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Asymmetric synthesis of novel 1,4-aminoalcohol ligands with norbornene and norbornane backbone: use in the asymmetric diethylzinc addition to benzaldehyde

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Abstract—The asymmetric synthesis of *cis*-1,4-aminoalcohols with norbornene and norbornane backbone was performed starting with (2*S*,3*R*)-(−)-*cis*-hemiester **1** (98% ee). Chemoselective amination with HMPTA followed by Grignard reactions and subsequent LAH reductions afforded compounds **5a**–**d**. *cis*-Hemiester **1** was also transformed into chiral ligands **7a**–**f** and **9a**–**d** with the DCC coupling method followed by LAH reduction using acyclic, heterocyclic amines and various aniline derivatives and *p*-toluenesulfonamide, respectively. The chiral ligands were subjected to asymmetric diethylzinc addition to examine their effectiveness as chiral catalysts. Among these, arylamine and tosyl substituted chiral ligands **9a**–**d** exhibited the highest selectivities (up to 97% ee).

1. Introduction

Aminoalcohols have been used extensively in asymmetric synthesis as chiral ligands[1] and auxiliaries.[2] The heteroatoms allow great ability to bind a transition metal or achiral starting compound. They also play an important role in asymmetric C–C bond forming reactions, which have always been one of the most challenging areas in organic synthesis. Among these, the enantioselective addition of diethylzinc to aldehydes catalyzed by chiral aminoalcohols which was initiated by Oguni and Omi with (*S*)-leucinol,[3] and followed by Noyori with DAIB,[4] has attracted considerable attention. Chiral 1,2-aminoalcohols indicate high chiral catalytic activity of enantioselective alkylation,[5] however, only a few examples of 1,4-aminoalcohols with high catalytic activity have been identified.[6] Most of the chiral 1,4-aminoalcohol ligands are derived from monoterpenes, that is, pulegone,[7] camphor,[8] fenchone,[9] and limonene,[10] and have successfully been used as chiral catalysts, although their use is limited, since in most cases, only one enantiomer of the starting compound is commercially available. In recent work, we described the synthesis of new chiral 1,4-aminoalcohols including a norbornene backbone with high yields and enantiomeric excesses (Fig. 1).[11] Their evaluation as chiral ligands in the addition of diethylzinc to benzaldehyde was also described, showing satisfactory results with compound (+)-**2a** (88% ee).

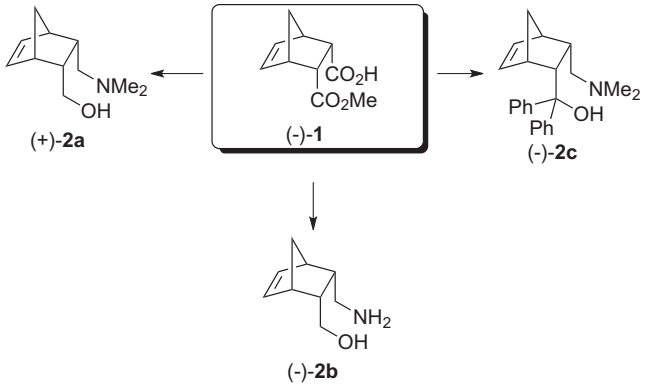

Figure 1. Synthesis of 1,4-aminoalcohols.

In connection with the aforementioned work,[11] we decided to synthesize a series of new enantiopure 1,4-aminoalcohol derivatives, which present the various substituents on a hydroxyl group attached to a methylene carbon and on the nitrogen moiety. Herein, we report the synthesis of novel functionalized derivatives and also the evaluation results

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as a chiral catalyst in the enantioselective addition of diethylzinc to benzaldehyde.

2. Results and discussion

2.1. Asymmetric synthesis of 1,4-aminoalcohols with norbornene and norbornane backbone

In our synthetic route to the novel chiral 1,4-aminoalcohols, homochiral *cis*-monoester (−)-**1** was chosen as the starting compound. Recently, Bolm et al.[12] reported a highly efficient and widely applicable method for the desymmetrization of *meso*-anhydrides via quinine- or quinidine-mediated opening with methanol. Although both enantiomers of *cis*-monoester-**1** could be synthesized with quite high enantiomeric excesses (up to 99% ee), in our study we only used *cis*-monoester (−)-**1** obtained from quinine-mediated desymmetrization of norborneneanhydride (98% ee). The data have previously been reported.[11]

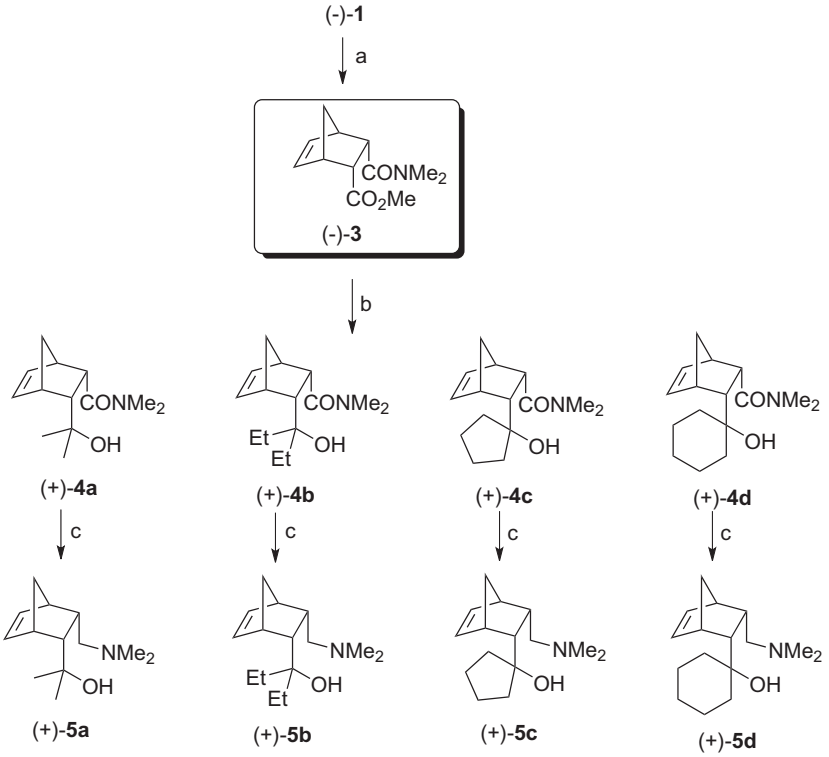
The main structural characteristic of the target 1,4-aminoalcohols **5a–d**, **7a–f**, **9a–d** is to possess various acyclic and cyclic substitutions on the methylene carbon bearing a hydroxyl group and an *N*,*N*-dialkyl, *N*-aryl and heterocyclic amine. Additionally, the catalytic activity has been evaluated and compared to those previously reported by us for (+)-**2a**, (−)-**2b**, and (−)-**2c**.[11] The obtained results are related to the previous studies reported by us, and allow us to compare the role of substitutions on both the hydroxymethylene side and the nitrogen moiety.

2.2. Asymmetric synthesis of 1,4-aminoalcohols having substituents on the hydroxymethylene carbon

In the synthesis of sterically and electronically modified chiral ligands, the *N*,*N*-dimethylamine moiety was kept constant, whereas the ester moiety was functionalized with various substituents. For this purpose, *cis*-monoester (−)-**1** was reacted with hexamethylphosphorus triamide, which transformed the carboxylic acid group into the corresponding *N*,*N*-dimethyl amide derivative (−)-**3** with a yield of 88%.[13] Using a Grignard method, the ester group of (−)-**3** was functionalized with methyl and ethylmagnesium iodide to give dimethyl and diethyl substituted derivatives (+)-**4a** and (+)-**4b**, respectively. The five- and six-membered ring construction on the ester carbon of (−)-**3** was accomplished by using 1,4-dibromobutane and 1,5-dibromopentane with magnesium in ether to afford (+)-**4c** and (+)-**4d**, respectively. Subsequent reduction of (+)-**4a–d** by $LiAlH_4$ in ether afforded the resultant chiral ligands (+)-**5a–d** (Scheme 1).

2.3. Asymmetric synthesis of *N*-functionalized 1,4-aminoalcohol derivatives

Following our synthetic work, we also synthesized a new set of novel chiral *N*-functionalized 1,4-aminoalcohols derived from *cis*-monoester (−)-**1**. The key step for the N-functionalization of (−)-**1** was the DCC coupling method, which transformed the carboxylic acid group into the corresponding *N*,*N*-disubstituted acyclic and cyclic amides (−)-**6a–c** by using diethyl, diallyl, and dibenzyl amines as

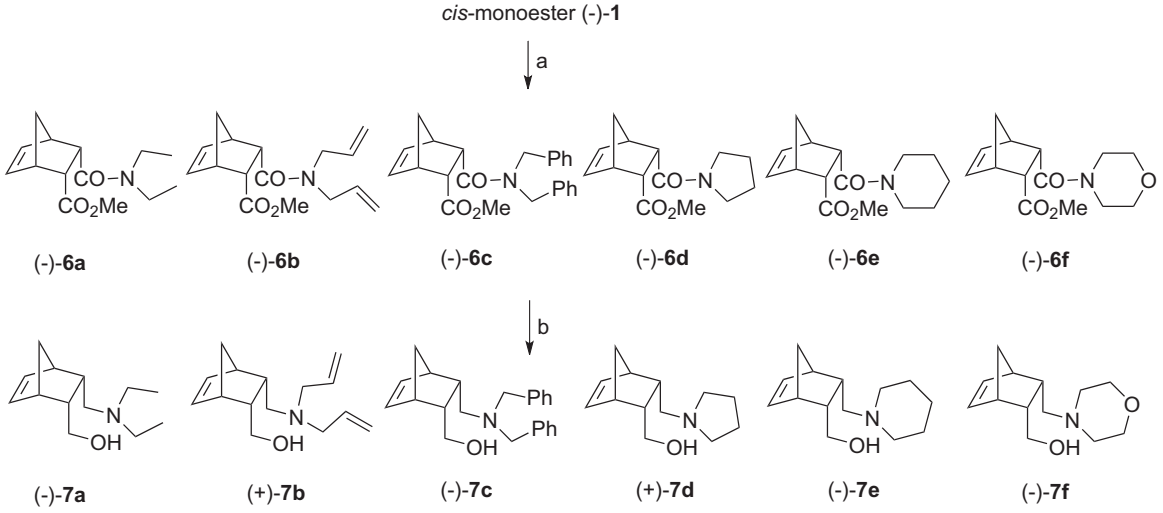


Scheme 1. Reagents and conditions: (a) HMPTA, benzene, reflux; (b) (i) MeI, Mg, Et_2O for (+)-**4a**; (ii) EtI, Mg, Et_2O for (+)-**4b**; (iii) 1,4-dibromobutane, Mg, Et_2O for (+)-**4c**; (iv) 1,5-dibromopentane, Mg, Et_2O for (+)-**4d**; (v) 1 M HCl for compounds (+)-**4a–d**; (c) $LiAlH_4$, Et_2O, reflux.

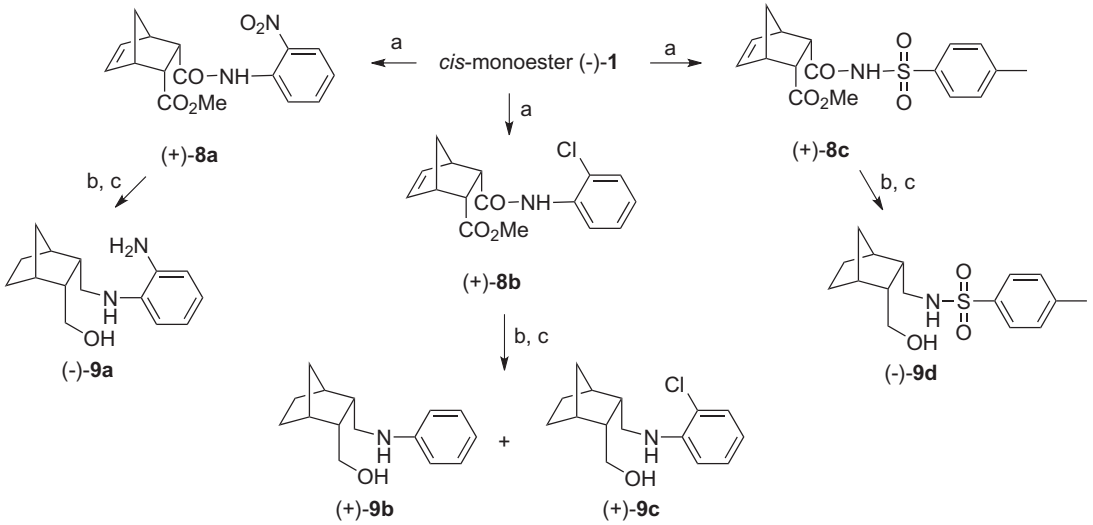
the first set and pyrrolidine, piperidine, and morpholine (−)-**6d**–**f** as the second set, respectively. Subsequent reduction of (−)-**6a**–**f** by $LiAlH_4$ in ether afforded the resultant chiral ligands (−)-**7a**, (+)-**7b**, (−)-**7c**, (+)-**7d**, (−)-**7e**, and (−)-**7f** (Scheme 2).

The next step consisted of preparing various *N*-aryl substituted 1,4-aminoalcohols. *cis*-Monoester (−)-**1** was coupled with *o*-, *m*-, and *p*-substituted aniline derivatives using the DCC method to obtain the desired amide ester products. Unfortunately, *m*- and *p*-substituted aniline derivatives, that is, *m*-nitroaniline, *p*-toluidine, *p*-chloroaniline, and aniline itself, afforded *meso*-imide type products, whereas only *o*-substituted derivatives *o*-nitro and *o*-chloro anilines except *o*-anisidine yielded the amide ester type products (+)-**8a** and (+)-**8b**, respectively. In addition to the aniline derivatives, *p*-toluenesulfonamide was also introduced to the carboxylic acid group of *cis*-monoester (−)-**1**. Since the secondary amine functionality of this group of 1,4-aminoalcohols can be useful chiral ligand candidates for asymmetric borane reduction reactions, after the LAH step, the norbornene backbone was subsequently transformed into the norbornane backbone via hydrogenation in the presence of Pd/C. In the LAH step, the nitro group of compound (+)-**8a** was reduced into the amine group, whereas the chloride substituted derivative (+)-**8b** afforded the corresponding dechlorinated and chlorinated products (+)-**9b** and (+)-**9c** in a 1:2 molar ratio, respectively, after the hydrogenation step (Scheme 3).

The absolute configurations of (+)-**5a**–**d**, (−)-**7a**, **7c**, **7e**, **7f**, (+)-**7b**, **7d**, and (−)-**9a**, **9d**, (+)-**9b**, **9c** were determined as (*S*) for the carboxylic acid group attached to the stereogenic center and as (*R*) for the ester group attached one, by comparing the specific rotation signs determined at equal concentrations in the same solvent with *cis*-monoester



Scheme 2. Reagents and conditions: (a) DCC, DMAP, CH_2Cl_2, secondary acyclic and cyclic amines; (b) $LiAlH_4$, Et_2O, reflux.



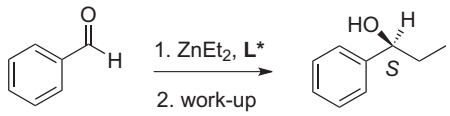
Scheme 3. Reagents and conditions: (a) DCC, DMAP, CH_2Cl_2; (i) *o*-nitroaniline for (+)-**8a**, (ii) *o*-chloroaniline for (+)-**8b**, (iii) *p*-toluenesulfonamide for (+)-**8c**; (b) $LiAlH_4$, Et_2O, reflux; (c) H_2, Pd/C, CH_2Cl_2.

(+)-**1**, which has already been reported in the literature.[12,14] In our synthetic route, the carboxylic acid group was transformed into the amine functionality and the ester group into the alcohol moiety of the target 1,4-aminoalcohols. Since the transformation of the *cis*-monoester (−)-**1** to chiral ligands (+)-**5a–d**, (−)-**7a**, **7c**, **7e**, **7f**, (+)-**7b**, **7d**, and (−)-**9a**, **9d**, (+)-**9b**, **9c** has no effect on the stereocenters of the norbornene backbone, the absolute configuration of each ligand was not altered during the transformation reactions.

2.4. Enantioselective addition of diethylzinc to benzaldehyde using 5a–d, 7a–f, and 9a–c

The catalytic properties of all new chiral 1,4-aminoalcohols **5a–d**, **7a–f**, and **9a–d** were studied in the asymmetric diethylzinc addition to benzaldehyde. As the first set of chiral 1,4-aminoalcohols, (+)-**5a–d** possessing various acyclic and cyclic substitutions on hydroxy methylene carbon were tested. The results are summarized in Table 1.

Table 1. Asymmetric diethylzinc addition to benzaldehyde using norbornene-based 1,4-aminoalcohol catalysts (+)-**5a–d**



L* = (+)-**5a-d**

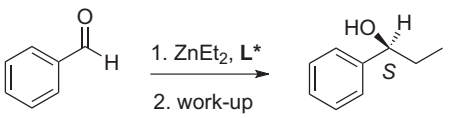
Entry	Ligand[a]	Solvent	Temperature (°C)	Yield[b] (%)	ee[c] (%)
1	(+)-**5a**	Toluene	0	78	53
2	(+)-**5b**	Toluene	0	38	15
3	(+)-**5c**	Toluene	0	89	11
4	(+)-**5d**	Toluene	0	78	65
5	(+)-**5a**	Toluene	−10	41	35
6	(+)-**5a**	Hexane	0	52	33
7	(+)-**5b**	THF	0	20	<5
8	(+)-**5b**	DCM	0	10	7
9	(+)-**5c**	THF	0	15	<5
10	(+)-**5c**	DCM	0	10	13
11	(+)-**5d**	Hexane	0	80	69

[a] 10 mol % of chiral catalysts was used.
[b] Yields were calculated after column chromatography.
[c] Enantiomeric ratios were determined by HPLC analysis using a chiral column. The major product has the (*S*)-configuration.

The asymmetric diethylzinc addition reactions were first carried out in toluene with 10 mol % of chiral catalysts (+)-**5a–d** at 0 °C and compared with the result of (−)-**2c** (49% ee), which has diphenyl substituents on the hydroxymethylene carbon reported in our previous study (entries 1–4).[11] The best results were obtained with aminoalcohol (+)-**5a** (53% ee), which has dimethyl substituents on the hydroxymethylene carbon (entry 1) and with (+)-**5d** (65% ee), which has a cyclohexyl moiety on the hydroxymethylene carbon (entry 4). Catalysts with diethyl and cyclopentyl substituents on the hydroxymethylene carbon (+)-**5b** and (+)-**5c**, respectively (entries 2 and 3), gave products with lower ee values. We investigated the conditions to improve the enantioselectivity of the chiral catalysts. For this purpose, the temperature and solvent dependence enantioselectivity of chiral ligand (+)-**5a** was explored. At −10 °C, catalyst (+)-**5a** gave 35% ee (entry 5) while in hexane at 0 °C afforded 33% ee (entry 6). Both the enantioselectivity and the chemical yield were lower than entry 1. We also examined the effect of the solvent using THF, DCM, and hexane for catalysts (+)-**5b–d**. In THF, both catalysts (+)-**5b** and (+)-**5c** gave <5% ee (entries 7 and 9, respectively). In DCM, 7% and 13% ee values were obtained for catalysts (+)-**5b** and (+)-**5c**, respectively (entries 8 and 10). The best result was obtained at the optimized temperature 0 °C in hexane for catalyst (+)-**5d** (69% ee) (Table 1, entry 11).

As the second set of chiral 1,4-aminoalcohols, the catalytic properties of **7a–d** possessing various acyclic and cyclic substituents on the nitrogen atom were explored again in asymmetric diethylzinc addition to benzaldehyde. The results are summarized in Table 2.

Table 2. Asymmetric diethylzinc addition to benzaldehyde using norbornene-based 1,4-aminoalcohol catalysts (−)-**7a**, (+)-**7b**, (−)-**7c**, (+)-**7d**, (−)-**7e**, and (−)-**7f**



L* = (-)-**7a**, (+)-**7b**, (-)-**7c** (+)-**7d**, (-)-**7e**, (-)-**7f**

Entry	Ligand[a]	Solvent	Temperature (°C)	Yield[b] (%)	ee[c] (%)
1	(−)-**7a**	Toluene	0	92	89
2	(−)-**7a**	Hexane	0	87	60
3	(+)-**7b**	Toluene	0	89	72
4	(−)-**7c**	Toluene	0	79	58
5	(+)-**7d**	Toluene	0	86	20
6	(+)-**7d**	Hexane	0	82	5
7	(−)-**7e**	Toluene	0	85	40
8	(−)-**7e**	Hexane	0	83	85
9	(−)-**7f**	Toluene	0	88	63
10	(−)-**7f**	Hexane	0	76	30

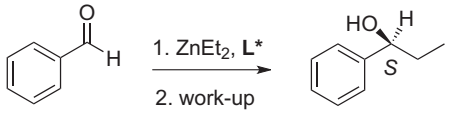
[a] 10 mol % of chiral catalysts was used.
[b] Yields were calculated after column chromatography.
[c] Enantiomeric ratios were determined by HPLC analysis using a chiral column. The major product has the (*S*)-configuration.

All the ligands exhibited acceptable enantioselectivities (up to 89% ee) and afforded (*S*)-1-phenylpropanol. The reactions were carried out at 0 °C and in two different solvents: toluene and hexane. The best results were obtained with aminoalcohol having diethyl substituents on the nitrogen atom (−)-**7a** and piperidinyl substituted aminoalcohol (−)-**7e** as 89% and 85% ee values, respectively (Table 2, entries 1 and 8). We observed high solvent dependence enantioselectivities for this set of chiral catalysts. Catalyst (−)-**7a** gave 89% ee in toluene (entry 1), but a drastic decrease of enantioselectivity was observed in hexane (entry 2). In contrast to this case, chiral catalyst (−)-**7e** afforded 40% ee in toluene (entry 7) and a sharp increase was observed in hexane with 85% ee (entry 8). Similar solvent dependence was observed for ligands (+)-**7d** and (−)-**7f** as 20% and 63% ee in toluene and 5% and 30% ee in

hexane, respectively (entries 5, 6, 9, and 10). Diallyl and dibenzyl substituted aminoalcohols (+)-**7b** and (−)-**7c** afforded acceptable enantioselectivities 72% and 58% ee at 0 °C and in toluene, respectively (entries 3 and 4).

In the last part, we explored the catalytic activities of **9a**–**d** having a secondary arylamine functionality and norbornane backbone in the asymmetric diethylzinc addition to benzaldehyde. The results are summarized in Table 3.

Table 3. Asymmetric diethylzinc addition to benzaldehyde using norbornene-based 1,4-aminoalcohol catalysts (−)-**9a**, (+)-**9b**, (+)-**9c**, and (−)-**9d**



L* = (-)-**9a**, (+)-**9b**, (+)-**9c**, (-)-**9d**

Entry	Ligand[a]	Solvent	Temperature (°C)	Yield[b] (%)	ee[c] (%)
1	(−)-**9a**	Hexane	0	93	91
2	(−)-**9a**	Toluene	0	97	95
3	(+)-**9b**	Hexane	0	87	84
4	(+)-**9b**	Toluene	0	91	92
5	(+)-**9c**	Hexane	0	79	76
6	(+)-**9c**	Toluene	0	82	80
7	(−)-**9d**	Hexane	0	96	97
8	(−)-**9d**	Toluene	0	97	96

[a] 10 mol % of chiral catalysts was used.
[b] Yields were calculated after column chromatography.
[c] Enantiomeric ratios were determined by HPLC analysis using a chiral column. The major product has the (*S*)-configuration.

All the catalysts were tested at 0 °C in hexane and toluene. *o*-Aminoaniline substituted chiral ligand (−)-**9a** gave 91% ee in hexane and 95% ee in toluene, respectively (Table 3, entries 1 and 2). A drastic increase was observed for aniline substituted ligand (+)-**9b** in hexane and toluene from 84% to 92% ee, respectively (entries 3 and 4), whereas *o*-chloro aniline substituted ligand (+)-**9c** showed a slight increase in hexane and toluene from 76% to 80% ee, respectively (entries 5 and 6). Tosyl substituted aminoalcohol catalyst (−)-**9d** afforded almost the same enantioselectivities 97–96% ee in hexane and toluene, respectively (entries 7 and 8).

3. Conclusion

We have synthesized a series of chiral norbornene-based 1,4-aminoalcohols (2*R*,3*S*)-**5a**–**d**, (2*R*,3*S*)-**7a**–**f**, (2*R*,3*S*)-**9a**–**c**, and (2*S*,3*R*)-**9d** where the amine moiety attached chiral center has (*S*)-configuration while the alcohol moiety attached stereogenic center has an (*R*)-configuration. These compounds were used as ligands in the asymmetric diethylzinc addition to benzaldehyde. Ligands (2*R*,3*S*)-**5a**–**d** possess various acyclic and cyclic substituents on hydroxymethylene carbon and gave moderate enantioselectivities (up to 69% ee). The other set of ligands (2*R*,3*S*)-**7a**–**f** was functionalized on the nitrogen atom by various acyclic substituents and heterocyclic systems, that is, pyrrolidine, piperidine, and morpholine, and afforded high enantioselectivities by comparing with hydroxymethylene substituted ligands (up to 89% ee). The best results were obtained with the secondary arylamine and tosyl amine substituted ligands (2*R*,3*S*)-**9a**–**c** and (2*S*,3*R*)-**9d** (up to 97% ee). We also examined the effect of the solvent using hexane, toluene, THF, and DCM and found out that hexane and toluene were the best solvents for these ligands. We concluded that the substitution on the nitrogen moiety is more preferable over substitution on the hydroxymethylene carbon.

4. Experimental

The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Brucker Spectrospin Avance DPX 400 spectrometer. Chemical shifts are given in ppm downfield from tetramethylsilane. Apparent splittings are given in all cases. Infrared spectra were obtained from KBr pellets on a Mattson 1000 FT-IR spectrophotometer. Mass spectra were recorded on a Varian MAT 212. Melting points are uncorrected. Optical rotations were measured in a 1 dm cell using a Rudolph Research Analytical Autopol III polarimeter at 20 °C. HPLC measurements were performed with ThermoFinnigan Spectra System instrument. Separations were carried out on Chiralcel OD-H analytical column (250 × 4.60 mm) with hexane/2-propyl alcohol as eluent. Column chromatography was performed on silica gel (60-mesh, Merck). TLC was carried out on Merck 0.2-mm silica gel 60 F_{254} analytical aluminum plates. Elemental analyses were carried out using a LECO 932-CHN instrument.

4.1. Synthesis of (2*R*,3*S*)-methyl 3-(dimethylcarbamoyl)-bicyclo[2.2.1] hept-5-ene-2-carboxylate (−)-3

To the solution of *cis*-monoester (−)-**1** (2.00 g, 10.2 mmol) in benzene (5 mL) was added hexamethylphosphorous triamide (1.85 mL, 5.1 mmol) at a rate that maintained the reflux of the reaction. After 2 h, the resulting cloudy solution was allowed to cool to room temperature and a saturated $NaHCO_3$ solution was added. The aqueous layer was extracted with DCM. The organic solutions were combined, dried over $MgSO_4$, and concentrated to give compound (−)-**3** (2.01 g, 88%). $[\alpha]_D^{20} = -39.1$ (c 2.03, $CHCl_3$); mp 78–79 °C; IR (KBr): 2998, 1742, 1637 cm^{-1}; ^{1}H NMR: δ 6.30 (dd, $J = 3.03$, 5.34 Hz, 1H), 6.12 (dd, $J = 2.93$, 5.39 Hz, 1H), 3.52 (s, 3H), 3.35 (dd, $J = 3.16$, 9.91 Hz, 1H), 3.19 (dd, $J = 3.48$, 9.92 Hz, 1H), 3.12 (s, 1H), 3.04 (s, 1H), 2.95 (s, 3H), 2.81 (s, 3H), 1.38 (d, $J = 8.5$ Hz, 1H), 1.27 (d, $J = 8.5$ Hz, 1H); ^{13}C NMR: δ 173.3, 172.4, 136.6, 133.9, 51.9, 49.2, 48.9, 47.3, 47.0, 46.9, 37.3, 36.0; HRMS calcd for $C_{12}H_{18}NO_3$ $(M+H)^+$, 224.1287; found, 224.1277.

4.2. General procedure for Grignard reactions

Haloalkane (7.7 mmol) was dissolved in 10 mL of anhydrous diethyl ether and placed into the addition funnel. This solution was added to magnesium (10.2 mmol) turnings. Once the reaction had begun, the rest of the haloalkane solution was added dropwise at a rate that

maintained gentle reflux. When the addition of the haloalkane solution was complete, the mixture was refluxed for 20 min. Compound (−)-**3** (2.6 mmol) was dissolved in 15 mL of anhydrous diethyl ether and added to the prepared Grignard mixture. After all of compound (−)-**3** solution had been added, the reaction mixture was refluxed for 2 h. The resultant mixture was poured into a mixture of ice (25 g) and 3 M H_2SO_4 (30 mL). The organic phase was washed with 5% $NaHCO_3$ and then with brine, after which it was dried over $MgSO_4$, the solvent evaporated and the crude product purified by column chromatography (EtOAc).

4.2.1. (2*S*,3*R*)-3-(2-Hydroxypropan-2-yl)-*N*,*N*-dimethylbicyclo[2.2.1]hept-5-ene-2-carboxamide (+)-4a. (0.38 g, 40%); mp 99–101 °C; $[\alpha]_D^{20} = +84.6$ (c 1.84, $CHCl_3$); ^{1}H NMR: δ 6.46 (dd, $J = 2.90$ Hz, 1H), 5.87 (dd, $J = 2.90$ Hz, 1H), 5.76 (s, 1H), 3.45 (dd, $J = 3.10$, 9.30 Hz, 1H), 3.20 (s, 3H), 3.09 (s, 1H), 2.96 (s, 4H), 2.36 (d, $J = 9.34$ Hz, 1H), 1.39 (d, $J = 8.10$ Hz, 1H), 1.32 (d, $J = 8.05$ Hz, 1H), 1.26 (s, 3H), 1.09 (s, 3H); ^{13}C NMR: δ 175.9, 137.4, 130.4, 69.5, 58.4, 49.6, 47.1, 46.1, 43.8, 38.3, 36.6, 31.1, 30.9.

4.2.2. (2*S*,3*R*)-3-(3-Hydroxypentan-3-yl)-*N*,*N*-dimethylbicyclo[2.2.1]hept-5-ene-2-carboxamide (+)-4b. (0.29 g, 34%); mp 82–83 °C; $[\alpha]_D^{20} = +80.8$ (c 2.11, $CHCl_3$); ^{1}H NMR: δ 6.37 (dd, $J = 3.10$, 5.20 Hz, 1H), 5.80 (dd, $J = 2.90$, 5.30 Hz, 1H), 5.56 (s, 1H), 3.36 (dd, $J = 3.10$, 9.30 Hz, 1H), 3.12 (s, 3H), 2.97 (s, 1H), 2.80 (s, 4H), 2.38 (dd, $J = 2.43$, 9.30 Hz, 1H), 1.65–1.55 (m, 2H), 1.45–1.36 (m, 2H), 1.32–1.16 (m, 2H), 0.78–0.72 (m, 6H); ^{13}C NMR: δ 176.0, 137.5, 130.2, 73.5, 54.8, 49.5, 47.1, 45.5, 43.6, 38.3, 36.6, 30.8, 30.1, 8.3,7.9.

4.2.3. (2*S*,3*R*)-3-(1-Hydroxycyclopentyl)-*N*,*N*-dimethylbicyclo[2.2.1]hept-5-ene-2-carboxamide (+)-4c. (0.21 g, 40%); mp 104–105 °C; $[\alpha]_D^{20} = +46.2$ (c 2.01, $CHCl_3$); ^{1}H NMR: δ 6.38 (dd, $J = 3.60$, 8.20 Hz, 1H), 5.80 (dd, $J = 3.50$, 5.20 Hz, 1H), 5.26 (s, 1H), 3.38 (dd, $J = 3.20$, 9.40 Hz, 1H), 3.12 (s, 3H), 2.98 (s, 1H), 2.87 (s, 4H), 2.31 (dd, $J = 2.53$, 9.40 Hz, 1H), 1.76–1.65 (m, 4H), 1.50–1.38 (m, 4H), 1.25 (d, $J = 5.50$ Hz, 1H), 1.22 (d, $J = 6.30$ Hz, 1H); ^{13}C NMR: δ 175.0, 138.0, 129.9, 80.8, 58.3, 50.0, 47.1, 47.0, 44.3, 41.6, 41.2, 38.2, 36.4, 24.3, 24.1.

4.2.4. (2*S*,3*R*)-3-(1-Hydroxycyclohexyl)-*N*,*N*-dimethylbicyclo[2.2.1]hept-5-ene-2-carboxamide (+)-4d. (0.28 g, 40%) colorless oil; $[\alpha]_D^{20} = +52.4$ (c 2.00, $CHCl_3$); ^{1}H NMR: δ 6.44 (dd, $J = 3.09$, 5.30 Hz, 1H), 5.98 (dd, $J = 2.90$, 5.20 Hz, 1H), 5.43 (s, 1H), 3.34 (dd, $J = 3.07$, 9.18 Hz, 1H), 3.11 (s, 3H), 3.02 (s, 1H), 2.88 (s, 4H), 2.31 (d, $J = 9.28$ Hz, 1H), 1.75–1.08 (m, 12H); ^{13}C NMR: δ 176.0, 137.5, 130.2, 70.1, 57.9, 49.5, 47.0, 45.0, 43.5, 39.0, 38.8, 38.3, 36.6, 26.2, 22.2, 21.9.

4.3. General procedure for DCC coupling reactions

cis-Monoester (−)-**1** (1.0 equiv) and amine (1.0 equiv) were dissolved in DCM at 0 °C under an argon atmosphere. Then, DCC (1.1 equiv) and DMAP (0.25 equiv) were added simultaneously at 0 °C. The mixture was stirred overnight at room temperature. DCC precipitated as dicyclohexylurea. The mixture was filtered and the filtrate was washed first with 1 M HCl, then with 1 M $NaHCO_3$ and finally with brine. The organic phase was dried over $MgSO_4$ and evaporation of the solvent afforded the desired amide ester product.

4.3.1. (2*R*,3*S*)-Methyl 3-(diethylcarbamoyl)bicyclo[2.2.1]-hept-5-ene-2-carboxylate (−)-6a. (0.45 g, 35%); mp: 65–68 °C; $[\alpha]_D^{20} = -32.4$ (c 3.00, $CHCl_3$); ^{1}H NMR: δ 6.30 (dd, $J = 3.03$, 5.34 Hz, 2H), 3.56 (s, 3H), 3.46–3.37 (m, 2H), 3.23–3.19 (m, 2H), 3.12 (d, $J = 3.43$ Hz, 1H), 3.10 (br s, 1H), 2.98 (br s, 1H), 1.45 (d, $J = 8.43$ Hz, 1H), 1.33 (d, $J = 8.40$ Hz, 1H), 1.21 (t, $J = 7.12$ Hz, 3H), 1.06 (t, $J = 7.07$ Hz, 3H); ^{13}C NMR: δ 173.0, 170.7, 135.2, 134.1, 51.2, 49.3, 48.6, 47.1, 46.3, 46.2, 41.5, 40.1, 14.5, 12.8.

4.3.2. (2*R*,3*S*)-Methyl 3-(diallylcarbamoyl)bicyclo[2.2.1]-hept-5-ene-2-carboxylate (−)-6b. (0.91 g, 65%) colorless oil; $[\alpha]_D^{20} = -43.90$ (c 2.03, $CHCl_3$); ^{1}H NMR: δ 6.27 (dd, $J = 3.95$, 14.80 Hz, 2H), 5.87–5.69 (m, 2H), 5.24 (t, $J = 4.45$ Hz, 2H), 5.11 (dd, $J = 2.98$, 14.8 Hz, 2H), 4.05 (dd, $J = 5.08$, 15.0 Hz, 1H), 3.99 (t, $J = 1.85$ Hz, 1H), 3.88 (dt, $J = 2.14$, 17.5 Hz, 1H), 3.78 (dd, $J = 6.47$, 15.0 Hz, 1H), 3.56 (s, 3H), 3.40 (dd, $J = 3.18$, 9.99 Hz, 1H), 3.22 (dd, $J = 3.29$, 9.97 Hz, 1H), 3.16 (s, 1H), 3.05 (s, 1H), 1.43 (d, $J = 8.43$ Hz, 1H), 1.32 (d, $J = 8.46$ Hz, 1H). ^{13}C NMR: δ 172.8, 171.9, 134.9, 134.3, 133.5, 133.2, 117.0, 116.5, 51.3, 49.3, 48.8, 48.6, 48.1, 47.1, 46.1, 20.8.

4.3.3. (2*R*,3*S*)-Methyl 3-(dibenzylcarbamoyl)bicyclo[2.2.1]-hept-5-ene-2-carboxylate (−)-6c. (1.03 g, 54%); mp 77–80 °C; $[\alpha]_D^{20} = -34.9$ (c 2.03, $CHCl_3$); ^{1}H NMR: δ 7.40–7.14 (m, 10H), 6.38 (dd, $J = 5.18$, 3.21 Hz, 1H), 6.23 (dd, $J = 5.25$, 2.99 Hz, 1H), 4.40–4.63 (m, 4H), 3.54 (s, 4H), 3.17 (s, 2H), 3.01 (s,1H), 1.43 (d, $J = 13.69$ Hz, 1H), 1.25 (d, $J = 8.34$ Hz, 1H). ^{13}C NMR: δ 173.0, 172.2, 137.6, 136.7, 135.3, 134.0, 129.0, 128.7, 128.4, 127.6, 127.3, 126.4, 51.3, 49.7, 49.4, 48.7, 48.4, 47.3, 46.2, 45.9.

4.3.4. (2*R*,3*S*)-Methyl 3-(pyrrolidine-1-carbonyl)bicyclo[2.2.1]-hept-5-ene-2-carboxylate (−)-6d. (0.50 g, 39%); mp 51–52 °C; $[\alpha]_D^{20} = -24.65$ (c 0.10, MeOH); ^{1}H NMR: δ 6.32 (dd, $J = 3.00$, 5.41 Hz, 1H), 6.26 (dd, $J = 2.94$, 5.42 Hz, 1H), 3.58 (s, 3H), 3.42 (dt, $J = 8.43$, 16.68 Hz, 4H), 3.33 (dd, $J = 3.17$, 10.00 Hz, 1H), 3.24 (dd, $J = 3.40$, 10.00 Hz, 1H), 3.17 (s, 1H), 3.10 (s, 1H), 1.93–1.91 (m, 2H), 1.84 (p, $J = 6.73$ Hz, 2H), 1.44 (dd, $J = 1.42$, 8.47 Hz, 1H), 1.32 (d, $J = 8.43$ Hz, 1H); ^{13}C NMR: δ 172.8, 170.4, 135.5, 133.9, 51.4, 48.7, 48.5, 48.1, 46.3, 46.2, 45.7, 26.1, 24.2.

4.3.5. (2*R*,3*S*)-Methyl 3-(piperidine-1-carbonyl)bicyclo-[2.2.1]hept-5-ene-2-carboxylate (−)-6e. (1.18 g, 88%); mp 77–78 °C; $[\alpha]_D^{20} = -21.95$ (c 2.00, MeOH); ^{1}H NMR: δ 6.21 (dd, $J = 3.02$, 5.19 Hz, 1H), 6.07 (dd, $J = 2.90$, 5.27 Hz, 1H), 3.62–3.58 (m, 1H), 3.46 (s, 3H), 3.42 (s, 1H), 3.29 (dd, $J = 2.91$, 9.78 Hz, 1H), 3.10 (dd, $J = 3.12$, 9.83 Hz, 3H), 3.04 (s, 1H), 2.95 (s, 1H), 1.54–1.43 (m, 6H), 1.32 (d, $J = 7.92$ Hz, 1H), 1.21 (d, $J = 1.21$ Hz,

1H); ^{13}C NMR: δ 172.9, 170.0, 135.8, 133.5, 51.3, 48.8, 48.3, 46.9, 46.8, 46.6, 42.7, 33.8, 26.3, 25.4, 25.0.

4.3.6. (2*R*,3*S*)-Methyl 3-(morpholine-4-carbonyl)bicyclo-[2.2.1]hept-5-ene-2-carboxylate (−)-6f. (1.00 g, 74%); mp 87–88 °C; $[\alpha]_D^{20} = -32.2$ (c 0.20, MeOH); ^{1}H NMR: δ 6.34 (dd, $J = 3.01$, 5.36 Hz, 1H), 6.10 (dd, $J = 2.92$, 5.40 Hz, 1H), 3.60 (d, $J = 7.73$ Hz, 4H), 3.50 (s, 3H), 3.47 (d, $J = 14.35$ Hz, 2H), 3.34 (d, $J = 9.13$ Hz, 2H), 3.28 (dd, $J = 3.12$, 9.84 Hz, 1H), 3.18 (dd, $J = 3.47$, 9.88 Hz, 1H), 3.12 (s, 1H), 3.02 (s, 1H), 1.40 (d, $J = 8.53$ Hz, 1H), 1.26 (d, $J = 8.50$ Hz, 1H); ^{13}C NMR: δ 172.2, 170.9, 136.3, 133.4, 66.8, 66.3, 51.5, 48.8, 48.4, 46.9, 46.8, 46.7, 45.8, 42.2.

4.3.7. (2*R*,3*S*)-Methyl 3-(2-nitrophenylcarbamoyl)bicyclo-[2.2.1]hept-5-ene-2-carboxylate (+)-8a. (0.97 g, 60%); mp 96–97 °C; $[\alpha]_D^{20} = +7.9$ (c 2.00, $CHCl_3$); ^{1}H NMR: δ 10.52 (s, 1H), 8.74 (d, $J = 8.54$ Hz, 1H), 8.21 (d, $J = 6.96$ Hz, 1H), 7.64 (t, $J = 7.14$ Hz, 1H), 7.18 (t, $J = 7.83$ Hz, 1H), 6.33 (dd, $J = 5.41$, 2.90 Hz, 1H), 6.19 (dd, $J = 5.37$, 2.70 Hz, 1H), 3.73 (s, 3H), 3.37 (t, $J = 4.1$ Hz, 1H), 3.31 (br s, 1H), 3.20 (br s, 1H), 2.72 (t, $J = 2.34$ Hz, 1H), 1.80 (d, $J = 8.75$ Hz, 1H), 1.55 (dd, $J = 8.80$, 1.45 Hz, 1H); ^{13}C NMR: δ 173.5, 173.2, 137.5, 136.7, 136.1, 135.7, 134.8, 125.7, 123.2, 122.5, 52.1, 50.6, 49.3, 47.5, 47.0, 45.0.

4.3.8. (2*R*,3*S*)-Methyl 3-(2-chlorophenylcarbamoyl)bicyclo-[2.2.1]hept-5-ene-2-carboxylate (+)-8b. (1.06 g, 68 %); mp 78–79 °C; $[\alpha]_D^{20} = +58.9$ (c 2.00, $CHCl_3$); ^{1}H NMR: δ 8.25 (d, $J = 8.06$ Hz, 1H), 8.20 (s, 1H), 7.25 (d, $J = 7.90$ Hz, 1H), 7.16 (t, $J = 8.00$ Hz, 1H), 6.91 (t, $J = 7.80$ Hz, 1H), 6.19 (dd, $J = 2.90$, 5.28 Hz, 1H), 6.07 (dd, $J = 2.95$, 5.32 Hz, 1H), 3.61 (s, 3H), 3.18 (d, $J = 4.57$ Hz, 2H), 3.01 (br s, 1H), 2.64 (t, $J = 1.63$ Hz, 1H), 1.70 (d, $J = 7.95$ Hz, 1H), 1.44 (d, $J = 8.05$ Hz, 1H); ^{13}C NMR: δ 174.0, 172.4, 137.7, 135.9, 135.0, 133.2, 127.6, 124.5, 122.8, 121.7, 49.8, 49.8, 48.9, 47.7, 47.5, 46.2.

4.3.9. (2*R*,3*S*)-Methyl 3-(tosylcarbamoyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (+)-8c. (1.46 g, 82%); mp 76 °C; $[\alpha]_D^{20} = +16.7$ (c 2.00, $CHCl_3$); ^{1}H NMR: δ 7.88 (d, $J = 8.28$ Hz, 2H), 7.24 (d, $J = 8.15$ Hz, 2H), 6.12 (dd, $J = 3.20$, 5.42 Hz, 1H), 6.01 (dd, $J = 3.17$, 5.48 Hz, 1H), 3.61 (s, 3H), 3.14 (br s, 1H), 3.10 (t, $J = 4.26$ Hz, 1H), 2.98 (br s, 1H), 2.38 (d, $J = 4.82$ Hz, 1H), 2.36 (s, 3H), 1.50 (dd, $J = 8.95$, 17.40 Hz, 1H), 1.33 (dd, $J = 8.62$, 16.85 Hz, 1H); ^{13}C NMR: δ 174.3, 171.8, 144.8, 137.5, 136.0, 135.7, 129.5, 128.3, 52.3, 49.2, 48.5, 47.3, 46.2, 44.9, 33.8.

4.4. General procedure for LAH reduction reactions

To a suspension of $LiAlH_4$ (3.0 equiv) in dry THF (10 mL) was added a solution of amide or amidoester (1.0 equiv) in THF (5 mL) at a rate which maintained gentle reflux. The mixture was then refluxed for 1 day and hydrolized by the cautious addition of water and 15% NaOH solution. The fine white precipitate, which formed, was washed with ether and discarded. The filtrate was concentrated and purified by column chromatography.

4.4.1. 2-((2*R*,3*S*)-3-((Dimethylamino)methyl)bicyclo[2.2.1]-hept-5-en-2-yl)propan-2-ol (+)-5a. (0.14 g, 30%) colorless oil; $[\alpha]_D^{20} = +17.4$ (c 1.37, $CHCl_3$); IR (KBr): 3445, 2968, 1729 cm^{-1}; ^{1}H NMR: δ 6.12 (dd, $J = 2.90$, 5.70 Hz, 1H), 5.97 (dd, $J = 2.90$, 5.30 Hz, 1H), 2.71 (br s, 1H), 2.63 (br s, 1H), 2.43 (s, 1H), 2.41 (s, 1H), 2.35 (dd, $J = 2.70$, 5.30 Hz, 1H), 2.16 (s, 6H), 2.09 (s, 1H), 2.02 (dd, $J = 2.90$, 12.70 Hz, 1H), 1.37 (q, $J = 6.20$ Hz, 2H), 1.19 (s, 3H), 0.95 (s, 3H); ^{13}C NMR: δ 135.6, 133.0, 70.3, 60.0, 54.5, 50.3, 46.7, 45.7, 43.8, 40.7, 31.9, 27.2. Anal. Calcd for $C_{13}H_{23}NO$: C, 74.59; H, 11.07; N, 6.69. Found: C, 74.27; H, 10.82; N, 6.53.

4.4.2. 3-((2*R*,3*S*)-3-((Dimethylamino)methyl)bicyclo[2.2.1]-hept-5-en-2-yl)pentan-3-ol (+)-5b. (0.10 g, 35%) colorless oil; $[\alpha]_D^{20} = +17.35$ (c 1.30, $CHCl_3$); IR (KBr): 3409, 2965, 1725 cm^{-1}; ^{1}H NMR: δ 6.30 (dd, $J = 3.20$, 5.30 Hz, 1H), 5.92 (dd, $J = 3.00$, 5.30 Hz, 1H), 5.53 (s, 1H), 3.54–3.51 (m, 1H), 3.35 (dd, $J = 3.20$, 9.80 Hz, 1H), 3.12 (br s, 1H), 3.08 (s, 3H), 2.97 (s, 1H), 2.90 (s, 1H), 2.88 (s, 3H), 2.43–2.37 (m, 1H), 1.59–1.48 (m, 2H), 1.40–1.18 (m, 4H), 0.89 (t, $J = 7.40$ Hz, 6H); ^{13}C NMR: δ 136.6, 134.4, 74.6, 61.0, 51.0, 50.9, 47.2, 45.8, 44.5, 41.0, 31.8, 31.6, 30.8, 7.9, 7.7. Anal. Calcd for $C_{15}H_{27}NO$: C, 75.90; H, 11.46; N, 5.90. Found: C, 75.67; H, 11.12; N, 5.53.

4.4.3. 1-((2*R*,3*S*)-3-((Dimethylamino)methyl)bicyclo[2.2.1]-hept-5-en-2-yl)cyclopentanol (+)-5c. (0.11 g, 54%) colorless oil; $[\alpha]_D^{20} = +11.1$ (c 2.56, $CHCl_3$); IR (KBr): 3409, 2960, 1464, 1074 cm^{-1}; ^{1}H NMR: δ 6.10 (dd, $J = 2.91$, 5.53 Hz, 1H), 5.99 (dd, $J = 2.86$, 5.53 Hz, 1H), 2.73 (br s, 1H), 2.64 (d, $J = 3.40$ Hz, 1H), 2.61 (d, $J = 2.55$ Hz, 1H), 2.59–2.51 (m, 1H), 2.30 (t, $J = 12.43$ Hz, 1H), 2.15 (br s, 7H), 1.95 (dd, $J = 2.40$, 12.40 Hz, 1H), 1.80–1.40 (m, 8H), 1.35 (d, $J = 7.96$ Hz, 2H); ^{13}C NMR: δ 135.6, 133.0, 70.3, 60.0, 54.5, 50.3, 46.7, 45.7, 43.8, 40.7, 31.9, 27.2. Anal. Calcd for $C_{15}H_{25}NO$: C, 76.55; H, 10.71; N, 5.95. Found: C, 76.67; H, 10.71; N, 5.64.

4.4.4. 1-((2*R*,3*S*)-3-((Dimethylamino)methyl)bicyclo[2.2.1]-hept-5-en-2-yl)cyclohexanol (+)-5d. (0.14 g, 52%) colorless oil; mp 67–68 °C; $[\alpha]_D^{20} = +3.7$ (c 2.16, $CHCl_3$), IR (KBr): 3506, 2954, 1556, 1094 cm^{-1}; ^{1}H NMR: δ 6.15 (dd, $J = 3.08$, 5.70 Hz, 1H), 5.95 (dd, $J = 2.70$, 5.70 Hz, 1H), 2.75 (br s, 1H), 2.62–2.55 (m, 2H), 2.39 (t, $J = 12.83$ Hz, 1H), 2.25 (dd, $J = 2.84$, 2.42 Hz, 1H), 2.15 (br s, 6H), 2.12 (s, 1H), 1.99 (dd, $J = 2.84$, 2.39 Hz, 1H), 1.79–1.16 (m, 6H), 1.12 (dd, $J = 3.93$, 3.95 Hz, 2H), 1.07–0.95 (m, 4H); ^{13}C NMR: δ 136.7, 133.9, 71.9, 61.5, 57.2, 51.3, 47.6, 46.0, 44.6, 41.8, 39.9, 36.1, 26.1, 22.0, 21.4. Anal. Calcd for $C_{16}H_{27}NO$: C, 77.06; H, 10.91; N, 5.62. Found: C, 76.81; H, 10.95; N, 5.67.

4.4.5. ((2*R*,3*S*)-3-((Dimethylamino)methyl)bicyclo[2.2.1]-hept-5-en-2-yl)methanol (−)-7a. (0.36 g, 95%) colorless oil; $[\alpha]_D^{20} = -6.4$ (c 1.80, $CHCl_3$); IR (KBr): 3412, 2968, 1645 cm^{-1}; ^{1}H NMR: δ 6.06 (s, 2H), 3.47 (d, $J = 11.30$ Hz, 1H), 3.19 (t, $J = 11.25$ Hz, 1H), 2.74–2.67 (m, 4H), 2.61–2.52 (m, 2H), 2.44–2.35 (m, 2H), 2.32 (d, $J = 7.50$ Hz, 2H), 1.40 (s, 2H), 1.02 (t, $J = 7.14$ Hz, 6H); ^{13}C NMR: δ 135.1, 134.0, 62.8, 54.2, 50.0, 47.7, 47.0, 46.4, 46.3, 39.4, 10.4. Anal. Calcd for $C_{13}H_{23}NO$: C,

74.59; H, 11.07; N, 6.69. Found: C, 73.93; H, 10.85; N, 6.48.

4.4.6. ((2*R*,3*S*)-3-((Diallylamino)methyl)bicyclo[2.2.1]hept-5-en-2-yl)methanol (+)-7b. (0.58 g, 75%) colorless oil; $[\alpha]_D^{20} = +15.7$ (c 1.00, $CHCl_3$); IR (KBr): 3458, 2962, 1642 cm^{-1}; ^1H NMR: δ 6.04 (dd, $J = 2.65$, 5.52 Hz, 2H), 5.89–5.79 (m, 2H), 5.19 (d, $J = 8.18$ Hz, 2H), 5.16 (d, $J = 8.18$ Hz, 2H), 3.48 (dd, $J = 2.95$, 11.65 Hz, 1H), 3.38 (d, $J = 5.47$ Hz, 1H), 3.34 (d, $J = 5.46$ Hz, 1H), 3.17 (t, $J = 11.40$ Hz, 1H), 2.87 (q, $J = 8.03$ Hz, 2H), 2.75 (br s, 1H), 2.69 (br s, 1H), 2.63–2.56 (m, 1H), 2.53–2.46 (m, 1H), 2.40 (t, $J = 12.60$ Hz, 1H), 2.29 (dd, $J = 2.94$, 12.78 Hz, 1H), 1.40 (dd, $J = 1.58$, 8.32 Hz, 2H); ^{13}C NMR: δ 135.4, 134.4, 133.7, 118.8, 62.9, 56.6, 54.4, 50.0, 47.7, 47.0, 46.3, 39.3. Anal. Calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 76.56; H, 10.13; N, 6.16.

4.4.7. ((2*R*,3*S*)-3-((Dibenzylamino)methyl)bicyclo[2.2.1]-hept-5-en-2-yl)methanol (−)-7c. (0.66 g, 72%); mp 92 °C; $[\alpha]_D^{20} = -33.0$ (c 2.00, $CHCl_3$); IR (KBr): 3230, 2965, 1599, 1451 cm^{-1}; ^1H NMR: δ 7.34–7.24 (m, 10H), 6.52 (br s, 1H), 6.02 (dd, $J = 7.00$, 9.94 Hz, 2H), 3.91 (s, 1H), 3.87 (s, 1H), 3.39 (d, $J = 11.58$ Hz, 1H), 3.24 (s, 1H), 3.21 (s, 1H), 2.86 (t, $J = 11.42$ Hz, 1H), 2.71 (s, 1H), 2.53–2.44 (m, 3H), 2.24 (dd, $J = 2.84$, 13.1 Hz, 2H), 1.36 (s, 2H); ^{13}C NMR: δ 136.9, 135.4, 134.3, 129.8, 128.4, 127.4, 62.7, 58.5, 55.6, 49.9, 47.9, 46.9, 46.4, 39.3. Anal. Calcd for $C_{23}H_{27}NO$: C, 82.84; H, 8.16; N, 4.20. Found: C, 82.20; H, 8.46; N, 4.45.

4.4.8. ((2*R*,3*S*)-3-(Pyrrolidin-1-ylmethyl)bicyclo[2.2.1]hept-5-en-2-yl)methanol (+)-7d. (0.39 g, 95%); mp 65–66 °C; $[\alpha]_D^{20} = +1.6$ (c 2.00, MeOH); ^1H NMR: δ 6.05 (s, 2H), 3.50 (t, $J = 6.87$ Hz, 1H), 3.22 (t, $J = 11.25$ Hz, 1H), 2.75 (s, 2H), 2.65–2.44 (m, 7H), 2.20 (d, $J = 12.54$ Hz, 1H), 1.76 (br s, 4H), 1.40 (s, 2H); ^{13}C NMR: δ 135.4, 134.3, 63.0, 56.8, 53.8, 49.9, 47.7, 46.9, 46.2, 41.0, 23.3. Anal. Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.11; H, 9.95; N, 6.57.

4.4.9. ((2*R*,3*S*)-3-(Piperidin-1-ylmethyl)bicyclo[2.2.1]hept-5-en-2-yl)methanol (−)-7e. (0.88 g, 89%); mp 61–62 °C; $[\alpha]_D^{20} = -3.6$ (c 2.00, MeOH); ^1H NMR: δ 6.05 (s, 2H), 3.50 (d, $J = 10.65$ Hz, 1H), 3.21 (t, $J = 11.45$ Hz, 1H), 2.75 (s, 1H), 2.68 (s, 1H), 2.64–2.47 (m, 4H), 2.28–2.17 (m, 4H), 1.64–1.49 (m, 4H), 1.43–1.37 (m, 2H), 1.26 (s, 2H); ^{13}C NMR: δ 135.3, 134.4, 63.1, 60.0, 50.1, 47.6, 47.0, 46.4, 38.8, 29.6, 25.6, 24.2. Anal. Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 75.32; H, 10.13; N, 6.17.

4.4.10. ((2*R*,3*S*)-3-(Morpholinomethyl)bicyclo[2.2.1]hept-5-en-2-yl)methanol (−)-7f. (0.59 g, 70%) colorless oil; $[\alpha]_D^{20} = -4.3$ (c 2.00, $CHCl_3$); ^1H NMR: δ 6.06 (s, 2H), 3.68 (br s, 4H), 3.50 (br s, 1H), 3.21 (t, $J = 11.21$ Hz, 1H), 2.75 (s, 1H), 2.71 (s, 1H), 2.57–2.47 (m, 4H), 2.34–2.26 (m, 4H), 1.43–1.38 (m, 2H); ^{13}C NMR: δ 134.9, 133.8, 66.0, 62.4, 59.3, 53.1, 49.5, 47.0, 46.4, 45.7, 37.6. Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.62; H, 9.13; N, 6.18.

4.5. General procedure for hydrogenation reactions

The compound was dissolved in CH_2Cl_2 (10 mL) at room temperature and Pd/C (10% (w/w)) was then added to this solution. H_2 gas was allowed to pass into the reaction vessel. The reaction was continued until the starting compound was consumed as monitored by TLC. The mixture was filtered on Celite and washed with CH_2Cl_2 (3×20 mL). Evaporation of the solvent afforded the desired product.

4.5.1. ((2*R*,3*S*)-3-((2-Aminophenylamino)methyl)bicyclo-[2.2.1]heptan-2-yl)methanol (−)-9a. (0.67 g, 90%); mp 85 °C; $[\alpha]_D^{20} = -116.0$ (c 0.10, $CHCl_3$); IR (KBr): 3364, 2959, 1603 cm^{-1}; ^1H NMR: δ 6.72 (t, $J = 6.25$ Hz, 1H), 6.58 (dd, $J = 1.42$, 7.41 Hz, 1H), 6.54 (d, $J = 7.30$ Hz, 1H), 6.50 (d, $J = 4.40$ Hz, 1H), 3.54 (dd, $J = 4.89$, 10.06 Hz, 1H), 3.27 (t, $J = 9.93$ Hz, 1H), 3.02 (dd, $J = 5.22$, 10.79 Hz, 1H), 2.60 (t, $J = 10.60$ Hz, 1H), 2.10 (br s, 1H), 1.99 (d, $J = 4.06$ Hz, 1H), 1.52 (dd, $J = 4.54$, 9.11 Hz, 1H), 1.51–1.43 (m, 1H), 1.39 (d, $J = 9.60$ Hz, 1H), 1.25–1.18 (m, 1H), 1.18 (br s, 1H), 1.12 (br s, 1H), 1.12–1.10 (m, 1H), 1.04–0.98 (m, 1H); ^{13}C NMR: δ 138.1, 133.2, 120.9, 117.6, 116.3, 111.0, 49.3, 49.2, 48.1, 41.3, 39.4, 37.6, 30.1, 25.9, 22.7. Anal. Calcd for $C_{15}H_{22}N_2O$: C, 77.13; H, 9.00; N, 11.37. Found: C, 76.93; H, 8.65; N, 10.98.

4.5.2. ((2*R*,3*S*)-3-((Phenylamino)methyl)bicyclo[2.2.1]heptan-2-yl)methanol (+)-9b. After LAH reduction of (+)-**8b**, without purification the mixture was subjected to hydrogenation. (0.24 g, 30%); mp 68–69 °C; $[\alpha]_D^{20} = +5.1$ (c 2.00, $CHCl_3$); IR (KBr): 3423, 2960, 1602 cm^{-1}; ^1H NMR: δ 7.08 (t, $J = 7.90$ Hz, 2H), 6.62 (t, $J = 6.95$ Hz, 1H), 6.51 (d, $J = 7.92$ Hz, 2H), 3.58 (dd, $J = 6.05$, 10.09 Hz, 1H), 3.43 (t, $J = 9.51$ Hz, 1H), 3.13 (br s, 1H), 3.00 (dd, $J = 6.21$, 11.56 Hz, 1H), 2.70 (dd, $J = 9.22$, 11.46 Hz, 1H), 2.19 (s, 1H), 2.02 (d, $J = 4.08$ Hz, 1H), 1.62–1.56 (m, 1H), 1.55–1.47 (m, 1H), 1.41 (d, $J = 9.84$ Hz, 1H), 1.32–1.22 (m, 3H), 1.17 (d, $J = 9.84$ Hz, 1H), 1.12–1.10 (m, 1H); ^{13}C NMR: δ 147.7, 128.2, 116.3, 111.9, 63.9, 48.4, 48.3, 46.9, 39.8, 38.0, 36.4, 28.9, 21.5. Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.70; H, 9.28; N, 6.11.

4.5.3. ((2*R*,3*S*)-3-((2-Chlorophenylamino)methyl)bicyclo-[2.2.1]heptan-2-yl)methanol (+)-9c. After LAH reduction of (+)-**8b**, without purification the mixture was subjected to hydrogenation. (0.59 g, 65%) colorless oil; $[\alpha]_D^{20} = +10.8$ (c 2.00, $CHCl_3$); IR (KBr): 3348, 2950, 1598 cm^{-1}; ^1H NMR: δ 7.15 (dd, $J = 6.25$, 7.30 Hz, 1H), 7.03 (t, $J = 7.07$ Hz, 1H), 6.52 (dd, $J = 7.33$, 13.54 Hz, 2H), 4.76 (br s, 1H), 3.61 (dd, $J = 6.87$, 9.98 Hz, 1H), 3.49 (t, $J = 9.41$ Hz, 1H), 3.00 (dd, $J = 6.70$, 11.62 Hz, 1H), 2.79 (dd, $J = 8.85$, 11.47 Hz, 1H), 2.21 (s, 1H), 2.06 (s, 1H), 1.64 (br s, 1H), 1.58–1.49 (m, 1H), 1.43 (d, $J = 9.90$ Hz, 1H), 1.39–1.24 (m, 3H), 1.19 (d, $J = 9.76$ Hz, 1H), 1.13–1.06 (m, 1H); ^{13}C NMR: δ 144.5, 129.1, 127.8, 119.1, 116.9, 111.2, 64.8, 49.0, 48.9, 47.2, 40.8, 38.9, 37.3, 29.9, 22.5. Anal. Calcd for $C_{15}H_{20}ClNO$: C, 67.79; H, 7.58; N, 5.27. Found: C, 67.59; H, 7.84; N, 5.42.

4.5.4. *N*-(((2*S*,3*R*)-3-(Hydroxymethyl)bicyclo[2.2.1]heptan-2-yl)methyl)-4-methylbenzenesulfonamide (−)-9d. (1.18 g, 91%); mp 75.0 °C; $[\alpha]_D^{20} = -13.2$ (c 1.00, $CHCl_3$); IR (KBr): 3459, 2958, 1627 cm^{-1}; ^1H NMR: δ 7.67 (d, $J = 8.12$ Hz, 2H), 7.21 (d, $J = 8.10$ Hz, 2H), 6.23 (br s, 1H), 3.61 (dd, $J = 4.50$, 9.44 Hz, 1H), 3.36 (t, $J = 10.09$ Hz, 1H), 2.91 (dd, $J = 4.65$, 15.83 Hz, 1H), 2.43 (t, $J = 10.96$ Hz, 1H), 2.34 (s, 3H), 2.09 (br s, 1H), 1.85 (br s, 1H), 1.44–1.35 (m, 2H), 1.23–1.13 (m, 4H), 1.07 (dd, $J = 13.50$, 24.50 Hz, 2H); ^{13}C NMR: δ 142.0, 135.9, 128.6, 126.1, 63.5, 48.0, 46.7, 46.6, 39.9, 38.3, 36.4, 28.9, 21.5, 20.5. Anal. Calcd for $C_{16}H_{23}NO_3S$: C, 62.11; H, 7.49; N, 4.53; S, 10.36. Found: C, 62.20; H, 7.82; N, 4.69; S, 9.92.

4.6. General procedure for diethylzinc addition reactions

The ligand (0.05 mmol) was dissolved in hexane (or toluene) (3 mL) at room temperature under argon atmosphere and diethyl zinc (1.0 mmol, 1 M in hexane) was then added to this solution. The mixture was stirred for 30 min, and then cooled to 0 °C. Benzaldehyde (0.5 mmol) was added to the mixture and the reaction mixture was stirred for 48 h at 0 °C. After adding 1 M HCl (10 mL), it was extracted with ethyl acetate (25 mL). The organic phase was then dried over $MgSO_4$ and the solvent was evaporated to give the corresponding alcohol. HPLC-analysis of 1-phenyl-1-propanol: Chiralcel OD-H at room temperature, n-hexane/2-propanol = 98:2, 1.0 mL/min, 254 nm, $t_1 =$ 26.3 min (R), $t_2 = 31.5$ min (S).

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References

1. (a) Corey, E. J.; Hannon, F. J. *Tetrahedron Lett.* **1987**, *28*, 5237–5240; (b) Zhang, H.; Xue, F.; Mak, T. C. W.; Chan, K. S. *J. Org. Chem.* **1996**, *61*, 8002–8003; (c) Zhang, H.; Chan, K. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 381–382; (d) Kang, S.-W.; Ko, D.-H.; Kim, K. H.; Ha, D.-C. *Org. Lett.* **2003**, *5*, 4517–4519.
2. For reviews of 1,2-aminoalcohols as chiral auxiliaries, see: (a) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835–875; (b) Senanayake, C. H. *Aldrichim. Acta* **1998**, *31*, 3–15; (c) Fache, F.; Schulz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159–2231; For reviews of 1,3-aminoalcohols, see: (d) Lait, S. M.; Rankic, D. A.; Keay, B. A. *Chem. Rev.* **2007**, *107*, 767–796.
3. Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823–2824.
4. (a) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071–6072; (b) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028–4036; (c) Noyori, R.; Suga, S.; Kaway, K.; Okada, S.; Kitamura, M.; Oguni, N.; Hayashi, N.; Kaneko, T.; Matsuda, Y. *J. Organomet. Chem.* **1990**, *382*, 19–37; (d) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49–69; (e) Kitamura, M.; Suga, S.; Niwa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 4832–4842; (f) Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327–6335; (g) Kitamura, M.; Suga, S.; Oka, H.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 9800–9809; (h) Yamakawa, M.; Noyori, R. *Organometallics* **1999**, *18*, 128–133; (i) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008–2022.
5. (a) Beliczey, J.; Giffels, G.; Kragl, U.; Wandrey, C. *Tetrahedron: Asymmetry* **1997**, *8*, 1529–1530; (b) Sola, L.; Vidal-Ferran, A.; Moyano, A.; Perkas, M. A.; Riera, A. *Tetrahedron: Asymmetry* **1997**, *8*, 1559–1568; (c) Cho, B. T.; Chun, Y. S. *Tetrahedron: Asymmetry* **1998**, *9*, 1489–1492; (d) Nugent, A. W. *J. Chem. Soc., Chem. Commun.* **1999**, 1369–1370.
6. (a) Genov, M.; Kostova, K.; Dimitrov, V. *Tetrahedron: Asymmetry* **1997**, *8*, 1869–1876; (b) Genov, M.; Dimitrov, V.; Ivanova, V. *Tetrahedron: Asymmetry* **1997**, *8*, 3703–3706; (c) Knollmüller, M.; Ferencic, M.; Gärtner, P. *Tetrahedron: Asymmetry* **1999**, *10*, 3969–3975; (d) Hanyu, N.; Aoki, T.; Mino, T.; Sakamoto, M.; Fujita, T. *Tetrahedron: Asymmetry* **2000**, *11*, 2971–2979; (e) Scarpi, D.; Galbo, F. L.; Occhiato, E. G.; Guarna, A. *Tetrahedron: Asymmetry* **2004**, *15*, 1319–1324; (f) Faux, N.; Razafimahefa, D.; Picart-Goetgheluck, S.; Brocard, J. *Tetrahedron: Asymmetry* **2005**, *16*, 1189–1197; (g) Kasashima, Y.; Hanyu, N.; Aoki, T.; Mino, T.; Sakamoto, M.; Fujita, T. *J. Oleo Sci.* **2005**, *54*, 495–504; (h) Zhong, J.; Wang, M.; Guo, H.; Yin, M.; Bian, Q.; Wang, M. *Synlett* **2006**, 1667–1670; (i) Martinez, A. G.; Vilar, E. T.; Fraile, A. G.; Cerero, S. M.; Ruiz, P. M.; Morillo, C. D. *Tetrahedron: Asymmetry* **2007**, *18*, 742–749.
7. He, X. C.; Eliel, E. L. *Tetrahedron* **1987**, *43*, 4979–4987.
8. Goldfuss, B.; Steigelman, M.; Khan, S. I.; Houk, K. N. *J. Org. Chem.* **2000**, *65*, 77–82.
9. Hanyu, N.; Aoki, T.; Mino, T.; Sakamoto, M.; Fujita, T. *Tetrahedron: Asymmetry* **2000**, *11*, 4127–4136.
10. Steiner, D.; Sethofer, S. D.; Goralski, C. T.; Singaram, B. *Tetrahedron: Asymmetry* **2002**, *13*, 1477–1483.
11. Tanyeli, C.; Sünbül, M. *Tetrahedron: Asymmetry* **2005**, *16*, 2039–2043.
12. (a) Bolm, C.; Gerlach, A.; Dinter, C. L. *Synlett* **1999**, 195–196; (b) Bolm, C.; Schiffers, I.; Dinter, C. L.; Gerlach, A. *J. Org. Chem.* **2000**, *65*, 6984–6991; (c) Bolm, C.; Schiffers, I.; Dinter, C. L.; Defrere, L.; Gerlach, A.; Raabe, G. *Synthesis* **2001**, 1719–1730; (d) Bolm, C.; Dinter, C. L.; Schiffers, I.; Defrere, L. *Synlett* **2001**, 1875–1877; (e) Bolm, C.; Schiffers, I.; Atodiresei, I.; Özçubukçu, S.; Raabe, G. *New J. Chem.* **2003**, *27*, 14–17; (f) Bolm, C.; Schiffers, I.; Atodiresei, I.; Hackenberger, C. P. R. *Tetrahedron: Asymmetry* **2003**, *14*, 3455–3467.
13. Middlemas, E. D.; Quin, L. D. *J. Org. Chem.* **1979**, *44*, 2587–2589.
14. Tanyeli, C.; Özçubukçu, S. *Tetrahedron: Asymmetry* **2003**, *14*, 1167–1170.