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β-Amino alcohols derived from (1*R*,2*S*)-norephedrine and (1*S*,2*S*)-pseudonorephedrine as catalysts in the asymmetric addition of diethylzinc to aldehydes

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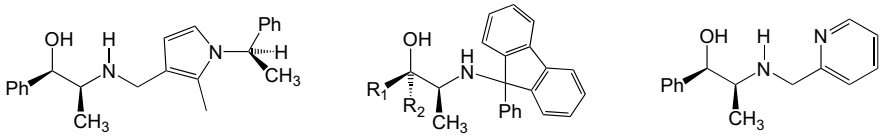
Abstract—A family of *N*-alkylnorephedrine and *N*-alkylpseudonorephedrine derived ligands were prepared and applied in the asymmetric alkylation of benzaldehyde using diethylzinc. The absolute configuration of the addition product was directed primarily by the benzylic position of the *Ephedra* alkaloid, while the magnitude of the enantiomeric ratio was heavily influenced by the nitrogen substituent. However, sterically demanding substituents at the nitrogen position caused the enantioselectivity to be the same for the two diastereomeric systems. Among the ligands that were prepared, it was determined that the *N*-cyclooctylpseudonorephedrine derivative **7b** yielded the highest enantiomeric ratios (87.5:12.5 to 91.0:9.0) when applied in the catalytic asymmetric addition of diethylzinc to aldehydes.

1. Introduction

The catalytic enantioselective addition of diorganozinc reagents to carbonyl compounds has been examined using many different types of β-aminoalcohols as asymmetric templates.[1–4] The β-aminoalcohols derived from the *Ephedra* alkaloids have enjoyed a large degree of success with their widespread use[5] in this field. Among the *Ephedra*-derived ligands that have been developed, the *N*,*N*-dialkylnorephedrine derivatives have been demonstrated to be very effective catalysts for the enantioselective addition of diorganozinc reagents to aldehydes and ketones.[5,6] In contrast, mono-*N*-alkylated norephedrine derivatives have exhibited only modest degrees of success in terms of their ability to induce asymmetry in this catalysis reaction (Fig. 1).[7]

In this context, Sardina et al. described a detailed study that evaluated the impact of the substituents about the β-aminoalcohol framework for a variety of *N*-fluorenylphenyl substrates.[7b] However, the work described by Sardina et al. only has two examples that represented mono-*N*-alkylated derivatives from the *Ephedra* family. We became interested in examining further the scope and utility of mono-*N*-alkylated *Ephedra* derivatives in the catalytic enantioselective addition of diethylzinc to aldehydes. Herein we report on the synthesis and testing of a series of



1[7a] (Unaleroglu et al.) **2a:** R_1 = Ph; R_2 = H[7b] (Sardina et al.) **2b:** R_1 = H; R_2 = Ph[7b] **3**[7c] (Wu et al.)

Figure 1.

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norephedrine and pseudonorephedrine-based derivatives in their ability to serve as catalysts.

2. Results and discussion

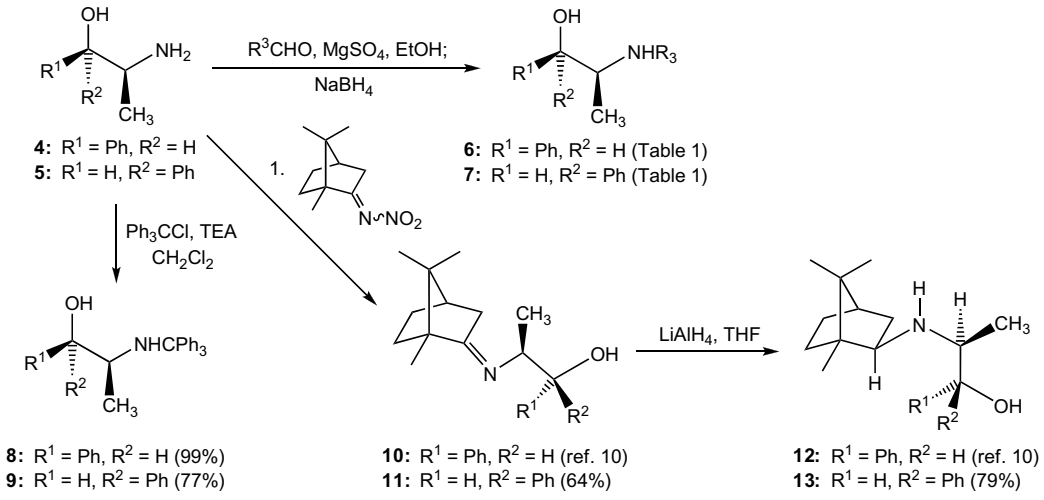
(1*R*,2*S*)-Norephedrine **4** and (1*S*,2*S*)-pseudonorephedrine **5**[8] were reductively alkylated with a variety of aldehydes and ketones to afford derivatives **6** and **7**, respectively (Scheme 1).[9] The norephedrine and pseudonorephedrine starting materials were also directly alkylated with triphenylmethyl chloride to yield derivatives **8** and **9**, respectively. In addition, the *Ephedra* alkaloids **4** and **5** were reacted with the *N*-nitroimine of D-camphor[10] to generate imines **10** and **11**. These products were reduced stereoselectively with lithium aluminum hydride to afford camphor-based β-aminoalcohols **12** and **13**. The chemical yields for these reactions are listed in Table 1.

Once the ligands had been prepared, they were employed in the asymmetric 1,2-addition of diethylzinc to benzaldehyde. The catalysts **6a**–**w**, **7a**–**c**, **8**, **9**, **12**, and **13** were employed at a level of 10 mol % with 3 equiv of Et_2Zn relative to benzaldehyde. The use of 3 equiv of Et_2Zn afforded slightly improved yields and enantiomeric ratios over the use of 2 equiv. (1*R*,2*S*)-Ephedrine **14** and (1*S*,2*S*)-pseudoephedrine **15** were also employed as catalysts as equivalents to *N*-methylnorephedrine and *N*-methylpseudonorephedrine, respectively. The results of these reactions are listed in Table 2. The (1*R*,2*S*)-norephedrine-derived catalysts **6a**–**w** primarily afforded the (*R*)-configuration in the product 1-phenyl-1-propanol, whereas the (1*S*,2*S*)-pseudonorephedrine-based catalysts **7a**–**c** provided the corresponding (*S*)-enantiomer. These observations were in agreement with the observations of Sardina et al.[7b] The norephedrine catalysts **6a**–**w** afforded an average enantiomeric ratio of 80:20. The examples that gave the lower enantiomeric ratios in this series included **6f**, **6g**, **6l**, and **6u**–**w**, with values ranging from 55:45 to 74:26. In the case of **6g**, the presence of the phenolic position most likely led to erosion of the enantioselectivity via deprotonation by diethylzinc, yielding a catalytic site remote from any asymmetry elements. All the remaining ligands, **6f**, **6l**, and **6u**–**w**, shared the common aspect of a nitrogen substituent that was sterically demanding (-anthryl, -*o*-phenylbenzyl, 2-indanyl, cyclooctyl, and -cyclopentyl, respectively). Interestingly, when the nitrogen substituent was cyclohexyl (catalyst **6t**), the enantiomeric ratio of the asymmetric addition was 84.5:15.5. Based on the proposed literature mechanisms[7b,11] of the ligand-catalyzed addition of diorganozinc compounds to aldehydes, it was proposed that the larger substituents on the nitrogen caused the putative intermediate **16a** responsible for the catalysis process to be less stable (Fig. 2). This would give

Table 1. Norephedrine and pseudonorephedrine derivatives

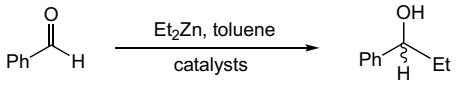
Entry	Ligand	R_3	Yield[a] (%)
1	**6a**	-$(CH_2)_7CH_3$	23
2	**6b**	-$CH_2C(CH_3)_3$	59
3	**6c**	-$CH_2C_6H_5$	99
4	**6d**	-1-$CH_2C_{10}H_7$(naphthyl)	63
5	**6e**	-2-$CH_2C_{10}H_7$(naphthyl)	79
6	**6f**	-9-$CH_2C_{14}H_9$(anthryl)	52
7	**6g**	-*o*-$CH_2C_6H_4OH$	58
8	**6h**	-*o*-$CH_2C_6H_4OCH_3$	61
9	**6i**	-*m*-$CH_2C_6H_4OCH_3$	71
10	**6j**	-3,4-$CH_2C_6H_4(OCH_3)_2$	31
11	**6k**	-*o*-$CH_2C_6H_4C_2H_5$	23
12	**6l**	-*o*-$CH_2C_6H_4C_6H_5$(biphenyl)	31
13	**6m**	-*p*-$CH_2C_6H_4C_6H_5$(biphenyl)	49
14	**6n**	-2,4,6-$CH_2C_6H_2(CH_3)_3$	77
15	**6o**	-3,5-di-*tert*-butyl-2-methoxybenzyl	59
16	**6p**	-2-OBn-3,5-di-*tert*-butylbenzyl	73
17	**6q**	-3,5-$CH_2C_6H_3Br_2$	85
18	**6r**	-$CH(CH_3)_2$	54
19	**6s**	-$CH(CH_2CH_3)_2$	40
20	**6t**	-cyclohexyl	85
21	**6u**	-2-indanyl	22
22	**6v**	-C_8H_{15}(-cyclooctyl)	39
23	**6w**	-C_5H_9(-cyclopentyl)	49
24	**7a**	-*o*-$CH_2C_6H_4OCH_3$	20
25	**7b**	-C_8H_{15}(-cyclooctyl)	39
26	**7c**	-9-$CH_2C_{14}H_9$(anthryl)	95

[a] Isolated yields after either flash chromatography or recrystallization.



Scheme 1. Norephedrine and pseudonorephedrine derivatives.

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



Entry	Ligand	er[b]	Config.[c]
1	**6a**	84.5:15.5	(*R*)
2	**6b**	85.0:15.0	(*R*)
3	**6c**	84.5:15.5	(*R*)
4	**6d**	75.0:25.0	(*R*)
5	**6e**	85.0:15.0	(*R*)
6	**6f**	67.5:32.5	(*R*)
7	**6g**	54.0:46.0	(*R*)
8	**6h**	83.0:17.0	(*R*)
9	**6i**	80.0:20.0	(*R*)
10	**6j**	82.5:17.5	(*R*)
11	**6k**	82.5:17.5	(*R*)
12	**6l**	74.0:26.0	(*R*)
13	**6m**	82.0:18.0	(*R*)
14	**6n**	80.0:20.0	(*R*)
15	**6o**	90.0:10.0	(*R*)
16	**6p**	89.5:10.5	(*R*)
17	**6q**	80.5:19.5	(*R*)
18	**6r**	87.0:13.0	(*R*)
19	**6s**	85.0:15.0	(*R*)
20	**6t**	84.5:15.5	(*R*)
21	**6u**	64.5:35.5	(*R*)
22	**6v**	55.0:45.0	(*R*)
23	**6w**	65.5:34.5	(*R*)
24	**7a**	56.0:44.0	(*S*)
25	**7b**	90.0:10.0	(*S*)
26	**7c**	74.0:26.0	(*R*)
27	**8**	60.0:40.0	(*S*)
28	**9**	94.0:6.0	(*S*)
29	**12**	73.5:26.5	(*R*)
30	**13**	73.5:26.5	(*R*)
31	**14**	78.5:21.5	(*R*)
32	**15**	57.5:42.5	(*S*)

[a] All reactions, except entries 27 and 28, went to completion as determined by ^{1} NMR spectroscopy.

[b] The enantiomeric ratios [er (major:minor)] were determined via CSP HPLC using a Chiralcel-OD column.

[c] The configuration was determined by comparison with HPLC literature values.[12]

rise to an alternate reaction pathway **20a→23a** where the asymmetric induction would be dependent on conformational factors associated with an open chain system. It would be likely that the open chain pathway would not exhibit the same level of stereoselectivity as the closed ring pathway **16a→19a**, and the prediction of the dominant stereoisomer would also be compromised.

In contrast to the enantioselectivities obtained with norephedrine catalysts **6**, the pseudonorephedrine-based catalysts **7** and **15** primarily yielded the (*S*)-configuration in the product. In addition, pseudonorephedrine-based catalyzed reactions exhibited enantioselectivities that were low when the nitrogen substituent was small and higher when the substituent was larger. Interestingly, the use of the pseudonorephedrine catalyst **7c** ($R_3 = CH_2$-9-anthryl) and the norephedrine catalyst **6f** ($R_3 = CH_2$-9-anthryl) each afforded the (*R*)-alcohol product in enantiomeric ratios of 74:26 and 67.5:32.5, respectively. In the same fashion, the norephedrine and pseudonorephedrine camphor-based derivatives **12** and **13** each gave the (*R*)-alcohol in an enantiomeric ratio of 73.5:26.5. From these examples, it would seem that the stereochemistry of the benzylic component of the catalysts has a compromised role in directing the asymmetric addition of the ethyl group to the benzaldehyde substrate when the nitrogen is sterically demanding. This observation is limited in that it only reveals a small part of a much larger question for which a complete mechanistic rationale has not been developed.

In the context of large nitrogen substituents, the *N*-trityl catalysts **8** and **9** generated the (*S*)-configured product in enantiomeric ratios of 60:40 and 94:6, respectively, when applied in the diethylzinc addition reaction. The change in the configuration of the product suggested a further change in the reaction pathway leading to product formation. These catalytic processes did not go to completion (32% completion for catalyst **8** and 76% completion for catalyst **9**), and generated significant amounts of benzyl alcohol (>10%), the product of direct reduction by diethylzinc.[13] Based on these combined results, it was determined that the *N*-trityl catalysts were not suitable for use in the enantioselective addition of diethylzinc to aldehydes.

The derivative that gave the best enantioselectivity was the *N*-cyclooctylpseudonorephedrine catalyst **7b**. This ligand was used to catalyze the asymmetric addition of diethylzinc to a series of aldehydes and this process afforded a range of enantiomeric ratios from 87.5:12.5 to 91.0:9.0 (Table 3). It is proposed that **7b** follows the mechanistic pathway as depicted in Figure 2 and that the dominant pathway is the closed ring system (**16b→19b**).

3. Conclusion

Norephedrine and pseudonorephedrine were employed as templates for the preparation of a variety of *N*-substituted *Ephedra* catalysts. It was determined that the norephedrine-based catalysts **6** afforded an average enantiomeric ratio of 80:20 when employed in the diethylzinc addition reaction with benzaldehyde. When the nitrogen substituent was large in size (-methylanthryl, -*o*-phenylbenzyl, -bornyl) the enantioselectivity was diminished. The pseudonorephedrine-based catalysts favored the formation of the (*S*)-alcohol product. Finally, sterically demanding substituents caused both diastereomeric derivatives to afford the alcohol product with the same configuration.

4. Experimental

4.1. General remarks

Toluene was purchased as an anhydrous reagent and used without further purification. All reactions were run under a nitrogen atmosphere. Unless otherwise noted, all ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using an NMR spectrometer operating at 400 MHz and 100 MHz, respectively. Chemical shifts are reported in parts per

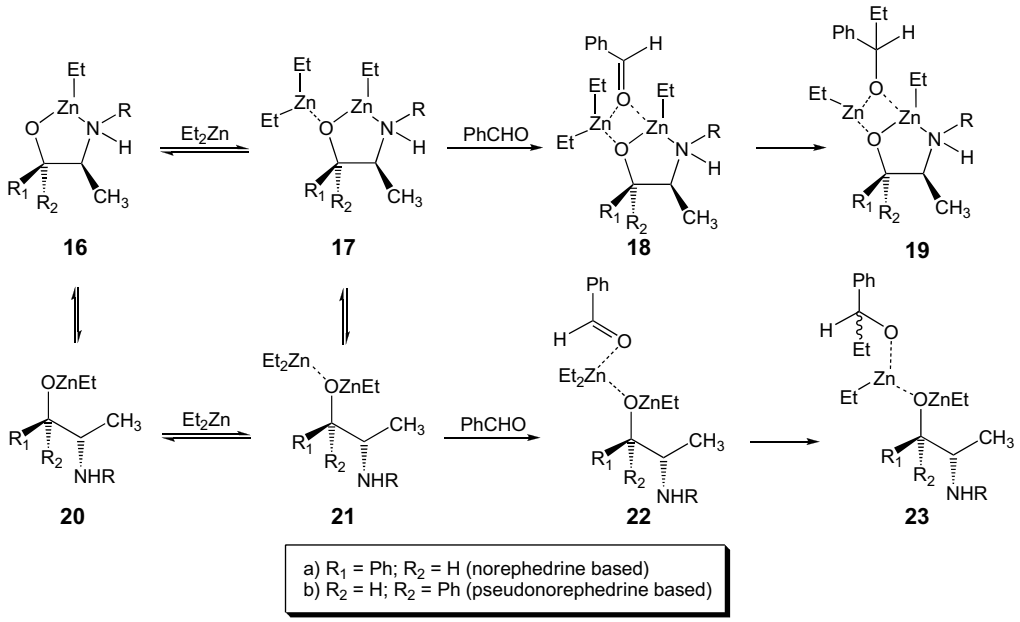
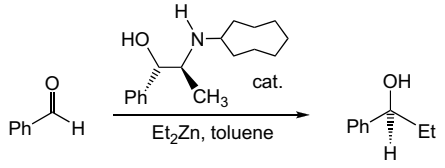


Figure 2. Proposed intermediates for the norephedrine-diethylzinc-based catalysis.

Table 3. Catalytic asymmetric addition of diethylzinc to benzaldehyde[a]



Entry	R	Yield[a] (%)	er[b]	Config.[c]
1	-C_6H_5	52	90.0:10.0	(*S*)
2	-1-$C_{10}H_9$(-1-naphthyl)	40	91.0:9.0	(*S*)
3	-2-$C_{10}H_9$(-2-naphthyl)	78	91.0:9.0	(*S*)
4	-*p*-$C_6H_4OCH_3$	40	89.5:10.5	(*S*)
5	-*trans*-CH=CHC_6H_5	73	87.5:12.5	(*S*)

[a] All yields are after flash chromatography.
[b] The enantiomeric ratios [er (major:minor)] were determined via CSP HPLC using a Chiralcel-OD column.
[c] The configuration was determined by comparison with HPLC literature values.[12]

million (δ scale), and coupling constants (J values) are listed 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 either as a Nujol mull, a neat liquid, or in $CHCl_3$. Melting points were recorded on a Mel-Temp apparatus and are uncorrected. Optical activities were measured at 589 nm using a digital polarimeter.

4.2. General procedure for the reductive alkylation of (1*R*,2*S*)-norephedrine

To a flame-dried, nitrogen-purged flask were added (1*R*,2*S*)-norephedrine (1.05 g, 6.96 mmol), ethanol (10 mL), and a selected aldehyde (10.4 mmol). The mixture was allowed to stir at room temperature for 18 h, and then cooled to 0 °C. After cooling, sodium borohydride (0.53 g, 13.9 mmol) was added and allowed to stir for 90 min. The reaction solvent was removed under reduced pressure. The product was extracted with ethyl acetate (50 mL × 3) and sodium hydroxide (1 M, 50 mL), washed with brine (50 mL), and dried with magnesium sulfate. The solvent was removed under reduced pressure and the product was recrystallized with ethyl ether and hexanes (1:2).

4.2.1. (1*R*,2*S*)-2-(*n*-Octylamino)-1-phenylpropan-1-ol 6a. Using octanal, the title compound was obtained as a white solid (23%). $[\alpha]_D^{25} = +15.1$ (c 0.12, $CHCl_3$). Mp = 52–53 °C. ^{1}H NMR ($CDCl_3$): δ 0.84 (d, $J = 6.6$ Hz, 3H), 0.88 (t, $J = 6.6$ Hz, 3H), 1.29 (m, 4H), 1.52 (m, 4H), 2.72 (m, 4H), 2.95 (dq, $J = 3.9$, 6.6 Hz, 1H), 4.83 (d, $J = 3.5$ Hz, 1H), 7.24–7.26 (m, 3H), 7.33 (d, $J = 4.3$ Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 14.1, 22.6, 27.3, 29.2, 29.4, 29.9, 30.0, 31.8, 47.1, 58.6, 72.7, 126.0, 127.0, 128.1, 141.3. IR ($CHCl_3$): 3438, 1132, 989, 741, 701 cm^{-1}. ESI-HRMS: ($M+H^+$) calcd for $C_{17}H_{30}NO$, 264.2327; found, 264.2324.

4.2.2. (1*R*,2*S*)-2-(2,2-Dimethylpropylamino)-1-phenyl-1-propanol 6b. Using pivaldehyde, the title compound was obtained as a white solid. Mp: 82–84 °C. $[\alpha]_D = -12.0$ (c 1.80, $CHCl_3$). Characterization data for this compound matched exactly with the identical compound found in the literature.[14a]

4.2.3. (1*R*,2*S*)-2-(Benzylamino)-1-phenyl-1-propanol 6c. Using benzaldehyde, the title compound was obtained as a clear oil (99%). $[\alpha]_D^{25} = -30.0$ (c 0.86, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.86 (d, $J = 6.6$ Hz, 3H), 3.01 (dq, $J = 3.9$, 6.6 Hz, 1H), 3.89 (s, 2H), 4.80 (d, $J = 3.2$ Hz, 1H), 7.26–7.35 (m, 10H). ^{13}C NMR ($CDCl_3$): δ14.7, 51.4, 58.1, 73.9, 126.6, 127.4, 127.5, 128.4, 128.5, 128.9, 140.3, 142.2. IR (neat): 3406, 1603, 1028, 910, 732, 700 cm^{-1}. ESI-HRMS: ($M+H^+$) calcd for $C_{16}H_{20}NO$, 242.1545; found, 242.1535.

4.2.4. (1*R*,2*S*)-2-(Naphthalen-1′-ylmethylamino)-1-phenylpropan-1-ol 6d. Using 1-naphthaldehyde, the title compound was obtained as a clear oil (63%). $[\alpha]_D^{25} = -28.2$ (*c* 0.59, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.90 (d, $J = 6.3$ Hz, 3H), 3.12 (dq, $J = 4.3$, 6.6 Hz, 1H), 4.34 (AB spin system, $J = 12.5$, 20.7 Hz, 2H), 4.88 (d, $J = 3.9$ Hz, 1H), 7.23–7.27 (m, 2H), 7.33 (d, $J = 4.3$ Hz, 3H), 7.42–7.57 (m, 4H), 7.80 (d, $J = 7.8$ Hz, 1H), 7.88 (d, $J = 7.8$ Hz, 1H), 8.12 (d, $J = 8.2$ Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 14.6, 49.1, 58.4, 73.3, 123.4, 125.3, 125.6, 126.0, 126.2, 126.9, 127.9, 128.0, 128.7, 131.6, 133.8, 135.5, 141.3. IR (neat): 3402, 1219, 1112, 755, 701 cm^{-1}. ESI-HRMS: ($M+H^+$) calcd for $C_{20}H_{22}NO$, 292.1701; found, 292.1711.

4.2.5. (1*R*,2*S*)-2-(Naphthalen-2′-ylmethylamino)-1-phenylpropan-1-ol 6e. Using 2-naphthaldehyde, the title compound was obtained as a white solid (79%). $[\alpha]_D^{25} = -11.4$ (*c* 0.64, $CHCl_3$). Mp = 84–86 °C. ^1H NMR ($CDCl_3$): δ 0.89 (d, $J = 6.6$ Hz, 3H), 3.04 (dq, $J = 3.9$, 6.3 Hz, 1H), 4.04 (s, 2H), 4.82 (d, $J = 3.9$ Hz, 1H), 7.24–7.32 (m, 3H), 7.45–7.49 (m, 2H), 7.75 (br s, 1H), 7.81–7.84 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 14.6, 51.2, 57.7, 73.2, 125.6, 126.1, 126.3, 126.4, 127.0, 127.6, 128.0, 128.2, 132.6, 133.3, 137.5, 141.3. IR ($CHCl_3$): 3304, 1601, 1139, 1000, 902, 819, 748, 702 cm^{-1}. ESI-HRMS: ($M+H^+$) calcd for $C_{20}H_{22}NO$, 292.1701; found, 292.1695.

4.2.6. (1*R*,2*S*)-2-(Anthracen-9′-ylmethylamino)-1-phenylpropan-1-ol 6f. Using 9-anthraldehyde, the title compound was obtained as a yellow solid (52%). $[\alpha]_D^{25} = -71.5$ (*c* 0.55, $CHCl_3$). Mp = 106–107 °C. ^1H NMR ($CDCl_3$): δ 0.93 (d, $J = 6.6$ Hz, 3H), 3.26 (dq, $J = 4.3$, 6.3 Hz, 1H), 4.80 (AB spin system, $J = 12.0$, 13.7 Hz, 2H), 4.98 (d, $J = 4.3$ Hz, 1H), 7.23–7.33 (m, 2H), 7.44–7.55 (m, 2H), 8.00 (d, $J = 8.6$ Hz, 2H), 8.28 (d, $J = 9.0$ Hz, 2H) 8.41 (s, 1H). ^{13}C NMR ($CDCl_3$; An extra aromatic signal is detected and is attributed to asymmetry): δ 14.9, 43.5, 59.3, 73.2, 123.7, 124.9, 126.1, 126.3, 127.0, 127.4, 128.1, 129.2, 130.2, 130.8, 131.5, 133.9, 141.2. IR ($CHCl_3$): 3410, 1603, 1159, 1029, 841, 728, 703 cm^{-1}. ESI-HRMS: ($M+H^+$) calcd for $C_{24}H_{24}NO$, 342.1858; found, 342.1848.

4.2.7. 2-{[(1*R*,2*S*)-1-Hydroxyl-1-phenylpropan-2-ylamino]-methyl}phenol 6g. Using salicylaldehyde, the title compound was obtained as a clear oil (58%). $[\alpha]_D^{25} = +11.2$ (*c* 0.57, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.05 (d, $J = 6.3$ Hz, 3H), 3.02 (dq, $J = 4.3$, 6.6 Hz, 1H), 4.04 (AB spin system, $J = 14.1$, 48.0 Hz, 2H), 4.87 (d, $J = 3.9$ Hz, 1H), 6.78 (t, $J = 7.4$ Hz, 1H), 6.83 (d, $J = 7.4$ Hz, 1H), 6.99 (d, $J = 8.6$ Hz, 1H), 7.17 (t, $J = 6.6$ Hz, 1H), 7.26–7.36 (m, 5H). ^{13}C {^1H} NMR ($CDCl_3$): δ 13.7, 49.8, 57.3, 75.1, 116.4, 119.0, 122.7, 126.1, 127.5, 128.1, 128.3, 128.6, 141.4, 158.0. IR (neat): 3420, 1590, 1103, 1035, 753, 702 cm^{-1}. ESI-HRMS: ($M+H^+$) calcd for $C_{16}H_{20}NO_2$, 258.1494; found, 258.1487.

4.2.8. (1*R*,2*S*)-2-(2′-Methoxybenzylamino)-1-phenylpropan-1-ol 6h. Using *o*-anisaldehyde, the title compound was obtained as a white solid (61%). $[\alpha]_D^{25} = -17.6$ (*c* 0.62, $CHCl_3$). Mp = 90–92 °C. ^1H NMR ($CDCl_3$): δ 0.81 (d, $J = 6.6$ Hz, 3H), 2.88 (dq, $J = 3.9$, 6.6 Hz, 1H), 3.75 (s, 3H), 3.84 (s, 2H), 4.77 (d, $J = 3.9$ Hz, 1H), 6.83 (d, $J = 8.2$ Hz, 1H), 6.91 (t, $J = 7.4$ Hz, 1H), 7.20–7.29 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 14.5, 46.5, 55.0, 57.1, 72.9, 110.2, 120.3, 126.0, 126.8, 127.9, 128.3, 129.7, 141.6, 157.6. IR (Nujol mull): 3302, 1600, 1244, 1053, 1029, 756, 700 cm^{-1}. ESI-HRMS: ($M+H^+$) calcd for $C_{17}H_{22}NO_2$, 272.1651; found, 272.1644.

4.2.9. (1*R*,2*S*)-2-(3′-Methoxybenzylamino)-1-phenylpropan-1-ol 6i. Using *m*-anisaldehyde, the title compound was obtained as a clear oil (71%). $[\alpha]_D^{25} = -11.9$ (*c* 0.63, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.85 (d, $J = 6.6$ Hz, 3H), 2.99 (dq, $J = 3.9$, 6.3 Hz, 1H), 3.81 (s, 3H), 3.85 (s, 2H), 4.78 (d, $J = 3.9$ Hz, 1H), 6.80–6.83 (m, 1H), 6.88–6.92 (m, 2H), 7.23–7.35 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 14.4, 50.9, 54.9, 57.5, 73.2, 112.3, 113.5, 120.1, 126.0, 126.8, 127.9, 129.3, 141.4, 141.6, 159.6. IR (neat): 3404, 1602, 1154, 1045, 780, 738, 701 cm^{-1}. ESI-HRMS: ($M+H^+$) calcd for $C_{17}H_{22}NO_2$, 272.1651; found, 272.1659.

4.2.10. (1*R*,2*S*)-2-(3′,4′-Dimethoxybenzylamino)-1-phenylpropan-1-ol 6j. Using 3,4-dimethoxybenzaldehyde, the title compound was obtained as a clear oil (47%). $[\alpha]_D^{25} = -11.2$ (*c* 0.60, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.86 (d, $J = 6.6$ Hz, 3H), 3.00 (dq, $J = 3.9$, 6.6 Hz, 1H), 3.83 (s, 2H), 3.88 (s, 3H), 3.90 (s, 3H), 4.79 (d, $J = 3.9$ Hz, 1H), 6.83–6.88 (m, 3H), 7.24–7.33 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.2, 50.5, 55.4, 55.5, 57.3, 73.2, 110.8, 111.0, 119.8, 125.8, 126.6, 127.7, 132.4, 141.4, 147.7, 148.7. IR (neat): 3388, 1592, 1139, 1029, 765, 702 cm^{-1}. ESI-HRMS: ($M+H^+$) calcd for $C_{18}H_{24}NO_3$, 302.1756; found, 302.1756.

4.2.11. (1*R*,2*S*)-2-(2′-Ethylbenzylamino)-1-phenylpropan-1-ol 6k. Using 2-ethylbenzaldehyde, the title compound was obtained as a clear oil (23%). $[\alpha]_D^{25} = -22.2$ (*c* 0.43, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.87 (d, $J = 6.6$ Hz, 3H), 1.25 (t, $J = 7.4$ Hz, 3H), 2.71 (q, $J = 7.4$ Hz, 2H), 3.03 (dq, $J = 3.9$, 6.3 Hz, 1H), 3.88 (AB spin system, $J = 12.5$, 17.5 Hz, 2H), 4.81 (d, $J = 3.9$ Hz, 1H), 7.18–7.33 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 14.7, 15.5, 25.3, 48.9, 58.5, 73.0, 126.0, 126.1, 127.0, 127.5, 128.1, 128.7, 129.0, 137.2, 141.2, 142.4. IR (neat): 3404, 1604, 1199, 756, 705 cm^{-1}. ESI-HRMS: ($M+H^+$) calcd for $C_{18}H_{24}NO$, 270.1858; found, 270.1862.

4.2.12. (1*R*,2*S*)-2-(*o*-Biphenylmethylamino)-1-phenylpropan-1-ol 6l. Using *o*-biphenylcarboxaldehyde, the title compound was obtained as a clear oil (31%). $[\alpha]_D^{25} = -12.7$ (*c* 0.51, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.65 (d, $J = 6.6$ Hz, 3H), 2.74 (dq, $J = 3.9$, 6.6 Hz, 1H), 3.83 (AB spin system, $J = 12.9$, 18.4 Hz, 2H), 4.57 (d, $J = 3.9$ Hz, 1H), 7.19–7.43 (m, 14H). ^{13}C NMR ($CDCl_3$): δ 14.3, 49.0, 57.8, 72.9, 126.0, 126.8, 127.1, 127.5, 127.9, 128.2, 128.7, 129.3, 130.1, 137.2, 141.1, 141.2, 141.9. IR (neat): 3419, 1600, 1198, 1010, 753, 701 cm^{-1}. ESI-HRMS: ($M+H^+$) calcd for $C_{22}H_{24}NO$, 318.1858; found, 318.1854.

4.2.13. (1*R*,2*S*)-2-(*p*-Biphenylmethylamino)-1-phenylpropan-1-ol 6m. Using *p*-biphenylcarboxaldehyde, the title compound was obtained as a white solid (49%). $[\alpha]_D^{25} = -22.9$ (*c* 0.61, $CHCl_3$). Mp = 84–86 °C. ^1H NMR ($CDCl_3$): δ 0.88 (d, $J = 6.6$ Hz, 3H), 3.04 (dq, $J = 3.9$, 6.3 Hz, 1H), 3.93 (s, 2H), 4.83 (d, $J = 3.5$ Hz, 1H), 7.24–7.46 (m,

10H), 7.57–7.61 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 14.7, 50.9, 57.8, 73.1, 126.1, 127.1, 127.3, 127.3, 128.1, 128.5, 128.8, 139.1, 140.2, 140.8, 141.2. IR (Nujol mull): 1601, 1120, 1072, 824, 754, 696 cm^{-1}. ESI-HRMS: ($M+H^+$) calcd for $C_{22}H_{24}NO$, 318.1858; found, 318.1861.

4.2.14. (1*R*,2*S*)-1-Phenyl-2-(2′,4′,6′-trimethylbenzylamino)-propan-1-ol 6n. Using mesitaldehyde, the title compound was obtained as a clear oil (77%). $[\alpha]_D^{25} = -32.7$ (*c* 0.61, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.86 (d, $J = 6.6$ Hz, 3H), 2.26 (s, 3H), 2.34 (s, 6H), 3.02 (dq, $J = 3.9$, 6.3 Hz, 1H), 3.82 (AB spin system, $J = 11.7$, 13.3 Hz, 2H), 4.80 (d, $J = 3.9$ Hz, 1H), 6.85 (s, 2H), 7.22–7.31 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.8, 19.4, 20.8, 45.5, 59.2, 73.0, 126.0, 127.0, 128.0, 129.0, 133.1, 136.7, 136.8, 141.2. IR (neat): 3417, 1613, 1217, 1109, 851, 758, 701 cm^{-1}. ESI-HRMS: ($M+H^+$) calcd for $C_{19}H_{26}NO$, 284.2014; found, 284.2015.

4.2.15. (1*R*,2*S*)-2-(3′,5′-Di-*tert*-butyl-2′-methoxybenzylamino)-1-phenylpropan-1-ol 6o. Using 3,5-di-*tert*-butyl-2-methoxybenzaldehyde, the title compound was obtained as a clear oil (59%). $[\alpha]_D^{25} = +1.7$ (*c* 0.56, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.84 (d, $J = 6.3$ Hz, 3H), 1.31 (s, 9H), 1.40 (s, 9H) 2.91 (dq, $J = 3.9$, 6.3 Hz, 1H), 3.77 (s, 3H), 3.94 (AB spin system, $J = 13.3$, 19.1 Hz, 2H), 4.82 (d, $J = 3.9$ Hz, 1H), 7.20–7.31 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 14.5, 31.1, 31.5, 34.5, 35.2, 47.0, 58.0, 61.7, 73.1, 123.3, 125.1, 126.1, 126.9, 128.0, 132.2, 141.4, 141.9, 145.8, 155.8. IR (neat): 3354, 1602, 1230, 1120, 881, 759, 701 cm^{-1}. ESI-HRMS: ($M+H^+$) calcd for $C_{25}H_{38}NO_2$, 384.2903; found, 384.2902.

4.2.16. (1*R*,2*S*)-2-(2′-(Benzyloxy)-3′,5′-di-*tert*-butyl-2′-methoxybenzylamino)-1-phenylpropan-1-ol 6p. Using 2-benzyloxy-3,5-di-*tert*-butylbezaldehyde, the title compound was obtained as a clear oil (73%). $[\alpha]_D^{25} = -2.7$ (*c* 0.61, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.75 (d, $J = 6.3$ Hz, 3H), 1.33 (s, 9H), 1.44 (s, 9H), 2.82 (dq, $J = 3.9$, 6.6 Hz, 1H), 3.95 (AB spin system, $J = 13.3$, 32.4 Hz, 2H), 4.74 (d, $J = 3.9$ Hz, 1H), 4.97 (s, 2H), 7.20–7.48 (m, 12H). ^{13}C NMR ($CDCl_3$): δ 14.2, 31.2, 31.5, 34.5, 35.4, 47.0, 57.9, 73.2, 75.4, 123.5, 125.3, 126.0, 126.4, 126.9, 127.5, 127.9, 128.4, 132.5, 137.8, 141.4, 142.1, 146.1, 154.2. IR (neat): 3408, 1604, 1124, 1017, 734, 701 cm^{-1}. ESI-HRMS: ($M+H^+$) calcd for $C_{31}H_{42}NO_2$, 460.3216; found, 460.3209.

4.2.17. (1*R*,2*S*)-2-(3,5-Dibromobenzylamino)-1-phenylpropan-1-ol 6q. Using 3,5-dibromobenzaldehyde, the title compound was obtained as a clear oil (85%). $[\alpha]_D^{25} = -5.4$ (*c* 0.81, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.89 (d, $J = 6.6$ Hz, 3H), 2.93 (dq, $J = 3.9$, 6.3 Hz, 1H), 3.79 (AB spin system, $J = 13.7$, 19.1 Hz, 2H), 4.72 (d, $J = 3.9$ Hz, 1H), 7.24–7.39 (m, 7H), 7.56 (t, $J = 2.0$ Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 14.6, 50.0, 57.7, 73.8, 122.9, 126.0, 127.2, 128.1, 129.7, 132.6, 141.1, 144.2. IR (neat): 3404, 1586, 1198, 1101, 853, 741, 702 cm^{-1}. EI-HRMS: ($M+H^+$) calcd for $C_{16}H_{18}NOBr_2$, 397.9755; found, 397.9746.

4.2.18. (1*R*,2*S*)-2-Isopropylamino-1-phenyl-1-propanol 6r. Using acetone, the title compound was obtained as a white solid. $[\alpha]_D^{25} = -15.9$ (*c* 0.69, $CHCl_3$). Mp = 99–101 °C. ^{1}H NMR: δ 0.80 (d, $J = 6.8$ Hz, 3H), 1.10 (t, $J = 7.2$ Hz, 6H), 2.97 (m, 1H), 3.05 (dq, $J = 3.6$, 6.4 Hz, 1H), 4.70 (d, $J = 4.4$ Hz, 1H), 7.23–7.35 (m, 5H). Characterization data for this compound matched exactly with the identical compound found in the literature.[14b]

4.2.19. (1*R*,2*S*)-2-(Pentan-3′-ylamino)-1-phenylpropan-1-ol 6s. Using 3-pentanone, the title compound was synthesized as a pale yellow solid (40%). $[\alpha]_D^{25} = -8.8$ (*c* 0.61, $CHCl_3$). Mp = 54–56 °C. ^{1}H NMR ($CDCl_3$): δ 0.77 (d, $J = 6.6$ Hz, 3H), 0.86 (t, $J = 7.4$ Hz, 3H), 0.91 (t, 7.4 Hz, 3H), 1.42 (m, 4H), 2.52 (q, 5.86 Hz, 1H), 2.99 (dq, $J = 3.9$, 6.6 Hz, 1H), 4.66 (d, $J = 3.9$ Hz, 1H), 7.22–7.32 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 9.6, 10.0, 15.1, 26.2, 26.7, 55.4, 57.00, 73.1, 126.00, 126.8, 127.7, 127.9, 141.5. IR ($CHCl_3$): 3402, 1604, 1121, 985, 745, 701 cm^{-1}. ESI-HRMS: ($M+H^+$) calcd for $C_{14}H_{24}NO$, 222.1858; found, 222.1868.

4.2.20. (1*R*,2*S*)-2-Cyclohexylamino-1-phenyl-1-propanol 6t. Using cyclohexanone, the title compound was obtained as a white solid (85%). $[\alpha]_D^{25} = +8.1$ (*c* 0.60, $CHCl_3$). Mp = 89–91 °C. ^{1}H NMR ($CDCl_3$): δ, 0.78 (d, $J = 6.8$ Hz, 3H), 1.00–1.34 (m, 7H), 1.59–1.64 (m, 1H), 1.71–1.75 (m, 1H), 1.85–1.96 (m, 1H), 2.52–2.59 (m, 1H), 3.05–3.11 (m, 1H), 4.66 (d, $J = 4.0$ Hz, 1H), 7.21–7.34 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 12.7, 24.8, 24.9, 25.5, 31.8, 32.5, 54.3, 55.8, 72.4, 126.0, 127.0, 128.0, 140.9. IR (Nujol mull): 3278, 1102, 738, 701 cm^{-1}. ESI-HRMS: ($M+H^+$) calcd for $C_{15}H_{24}NO$, 234.1858; found, 234.1858.

4.2.21. (1*R*,2*S*)-2-(2,3-Dihydro-1*H*-inden-2-ylamino)-1-phenylpropan-1-ol 6u. Using 2-indanone, the title compound was obtained as a light brown solid (22%). $[\alpha]_D^{25} = -22.2$ (*c* 0.18, $CHCl_3$). Mp = 118–120 °C. ^{1}H NMR ($CDCl_3$): δ 0.85 (d, $J = 6.6$ Hz, 3H), 2.76 (m, 2H), 3.10 (dq, $J = 3.9$, 6.2 Hz, 1H), 3.21 (m, 2H), 3.81 (pentet, $J = 7.0$ Hz, 1H), 4.75 (d, $J = 3.9$ Hz, 1H), 7.15–7.34 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 15.0, 40.4, 40.5, 56.5, 56.8, 73.4, 124.6, 124.7, 126.1, 126.4, 126.5, 127.0, 128.0, 141.3, 141.5. IR ($CHCl_3$): 3278, 1604, 1145, 1026, 746, 701 cm^{-1}. ESI-HRMS: ($M+H^+$) calcd for $C_{18}H_{22}NO$, 268.1701; found, 268.1705.

4.2.22. (1*R*,2*S*)-2-(Cyclooctylamino)-1-phenylpropan-1-ol 6v. Using cyclooctanone, the title compound was obtained as a white solid (39%). $[\alpha]_D^{25} = +27.7$ (*c* 0.10, $CHCl_3$). Mp = 115–116 °C. ^{1}H NMR ($CDCl_3$): δ 0.84 (d, $J = 6.6$ Hz, 3H), 1.49–1.87 (m, 14H), 2.89 (pentet, $J = 4.3$ Hz, 1H), 3.09 (dq, $J = 3.5$, 6.3 Hz, 1H), 4.75 (s, 1H), 7.23–7.36 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.5, 23.7, 24.0, 25.6, 27.2, 27.3, 32.2, 32.5, 54.7, 55.5, 73.0, 126.1, 127.0, 128.0, 141.3. IR ($CHCl_3$): 3428, 912, 741, 702 cm^{-1}. ESI-HRMS: ($M+H^+$) calcd for $C_{17}H_{28}NO$, 262.2171; found, 262.2165.

4.2.23. (1*R*,2*S*)-2-(Cyclopentylamino)-1-phenylpropan-1-ol 6w. Using cyclopentanone, the title compound was obtained as a white solid (47%). $[\alpha]_D^{25} = -2.8$ (*c* 0.70, $CHCl_3$). Mp = 121–123 °C. ^{1}H NMR ($CDCl_3$): δ 0.81 (d, $J = 6.6$ Hz, 3H), 1.26–1.40 (m, 2H), 1.52–1.60 (m, 2H), 1.68–1.72 (m, 2H), 1.81–1.92 (m, 2H), 3.00 (dq, $J = 4.3$, 6.6 Hz, 1H), 3.24 (pentet, $J = 7.0$ Hz, 1H), 4.71 (d, $J = 3.9$ Hz, 1H), 7.24–7.35 (m, 5H). ^{13}C NMR ($CDCl_3$):

δ 15.0, 23.6, 23.7, 33.3, 33.6, 56.6, 56.8, 73.4, 126.1, 126.8, 127.9, 141.6. IR (Nujol mull): 3280, 1604, 998, 745, 703 cm^{-1}. ESI-HRMS: ($M+H^+$) calcd for $C_{14}H_{22}NO$, 220.1701; found, 220.1699.

4.2.24. (1*S*,2*S*)-2-(2′-Methoxybenzylamino)-1-phenylpropan-1-ol 7a. Using *o*-anisaldehyde, the title compound was obtained as colorless prisms (20%), $[\alpha]_D^{25} = +87.1$ (*c* 0.64, $CHCl_3$), mp = 70–72 °C. ^1H NMR ($CDCl_3$): δ 0.96 (d, *J* = 6.3 Hz, 3H), 2.73 (pentet, *J* = 6.6 Hz, 1H), 3.77 (s, 3H), 3.69 (d, *J* = 12.9 Hz, 1H), 3.86 (d, *J* = 12.9 Hz, 1H), 4.18 (d, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.90 (t, *J* = 7.4 Hz, 1H), 7.17–7.35 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 16.7, 47.1, 55.0, 59.2, 77.6, 110.1, 120.3, 126.8, 127.3, 128.1, 128.1, 128.3, 129.7, 142.5, 157.6. IR ($CHCl_3$): 3313, 1602, 1243, 1048, 1029, 753, 702 cm^{-1}. ESI-HRMS: ($M+H^+$) calcd for $C_{17}H_{22}NO_2$, 272.1651; found, 272.1644.

4.2.25. (1*S*,2*S*)-2-(Cyclooctylamino)-1-phenyl-1-propanol 7b. Using cyclooctanone, the title compound was obtained as a clear oil (39%).$[\alpha]_D^{25} = +84.8$ (*c* 0.91, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.94 (d, *J* = 6.3 Hz, 3H), 1.44–1.84 (m, 14H), 2.67 (pentet, *J* = 6.8 Hz, 1H), 2.73 (br s, 1H), 3.78–3.84 (m, 1H), 4.04 (d, *J* = 8.2 Hz, 1H), 7.23–7.36 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 12.7, 24.8, 24.9, 25.5, 31.8, 32.5, 54.3, 55.8, 72.4, 126.0, 127.0, 128.0, 140.9. IR (Nujol mull): 3372, 1056, 734, 701 cm^{-1}. ESI-HRMS: ($M+H^+$) calcd for $C_{17}H_{28}NO$, 26.2171; found, 262.2167.

4.2.26. (1*S*,2*S*)-2-(Anthracen-9′-ylmethylamino)-1-phenylpropan-1-ol 7c. Using 9-anthraldehyde, the titled compound was obtained as a yellow solid (95%), $[\alpha]_D^{25} = +133.9$ (*c* 0.66, $CHCl_3$), mp = 104–106 °C. ^1H NMR ($CDCl_3$): δ 1.21 (d, *J* = 6.6 Hz, 3H), 3.05 (dq, *J* = 6.6, 8.2 Hz, 1H), 4.21 (d, *J* = 7.8 Hz, 1H), 4.60 (d, *J* = 12.1 Hz, 1H), 4.87 (d, *J* = 11.7 Hz, 1H), 7.24–7.56 (m, 9H), 8.01 (d, *J* = 9.4 Hz, 2H), 8.30 (d, *J* = 9.8 Hz, 2H), 8.42 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 16.9, 43.3, 60.6, 77.6, 123.8, 124.9, 126.2, 126.9, 127.4, 127.6, 128.2, 129.1, 130.1, 130.9, 131.5, 142.1. IR ($CHCl_3$): 3304, 1624, 1138, 1026, 732, 701 cm^{-1}. ESI-HRMS: ($M+H^+$) calcd for $C_{24}H_{24}NO$, 342.1858; found, 342.1866.

4.3. General procedure for N-alkylation of (1*R*,2*S*)-norephedrine or (1*S*,2*S*)-pseudonorephedrine via nucleophilic substitution

To a flame-dried, nitrogen-purged flask were added (1*R*,2*S*)-norephedrine (1.02 g, 6.76 mmol) and anhydrous methylene chloride (22 mL). Triethylamine (1.4 mL, 10.1 mmol) was added via syringe and allowed to stir for 24 h at room temperature. The reaction was quenched via saturated ammonium chloride solution (50 mL) and the product was extracted with methylene chloride (50 mL × 2), washed with brine, dried with magnesium chloride, and gravity filtered. The solvent was removed under reduced pressure.

4.3.1. (1*R*,2*S*)-1-Phenyl-2-(tritylamino)propan-1-ol 8. Using trityl chloride, the title compound was obtained as a yellow oil (99%). $[\alpha]_D^{25} = +74.5$ (*c* 0.64, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.63 (d, *J* = 6.6 Hz, 3H), 2.21 (br s, 1H), 2.65 (br d, *J* = 2.7 Hz, 1H), 2.95 (dq, *J* = 3.1, 6.6 Hz, 1H), 3.87 (s, 1H), 7.04–7.32 (m, 14H), 7.58 (d, *J* = 9.4 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 15.1, 53.9, 71.5, 74.4, 125.5, 126.5, 127.8, 127.9, 128.8, 142.1, 146.6. IR (neat): 3451, 1596, 1217, 992, 747, 704 cm^{-1}. ESI-HRMS: ($M+H^+$) calcd for $C_{28}H_{28}NO$, 394.2171; found, 394.2175.

4.3.2. (1*S*,2*S*)-1-Phenyl-2-(tritylamino)propan-1-ol 9. Using trityl chloride, the title compound was obtained as a white solid after recrystallization from hexanes and ethyl acetate (77%). $[\alpha]_D^{25} = -0.2$ (*c* 0.72, $CHCl_3$), mp = 135–137 °C. ^1H NMR ($CDCl_3$): δ 0.25 (d, *J* = 6.3 Hz, 3H), 2.89 (dq, *J* = 3.7, 6.3 Hz, 1H), 4.34 (d, *J* = 7.0 Hz, 1H), 7.16–7.32 (m, 14H), 7.55 (d, *J* = 7.8 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 17.9, 54.5, 71.1, 78.7, 126.5, 127.3, 127.5, 127.9, 128.1, 128.9, 142.0, 146.6. IR ($CHCl_3$): 3402, 1596, 1137, 1034, 735 cm^{-1}. ESI-HRMS: ($M+H^+$) calcd for $C_{28}H_{28}NO$, 394.2171; found, 394.2175.

4.3.3. (1*S*,2*S*)-1-phenyl-2-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylideneamino)-1-propanol 11. Using (1*S*,2*S*)-pseudonorephedrine and the literature experimental,[10] the title compound was obtained as a clear oil (64%). $[\alpha]_D^{25} = +90.3$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.72 (s, 3H), 0.89 (s, 3H), 0.96 (s, 3H), 1.08 (d, *J* = 6.6 Hz, 3H), 1.14–1.21 (m, 1H), 1.55–1.65 (m, 2H), 1.70–1.84 (m, 2H), 2.16–2.22 (m, 2H), 3.44 (pentet, *J* = 6.0 Hz, 1H), 3.52 (d, *J* = 8.0 Hz, 1H), 4.61 (t, *J* = 8.1 Hz, 1H), 7.22–7.31 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 11.4, 17.8, 18.7, 19.2, 27.1, 32.1, 35.2, 43.4, 46.8, 53.5, 62.2, 77.8, 126.3, 126.9, 127.7, 142.9, 183.0. IR (Nujol mull): 3419, 1682, 1053, 737, 704 cm^{-1}. ESI-HRMS: ($M+H^+$) calcd for $C_{19}H_{28}NO$, 286.2171; found, 286.2168.

4.3.4. (1*S*,2*S*)-1-Phenyl-2-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylamino)-1-propanol 13. Using the literature experimental[10] for reduction, the title compound was obtained as a white solid (79%). Mp = 63–65 °C. $[\alpha]_D^{25} = +144.4$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.83 (s, 3H), 0.87 (s, 3H), 0.88 (s, 3H), 0.92 (d, *J* = 6.0 Hz, 3H), 0.95–0.97 (m, 1H), 1.19–1.31 (m, 2H), 1.64–1.74 (m, 2H), 1.89–1.96 (m, 1H), 2.04–2.09 (m, 1H), 2.58 (pentet, *J* = 6.4 Hz, 1H), 2.99 (dd, *J* = 2.4 Hz and *J* = 9.2 Hz, 1H), 4.07 (d, *J* = 9.0 Hz, 1H), 7.25–7.38 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 17.2, 22.6, 23.6, 25.1, 25.5, 27.2, 27.3, 27.4, 31.4, 34.0, 34.6, 54.9, 57.3, 72.0, 77.7, 126.9, 127.4, 128.1, 142.4. IR (Nujol mull): 3366, 1148, 1043, 735, 709 cm^{-1}. ESI-HRMS: ($M+H^+$) calcd for $C_{19}H_{30}NO$, 288.2327; found, 288.2329.

5. General procedure for the asymmetric 1,2-addition with diethylzinc and benzaldehyde

(1*R*,2*S*)-2-(Benzylamino)-1-phenyl-1-propanol **8** (0.085 g, 0.313 mmol) was added to a flame-dried round-bottomed flask with toluene (4.1 mL) in an inert atmosphere. To the flask was added a solution of diethylzinc in hexanes (1 M, 9.4 mL) and the mixture was allowed to stir at room temperature for 25 min. Benzaldehyde (0.32 mL, 3.13 mmol) was then added and allowed to stir at room temperature for 24 h. The reaction was quenched with a saturated solution of ammonium chloride (50 mL) and

extracted with ethyl acetate (50 mL × 2). The organic solution was washed with brine, dried over $MgSO_4$, gravity filtered, and concentrated under reduced pressure to afford enantiomerically enriched 1-phenyl-1-propanol. The enantioselectivity of this process was immediately determined via chiral stationary phase HPLC.

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