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Catalytic asymmetric addition of diethylzinc to aldehydes via chiral, non-racemic β-hydroxy and β-methoxy salicylhydrazone catalysts

Sucharita Banerjee, Gregory M. Ferrence, Shawn R. Hitchcock *

Department of Chemistry, Illinois State University, Normal, IL 61790-4160, USA

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ABSTRACT

(1*S*,2*S*)-Pseudoephedrine and (1*S*,2*S*)-pseudonorephedrine have been converted to their corresponding hydrazines and condensed with either *o*-salicylaldehyde or 2-hydroxy-1-naphthaldehyde to afford a series of β-hydroxysalicylhydrazones that have been employed in the asymmetric addition of diethylzinc to 2-naphthaldehyde in up to 56% ee. In addition to this, the *Ephedra* hydrazines were also condensed with the *o*-hydroxyacetophenone derivative to form related hydrazones. The use of these corresponding hydrazones in the asymmetric addition reaction with the diethylzinc did not yield improved enantioselectivities. Finally, Enders' hydrazine was used as a chiral scaffold for the synthesis of β-methoxysalicylhydrazones. These compounds were employed in the asymmetric addition of diethylzinc to a variety of aromatic aldehydes with enantiomeric excesses as high as 68% ee.

1. Introduction

Chiral, non-racemic hydrazones have recently been reported as useful catalytic ligands in the addition of diethylzinc to aldehydes.[1–3] Mino et al. were the first to develop chiral hydrazone ligands for this purpose.[1] Arai et al. developed related salicylhydrazone derivatives using a binaphthyl template (Fig. 1).[2] When employed in the asymmetric 1,2-addition of diethylzinc, these ligands afforded enantiomeric excesses as high as 80% ee. In related work, Hayashi and co-workers[3] disclosed that a β-hydroxyimine derived from *tert*-leucinol was also an effective catalyst for the asymmetric addition of diethylzinc to aldehydes.[3] Previously, we prepared a series of tridentate β-hydroxysalicylhydrzone ligands from (1*R*,2*S*)-ephedrine and (1*R*,2*S*)-norephedrine and tested these compounds in the catalytic asymmetric addition of diethylzinc to aldehydes. These reactions exhibited enantiomeric ratios ranging from 89:11 to 96:4.[4]

Based on the earlier work with β-hydroxysalicylhydrazones by Arai, Hayashi, and based on our own efforts, we developed an interest in the synthesis and application of other derivatives of the β-hydroxysalicylhydrazone families of compounds having significant structural differences that could be exploited for enhanced enantioselectivities. In particular we became interested in preparing a series of hydrazones using the *Ephedra* alkaloids (1*S*,2*S*)-pseudoephdrine and (1*S*,2*S*)-pseudonorephedrine as scaffolds. Herein, we describe the synthesis of variety of salicylhydrazone ligands and their structural modifications and their application in the catalytic asymmetric addition of diethylzinc to aldehydes.

2. Results and discussion

The synthesis of the β-hydroxysalicylhydrazones was initiated by reaction of (1*S*,2*S*)-pseudonorephedrine[5] with acetone or benzaldehyde followed by treatment with sodium borohydride to generate the N-alkylated derivatives **7b** and **7c** (Scheme 1). Pseudoephedrine **7a** and derivatives **7b–c** were then N-nitrosated to produce *N*-nitrosamines **8a–c**,[6] and subsequently reduced to the corresponding β-hydroxyhydrazine by **9a–c**. These hydrazines were then condensed with either salicylaldehyde **10a** or 2-hydroxy-1-naphthaldehyde **10b** to form hydrazones **11–15** which were purified by chromatography (Scheme 1). These hydrazones presumably formed with *trans*-configured geometry about the C=N bond.[7] This geometry was observed in the solid state for ligand **14** as evidenced by single crystal X-ray crystallography (Fig. 2).[8] There was also an interest in synthesizing a ligand similar to *Ephedra*-based salicylhydrazones but with restricted rotation of the hydroxyl and amine moieties.

Attention was focused on the use of the commercially available, conformationally rigid *cis*-1-amino-2-indanol. The synthesis of the indanol-based salicylhydrazone was initiated by the acylation of (1*R*,2*S*)-*cis*-1-amino-2-indanol **16** (Scheme 2). The product of the acylation was reduced with $LiAlH_4$ to generate the *N*-methyl derivative **18**. This secondary amine was then N-nitrosated with sodium nitrite and HCl to afford **19** in 76% yields. The *N*-nitrosamine was reduced with lithium aluminum hydride to produce hydrazine **20** and the resultant hydrazine was then condensed with 2-hydroxy-1-naphthaldehyde to form the salicylhydrazone ligand **21**. The yield of the condensation was very low (9%). It was assumed that the low stability of the hydrazine and steric environment of the ligand were responsible for the low yield of **21**.

* Corresponding author.
E-mail address: hitchcock@ilstu.edu (S.R. Hitchcock).

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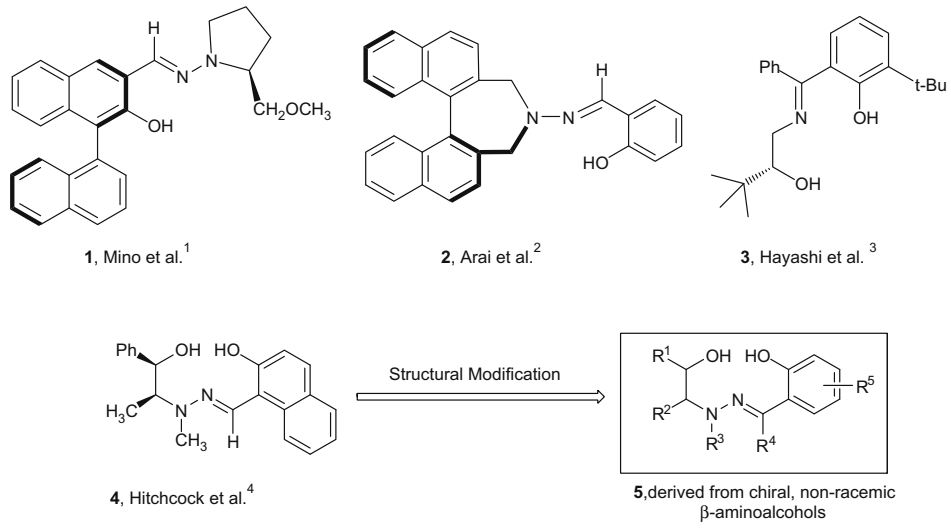
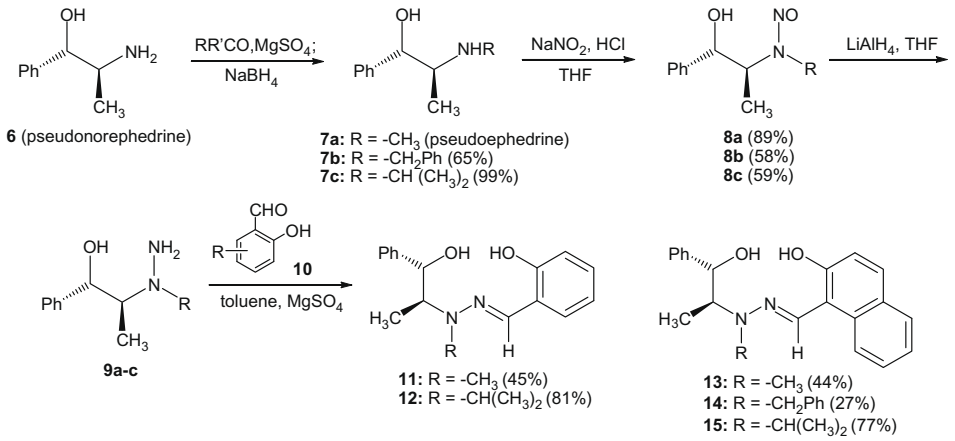


Figure 1. β-Hydroxysalicylhydrazone examples.



Scheme 1. Synthesis of β-hydroxysalicylhydrazones **11–15**.

The synthesis of salicylhydrazones using the (1*S*,2*S*)-pseudoephedrine **9a** and (1*R*,2*S*)-ephedrine-based hydrazines **22** and the methyl ketone analog of salicylaldehyde was also pursued. Based on this idea, 1-(2-hydroxy-5-methylphenyl)ethanone **23** was condensed with the *Ephedra*-derived hydrazines to form hydrazones **24** and **25** (Scheme 3). With compounds **11–15**, **21**, **24**, and **25** in hand, we pursued the hydrazone ligand-catalyzed asymmetric addition of diethylzinc to 2-naphthaldehyde. The results of these reactions are collected in Table 1.

The asymmetric 1,2-addition process yielded enantioselectivities that ranged from 4% to 56% ee. Of the salicylaldehyde and 2-hydroxy-1-naphthaldehyde-derived hydrazones, the maximum enantiomeric excess was generated by the use of the *N*-isopropylsalicylhydrazone ligand **12**. The hydrazone ligands **24** and **25** also afforded the desired product in low enantiomeric excess in addition to the 2-naphthylmethanol, the product of reduction as evidenced by ^{1}H NMR spectroscopy. Ultimately, none of the (1*S*,2*S*)-pseudoephedrine-based hydrazone ligands or the related ligands in this work proved to be superior to the diastereomeric (1*R*,2*S*)-ephedrine that was previously prepared. The lower enantiomeric excess was attributed to multiple intermediates that may be accessible with the pseudoephedrine configuration versus that of the ephedrine configuration (Scheme 4).

At this stage, it was determined that (1*R*,2*S*)-ephedrine-based salicylhydrazones were more effective at carrying out 1,2-asymmetric addition reactions compared to (1*S*,2*S*)-pseudoephedrine-based salicylhydrazones. So, attention was focused on the structural modification of the ephedrine-based salicylhydrazone with the goal of improving the observed enantiomeric excesses from the addition process. In this context, the impact of removal of the hydroxy group from the naphtholic ring and the removal of the imine bond were explored. This effort was initiated by condensation of the ephedrine hydrazine **22** with either 2-hydroxy-1-napthaldehyde or 1-naphthaldehyde to form hydrazones **28** and **29** (Scheme 5). The resultant hydrazones were reduced with lithium aluminum hydride to form hydrazines **30** and **31**. Hydrazone **28** was employed as a ligand in our previous work.[4] Hydrazone **29** and hydrazines **30** and **31** were tested as ligands in the asymmetric addition process (Table 2). The results from this work suggested that hydrazine that did not have the naphtholic hydroxyl group was the superior catalyst over the systems that were prepared. The improved enantioselectivity was a positive sign, but the ligand itself proved to have low stability (observable degradation by ^{1}H NMR spectroscopy when the material was stored at 0 °C). Nonetheless, this work suggested that the coordinating hydroxyl group could be contributing to compromised selectivities.

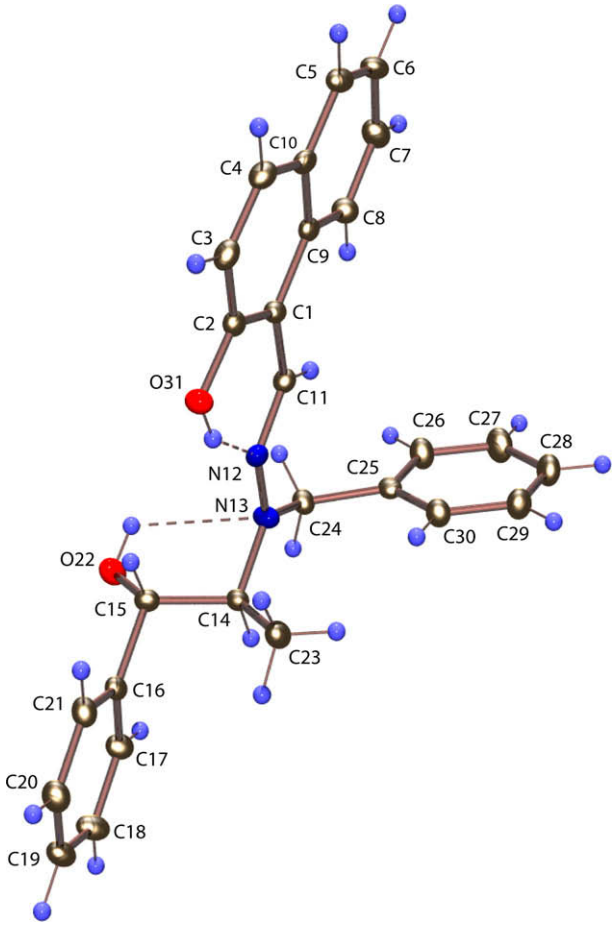
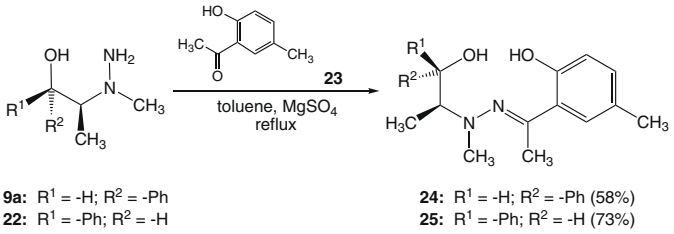


Figure 2. ORTEP-III diagram of **14** with the atomic numbering scheme and intramolecular H-bonding. Displacement ellipsoids are drawn at the 50% probability level.

To circumvent the problem of the free alcohol, a commercially available, enantiomerically pure, stable hydrazine was sought as a scaffold for the synthesis of hydrazones that would not have a free hydroxyl group. Inspired by Mino's earlier work,[1] Enders' hydrazine[9] was selected and employed as a template for the formation of a series of ligands for the asymmetric addition process. The synthesis of the hydrazones was carried out by condensation of **32** with salicylaldehyde and other related aldehyde derivatives to give hydrazones **33–35** in yields of 90–93% (Scheme 6).

Once these ligands were synthesized, a series of reactions were carried out in which the ligands were employed as catalysts in the asymmetric addition of diethylzinc to a variety of aromatic aldehydes (Table 3). The hydrazone derived from the condensation of Enders' hydrazine with 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde **(35)** afforded an enantiomeric excess of 58% ee in the asymmetric addition of diethylzinc with 2-naphthaldehyde.



9a: R^1 = -H; R^2 = -Ph
22: R^1 = -Ph; R^2 = -H

24: R^1 = -H; R^2 = -Ph (58%)
25: R^1 = -Ph; R^2 = -H (73%)

Scheme 3. Synthesis of ketone-based salicylhydrazones **24** and **25**.

Salicylhydrazone **35** was also employed with other aldehydes, although the enantioselectivities were not as high. An interesting observation from this work was that the absolute configuration of the alcohol product was determined to be the (*R*)-configuration when ligands **33** and **34** were employed; the alcohol product was determined to be the (*S*)-configuration when ligand **35** was used. It is proposed that the ligands **33** and **34** involve the formation of intermediates where diethylzinc coordination occurs at the phenolic oxygen (Scheme 7). In contrast, ligand **35** inhibits coordination at the phenolic oxygen due to the presence of the *tert*-butyl group at the *ortho*-position.

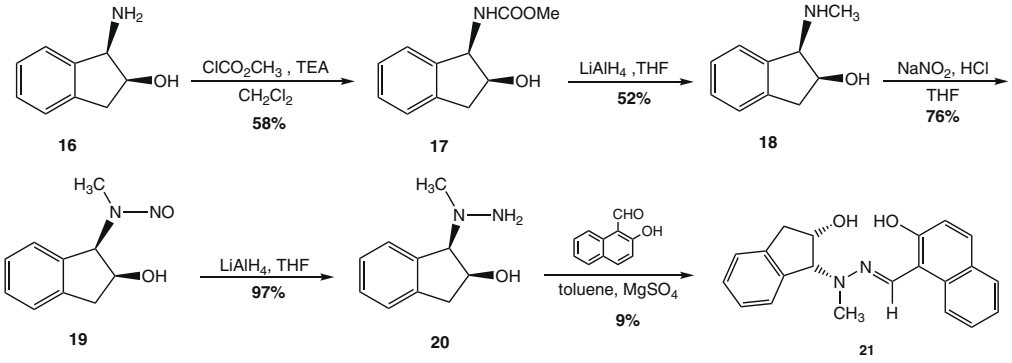
3. Conclusions

A series of β-hydroxysalicylhydrazones based on the *Ephedra* alkaloids (1*S*,2*S*)-pseudoephedrine and (1*S*,2*S*)-pseudonorephedrine have been synthesized and applied in the asymmetric addition of diethylzinc. The observed enantioselectivities for the alcohol products were not as high as those observed for diastereomeric (1*R*,2*S*)-ephedrine. Modification of the β-hydroxy salicylhydrazones either by the introduction of ketone as starting materials or by the reduction of the hydrazone functional group, in some cases, improved the enantioselectivity of product formation. Unfortunately, some of the modified compounds proved to have low stability. Enders' hydrazine was used in the synthesis of β-methoxysalicylhydrazones that proved to have better stability, although the enantioselectivities of the product were only moderate.

4. Experimentals

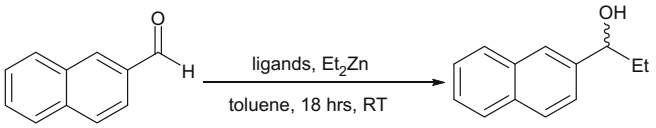
4.1. General remarks

Toluene was purchased as an anhydrous reagent and used without further purification. Diethylzinc was directly purchased from



Scheme 2. An indanol derivative of salicylhydrazone.

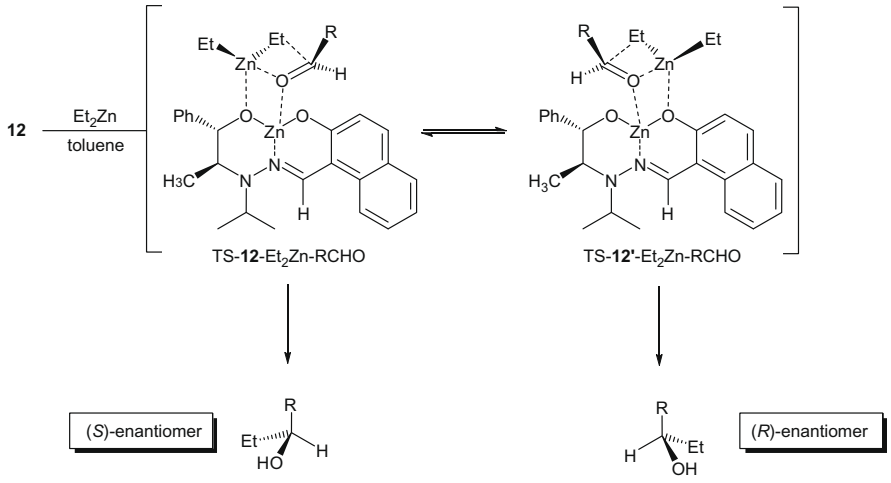
Table 1
Catalytic asymmetric addition of diethylzinc to 2-naphthaldehyde



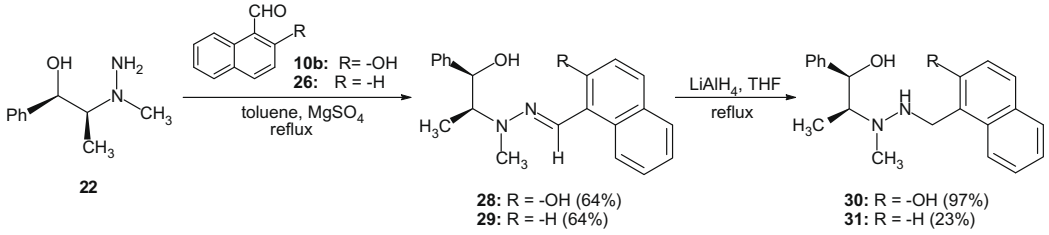
26 **27**

Entry	Ligand	Yield[a] (%)	Enantiomeric ratio *S*:*R*[b] (%ee)	Absolute configuration[c]
1	**11**	56	52.0:48.0 (4)	*S*
2	**12**	94	78.1:21.9 (56)	*S*
3	**13**	90	63.0:37.0 (26)	*S*
4	**14**	47	63.4:37.6 (26)	*S*
5	**15**	46	69.0:31.1 (38)	*S*
6	**21**	90	63.4:36.6 (27)	*S*
7	**24**	58[d]	65.6:34.4 (31)	*S*
8	**25**	66[d]	43.6:56.4 (13)	*R*

[a] All reactions went to completion as determined by ^{1}H NMR spectroscopy and HPLC.
[b] The enantiomeric ratio (er) values were determined via CSP HPLC using a Chiralcel-OD column.
[c] The configuration was determined by comparison of the literature values (see Ref. 4).
[d] Combined yield of addition and reduction product.



Scheme 4. Proposed transition states for the reaction of **12** with diethylzinc.



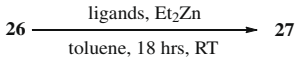
Scheme 5. Synthesis of ligand **30** and **31**.

Aldrich. 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 in 500 MHz or 400 MHz, 125 MHz or 100 MHz, respectively. Chemical shifts were reported in parts per million (δ scale), and coupling constant (J values) were listed in hertz (Hz). Tetramethylsilane (TMS) was used as internal standard (δ = 0 ppm). Infrared spectra are reported in reciprocal centimeters (cm^{-1}) and are measured either as Nujol mull or as a neat liquid. Melting points were recorded on a Mel-Temp apparatus and are uncorrected. Optical activities were measured at 589 nm using a digital polarimeter. Enantiomeric ratio of the catalysis was determined using chiral phase HPLC using AD, AS, or OD column. High resolution mass spectra were obtained from the mass Spectrometry laboratory, School of Chemical Science, University of Illinois, Urbana-Champaign. Anhydrous toluene was used for the catalysis reaction.

4.2. General procedure for reductive alkylation to form 7b and 7c

In a 250 mL round-bottomed flask were added (1*S*,2*S*)-pseudoephedrine (5.00 g, 33.1 mmol), ethanol (100 mL), and the selected

Table 2
Catalytic asymmetric addition of diethylzinc to 2-naphthaldehyde



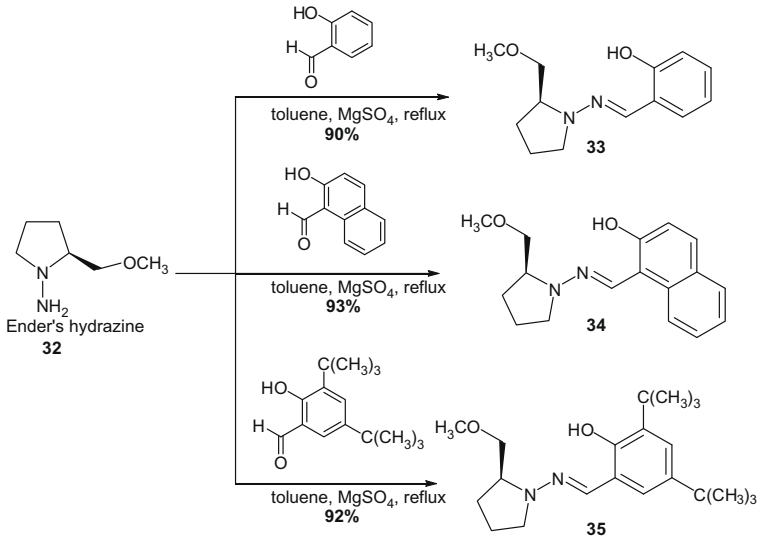
Entry	Ligand	Yield[a] (%)	Enantiomeric ratio *S*:*R*[b] (%ee)	Absolute configuration[c]
1	**29**	38	33.3:66.7 (33)	*R*
1	**30**	92	42.7:57.3 (15)	*R*
2	**31**	96	16.0:84.0 (68)	*R*

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

carbonyl compound (9.00 mL, 82.7 mmol). The reaction mixture was stirred overnight at room temperature. Sodium borohydride (2.50 g, 66.1 mmol) was added and the reaction mixture was stirred overnight. The reaction mixture was diluted with a 20% aqueous solution of sodium hydroxide (50 mL) and extracted with ethyl acetate (2 × 50 mL). The organic layer was then treated with brine (100 mL) and dried over magnesium sulfate ($MgSO_4$).

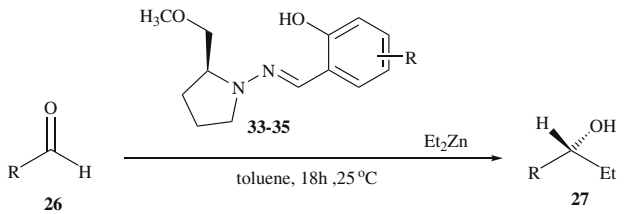
4.2.1. (1*S*,2*S*)-2-(Benzylamino)-1-phenyl-1-propanol, 7b

Benzaldehyde was employed as the selected carbonyl compound. The solvent was evaporated via rotary evaporation. The white residue was purified by flash chromatography using (7:3) hexanes/ethyl acetate. The title compound was obtained as a white solid (65%). $[\alpha]_D^{25} = +135.9$ (*c* 1.0, $CHCl_3$). Mp = 143–146 °C. ^{1}H (500 MHz, $CDCl_3$), (δ ppm): 0.88 (d, *J* = 6.4 Hz, 3H), 2.69–2.75 (m, 1H), 3.60 (d, *J* = 13.0 Hz, 1H), 3.81 (d, *J* = 13.0 Hz, 1H), 4.13 (d, *J* = 8.2 Hz, 1H), 7.19–7.26 (m, 10H). ^{13}C (125 MHz, $CDCl_3$), (δ ppm): 16.1, 50.9, 58.9, 77.4, 126.7, 126.8, 127.3, 127.9, 128.0, 128.2, 139.8, 142.2. IR (nujol): 3292, 1382, 1042, 759 cm^{-1}. ESI-HRMS calcd for $C_{16}H_{20}NO$ $(M+H)^+$: 242.1545. Found: 242.1542.



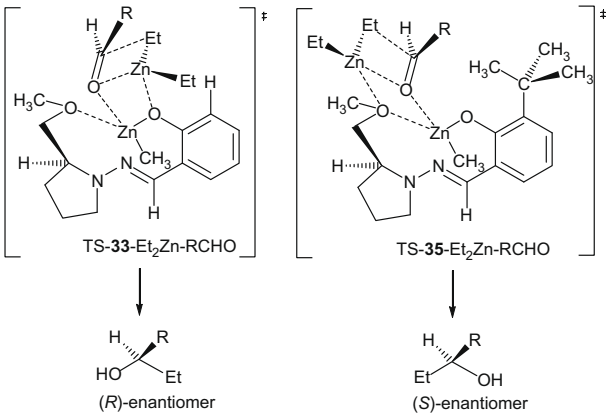
Scheme 6. Synthesis of hydrazones **33–35**.

Table 3
1,2-Asymmetric addition of diethylzinc to aldehydes



Entry	Ligand	RCHO	Yield[a] (%)	Enantiomeric ratio[b] (%ee)	Absolute configuration[c]
1	**33**	2-$C_{10}H_7$–	71	45.8:54.2 (8)	*R*
2	**33**	*t*-PhCH=CH–	44	45.8:54.2 (8)	*R*
3	**34**	2-$C_{10}H_7$–	66	48.8:51.2 (2)	*R*
4	**34**	*t*-PhCH=CH–	81	52.3:47.7 (5)	*R*
5	**35**	2-$C_{10}H_7$–	61	78.7:21.2 (58)	*S*
6	**35**	*t*-PhCH=CH–	63	46.2:53.8 (8)	*S*
7	**35**	1-$C_{10}H_7$–	65	64.6:35.4 (29)[c]	*S*
8	**35**	C_6H_5–	76	32.7:67.3 (35)[b]	*S*
9	**35**	4-MeO-C_6H_5–	71	29.8:70.2 (40)[b]	*S*

[a] Yield was reported after purification via flash chromatography.
[b] Enantiomeric excess was determined by CSP HPLC using OD column.
[c] Absolute configuration was determined from the literature.



Scheme 7. Proposed mechanisms for the addition reactions of **33** and **35**.

4.2.2. (1*S*,2*S*)-2-(Isopropylamino)-1-phenyl-1-propanol, 7c

Acetone was employed as the selected carbonyl compound. The solvent was evaporated via rotary evaporation. A colorless liquid was obtained in quantitative yield. $[\alpha]_D^{25} = +53.6$ (*c* 0.5, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$), (δ ppm): 0.85 (d, *J* = 6.3 Hz, 3H), 1.01 (d, *J* = 6.2 Hz, 3H), 1.05 (d, *J* = 6.2 Hz, 3H), 2.64–2.69 (m, 1H), 2.83–2.87 (m, 1H), 3.15 (s, 1H), 4.04 (d, *J* = 8.3 Hz, 1H), 7.21–7.31 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$), (δ ppm): 16.5, 22.2, 23.8, 45.66, 56.8, 126.7, 127.0, 127.7, 142.1. IR (neat): 3389, 2924, 1650, 759 cm^{-1}. ESI-HRMS calcd for $C_{12}H_{20}NO$ $(M+H^+)$: 194.1545. Found: 194.1541.

4.3. General procedure for N-nitrosation for the formation of 8a–c

In a 250 mL round-bottomed flask were placed **8a,b** or **c** (4.60 g, 19.1 mmol), THF (10 mL), $NaNO_2$ (1.51 g, 22.0 mmol), and HCl (3 M, 8.8 mL). The reaction mixture was stirred 18 h at room temperature and the reaction was quenched with KOH solution (20%, 50 mL), and the reaction mixture was extracted with ethyl acetate (100 mL). The organic layer was washed with brine (100 mL) and dried over $MgSO_4$. The solvent was removed via rotary evaporation to yield the crude nitrosamine.

4.3.1. (1*S*,2*S*)-2-(*N*-Methyl-*N*-nitrosamino)-1-phenyl-1-propanol, 8a

Using pseudoephedrine **(7a)** as the starting material, the title compound was obtained as viscous yellow residue (89%). The ^1H and ^{13}C NMR spectroscopic data matched the literature values for this compound.[6]

4.3.2. (1*S*,2*S*)-2-(*N*-Benzyl-*N*-nitrosamino)-1-phenyl-1-propanol, 8b

Using **7b**, the title compound was obtained as white solid (58%) after recrystallization from ethyl acetate and hexanes. $[\alpha]_D^{25} = +204.7$ (*c* 1.0, $CHCl_3$). Mp: 90–92 °C. ^1H (500 MHz, $CDCl_3$, extra peaks were present due to the presence of two stereoisomers), (δ ppm): 1.26 (d, *J* = 7.1 Hz, 3H), 2.69 (d, *J* = 4.5 Hz, 1H), 4.40–4.46 (m, 1H), 4.45 (d, *J* = 14.8 Hz, 1H), 5.20 (d, *J* = 14.8 Hz, 1H), 5.33 (d, *J* = 15.1 Hz, 1H), 7.25–7.37 (m, 10H). ^{13}C (125 MHz, $CDCl_3$, extra peaks were due to the presence of two stereoisomers), (δ ppm): 17.6, 48.3, 64.3, 77.7, 126.5, 127.7, 128.1, 128.4, 128.7, 128.9, 134.6, 140.9. IR (nujol) cm^{-1}: 3496, 1374, 766. ESI-HRMS calcd for $C_{16}H_{19}N_2O_2$ $(M+H)^+$: 271.1447. Found: 271.1447.

4.3.3. (1*S*,2*S*)-2-(*N*-Isopropyl-*N*-nitrosamino)-1-phenyl-1-propanol, 8c

Using **7c**, the title compound was obtained as white solid (59%) after recrystallization from ethyl acetate and hexanes. $[\alpha]_D^{25} = +188.0$ (*c* 0.2, $CHCl_3$). Mp = 92–95 °C. ^1H NMR (500 MHz, $CDCl_3$, dominant peaks were only reported as there are two stereoisomer's present), (δ ppm): 0.92 (d, *J* = 6.8 Hz, 3H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.21 (d, *J* = 6.9 Hz, 3H), 4.14–4.19 (m, 1H), 4.26–4.31 (m, 1H), 4.85 (s, 1H), 5.04–5.10 (m, 1H), 7.26–7.36 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$), (δ ppm): 13.8, 18.3, 20.3, 45.2, 60.1, 75.3, 126.2, 128.1, 128.5, 141.5. IR (nujol) cm^{-1}: 3258, 1353, 1055, 754. ESI-HRMS calcd for $C_{12}H_{19}N_2O_2$ $(M+H)^+$: 223.1447. Found: 223.1438.

4.4. General procedure for *N*-nitrosamine reduction to form hydrazines 9a–c

In a 1 L round-bottomed flask were added lithium aluminum hydride (200 mmol) and THF (500 mL). The reaction mixture was then heated to 50 °C. To the reaction mixture a solution of *N*-nitrosamine **8a**, **8b**, **or 8c** (100 mmol) in THF (100 mL) was added dropwise in about 20 min. The reaction mixture was heated for 2 h and then cooled to 0 °C. An aqueous solution of NaOH (1 M, 150 mL) was added dropwise to the reaction mixture (caution: this process is highly exothermic). The solvents were removed by rotary evaporation and the residue was extracted with ethyl acetate (2 × 300 mL) and NaOH solution (1 M, 150 mL). The organic layer was washed with brine and dried over magnesium sulfate. The solvent was evaporated via rotary evaporation. This process afforded hydrazines **9a–c**. The hydrazines were not characterized due to their low stability and were used immediately to create the hydrazones **11–15**.

4.5. General procedure for the formation of salicylhydrazones 11 and 12

In 250 mL round-bottomed flask were added toluene (120 mL), hydrazine **9a** or **9c** (2.00 g, 11.0 mmol), salicylaldehyde (11.0 mmol), and magnesium sulfate (2 g). The reaction mixture was heated up to reflux and stirred 18 h at reflux. It was then allowed to cool to room temperature. The reaction mixture was extracted with ethyl acetate (150 mL) and brine (100 mL). The organic layer was then dried over magnesium sulfate and filtered. The solvent was removed via rotary evaporation.

4.5.1. 2-((*E*)-(2-((1*S*,2*S*)-1-Hydroxy-1-phenyl-2-propyl)-2-methylhydrazono)methyl) phenol, 11

Hydrazine **9a** was employed in the condensation reaction. The crude product was purified with flash chromatography using 9:1 hexanes and ethyl acetate. The chromatographed product was then recrystallized from hexanes and ethyl acetate. The title compound was obtained as a white solid (45%). $[\alpha]_D^{20} = -13.9$ (*c* 1.0, $CHCl_3$). Mp = 95–98 °C. ^1H NMR (500 MHz, $CDCl_3$), δ (ppm): 0.89 (d, *J* = 6.7 Hz, 3H), 2.96 (s, 3H), 3.07 (s, 1H), 3.43–3.48 (m, 1H), 4.71 (d, *J* = 9.3 Hz, 1H), 6.86–6.96 (m, 5H), 7.15–7.41 (m, 4H), 7.52 (s, 1H), 11.46 (s, 1H). ^{13}C (125 MHz, $CDCl_3$) δ (ppm): 12.6, 36.5, 69.3, 76.5, 116.4, 119.2, 119.7, 127.2, 128.2, 128.5, 129.0, 129.1, 138.7, 140.9, 156.9. IR (nujol): 3491, 1595, 1276, 1060, 761 cm^{-1}. ESI-HRMS calcd for $C_{17}H_{21}N_2O_2$ $(M+H)^+$: 285.1603. Found: 285.1591.

4.5.2. 2-((*E*)-(2-((1*S*,2*S*)-1-Hydroxy-1-phenyl-2-propyl)-2-isopropylhydrazono)methyl) phenol, 12

Hydrazine **9c** was employed in the condensation reaction. The crude product was purified with flash chromatography using 9:1 hexanes and ethyl acetate. The title compound was obtained as a yellow liquid (81%). $[\alpha]_D^{23} = +17.1$ (*c* 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$), (δ ppm): 0.95 (d, *J* = 6.7 Hz, 3H), 1.11 (d, *J* = 6.6 Hz, 3H), 1.33 (d, *J* = 6.6 Hz, 3H), 3.54–3.60 (m, 1H), 3.95–4.00 (m, 1H), 4.60 (d, *J* = 8.9 Hz, 1H), 6.85 (t, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 8.1 Hz, 1H), 7.10 (d, 7.6 Hz, 1H), 7.15 (m, 1H), 7.26–7.39 (m, 5H), 7.56 (s, 1H). ^{13}C (125 MHz, $CDCl_3$), (δ ppm): 14.9, 18.2, 21.1, 48.2, 59.4, 76.1,

116.3, 119.1, 119.7, 127.3, 128.0, 128.4, 128.9, 129.0, 138.5, 141.0, 157.0. IR (nujol): 3468, 1622, 1377, 761 cm^{-1}. ESI-HRMS calcd for $C_{19}H_{25}N_2O_2$ $(M+H)^+$: 312.1827. Found: 312.1830.

4.6. General procedure for the formation of hydrazones 13–15

In 250 mL round-bottomed flask were added toluene (120 mL), hydrazine **9a,b** or **c** (11.0 mmol), 2-hydroxy-1-naphthaldehyde (1.90 g. 11.0 mmol), and magnesium sulfate (2 g). The reaction mixture was heated up to reflux and stirred 18 h at reflux. It was then allowed to cool to room temperature. The reaction mixture was extracted with ethyl acetate (150 mL) and brine (100 mL). The organic later was then dried over magnesium sulfate and filtered. The solvent was evaporated via rotary evaporation.

4.6.1. 1-((*E*)-(2-((1*S*,2*S*)-1-Hydroxy-1-phenyl-2-propyl)-2-methylhydrazono)methyl)-2-naphthol, 13

The residue was purified by flash chromatography using (9:1) hexanes/ethyl acetate followed by recrystallization using hexanes and ethyl acetate (44%). $[\alpha]_D^{20} = -29.5$ (*c* 1.0, $CHCl_3$). Mp = 143–146 °C. ^{1}H NMR (500 MHz, $CDCl_3$), (δ ppm): 0.94 (d, *J* = 6.7 Hz, 3H), 3.07 (s, 3H), 3.50–3.54 (m, 1H), 4.77 (d, *J* = 9.3 Hz, 1H), 7.19–7.24 (m, 3H), 7.29–7.38 (m, 3H), 7.42–7.49 (m, 3H), 7.69 (d, *J* = 8.7, 1H), 7.6 Hz (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 8.7 Hz, 1H), 8.35 (s, 1H), 12.70 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$), (δ ppm): 12.6, 36.7, 69.5, 109.9, 119.0, 120.1, 123.1, 126.8, 127.3, 128.2, 128.4, 128.9, 129.0, 130.4, 131.5, 135.0, 135.2, 140.8, 156.3. IR (nujol): 3475, 1621, 1454, 1039, 742 cm^{-1}. ESI-HRMS calcd for $C_{21}H_{23}N_2O_2$ $(M+H)^+$: 335.1760. Found: 335.1753.

4.6.2. 1-((*E*)-(2-((1*S*,2*S*)-1-Hydroxy-1-phenyl-2-propyl)-2-isopropylhydrazono)methyl)-2-naphthol, 15

The residue was purified by flash chromatography using (9:1) hexanes/ethyl acetate. The title compound was obtained as a yellow liquid (77%). $[\alpha]_D^{25} = +43.4$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$), (δ ppm): 1.01 (d, *J* = 6.6 Hz, 3H), 1.21 (d, *J* = 6.6 Hz, 3H), 1.38 (d, *J* = 6.6 Hz, 3H), 3.43 (s, 1H), 3.58–3.64 (m, 1H), 4.04–4.11 (m, 1H), 4.63 (d, *J* = 9.0 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.28–7.456 (m, 7H), 7.67 (d, *J* = 8.7 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.95 (d, *J* = 8.7 Hz, 1H), 8.56 (s, 1H), 13.05 (s, 1H). ^{13}C (100 MHz, $CDCl_3$), (δ ppm): 14.5, 18.6, 21.3, 49.3, 60.2, 76.2, 109.7, 119.1, 119.9, 123.1, 126.9, 127.4, 128.1, 128.5, 129.1, 130.7, 131.6, 138.1, 141.1, 157.3, 170.2. IR (nujol): 3468, 1622, 1377, 761 cm^{-1}. ESI-HRMS calcd for $C_{23}H_{27}N_2O_2$ $(M+H^+)$: 363.2073. Found: 363.2065.

4.6.3. 1-((*E*)-(2-Benzyl-2-((1*S*,2*S*)-1-hydroxy-1-phenyl-2-propyl)-hydrazono)methyl)-2-naphthol, 14

The residue was purified by flash chromatography using (9:1) hexanes/ethyl acetate followed by recrystallization using hexanes and ethyl acetate. The title compound was obtained as a white solid (27%). $[\alpha]_D^{25} = +11.5$ (*c* 1.0, $CHCl_3$). Mp = 128–131 °C. ^{1}H (500 MHz, $CDCl_3$), (δ ppm): 1.12 (d, *J* = 6.7 Hz, 3H), 2.92 (s, 1H), 4.40–4.46 (m, 1H), 3.59–3.64 (m, 1H), 4.55 (d, *J* = 15.0 Hz, 1H), 4.60 (d, *J* = 15.0 Hz, 1H), 4.85 (d, *J* = 8.9 Hz, 1H), 7.16–7.71 (m, 11H), 8.17 (s, 1H), 12.67 (s, 1H). ^{13}C (125 MHz, $CDCl_3$), (δ ppm): 14.2, 56.6, 68.4, 78.2, 110.1, 119.0, 120.0, 122.9, 126.6, 126.8, 127.1, 127.6, 128.0, 128.2, 128.5, 128.8, 129.1, 130.2, 131.3, 136.1, 137.0, 141.3, 156.3. IR (nujol): 3400, 1459, 769 cm^{-1}. ESI-HRMS calcd for $C_{27}H_{19}N_2O_2$ $(M+H)^+$: 411.2073. Found: 411.2080.

4.6.4. Methyl (1*R*,2*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-ylcarbamate, 17

In a 250 mL round-bottomed flask were added (1*R*,2*S*)-*cis*-1-amino-2-indanol (5.02 g, 33.5 mmol), dichloromethane (100 mL), methyl chloroformate (2.72 mL, 35.2 mmol), and triethylamine (9.30 mL, 67.0 mmol). The reaction mixture was stirred for 18 h at ambient temperature and then the reaction was quenched with 1 M HCl (100 mL). The reaction mixture was extracted with dichloromethane (100 mL). The organic layer was washed with brine (100 mL) and dried over magnesium sulfate. The solvents were removed via rotary evaporation. The residue was recrystallized with ethyl acetate and hexanes. The product was obtained in 58% yield. $[\alpha]_D^{23} = +19.1$ (*c* 1.0, $CHCl_3$). Mp: 95–98 °C. The 500 MHz NMR spectrum indicated the presence of a mixture of diastereomers in a ratio of 55:45 that complicated interpretation. ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 2.87–3.09 (m, 2H), 3.27–3.39 (m, 1H), 3.70 (s, 3H), 5.09 (d, *J* = 7.2 Hz, 1H), 5.61 (s, 1H), 7.00 (s, 1H), 7.20–7.29 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$), (δ ppm): 8.4, 38.7, 39.4, 45.7, 52.2, 59.1, 61.1, 73.2, 80.4, 124.3, 124.8, 125.12, 125.4, 126.9, 127.7, 127.9, 129.2, 139.6, 139.8, 140.2, 140.7. IR (nujol): 3440, 3327, 1751, 752 cm^{-1}. ESI-HRMS calcd for $C_{11}H_{13}NO_3Na$ $(M+H)^+$: 230.0793. Found: 230.0792.

4.6.5. (1*R*,2*S*)-1-(Methylamino)-2,3-dihydro-1*H*-inden-2-ol, 18

In a 500 mL round-bottomed flask were added $LiAlH_4$ (1.45 g, 38.2 mmol) and THF (450 mL). The reaction mixture was heated to reflux. A solution of **17** (3.50 g, 19.1 mmol) in THF (50 mL) was added dropwise to the reaction mixture. The reaction mixture was then heated to reflux for 18 h. The reaction mixture was then cooled to 0 °C. Water (300 mL) was added dropwise to quench the reaction. The reaction solvent was removed by rotary evaporation and the reaction mixture was extracted with 1 M NaOH (150 mL) and ethyl acetate (100 mL). The aqueous layer was extracted with ethyl acetate (50 mL). The combined organic layers were washed with brine (150 mL) and dried over magnesium sulfate. The solvent was removed by rotary evaporation. The brown residue was recrystallized with ethyl acetate and hexanes. The titled compound was obtained as an off-white solid (52%). $[\alpha]_D^{24} = -10.2$ (*c* 1.0, $CHCl_3$). Mp: 108–110 °C. ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 2.61 (s, 3H), 2.97 (dd, *J* = 16.4 Hz, *J* = 4.0 Hz, 1H), 3.06 (dd, *J* = 16.4 Hz, 4.0 Hz, 1H), 3.96 (d, *J* = 5.2 Hz, 1H), 4.44–4.47 (m, 1H), 7.23–7.26 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$), (δ ppm): 35.3, 39.7, 67.7, 70.3, 123.6, 125.6, 126.6, 128.0, 141.1, 142.1. IR (nujol): 3309, 1457, 737 cm^{-1}. ESI-HRMS calcd for $C_{10}H_{14}NO$ $(M+H)^+$: 164.1075. Found: 164.1077.

4.6.6. *N*-((1*R*,2*S*)-2-Hydroxy-2,3-dihydro-1*H*-inden-1-yl)-*N*-methylnitrous amide, 19

In a 250 mL round-bottomed flask were added (1*R*,2*S*)-1-(methylamino)-2,3-dihydro-1*H*-inden-2-ol (2.25 g, 13.97 mmol), THF (20 mL), HCl (10 mL, 3 M), and sodium nitrite (1.15 g, 18.80 mmol). The reaction mixture was stirred for 18 h at ambient temperature and the reaction was quenched with HCl (1 M, 25 mL) and ethyl acetate (50 mL). The organic layer was washed with brine and dried over magnesium sulfate. The solvent was evaporated via rotary evaporation. The residue was recrystallized with ethyl acetate and hexanes. The title compound was obtained as a yellow solid (76%). $[\alpha]_D^{24} = +60.4$ (*c* 1.1, $CHCl_3$). Mp = 91–93 °C. ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 2.92 (s, 3H), 3.07 (dd, *J* = 16.8 Hz, *J* = 5.9 Hz, 1H), 3.37 (dd, *J* = 16.8 Hz, *J* = 5.9 Hz, 1H), 4.98–5.02 (m, 1H), 6.18 (d, *J* = 6.6 Hz, 1H), 7.19–7.37 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$), (δ ppm): 31.8, 39.9, 70.2, 73.6, 125.5, 125.6, 127.6, 129.4, 136.5 and 140.9. IR (nujol): 3331, 1460, 751 cm^{-1}. ESI-HRMS calcd for $C_{10}H_{13}N_2O_2$ $(M+H)^+$: 193.0977. Found: 193.080.

4.6.7. (1*R*,2*S*)-1-(1-Methylhydrazinyl)-2,3-dihydro-1*H*-inden-2-ol, 20

In a 250 mL round-bottomed flask were added $LiAlH_4$ (0.52 g, 10.4 mmol) and THF (30 mL). A solution of **19** (1.0 g, 5.2 mmol) in THF (15 mL) was added dropwise to the reaction mixture in 20 min. The reaction was stirred for 2 h. The reaction was cooled to 0 °C and water (50 mL) was added dropwise to quench the reac-

tion. The solvent was removed via rotary evaporation. The reaction was extracted with NaOH (1 M, 25 mL) and Ethyl acetate (25 mL). The aqueous layer was extracted with ethyl acetate (25 mL). The combined organic layer was washed with brine (50 mL) and dried over magnesium sulfate. The solvent was evaporated via rotary evaporation. The title compound was obtained as a yellow liquid (97%). This material was used without further purification due to stability concerns.

4.6.8. (1-((*E*)-(2-((1*R*,2*S*)-2-Hydroxy-2,3-dihydro-1*H*-inden-1-yl)-2-methylhydrazono) methyl)-2-naphthol, 21

Toluene (46 mL), hydrazine **20** (0.93 g, 5.20 mmol), 2-hydroxy-1-naphthaldehyde (0.90 g, 5.20 mmol), and magnesium sulfate (1 g) were combined in a 250 mL round-bottomed flask and the reaction mixture was heated to reflux and stirred 18 h. It was then allowed to cool to room temperature. The reaction mixture was extracted with ethyl acetate (50 mL) and brine (50 mL). The organic later was then dried over magnesium sulfate and filtered. The solvent was removed via rotary evaporation. The residue was purified by flash chromatography using (9:1) hexanes/ethyl acetate followed by recrystallization using hexanes and ethyl acetate. The title compound was obtained as a light brown solid (9%). $[\alpha]_D^{23} = +122.7$ (*c* 0.2, $CHCl_3$). Mp = 145–148 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 3.02 (dd, *J* = 16.6 Hz, *J* = 4.7 Hz, 1H), 3.16 (s, 3H), 3.28 (dd, *J* = 16.6, 4.7 Hz, 1H), 4.83–4.88 (m, 1H), 5.02 (d, *J* = 6.4 Hz, 1H), 7.12 (d, *J* = 8.8 Hz, 1H), 7.29–7.36 (m, 4H), 7.44–7.48 (m, 1H), 7.63 (d, *J* = 8.8 Hz, 1H), 7.74 (d, *J* = 7.7 Hz, 1H), 8.01 (d, *J* = 8.8 Hz, 1H), 8.31 (s, 1H), 12.00 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 36.8, 40.6, 73.6, 74.7, 110.1, 119.1, 120.2, 122.9, 125.7, 125.9, 126.6, 127.3, 128.3, 128.9, 129.0, 129.8, 131.4, 132.5, 138.5, 140.6, 155.9. IR (nujol): 3490, 1620, 1377, 741 cm^{-1}. ESI-HRMS calcd for $C_{21}H_{21}N_2O_2$ (M+H)$^+$: 333.1603. Found: 333.1605.

4.7. General procedure for the formation of hydrazones 24 and 25

In 250 mL round-bottomed flask were added toluene (110 mL), hydrazine **9a** or **22** (2.00 g, 11.1 mmol), 1-(2-hydroxy-5-methylphenyl)ethanone (1.67 g, 11.1 mmol), and magnesium sulfate (2 g). The reaction mixture was heated up to reflux and stirred 18 h at reflux. It was then allowed to cool to room temperature. The reaction mixture was extracted with ethyl acetate (100 mL) and brine (100 mL). The organic later was then dried over magnesium sulfate and filtered. The solvent was evaporated via rotary evaporation.

4.7.1. 2-((*E*)-1-(2-((1*R*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl)-2-methylhydrazono)ethyl)-4-methylphenol, 25

The residue was purified by flash chromatography using (9:1) hexanes/ethyl acetate. The title compound was obtained as a yellow solid (29%). $[\alpha]_D^{25} = +59.6$ (*c* 1.0, $CHCl_3$). Mp = 143–146 °C. ^{1}H NMR (500 MHz, $CDCl_3$), (δ ppm): 1.11 (d, *J* = 6.7 Hz, 3H), 2.30 (s, 3H), 2.36 (s, 3H), 2.54 (s, 3H), 3.14–3.18 (m, 1H), 4.88 (d, *J* = 7.4 Hz, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 7.09 (d, *J* = 8.3 Hz, 1H), 7.25–7.32 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$), (δ ppm): 9.7, 14.4, 20.6, 42.5, 67.8, 74.5, 117.4, 118.8, 126.1, 127.1, 127.5, 128.1, 128.4, 132.4, 141.9, 158.1, 169.9. IR (nujol): 3463, 1602, 1363, 761 cm^{-1}. ESI-HRMS calcd for $C_{19}H_{25}N_2O_2$ (M+H)$^+$: 313.1916. Found: 313.1908.

4.7.2. 2-((*E*)-1-(2-((1*S*,2*S*)-1-Hydroxy-1-phenyl-2-propyl)-2-methylhydrazono)ethyl)-4-methylphenol, 24

The residue was purified by flash chromatography using (9:1) hexanes/ethyl acetate. The title compound was obtained as a yellow liquid (58%). $[\alpha]_D^{25} = -371.9$ (*c* 1.1, $CHCl_3$). ^{1}H (500 MHz, $CDCl_3$), δ (ppm): 1.01 (d, *J* = 6.6 Hz, 3H), 2.31 (s, 3H), 2.54 (s, 3H), 2.64 (s, 3H), 2.98–3.05 (m, 1H), 4.04 (s, 1H), 4.29 (d, *J* = 9.7 Hz, 1H), 6.89 (d, *J* = 8.3 Hz, 1H), 7.10–7.12 (m, 1H), 7.24 (s, 1H), 7.34–7.36 (m, 5H), 13.4 (s, 1H). ^{13}C (125 MHz, $CDCl_3$), (δ ppm): 8.9, 14.7, 20.6, 41.5, 68.3, 76.3, 117.4, 118.8, 127.4, 127.9, 128.2, 128.3, 132.6, 140.8, 157.9, 169.7. IR (nujol): 3447, 1600, 754 cm^{-1}. ESI-HRMS calcd for $C_{19}H_{25}N_2O_2$ (M+H)$^+$: 313.1916. Found: 313.1919.

4.7.3. ((1*R*,2*S*)-2-((*E*)-1-Methyl-2-(1-naphthylmethylene)-hydrazinyl)-1-phenyl-1-propanol, 29

Hydrazine **22** (1.50 g, 8.30 mmol), 2-naphthaldehyde (1.30 g, 8.30 mmol), toluene (85 mL), and magnesium sulfate (2 g) were combined in a 250 mL round-bottomed flask. The reaction mixture was heated to reflux and then stirred overnight at reflux temperature. The reaction mixture was then cooled to room temperature. The reaction was quenched with brine (100 mL) and ethyl acetate (100 mL). The organic layer was dried over magnesium sulfate. The solvent was evaporated via rotary evaporation. The residue was purified by recrystallization from hexanes and ethyl acetate. The title compound was obtained as a white solid (64%). $[\alpha]_D^{24} = +169.5$ (*c* 1.0, $CHCl_3$). Mp = 128–130 °C. ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 1.09 (d, *J* = 6.7 Hz, 3H), 2.95 (s, 3H), 3.41–3.45 (m, 1H), 4.92 (s, 1H), 5.36 (d, *J* = 2.2 Hz, 1H), 7.21–7.80 (m, 12H). ^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): 9.4, 37.8, 67.5, 76.7, 122.5, 125.6, 125.7, 125.8, 126.1, 126.3, 127.0, 127.8, 127.9, 128.1, 128.4, 132.9, 133.1, 133.6, 134.0, 141.9. IR (nujol): 3423, 1461, 874 cm^{-1}. ESI-HRMS calcd for $C_{21}H_{23}N_2O$ (M+H)$^+$: 319.1810. Found: 319.1809.

4.7.4. 1-((2-((1*R*,2*S*)-1-Hydroxy-1-phenyl-2-propyl)-2-methylhydrazinyl)methyl)-2-naphthol, 30

In a 250 mL round-bottomed flask were added $LiAlH_4$ (0.12 g, 3.00 mmol) and THF (8 mL). The reaction mixture was heated up to 50 °C. A solution of (1*R*,2*S*)-salicylhydrazone (0.50 g, 1.50 mmol) in THF (5 mL) was added to the reaction mixture dropwise in about 20 min. The reaction mixture was heated up to reflux after addition and allowed to run at reflux for 18 h. The reaction mixture was cooled to room temperature and then to 0 °C. Water (20 mL) was added dropwise to the reaction mixture (highly exothermic). THF was completely evaporated via rotary evaporation. The residue was treated with 1 M NaOH (50 mL) and ethyl acetate (50 mL). The aqueous layer was again extracted with ethyl acetate (10 mL). The combined organic layer was washed with brine (150 mL) and dried over magnesium sulfate. The solvent was completely evaporated via rotary evaporation. The residue was recrystallized using hexanes and ethyl acetate (8:2). The titled compound was obtained as an off-white solid (97%). $[\alpha]_D^{24} = +123.4$ (*c* 0.3, $CHCl_3$). Mp = 129–132 °C. ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 0.94 (d, *J* = 6.7 Hz, 3H), 3.07 (s, 3H), 3.50–3.54 (m, 1H), 4.77 (d, *J* = 9.3 Hz, 1H), 7.19–7.24 (m, 3H), 7.29–7.38 (m, 3H), 7.42–7.49 (m, 3H), 7.69 (d, *J* = 8.7 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 8.7 Hz, 1H), 8.35 (s, 1H), 12.70 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): 12.6, 36.7, 69.5, 109.9, 119.0, 120.1, 123.1, 126.8, 127.3, 128.2, 128.4, 128.9, 129.0, 130.4, 131.5, 135.0, 135.2, 140.8, 156.3. IR (nujol): 3230, 1620, 1376, 767 cm^{-1}. ESI-HRMS calcd for $C_{21}H_{25}N_2O_2$ (M+H)$^+$: 337.1916. Found: 337.1903.

4.7.5. (1*R*,2*S*)-2-(1-Methyl-2-(naphthylmethyl)hydrazinyl)-1-phenyl-1-propanol, 31

In a 500 mL round-bottomed flask were added $LiAlH_4$ (0.22 g, 5.97 mmol) and THF (200 mL). The reaction mixture was heated up to 50 °C. A solution of **29** (1.00 g, 2.98 mmol) in THF (50 mL) was added to the reaction mixture dropwise in about 20 min. The reaction mixture was heated up to reflux after addition and allowed to run at reflux for 18 h. The reaction mixture was cooled to room temperature and then to 0 °C. Water (50 mL) was added dropwise to the reaction mixture (highly exothermic). The solvent was removed via rotary evaporation. The residue was treated with

1 M NaOH (100 mL) and ethyl acetate (100 mL). The aqueous layer was again extracted with ethyl acetate (50 mL). The combined organic layer was washed with brine (150 mL) and dried over magnesium sulfate. The solvent was removed via rotary evaporation and the residue was recrystallized using ethyl acetate and hexanes. The title compound was obtained as white solid (54%). $[\alpha]_D^{25} = +43.4$ (c 1.0, $CHCl_3$). Mp = 95–98 °C. ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 0.81 (d, J = 6.7 Hz, 3H), 2.61 (s, 3H), 2.76–2.81 (m, 1H), 4.13 (s, 2H), 5.25 (s, 1H), 6.01 (s, 1H), 7.18–7.50 (m, 7H), 7.76–7.82 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$), (δ ppm): 3.5, 42.0, 54.1, 65.0, 77.4, 125.9, 126.1, 126.6, 127.0, 127.6, 127.7, 127.8, 127.9, 128.3, 132.8, 133.3, 134.8, 142.5. IR (nujol): 3314, 1601, 1372, 763, 701 cm^{-1}. ESI-HRMS calcd for $C_{21}H_{25}N_2O$ (M+H)$^+$: 321.1967. Found: 321.1968.

4.8. General procedure for the synthesis of the hydrazones 33–35

In a 250 mL round-bottomed flask were added Enders' hydrazine (1.00 g, 7.68 mmol), salicylaldehyde (1.32 g, 7.68 mmol), toluene (77 mL), and $MgSO_4$ (2 g). The reaction mixture was heated to reflux for 18 h and then cooled to 25 °C. A brine solution was added and the mixture was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed by rotary evaporation.

4.8.1. (*S,E*)-2-((2-(Methoxymethyl)pyrrolidinyl-1-imino)methyl)-phenol, 33

The solvent was evaporated via rotary evaporation and the residue was purified by flash chromatography using 95:05 (hexanes/ethyl acetate). The product was obtained as yellow liquid (57%). $[\alpha]_D^{23} = -202.9$ (c 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.76–1.83 (m, 1H), 1.90–2.04 (m, 3H), 2.93–2.99 (m, 1H), 3.37 (s, 3H), 3.45–3.60 (m, 4H), 6.81 (td, J = 7.8 Hz, 1.0 Hz, 1H), 6.90 (dd, J = 7.8 Hz, J = 1.0 Hz, 1H), 7.05–7.12 (m, 2H), 7.33 (s, 1H), 11.44 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) (δ ppm): 21.8, 26.4, 48.7, 59.0, 63.1, 74.4, 116.2, 118.9, 119.9, 136.6 and 156.5. IR (neat) cm^{-1}: 3463, 3002, 2998, 1602, 1252, 761. ESI-HRMS calcd for $C_{13}H_{19}N_2O_2$ (M+H$^+$): 235.1447. Found: 235.1449.

4.8.2. (*S,E*)-1-((2-(Methoxymethyl)pyrrolidin-1-ylimino)methyl)-naphthalen-2-ol, 34

Using 2-hydroxy-1-naphthaldehyde the solvent was evaporated via rotary evaporation and the residue was purified by flash chromatography using 99:1 (hexanes/ethyl acetate). The product was obtained as yellow solid (92%). $[\alpha]_D^{23} = -225.6$ (c 1, $CHCl_3$). Mp = 78–80 °C. ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 1.80–1.90 (m, 1H), 1.97–2.09 (m, 3H), 3.11 (q, J = 7.3 Hz, 1H), 3.42 (s, 3H), 3.55–3.62 (m, 3H), 3.68 (p, J = 5.4 Hz, 1H), 7.18 (d, J = 8.9 Hz, 1H), 7.29 (t, J = 7.5 Hz, 1H), 7.43–7.46 (m, 1H), 7.64 (d, J = 8.9 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.98 (d, J = 8.6 Hz, 1H), 8.21 (s, 1H), 12.60 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) (δ ppm): 22.2, 26.7, 49.5, 59.3, 63.7, 74.8, 110.4, 119.1, 120.3, 122.8, 126.5, 128.3, 129.0, 129.5, 131.4, 133.8 and 156.1. IR (nujol) cm^{-1}: 3463, 1602, 1252, 765. ESI-HRMS calcd for $C_{17}H_{21}N_2O_2$ (M+H)$^+$: 285.1603. Found: 285.1600.

4.8.3. (*S,E*)-2,4-Di-*tert*-butyl-6-((2-(methoxymethyl)pyrrolidin-1-ylimino)methyl)phenol, 35

Using 2-hydroxy-3,5-di-*tert*-butylbenzaldehyde, the residue was purified by flash chromatography using 9:1 (hexanes/ethyl acetate). The product was obtained as yellow solid (93%). $[\alpha]_D^{23} = -126.5$ (c 1.0, $CHCl_3$). Mp = 95–97 °C. ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 1.30 (s, 9H), 1.45 (s, 9H), 1.84–1.87 (m, 1H), 1.96–2.07 (m, 3H), 3.41 (s, 3H), 3.49–3.54 (m, 1H), 3.58–3.61 (m, 3H), 6.96 (d, J = 2.4 Hz, 1H), 7.21 (m, J = 2.4 Hz, 1H), 7.45 (s, 1H), 7.45 (s, 1H), 11.68 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): 22.1, 26.6, 29.5, 31.6, 34.1, 35.0, 49.5, 59.3, 63.5, 74.5, 119.0, 123.3, 123.9, 135.9, 139.3, 140.3 and 153.7. IR (nujol) cm^{-1}: 3463, 1602, 1248, 761. ESI-HRMS calcd for $C_{21}H_{35}N_2O_2$ (M+H$^+$): 347.2699. Found: 347.2693.

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References

1. (a) Mino, T.; Suzuki, A.; Yamashita, M.; Narita, S.; Shirae, Y.; Sakamoto, M.; Fujita, T. *J. Organomet. Chem.* **2006**, *691*, 4297–4303; (b) Mino, T.; Shiotsuki, M.; Yamamoto, N.; Suenaga, T.; Sakamoto, M.; Fujita, T.; Yamashita, M. *J. Org. Chem.* **2001**, *66*, 1795.
2. Arai, T.; Endo, Y.; Yanagisawa, A. *Tetrahedron: Asymmetry* **2007**, *18*, 165–169.
3. Tanaka, T.; Yasuda, Y.; Hayashi, M. *J. Org. Chem.* **2006**, *71*, 7091–7093.
4. Parrott, R. W.; Dore, D. D.; Chandrashekar, S. P.; Bentley, J. T.; Morgan, B. S.; Hitchcock, S. R. *Tetrahedron: Asymmetry* **2008**, *19*, 607–611.
5. Groeper, J. A.; Hitchcock, S. R.; Ferrence, G. M. *Tetrahedron: Asymmetry* **2006**, *17*, 2884–2889.
6. Hitchcock, S. R.; Nora, G. P.; Casper, D. M.; Squire, M. D.; Maroules, C. D.; Ferrerence, G. M.; Szczepura, L. F.; Standard, G. M. *Tetrahedron* **2001**, *57*, 9789–9798.
7. Takahashi and co-workers studied *Ephedra* based hydrazones in an unrelated study and determined by ^{1}H NMR spectroscopy that these compounds have a strong preference for the formation of the *trans*-configured product. Please see: (a) Takahayashi, H.; Tomita, K.; Noguchi, H. *Chem. Pharm. Bull.* **1981**, *29*, 3387; (b) Takahayashi, H.; Inagaki, H. *Chem. Pharm. Bull.* **1982**, *30*, 922.
8. X-ray quality crystals were grown by evaporation of an ethyl acetate/hexanes solution of the compound. Crystallographic data (excluding structure factors) for **14** has been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 770158.
9. (a) Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253; (b) Vicario, J. L.; Job, A.; Wolberg, M.; Muller, M.; Enders, D. *Org. Lett.* **2002**, *4*, 1023.