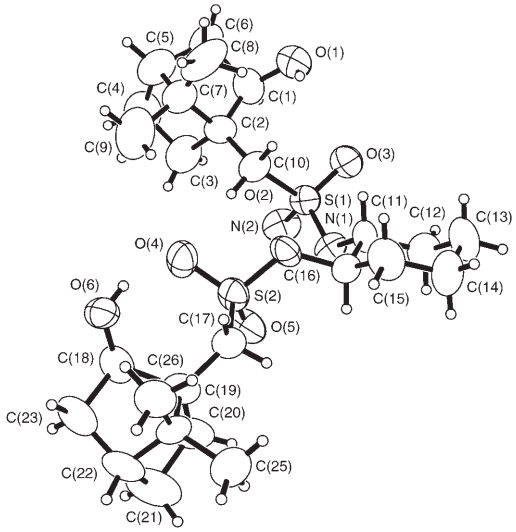


Figure 1. ORTEP drawing of HOCSAC ligand (**6c**).

cates its high stability, providing indirect proof of the possible existence of bimetallic complexes as the truly catalytic active species and validated our proposal for ligand design.

Conclusion

We describe here the preparation of different *trans*-1-sulfonylamino-2-isoborneolaminocyclohexane derivatives able to chelate two titanium atoms at the same time. These ligands have been successfully used in the uncommon catalytic enantioselective addition of organozinc reagents to ketones. The procedures permitted not only the use of commercially available dialkylzinc reagents but also of other zinc reagents obtained through different transmetallation processes from arylboronic acids, arylboranes, arylmagnesiums, allylesters, and alkenylzirconiums. The enantioselectivity found for tertiary alcohols obtained after an alkylation or an arylation process was unsurpassable (only one enantiomer detected). Enantioselectivity was excellent for the alkenylation process (up to 94 % *ee*), whereas the enantiomeric excesses for related alcohols obtained through an alkynylation or allylation process were modest. Some evidence for the presence of a complex bearing two titanium atoms and a ligand molecule in the mechanistic pathway were found through ^{1}H NMR spectroscopic studies, this being the driving force behind our ligand design.

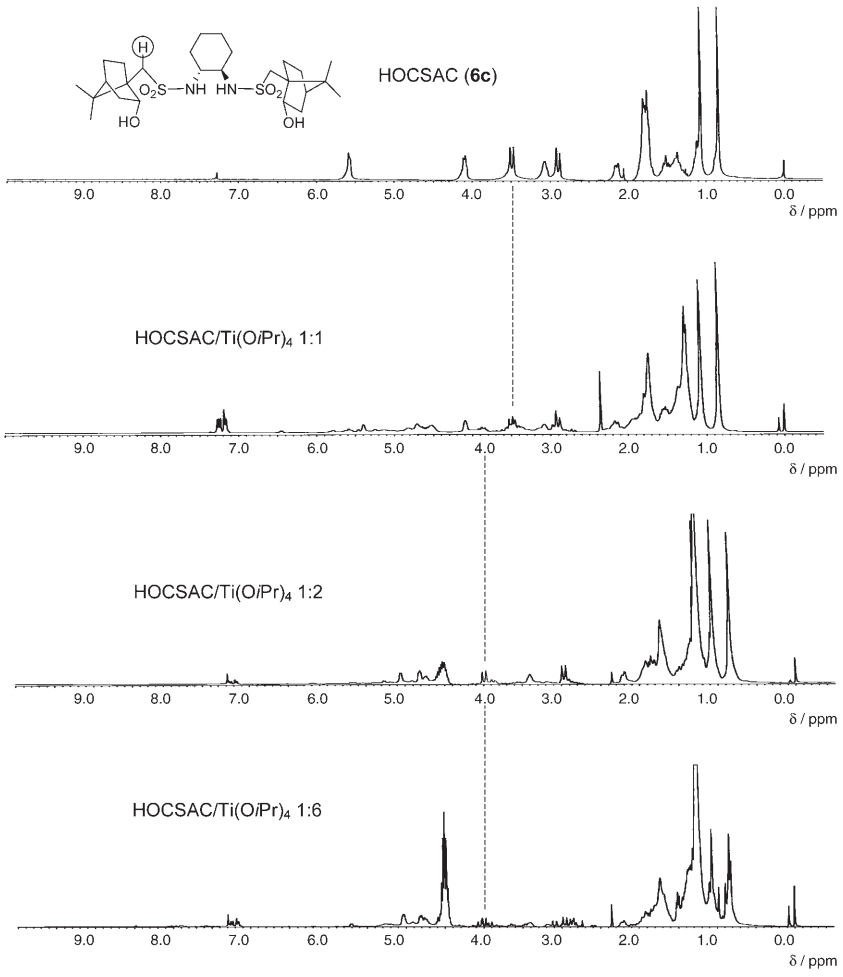


Figure 2. ^{1}H NMR spectra in $CDCl_3$ at room temperature of HOCSAC/Ti(O*i*Pr)$_4$ at different ratios.

Experimental Section

Chemicals and instrumentation: 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. $[\alpha]_D$ were recorded at room temperature (ca. 25 °C) in a DIP-1000 JASCO polarimeter (p.a. solvents, Panreac). FTIR spectra were obtained on a Nicolet Impact 400 D spectrophotometer. NMR spectra were recorded on a Bruker AC-300 (300 MHz for ^{1}H and 75 MHz for ^{13}C spectra) by using $CDCl_3$ as the solvent and TMS as the internal standard; chemical sifts are given in δ (ppm) and coupling constants (J) in Hz. Mass spectra (EI) were obtained at 70 eV on a Shimazdu QP-5000 spectrometer, giving fragment ions in m/z with relative intensities (%) in parentheses. High resolution mass spectra and X-ray experiments were performed by the corresponding Mass Spectrometry and Crystallographic Service at the University of Alicante. The purity of volatile products and the chromatographic analyses (GLC) were determined with a Hewlett Packard HP-5890 instrument equipped with a flame ionization detector and 12 m HP-1 capillary column (0.2 mm diameter, 0.33 mm film thickness, OV-1 stationary phase), by using nitrogen (2 mL min^{-1}) as the carrier gas

($T_{injector}=275\,°C$, $T_{detector}=300\,°C$, $T_{column}=80\,°C$ (3 min) and 60–270 °C (15 °C min^{-1}), $p=40$ kPa; t_r values are given in min under these conditions). The enantiomeric ratios (*er*) for the calculation of the enantiomeric excess of tertiary alcohols were determined with the aforementioned apparatus by using either 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) with nitrogen as the carrier gas ($T_{injector}=250\,°C$, $T_{detector}=260\,°C$; A conditions: $T_{column}=100\,°C$ (20 min) and 220 °C (0.3 °C min^{-1}), $P=$ 120 kPa) or a 50 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; B conditions: $T_{column}=90\,°C$ (5 min) and 180 °C (0.1 °C min^{-1}), $P=$ 120 kPa). Alternatively, the enantiomeric ratios were determined by HPLC analyses in a HP-1100 or Jasco P-1030 apparatus by using hexane/2-propanol mixtures as solvents, and as chiral columns: Chiralcel OD-H (ODH), Chiralpak AD (AD), Chiralpak AS (AS), and Chiralcel OJ (OJ), indicating in each case the column and solvent ratio used. The $t_r(R)$ and $t_r(S)$ values are given in min under these conditions. TLC was carried out on Schleicher & Schuell F1400/LS 254 plates coated with a 0.2 mm layer of silica gel; detection by UV_{254} light, staining with phosphomolybdic acid (25 g phosphomolybdic acid, 10 g $Ce(SO_4)_2{\cdot}4H_2O$, 60 mL concentrated H_2SO_4 and 940 mL H_2O) or with I_2; R_f values are given under these conditions. Column chromatography was carried out by using silica gel 60 of 35–70 mesh. (*E*)-1-Phenylhept-1-en-3-one[42] and cyclohexyl but-1-yl ketone[43] were prepared by reaction of the corresponding acyl chloride with morpholine, followed by addition of *n*-butyllithium. All reagents were commercially available (Acros, Aldrich, Strem) and were used as received. Solvents were dried by standard procedures.[44]

General procedure for the synthesis of isoborneol sulfonamide derivatives 6 and 11: A solution of DMAP (0.66 g, 5.4 mmol, 0.45 equiv), Et_3N (3.5 mL, 25 mmol, 2.1 equiv), and the corresponding ethylendiamine **4** (12 mmol, 1 equiv) or cyclohexylamine (24 mmol, 2 equiv) in CH_3CN (25 mL mmol^{-1}) was added to a solution of (1*S*)-(+)-10-camphorsulfonyl chloride (**5**) or its enantiomer (1*R*)-(−)-10-camphorsulfonyl chloride (*ent*-**5**) (6.25 g, 25 mmol, 2.1 equiv) in CH_3CN (25 mL) at 0 °C. The mixture was stirred for 24 h and the temperature allowed to rise to 25 °C. Then, the mixture was quenched by the addition of an aqueous solution of NaOH (3 M, 25 mL) and extracted with EtOAc (3×30 mL). The combined organic layers were washed with a HCl solution (2 M, 50 mL), dried over Na_2SO_4, and concentrated. Finally, the crude residue was dissolved in ethanol (60 mL) and treated with $NaBH_4$ (1.82 g, 6 equiv) at 0 °C. The reaction mixture was warmed up to room temperature and stirred for 24 h. After this time, ethanol was removed under reduced pressure (15 Torr) and the resulting residue was dissolved in a saturated solution of NH_4Cl (50 mL) and extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated. The residue was purified by flash chromatography on silica gel (hexane/EtOAc) to give isoborneolsulfonamides **6a–f** and **11**. Yields are included in Table 1 and in the Results and Discussion section.

(1*S*,2*R*,4*S*,1″*S*,2″*R*,4″*S*)-*N*-{*trans*-2′-[2″-Hydroxy-7″,7″-dimethylbicyclo-[2.2.1]hept-1″-ylmethylsulfonamino]ethyl}-2-hydroxy-7,7-dimethylbicyclo-[2.2.1]hept-1-ylmethanesulfonamide (6a):[45] White solid; $R_f=0.36$ (hexane/AcOEt 1:1); m.p. 134–136 °C (AcOEt/hexane); $[\alpha]_D=-95.3$ ($c=$ 1.04 in $CHCl_3$); ^{1}H NMR: $\delta=0.84$, 1.07 (2 s, 6 H each; 4×CH_3), 1.45–1.80 (m, 14 H; 2× $CH_2CH(CH_2)_2$), 2.94, 3.50 (2 d, $J=13.9$ Hz, 2 H each; 2× CH_2S), 3.36 (br s, 2 H; 2×OH), 3.30–3.40 (m, 4 H; 2×CH_2N), 4.05–4.10 (m, 2 H; 2×CHO), 5.55–5.65 ppm (m, 2 H; 2×NH); ^{13}C NMR: $\delta=19.8$ (2 C), 20.5 (2 C), 27.3 (2 C), 30.3 (2 C), 39.2 (2 C), 43.5 (2 C), 44.3 (2 C), 48.8 (2 C), 50.3 (2 C), 52.1 (2 C), 76.2 ppm (2 C); IR (KBr): $\tilde{\nu}=3530$, 3284 (NH, OH), 1148, 1066 cm^{-1} (C–O); MS (EI): *m*/*z* (%): 492 (<1) $[M-H_2O]^+$, 183 (100); HRMS: *m*/*z*: calcd for $C_{22}H_{40}N_2O_6S_2{\cdot}H_2O$: 474.2209; found: 474.2222.

(1*S*,2*R*,4*S*,1′*R*,2′*R*,1″*S*,2″*R*,4″*S*)-*N*-{*trans*-2′-[2″-Hydroxy-7″,7″-dimethylbicyclo[2.2.1]hept-1″-ylmethylsulfonamino]-1′,2′-diphenylethyl}-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide (6b): White solid; $R_f=0.72$ (hexane/AcOEt 1:1); m.p. 181–183 °C (AcOEt/hexane); $[\alpha]_D=-11.5$ ($c=1.9$ in $CHCl_3$); ^{1}H NMR: $\delta=0.40$, 0.78 (2 s, 6 H each; 4×CH_3), 0.95–1.70 (m, 14 H; 2×$CH_2CH(CH_2)_2$), 1.94, 2.94 (2 d, $J=$ 13.7 Hz, 2 H each; 2×CH_2S), 3.45 (s, 2 H; 2×OH), 4.00–4.50 (m, 2 H; 2× CHO), 4.85–4.86 (m, 2 H; 2×CHN), 6.42 (s, 2 H; 2×NH), 7.20–7.25 ppm (m, 10 H; 2×Ph); ^{13}C NMR: $\delta=19.6$ (2 C), 20.10 (2 C), 27.3 (2 C), 29.9 (2 C), 39.2 (2 C), 44.1 (2 C), 48.4 (2 C), 50.2 (2 C), 53.85 (2 C), 62.3 (2 C), 75.95 (2 C), 128.3 (4 C), 128.4 (2 C), 128.7 (4 C), 138.0 (2 C); IR (KBr): $\tilde{\nu}=3562$, 3416, 3259 (NH, OH), 3030 (C=CH), 1334, 1146 (SO_2N), 1074 cm^{-1} (C–O); MS (EI): *m*/*z* (%): 642 (<1) $[M-2H]^+$, 106 (100); HRMS: *m*/*z*: calcd for $C_{34}H_{48}N_2O_6S_2{\cdot}C_{10}H_7N_2O_3S$: 427.2055; found: 427.2055.

(1*S*,2*R*,4*S*,1′*R*,2′*R*,1″*S*,2″*R*,4″*S*)-*N*-{*trans*-2′-[2″-Hydroxy-7″,7″-dimethylbicyclo[2.2.1]hept-1″-ylmethylsulfonamino]cyclohexyl}-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide (6c): White crystals; $R_f=0.51$ (hexane/AcOEt 1:1); m.p. 175–177 °C (AcOEt/hexane); $[\alpha]_D=-37.19$ ($c=2.1$ in $CHCl_3$); ^{1}H NMR: $\delta=0.83$, 1.06 (2 s, 6 H each; 4×CH_3), 1.10–2.15 (m, 24 H; $CH(CH_2)_4CH$, 2×$(CH_2)_2CHCH_2$), 2.89, 3.47 (2 d, $J=13.6$ Hz, 2 H each; 2×CH_2S), 3.05 (br s, 2 H; 2×OH), 4.05–4.10 (m, 2 H; 2×CHO), 5.50–5.55 ppm (m, 2 H; 2×NH); ^{13}C NMR: $\delta=19.8$ (2 C), 20.45 (2 C), 24.65 (2 C), 27.25 (2 C), 30.5 (2 C), 34.6 (2 C), 38.95 (2 C), 44.35 (2 C), 48.7 (2 C), 50.5 (2 C), 53.85 (2 C), 57.65 (2 C), 76.55 ppm (2 C); IR (KBr): $\tilde{\nu}=3529$, 3214, (OH), 1140, 1073 cm^{-1} (CO); MS (EI): *m*/*z* (%): 528 (<1) $[M-H_2O]^+$, 93 (100); HRMS: *m*/*z*: calcd for $C_{26}H_{46}N_2O_6S_2{\cdot}H_2O$: 528.2691; found: 528.2673; crystal data: $C_{26}H_{46}N_2O_6S_2$, $M=546.77$; orthorhombic, $a=12.903(2)$, $b=20.813(4)$, $c=$ 23.066(4) Å; $V=6194(4)$ Å^3; space group $P2(1)2(1)2$; $Z=8$; $\rho_{calcd}=$ 1.173 Mg m^{-3}; $\lambda=0.71073$ Å; $\mu=0.210$ mm^{-1}; $F(000)=2368$; $T=-100\pm$ 1 °C. Data collection based on three ω-scan runs (starting with $\omega=-34°$) at values of $\varphi=0$, 120, 240° with the detector at $2\theta=-32°$. An additional run of 100 frames at $2\theta=-32$, $\omega=-34$, and $\varphi=0°$ was acquired to improve redundancy. For each of these runs, 606 frames were collected at 0.3° intervals and 30 s per frame. The diffraction frames were integrated by using the program SAINT and the integrated intensities were corrected for Lorentz-polarization effects with SADABS. The structure was solved by direct methods[3] and refined to all 10802 unique F_o^2 by full matrix least squares. All of the hydrogen atoms were placed at idealized positions and refined as rigid atoms. Final $wR2=0.1260$ for all data and 705 parameters; $R1=0.0704$ for 5413 $F_o>4\sigma(F_o)$.

(1*S*,2*R*,4*S*,1′*S*,2′*S*,1″*S*,2″*R*,4″*S*)-*N*-{*trans*-2′-[2″-Hydroxy-7″,7″-dimethylbicyclo[2.2.1]hept-1″-ylmethylsulfonamino]-1′,2′-diphenylethyl}-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide (6d): White solid; $R_f=0.8$ (hexane/AcOEt 1:1); m.p. 181–183 °C (AcOEt/hexane); $[\alpha]_D=-97.7$ ($c=1.9$ in $CHCl_3$); ^{1}H NMR: $\delta=0.55$, 0.71 (2 s, 6 H each; 4×CH_3), 0.80–1.50 (m, 14 H; 2×$(CH_2)_2CHCH_2$), 2.46, 2.88 (2 d, $J=$ 13.7 Hz, 2 H each; 2×CH_2S), 2.97 (s, 2 H; 2×OH), 3.95–4.50 (m, 2 H; 2× CHO), 4.70–4.85 (m, 2 H; 2×CHN), 5.70 (s, 2 H; 2×NH), 7.10–7.30 ppm (m, 10 H; 2×Ph); ^{13}C NMR: $\delta=19.4$ (2 C), 21.05(2 C), 27.3 (2 C), 30.10 (2 C), 39.05 (2 C), 44.15 (2 C), 48.5 (2 C), 50.2 (2 C), 53.8 (2 C), 62.4 (2 C), 75.95 (2 C), 127.8 (4 C), 128.5 (2 C), 128.8 (4 C), 137.6 ppm (2 C); IR (KBr): $\tilde{\nu}=3513$, 3431, 3278 (NH, OH), 3060 (C=CH), 1142, 1077 cm^{-1} (C–O); MS (EI): *m*/*z* (%): 626 (<1) $[M-H_2O]^+$, 106 (100); HRMS: *m*/*z*: calcd for $C_{34}H_{48}N_2O_6S_2{\cdot}C_{17}H_{24}NO_3S$: 322.1471; found: 322.1432.

(1*R*,2*S*,4*R*,1′*R*,2′*R*,1″*R*,2″*S*,4″*R*)-*N*-{*trans*-2′-[2″-Hydroxy-7″,7″-dimethylbicyclo[2.2.1]hept-1″-ylmethylsulfonamino]cyclohexyl}-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide (6e): White solid; $R_f=0.59$ (hexane/AcOEt 1:1); m.p. 209–211 °C (AcOEt/hexane); $[\alpha]_D=-54.7$ ($c=1.7$ in $CHCl_3$); ^{1}H NMR: $\delta=0.83$, 1.07 (2 s, 6 H each; 4×CH_3), 1.10–2.20 (m, 24 H; $CH(CH_2)_4CH$, 2×$(CH_2)_2CHCH_2$), 2.96, 3.49 (2 d, $J=13.7$ Hz, 2 H each; 2×CH_2S), 3.10–3.25 (m, 2 H; 2× OH), 4.05–4.10 (m, 2 H; 2×CHO), 4.90–4.95 ppm (m, 2 H; 2×NH); ^{13}C NMR: $\delta=19.85$ (2 C), 20.5 (2 C), 24.5 (2 C), 27.35 (2 C), 30.45 (2 C), 34.2 (2 C), 39.05 (2 C), 44.35 (2 C), 48.75 (2 C), 50.45 (2 C), 54.15 (2 C), 57.45 (2 C), 76.25 ppm (2 C); IR (KBr): $\tilde{\nu}=3466$, 3212 (NH, OH), 1142, 1072 cm^{-1} (C–O); MS (EI): *m*/*z* (%): 545 (<1) $[M-H]^+$, 135 (100); HRMS: *m*/*z*: calcd for $C_{26}H_{46}N_2O_6S_2$: 528.2797; found: 528.2758.

(1*S*,2*R*,4*S*,1′*R*,2′*R*,1″*S*,2″*R*,4″*S*)-*N*-{*cis*-2′-[2″-Hydroxy-7″,7″-dimethylbicyclo[2.2.1]hept-1″-ylmethylsulfonamino]cyclohexyl}-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide (6f): White solid; $R_f=0.5$ (hexane/AcOEt 1:1); m.p. 170–172 °C (AcOEt/hexane); $[\alpha]_D=-40.5$ ($c=1.44$ in $CHCl_3$); ^{1}H NMR: $\delta=0.83$, 1.06, 1.07

(3s, 6H, 3H, 6H; 4×CH_3), 1.15–2.1 (m, 24H; $CH(CH_2)_4CH$, 2×$(CH_2)_2CHCH_2$), 2.90, 3.03, 3.47, 3.52 (4d, J=13.7 Hz, 1H each; 2×CH_2S), 3.19, 3.63 (2s, 1H each; 2×OH), 4.05–4.10 (m, 2H; 2×CHO), 5.50–5.70 ppm (m, 2H; 2×NH); ^{13}C NMR: δ=19.75, 19.8, 20.35, 20.45, 20.95, 21.95, 27.25, 29.6, 30.05, 30.3, 30.45, 39.0, 40.0, 44.3, 44.35, 48.65, 48.7, 50.35, 50.45, 53.2, 53.5, 54.0, 54.15, 60.3, 76.25, 76.35 ppm; IR (KBr): $\tilde{\nu}$=3533, 3300 (NH, OH), 1144 cm^{-1} (C–O); MS (EI): m/z (%): 528 (<1) $[M-H_2O]^+$, 135 (99), 114 (98), 93 (100); HRMS: m/z: calcd for $C_{26}H_{46}N_2O_6S_2{\cdot}H_2O$: 528.2691; found: 528.2695.

(1*S*,2*R*,4*S*)-*N*-Cyclohexyl-(2-Hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-yl)methanesulfonamide (11): Pale yelow oil; R_f=0.70 (hexane/AcOEt 3:2); $[\alpha]_D$=−46.4 (c=1.68 in $CHCl_3$); ^{1}H NMR: δ=0.82, 1.07 (2s, 3H each; 2×CH_3), 1.10–2.05 (m, 18H; $(CH_2)_5CH$, $(CH_2)_2CHCH_2$), 2.86, 3.43 (2d, J=13.7 Hz, 1H each; CH_2S), 3.30 (s, 1H; OH), 4.10–4.15 (m, 1H; CHO), 4.76 ppm (d, J=7.4 Hz, 1H; NH); ^{13}C NMR: δ=19.8, 20.45, 24.7, 24.8, 25.05, 27.25, 30.5, 34.45, 34.5, 38.85, 44.3, 48.5, 50.4, 52.8, 53.85, 76.3 ppm; IR (KBr): $\tilde{\nu}$=3541, 3281 (NH, OH), 1137, 1175 cm^{-1} (C–O); MS (EI): m/z (%): 314 (<1) $[M-H]^+$, 99 (100); HRMS: m/z: calcd for $C_{16}H_{29}NO_3S$: 315.1868; found: 315.1878.

General procedure for the synthesis of canforsulfonamide derivatives 8: An aqueous solution of NaOH (2M, 15 mL) was added to a solution of (1*R*,2*R*)-*trans*-(+)diaminocyclohexane (1.37 g, 12 mmol, 1 equiv) in CH_2Cl_2 (15 mL) at 0°C. A solution of the corresponding arenesulfonyl chloride **7** (12 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) was then slowly added to the resulting biphasic mixture (this mixture was stirred strongly) and the temperature was allowed to rise to 25°C over 6 h. After this time, the reaction was quenched by the addition of HCl (2M) until the mixture reached an acidic pH. The organic layer was then decanted and discarded. The acid aqueous layer was basified by the addition of an aqueous solution of NaOH (3M) and extracted with CH_2Cl_2 (4×50 mL). The resulting organic layers were dried over anhydrous Na_2SO_4, filtered, and then concentrated. DMAP (0.73 mg, 0.5 equiv) and Et_3N (7.6 mL, 4.5 equiv) were added to a solution of the resulting crude residue in CH_3CN (25 mL) at 0°C. A solution of (1*S*)-(+)-10-camphorsulfonyl chloride (**5**, 4.51 g, 18 mmol, 1.5 equiv) in CH_3CN (25 mL) was slowly added to the above solution at 0°C. After 24 h, the temperature of the mixture was allowed to rise to 25°C and the reaction mixture was then quenched by the addition of an aqueous solution of NaOH (3M, 50 mL). This mixture was extracted with EtOAc (4×40 mL) and the resulting organic layers were washed with HCl (2M), dried over anhydrous Na_2SO_4, filtered, and then concentrated. The residue was purified by flash chromatography on silica gel (hexane/EtOAc) to give ketones **8**. Yields are included in Scheme 4.

(1*S*,4*S*,1′*R*,2′*R*)-*N*-{*trans*-2′-[7,7-Dimethyl-2-oxobicyclo[2.2.1]hept-1-ylmethylsulfonamino]cyclohexyl}-4″-methylbenzenesulfonamide (8a): White solid; R_f=0.41 (hexane/AcOEt 1:1); m.p. 67–69°C (AcOEt/hexane); $[\alpha]_D$=+23.3 (c=1.2 in $CHCl_3$); ^{1}H NMR: δ=0.97, 1.11 (2s, 3H each; $C(CH_3)_2$), 1.15–2.30 (m, 17H; $CH(CH_2)_4CH$, $(CH_2)_2CHCH_2$), 2.35 (s, 3H; CH_3Ar), 2.75–2.85, 3.10–3.20 (2m, 1H each; 2×CHN), 3.01, 3.42 (2d, J=15.1 Hz, 1H each; CH_2S), 5.19 (d, J=7.0 Hz, 1H; NH), 5.55 (d, J=5.8 Hz, 1H; NH), 7.28, 7.78 ppm (2d, J=8.1 Hz, 2H each; Ar); ^{13}C NMR: δ=19.50, 19.80, 21.5, 24.1, 24.5, 27.0, 33.6, 42.65, 42.9, 48.7, 51.2, 56.9, 57.3, 59.3, 60.35, 127.2 (2C), 129.6 (2C), 137.3, 143.2, 216.7 ppm; IR (KBr): $\tilde{\nu}$=3273 (NH, OH), 1744 cm^{-1} (C=O); MS (EI): m/z (%): 482 (<1) $[M]^+$, 96 (100); HRMS: m/z: calcd for $C_{23}H_{34}N_2O_5S_2$: 482.1909; found: 482.1899.

(1*S*,4*S*,1′*R*,2′*R*)-*N*-{*trans*-2′-[7,7-Dimethyl-2-oxobicyclo[2.2.1]hept-1-ylmethylsulfonamino]cyclohexyl}-4″-methoxybenzenesulfonamide (8b): White solid; R_f=0.43 (hexane/AcOEt 1:1); m.p. 67–69°C (AcOEt/hexane); $[\alpha]_D$=+22.4 (c=1.2 in $CHCl_3$); ^{1}H NMR: δ=090, 1.04 (2s, 3H each; $C(CH_3)_2$), 1.05–2.40 (m, 17H; $CH(CH_2)_4CH$, $(CH_2)_2CHCH_2$), 2.75–2.80, 3.10–3.15 (2m, 1H each; 2×CHN), 3.02, 3.44 (2d, J=15.0 Hz, 1H each; CH_2S), 3.86 (s, 3H; CH_3O), 5.24 (d, J=7.0 Hz, 1H; NH), 5.58 (d, J=5.8 Hz, 1H; NH), 6.97, 7.83 ppm (2d, J=8.9 Hz, 2H each; Ar); ^{13}C NMR: δ=19.50, 19.80, 24.1, 24.4, 26.4, 27.0, 33.55, 42.6, 42.8, 48.7, 51.2, 55.5, 56.9, 57.2, 59.2, 114.15 (2C), 129.3 (2C), 131.85, 162.7, 216.7 ppm; IR (KBr): $\tilde{\nu}$=3290 (NH, OH), 1744 cm^{-1} (C=O); MS (EI): m/z (%): 327 (16), 96 (100); HRMS: m/z: calcd for $C_{23}H_{34}N_2O_6S_2$: 498.1858; found: 498.1845.

General procedure for the synthesis of isoborneol derivatives 10a,b: $NaBH_4$ (2.27 g, 60 mmol, 6 equiv) was added to a solution of the corresponding pure ketone **8** (10 mmol, 1.0 equiv) in ethanol (50 mL) at 0°C. The reaction temperature was then allowed to rise to 25°C and the reaction mixture was stirred for 24 h. After this time, the reaction was quenched with saturated NH_4Cl and extracted with EtOAc (4×40 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated. The residue was purified by flash chromatography on silica gel (hexane/EtOAc) to give isoborneolsulfonamides **10a**,**b**. Yields are included in Scheme 4.

(1*S*,2*R*,4*S*,1′*R*,2′*R*)-*N*-{*trans*-2′-[2-Hydroxy-7,7-dimethylbicyclo-[2.2.1]hept-1-ylmethylsulfonamino]cyclohexyl}-4″-methylbenzenesulfonamide (10a): White solid; R_f=0.63 (hexane/AcOEt 1:1); m.p. 90–92°C (AcOEt/hexane); $[\alpha]_D$=+7.8 (c=2.1 in $CHCl_3$); ^{1}H NMR: δ=0.87, 1.10 (2s, 3H each; $C(CH_3)_2$), 1.15–2.20 (m, 17H; $CH(CH_2)_4CH$, $(CH_2)_2CHCH_2$), 2.43 (s, 3H; CH_3Ar), 2.82–2.86, 3.08–3.12 (2m, 1H each; 2×CHN), 2.99, 3.59 (2d, J=13.7 Hz, 1H each; CH_2S), 3.40 (d, J=3.8 Hz, 1H; CHO), 4.10 (s, 1H; OH), 4.97 (d, J=7.2 Hz, 1H; NH), 5.18 (d, J=7.8 Hz, 1H; NH), 7.31, 7.75 ppm (2d, J=8.1 Hz, 2H each; Ar); ^{13}C NMR: δ=19.9, 21.45, 21.5, 24.4, 24.6, 27.3, 30.6, 33.2, 35.0, 39.0, 44.4, 48.8, 50.5, 53.7, 57.0, 57.7, 60.4, 126.9 (2C), 129.8 (2C), 137.6, 143.6 ppm; IR (KBr): $\tilde{\nu}$=3535, 3290 (NH, OH), 1088 cm^{-1} (C–O); MS (EI): m/z (%): 483 (<1) $[M-H]^+$, 96 (100); HRMS: m/z: calcd for $C_{23}H_{36}N_2O_5S_2$: 484.2066; found: 484.2054.

(1*S*,2*R*,4*S*,1′*R*,2′*R*)-*N*-{*trans*-2′-[2-Hydroxy-7,7-dimethylbicyclo-[2.2.1]hept-1-ylmethylsulfonamino]cyclohexyl}-4″-methoxybenzenesulfonamide (10b): White solid; R_f=0.29 (hexane/AcOEt 1:1); m.p. 85–87°C (AcOEt/hexane); $[\alpha]_D$=+9.2 (c=0.77 in $CHCl_3$); ^{1}H NMR: δ=0.86, 1.10 (2s, 3H each; $C(CH_3)_2$), 1.10–2.15 (m, 17H; $CH(CH_2)_4CH$, $(CH_2)_2CHCH_2$), 2.80–2.85, 3.10–3.15 (2m, 1H each; 2×CHN), 2.97, 3.59 (2d, J=13.7 Hz, 1H each; CH_2S), 3.45 (brs, 1H; OH), 3.87 (s, 3H; CH_3O), 5.10 (d, J=7.2 Hz, 1H; NH), 5.33 (d, J=7.8 Hz, 1H; NH), 6.98, 7.81 ppm (2d, J=8.9 Hz, 2H each; Ar); ^{13}C NMR: δ=19.9, 20.4, 24.4, 24.6, 27.3, 30.55, 33.1, 34.85, 39.0, 44.4, 48.75, 50.5, 53.7, 55.6, 56.9, 57.6, 76.6, 114.3 (2C), 129.1 (2C), 132.2, 162.9 ppm; IR (KBr): $\tilde{\nu}$=3529, 3286 (NH, OH), 1164 cm^{-1} (C–O); MS (EI): m/z (%): 500 (<1) $[M]^+$, 96 (100); HRMS: m/z: calcd for $C_{23}H_{36}N_2O_6S_2{\cdot}H$: 499.1931; found: 499.1931.

(1*S*,2*R*,4*S*,1′*R*,2′*R*)-*N*-{*trans*-2′-[2-Hydroxy-7,7-dimethylbicyclo-[2.2.1]hept-1-ylmethylsulfonamino]cyclohexyl}methanesulfonamide (10c): A solution of (1*S*)-(+)-10-camphorsulfonyl chloride (**5**, 3.10 g, 12.5 mmol, 1.05 equiv) in CH_3CN (25 mL) was added to a solution of (1*R*,2*R*)-*trans*-(+)diaminocyclohexane (**4c**, 1.37 g, 12 mmol, 1 equiv), DMAP (0.66 g, 0.5 equiv), and Et_3N (7.6 mL, 4.5 equiv) in CH_3CN (25 mL) at 0°C. The reaction mixture stirred for 24 h and the reaction temperature allowed to rise to 25°C. After this time, the reaction was quenched by the addition of an aqueous solution of NaOH (3M, 25 mL) and was extracted with EtOAc (4×40 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated. The resulting crude residue was dissolved in THF (25 mL) and Et_3N (1.8 mL, 13 mmol, 1.1 equiv) was added at 0°C. Then, methanesulfonyl chloride (**9**, 1.01 mL, 13.0 mmol, 1.1 equiv) was slowly added at the same temperature. The reaction temperature was allowed to rise to 25°C and the mixture was stirred for 24 h. After this time, the reaction mixture was quenched by the addition of an aqueous solution of NaOH (3M) and was extracted with EtOAc. The combined organic layers were washed with HCl (1M), dried over anhydrous Na_2SO_4, filtered, and then concentrated. DIBAL (1M in hexane, 35 mL, 35 mmol, 3.5 equiv) was added to a solution of the resulting residue in anhydrous THF (50 mL) under an argon atmosphere at −78°C. The reaction mixture was then warmed to room temperature and after 24 h stirring, was quenched with HCl (2M) and extracted with CH_2Cl_2 (3×25 mL). The organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated. The residue was purified by flash chromatography on silica gel (hexane/EtOAc) to give the title compound **10c**. The yield of the reaction is included in Scheme 4. White solid; R_f=0.24 (hexane/AcOEt 1:1); m.p. 185–187°C (AcOEt/hexane); $[\alpha]_D$=−29.8 (c=1.24 in $CHCl_3$);

^{1}H NMR: $\delta = 0.84$, 1.07 (2s, 3H each; $C(CH_3)_2$), 1.10–2.75 (m, 17H; $CH(CH_2)_4CH$, $(CH_2)_2CHCH_2$), 2.90, 3.54 (2d, $J = 13.7$ Hz, 1H each; CH_2S), 3.30 (s, 3H; CH_3S), 3.08 (s, 1H; OH), 4.05–4.10 (m, 1H; CHO), 5.45–5.50 ppm (m, 2H; 2×NH); ^{13}C NMR: $\delta = 19.85$, 20.4, 24.55, 24.6, 27.25 30.45, 34.2, 34.5 39.0, 41.7, 44.35, 48.65, 50.55, 53.95, 57.45, 57.55, 76.55 ppm; IR (KBr): $\tilde{\nu} = 3527$, 3292 (NH, OH), 1150, 1075 cm^{-1} (C–O); MS (EI): m/z (%): 329 (<1) $[M-CH_3SO_2]^+$, 96 (100); HRMS: m/z: calcd for $C_{17}H_{32}N_2O_5S_2$: 408.1753; found: 408.1769.

General procedure for the enantioselective addition of commercially available diorganozinc reagents to ketones: A solution of the diorganozinc reagent (**13**, 12 mmol, 2.4 equiv) in toluene (4.5–20 mL, depending on the commercial source) was added to a solution of corresponding chiral ligand **6**, **10**, or **11** (0.5 mmol, 0.05 equiv) in toluene (10 mL) under an argon atmosphere. After 5 min stirring at 25 °C, a new solution of Ti(O*i*Pr)$_4$ (1.6 mL, 5.5 mmol, 1.1 equiv) was added, followed by the corresponding ketone (**12**, 5 mmol, 1.0 equiv). The reaction mixture was stirred for several hours/days (see Tables 2, 3, and the Results and Discussion section) at the same temperature and finally quenched by the successive addition of methanol (1 mL) and a saturated solution of NH_4Cl (15 mL). The mixture was filtered through Celite and the resulting solution was extracted with EtOAc (3×50 mL). The organic layers were dried over anhydrous Na_2SO_4, filtered, and then concentrated. The residue was purified by bulb-to-bulb distillation or flash chromatography (hexane/EtOAc) to give chiral tertiary alcohols **14a–i** and **15a–d**. Yields and *ee* values are included in Tables 2, 3, and the Results and Discussion. Compounds **14a–c**,**f**[11b] and **14d**,**e**,[14] which have been previously fully described by us, were characterized by comparison of their spectroscopic (^{1}H and ^{13}C NMR, IR, and mass spectra) and chromatographic data with those of the reported alcohols. For the other cases, physical and spectroscopic data, including literature references for known compounds follow.

(*E*)-3-Ethyl-1-phenylhept-1-en-3-ol (14g):[46] Pale yellow oil; $R_f = 0.67$ (hexane/AcOEt 7:3); t_r (GC) = 11.2 min; HPLC (ODH, UV 225 nm, hexane/2-propanol 98:2, flow 1 mL min^{-1}): t_r (1st) = 12.8, t_r (2nd) = 13.8 min; $[\alpha]_D = +7.6$ ($c = 1.84$ in $CHCl_3$); *er* 1st/2nd 92.5:7.5; ^{1}H NMR: $\delta = 0.85$–1.70 (m, 15H; $CH_3CH_2C(OH)(CH_2)_3CH_3$), 6.18 (d, $J = 16.1$ Hz, 1H; C*H*CPh), 6.57 (d, $J = 16.1$ Hz, 1H; C*H*Ph), 7.15–7.40 ppm (m, 5H; Ph); ^{13}C NMR: $\delta = 7.8$, 14.0, 23.15, 25.75, 33.7, 40.65, 75.55, 126.25 (2C), 127.15, 127.75, 128.45 (2C), 135.6, 137.15 ppm; IR (film): $\tilde{\nu} = 3444$ (OH), 1449 cm^{-1} (C=CH); MS (EI): m/z (%): 219 (<1) $[M]^+$, 129 (100).

3-Methyl-1-phenyl-1-pentyn-3-ol (14h):[47] Pale yellow oil; $R_f = 0.85$ (hexane/AcOEt 7:3); b.p. 155–160 °C (0.1 Torr); t_r (GC) = 10.47 min; GC (B conditions): t_r (1st) = 175.2, t_r (2nd) = 176.1 min; $[\alpha]_D = +160.0$ ($c = 1.9$ in EtOH); *er* 1st/2nd >99:<1; ^{1}H NMR: $\delta = 1.10$ (t, $J = 7.4$ Hz, 3H; CH_2CH_3), 1.56 (s, 3H; CCH_3), 1.78 (q, $J = 7.4$ Hz, 2H; CH_2), 2.10 (s, 1H; OH), 7.25–7.30, 7.40–7.45 ppm (2m, 3H, 2H; Ph); ^{13}C NMR: $\delta = 9.05$, 29.25, 36.6, 69.05, 83.3, 92.7, 122.8, 128.15, 128.2 (2C), 131.6 ppm (2C); IR (film): $\tilde{\nu} = 3404$ (OH), 3049, 1636 (C=CH), 2196 (C=C), 1118 cm^{-1} (C–O); MS (EI): m/z (%): 174 (5) $[M]^+$, 145 (100).

2-Cyclohexyl-2-hexanol (14i):[48] $R_f = 0.74$ (hexane/AcOEt 7:3); b.p. 130–135 °C (0.1 Torr); t_r (GC) = 10.18 min; GC (A conditions): t_r (1st) = 94.91, t_r (2nd) = 95.81 min; $[\alpha]_D = -7.0$ ($c = 0.37$ in $CHCl_3$); *er* 1st/2nd 82.5:17.5; ^{1}H NMR: $\delta = 0.91$ (t, $J = 6.7$ Hz, 3H; CH_2CH_3), 0.96–1.90 ppm (m, 21H; $(CH_2)_5CHCCH_3(OH)(CH_2)_3$); ^{13}C NMR: $\delta = 14.1$, 23.35, 23.95, 25.45, 26.55, 26.75, 26′8, 26.85, 27.5, 39.6, 47.2, 74.35 ppm; IR (film): $\tilde{\nu} = 3434$ (OH), 1143 cm^{-1} (C–O); MS (EI): m/z (%): 169 (15) $[M-CH_3]^+$, 101 (100), 71 (100).

1-(4′-Methylphenyl)-1-phenylethanol (*ent*-15a):[49] Pale yellow oil; $R_f = 0.44$ (hexane/AcOEt 4:1); t_r (GC) = 10.74 min; HPLC (AD, UV 225 nm, hexane/2-propanol 97:3, flow 1 mL min^{-1}): t_r (1st) = 12.7, t_r (2nd) = 13.5 min; $[\alpha]_D = +16.0$ ($c = 1.2$ in CH_2Cl_2); *er* 1st/2nd 98:2; ^{1}H NMR: $\delta = 1.92$ (s, 3H; CH_3CO), 2.18 (br s, 1H; OH), 2.32 (s, 3H; CH_3Ar), 7.20–7.40 ppm (m, 9H; ArH); ^{13}C NMR: $\delta = 20.95$, 30.8, 76.05, 125.8 (4C), 126.8, 128.1 (2C), 128.8 (2C), 136.6, 145.1, 148.2 ppm; IR (film): $\tilde{\nu} = 3437$ (OH), 1518 (C=CH), 1075 cm^{-1} (C–O); MS (EI): m/z (%): 213 (1) $[M+H]^+$, 212 (6) $[M]^+$, 197 (100).

1-(4′-Bromophenyl)-1-phenylethanol (15b):[50] Pale green oil; $R_f = 0.5$ (hexane/AcOEt 4:1); t_r (GC) = 15.10 min; HPLC (ODH, UV 235 nm, hexane/2-propanol 99:1, flow 1 mL min^{-1}): t_r (1st) = 41.8, t_r (2nd) = 49.9 min; $[\alpha]_D = +9.6$ ($c = 2.0$ in CH_2Cl_2); *er* 1st/2nd >99:<1; ^{1}H NMR: $\delta = 1.92$ (s, 3H; CH_3), 2.55 (s, 1H; OH), 7.25–7.40 ppm (m, 9H; ArH); ^{13}C NMR: $\delta = 30.7$, 75.85, 120.85, 125.7 (2C), 127.2 (2C), 127.65, 128.3 (2C), 131.1 (2C), 147.05, 147.3 ppm; IR (film): $\tilde{\nu} = 3437$ (OH), 1678 (C=CH), 1011 cm^{-1} (C–O); MS (EI): m/z (%): 278 (7) $[M+H]^+$, 277 (1) $[M]^+$, 261 (100).

1-(4′-Trifluoromethylphenyl)-1-phenylethanol (15c):[51] Pale yellow oil; $R_f = 0.48$ (hexane/AcOEt 4:1); t_r (GC) = 10.33 min; HPLC (AD, UV 225 nm, hexane/2-propanol 99:1, flow 1 mL min^{-1}): t_r (1st) = 13.1, t_r (2nd) = 15.4 min; $[\alpha]_D = +19.9$ ($c = 1.37$ in CH_2Cl_2); *er* 1st/2nd 4:96; ^{1}H NMR: $\delta = 1.91$ (s, 3H; CH_3), 2.44 (s, 1H; OH), 7.20–7.40, 7.50, 7.53 ppm (m, 2d, $J = 8.8$ Hz, 9H; ArH); ^{13}C NMR: $\delta = 30.15$, 75.54, 124.25 (q, ^1J(C,F) = 274.0 Hz), 125.05 (q, ^3J(C,F) = 4.4 Hz), 125.8 (2C), 126.1 (2C), 127.35, 128.35, 129.0 (q, ^2J(C,F) = 31.8), 147.0, 152.0 ppm; IR (film): $\tilde{\nu} = 3453$ (OH), 1366 (C=CH), 1126 (C–F), 1071 cm^{-1} (C–O); MS (EI): m/z (%): 268 (<1) $[M+2H]^+$, 267 (<1) $[M+H]^+$, 266 (2) $[M]^+$, 251 (100).

1-(4′-Bromophenyl)-1-phenyl-1-propanol (15d):[52] Pale yellow oil; $R_f = 0.57$ (hexane/AcOEt 4:1); t_r (GC) = 13.15 min; HPLC (AD, UV 225 nm, hexane/2-propanol 97:3, flow 1 mL min^{-1}): t_r (1st) = 10.1, t_r (2nd) = 11.7 min; $[\alpha]_D = +9.9$ ($c = 1.65$ in CH_2Cl_2); *er* 1st/2nd 10:90; ^{1}H NMR: $\delta = 0.85$ (t, $J = 7.3$ Hz, 3H; CH_3), 2.04 (s, 1H; OH), 2.26 (q, $J = 7.2$ Hz, 2H; CH_2), 7.15–7.40 ppm (m, 9H; ArH); ^{13}C NMR: $\delta = 8.0$, 34.25, 78.15, 120.65, 125.95 (2C), 127.0, 127.95, 128.25, 131 (2C), 145.85 (2C), 146.4 ppm (2C); IR (film): $\tilde{\nu} = 3583$ (OH), 1483 (C=CH), 1005 cm^{-1} (C–O); MS (EI): m/z (%): 293 (<1) $[M+2H]^+$, 292 (<1) $[M+H]^+$, 291 (<1) $[M]^+$, 260 (100).

General procedure for the enantioselective addition of organozinc reagents prepared from arylboronic acids to ketones: A solution of Et_2Zn (1.1 M in toluene, 6.5 mL, 7.2 mmol, 7.2 equiv) was slowly added to a pressure tube charged with the corresponding arylboronic acid (**16**, 2.4 mmol, 2.4 equiv) at 0 °C under argon atmosphere. The resulting solution was warmed to 70 °C and stirred for 16 h. Then, the mixture was cooled to 0 °C, and HOCSAC ligand (**6c**) (0.027 g, 0.05 mmol, 0.05 equiv) and Ti(O*i*Pr)$_4$ (0.39 mL, 1.3 mmol, 1.3 equiv) were successively added. After 15 min stirring allowing the temperature to rise to 25 °C, the corresponding ketone (**12**, 1 mmol, 1 equiv) was added. The reaction mixture was stirred at the same temperature for 24 h, and was then quenched by the successive addition of methanol (1 mL) and a saturated solution of NH_4Cl (15 mL). The mixture was filtered through Celite and the resulting solution was extracted with EtOAc (3×15 mL). The organic layers were dried over anhydrous Na_2SO_4, filtered, and then concentrated. The residue was purified by bulb-to-bulb distillation or flash chromatography (hexane/EtOAc) to give chiral tertiary alcohols **14a**,**j** and **15a–d**. Yields and *ee* values are included in Table 4. Compounds **14a**,**j**[11b] have been previously fully described by us, and were characterized by the comparison of their spectroscopic (^{1}H and ^{13}C NMR, IR, and mass spectra) and chromatographic data with those of the reported alcohols. Alcohols **15a–d** have already been described in the previous section.

General procedure for the enantioselective addition of organozinc reagents prepared from triphenylborane (18) to ketones: As in the previous general procedure, but charging the pressure tube with triphenylborane (**18**, 0.387 g, 1.6 mmol, 4.8 equiv) and a solution of Et_2Zn (1.1 M in toluene, 6.5 mL, 7.2 mmol, 7.2 equiv). Yields and *ee* values are included in Table 5. Compound **14j**[11b] has been previously fully described by us, and was characterized by the comparison of its spectroscopic (^{1}H and ^{13}C NMR, IR, and mass spectra) and chromatographic data with those of the reported alcohol. Alcohols **15a–d** have been already described in the previous section.

General procedure for the enantioselective addition of organozinc reagents prepared from arylmagnesium derivatives (19) to ketones: The corresponding arylmagnesium halide (**19**, 7.75 mmol, 3.1 equiv) was added to a solution of BF_3OEt_2 (**20**, 0.314 mL, 2.5 mmol, 1 equiv) in Et_2O (7.5 mL) at 25 °C under an argon atmosphere, and the resulting mixture was stirred at the same temperature for 24 h. After this time, the solution was filtered off and the solvent in the clear solution was removed in vacuo. This crude residue was dissolved in toluene (7.5 mL), stirred at room temperature for 24 h, and filtered off again under an

argon atmosphere. Finally, the removal of toluene in vacuo produced the corresponding triarylborane, which was treated with a solution of Et_2Zn (1.1 M in toluene, 6.5 mL, 7.2 mmol, 7.2 equiv), following the same protocol as in the previous procedure to obtain the diarylalkanols **15a**,**e**–**g**. Yields and *ee* values are included in Table 6. Alcohol **15a** has been already described in the previous section. For other cases, physical and spectroscopic data, including literature references for known compounds follow.

1-(3′-Methylphenyl)-1-phenylethanol (15e):[53] Pale yellow oil; $R_f = 0.61$ (hexane/AcOEt 7:3); t_r (GC) = 11.03 min; HPLC (AD, UV 225 nm, hexane/2-propanol 99:1, flow 1 mL min^{-1}): t_r (1st) = 27.7, t_r (2nd) = 31.3 min; $[\alpha]_D = -14.3$ ($c = 1.2$ in CH_2Cl_2); *er* 1st/2nd 7:93; ^{1}H NMR: $\delta =$ 1.89 (s, 3H; CH_3CO), 2.30 (s, 3H; $ArCH_3$), 2.32 (brs 1H; OH), 7.10–7.40 ppm (m, 9H; ArH); ^{13}C NMR: $\delta = 21.5$, 30.7, 76.1, 122.85, 125.75 (2C), 126.45, 127.6, 127.95, 128.05 (2C), 137.6, 147.85, 148.0 ppm; IR (film): $\tilde{\nu} = 3435$ (OH), 1606 (C=CH), 1379 cm^{-1} (C–O); MS (EI): *m*/*z* (%): 213 (2) $[M+H]^+$, 212 (7) $[M]^+$, 197 (100).

1-(4′-Chlorophenyl)-1-phenylethanol (15f):[52] Pale yellow oil; $R_f = 0.59$ (hexane/AcOEt 7:3); t_r (GC) = 11.02 min; HPLC (AD, UV 225 nm, hexane/2-propanol 99:1, flow 1 mL min^{-1}): t_r (1st) = 35.7, t_r (2nd) = 40.6 min; $[\alpha]_D = -5.3$ ($c = 0.2$, $CHCl_3$); *er* 1st/2nd 44:56; ^{1}H NMR: $\delta =$ 1.90 (s, 3H; CH_3), 2.28 (s, 1H; OH), 7.20–7.40 ppm (m, 9H; ArH); ^{13}C NMR: $\delta = 30.7$, 30.8, 75.8, 125.7 (2C), 127.15, 127.3 (2C), 128.2 (2C), 128.25 (2C), 132.65, 146.5, 147.4 ppm; IR (film): $\tilde{\nu} = 3416$ (OH), 1502 cm^{-1} (C=CH); MS (EI): *m*/*z* (%): 233 (1) $[M+H]^+$, 232 (7) $[M]^+$, 217 (100).

1-(4′-Fluorophenyl)-1-phenylethanol (15g):[52] Pale yellow oil; $R_f = 0.57$ (hexane/AcOEt 7:3); t_r (GC) = 9.29 min; HPLC (AD, UV 217 nm, hexane/2-propanol 99:1, flow 0.8 mL min^{-1}): t_r (1st) = 37.9, t_r (2nd) = 39.4 min; $[\alpha]_D = -4.9$ ($c = 1.06$, $CHCl_3$; *er* 1st/2nd 92:8; ^{1}H NMR: $\delta = 1.92$ (s, 3H; CH_3), 2.15 (s, 1H; OH), 6.95–7.0, 7.20–7.40 ppm (2m, 5H, 4H; ArH); ^{13}C NMR: $\delta = 31.0$, 75.8, 114.8 (d, ^2J(C,F) = 20.9 Hz), 125.7 (2C), 127.1 (2C), 127.6 (d, ^3J(C,F) = 7.7 Hz), 128.2 (2C), 143.8 (d, ^4J(C,F) = 3.3 Hz), 147.7, 161.7 ppm (d, ^1J(C,F) = 244.8 Hz); IR (film): $\tilde{\nu} = 3431$ (OH), 1518 cm^{-1} (C=CH); MS (EI): *m*/*z* (%): 216 (5) $[M]^+$, 201 (100).

General procedure for the enantioselective allylation of acetophenone (12a): A solution of $[Pd(PPh_3)_4]$ (11.5 mg, 0.01 mmol, 0.01 equiv), either allyl carbonate (**21a**, 0.43 mL, 3 mmol, 3 equiv) or cynnamyl acetate (**21b**, 1.0 mL, 6 mmol, 6 equiv), and diethylzinc (1.1 M in toluene, 8.2 mL, 9 mmol, 9 equiv) was stirred at 70 °C for 16 h in a pressure tube under an argon atmosphere. After this time, the mixture was cooled to 0 °C, and the corresponding chiral ligand **6c**, **10a**, or **b** (0.05 mmol, 0.05 equiv) and $Ti(OiPr)_4$ (0.35 mL, 1.1 mmol, 1.1 equiv) were successively added. After 15 min stirring allowing the temperature to rise to 25 °C, acetophenone (**12a**, 0.12 mL, 1 mmol, 1 equiv) was added. The reaction mixture was stirred at the same temperature for several hours, and then quenched by the successive addition of methanol (1 mL) and a saturated solution of NH_4Cl (15 mL). The mixture was filtered through Celite and the resulting solution was extracted with EtOAc (3 × 15 mL). The organic layers were dried over anhydrous Na_2SO_4, filtered, and then concentrated. The residue was purified by flash chromatography (hexane/EtOAc) to give chiral tertiary alcohols **22**. Yields and *ee* values are included in Scheme 5.

2-Phenyl-4-penten-2-ol (22a):[54] Pale yellow oil; $R_f = 0.54$ (hexane/AcOEt 7:3); t_r (GC) = 9.27 min; HPLC (AS, UV 208 nm, hexane/2-propanol 99.5:0.5, flow 0.6 mL min^{-1}): t_r ((*R*)-**22a**) = 12.29, t_r ((*S*)-**22a**) = 13.22 min; $[\alpha]_D = -2.6$ ($c = 0.85$ in $CHCl_3$) *er* *R*/*S* 48:52; ^{1}H NMR: $\delta =$ 1.55 (s, 3H; CH_3), 2.05 (s, 1H; OH), 2.50, 2.69 (2dd, $J = 8.3$, 13.7 Hz, $J =$ 6.4, 13.7 Hz; 1H each; CH_2CO), 5.10–5.15 (m, 2H; CH_2=CH), 5.55–5.70 (m, 1H; CH_2=C*H*), 7.40–7.45 ppm (m, 5H; Ph); ^{13}C NMR: $\delta = 29.9$, 48.4, 73.6, 119.4, 124.7 (2C), 126.6, 128.13 (2C), 133.6, 147.6 ppm; IR (film): $\tilde{\nu} = 3415$ (OH), 1684 (C=CH), 1208 cm^{-1} (C–O); MS (EI): *m*/*z* (%): 160 (<1) $[M-2H]^+$, 121 (100).

2,3-Diphenyl-4-penten-2-ol (*syn*-22b):[55] Pale yellow oil; $R_f = 0.22$ (hexane/AcOEt 4:1); t_r (GC) = 13.16 min; HPLC (AD, UV 254 nm, hexane/2-propanol 98:2, flow 1 mL min^{-1}): t_r (1st) = 15.7, t_r (2nd) = 21.5 min; $[\alpha]_D = -1.1$ ($c = 1.22$, $CHCl_3$); *er* 1st/2nd 79:21; ^{1}H NMR: $\delta =$ 1.23 (s, 3H; CH_3), 3.37 (d, $J = 9.5$ Hz, 1H; C*H*Ph), 5.05–5.25 (m, 2H; CH=CH_2), 6.20–6.45 (m, 1H; C*H*=CH_2), 7.20–7.35 ppm (m, 10H; 2 × Ph); ^{13}C NMR: $\delta = 25.3$, 60.3, 74.1, 117.75, 125.6, 126.1 (2C), 127.2, 128.3 (2C), 128.5 (2C), 129.2 (2C), 133.55, 137.6, 141.0 ppm; IR (film): $\tilde{\nu} =$ 3456 (OH), 1606 cm^{-1} (C=CH); MS (EI): *m*/*z* (%): 239 (<1) $[M+2H]^+$, 117 (100).

2,3-Diphenyl-4-penten-2-ol (*anti*-22b):[55] Pale yellow oil. $R_f = 0.22$ (hexane/AcOEt: 4/1); t_r (GC) = 13.10 min; HPLC (AD, UV 254 nm, hexane/2-propanol 98:2, flow 1 mL min^{-1}): t_r (1st) = 15.1, t_r (2nd) = 28.9 min; $[\alpha]_D = +0.5$ ($c = 3.44$, $CHCl_3$); *er* 1st/2nd 61:39; ^{1}H NMR $\delta =$ 1.11 (s, 3H; CH_3), 3.36 (d, $J = 9.5$ Hz, 1H; C*H*Ph), 5.13–5.25 (m, 2H; CH=CH_2), 6.24–6.45 (m, 1H; C*H*=CH_2), 7.18–7.38 ppm (m, 10H; 2 × Ph); ^{13}C NMR: $\delta = 25.15$, 60.3, 74.0, 117.7, 125.6, 126.1 (2C), 127.15, 128.3 (2C), 128.5 (2C), 129.4 (2C), 133.5, 137.6, 140.8 ppm; IR (film): $\tilde{\nu} = 3465$ (OH), 1606 cm^{-1} (C=CH); MS (EI): *m*/*z* (%): 239 (<1) $[M+2H]^+$, 117 (100).

Preparation of 2,4-diphenyl-3-butyn-2-ol (24) by enantioselective alkynylation of acetophenone (12a): A solution of phenylacetylene (**23a**, 0.33 mL, 3 mmol, 3 equiv) and diethylzinc (1.1 M in toluene, 2.7 mL, 3 mmol, 3 equiv) in toluene (0.5 mL) was stirred at room temperature for 3 h under an argon atmosphere. After this time, the corresponding chiral ligand **6c**, **10a**, or **10b** (0.05 mmol, 0.05 equiv), $Ti(OiPr)_4$ (0.03 mL, 0.1 mmol, 0.1 equiv), and toluene (2 mL) were successively added. The resulting solution was stirred for 1 h and acetophenone (**12a**, 0.12 mL, 1 mmol, 1 equiv) was added. The reaction mixture was stirred at the same temperature for several hours, before being quenched by the successive addition of methanol (1 mL) and a saturated solution of NH_4Cl (15 mL). The mixture was filtered through Celite and the resulting solution was extracted with EtOAc (3 × 15 mL). The organic layers were dried over anhydrous Na_2SO_4, filtered, and then concentrated. The residue was purified by flash chromatography (hexane/EtOAc) to give the title alcohol **24**.[56] Yields and *ee* values are included in Scheme 6. Pale yellow oil; $R_f = 0.41$ (hexane/AcOEt 4:1); t_r (GC) = 12.3 min; HPLC (AD, UV 235 nm, hexane/2-propanol 99:1, flow 1 mL min^{-1}): t_r (1st) = 36.7, t_r (2nd) = 44.4 min; $[\alpha]_D = -4.0$ ($c = 1.85$ in $CHCl_3$); *er* 1st/2nd 76.5:23.5; ^{1}H NMR: $\delta = 1.87$ (s, 3H; CH_3), 2.50 (brs, 1H; OH), 7.25–7.50, 7.70–7.75 ppm (2m, 5H each; 2 × Ph); ^{13}C NMR: $\delta = 33.3$, 70.4, 84.9, 92.4, 122.5, 124.9 (2C), 127.7, 128.3, 128.35 (2C), 128.5 (2C), 131.7 (2C), 145.6 ppm; IR (film): $\tilde{\nu} = 3380$ (OH), 3388 (C=C), 1493 cm^{-1} (C=CH); MS (EI): *m*/*z* (%): 222 (31) $[M]^+$, 207 (100).

General procedure for the enantioselective alkenylation of ketones: The corresponding alkyne **23** (1.2 mmol, 1.2 equiv) was added to a suspension of Cp_2ZrHCl (**25**, 309 mg, 1.2 mmol, 1.2 equiv), in CH_2Cl_2 (4 mL) under an argon atmosphere. The reaction mixture was stirred for 20 min at room temperature, and then the solvent was removed in vacuo. The resulting residue was dissolved in toluene (5 mL), cooled to −78 °C, and treated with Me_2Zn (2.0 M in toluene, 0.600 mL, 1.2 mmol, 1.2 equiv) for 30 min. The corresponding chiral ligand **6c**, **10a**, or **10b** (0.05 mmol, 0.05 equiv) and $Ti(OiPr)_4$ (0.33 mL, 1.10 mmol, 1.1 equiv) were mixed in toluene (2 mL) at room temperature in another Schlenk flask for 15 min under argon atmosphere. This solution was then added to the previous Schlenk flask containing the dimethylzinc at −78 °C. After the addition, the solution was warmed to 0 °C and added the corresponding ketone (**12**, 1 mmol, 1 equiv). The reaction mixture was then warmed to room temperature and stirred for several hours, followed by the successive addition of methanol (1 mL) and a saturated solution of NH_4Cl (15 mL) to quench the reaction. The mixture was filtered through Celite and the resulting solution was extracted with EtOAc (3 × 15 mL). The organic layers were dried over anhydrous Na_2SO_4, filtered, and then concentrated. The residue was purified by flash chromatography (hexane/EtOAc) to give chiral tertiary alcohols **26**. Yields and *ee* values are included in Table 7.

2-Phenyl-4-trimethylsilyl-3-buten-2-ol (26a): Pale yellow oil; $R_f = 0.6$ (hexane/AcOEt 7:3); t_r (GC) = 7.14 min; HPLC (OJ, UV 231 nm, hexane/2-propanol 99:1, flow 0.5 mL min^{-1}): t_r (1st) = 12.4, t_r (2nd) = 19.3 min; $[\alpha]_D = -13.4$ ($c = 0.55$ in $CHCl_3$); *er* 1st/2nd 3:97; ^{1}H NMR: $\delta =$ 0.13 (s, 9H; $Si(CH_3)_3$), 1.67 (s, 3H; CH_3CO), 2.05 (s, 1H; OH), 5.98 (d, $J = 8.8$ Hz, 1H; CH=C*H*Si), 6.36 (d, $J = 8.8$ Hz, 1H; C*H*=CHSi), 7.25–7.50 ppm (m, 5H; Ph); ^{13}C NMR: $\delta = -1.3$ (3C), 29.3, 75.5, 125.2 (2C), 126.2, 126.85, 128.2 (2C), 146.5, 151.6 ppm; IR (film): $\tilde{\nu} = 3388$ (OH),

1606 (C=CH), 840, 765 cm^{-1} ($Si(CH_3)_3$); MS (EI): *m/z* (%): 222 (<1) $[M+2H]^+$, 221 (3) $[M+H]^+$, 220 (14) $[M]^+$, 205 (100); HRMS: *m/z*: calcd for $C_{13}H_{20}OSi$: 220.1283; found: 220.1269.

2,4-Diphenyl-3-buten-2-ol (26b):[40d] Pale yellow oil; R_f=0.5 (hexane/AcOEt 7:3); t_r (GC)=10.28 min; HPLC (ODH, UV 254 nm, hexane/2-propanol 92:8, flow 0.8 mL min^{-1}): t_r ((*R*)-**26b**)=14.1, t_r ((*S*)-**26b**)=17.1 min; $[\alpha]_D$=+6.0 (*c*=0.44 in $CHCl_3$); *er R/S* 11.0:89.0; ^{1}H NMR: δ=1.76 (s, 3H; CH_3), 2.03 (s, 1H; OH), 6.58 (d, *J*=16.0 Hz, 1H; CH=C*H*CO), 6.65 (d, *J*=16.0 Hz, 1H; C*H*=CHCO), 7.20–7.40, 7.52 ppm (m, d, *J*=7.2 Hz, 8H, 2H; 2×Ph); ^{13}C NMR δ=29.8, 74.7, 125.2 (2C), 126.5 (2C), 127.1, 127.6, 127.65, 128.3 (2C), 128.55 (2C), 136.3, 136.65, 146.5 ppm; IR (film): $\tilde{\nu}$=3388 (OH), 3028, 1499 cm^{-1} (C=CH); MS (EI): *m/z* (%): 225 (2) $[M+H]^+$, 224 (12) $[M]^+$, 181 (100).

2-Phenyl-3-octen-2-ol (26c):[40d] Pale yellow oil; R_f=0.64 (hexane/AcOEt 7:3); t_r (GC)=7.82 min; HPLC (OJ, UV 220 nm, hexane/2-propanol 97:3, flow 1 mL min^{-1}): t_r ((*R*)-**26c**)=5.8, t_r ((*S*)-**26c**)=7.2 min; $[\alpha]_D$=−2.9 (*c*=1.3 in $CHCl_3$); *er R/S* 3.0:97.0; ^{1}H NMR: δ=0.89 (t, *J*=6.7 Hz, 3H; C$H_3$$CH_2$), 1.25–1.40 (m, 4H; ($CH_2$)$_2$$CH_3$), 1.63 (s, 3H; CH_3CO), 1.85 (s, 1H; OH), 2.05–2.10 (m, 2H; CH_2CH=CH), 5.60–5.70 (m, 1H; CH=C*H*CO), 5.77 (d, *J*=15.6 Hz, 1H; C*H*=CHCO), 7.20–7.25, 7.25–7.35, 7.46 ppm (2m, d, *J*=7.2 Hz, 1H, 2H, 2H; Ph); ^{13}C NMR: δ=13.9, 22.25, 29.9, 31.4, 31.9, 74.4, 125.2 (2C), 126.7, 128.1 (2C), 129.2, 136.8, 147.3 ppm; IR (film): $\tilde{\nu}$=3403 (OH), 3034, 1499 cm^{-1} (C=CH); MS (EI): *m/z* (%): 204 (<1) $[M]^+$, 147 (100).

3-Methyl-1-phenylnon-4-en-1-yn-3-ol (26d):[40d] Pale yellow oil; R_f=0.58 (hexane/AcOEt 7:3); t_r (GC)=9.64 min; HPLC (ODH, UV 251 nm, hexane/2-propanol 97:3, flow 0.5 mL min^{-1}): t_r (1st)=14.7, t_r (2nd)=19.1 min; $[\alpha]_D$=−7.6 (*c*=4.5 in $CHCl_3$); *er* 1st/2nd 13:87; ^{1}H NMR: δ=0.91 (t, *J*=7.2 Hz, 3H; C$H_3$$CH_2$), 1.30–1.45 (m, 4H; ($CH_2$)$_2$$CH_3$), 1.64 (s, 3H; CH_3CO), 2.05–2.10 (m, 2H; CH_2CH=CH), 2.21 (br s, 1H; OH), 5.66 (d, *J*=15.5 Hz, 1H; CH=C*H*CO), 6.04 (dt, *J*=15.5 Hz, 1H; C*H*=CHCO), 7.25–7.35, 7.40–7.45 ppm (2m, 3H, 2H; Ph); ^{13}C NMR: δ=13.9, 22.2, 30.45, 31.1, 31.5, 68.3, 84.4, 91.6, 122.7, 128.2 (2C), 130.7, 131.6 (2C), 133.9 ppm; IR (film): $\tilde{\nu}$=3376 (OH), 1494 (C=CH), 1106, 1077 cm^{-1} (C–O); MS (EI): *m/z* (%): 230 (<1) $[M+2H]^+$, 229 (<1) $[M+H]^+$, 228 (2) $[M]^+$, 227 (3) $[M-H]^+$, 171 (100).

3-Phenylnon-4-en-3-ol (26e):[40d] Pale yellow oil; R_f=0.74 (hexane/AcOEt 7:3); t_r (GC)=12.70 min; HPLC (OJ, UV 217 nm, hexane/2-propanol 97:3, flow 1 mL min^{-1}): t_r ((*R*)-**26e**)=5.7, t_r ((*S*)-**26e**)=7.4 min; $[\alpha]_D$=−10.3 (*c*=1.1 in $CHCl_3$) *er R/S* 5.0:95.0; ^{1}H NMR: δ=0.85, 0.91 (2t, *J*=7.3, 6.9 Hz, 3H each; 2×CH_3), 1.30–1.40 (m, 4H; (CH_2)$_2$$CH_3$), 1.79 (s, 1H; OH), 1.85–2.0 (m, 2H; CH_2CO), 2.05–2.10 (m, 2H; CH_2CH=CH), 5.65–5.70 (m, 1H; C*H*=CHCO), 5.82 (d, *J*=15.5 Hz, 1H; CH=C*H*CO), 7.25, 7.36, 7.45 ppm (2t, d, *J*=7.2, 7.5, 7.6 Hz, 1H, 2H, 2H; Ph); ^{13}C NMR: δ=8.0, 13.9, 22.2, 31.4, 32.0, 35.1, 76.75, 125.5 (2C), 126.5, 128.0 (2C), 129.4, 136.05, 146.2 ppm; IR (film): $\tilde{\nu}$=3471 (OH), 1499 cm^{-1} (C=CH); MS (EI): *m/z* (%): 218 (<1) $[M]^+$, 217 (<1) $[M-H]^+$, 189 (100).

CCDC-289391 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambrigde Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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