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A structural examination of the impact of oxygenated side chains in *Ephedra* compounds in the catalytic asymmetric addition of diethylzinc to aldehydes

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ABSTRACT

An investigation of the impact of oxygenated side chains in *Ephedra* compounds on the catalytic asymmetric addition of diethylzinc to aldehydes has been conducted. (1*R*,2*S*)-Ephedrine and (1*S*,2*S*)-pseudoephedrine were alkylated with either alkyl halides or β-alkoxyalkyl halides to afford a series of ligands **9a**–**h** and **10a**–**h**. These compounds were employed in the enantioselective addition of diethylzinc to a variety of aldehydes. It was determined that the presence of oxygen could have a negative effect in terms of obtaining high levels of enantiomeric discrimination, but the effect is diminished with higher levels of substitution near the oxygen.

1. Introduction

The synthesis and application of chiral auxiliaries and chiral catalysts for conducting asymmetric synthesis remains as a source of continued interest for the synthetic community.[1] There are a number of such ligands that have been designed and successfully employed in asymmetric reactions that involve additional coordination as a means of enhancing the observed stereoselection. Meyers' oxazoline,[2] Whitesell's amide,[3] and Enders' hydrazone[4] are examples of chiral auxiliaries that possess an ether component capable of contributing to a more well-defined region where the process of asymmetric induction may take place (Fig. 1). In each of these examples, the stereoelectronic properties of the chiral auxiliaries contribute to high levels of diastereoselectivity in a variety of reactions such as the aldol reaction, alkylation, and conjugate addition.[5] Ultimately, the presence of the coordinating ether group has a positive impact on the overall success of these reactions. We became interested in determining if the same type of coordination might be exploited in the design of ligands for the asymmetric addition of diethylzinc to aldehydes. The chiral auxiliaries that employ this mode of coordination often involve the use of lithium bases (e.g., *n*-BuLi, LDA, and LiHMDS). Lithium is considered to be a hard Lewis acid and a very effective coordinating metal, whereas zinc is considered to be 'borderline' hard Lewis acid. Nonetheless, we wanted to explore the concept of using ether linkages in chiral, non-racemic ligands as a means of controlling the stereochemical outcome of the zinc-mediated asymmetric addition reaction. In this regard, β-amino alcohols have enjoyed much success in diorganozinc alkylation reactions, and ligands derived from *Ephedra* alkaloids have been part of this success.[6] Much of the success associated with the use of these compounds is based on the fact that varying the substituents appended to the nitrogen of the *Ephedra* template has a measurable impact on the level of stereoselectivity observed in the addition reaction.[7] Thus, we began an investigation directed at examining the impact of having ether *N*-β-alkoxyalkyl side chains and their *N*-alkyl analog derivatives appended to the *Ephedra* template.

2. Results and discussion

We began our investigation by alkylating (1*R*,2*S*)-ephedrine **7** or (1*S*,2*S*)-pseudoephedrine **8** with a variety of alkyl halides and β-alkoxylalkyl halides in the presence of potassium carbonate (Scheme 1). This process afforded ephedrine derivatives **9a**–**h** and pseudoephedrine derivatives **10a**–**h** in good chemical yields after flash chromatography (Table 1). With these ligands in hand, the asymmetric 1,2-addition of diethylzinc to benzaldehyde was conducted as a test reaction. The results of these test reactions using ligands **9a**–**h** and **10a**–**h** are reported in Table 2. The (1*R*,2*S*)-ephedrine-derived ligands **9a**–**h** afforded the (*R*)-configuration in the product 1-phenyl-1-propanol, whereas the (1*S*,2*S*)-pseudoephedrine-based ligands **10a**–**h** provided the corresponding (*S*)-configuration. In using ligand **9e** (Table 2, entry 10), it was determined that lowering the temperature of the reaction led to slightly lower enantiomeric excess. In addition, it was determined that the use of 20 mol % (0.2 equiv) of the ligand **9e** (Table 2, entry 11) afforded the same level of enantioselection as when the catalyst was used in 10 mol %.

There was a clear difference in the level of enantioselection depending on the nitrogen substituent that was present. In the case of ligands **9a** and **10a**, the enantioselectivity was measured to be 73% and 80%, respectively. The oxygenated versions of these

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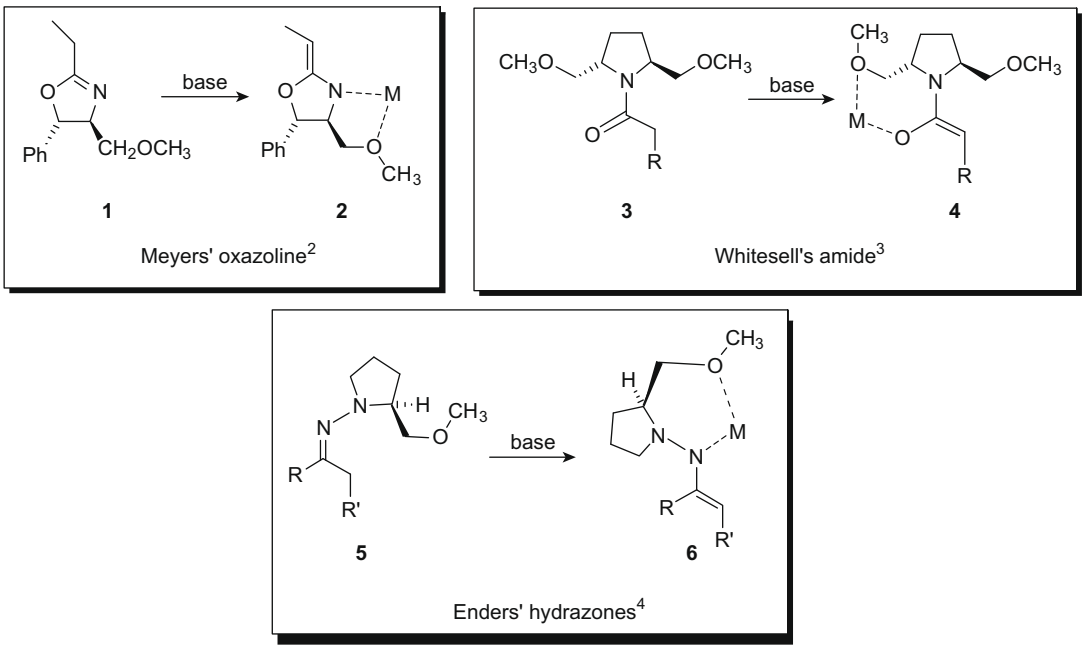
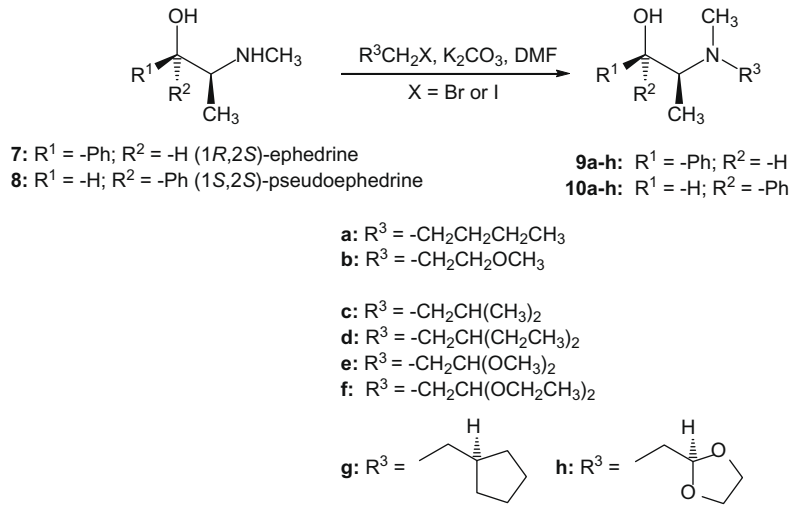


Figure 1. Chiral auxiliaries with proposed modes of coordination.



Scheme 1. Synthesis of *N*-alkyl and *N*-β-alkoxyalkyl *Ephedra* ligands **9a–h** and **10a–h**.

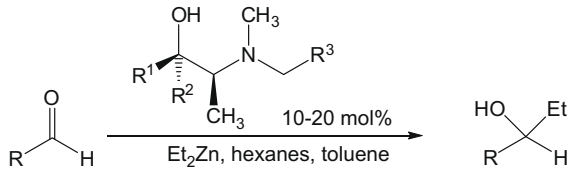
Table 1
Chemical yields for *N*-alkyl and *N*-alkoxyalkyl *Ephedra* ligands **9a–h** and **10a–h**

Entry	Ligand	Yield (%)
1	**9a**	73
2	**9b**	75
3	**9c**	77
4	**9d**	67
5	**9e**	52
6	**9f**	81
7	**9g**	53
8	**9h**	60
9	**10a**	75
10	**10b**	73
11	**10c**	89
12	**10d**	72
13	**10e**	78
14	**10f**	78
15	**10g**	52
16	**10h**	72

ligands **9b** and **10b** gave substantially lower enantiomeric ratios, that is, 30% and 32%ee, respectively. It is proposed that the ethereal linkages may contribute an alternate transition state that compromises the overall selectivity of the asymmetric addition process (Fig. 2).[8] This would ultimately suggest that either the oxygen of the five-membered ring zinc chelate is more Lewis basic than the ethereal oxygen of the side chain or the formation of the four-membered ring zincate is more favored than the formation of the seven-membered ring chelate.

When the nitrogen substituent was changed to the 2-ethylbutyl side chain in the ephedrine and pseudoephedrine derivatives **9d** and **10d**, the enantiomeric ratio of the product was determined to be 73% and 57%ee, respectively. Interestingly, the oxygenated versions of **9d** and **10d**, namely, the 2,2-dimethoxyethyl-substituted derivatives **9e** and **10e** gave enantiomeric excesses that were comparable. The same observation was made in the case of the alkyl derivatives **9g** and **10g** and their oxygenated derivatives **9h** and

Table 2
Catalytic asymmetric addition of diethylzinc to benzaldehyde[a]



11 **9a-h:** R_1 = -Ph; R_2 = -H **12**
10a-h: R_1 = -H; R_2 = -Ph

Entry	Ligand	Temp. (°C)	Equiv (%)	er, *R*:*S*, ($\|R - S\|$)[b]	Config.[c]
1	**9a**	25	10	86.5:13.5 (73)	*R*
2	**10a**	25	10	10:90 (80)	*S*
3	**9b**	25	10	66:34 (32)	*R*
4	**10b**	25	10	35:65 (30)	*S*
5	**9c**	25	10	76:24 (52)	*R*
6	**10c**	25	10	16.5:83.5 (67)	*S*
7	**9d**	25	10	86.5:13.5 (73)	*R*
8	**10d**	25	10	21.5:78.5 (57)	*S*
9	**9e**	25	10	90:10 (80)	*R*
10	**9e**	0	10	87:13 (74)	*R*
11	**9e**	25	20	90:10 (80)	*R*
12	**10e**	25	10	21.5:78.5 (57)	*S*
13	**9f**	25	10	66.5:33.5 (33)	*R*
14	**10f**	25	10	30.5:69.5 (39)	*S*
15	**9g**	25	10	90:10 (80)	*R*
16	**10g**	25	10	13:87 (74)	*S*
17	**9h**	25	10	91:9 (82)	*R*
18	**10h**	25	10	10:90 (80)	*S*

[a] All reactions went to completion as determined by ^{1}H NMR spectroscopy and CSP HPLC.
[b] The enantiomeric ratios were determined by HPLC using a Chiralcel-OD column, 2% IPA in hexanes. Flow rate: 1 mL/min, UV detector (254 nm). t_R = 11.8 (*R*) and 14.8 (*S*) min.
[c] The configuration was determined by comparison of literature values (see Ref. 7).

10h. The argument made for these results is that the steric volume of the oxygenated nitrogen substituents diminished their ability to effectively coordinate with the diethylzinc (Fig. 3).

Finally, the *Ephedra* ligands **9f** and **10f** which contained a 2,2-diethoxyethyl nitrogen substituent performed poorly and this is believed to be due not to the contribution of the putative minor pathway described in Figure 3, but to steric forces associated with a longer side chain contributing to poor facial selectivity with the aldehyde substrate.

Ephedra ligand **9h** was used to catalyze the asymmetric addition of diethylzinc to a series of aldehydes (Table 3) and this process afforded a range of enantiomeric ratios from 81.5:18.5 (63%ee) to 95:5 (90%ee). The lowest enantiomeric excess was generated from the substrate *trans*-cinnamaldehyde and the highest was the *o*-chlorobenzaldehyde. It is presumed that the stereoelectronic differences between these substrates are responsible for the differences in the observed selectivities.

3. Conclusion

We have developed (1*R*,2*S*)-ephedrine and (1*S*,2*S*)-pseudoephedrine-derived chiral ligands that have a variety of *N*-β-alkyoxyalkyl and *N*-alkyl side chains. It was determined that when the ephedrine-derived ligands **9a**–**h** were used in an asymmetric 1,2-addition of diethylzinc to benzaldehyde the (*R*)-configuration of the product was obtained, whereas when the pseudoephedrine-derived ligands **10a**–**h** were used in the same process the (*S*)-configuration of the product was afforded. The application of the methoxyethyl side chain of **9b** in the addition reaction afforded lower enantioselectivities and the application of the acetal bearing side chains of **9e** and **9h** yielded enantioselectivities comparable to their non-oxygenated side chain analogs.

4. Experimentals

4.1. General information

Toluene was purchased as an anhydrous reagent and was used without further purification. All reactions were run under a nitrogen atmosphere. ^{1}H and ^{13}C spectra were measured with a 400 MHz NMR spectrometer using $CDCl_3$ at room temperature.

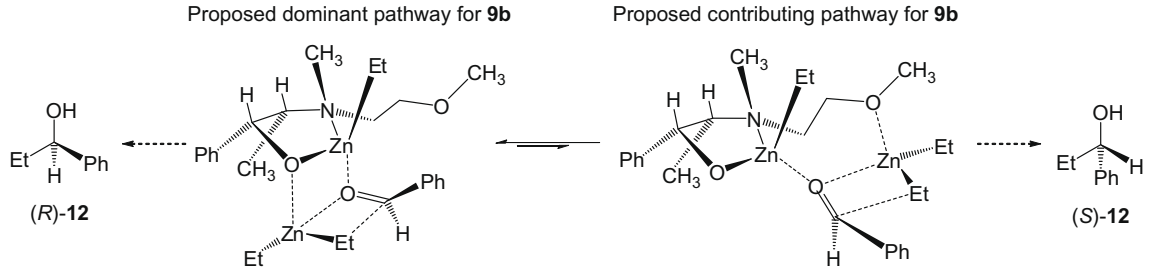


Figure 2. Proposed transition states for enantioselection with the *Ephedra* ligand **9b** in combination with diethylzinc and benzaldehyde.

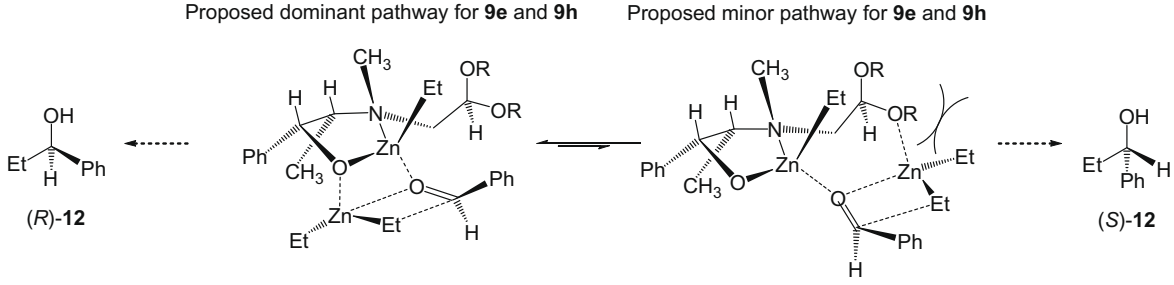
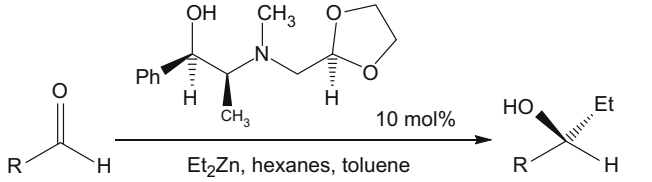


Figure 3. Proposed transition states for enantioselection with the *Ephedra* ligands **9e** and **9h** in combination with diethylzinc and benzaldehyde.

Table 3
Catalytic asymmetric addition of diethylzinc to aldehydes[a]



Entry[a]	RCHO, R– =	Yield (%)	er, *R*:*S*, ($\|R-S\|$)[b]	Config.[c]
1	$-C_6H_5$	84	91:9 (82)	*R*
2	$-2-C_{10}H_7$ (–2-naphthyl)	96	91:9 (82)	*R*
3	$-1-C_{10}H_7$ (–1-naphthyl)	97	88.5:11.5 (77)	*R*
4	–*trans*-CH=CHC_6H_5	82	81.5:18.5 (63)	*R*
5	*o*-C_6H_4Cl	89	95:5 (90)	*R*

[a] All reactions went to completion as determined by ^{1}H NMR spectroscopy and CSP HPLC.
[b] The enantiomeric ratio values were determined by CSP HPLC using a Chiralcel-OD column.
[c] The configuration was determined by comparison of literature values (see Ref. 7).

Chemical shifts are reported in parts per million (δ scale), and coupling constants (*J* values) are listed out in hertz (Hz). Tetramethylsilane (TMS) was used as the internal standard ($\delta = 0$ ppm). Infrared spectra are reported in reciprocal centimeters (cm^{-1}) and are measured as a neat liquid. Observed rotations were measured using a Jasco P-2000 polarimeter. Measurements of the observed rotation were made at 589 nm.

4.2. Preparation of (1*R*,2*S*)-ephedrine and (1*S*,2*S*)-pseudoephedrine derivatives 9a–h and 10a–h

In a 100 mL round-bottomed flask were placed (1*R*,2*S*)-ephedrine (2.00 g, 12.1 mmol), 2-bromomethyl-1,3-dioxalane (1.95 mL, 12.7 mmol), and potassium carbonate (3.34 g, 24.2 mmol) with dmf (12 mL). The solution was heated to reflux and was stirred overnight. The solution was then cooled to room temperature and quenched with 1 M HCl (75 mL). The organic layer was then diluted and extracted with ethyl ether (2 × 75 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$), and the solvent was removed by rotary evaporation to afford the desired material.

4.2.1. (1*R*,2*S*)-2-Butyl(methyl)amino)-1-phenylpropan-1-ol (9a)

Using (1*R*,2*S*)-ephedrine and 1-bromobutane as substrates. The title compound was purified by flash column chromatography (EtOAc) and 2.5% triethylamine. Colorless oil (0.97 g, 73%). $[\alpha]_D^{25} = -184$ (*c* 0.71, $CHCl_3$). IR (neat): 3350, 2958, 1040, 755, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.85 (d, *J* = 6.6 Hz, 3H), 0.91 (t, *J* = 7.0 Hz, 3H), 1.24–1.33 (m, 2H), 1.42–1.50 (m, 2H), 2.24 (s, 3H), 2.39–2.52 (m, 4H), 2.77–2.81 (m, 1H), 3.89 (br s, 1H), 4.80 (d, *J* = 4.3, 1H), 7.22–7.32 (m, 5H). ^{13}C NMR ($CDCl_3$) δ (ppm): 9.7, 13.9, 20.3, 29.4, 38.6, 54.4, 63.4, 72.7, 125.9, 126.5, 127.7, 142.5. HRMS Calcd for $C_{14}H_{24}NO$: 222.1858. Found: 222.1853.

4.2.2. (1*S*,2*S*)-2-Butyl(methyl)amino)-1-phenylpropan-1-ol (10a)

Using (1*S*,2*S*)-pseudoephedrine and 1-bromobutane as substrates. The title compound was purified by flash column chromatography (hexanes/EtOAc, 9:1, 2.5% triethylamine). Colorless oil (1.01 g, 75%). $[\alpha]_D^{25} = -84$ (*c* 0.85, $CHCl_3$). IR (neat): 3348, 2956, 1041, 755, 700. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.37 (d, *J* = 6.6 Hz, 3H), 0.97 (t, *J* = 7.1 Hz, 3H), 1.35–1.44 (m, 2H), 1.51–1.60 (m, 2H), 2.56 (s, 3H), 2.32–2.40 (m, 2H), 2.51–2.59 (m, 2H), 2.61–2.69 (m, 1H), 4.23 (d, *J* = 9.8, 1H), 5.24 (br s, 1H), 7.26–7.39 (m, 5H). ^{13}C NMR ($CDCl_3$) δ (ppm): 6.9, 13.8, 20.1, 30.1, 35.5, 53.0, 65.3, 74.4, 127.0, 127.3, 127.8, 142.0. HRMS Calcd for $C_{14}H_{24}NO$: 222.1858. Found: 222.1857.

4.2.3. (1*R*,2*S*)-2-((2-Methoxyethyl)(methyl)amino)-1-phenylpropan-1-ol (9b)

Using (1*R*,2*S*)-ephedrine and 1-bromo-2-methoxyethane as substrates. The title compound was purified by flash column chromatography (hexanes/EtOAc, 1:1, 2.5% triethylamine). Colorless oil (2.02 g, 75%). $[\alpha]_D^{25} = -196$ (*c* 0.71, $CHCl_3$). IR (neat): 3422, 1602, 1450, 1119, 756, 701 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.86 (d, *J* = 7.0 Hz, 3H), 2.30 (s, 3H), 2.67- 2.81 (m, 2H), 2.84–2.90 (m, 2H), 3.38 (s, 3H), 4.84 (d, *J* = 3.9 Hz, 1H), 7.12–7.33 (m, 5H). ^{13}C NMR ($CDCl_3$) δ (ppm): 9.0, 39.5, 53.2, 58.2, 63.4, 70.7, 73.3, 125.6, 126.2, 127.3, 142.3. HRMS Calcd for $C_{13}H_{22}NO_2$: 224.1651. Found: 224.1644.

4.2.4. (1*S*,2*S*)-2-((2-Methoxyethyl)(methyl)amino)-1-phenylpropan-1-ol (10b)

Using (1*S*,2*S*)-pseudoephedrine and 1-bromo-2-methoxyethane as substrates. The title compound was purified by flash column chromatography (EtOAc, 2.5% triethylamine). Clear liquid (1.97 g, 73%). $[\alpha]_D^{25} = -553$ (*c* 0.107, $CHCl_3$). IR (neat): 3376, 1604, 1452, 1120, 752, 701 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.74 (d, *J* = 6.6 Hz, 3H), 2.35 (s, 3H), 2.53 (dt, *J* = 13.3, 5.1 Hz, 1H), 2.66 (dq, *J* = 9.6, 6.6 Hz, 1H), 2.78–2.84 (m, 1H), 3.40 (s, 3H), 3.49–3.56 (m, 2H), 4.21 (d, *J* = 9.6 Hz, 1H), 7.27–7.37 (m, 5H). ^{13}C NMR ($CDCl_3$) δ (ppm): 6.9, 36.5, 51.4, 57.9, 65.0, 70.2, 74.1, 126.6, 126.8, 127.3, 141.6. HRMS Calcd for $C_{13}H_{22}NO_2$: 224.1651. Found: 224.1656.

4.2.5. (1*R*,2*S*)-2-(Isobutyl(methyl)amino)-1-phenylpropan-1-ol (9c)

Using (1*R*,2*S*)-ephedrine and 1-bromo-2-methylpropane as substrates. The title compound was purified by flash column chromatography (hexanes/EtOAc, 9:1, 2.5% triethylamine). Colorless oil (1.03 g, 77%). $[\alpha]_D^{25} = -165$ (*c* 0.83, $CHCl_3$). IR (neat): 3424, 2955, 1047, 758, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.84–0.89 (m, 9H), 1.76 (n, *J* = 7.4 Hz,1H), 2.17 (s, 3H), 2.21–2.51 (m, 2H), 2.75–2.78 (m, 1H), 4.79 (d, *J* = 4.7 Hz, 1H), 7.23–7.33 (m, 5H). ^{13}C NMR ($CDCl_3$) δ (ppm): 9.8, 20.4, 20.6, 26.3, 38.4, 63.6, 64.2, 73.1, 126.0, 126.6, 127.7, 142.5. HRMS Calcd for $C_{14}H_{24}NO$: 252.1858. Found: 252.1860.

4.2.6. (1*S*,2*S*)-2-(Isobutyl(methyl)amino)-1-phenylpropan-1-ol (10c)

Using (1*S*,2*S*)-pseudoephedrine and 1-bromo-2-methylpropane as substrates. The title compound was purified by flash column chromatography (hexanes/EtOAc, 9:1, 2.5% triethylamine). Clear liquid (1.19 g, 89%). $[\alpha]_D^{25} = -136$ (*c* 0.61, $CHCl_3$). IR (neat): 3356, 2957, 1039, 754, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.73 (d, *J* = 6.7 Hz, 3H), 0.96 (app. t, *J* = 6.2 Hz, 6H), 1.77–1.87 (m, 1H), 2.17 (dd, *J* = 12.1, 6.6 Hz, 1H), 2.24 (s, 3H), 2.28 (dd, *J* = 12.5, 8.2 Hz, 1H), 2.55–2.63 (m, 1H), 4.23 (d, *J* = 9.8 Hz, 1H), 7.24–7.37 (m, 5H). ^{13}C NMR ($CDCl_3$) δ (ppm): 6.9, 20.4, 20.5, 25.9, 35.8, 61.6, 65.9, 74.6, 127.1, 127.4, 127.9, 142.0. HRMS Calcd for $C_{14}H_{24}NO$: 252.1858. Found: 252.1849.

4.2.7. (1*R*,2*S*)-2-((2-Ethylbutyl)(methyl)amino)-1-phenylpropan-1-ol (9d)

Using (1*R*,2*S*)-ephedrine and 1-bromo-2-ethylbutane as substrates. The title compound was purified by flash column chromatography (hexanes/EtOAc, 95:5, 2.5% triethylamine). Clear liquid (1.01 g, 67%). $[\alpha]_D^{25} = -225$ (*c* 0.61, $CHCl_3$). IR (neat): 3424, 1039, 758, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.82–0.90 (m, 9H), 1.22–1.49 (m, 5H), 2.16 (s, 3H), 2.30 (dd, *J* = 6.6, 4.6 Hz, 1H), 2.75 (dd, *J* = 6.6, 5.1 Hz, 1H), 3.67 (br s, 1H), 4.77 (d, *J* = 4.7 Hz, 1H), 7.23–7.33 (m, 5H). ^{13}C NMR ($CDCl_3$) δ (ppm): 9.8, 10.4, 10.8, 23.4,

23.7, 38.4, 38.6, 59.5, 64.4, 73.2, 126.1, 126.7, 127.8, 142.5. HRMS Calcd for $C_{16}H_{28}NO$: 250.2147. Found: 250.2163.

4.2.8. (1*S*,2*S*)-2-((2-Ethylbutyl)(methyl)amino)-1-phenylpropan-1-ol (10d)

Using (1*S*,2*S*)-pseudoephedrine and 1-bromo-2-ethylbutane as substrates. The title compound was purified by flash column chromatography (hexanes/EtOAc, 9.5:0.05, 2.5% triethylamine). Colorless oil (1.08 g, 72%). $[\alpha]_D^{25} = -166$ (*c* 0.55, $CHCl_3$). IR (neat): 3360, 1605, 1454, 754, 700 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 0.74 (d, *J* = 6.6 Hz, 3H), 0.87–0.95 (m, 6H), 1.33–1.53 (m, 5H), 2.23 (s, 3H), 2.24 (dd, *J* = 12.5, 6.64 Hz, 1H), 2.37 (dd, *J* = 11.1, 7.0 Hz, 1H), 2.56–2.63 (m, 1H), 4.23 (d, *J* = 9.77 Hz, 1H), 5.20 (br s, 1H), 7.25–7.38 (m, 5H). ^{13}C NMR ($CDCl_3$) δ (ppm): 7.1, 10.6, 23.6, 35.6, 38.3, 57.8, 65.9, 74.8, 127.3, 127.5, 128.1, 142.2. HRMS Calcd for $C_{16}H_{28}NO$: 250.2147. Found: 250.2183.

4.2.9. (1*R*,2*S*)-2-((2,2-Dimethoxyethyl)(methyl)amino)-1-phenylpropan-1-ol (9e)

Using (1*R*,2*S*)-ephedrine and 2-bromo-1,1-dimethoxyethane as substrates. The title compound was purified by flash column chromatography (hexanes/EtOAc, 1:1, 2.5% triethylamine). Clear liquid (1.60 g, 52%). $[\alpha]_D^{25} = -337$ (*c* 0.40, $CHCl_3$). IR (neat): 3431, 1637, 1451, 1126, 750, 702 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 0.87 (d, *J* = 7.0 Hz, 3H), 2.30 (s, 3H), 2.63 (dd, *J* = 14.2, 5.2 Hz, 1H), 2.73 (dd, *J* = 14.2, 5.6 Hz, 1H), 2.82–2.88 (m, 1H), 3.37 (appt. d, *J* = 8.2 Hz, 6H), 3.81 (br s, 1H), 4.44 (t, *J* = 5.5 Hz, 1H), 4.81 (d, *J* = 3.9 Hz, 1H), 7.20–7.37 (m, 5H). ^{13}C NMR ($CDCl_3$) δ (ppm): 9.4, 40.7, 53.6, 53.9, 56.3, 64.2, 74.1, 103.5, 126.0, 126.7, 127.8, 142.3. HRMS Calcd for $C_{14}H_{24}NO_3$: 254.1756. Found: 254.1756.

4.2.10. (1*S*,2*S*)-2-((2,2-Dimethoxyethyl)(methyl)amino)-1-phenylpropan-1-ol (10e)

Using (1*R*,2*S*)-pseudoephedrine and 2-bromo-1,1-dimethoxyethane as substrates. The title compound was purified by flash column chromatography (hexanes/EtOAc, 7:3, 2.5% triethylamine). Colorless oil (2.39 g, 78%). $[\alpha]_D^{25} = -45.6$ (*c* 1.13, $CHCl_3$). IR (neat): 3385, 1604, 1127, 755, 702 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 0.74 (d, *J* = 6.3 Hz, 3H), 2.38 (s, 3H), 2.50 (dd, *J* = 13.4, 3.9 Hz, 1H), 2.64–2.68 (m, 1H), 2.72 (dd, *J* = 13.4, 5.9 Hz, 1H), 3.42 (appt. d, *J* = 5.9 Hz, 6H), 4.21 (d, *J* = 9.8 Hz, 1H), 4.54 (t, *J* = 4.7 Hz, 1H), 7.29–7.35 (m, 5H) ^{13}C NMR ($CDCl_3$) δ (ppm): 7.0, 37.0, 52.7, 52.9, 53.8, 65.5, 74.1, 102.3, 126.6, 126.8, 127.3, 141.3. HRMS Calcd for $C_{14}H_{24}NO_3$: 254.1756. Found: 254.1750.

4.2.11. (1*R*,2*S*)-2-((2,2-Diethoxyethyl)(methyl)amino)-1-phenylpropan-1-ol (9f)

Using (1*R*,2*S*)-ephedrine and 2-bromo-1,1-diethoxyethane as substrates. The title compound was purified by flash column chromatography (hexanes/EtOAc, 7:3, 2.5% triethylamine). Colorless oil (2.75 g, 81%). $[\alpha]_D^{25} = -170$ (*c* 0.81, $CHCl_3$). IR (neat): 3441, 1602, 1451, 1127, 756, 701 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 0.85 (d, *J* = 7.0 Hz, 3H), 1.24 (appt. q, *J* = 7.0 Hz, 6H), 2.32 (s, 3H), 2.62 (dd, *J* = 14.1, 5.0 Hz, 1H), 2.77 (dd, *J* = 13.7, 5.5 Hz, 1H), 2.84–2.87 (m, 1H), 3.53–3.59 (m, 2H), 3.70–3.74 (m, 2H), 4.58 (t, *J* = 5.5 Hz, 1H), 4.83 (d, *J* = 3.9 Hz, 1H), 7.21–7.34 (m, 5H). ^{13}C NMR ($CDCl_3$) δ (ppm): 8.9, 14.9, 40.4, 56.8, 61.6, 62.0, 63.9, 73.9, 101.6, 125.7, 126.2, 127.3, 142.1. HRMS Calcd for $C_{16}H_{28}NO_3$: 282.2069. Found: 282.2067.

4.2.12. (1*S*,2*S*)-2-((2,2-Diethoxyethyl)(methyl)amino)-1-phenylpropan-1-ol (10f)

Using (1*S*,2*S*)-pseudoephedrine and 2-bromo-1,1-diethoxyethane as substrates. The title compound was purified by flash column chromatography (hexanes/EtOAc, 8:2, 2.5% triethylamine). Colorless oil (2.64 g, 78%). $[\alpha]_D^{25} = -138$ (*c* 0.65, $CHCl_3$). IR (neat): 3408, 1604, 1452, 1129, 755, 701 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 0.73 (d, *J* = 6.6 Hz, 3H), 1.24–1.28 (m, 6H), 2.39 (s, 3H), 2.48 (dd, *J* = 13.3, 4.7 Hz, 1H), 2.64–2.68 (m, 1H), 2.73 (dd, *J* = 13.3, 6.Hz, 1H), 3.55–3.63 (m, 2H), 3.69–3.79 (m, 2H), 4.22 (d, *J* = 9.8 Hz, 1H), 4.63–4.67 (m, 1H), 7.28–7.37 (m, 5H). ^{13}C NMR ($CDCl_3$) δ (ppm): 7.1, 14.6, 31.2, 37.5, 54.6, 61.3, 61.6, 65.6, 74.2, 100.7, 126.6, 126.8, 127.4, 141.4. HRMS Calcd for $C_{16}H_{28}NO_3$: 282.2069. Found: 282.2078.

4.2.13. (1*R*,2*S*)-2-((Cyclopentylmethyl)(methyl)amino)-1-phenylpropan-1-ol (9g)

Using (1*R*,2*S*)-ephedrine and iodomethylcyclopentane as substrates. The title compound was purified by flash column chromatography (hexanes/EtOAc, 7:3, 2.5% triethylamine). Clear liquid (0.59 g, 53%). $[\alpha]_D^{25} = -211$ (*c* 0.65, $CHCl_3$). IR (neat): 3418, 2949, 1041, 759, 700 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 0.86 (d, *J* = 7.0, 3H), 1.11–1.18 (m, 2H), 1.50–1.61 (m, 4H), 1.68–1.74 (m, 2H), 1.97–2.09 (m,1H), 2.18 (s, 3H), 2.32 (dd, *J* = 12.5, 7.4 Hz, 1H), 2.39 (dd, *J* = 12.5, 7.8 Hz, 1H), 2.76 (m, 1H), 4.04 (br s, 1H), 4.74 (d, *J* = 4.7 Hz, 1H), 7.19- 7.35 (m, 5H). ^{13}C NMR ($CDCl_3$) δ (ppm): 9.6, 24.9, 30.7, 37.9, 38.4, 60.8, 63.7, 72.8, 125.9, 126.4, 127.6, 142.5. HRMS Calcd for $C_{16}H_{26}NO$: 248.2014. Found: 248.2011.

4.2.14. (1*S*,2*S*)-2-((Cyclopentylmethyl)(methyl)amino)-1-phenylpropan-1-ol (10g)

Using (1*S*,2*S*)-pseudoephedrine and iodomethylcyclopentane as substrates. The title compound was purified by flash column chromatography (hexanes/EtOAc, 7:3, 2.5% triethylamine). Colorless oil (0.582 g, 52%). $[\alpha]_D^{25} = -173$ (*c* 0.52, $CHCl_3$). IR (neat): 3346, 2949, 1038, 754, 700 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 0.73 (d, *J* = 6.6 Hz, 3H), 1.20–1.26 (m, 2H), 1.54–1.64 (m, 4H), 1.78–1.85 (m, 2H), 2.06–2.17 (m, 1H), 2.56 (s, 3H), 2.32 (dd, *J* = 12.1, 7.0 Hz, 1H), 2.41 (dd, *J* = 11.7, 8.2 Hz, 1H), 2.58–2.65 (m, 1H), 4.22 (d, *J* = 9.8 Hz, 1H), 5.24 (br s, 1H), 7.24–7.37 (m, 5H). ^{13}C NMR ($CDCl_3$) δ (ppm): 7.0, 25.1, 30.9, 36.0, 37.8, 59.4, 65.5, 74.6, 127.2, 127.5, 128.0, 142.2. HRMS Calcd for $C_{16}H_{26}NO$: 248.2014. Found: 248.2024.

4.2.15. (1*R*,2*S*)-2-(((1,3-Dioxolan-2-yl)methyl)(methyl)amino)-1-phenylpropan-1-ol (9h)

Using (1*R*,2*S*)-ephedrine and 2-(bromomethyl)-1,3-dioxolane as substrates. The title compound was purified by flash column chromatography (hexanes/EtOAc, 5.5:4.5, 2.5% triethylamine). Clear liquid (1.82 g, 60%). $[\alpha]_D^{25} = -126$ (*c* 1.15, $CHCl_3$). IR (neat): 3445, 3062, 1030, 751, 702 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 0.87 (d, *J* = 6.3 Hz, 3H), 2.38 (s, 3H), 2.71 (dd, *J* = 14.0, 4.3 Hz, 1H), 2.81 (dd, *J* = 14.0, 4.3 Hz, 1H), 2.85–2.91 (m, 1H), 3.72 (br s, 1H), 3.86–3.88 (m, 2H), 3.98–4.01 (m, 2H), 4.86 (d, *J* = 3.9 Hz, 1H), 4.97 (t, *J* = 4.4 Hz, 1H), 7.22–7.34 (m, 5H). ^{13}C NMR ($CDCl_3$) δ (ppm): 8.9, 40.6, 56.4, 64.1, 64.3, 64.4, 73.5, 103.1, 125.6, 126.3, 127.4, 142.4. HRMS Calcd for $C_{14}H_{24}NO$: 252.1600. Found: 252.1600.

4.2.16. (1*S*,2*S*)-2-(((1,3-Dioxolan-2-yl)methyl)(methyl)amino)-1-phenylpropan-1-ol (10h)

Using (1*S*,2*S*)-pseudoephedrine and 2-(bromomethyl)-1,3-dioxolane as substrates. The title compound was purified by flash column chromatography (hexanes/EtOAc, 7:3, 2.5% triethylamine). Colorless oil (2.20 g, 72%). $[\alpha]_D^{25} = -51$ (*c* 1.08, $CHCl_3$). IR (neat): 3398, 3062, 1041, 758, 702 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 0.72 (d, *J* = 6.6 Hz, 3H), 2.40 (s, 3H), 2.56 (dd, *J* = 13.7, 3.9 Hz, 1H), 2.66–2.71 (m,1H), 2.76 (dd, *J* = 13.7, 4.7 Hz, 1H), 3.84–3.86 (m, 2H), 3.96–3.99 (m, 2H), 4.20 (d, *J* = 9.8 Hz, 1H), 4.87 (br s, 1H), 5.02 (t, *J* = 4.3 Hz, 1H) 7.25–7.36 (m, 5H). ^{13}C NMR ($CDCl_3$) δ (ppm): 7.3, 37.8, 54.9, 64.2, 64.5, 65.9, 74.4, 103.0, 126.9, 127.1, 127.6, 141.5. HRMS Calcd for $C_{14}H_{22}NO_3$: 252.1600. Found: 252.1591.

4.3. General procedure for the addition of diethylzinc to aldehydes

In a nitrogen purged, flame-dried 100 mL round-bottomed flask was placed the chiral ligand **9a** (0.075 g, 0.34 mmol) and anhydrous toluene (5 mL). The solution was cooled to 0 °C and diethylzinc (10.2 mL, 1 M in hexane) was added with a syringe. After stirring for 1 h, benzaldehyde (0.40 mL, 3.4 mmol) was added to the reaction mixture. The solution was allowed to stir overnight at ambient temperature and the reaction was quenched by the addition of 1 M HCl (100 mL). The organic layer was extracted with dichloromethane (2×40 mL). The combined organic layers were washed with brine (50 mL), dried with $MgSO_4$, and the solvent was removed by rotary evaporation. If necessary, the crude product was purified by flash column chromatography using appropriate eluents (hexanes/EtOAc). The enantiomeric excess was determined with CSP HPLC using a Chiracel OD column.

4.4. Chiral HPLC analyses of 1-arylpopan-1-ols

A Chiracel OD column was used in all cases, temp. = 25 °C, UV detection, $\lambda = 254$ nm. The solvent systems were HPLC grade hexanes and isopropanol (IPA).

4.4.1. 1-Phenylpropan-1-ol

Hexanes/IPA, 98:2; 1 mL/min. t_r (*R*)-enantiomer (min) = 11.3, t_r (*S*)-enantiomer (min) = 15.0.

4.4.2. 1-(2′-Naphthyl)propan-1-ol

Hexanes/IPA, 98:2; 1 mL/min. t_r (*S*)-enantiomer (min) = 25.1, t_r (*R*)-enantiomer (min) = 27.9.

4.4.3. (*E*)-1-Pheny-1-penten-3-ol

Hexanes/IPA, 98:2; 1 mL/min. t_r (*S*)-enantiomer (min) = 12.7, t_r (*R*)-enantiomer (min) = 25.4.

4.4.4. 1-(3-Chlorophenyl)propan-1-ol

Hexanes/IPA, 98:2; 1 mL/min. t_r (*R*)-enantiomer (min) = 11.3, t_r (*S*)-enantiomer (min) = 14.8.

4.4.5. 1-(1′-Naphthyl)propan-1-ol

Hexanes/IPA, 90:10; 1 mL/min. t_r (*S*)-enantiomer (min) = 9.0, t_r (*R*)-enantiomer (min) = 19.7.

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