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Synthesis of camphorsulfonamide-based quinoline ligands and their N-oxides: first use in the enantioselective addition of organozinc reagents to aldehydes

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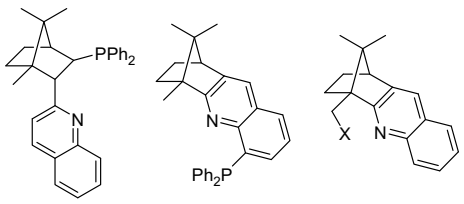
ABSTRACT

The preparation of several camphorsulfonamide-based quinoline derivatives and their N-oxides was accomplished via an indirect Friedländer synthesis using aminobenzylic alcohols and $RuCl_2(DMSO)_4$ as a catalyst. These ligands were tested in the enantioselective addition of dialkylzinc reagents to aldehydes, with enantiomeric excesses up to 96%. A similar protocol using triphenylborane and diethylzinc gave the corresponding phenylation process.

1. Introduction

Chiral ligands bearing nitrogen chelating donor atoms are of great interest nowadays[1] due to their easy preparation and availability. Furthermore, they are easily recovered from the reaction media generally by an acidic–basic extraction. In this context, the most used chiral nitrogen-donor ligands are those that involve the pyridine ring.[2] The related quinoline derivatives are less developed and only a few examples with the monoterpene camphor skeleton have been recently described.[3] The synthesis of ligands **1**,[4] **2**,[5] and **3**[6] always involves an important number of synthetic steps under very challenging reaction conditions, which hamper down their possible applications.



1 **2** **3a**: X = PPh_2 **3b**: X = SPh

On one hand, we have described different isoborneolsulfonamide ligands,[7] which have proven to be very useful as promoters of the addition of organozinc reagents to ketones.[8] On the other hand, we have recently described an easy entry to the indirect Friedländer synthesis of quinoline derivatives, starting from 2-aminobenzylic alcohol derivatives and ketones or alcohols, catalyzed by ruthenium.[9,10]

Herein, we would like to introduce a new and straightforward pathway to the synthesis of a new class of camphorsulfonamide-based quinoline ligands, as well as of their corresponding N-oxides, and their use in the enantioselective addition of organozinc reagents to aldehydes[11] in the presence of titanium tetraisopropoxide.[12]

2. Results and discussion

The previous success in the use of camphorsulfonamide-based ligands in the enantioselective alkylation of aldehydes[13] prompted us to modify this structure. The addition of a chelating group, such as a nitrogen atom, might modulate the activity of catalysts and therefore its reactivity.

2.1. Synthesis of chiral ligands

Our previous experience with isoborneolsulfonamide ligands has taught us that the reactivity of the ligands was strongly dependent on the presence of one or two units of the isoborneol moiety, even in the presence of an extra-sulfonamide unit (first,[14] second,[15] and third generation[16] isoborneolsulfonamide ligands). With this fact in mind, we synthesized the three related types of ligands. The first class of ligands **7** (C_1-symmetry) was prepared by reaction of chiral camphorsulfonyl chloride **4** with the ketones corresponding amine **5**, and without a further purification the obtained produces were annulated by reaction with the aminobenzyl

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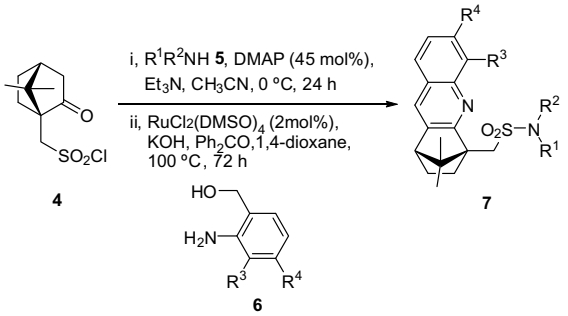
Table 1
Synthesis of monoquinoline camphorsulfonamide ligands **7**

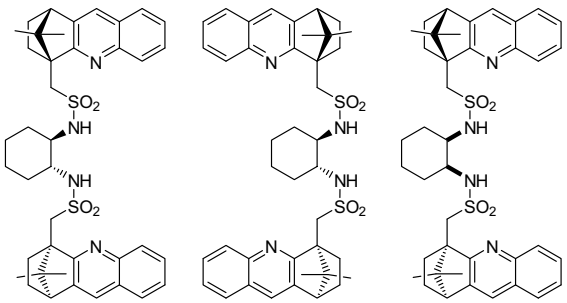


Entry	R^1	R^2	R^3	R^4	No	Yield[a] (%)
1	H	Bn	H	H	**7a**	71
2	H	Bn	CH=CHCH=CH		**7b**	54
3	H	$(CH_2)_2NMe_2$	H	H	**7c**	77
4	Me	$(CH_2)_2NMe_2$	H	H	**7d**	74

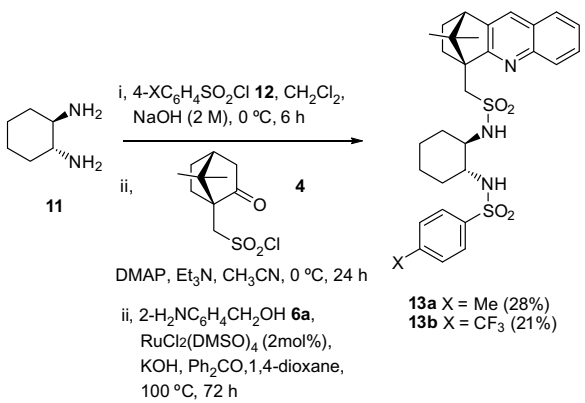
[a] Isolated yield after column chromatography.

alcohol **6** (see Table 1). The yields obtained were homogeneous independently of the initial amine.

The second type of ligands **8–10** (C_2-symmetry) were prepared in a similar way, but using 1,2-cyclohexanodiamine derivatives and a double amount of all reagents. It should be noted that the yields obtained in these cases were slightly higher than those presented in Table 1.



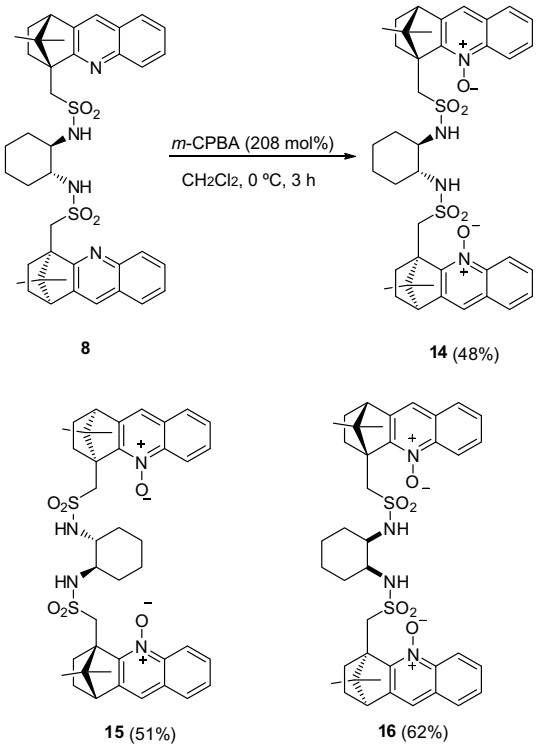
The third class of quinoline ligands **13** was prepared starting from chiral diamine **11** by reaction with the corresponding arenesulfonyl chloride (**12**) in two phases media, followed by a standard reaction with the chiral camphorsulfonyl chloride (**4**). The final indirect Friedländer annulation using 2-aminobenzyl alcohol (**6a**)



Scheme 1. Synthesis of compounds **13**.

catalyzed by ruthenium gave the expected compounds **13**, with moderated overall yields (Scheme 1).

The related N-dioxides, which appear in Scheme 2, were easily prepared from the corresponding C_2-ligands by oxidation with *m*-CPBA in methylenechloride at 0 °C according to the previously described protocol.[17] The resulting derivatives **14–16** were stable enough to be purified by column chromatography.

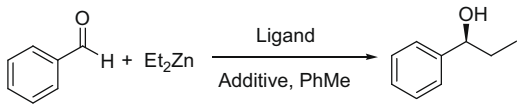


Scheme 2. Synthesis of N-oxide derivatives **14–16**.

2.2. Enantioselective addition of orgnaozinc reagents to aldehydes

Once the different types of ligands were synthesized, they were tested in the enantioselective addition of diethylzinc **18a** to benzaldehyde **17a** as shown in Table 2.

Table 2
Optimization of the enantioselective addition of diethylzinc to benzaldehyde

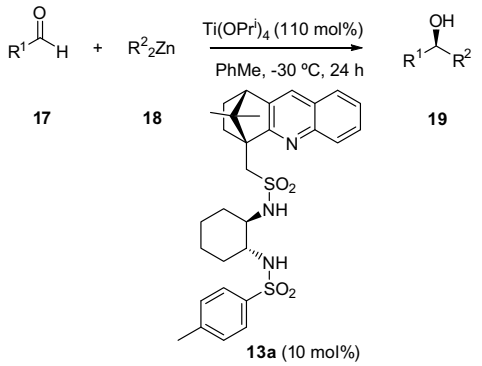


17a **18a** (240 mol%) **19a**

Entry	Ligand[a]	T (°C)	T (h)	Additive[b]	Yield[c] (%)	ee[d] (%)
1	**7a** (10)	−10	16	$Ti(OPr^i)_4$ (110)	95	24 (*R*)
2	**7b** (10)	−10	16	$Ti(OPr^i)_4$ (110)	>95	15 (*S*)
3[b]	**7c** (10)	−10	16	$Ti(OPr^i)_4$ (110)	>95	0 (—)
4	**7d** (10)	−10	16	$Ti(OPr^i)_4$ (110)	>95	0 (—)
5	**8** (10)	−10	16	$Ti(OPr^i)_4$ (110)	89	31 (*S*)
6	**9** (10)	−10	16	$Ti(OPr^i)_4$ (110)	95	17 (*S*)
7	**10** (10)	−10	16	$Ti(OPr^i)_4$ (110)	>95	9 (*R*)
8	**13a** (10)	−10	16	$Ti(OPr^i)_4$ (110)	>95	89 (*S*)
9	**13b** (10)	−10	16	$Ti(OPr^i)_4$ (110)	>95	65 (*S*)
10	**14** (10)	−10	16	$Ti(OPr^i)_4$ (110)	93	2 (*R*)
11	**15** (10)	−10	16	$Ti(OPr^i)_4$ (110)	90	9 (*S*)
12	**16** (10)	−10	16	$Ti(OPr^i)_4$ (110)	94	14 (*R*)
13	**8** (10)	−10	16	—	38	6 (*S*)
14	**8** (10)	−10	16	$Ti(OPr^i)_4$ (10)	50	21 (*S*)
15	**13a** (10)	−10	48	—	24	30 (*S*)
16	**13a** (10)	−10	16	$Ti(OPr^i)_4$ (10)	14	0 (—)
17	**13a** (10)	−10	16	$Cu(OTf)_2$ (10)	21	50 (*S*)
18	**13a** (10)	25	6	$Ti(OPr^i)_4$ (110)	>95	31 (*S*)
19	**13a** (10)	−30	24	$Ti(OPr^i)_4$ (110)	>95	92 (*S*)
20	**13a** (5)	−30	40	$Ti(OPr^i)_4$ (110)	67	85 (*S*)
21[e]	**13a** (10)	−30	24	$Ti(OPr^i)_4$ (110)	86	95 (*S*)
22	**13b** (10)	−30	24	$Ti(OPr^i)_4$ (110)	>95	91 (*S*)

[a] The amount of ligand is reported in parentheses.
[b] The amount of additive is reported in parentheses.
[c] Yield of isolated alcohol **19a** after bulb to bulb distillation.
[d] Enantiomeric excess obtained by HPLC (chiracel OD-H). The absolute configuration is reported in parentheses.
[e] The amount of diethylzinc **18a** was reduced to 180 mol %.

Table 3
Enantioselective addition of dialkylzinc reagents to aldehydes



17 **18** **19**

13a (10 mol%)

Entry	R^1	R^2	No	Yield[a] (%)	ee[b] (%)
1	Ph	Et	**19a**	>95	92 (*S*)
2	Ph	Me	**19b**	94[c]	80 (*S*)
3	4-ClC_6H_4	Et	**19c**	89	90 (*S*)
4	4-NCC_6H_4	Et	**19d**	56[c]	75 (*S*)
5	4-$CF_3C_6H_4$	Et	**19e**	>95	87 (*S*)
6	4-$MeOC_6H_4$	Et	**19f**	>95	89 (*S*)
7	1-Naphthyl	Et	**19g**	>95	96 (*S*)
8	(*E*)-PhCH=CH	Et	**19h**	65	63 (*S*)
9	PhC≡C	Et	**19i**	82	50 (*S*)
10	$PhCH_2CH_2$	Et	**19j**	86[c]	93 (*S*)

[a] Isolated yield after column chromatography.
[b] Enantiomeric excess obtained by HPLC (see Section 4). The absolute configuration is reported in parentheses.
[c] Values after 48 h reaction time.

The initial reaction conditions, as well as reagent ratios, were chosen from our standard protocols (a large excess of diethylzinc, nearly stoichiometric amount of titanium tetraisopropoxide, 10 mol % of ligand in toluene at low temperature).[18] The ethylation took place in 16 h under these conditions using simple quinoline derivative **7a**, giving the expected secondary alcohol **19a** in nearly quantitative yield but in low enantiomeric excess (Table 2, entry 1). The same reaction using the most hindered benzo[*h*]quinoline ligand **7b** also gave a modest enantioselectivity, with the absolute configuration of the secondary alcohol **19a** surprisingly being the opposite one (entry 2). The presence of an extra chelating nitrogen atom different from the quinoline one had an important negative effect on the enantiomeric excess of the secondary alcohol (entries 3 and 4). The use of the C_2-symmetric ligands did not improve the previous results, although they showed that the absolute configuration of the secondary alcohol **19a** was dictated by the diamine unit and not by the camphor moiety with these ligands (entries 8–10). The reaction using the C_1-ligand **13a**, bearing only one camphor–quinoline unit, gave a good result not only in terms of yield but also in enantioselectivity (entry 8). The related more acidic ligand **13b** gave, however, a lower enantiomeric excess (entry 9).

It should be noted that the N-dioxide derivatives **14**–**16** gave even worse results than the initial C_2-symmetric ligands (compare entries 5–7 and 10–12).

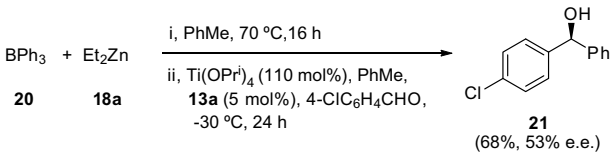
When the reaction was performed in the absence of titanium tetraisopropoxide, or using substoichiometric amounts of either this Lewis acid or copper(II) triflate, the results were clearly inferior (entries 13–17).

The effect of temperature was the classical one, a lower temperature gave a higher enantioselectivity and reaction time (compare entries 8, 18, and 19).

While a decrease in the amount of catalyst **13a** at −30 °C seemed to have a negative impact on the results, the same was not true for the amount of diethylzinc (compare entries 19–21).

Finally, it should be noted that, whereas at −10 °C the behavior of both ligands **13** was different (entries 8 and 9), the reaction at −30 °C gave similar results independent of the ligand used (entries 19 and 22).

Once the best conditions were found (Table 2, entry 19), the scope of the reaction was studied, with the results shown in Table 3. The results were similar using different sources of nucleophiles, such as diethylzinc and dimethylzinc (compare entries 1 and 2). The electronic character of the arenecarbaldehyde derivative seemed not to have any important impact on the results, since *para*-substituted benzaldehyde derivatives with either electron-withdrawing or electron-donating groups gave results similar to those found with benzaldehyde (compare entries 1 and 3–6). The possible differences might be due to the presence of a new chelating group, with the cyano derivative giving the lowest results in this series by competing with the oxygen atom of the carbonyl group for complexation with the Lewis acid center. The best result was obtained when the highly hindered naphtha-1-ylcarbaldedyde was used as the electrophile (entry 7). Surprisingly, when the reaction was carried out using α,β-unsaturated aldehydes the results were lower. However, the reaction using the related saturated



20 **18a** **21** (68%, 53% e.e.)

Scheme 3. Phenylation of 4-chlorobenzaldehyde.

aliphatic aldehyde gave high levels of enantioselectivity (compare entries 8–10).

The final process studied was the phenylation of aldehydes as shown in Scheme 3. It has been established that the transmetallation of triphenylborane **20** with diethylzinc **18a** gave a new organozinc reagent bearing both ethyl and phenyl groups. This new organozinc reagent has been used as an efficient phenylating agent.[19,20] In fact, after the transmetallation process at 70 °C, the standard reaction with 4-chlorobenzaldehyde **17b** in the presence of titanium tetraisopropoxide and chiral ligand **13a** gave, after hydrolysis, alcohol **21** as the only secondary alcohol isolated. In fact, we were unable detect the corresponding alcohol **19c** by GC-analysis of the crude mixture. This result showed that the change of the source of the nucleophilic zinc reagent has an important effect on the level of enantioselectivity previously reached, with this lower enantioselectivity seemingly due to the higher volume of nucleophile.

3. Conclusions

In conclusion, we have described the synthesis of a new class of chiral quinoline ligands, which were prepared by the reaction of camphorsulfonyl chloride with different amines and final indirect Firedländer annulation catalyzed by ruthenium. These compounds have been used as ligands in the enantioselective addition of organozinc reagents to aldehydes, giving good enantioselectivities in the case of using either aromatic or aliphatic ones.

4. Experimental

Melting points were obtained with a Reichert Thermovar apparatus. $[\alpha]_D$ were recorded at room temperature (ca. 25 °C) in a DIP-1000 JASCO polarimeter. FT-IR spectra were obtained on a Nicolet Impact 400D spectrophotometer. NMR spectra were recorded on a Bruker AC-300 (300 MHz for ^1H and 75 MHz for ^{13}C) using $CDCl_3$ as solvent and TMS as 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 (%) that are given in parentheses. The high resolution mass spectroscopy was performed by the corresponding Mass Spectrometry 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 diam, 0.33 mm film thickness, OV-1 stationary phase), using nitrogen (2 mL/min) as carrier gas, $T_{injector}$ = 275 °C, $T_{detector}$ = 300 °C, T_{column} = 60 °C (3 min) and 60–270 °C (15 °C/min), P = 40 kPa; t_r values are given in min under these conditions. The enantiomeric ratios (e.r.) for the calculation of enantiomeric excess of tertiary alcohols were determined by HPLC analysis in a HP-1100 or a Jasco P-1030 apparatus by using hexane/2-propanol mixtures as solvents, and Chiralcel OD-H (ODH) and Chiralcel OJ (OJ) as chiral columns, 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. Thin layer chromatography (TLC) was carried out on Schleicher & Schuell F1400/LS 254 plates coated with a 0.2 mm layer of silica gel; detection by UV_{254} light, staining with phosphomolybdic acid (25 g phosphomolybdic acid, 10 g $Ce(SO_4)_2 \cdot 4H_2O$, 60 mL concentrated H_2SO_4 and 940 mL H_2O); R_f values are given under these conditions. Column chromatography was performed using silica gel 60 of 35–70 mesh. All reagents were commercially available (Acros, Aldrich, Strem) and were used as received. Solvents were dried by standard procedures.

4.1. General procedure for the preparation of compounds 7a–d and 8–10

To a solution of the corresponding amine **5** (15 mmol, 7.5 mmol for compounds **8–10**), triethylamine (15.6 mmol) and dimethylaminopyridine (6.75 mmol) in acetonitrile (30 mL) at 0 °C was added dropwise a solution of (1*S*)-(+)-10-camphorsulfonylchloride **4** (15.6 mmol) in acetonitrile (30 mL). The solution was stirred for 24 h allowing the temperature to reach 25 °C. Then, the mixture was quenched by the addition of a 3 M solution of NaOH (30 mL) and the resulting mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with a 2 M solution of HCl (60 mL), dried over anhydrous Na_2SO_4, and filtered. Finally, the solvent was removed under reduced pressure to afford the corresponding camphorsulfonamides. Then, to a solution of $RuCl_2(DMSO)_4$ (0.3 mmol) and KOH (45 mmol) in 1,4-dioxane (50 mL) was added the corresponding camphorsulfonamide (ca. 15 mmol) followed by the corresponding alcohol **6** (22.5 mmol) and benzophenone (22.5 mmol). The mixture was stirred and heated at 100 °C for a period of 72 h. After this period of time, the mixture was filtered through Celite and the solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using suitable mixtures of either hexane/EtOAc (for compounds **7a**,**b**, **8–10**) or EtOAc/MeOH (for compounds **7c**,**d**) to afford the corresponding quinoline derivatives **7–10**. Yields are reported in Table 1 and text. Spectroscopic and analytical data follow.

4.1.1. *N*-Benzyl-(1*S*,12*S*)-15,15-dimethyl-3-azatetracyclo[10.2.1.0^{2,11}.0^{4,9}]pentadeca-2(11),3,5,7,9-pentaen-1-ylmethanesulfonamide 7a

R_f 0.54 (hexane/EtOAc: 3/2); $[\alpha]_D^{20} = +76.9$ (c 8.5, $CHCl_3$); ν (film) 3068, 1634, 1581 cm^{-1} (C=CH); δ_H 0.50 and 1.01 (3 and 3H, respectively, 2s, 2 × CH_3), 1.20–1.30, 2.00–2.05, 2.15–2.25 (1, 1 and 2H, respectively, 3m, CH_2CH_2), 2.97 (1H, d, J = 3.3 Hz, C*H*CH_2), 3.22 and 3.55 (1 and 1H, respectively, 2d, J = 15.2 Hz, CH_2SO_2), 4.35–4.45 and 4.55–4.60 (1 and 1H, 2m, CH_2N), 7.25–7.45 and 7.70–7.75 (8 and 2H, respectively, 2m, ArH), 9.51 (1H, t, J = 6.3 Hz, NH); δ_C 19.0, 20.4, 26.5, 30.25, 48.25, 50.55, 51.75, 55.45, 57.6, 126.15, 127.6, 127.65, 127.7, 127.75, 128.35, 128.7 (2C), 128.75 (2C), 128.8, 137.4, 139.4, 145.15, 168.45; m/z 238 (M^+−168, 10%), 237 (70), 236 (100), 220 (11), 209 (18), 208 (14), 195 (19), 194 (50), 193 (14), 192 (14), 180 (21); HRMS: M^+ found 406.1722. $C_{24}H_{26}SN_2O_2$ requires 406.1715.

4.1.2. *N*-Benzyl-(1*S*,16*S*)-19,19-dimethyl-3-azapentacyclo[14.2.1.0^{4,13}.0^{5,10}]nonadeca-2(15),3,5(10),6,8,11,13-heptaen-1-ylmethanesulfonamide 7b

R_f 0.52 (hexane/EtOAc: 6/4); $[\alpha]_D^{2.} = +28.0$ (c 13.5, $CHCl_3$); ν (film) 3295 (NH), 3060, 1613, 1563 (SO_2) cm^{-1} (C=CH); δ_H 0.48 and 1.04 (3 and 3H, respectively, 2s, 2 × CH_3), 1.22–1.32, 1.95–2.00 and 2.20–2.40 (1, 1 and 2H, respectively, 3m, CH_2CH_2), 3.00 (1H, d, J = 3.7 Hz, C*H*CH_2), 3.30 and 3.67 (2H, 2d, J = 15.1 Hz, CH_2SO_2), 4.48–4.63 (2H, m, CH_2N), 7.15–7.40, 7.50–7.65, 7.75–7.85 and 8.78 (6, 2, 3 and 1H, respectively, 3m and d, respectively, J = 8.3 Hz, ArH), 8.82 (1H, t, J = 6.6 Hz, NH); δ_C 19.3, 20.15, 26.25, 29.0, 47.5, 50.5, 52.35, 55.75, 58.05, 123.35, 125.4, 125.6, 126.8, 127.05, 127.3, 127.4, 128.0 (2C), 128.2, 128.3 (2C), 128.45, 130.75, 133.25, 137.35, 139.95, 143.3, 166.85; m/z 288 (M^+−168, 11%), 287 (68), 286 (100), 285 (14), 258 (14), 245 (17), 244 (45), 243 (18), 242 (25), 230 (21), 106 (11), 91 (10); HRMS: M^+−$C_7H_8NO_2S$ found 286.1593. $C_{21}H_{20}N$ requires 286.1596.

4.1.3. *N*-(2-Dimethylaminoethyl)-(1*S*,12*S*)-15,15-dimethyl-3-azatetracyclo[10.2.1.0^{2,11}.0^{4,9}]pentadeca-2(11),3,5,7,9-pentaen-1-ylmethanesulfonamide 7c

R_f 0.55 (MeOH); $[\alpha]_D^{20} = +76.2$ (*c* 1.0, $CHCl_3$); *v* (film) 3063, 1644, 1578 (C=CH), 1325, 1145 (SO_2) cm^{-1}; δ_H 0.64 and 1.08 (3H each one, 2s, 2 × CH_3), 1.30–1.35, 2.00–2.10 and 2.20–2.30 (1, 1 and 2H, respectively, 3m, CH_2CH_2), 2.17 (6H, s, NMe_2), 2.45–2.55 and 2.70–2.75 (1 and 1H, respectively, 2m, C*H*$_2$NMe$_2$), 3.00 (1H, d, *J* = 3.3 Hz, C*H*CH$_2$), 3.35–3.45 (2H, m, C*H*$_2$NH), 3.26 and 3.92 (1H each one, 2d, *J* = 14.9 Hz, CH_2SO_2), 7.45–7.50, 7.55–7.65, 7.75, 7.80 and 8.10 (1H each one, 2m, d, s and d, respectively, *J* = 7.8 and 8.3 Hz, respectively, ArH), 8.71 (1H, s, NH); δ_C 19.05, 20.25, 26.30, 29.85, 41.45, 45.00 (2C), 50.45, 50.70, 55.30, 57.25, 58.75, 125.80, 127.20, 127.25, 127.50, 127.85, 128.20, 139.10, 145.40, 168.25; *m/z* 330 (M$^+$−57, 22%), 329 (78), 279 (10), 237 (15), 236 (25), 194 (24), 193 (12), 192 (14), 180 (13), 58 (100); HRMS: $C_{21}H_{29}N_3O_2S$ found 387.1978. $C_{21}H_{29}N_3O_2S$ requires 387.1980.

4.1.4. *N*-(2-Dimethylaminoethyl)-*N*-methyl-(1*S*,12*S*)-15,15-dimethyl-3-azatetracyclo[10.2.1.0^{2,11}.0^{4,9}]pentadeca-2(11),3,5,7,9-pentaen-1-ylmethanesulfonamide 7d

R_f 0.36 (MeOH); $[\alpha]_D^{20} = +17.0$ (*c* 1.2, $CHCl_3$); *v* (film) 3043, 1638, 1582 (C=CH), 1346, 1147 (SO_2) cm^{-1}; δ_H 0.60 and 1.27 (3H each one, 2s, 2 × CH_3), 1.20–1.35, 1.45–1.55, 2.25–2.30, 2.75–2.90 and 2.95 (1H each one, 4m and d, *J* = 3.7 Hz, CH_2CH_2CH), 2.30 (6H, s, NMe_2), 2.50–2.65 (2H, m, C*H*$_2$NMe$_2$), 3.11 (3H, s, NMe), 3.35–3.45, 3.50–3.60 (1H each one, 2m, C*H*$_2$NMe), 3.38 and 4.19 (1H each one, 2d, *J* = 14.9 Hz, CH_2SO_2), 7.45–7.50, 7.55–7.65, 7.70–7.75 and 8.10 (1, 1, 2 and 1H, respectively, 3m and d, respectively, *J* = 8.3 Hz, ArH); δ_C 19.95, 20.00, 26.20, 27.40, 35.05, 45.20 (2C), 47.05, 48.05, 50.95, 54.40, 56.80, 57.55, 125.50, 126.30, 127.40, 127.70, 127.80, 128.55, 138.05, 146.25, 169.45; *m/z* 279 (M$^+$−122, 17%), 237 (19), 236 (23), 194 (15), 58 (100); HRMS: M$^+$−$C_5H_{13}N_2O_2S$ found 236.1441. $C_{17}H_{18}N$ requires 236.1439.

4.1.5. *N*-{(1*R*,2*R*)-2-[(1*S*,12*S*)-15,15-Dimethyl-3-azatetracyclo[10.2.1.0^{2,11}.0^{4,9}]pentadeca-2(11),3,5,7,9-pentaen-1-ylmethylsulfonamido]cyclohexyl}-(1*S*,12*S*)-15,15-dimethyl-3-azatetracyclo[10.2.1.0^{2,11}.0^{4,9}]pentadeca-2(11),3,5,7,9-pentaen-1-ylmethanesulfonamide 8

Mp 163–165 °C; R_f 0.61 (hexane/EtOAc: 1/1); $[\alpha]_D^{20} = +60.8$ (*c* 1.1, $CHCl_3$); *v* (KBr) 3048, 1632, 1588 (C=CH), 1340, 1147 (SO_2) cm^{-1}; δ_H 0.59 and 1.10 (6H each one, 2s, 4 × CH_3), 1.20–1.35, 1.45–1.50, 1.60–1.65, 1.75–1.80, 1.95–2.00, 2.20–2.40 and 2.97 [2, 2, 2, 2, 2, 6 and 2H, respectively, 6m and d, respectively, *J* = 3.7 Hz, $(CH_2)_4$ and 2 × CH_2CH_2CH)], 3.41 and 4.08 (2H each one, 2d, *J* = 14.9 Hz, 2 × CH_2SO_2), 3.65–3.75 (2H, m, 2 × CHN), 7.35–7.45, 7.70–7.75, 7.93 and 8.07 (4, 4, 2 and 2H, respectively, 2m and 2d, respectively, *J* = 3.8 and 8.1 Hz, ArH and 2 × NH); δ_C 14.15 (2C), 19.30 (2C), 20.25 (2C), 24.20 (2C), 26.40 (2C), 29.35 (2C), 50.60 (2C), 52.60 (2C), 55.15 (2C), 57.40 (2C), 57.45 (2C), 125.80 (2C), 127.05 (2C), 127.50 (2C), 127.75 (2C), 128.10 (2C), 128.15 (2C), 139.50 (2C), 145.60 (2C), 168.65 (2C); *m/z* 413 (M$^+$−299, 29%), 412 (100), 317 (30), 301 (17), 300 (88), 237 (47), 236 (68), 220 (16), 209 (14), 208 (16), 206 (11), 195 (20), 194 (74), 193 (20), 192 (15), 181 (10), 180 (40); HRMS: M$^+$−$C_{23}H_{30}N_3O_4S_2$ found 236.1430. $C_{17}H_{18}N$ requires 236.1439.

4.1.6. *N*-{(1*R*,2*R*)-2-[(1*R*,12*R*)-15,15-Dimethyl-3-azatetracyclo[10.2.1.0^{2,11}.0^{4,9}]pentadeca-2(11),3,5,7,9-pentaen-1-ylmethylsulfonamido]cyclohexyl}-(1*R*,12*R*)-15,15-dimethyl-3-azatetracyclo[10.2.1.0^{2,11}.0^{4,9}]pentadeca-2(11),3,5,7,9-pentaen-1-ylmethanesulfonamide 9

Mp 125–127 °C; R_f 0.52 (hexane/EtOAc: 1/1); $[\alpha]_D^{20} = -67.2$ (*c* 1.0, $CHCl_3$); *v* (KBr) 3056, 2962, 1638, 1570, 1513, (C=CH), 1399, 1149 (SO_2) cm^{-1}; δ_H 0.38 and 1.02 (6H each one, 2s, 4 × CH_3), 1.20–1.30, 1.40–1.50, 1.60–1.65, 1.80–1.90, 2.15–2.25, 2.35–2.45 and 2.90 [2, 2, 2, 4, 2, 4 and 2H, respectively, 6m and d, respectively, *J* = 3.9 Hz, $(CH_2)_4$ and 2 × CH_2CH_2CH)], 3.33 and 4.13 (2H each one, 2d, *J* = 15.2 Hz, 2 × CH_2SO_2), 3.65–3.70 (2H, m, 2 × CHN), 7.45–7.50, 7.55–7.60, 7.70–7.75, 7.94 and 8.44 (2, 2, 4, 2 and 2H, respectively, 3m and 2d, respectively, *J* = 3.8 and 8.1 Hz, ArH and 2 × NH); δ_C 19.20 (2C), 20.25 (2C), 24.20 (2C), 26.30 (2C), 28.75 (2C), 33.75 (2C), 50.60 (2C), 53.35 (2C), 55.00 (2C), 56.15 (2C), 57.40 (2C), 125.90 (2C), 127.15 (2C), 127.55 (2C), 127.75 (2C), 127.95 (2C), 128.25 (2C), 139.30 (2C), 145.40 (2C), 168.75 (2C); *m/z* 413 (M$^+$+1, 29%), 412 (100), 317 (31), 301 (14), 300 (76), 238 (11), 237 (58), 236 (51), 220 (10), 209 (11), 208 (13), 206 (11), 195 (14), 194 (49), 193 (13), 192 (10), 180 (25); M$^+$−$C_{23}H_{30}N_3O_4S_2$ found 236.1445. $C_{17}H_{18}N$ requires 236.1439.

4.1.7. *N*-{(1*R*,2*S*)-2-[(1*S*,12*S*)-15,15-Dimethyl-3-azatetracyclo[10.2.1.0^{2,11}.0^{4,9}]pentadeca-2(11),3,5,7,9-pentaen-1-ylmethylsulfonamido]cyclohexyl}-(1*S*,12*S*)-15,15-dimethyl-3-azatetracyclo[10.2.1.0^{2,11}.0^{4,9}]pentadeca-2(11),3,5,7,9-pentaen-1-ylmethanesulfonamide 10

Mp 248–250 °C; R_f 0.55 (hexane/EtOAc: 1/1); $[\alpha]_D^{20} = +142.0$ (*c* 1.0, $CHCl_3$); *v* (KBr) 3138, 3065, 2949, 1640, 1574, 1507, (C=CH), 1407, 1140 (SO_2) cm^{-1}; δ_H 0.55, 0.60, 1.01 and 1.04 (3H each one, 4s, 4 × CH_3), 1.15–1.40, 1.60–2.00, 2.00–2.35, 2.90–2.95 [3, 7, 6 and 2H, respectively, 4m, $(CH_2)_4$ and 2 × CH_2CH_2CH)], 3.20, 3.43, 3.65 and 4.73 (1H each one, 4d, *J* = 15.1 Hz, 2 × CH_2SO_2), 3.65–3.70 and 4.40–4.45 (1H each one, 2m, 2 × CHN), 6.65–6.70 and 6.85–6.90 (1H each one, 2m, 2 × NH), 7.25–7.30, 7.50–7.55, 7.60–7.70, 7.80–7.85, 8.05–8.10 and 8.50–8.55 (1, 2, 2, 2, 1 and 2H, respectively, 6m, ArH); δ_C 19.10, 19.20, 20.25, 20.30, 20.70, 23.70, 26.25, 26.50, 27.95, 30.00, 30.40, 31.80, 50.45, 50.75, 51.70, 54.10, 55.05, 55.40, 55.90, 56.00, 57.25, 57.55, 125.75, 125.80, 126.95, 127.25, 127.40, 127.45, 127.50, 127.70, 127.80, 128.00, 128.05, 128.10, 139.20, 140.10, 144.75, 145.60, 168.35, 169.45; *m/z* 413 (M$^+$−299, 33%), 412 (100), 317 (27), 302 (12), 301 (16), 300 (85), 237 (40), 236 (56), 220 (12), 209 (11), 208 (14), 195 (15), 194 (57), 193 (16), 192 (12), 180 (29); M$^+$−$C_{23}H_{30}N_3O_4S_2$ found 236.1434. $C_{17}H_{18}N$ requires 236.1439.

4.2. General procedure for the preparation of compounds 13

To a mixture of (1*R*,2*R*)-1,2-diaminocyclohexane **11** (12 mmol) in a biphasic system of a 2 M solution of NaOH (15 mL) and CH_2Cl_2 (15 mL) at 0 °C, a solution of the corresponding arenesulfonyl chloride **12** (12 mmol) in CH_2Cl_2 (15 mL) was added dropwise over a period of 20 min. The resulting mixture was stirred and left to reach room temperature for a period of 6 h. Then, to this solution was added a 2 M solution of HCl until the pH was acid. The organic layer was rejected and the aqueous phase was basified using a 6 M solution of NaOH until basic pH and extracted with CH_2Cl_2 (4 × 60 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. Finally, the solvent was removed under reduced pressure and the residue was obtained. Then, to a solution of the above residue, triethylamine (54 mmol) and dimethylaminopyridine (6 mmol) in acetonitrile (25 mL) at 0 °C was added dropwise a solution of (1*S*)-(+)-10-camphorsulfonylchloride **4** (18 mmol) in acetonitrile (25 mL). The resulting solution was stirred for 24 h allowing the temperature to reach to 25 °C. Then, the mixture was quenched by the addition of a 3 M solution NaOH (50 mL) and it was extracted with EtOAc (4 × 40 mL). The combined organic layers were washed with a 2M solution of HCl (60 mL), dried over anhydrous Na_2SO_4, and filtered. Finally, the solvent was removed under reduced pressure to give a new residue. Finally, to a solution of $RuCl_2(DMSO)_4$ (0.2 mmol) and KOH (40 mmol) in 1,4-dioxane (50 mL) was added the above residue

(ca. 10 mmol) followed by 2-aminobenzyl alcohol (30 mmol) and benzophenone (30 mmol). The resulting mixture was stirred and heated at 100 °C for a period of 72 h. After this period, the mixture was filtered through Celite and the solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using suitable mixtures of hexane/EtOAc to afford the corresponding quinolines **13**. Yields are reported in Scheme 1. Spectroscopic and analytical data follow.

4.2.1. *N*-[(1*R*,2*R*)-2-(4-Methylphenylsulfonamido)cyclo-hexyl]-(1*S*,12*S*)-15,15-dimethyl-3-azatetracyclo[10.2.1.$0^{2,11}$.$0^{4,9}$]pentadeca-2(11),3,5,7,9-pentaen-1-ylmethanesulfonamide 13a

Mp 105–107 °C; R_f 0.53 (hexane/EtOAc: 1/1); $[\alpha]_D^{20} = -0.7$ (*c* 1.6, $CHCl_3$); *v* (KBr) 2942, 1648, 1613 (C=CH), 1332, 1159 (SO_2) cm^{-1}; δ_H 0.60, 1.07 and 2.19 (3H each one, 3s, 3 × CH_3), 1.20–1.40, 1.60–1.70, 1.90–2.10, 2.15–2.30, 2.40–2.45 and 3.02 [5, 2, 2, 2, 1 and 1H, respectively, 5m and d, respectively, *J* = 3.7 Hz, $(CH_2)_4$ and CH_2CH_2CH)], 2.80–2.90 and 3.20–3.30 (1H each one, 2m, 2 × CHN), 3.35 and 3.52 (1H each one, 2d, *J* = 15.1 Hz, CH_2SO_2), 5.75 (1H, d, *J* = 3.4 Hz, NH), 7.20 and 7.89 (2H each one, 2d, *J* = 8.1 Hz, $C_6H_4CH_3$), 7.40–7.60 and 7.75–7.80 (3 and 2H, respectively, 2m, ArH), 8.80 (1H, d, *J* = 7.2 Hz, NH); δ_C 18.95, 20.15, 21.20, 23.80, 24.70, 26.30, 30.20, 32.45, 33.75, 50.30, 53.35, 55.35, 56.75, 57.30, 58.20, 126.05, 126.85, 127.55 (2C), 127.65 (2C), 128.30, 136.50 (2C), 139.40, 142.80 (2C), 144.60 (2C), 167.85; *m/z* 413 (M^+−154, 19%), 412 (70), 317 (32), 301 (19), 300 (100), 237 (42), 236 (69), 220 (12), 208 (13), 195 (14), 194 (54), 193 (17), 192 (13), 180 (29), 96 (26), 91 (23); HRMS: $M^+-C_{13}H_{19}N_2O_4S_2$ found 236.1468. $C_{17}H_{18}N$ requires 236.1439.

4.2.2. *N*-[(1*R*,2*R*)-2-(4-Trifluoromethylphenylsulfonamido)-cyclohexyl]-(1*S*,12*S*)-15,15-dimethyl-3-azatetracyclo-[10.2.1.$0^{2,11}$.$0^{4,9}$]pentadeca-2(11),3,5,7,9-pentaen-1-ylmethanesulfonamide 13b

Mp 113–115 °C; R_f 0.56 (hexane/EtOAc: 1/1); $[\alpha]_D^{20} = -1.1$ (c 1.0, $CHCl_3$); *v* (KBr) 2944, 1619, 1583 (C=CH), 1323, 1173 (SO_2) cm^{-1}; δ_H 0.60 and 1.06 (3H each one, 2s, 2 × CH_3), 1.30–1.40, 1.60–1.70, 1.90–2.00, 2.15–2.30, 2.35–2.40 and 3.01 [5, 2, 2, 2, 1 and 1H, respectively, 5m and d, respectively, *J* = 3.7 Hz, $(CH_2)_4$ and CH_2CH_2CH)], 2.90–2.95 and 3.20–3.30 (1H each one, 2m, 2 × CHN), 3.37 and 3.50 (1H each one, 2d, *J* = 15.1 Hz, CH_2SO_2), 6.17 (1H, d, *J* = 4.4 Hz, NH), 7.45–7.60 and 7.75–7.80 (3 and 2H, respectively, 2m, ArH), 7.66 and 8.16 (2H each one, 2d, *J* = 8.3 Hz, $C_6H_4CF_3$), 8.98 (1H, d, *J* = 6.8 Hz, NH); δ_C 19.00, 20.20, 23.95, 24.80, 26.30, 30.35, 32.45, 34.25, 50.40, 53.45, 55.45, 56.95, 57.35, 58.80, 120.45 (q, $J_{1,2}$ = 272.9 Hz, CF_3), 125.75, 125.80, 125.85, 126.15, 126.80, 127.60, 127.70, 127.75, 128.30, 128.45, 133.60 (q, $J_{1,3}$ = 33.7 Hz, CCF_3), 139.35, 143.40, 144.60, 167.80; *m/z* 413 (M^+−208, 19%), 412 (70), 317 (32), 301 (20), 300 (100), 237 (26), 236 (66), 222 (11), 220 (11), 208 (12), 195 (12), 194 (51), 193 (16), 192 (12), 180 (27), 145 (15), 138 (42), 96 (18), 83 (10), 55 (12) 43 (12); HRMS: $M^+-C_7H_4F_3O_2S$ found 412.2083. $C_{23}H_{30}N_3O_2S$ requires 412.2059.

4.3. General procedure for the preparation of N-oxides 14–16

To a solution of the corresponding quinolines **8–10** (5 mmol) in CH_2Cl_2 (35 mL s) was added *m*-chloroperbenzoic acid (10.85 mmol) at 0 °C. The resulting mixture was allowed to rise to room temperature. After 3 h, the mixture was quenched by addition of a saturated solution of NaCl (30 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. Finally, the solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography on silica gel using suitable mixtures of EtOAc/MeOH to afford the corresponding N-oxides **14–16**. Yields are reported in Scheme 2. Spectroscopic and analytical data follow.

4.3.1. 1-{(1*R*,2*R*)-2-[(1*S*,12*S*)-15,15-Dimethyl-3-olato-3-azonia-tetracyclo[10.2.1.$0^{2,11}$.$0^{4,9}$]pentadeca-2(11),3,5,7,9-pentaen-1-ylmethylsulfonamido]cyclohexylsulfamoylmethyl}-(1*S*,12*S*)-15,15-dimethyl-3-azoniatetracyclo[10.2.1.$0^{2,11}$.$0^{4,9}$]pentadeca-2(11),3,5,7,9-pentaen-3-olate 14

Mp 150–152 °C; R_f 0.79 (EtOAc/MeOH: 9/1); $[\alpha]_D^{20} = -4.5$ (*c* 1.1, $CHCl_3$); *v* (KBr) 3077, 2971, 2920, 2859, 1635, 1584, 1501 (C=CH), 1273, 1156 (SO_2) cm^{-1}; δ_H 0.75 and 1.15 (6H each one, 2*s*, 4 × CH_3), 1.20–1.55, 1.70–1.80, 1.90–2.00, 2.15–2.30, 2.60–2.70 and 2.93 [6, 2, 2, 4, 2 and 2H, respectively, 5m and d, *J* = 3.7 Hz, $(CH_2)_4$ and 2 × CH_2CH_2CH)], 3.50–3.55 (2H, m, 2 × CHN), 3.73 and 4.14 (2H each one, 2d, *J* = 15.0 Hz, 2 × CH_2SO_2), 7.15 (2H, s, 2 × NH), 7.47, 7.55–7.65, 7.75 and 8.68 (2, 4, 2 and 2H, respectively, s, m and 2d, respectively, *J* = 7.6 and 8.4 Hz, ArH); δ_C 19.05 (2C), 20.70 (2C), 24.05 (2C), 26.05 (2C), 28.25 (2C), 51.65 (2C), 52.05 (2C), 55.50 (2C), 55.75 (2C), 57.80 (4C), 119.25 (2C), 119.35 (2C), 127.50 (2C), 128.05 (2C), 129.05 (2C), 129.60 (2C), 140.95 (2C), 141.85 (2C), 151.20 (2C); *m/z* 412 (M^+−332, 19%), 238 (15), 237 (87), 236 (100), 235 (14), 234 (13), 222 (20), 220 (19), 209 (22), 208 (23), 206 (12), 204 (11), 195 (24), 194 (72), 193 (22), 192 (21), 181 (10), 180 (34); HRMS: $M^+-C_{23}H_{30}N_3O_3S$ found 316.1053. $C_{17}H_{18}NO_3S$ requires 316.1007.

4.3.2. 1-{(1*R*,2*R*)-2-[(1*R*,12*R*)-15,15-Dimethyl-3-olato-3-azoniatetracyclo[10.2.1.$0^{2,11}$.$0^{4,9}$]pentadeca-2(11),3,5,7,9-pentaen-1-ylmethylsulfonamido]cyclohexylsulfamoylmethyl}-(1*R*,12*R*)-15,15-dimethyl-3-azoniatetracyclo[10.2.1.$0^{2,11}$.$0^{4,9}$]-pentadeca-2(11),3,5,7,9-pentaen-3-olate 15

Mp 152–154 °C; R_f 0.71 (EtOAc/MeOH: 9/1); $[\alpha]_D^{20} = +44.0$ (*c* 1.0, $CHCl_3$); *v* (KBr) 3067, 2958, 2926, 2853, 1633, 1579, 1501 (C=CH), 1274, 1146 (SO_2) cm^{-1}; δ_H 0.65 and 0.95 (6H each one, 2*s*, 4 × CH_3), 1.10–1.30, 1.40–1.55, 1.75–1.80, 1.90–2.00, 2.10–2.20, 2.45–2.50, 2.65–2.75 and 2.90 [2, 4, 2, 2, 2, 2, 2 and 2H, respectively, 7m and d, *J* = 3.9 Hz, $(CH_2)_4$ and 2 × CH_2CH_2CH)], 3.45–3.55 (2H, m, 2 × CHN), 3.55 and 5.34 (2H each one, 2d, *J* = 15.2 Hz, 2 × CH_2SO_2), 6.90 (2H, s, 2 × NH), 7.48, 7.50–7.55, 7.60–7.65, 7.75–7.80 and 8.73 (2H each one, 3m and d, respectively, *J* = 8.4 Hz, ArH); δ_C 18.70 (2C), 20.50 (2C), 24.50 (2C), 26.10 (2C), 27.05 (2C), 34.75 (2C), 50.45 (2C), 51.30 (2C), 55.45 (2C), 56.40 (2C), 57.25 (2C), 118.95 (2C), 119.10 (2C), 127.55 (2C), 127.85 (2C), 128.95 (2C), 129.55 (2C), 140.95 (2C), 141.85 (2C), 151.00 (2C); *m/z* 412 (M^+−332, 7%), 333 (12), 253 (23), 252 (10), 238 (15), 237 (89), 222 (21), 220 (16), 209 (23), 208 (27), 206 (12), 204 (10), 195 (24), 194 (71), 193 (22), 192 (20), 181 (10), 180 (35), 167 (12); HRMS: $M^+-C_{23}H_{30}N_3O_5S_2$ found 252.1351. $C_{17}H_{18}NO$ requires 252.1388.

4.3.3. 1-{(1*R*,2*S*)-2-[(1*S*,12*S*)-15,15-Dimethyl-3-olato-3-azoniatetracyclo[10.2.1.$0^{2,11}$.$0^{4,9}$]pentadeca-2(11),3,5,7,9-pentaen-1-ylmethylsulfonamido]cyclohexylsulfamoylmethyl}-(1*S*,12*S*)-15,15-dimethyl-3-azoniatetracyclo[10.2.1.$0^{2,11}$.$0^{4,9}$]-pentadeca-2(11),3,5,7,9-pentaen-3-olate 16

Mp 145–147 °C; R_f 0.65 (EtOAc/MeOH: 9/1); $[\alpha]_D^{20} = -32.5$ (c 1.1, $CHCl_3$); *v* (KBr) 3060, 2965, 2932, 2859, 1629, 1579, 1507 (C=CH), 1268, 1150 (SO_2) cm^{-1}; δ_H 0.75, 0.79, 1.09 and 1.11 (3H each one, 4s, 4 × CH_3), 1.20–1.50, 1.65–2.00, 2.10–2.25, 2.60–2.70 and 2.95 [7, 5, 2, 2 and 2H, respectively, 4m and d, respectively, *J* = 4.0 Hz, $(CH_2)_4$ and 2 × CH_2CH_2CH)], 3.55 and 4.74 (1H each one, 2d, *J* = 15.3 Hz, CH_2SO_2), 3.70 and 4.85 (1H each one, 2d, *J* = 15.1 Hz, CH_2SO_2), 4.03 (2H, s, 2 × CHN), 7.50–7.70, 7.80 and 8.10–8.80 (6, 2 and 2H, respectively, m, d and m, respectively, *J* = 7.5 Hz, ArH); δ_C 18.75 (2C), 20.65, 20,70, 23.55, 25.90, 26.05, 28.00, 30.45, 30.50, 38.50, 50.95, 51.05, 51.30, 52.55, 53.35,

55.25, 55.35, 57.70, 57.85, 67.95, 119.05 (2C), 119.10, 127.55 (2C), 127.90, 128.00, 128.85, 129.00, 129.50, 129.55 (2C), 140.60, 140.70, 141.65, 141.75 (2C), 150.85; *m/z* 412 (M^+-332, 30%), 317 (11), 300 (25), 238 (15), 237 (84), 236 (100), 235 (13), 234 (12), 222 (21), 220 (20), 209 (23), 208 (24), 206 (13), 204 (11), 195 (26), 194 (80), 193 (25), 192 (23), 181 (11), 180 (37), 167 (14); HRMS: $M^+-C_{23}H_{30}N_3O_5S_2$ found 252.1316. $C_{17}H_{18}NO$ requires 252.1388.

4.4. General procedure for the enantioselective addition of dialkylzinc reagents to aldehydes

To a solution of corresponding ligand **13** (0.057 g, 0.1 mmol) in toluene (2 mL) under a nitrogen atmosphere was added the corresponding solution of dialkylzinc reagent (9 mmol, 4.5 mL, ca. 2M) at −30 °C. After 10 min, $Ti(OPr^i)_4$ (1.1 mmol, 0.33 mL) was added to the above solution and after 10 additional min, the corresponding aldehyde (1 mmol) was successively added. The resulting mixture was stirred at the same temperature for 24 h. Then, methanol (ca. 1 mL) and saturated NH_4Cl solution (ca. 20 mL) were successively added, the mixture was filtered through Celite and extracted with ethyl acetate (3 × 50 mL), and the organic layer was dried over Na_2SO_4. The solvents were removed under reduced pressure (15 Torr) and the residue was distilled bulb to bulb to yield the expected alcohols. Yields and enantiomeric excesses are shown in Tables 2 and 3. Compounds **19a–d** and **19f**,[13a] as well as **19e**[18] and **19h–j**[13b] were already described by us and were characterized by comparison of their physical and spectroscopic data with those reported in the literature. Spectroscopic and physical data, as well as literature reference for compound **19g** follow.

4.4.1. (*S*)-1-(Naphthalen-1-yl)propan-1-ol 19g[21]

Pale yellow oil, R_f 0.44 (hexane/EtOAc: 8/2); t_r (GC) = 13.2 min; HPLC (OD-H, UV 210 nm, hexane/2-propanol: 90/10, flow 1 mL/min) t_r (*S*) 10.1, t_r (*R*) 16.7; $[\alpha]_D = -38.0$ (*c* 3.8, $CHCl_3$) e.r. (*S*/*R*): 98/2; *v* (film) 3477 (OH), 1088 cm^{-1} (CO); δ_H 0.94 (t, *J* = 7.3 Hz, 3H; CH_3), 1.75–2.00 (m, 2H, CH_2), 2.17 (s, 1H, OH), 5.12 (dd, *J* = 5.1 and 7.6 Hz, 1H, CHO), 7.39–7.45, 7.53, 7.63 and 7.70–7.85 (m, d, d, m and m, respectively, *J* = 6.6 and 8.1 Hz, respectively, 3, 1, 1 1 and 1H, respectively, ArH); δ_C 11.10, 31.70, 73.10, 123.50, 123.90, 126.00, 126.10, 126.50, 128.40, 129.50, 131.10, 134.40, 140.80; *m/z* 186 (M^+, 3%), 168 (55), 167 (31), 165 (28), 154 (13), 153 (11), 152 (35), 129 (10).

4.5. Procedure for the sythesis of 1-(4-chlorophenyl)-1-phenylmethanol 21[22]

In a pressure tube charged with triphenylborane **20** (0.387 g, 1.6 mmol), a solution of Et_2Zn (1.1 M in toluene, 6.5 mL, 7.2 mmol) was slowly added at 0 °C under argon atmosphere. The resulting solution was warmed up to 70 °C and stirred for 16 h. Then, the mixture was cooled down to 0 °C, and ligand **13a** (0.029 g, 0.05 mmol) and $Ti(OPr^i)_4$ (0.33 mL, 1.1 mmol) were successively added. After 15 min of stirring and allowing the temperature to rise to 25 °C, 4-chlorobenzaldedhyde **17b** (1 mmol) was added. The reaction mixture was stirred at the same temperature for 24 h, 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 concentrated. The residue was purified by flash chromatography (hexane/EtOAc) to give the title compound. Yield and enantiomeric excesses are included in Scheme 3. Physical and spectroscopic data follow: Colorless oil. R_f 0.41 (hexane/EtOAc: 8/2); t_r (GC) = 14.3 min; HPLC (AD-H, UV 210 nm, hexane/2-propanol: 95/5, flow 0.8 mL/min) t_r (*R*) 17.5, t_r (*S*) 19.2; $[\alpha]_D$ = +6.5 (*c* 2.4, $CHCl_3$) e.r.(*S*/*R*): 76.5/23.5; *v* (film) 3427 (OH), 1089 cm^{-1} (CO); δ_H 2.37 (d, *J* = 3.3 Hz, 1H, OH), 5.78 (d, *J* = 3.1 Hz, 1H, CHO), 7.25–7.35 (m, 9H, ArH); δ_C 75.55, 126.50 (2C), 127.30, 127.85 (2C), 128.50, 128.55 (2C), 128.60 (2C), 142.15, 143.35; *m/z* 218 (M^+, 24%), 217 (13), 216 (41), 181 (12), 167 (16), 166 (10), 165 (23), 152 (11), 141 (26), 139 (67), 113 (12), 111 (24), 106 (11), 105 (100), 78 (10), 77 (50), 76 (10), 75 (19), 51 (19).

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