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Aromatic motifs in the design of *Ephedra* ligands for application in the asymmetric addition of diethylzinc to aldehydes and diphenylphosphinoylimines

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ABSTRACT

Using *N*-benzylephedrine as a model, a collection of *N*-arylmethylephedrine derivatives has been prepared. These derivatives were prepared by treatment of ephedrine with selected aldehydes to create oxazolidines **8a–e**. Reduction of the oxazolidines with lithium aluminum hydride afforded the target β-amino alcohols **9a–e**. When applied in the catalytic asymmetric addition of diethylzinc to aldehydes and diphenylphosphinoylimines, the derivatives yielded product enantioselectivities that were comparable to those of *N*-benzylephedrine. An *N*-cyclohexylmethylephedrine derivative was also prepared; this β-aminoalcohol did not perform well in the catalytic addition of diethylzinc to 2-naphthaldehyde, thus suggesting that the aromatic motif is important in terms of maintaining a reasonable level of asymmetric induction. Finally, *N*-benzyl-*N*-methyl-2-amino-1,2-diphenyl-1-ethanol, an analogue of the *N*-benzylephedrine derivative, was prepared. This compound yielded comparable enantioselectivities in the catalytic asymmetric addition when employed as a ligand.

1. Introduction

Investigations concerning the catalytic asymmetric addition of diorganozinc reagents to carbonyl compounds and imines have been primarily focused on the careful design, synthesis, and application of chiral ligands that possess the ability to effectively transfer asymmetry.[1] These studies have led to the creation of a vast array of ligands capable of inducing very high levels of enantioselection in asymmetric alkylation reactions.[2] The *Ephedra* alkaloids have been used to create a number of ligands for the enantioselective addition process (Fig. 1). These ligands include *N*-benzylephedrine **1** and its polymer-bound variants,[3] *N*-pyridylmethylephedrines **2**,[4] *N*-β-alkoxyethylephedrines **3**,[5] *N*-(*N*-tolylsulfonylethyl)ephedrines **4**,[6] *N*-(pyrazolylethyl) pseudoephedrine **5**,[7] *N*-(α-pyrrolylethyl)ephedrine **6**,[8] and a series of related derivatives.[9]

These *Ephedra* ligands have provided a wealth of information in the asymmetric addition reaction with diorganozinc reagents and carbonyl compounds, either from the standpoint of high enantioselectivities of the products or from the standpoint of mechanistic insights. In this context we became interested in developing a series of *Ephedra* ligands to explore derivatives similar to the *N*-benzylephedrine system **1**. In particular, we were interested in introducing a series of aryl moieties in the place of the phenyl ring of **1**. These aryl systems would vary in structure and electronic properties and might provide data pertaining to the effectiveness of bringing such groups into the chiral ligand framework. Herein we report our efforts in this area by the introduction of naphthyl groups and biphenyl groups in place of the phenyl for the increased steric projection of the aromatic motif. A *p*-fluorophenyl system as well as other ligands that were developed over the course of this work is described.

2. Results and discussion

The synthesis of the *Ephedra* ligands was initiated by the treatment of (1*R*,2*S*)-ephedrine with a variety of aromatic aldehydes (Scheme 1). This process afforded oxazolidines **8a–e** as mixtures of diastereomers (ca. 6:1) as determined by ^{1}H NMR spectroscopy. Chromatographic purification of the diastereomers was not viable as the oxazolidines would undergo ring opening to form the original starting materials. Fortunately, oxazolidines **8a–b** and **8d–e** underwent recrystallization. Derivative **8c** could not be recrystallized and was carried on to the next reaction where purification could be more readily achieved. Even though the oxazolidines were only intermediates in the synthesis of the targeted *Ephedra* derivatives, we were still interested in determining the relative and absolute configuration of the oxazolidine ring. Thus, oxazolidine **8b** was analyzed by single crystal X-ray crystallographic analysis[10] and it was determined that the C_2-naphthyl substituent occupied the same face of the ring as the C_5-phenyl position (Fig. 2). Based on this analysis and correlation with the associated NMR spectra

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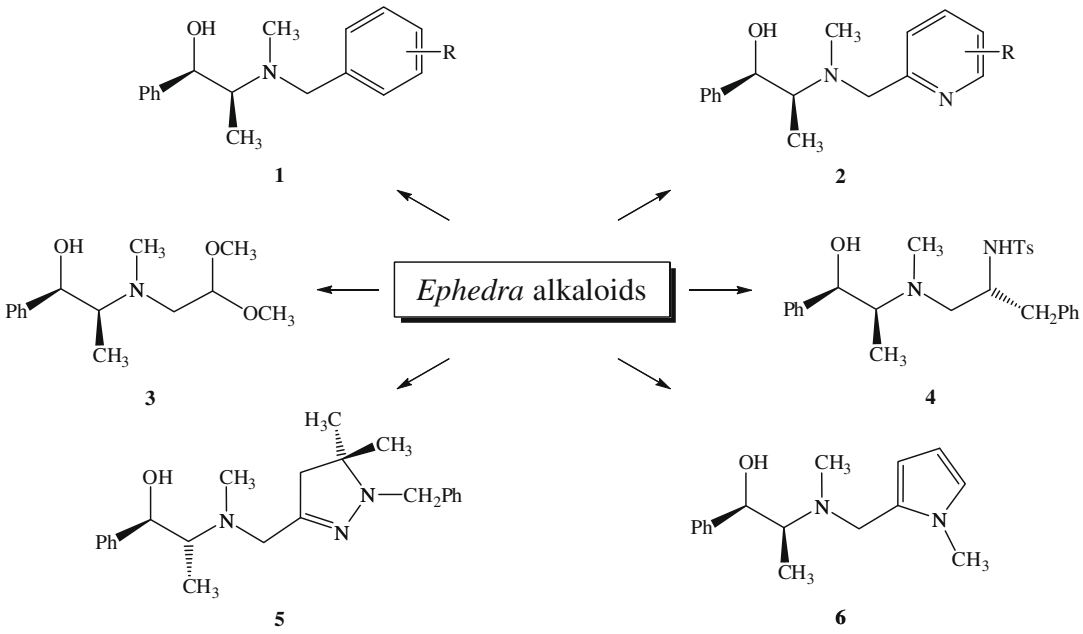
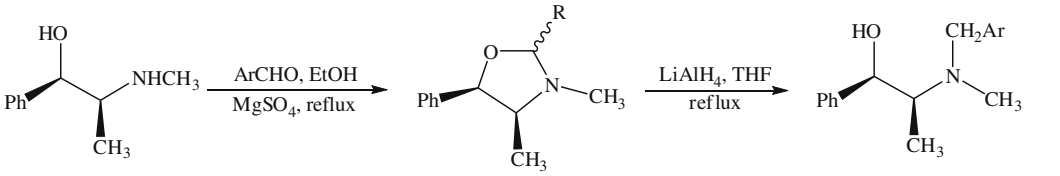


Figure 1. *Ephedra*-based ligands **1**–**6**.



a: R = -1-naphthyl (99%)
b: R= -2-naphthyl (70%)
c: R= -2-biphenyl (99%)
d: R = -4-biphenyl (74%)
e: R = -4-fluorophenyl (64%)

a: R = -1-naphthyl (80%)
b: R= -2-naphthyl (77%)
c: R= -2-biphenyl (26%)
d: R = -4-biphenyl (73%)
e: R = -4-fluorophenyl (28%)

Scheme 1. Synthesis of oxazolidines.

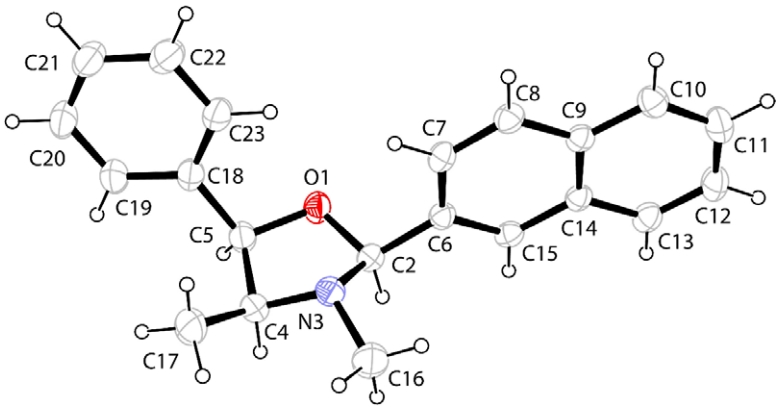
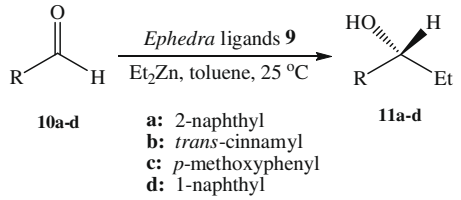


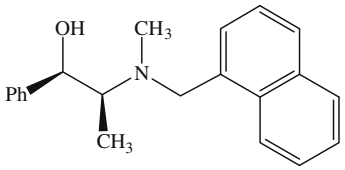
Figure 2. X-ray crystal structure of oxazolidine **8b** at 50% probability level. Hydrogens are drawn arbitrarily small for clarity.

(observed methine doublet at ca. 5.2 ppm in the oxazolidine examples **8a**–**e**), it was determined that the major oxazolidine isomer in all cases possessed a *cis*-configuration (Scheme 1).

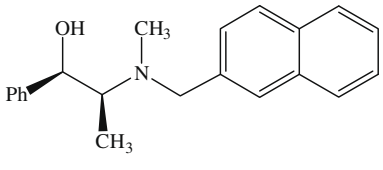
At this stage, oxazolidines **8a**–**e** were reduced by reaction with lithium aluminum hydride to the corresponding β-amino alcohol ligands **9a**–**e** in isolated yields ranging from 26% to 80% after purification. These ligands were then employed in the asymmetric 1,2 addition of diethylzinc to different aldehydes as shown in Table 1. The enantiomeric excesses for the enantioselective addition reactions ranged from 56% to 86%ee. In the case of the catalytic

Table 1
Asymmetric 1,2 addition of diethylzinc to aldehydes using ligands **9a–e**

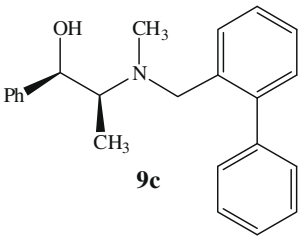




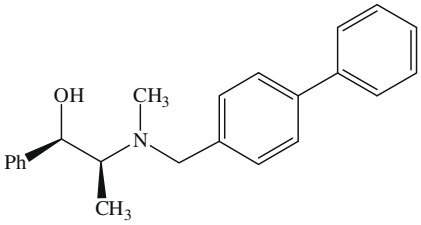
9a



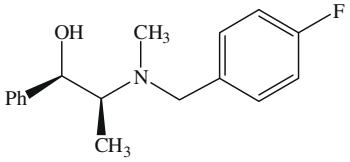
9b



9c



9d



9e

Entry	Ligand	RCHO R–	Yield[a] (%)	Enantiomeric ratio *R*:*S*[b] (%ee)	Absolute configuration[c]
1	**1** (R = –H)	–2-$C_{10}H_7$	88	91.1:8.9 (82)[b]	(*R*)
2	**1** (R = –H)	–*t*-CH=CHC_6H_5	82	84.9:15.1 (70)[b]	(*R*)
3	**9a**	–2-$C_{10}H_7$	50	90.4:9.6 (81)	(*R*)
4	**9a**	–*p*-$C_6H_4OCH_3$	66	85.6:14.4 (71)	(*R*)
5	**9a**	–*t*-CH=CHC_6H_5	81	81.9:18.1 (64)	(*R*)
6	**9b**	–2-$C_{10}H_7$	78	91.9:8.1 (84)	(*R*)
7	**9b**	–1-$C_{10}H_7$	69	93.6:6.4 (87)	(*R*)
8	**9b**	–*t*-CH=CHC_6H_5	59	85.3:14.7 (71)	(*R*)
9	**9c**	–2-$C_{10}H_7$	50	89.8:10.2 (80)	(*R*)
10	**9d**	–2-$C_{10}H_7$	74	92:8 (84)	(*R*)
11	**9d**	–*t*-CH=CH-Ph	78	84:16 (68)	(*R*)
12	**9d**	–*p*-$C_6H_4OCH_3$	72	88:12 (76)	(*R*)
13	**9e**	–2-$C_{10}H_7$	75	92:8 (84)	(*R*)
14	**9e**	–1-$C_{10}H_7$	37	93:7 (86)	(*R*)
15	**9e**	–*t*-CH=CHC_6H_5	61	81:19 (62)	(*R*)

[a] Yield was reported after purification via flash chromatography.
[b] Enantiomeric excess was determined using chiralcel HPLC with OD column in 98:2 hexanes/IPA.
[c] Absolute configuration was determined from the literature.

asymmetric addition of diethylzinc to 2-naphthaldehyde, the model system *N*-benzylephedrine **1** yielded the alcohol product in 82%ee. The same process catalyzed by ligands **9a–e** ranged from 80% to 86%ee. This suggested that the introduction of the different aromatic motifs did not enhance or compromise the overall transmission of chirality. The other examples including *trans*-cinnamaldehyde, 1-naphthaldehyde, and *p*-anisaldehyde were also consistent in terms of the enantiomeric purity of the alcohol product.

Based on the results of the asymmetric addition reaction, a tentative model of potential transition states has been proposed using the **9a**–Et_2Zn–RCHO adduct as a guide (Fig. 3). There are a multitude of factors that must be considered in determining which proposed transition state is the most viable; from the four putative systems listed here, **12** and **13** are more likely to contribute to the stereochemical outcome of the addition process. Since the values for the enantioselectivities are nearly the same, it is possible that the steric volume of the appendant nitrogen substituent apparently must be directed away from the chiral 'pocket' where the asymmetric induction takes place.

To further investigate the efficacy of ligands **9a–e**, the asymmetric addition of diorganozinc reagents to diphenylphosphinoylimines was pursued. The phosphinoylimines were prepared as mentioned before[4a] (Scheme 2) and were employed in the addition reaction (Table 2).

The consistent results obtained in the asymmetric addition reaction with the diphenyl phosphinoylimines would suggest that the various aromatic motifs of ligands **9a–e** make a similar contribution to the transmission of asymmetry in the transition state.

The collected results from the application reactions suggested that varying the aromatic substituent did not lead to either significant enhancement or diminishment of the enantioselectivity of the products. Nonetheless, there was still an interest in varying the substituent on the ephedrine scaffold to enhance the enantio-

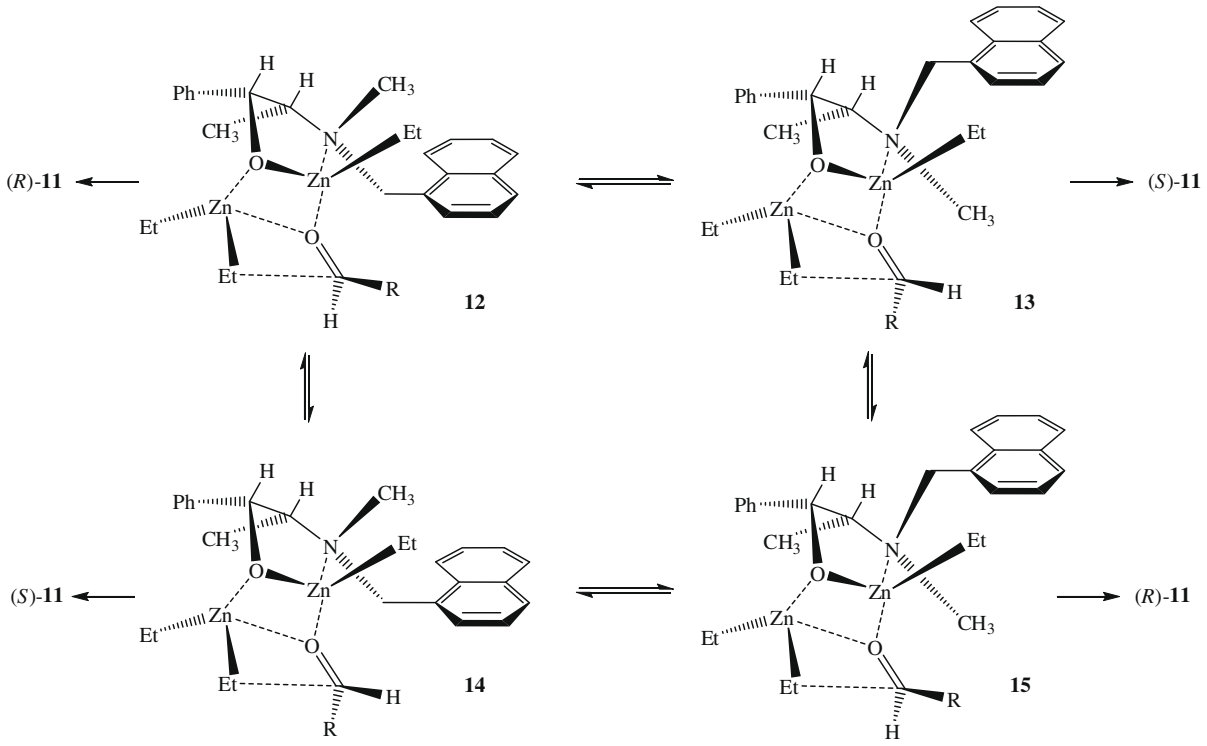
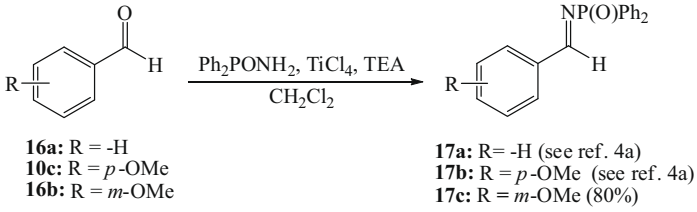
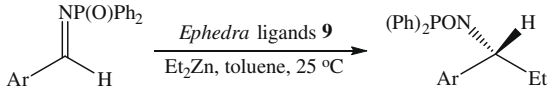


Figure 3. Proposed transition states **12**–**15**.



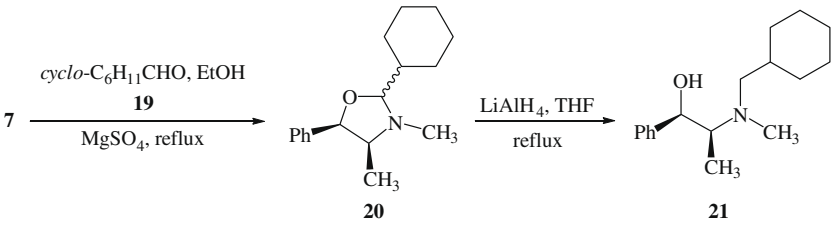
Scheme 2. Synthesis of phosphinoylimines.

Table 2
Asymmetric additions to diphenylphosphinoylimines using ligands **9a**–**e**



Entry	Ligand	R_2Zn R =	ArCH=NP(O)Ph_2	Yield[a] (%)	Enantiomeric ratio *R*:*S*[b] (%ee)	Absolute configuration[c]
1	**1**	Et	–*p*-$C_6H_4OCH_3$	42	97.2:2.8 (94)[b]	(*R*)
2	**9a**	Et	–C_6H_5	75	97:3 (94)	(*R*)
3	**9a**	Et	–*p*-$C_6H_4OCH_3$	79	98:2 (96)	(*R*)
4	**9a**	Me	–*m*-$C_6H_4OCH_3$	65	94.7:5.3 (89)	(*R*)
5	**9b**	Me	–*m*-$C_6H_4OCH_3$	61	94.5:5.5 (89)	(*R*)
6	**9c**	Me	–*m*-$C_6H_4OCH_3$	44	93.9:6.1 (88)	(*R*)
7	**9d**	Me	–*m*-$C_6H_4OCH_3$	44	93.9:6.1 (88)	(*R*)
8	**9d**	Et	–*p*-$C_6H_4OCH_3$	99	97.0:3.0 (94)	(*R*)
9	**9e**	Me	–*m*-$C_6H_4OCH_3$	51	95.1:4.9 (90)	(*R*)

[a] Yields are reported after purification via flash chromatography using 4:6 hexanes and ethylacetate.
[b] Enantiomeric excesses were determined via chiralcel HPLC using AD column in 80:20 hexanes and IPA.
[c] Absolute configurations were determined from HPLC data in the literature.



Scheme 3. Synthesis of saturated *N*-cyclohexylmethylephedrine **21**.

selection. To this end, (1*R*,2*S*)-ephedrine was reacted with cyclohexanecarbaldehyde to form oxazolidine **20** in 90% isolated yield (Scheme 3). This oxazolidine was reduced with lithium aluminum hydride to afford the target β-amino alcohol **21** in 32% yield after chromatography.

This ligand was then employed for the asymmetric 1,2 addition of diethylzinc to *trans*-cinnamaldehyde and 2-naphthaldehyde (Scheme 4). It was determined that this ligand was not suitable for the process of catalyzing the addition reaction. The ^{1}H NMR spectroscopic analysis revealed that the addition reaction did occur, but the addition product was contaminated with the reduction product (>40%). The reduction product arises from the transfer of a hydride to the aldehyde substrate from the diethylzinc with the release of ethene. It could be that the steric bulk of the cyclohexylmethyl component was responsible for the formation of the reduced product. In contrast, this ligand afforded a 95.4:4.6 (91% ee) enantiomeric ratio in the asymmetric addition of dimethylzinc to *m*-anisulfosphinoylimine with a yield of 36%. The low yield may be a reflection of the limitation of the effectiveness of this particular ligand.

Finally, there was an interest in determining whether a structural change in the *Ephedra* scaffold would improve the observed product enantioselectivities. This was accomplished by employing (1*R*,2*S*)-2-amino-1,2-diphenyl-1-ethanol **23** where the carbon bearing the nitrogen possesses a phenyl group as compared to the methyl group present in the *Ephedra* series. This material has previously been employed for the process of asymmetric addition of diorganozinc reagents to diphenylphosphinoylimines, but has not been employed in the aldehyde addition process.[11] The *N*-benzyl-*N*-methyl derivative was of interest as this aromatic motif was the simplest of the collection. This derivative was prepared by reacting **23** with methyl chloroformate and reducing with lithium aluminum hydride to generate the *N*-methyl derivative **24** in 96% yield (Scheme 5). This compound was then alkylated with benzyl bromide to afford the target in 64% isolated yield. With this material in hand, we applied it to the asymmetric addition reaction with aldehydes **10a** and **10b**, and with diphenylphosphinoylimine **17c**. It was determined that the change of the scaffold did not significantly change the observed product enantioselectivities despite the presence of a phenyl ring in the place of the methyl substituent of the *Ephedra* system.

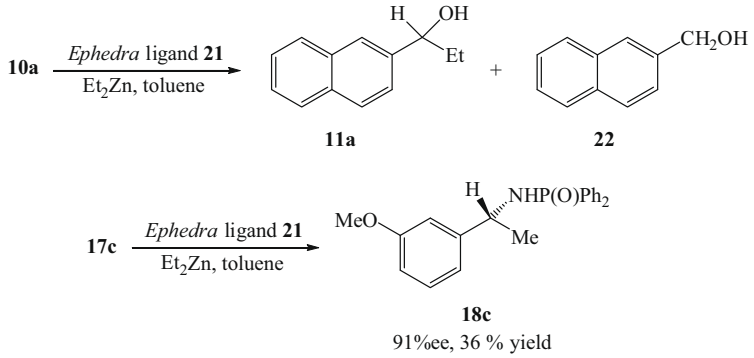
3. Conclusion

A series of *Ephedra* derivatives with varying aromatic motifs (-1-naphthylmethyl, -2-naphthylmethyl, 2-biphenylmethyl, -4-biphenylmethyl, and 4-fluorophenylmethyl) appended to the nitrogen have been employed in the asymmetric addition reaction of diorganozinc reagents to aldehydes and diphenylphosphinoylimines. With regard to the asymmetric induction observed in these reactions, the *Ephedra* derivatives were remarkably consistent in the addition reaction when compared against the model system of *N*-benzylephedrine as a model. The synthesis and application of the *N*-cyclohexylmethylephedrine derivative led to compromised reactions where either the enantioselectivity could not be measured accurately or the isolated chemical yield was low. The preparation and use of *N*-benzyl-*N*-methyl-2-amino-1,2-diphenyl-1-ethanol yielded comparable enantioselectivies in the catalytic asymmetric addition when employed as a ligand indicating that the group appended to the carbon bearing the nitrogen did not significantly change the overall efficacy of asymmetric induction.

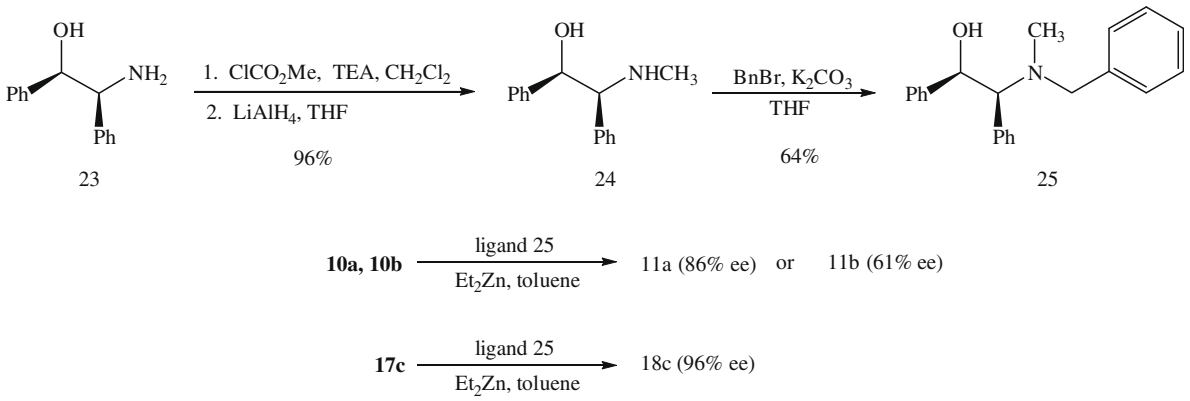
4. Experimentals

4.1. General remarks

All reactions were run under a nitrogen atmosphere. Anhydrous toluene was purchased and stored under a nitrogen atmosphere. Dimethylzinc was purchased as a 1.2 M solution in hexanes and diethylzinc was purchased as a 1.0 M solution in hexanes. All ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker Avance spectrometer at 25 °C in $CDCl_3$ operating at 500 MHz and 125 MHz, respectively, or a Varian spectrometer operating at 400 MHz (^{1}H) and 100 MHz (^{13}C). Chemical shifts are recorded in parts per million (δ scale), and the coupling constant (J values) are listed in hertz (Hz). Optical activities are measured using 589 nm using a Jasco digital polarimeter. Infrared spectra are re-



Scheme 4. Application reactions of *Ephedra* ligand **21**.



Scheme 5. Synthesis and application of *N*-benzyl-*N*-methyl-2-amino-1,2-diphenyl-1-ethanol.

ported in reciprocal centimeters (cm^{-1}). Flash chromatography was conducted with an Analogix flash chromatograph. Mass spectral analyses were conducted by the mass spectrometry analytical laboratories of the University of Illinois at Urbana-Champaign using quadruple time of flight mass spectrometer hybrid with MS/MS capability. Enantiomeric ratios were determined using a Shimadzu HPLC with chiral stationary phase Chiralcel AD column or OD column.

4.2. General procedure for the formation of oxazolidines 8a–e

In a 1 L round-bottomed flask, (1*R*,2*S*)-ephedrine (5.00 g, 30.26 mmol) and 1-naphthaldehyde (4.31 mL, 31.77 mmol) were placed into toluene (200 mL) and $MgSO_4$ (2 g). The reaction mixture was heated at reflux and allowed to run for 24 h. The reaction mixture was gravity filtered to remove $MgSO_4$. The filtrate was collected and the solvent was removed.

4.2.1. (4*S*,5*R*)-3,4-Dimethyl-2-(1-naphthyl)-5-phenyloxazolidine 8a

Recrystallized from dichloromethane and hexanes. White solid (49%). Mp = 79–81 °C. $[\alpha]_D^{24} = -123.9$ (*c* 1.00, $CHCl_3$). IR ($CHCl_3$): 1331, 1055, 713. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.86 (d, *J* = 10.0 Hz, 3H), 3.32 (s, 3H), 3.13–3.17 (m, 1H), 5.25 (d, *J* = 10.0 Hz, 1H), 5.55 (s, 1H), 7.33 (d, *J* = 5.0 Hz, 2H), 7.46–7.61 (m, 5H), 7.89 (d, *J* = 5.0 Hz, 1H), 8.07 (d, *J* = 10.0 Hz, 2H), 8.41 (d, *J* = 10.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 15.1, 36.8, 64.1, 83.0, 94.9, 123.9, 125.0, 125.5, 125.6, 126.2, 127.5, 127.8, 128.6, 129.3, 132.7, 133.1, 134.0. ESI-HRMS calcd for $C_{21}H_{22}NO$ $(M+H)^+$: 304.1701. Found: 304.1698.

4.2.2. (4*S*,5*R*)-3,4-Dimethyl-2-(2-naphthyl)-5-phenyloxazolidine 8b

The resultant white residue was recrystallized from dichloromethane and hexanes. The product was obtained as a white solid (64%). Mp = 127–129 °C. $[\alpha]_D^{22} = -66.7$ (*c* 1.02, $CHCl_3$). IR (Nujol): 1060, 712. ^{1}H NMR (500 MHz, CDC_{l3}) δ (ppm): 0.82 (d, *J* = 6.5 Hz, 3H), 2.20 (s, 3H), 2.98–3.03 (m, 1H), 4.84 (s, 1H), 5.18(d, *J* = 8.4 Hz, 1H),7.21–7.29 (m, 2H), 7.33–7.36(m, 3H), 7.46–7.49(m, 3H), 7.83–8.02(m, 4H) . ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 15.1, 37.8, 64.0, 82.5, 99.0, 125.5, 126.0, 126.2, 127.6, 127.7, 127.9, 128.0, 128.2, 128.4, 133.1, 134.0, 135.6, 139.8. ESI-HRMS calcd for $C_{21}H_{22}NO$ $(M+H)^+$: 304.1701. Found: 304.1694.

4.2.3. (4*S*,5*R*)-2-(2-Biphenyl)-3,4-dimethyl-5-phenyloxazolidine 8c

A colorless oil was obtained that could not be recrystallized. Due to the reactive nature of the oxazolidine, it was not purified but immediately reduced with lithium aluminum hydride.

4.2.4. (4*S*,5*R*)-2-(4-Biphenyl)-3,4-dimethyl-5-phenyloxazolidine 8d

The resultant white residue was recrystallized from dichloromethane and hexanes. White solid (74%). $[\alpha]_D^{24} = -59.5$ (*c* 1.0, $CHCl_3$). MP: 129–131 °C. IR (Nujol): 1378, 1063, 727. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.81 (d, *J* = 7.0 Hz, 3H), 2.23 (s, 3H), 2.96–3.02 (m, 1H), 4.75 (s, 1H), 5.15 (d, *J* = 8.0 Hz, 1H), 7.26–7.30 (tt, *J* = 7.5 Hz, 1.0 Hz, 1H), 7.32–7.38 (m, 3H), 7.43–7.47 (m, 4H), 7.59–7.67 (m, 4H), 7.71–7.73 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 15.1, 35.8, 64.1, 77.2, 82.5, 98.6, 127.2, 127.3, 127.4, 127.6, 127.9, 128.0, 128.8, 137.2, 140.0, 141.0, 142.1. ESI-HRMS calcd for $C_{23}H_{24}NO$ $(M+H)^+$: 330.1858. Found: 330.1858.

4.2.5. (4*S*,5*R*)-2-(4-Fluorophenyl)-3,4-dimethyl-5-phenyloxazolidine 8e

Recrystallization from hexanes and ethyl acetate. White solid (64%). Mp = 90–91 °C. $[\alpha]_D^{22} = -32.7$ (*c* 0.5, $CHCl_3$). IR (Nujol): 1604, 1217 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.78–0.79 (d, *J* = 6.5 Hz, 3H), 2.17 (s, 3H), 2.94–3.01 (m, 1H), 4.68 (s, 1H), 5.13–5.15 (d, *J* = 8.32 Hz, 1H), 7.09–7.13 (m, 2H), 7.28–7.30 (m, 1H), 7.32–7.38 (m, 2H), 7.40–7.42 (m, 2H), 7.61–7.64 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 15.0, 35.7, 63.9, 82.5, 98.1, 115.3, 115.5, 126.2, 127.7, 127.9, 128.1, 130.1, 130.2, 134.0, 139.7, 162.1, 164.6. ESI-HRMS calcd for $C_{17}H_{18}FNO$ $(M+H)^+$: 272.1451. Found: 272.1450.

4.3. General procedure for the formation of β-amino alcohols 9a–e

(4*S*,5*R*)-3,4-Dimethyl-2-(2-naphthyl)-5-phenyloxazolidine (3.94 g, 12.1 mmol), lithium aluminum hydride (0.915 g, 24.1 mmol), and THF (400 mL) were combined in a 2 L round-bottomed flask. The reaction mixture was heated at reflux and allowed to run for 24 h. The reaction mixture was cooled to 0 °C and the reaction was quenched by the slow addition of 1 M NaOH (150 mL). The mixture was diluted with ethyl acetate (300 mL), washed with Rochelle's salt (100 mL), and brine (100 mL), and dried ($MgSO_4$). The solvents were removed by rotary evaporation and the product was purified.

4.3.1. (1*R*,2*S*)-2-((Methyl(-1-naphthyl)(methyl)amino)-1-phenyl-1-propanol 9a

The product was purified by recrystallization by hexanes and dichloromethane. White solid (80%). MP = 83–85 °C. $[\alpha]_D^{24} = -23.2$ (*c* 1.0, $CHCl_3$). IR ($CHCl_3$): 3421, 3014, 1216 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.11 (d, *J* = 6.8 Hz, 3H), 2.18 (s, 3H), 3.04 (m, 1H), 4.04 (m, 1H), 4.38 (d, *J* = 5.3 Hz, 1H), 5.30 (s, 2H), 7.22–7.31 (m, 2H), 7.37–7.41 (m, 2H), 7.41–7.49 (m, 3H), 7.74–7.80 (m, 1H), 7.81–7.86 (dd, *J* = 7.7, 1.7 Hz, 2H), 8.01–8.06 (dd,

J = 7.9, 0.9 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): 9.5, 38.1, 58.1, 63.6, 74.3, 124.1, 25.1, 125.6, 126.0, 126.3, 127.0, 127.3, 128.0, 128.0, 128.5, 132.3, 133.9, 134.8, 142.7. ESI- HRMS calcd for $C_{21}H_{24}NO$ $(M+H)^+$: 306.1858. Found: 306.1847.

4.3.2. (1*R*,2*S*)-2-(Methyl(-2-naphthylmethyl)amino)-1-phenyl-1-propanol 9b

The product was recrystallized using dichloromethane and hexanes and was obtained as a white solid (77%). Mp = 86–88 °C. $[\alpha]_D^{23.6} = -43.5$ (c 1.0, $CHCl_3$). IR (Nujol): 3421, 1620, 796 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.04 (d, J = 6.8 Hz, 3H), 1.82 (s, 1H), 2.22 (s, 3H), 2.95–2.99 (m, 1H), 3.76 (dd, J = 19.8, 6.3 Hz, 2H), 4.90 (d, J = 5.1 Hz, 1H), 7.24–7.37 (m, 4H), 7.42–7.46 (m, 3H), 7.63–7.82(m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 9.7, 38.5, 59.2, 63.5, 73.8, 125.4, 125.8, 126.2, 126.8, 126.9, 127.0, 127.6, 127.8, 127.9, 132.6, 133.2, 137.0, 142.6. ESI-HRMS calcd for $C_{21}H_{24}NO$ $(M+H)^+$: 306.1858. Found: 306.1862.

4.3.3. (1*R*,2*S*)-2-((2-Biphenylmethyl)(methyl)amino)-1-phenyl-1-propanol 9c

Yellow oil, 26%. $[\alpha]_D^{22} = +0.4$ (c 1.0, $CHCl_3$). IR: 3409, 3060, 1599, 1218, 1038, 753 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.77–0.79 (d, J = 6.8 Hz, 3H), 1.98 (s, 1H), 2.68–2.74 (dq, J = 6.8, 4.8 Hz, 1H), 3.06 (s, 1H), 3.49–3.56 (ABq, J = 13.6 Hz, 2H), 4.60–4.62 (d, J = 4.8 Hz, 1H), 7.09–7.16 (m, 5H), 7.27–7.36 (m, 4H), 7.33–7.38 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): 9.6, 38.4, 56.7, 63.5, 73.3, 125.9, 126.4, 126.6, 126.8, 127.1, 127.2, 127.4, 127.6, 127.8, 128.1, 128.2, 128.3, 128.6, 128.7, 128.9, 129.4, 129.9, 129.9. ESI-HRMS calcd for $C_{23}H_{25}NO$ $(M+H)^+$: 332.2001. Found: 332.2014.

4.3.4. (1*R*,2*S*)-2-((4-Biphenylmethyl)(methyl)amino)-1-phenyl-1-propanol 9d

The product was purified by recrystallization from hexanes and dichloromethane. Solid flakes (73%). $[\alpha]_D^{24} = -43.5$ (c 1.0, $CHCl_3$). Mp = 65–68 °C. IR ($CHCl_3$): 3422, 3028, 1039 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.01 (d, J = 5.4 Hz, 3H), 1.43 (s, 2H), 2.23 (s, 3H), 2.93–3.00 (m, 1H), 3.65 (d, J = 6.3 Hz, 1H), 4.90 (d, J = 4.0, 1H), 7.24–7.26 (m, 1H), 7.28–7.32 (m, 2H), 7.32–7.36 (m, 4H), 7.41–7.46 (m, 3H), 7.51–7.55 (m, 2H), 7.58–7.61 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 10.0, 38.8, 58.9, 63.5, 73.8, 126.3, 127.0, 127.1, 127.2, 127.3, 128.1, 128.8, 129.1, 138.6, 140.0, 141.0, 142.6. ESI-HRMS calcd for $C_{23}H_{26}NO$ $(M+H)^+$: 332.2014. Found: 332.2016.

4.3.5. (1*R*,2*S*)-2-((4-Fluorobenzyl)(methyl)amino)-1-phenyl-1-propanol 9e

White solid (28%). Mp = 61–62 °C. $[\alpha]_D^{23} = -22.6$ (c 1.0, $CHCl_3$). IR (Nujol): 3304, 2923, 2360, 1602, 1507, 1455, 1221 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.99–1.01 (d, J = 6.8 Hz, 3H), 2.17 (s, 3H), 2.90–2.93 (dq, J = 5.1, 6.8 Hz, 1H), 3.20 (br s, 1H), 3.56–3.57 (AB q, J = 13.4 Hz, 2H), 4.85–4.86 (d, J = 5.1 Hz, 1H), 6.94–6.99 (m, 2H), 7.14–7.17 (m, 2H), 7.27–7.32 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): 9.8, 38.4, 58.4, 63.5, 73.6, 114.9, 115.2, 126.2, 127.1, 128.1, 128.3, 130.0, 130.1, 135.2, 142.5, 142.6, 160.7, 163.1. ESI-HRMS calculated for $C_{17}H_{20}NOF$ $(M+H)^+$: 274.1597. Found: 274.1607.

4.4. (4*S*,5*R*)-2-Cyclohexyl-3,4-dimethyl-5-phenyloxazolidine 20

In a 500 mL round-bottomed flask were added toluene (152 mL), (1*R*,2*S*)-ephedrine (5.00 g, 30.3 mmol), cyclohexane–carboxaldehyde (3.64 mL, 30.3 mmol), and magnesium sulfate (2 g). The reaction mixture was heated at reflux overnight. Then it was cooled to ambient temperature and filtered. The filtrate was evaporated via rotary evaporation. The product was obtained as a yellow liquid (90%). $[\alpha]_D^{23} = -41.3$ (c 0.4, $CHCl_3$). ^{1}H (400 MHz, minor diastereomers were not characterized, $CDCl_3$) δ (ppm): 0.66 (d, J = 6.67 Hz, 3H), 1.13–1.42 (m, 4H), 1.59–1.84 (m, 6H), 1.98–2.02 (m, 1H), 2.27 (s, 3H), 2.73–2.80 (m, 1H), 3.68 (d, J = 2.7 Hz, 1H), 4.94 (d, J = 8.0 Hz, 1H), 7.22–7.33 (m, 5H). ^{13}C (125 MHz, minor diastereomers were not characterized, $CDCl_3$) δ (ppm): 15.5, 26.0, 26.3, 26.6, 26.8, 29.7, 37.4, 40.2, 64.2, 80.9, 101.0, 127.4, 127.8, 127.9, and 139.8. IR (neat) cm^{-1}: 3332, 2927, 1215, 756. ESI-HRMS calcd for $C_{17}H_{26}NO$ $(M+H)^+$: 260.2014. Found: 260.2013.

4.5. (1*R*,2*S*)-2-((Cyclohexylmethyl)(methyl)amino)-1-phenyl-1-propanol 21

In a 500 mL round-bottomed flask were added lithium aluminum hydride (2.00 g, 53.6 mmol) and THF (145 mL). The reaction mixture was heated to 50 °C. To the reaction mixture was added a solution of (4*S*,5*R*)-2-cyclohexyl-3,4-dimethyl-5-phenyloxazolidine (7.00 g, 26.8 mmol) in THF (100 mL) dropwise over a 20-min period. The reaction mixture was then heated at reflux and stirred overnight. Then it was cooled to 0 °C. Water (100 mL) was added drop wise to quench the lithium aluminum hydride. Next, THF was evaporated completely via rotary evaporation. The reaction was quenched with 1 M sodium hydroxide (250 mL) solution and the residue was extracted with ethyl acetate (2 × 250 mL). The organic layer was washed with brine (250 mL) and dried over magnesium sulfate. The solvent was evaporated via rotary evaporation. The residue was purified by flash chromatography using hexanes/ethyl acetate (75:25). The product was obtained as a colorless liquid (32%). $[\alpha]_D^{23} = -17.2$ (c 1.0, $CHCl_3$). ^{1}H (500 MHz, $CDCl_3$) δ (ppm): 0.85 (d, J = 6.9 Hz, 3H), 1.11–1.26 (m, 4H), 1.43 (s, 2H), 1.44–1.49 (m, 1H), 1.66–1.79 (m, 2H), 2.17 (s, 3H), 2.20–2.24 (m, 2H), 2.27–2.33 (m, 2H), 2.71–2.76 (m, 1H), 3.77 (s, 1H), 4.79 (d, J = 4.6 Hz, 1H), 7.20–7.32 (m, 5H). ^{13}C (125 MHz, $CDCl_3$) δ (ppm): 10.1, 26.1, 30.3, 31.4, 31.7, 36.1, 38.8, 62.6, 64.3, 73.1, 126.1, 126.7, 127.9 and 142.4. IR (neat) cm^{-1}: 3411, 2848, 1449, 1040. ESI-HRMS calcd for $C_{17}H_{28}NO$ $(M+H)^+$: 262.2171. Found: 262.2182.

4.6. (1*R*,2*S*)-2-(Methylamino)-1,2-diphenylethanol 24

In a 250 mL round-bottomed flask were placed dichloromethane (117.0 mL) and (1*R*,2*S*)-2-amino-1,2-diphenyl-1-ethanol (5.00 g, 23.4 mmol). The reaction mixture was cooled to 0 °C. To the reaction mixture were added triethylamine (6.60 mL, 46.9 mmol) and methyl chloroformate (1.91, 24.6 mmol). The temperature of the reaction mixture was raised to room temperature and it was allowed to run overnight. The reaction was quenched by the addition of 1 M HCl (100 mL) and the reaction mixture was extracted with dichloromethane (100 mL). The organic layer was washed with brine (50 mL) and dried ($MgSO_4$). The solvents were removed via rotary evaporation and the product was purified by recrystallization (hexanes/EtOAc). The product was obtained as a white solid (88%). The white solid was then dissolved in THF (100 mL) and added dropwise to a preheated 500 mL round-bottomed flask having THF (500 mL) and lithium aluminum hydride (1.56 g, 41.3 mmol) in about 20 min. The reaction mixture was then raised to reflux temperature and stirred overnight. The reaction was quenched by the addition of water (100 mL) at 0 °C. The solvent was evaporated completely via rotary evaporation. The reaction was quenched with 1 M NaOH solution (300 mL) and the residue was extracted with ethyl acetate (250 mL) and the organic layer was washed with brine (200 mL) and dried over magnesium sulfate. The solvent was completely evaporated via rotary evaporation. The residue was recrystallized with ethyl acetate and hexane. The product was obtained as an off-white solid (96%). $[\alpha]_D^{23} = -37.3$ (c 1.0, $CHCl_3$). IR (Nujol): 3510, 1454, 1376, 1056, 698 cm^{-1}. ^{1}H (500 MHz, $CDCl_3$) δ (ppm): 2.28 (s, 3H), 3.77

(d, J = 5.9 Hz, 1H), 4.81 (d, J = 5.9 Hz, 1H), 7.13–7.15 (m, 5H), 7.23–7.28 (m, 5H). ^{13}C (125 MHz, $CDCl_3$) δ (ppm): 34.4, 71.0, 76.6, 126.8, 127.6, 127.7, 128.1, 128.2, 128.3, 139.1, and 140.6. ESI-HRMS calcd for $C_{15}H_{18}NO$ $(M+H)^+$: 228.1388. Found: 228.1395.

4.7. (1*R*,2*S*)-2-(Benzyl(methyl)amino)-1,2-diphenylethanol 25

In a 250 mL round-bottomed flask were added THF (60 mL), (1*R*,2*S*)-2-(benzyl(methyl)amino)-1,2-diphenylethanol (4.00 g, 17.6 mmol), benzyl bromide (2.21 mL, 18.5 mmol), and potassium carbonate (7.30 g, 52.9 mmol). The reaction temperature was raised to reflux temperature and allowed to run for 48 h. The reaction was then cooled to 0 °C. The reaction was quenched with brine (150 mL) and the reaction mixture was extracted with ethyl acetate (150 mL). The organic layer was dried over magnesium sulfate and the solvent was evaporated via rotary evaporation. The yellow residue was purified via flash chromatography using hexane/ethyl acetate (8:2). The product was obtained as a yellow liquid (64%). $[\alpha]_D^{23} = -53.6$ (c 1.2, $CHCl_3$). IR (Nujol): 3510, 705 cm^{-1}. ^{1}H (500 MHz, $CDCl_3$) δ (ppm): 2.21 (s, 3H), 3.26 (d, J = 13.6 Hz, 1H), 3.58 (t, J = 21.1, J = 6.3 Hz, 2H), 5.28 (d, J = 6.3 Hz, 1H), 7.05–7.22 (m, 15H). ^{13}C (125 MHz, $CDCl_3$) δ (ppm): 38.9, 59.4, 72.5, 74.6, 126.5, 126.8, 126.9, 127.3, 127.6, 127.7, 128.0, 128.5, 129.4, 135.9, 138.9, and 141.7. ESI-HRMS calcd for $C_{22}H_{24}NO$ $(M+H)^+$: 318.1858. Found: 318.1859.

4.8. General procedure for the asymmetric 1,2 addition of diethylzinc to aldehydes [(*R*)-1-(2-naphthyl)propan-1-ol 11a–d]

In a 100 mL round-bottomed flask were added ligand (0.098 g, 0.320 mmol), toluene (16 mL), and Et_2Zn (9.6 mL, 9.6 mmol). The reaction mixture was stirred for 30 min at room temperature. To the reaction mixture was added 2-naphthaldehyde (0.5 g, 3.20 mmol). The reaction mixture was allowed to run for 18 h at room temperature and the reaction was quenched with HCl (1 M, 50 mL). The reaction mixture was extracted with EtOAc (50 mL). The organic layer was washed with brine (50 mL) and dried over $MgSO_4$. The solvent was evaporated via rotary evaporation and the product was purified by flash chromatography (hexanes/EtOAc, 98:2). The product was obtained as a colorless oil (88%). $[\alpha]_D^{24.4} = -40.4$ (c 1.38, $CHCl_3$). IR (Nujol): 3257.50, 16001, 1018, 827, 746 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.80 (t, J = 7.5 Hz, 3H), 1.64–1.79 (m. 2H), 3.13 (s, 1H), 4.50 (t, J = 6.6 Hz, 1H), 7.29–7.71 (m, 7H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 9.9, 31.5, 75.6, 124.1, 124.5, 125.5, 125.8, 127.5, 127.7, 127.9, 132.7, 133.0, 141.8.

4.9. *N*-(3-Methoxybenzylidene)-*P*,*P*-diphenylphosphinic amide 17c

In a 250 mL round-bottomed flask were added diphenylphosphinamide (3.00 g, 13.8 mmol) and dichloromethane (55 mL) and cooled to 0 °C. Then triethylamine (5.80 mL, 41.3 mmol), titanium tetrachloride (0.90 mL, 8.3 mmol), and *m*-anisaldehyde (1.70 mL, 13.8 mmol) were added. The reaction mixture was allowed to warm to ambient room temperature, stirred for 1.5 h, and then gravity filtered to remove titanium dioxide. The filtrate was collected and the solvent was removed by rotary evaporation. The residue was treated with diethyl ether (40 mL) and filtered to remove triethylammonium chloride. The filtrate from this process was collected and the solvent was removed. The resultant yellow residue was purified by flash chromatography (hexanes/EtOAc, 4:6). The product was obtained as a yellow liquid (80%). IR (Nujol): 3100, 2998, 1600, 1200 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.85 (s, 3H), 7.09–7.12 (m, 1H), 7.43–7.58 (m, 9H) 7.92–7.96 (m, 4H), 9.26–9.32 (d, J = 30.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, ^{13}C and ^{31}P nuclei coupling observed): 55.3, 113.5, 119.9, 123.5, 128.3, 128.4, 129.8, 131.4, 131.5, 131.6, 131.7, 132.2, 133.2, 136.9, 137.1, 159.9, 173.5, and 173.6. ESI-HRMS calcd for $C_{20}H_{19}NO_2P$ $(M+H)^+$: 336.1153. Found: 336.1148.

4.10. General procedure for the asymmetric 1,2 addition of diethylzinc to diphenylphosphinylimines (*R*)-*P*,*P*-diphenyl-*N*-(1-phenylbutyl)phosphinic amide

In a 100 mL round-bottomed flask were placed toluene (13.0 mL), ligand (0.167 g, 0.66 mmol), *N*-benzylidene-*P*,*P*-diphenylphosphinic amide (0.20 g, 0.66 mmol), and diethylzinc (3.3 mL, 3.3 mmol). The reaction mixture was stirred for 48 h and the reaction was quenched by the addition of an aqueous solution of ammonium chloride (50 mL). The organic layer was diluted with ethyl acetate (50 mL), washed with brine (50 mL), and dried ($MgSO_4$). The solvents were removed via rotary evaporation and the product was purified by flash chromatography (hexanes/EtOAc, 4:6). Colorless oil (53%). Mp: 148–150 °C. $[\alpha]_D^{24.3} = +20.4$ (c 0.6, $CHCl_3$). IR (Nujol): 3161, 1186, 1056, 760 and 723. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.79(t, J = 7.4 Hz, 3 H), 1.79–1.88 (m, 1H), 1.97–2.05 (m, 1H), 3.29 (t, 1H), 4.06–4.13 (m, 1H), 7.14–7.16 (m, 2H), 7.22–7.34 (m, 8H), 7.41–7.49 (m, 1H), 7.73–7.78(m, 2H), 7.84–7.88 (m, 2H). ESI-HRMS calcd for C_{21} $H_{23}NOP$ $(M+H)^+$: 336.1517. Found: 336.1506.

4.11. General procedure for the asymmetric 1,2 addition of dimethylzinc to diphenylphosphinylimines [(*R*)-*N*-(1-(3-Methoxyphenyl)ethyl)-*P*,*P*-diphenylphosphinic amide]

In a 100 mL round-bottomed flask were placed toluene (7.5 mL), the chiral ligand (0.380 g, 1.5 mmol), *N*-(3-methoxybenzylidene)-*P*,*P*-diphenylphosphinic amide (0.50 g, 1.5 mmol), and dimethylzinc (6.3 mL, 7.5 mmol). The reaction mixture was stirred for 48 h and the reaction was quenched by the addition of an aqueous solution of ammonium chloride (50 mL). The organic layer was diluted with ethyl acetate (50 mL), washed with brine (50 mL), and dried ($MgSO_4$). The solvents were removed via rotary evaporation and the product was purified by flash chromatography (hexanes/EtOAc, 4:6). Colorless oil (81%). $[\alpha]_D^{25} = +26.3$ (c 1.03, $CHCl_3$). HPLC (Chiralcel AD column, 80:20 (hexanes/IPA), 1.0 mL/min): t_R (7.0) and t_S (10.3). IR (Nujol): 3200, 3010, 2990, 1580, 1200 (cm^{-1}). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.54 (d, J = 6.8 Hz, 3H), 3.45 (s, 1H), 3.75 (s, 3H), 4.31–4.38 (m, 1H), 6.75- 6.88 (m, 1H), 7.19–7.47 (m, 9H), 7.79–7.91 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) 25.9, 51.1, 55.2, 55.5, 111.8, 112.1, 118.1, 128.1, 128.2, 128.3, 129.4, 131.4, 131.5, 131.6, 1321.8, 132.3, 146.6, 146.7, 159.5. ESI-HRMS calcd for $C_{21}H_{23}NO_2P$ $(M+H)^+$: 352.1466. Found: 352.1463.

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