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Enantioselective diethylzinc addition to aldehydes via chiral, non-racemic β-hydroxysalicylhydrazone catalysts

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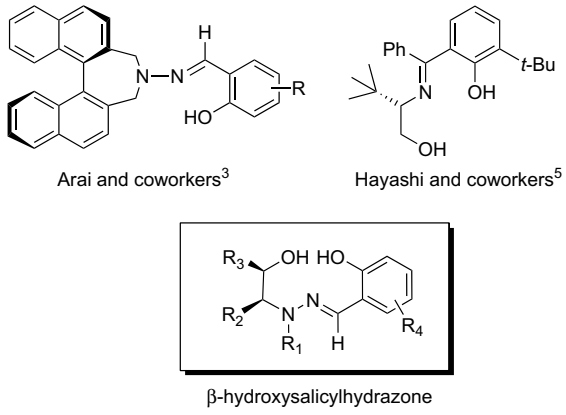
Abstract—A series of tridentate β-hydroxysalicylhydrazone ligands have been prepared from (1*R*,2*S*)-ephedrine and (1*R*,2*S*)-norephedrine and tested in the catalytic asymmetric addition of diethylzinc to aldehydes. The isolated chemical yields of the addition products ranged from 50% to 84%. The reactions exhibited very good enantioselectivity with enantiomeric ratios ranging from 89:11 to 96:4.

1. Introduction

The catalytic asymmetric addition of diorganozinc reagents to carbonyl compounds is a well established reaction pathway in synthetic organic chemistry.[1] This process is driven by the coordination of the diethylzinc species with an appropriate ligand, often a chiral, non-racemic β-amino alcohol.[2] To this end, many different research groups have sought to develop unique ligands that can serve as molecular scaffolds for the transfer of asymmetry.[1–4] Among the ligands that have been synthesized and applied in diethylzinc addition reactions, salicylhydrazones represent a class of compounds that have not been studied extensively. The most notable literature examples have been developed by Arai et al.[3] The template developed by Arai et al. possess an axially chiral binaphthyl linker as the foundation of the catalyst (Fig. 1). When employed in the asymmetric addition of diethylzinc to benzaldehyde, this particular catalyst afforded the addition product 1-phenyl-1-propanol with an enantiomeric ratio of 79.0:21.0 favoring the (*S*)-enantiomer. Arai et al. also prepared other catalyst derivatives of a similar design and were able to obtain enantiomeric ratios as high as 90.0:10.0.[3] In a related body of work, Hayashi et al. disclosed that β-hydroxysalicylimines derived from *tert*-leucinol were effective catalysts for the asymmetric addition of diethylzinc to aldehydes.[5] We became interested in developing a structurally new family of catalysts that combine the best elements of both the Arai salicylhydrazone catalysts and the Hayashi β-hydroxysalicylimines. The introduction of a chiral, non-racemic β-amino alcohol foundation for the salicylhydrazone was considered to be a potential means of enhancing the observed asymmetric induction. This presumption was based on a variety of literature examples involving β-hydroxysalicylimines (Schiff bases) as successful asymmetric catalysts.[5–7]



Fgure 1.

Based on our work with the β-amino alcohols derived from the *Ephedra* alkaloids,[8] we sought to employ (1*R*,2*S*)-ephedrine and (1*R*,2*S*)-norephedrine as chiral foundations.

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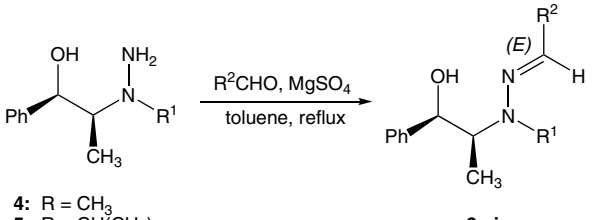
Herein, we report the preparation of β-hydroxysalicylhydrazones and their application in the catalytic enantioselective addition of diethylzinc to aldehydes.

2. Results and discussion

The hydrazines of (1*R*,2*S*)-ephedrine and (1*R*,2*S*)-*N*-isopropyl-norephedrine were prepared as previously described and then condensed with a variety of aromatic aldehydes to produce hydrazone derivatives **6a–j** (Table 1).[8,9] In all cases, the (*E*)-stereoisomer of the β-hydroxysalicylhydrazones was the major isomer detected by ^{1}H NMR spectroscopy. The stereochemical assignment was determined based on the earlier work of Takahashi et al.[10] The hydrazone ligands were subsequently applied in the asymmetric 1,2-addition of diethylzinc to benzaldehyde. It was determined that 3 equiv of diethylzinc at room temperature with 10 mol % loading of the catalyst resulted in the optimal results for both yield and enantioselectivity (see Scheme 1).

When employed in the catalytic asymmetric addition of diethylzinc to benzaldehyde, salicylhydrazone catalyst **6a** generated an enantiomeric ratio of 82.5:17.5 (*S*:*R*). In contrast, the benzylidene hydrazone catalyst **6b** generated a mixture of products that included the desired product (1-phenyl-1-propanol), benzyl alcohol and the starting material. The presence of the benzyl alcohol is indicative of the failure of catalyst **6b**, as benzyl alcohol is the direct product of the reduction of benzaldehyde by diethylzinc.[11] Ultimately, the results from entries 1 and 2 in Table 2 suggest that the presence of the phenolic unit is crucial for stable catalytic activity and enantioselection. Salicylhydrazone catalysts **6c–e** (Table 2, entries 3–5) exhibited

Table 1. β-Hydroxysalicylhydrazone synthesis

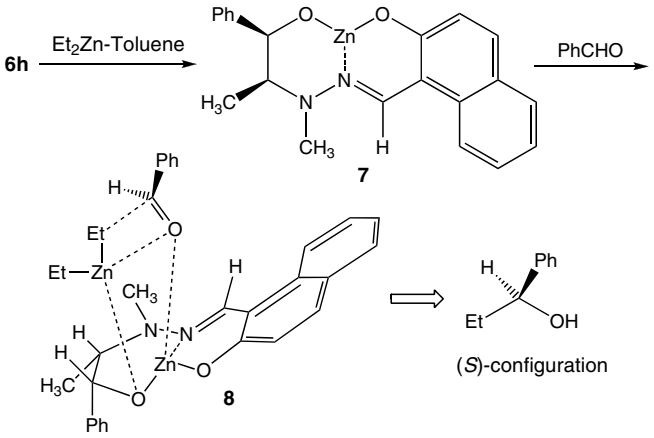


4: R = CH_3
5: R = $CH(CH_3)_2$

6a-j
28-80%

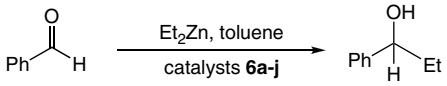
Entry	Ligand	R_1	R_2	Yield (%)
1	**6a**	$-CH_3$	–2-Hydroxyphenyl	43[a]
2	**6b**	$-CH_3$	–Phenyl	54[b]
3	**6c**	$-CH_3$	–2-Hydroxy-3-methylphenyl	51[a]
4	**6d**	$-CH_3$	–3-*t*-Butyl-2-hydroxyphenyl	48[b]
5	**6e**	$-CH_3$	–3,5-Di-(*t*-butyl)-2-hydroxyphenyl	28[a]
6	**6f**	$-CH_3$	–2-Hydroxy-5-nitrophenyl	43[b]
7	**6g**	$-CH_3$	–2-Hydroxy-5-methoxyphenyl	74[a]
8	**6h**	$-CH_3$	–2-Hydroxy-1-naphthyl	46[b]
9	**6i**	–*i*Pr	–2-Hydroxyphenyl	49[a]
10	**6j**	–*i*Pr	–2-Hydroxy-1-naphthyl	80[a]

[a] Derivative was purified by flash chromatography (hexanes–ethyl acetate, 4:1).
[b] Derivative was purified by recrystallization (ether–hexanes, 1:2).



Scheme 1. Proposed intermediate for catalyst **6h**.

Table 2. Catalytic asymmetric additions of diethylzinc



Entry	Catalyst[a]	er ($\lvert R–S \rvert$)[b]	Config.[c]
1	**6a**	82.5:17.5 (65)	(*S*)
2	**6b**	nd[d]	nd[d]
3	**6c**	44.5:55.5 (11)	(*R*)
4	**6d**	nd[d]	nd[d]
5	**6e**	nd[d]	nd[d]
6	**6f**	89:11 (78)	(*S*)
7	**6g**	80.5:19.5 (61)	(*S*)
8	**6h**	94:6 (88)	(*S*)
9	**6i**	61:39 (22)	(*S*)
10	**6j**	82.5:17.5 (65)	(*S*)

[a] All reactions went to completion as determined by ^{1}H NMR spectroscopy and CSP HPLC.
[b] The enantiomeric ratio (er) values were determined via CSP HPLC using a Chiralcel-OD column.
[c] The configuration was determined by comparison with literature values for retention times.[12]
[d] The er could not be determined due to the significant amount of benzyl alcohol present.

poor reactivity and low enantioselectivity when compared to the parent catalyst **6a**. All these derivativesshare a common structural feature of substitution at the *ortho*-position relative to the phenolic alcohol. The introduction of the *ortho*-substituent caused the enantiomeric ratio to favor the (*R*)-enantiomer in contrast to the principal formation of the (*S*)-enantiomer in all other cases. Hayashi et al.[5] observed a similar pattern of reactivity with their tridentate β-hydroxysalicylimine derivatives. This suggested that the region near the phenolic position must be free of steric interference in order for the catalytic process to occur efficiently.

Salicylhydrazone catalysts **6f** and **6g** were prepared to examine the effects of different electronic substituents (Table 2, entries 6 and 7). In contrast, the electronic effect of the methoxy substituent was not significant in terms of having an influence over the enantioselection. The intro-

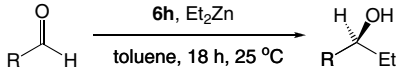
duction of a nitro group onto the aromatic ring at the *para*-position of the salicylhydrazone (entry 7) improved the enantioselection of the catalysis process to a ratio of 89.0:11.0. It is proposed that the origin of the increase might be related to the pK_a difference between *p*-nitrophenol and phenol (i.e., 7.2 vs 9.9), as well as the different binding abilities of the phenoxide system versus a *p*-nitrophenoxide system.[13]

To expand on the variety of the salicylaldehyde derivatives, 2-hydroxy-1-naphthaldehyde was employed as the aromatic base of salicylhydrazone catalyst **6h**. This derivative afforded the highest enantioselection for catalysis of the asymmetric addition of diethylzinc to benzaldehyde with a ratio of 94:6. The presence of the extended aromatic ring system apparently provides an environment, that is, conducive to catalysts.

In an effort to further enhance the stereoselectivity of the catalytic process, the *N*-isopropylnorephedrine catalysts were employed. It was anticipated that the *N*-isopropyl group of the norephedrine derivative would be more effective than the *N*-methyl group of ephedrine. However, the result of applying the norephedrine based catalysts **6i** and **6j** indicated otherwise. The salicylaldehyde derived **6i** yielded an enantiomeric ratio of 61:39. This was a significant decrease in enantioselection when compared to the case of the salicylaldehyde derived **6a**. The decrease in enantioselectivity was also observed with catalyst **6j**. These collected results suggested that the presence of a larger substituent on the nitrogen has a negative impact on the stereochemical outcome of the catalyst, perhaps through a conformational change in the catalyst structure.

Ultimately, catalyst **6h**, a (1*R*,2*S*)-ephedrine based salicylhydrazone with the naphthyl unit as the aromatic foundation, proved to be the most effective catalyst in the family of β-hydroxysalicylhydrazones and was tested with a series of aldehydes (Table 3). The isolated yield of the addition products ranged from 50% to 84% after chromatography, while the enantiomeric ratios ranged from 89:11 to 96:4. With regard to the mechanism of this catalytic process, it is proposed that catalyst **6h** undergoes a reaction with a single equivalent of diethylzinc to form a tridentate catalyst, similar to the Hayashi catalyst.[5]

Table 3. Catalytic asymmetric additions of Et_2Zn with β-hydroxysalicylhydrazone **6h**



Entry	R	Yield (%)	(|*R*–*S*|)[a]	Config.[b]
1	$-C_6H_5$	74	94:6 (88)	(*S*)
2	$-C_6H_4Cl$	50	96:4 (92)	(*S*)
3	$-1\text{-}C_{10}H_7$	84	92:8 (84)	(*S*)
4	$-1\text{-}C_{10}H_7$	63	95:4 (91)	(*S*)
5	–*t*-CH=CHPh	67	89:11 (78)	(*S*)

[a] The enantiomeric ratio (er) values were determined via CSP HPLC using a Chiralcel-OD column.

[b] The configuration was determined by comparison of literature values for optical activity.[12]

3. Conclusion

There are mechanistic factors that are involved but are not clear at this time. These include the impact of *ortho*-substituents on the phenolic ring, the impact of electronic tuning of the phenolic ring, and the difference in enantioselectivity based on the *Ephedra* nitrogen substituent (methyl vs isopropyl). Studies are currently underway to address these aspects in the context of the catalytic ability of the β-hydroxysalicylhydrazones.

4. Experimental

4.1. General

All reactions were run under a nitrogen atmosphere. Anhydrous toluene was purchased and stored under a nitrogen atmosphere. Diethylzinc was purchased as a 1 M solution in hexanes. Unless otherwise noted, all ^1H and ^{13}C NMR spectra were recorded at 25 °C in $CDCl_3$ operating at 400 MHz and 100 MHz, respectively. Chemical shifts are reported in parts per million (δ scale), and coupling constants (J values) are listed in Hertz (Hz). Infrared spectra are reported in reciprocal centimeters (cm^{-1}) and are measured either as a neat liquid or as a KBr window. Melting points were recorded on a Mel-Temp apparatus and are uncorrected. Mass spectral analyses were conducted by the mass spectrometry analytical laboratories of the University of Illinois at Urbana-Champaign using a quadrapole time of flight mass spectrometer hybrid with MS/MS capability. Optical activities were measured at 589 nm using a Jasco digital polarimeter purchased with NSF Grant #CHE 644950.

4.2. General procedure for the synthesis of β-hydroxysalicylhydrazones

Either the β-hydroxyhydrazine derived from (1*R*,2*S*)-ephedrine **4** or β-hydroxyhydrazine **5** derived from (1*R*,2*S*)-*N*-isopropyl-norephedrine (1.62 g, 8.98 mmol) was dissolved in toluene (10 mL) in a flame dried flask under an inert atmosphere. The aldehyde (8.98 mmol) of choice was added and allowed to stir for 22 h at reflux. Toluene was removed under reduced pressure and the hydrazone was extracted with ethyl acetate (50 mL × 2), washed with brine, dried with magnesium chloride, gravity filtered, and concentrated under reduced pressure. The hydrazones were either recrystallized in ether and hexanes (1:2) or purified via flash chromatography.

4.2.1. 2-[(*E*)-(2-((1*R*,2*S*)-1-Hydroxy-1-phenyl-2-propyl)-2-methylhydrazono)methyl]phenol 6a. (1*R*,2*S*)-Ephedrine **4** and 2-hydroxybenzaldehyde were reacted to yield compound **6a** as a yellow oil after chromatography (43%). $[\alpha]_D^{25} = +233.6$ (*c* 0.62, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.33 (d, $J = 6.6$ Hz, 3H), 2.13 (br s, 1H), 2.72 (s, 3H), 3.55 (pentet, $J = 6.6$ Hz, 1H), 4.87 (d, $J = 5.1$ Hz, 1H), 6.82–6.93 (m, 2H), 7.07–7.32 (m, 7H), 11.54 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 12.9, 35.8, 67.7, 76.2, 116.1, 119.0, 120.1, 126.1, 127.5, 128.0, 128.2, 128.4, 133.9, 142.4, 156.2. IR

(neat): 3438, 1034, 911, 752, 702 cm^{-1}. ESI-HRMS calcd for $C_{17}H_{21}N_2O_2$ ($M+H^+$): 285.1603. Found: 285.1602.

4.2.2. (1*R*,2*S*)-2-[(*E*)-2-Benzylidene-1-methylhydrazinyl]-1-phenylpropan-1-ol 6b. (1*R*,2*S*)-Ephedrine **4** and benzaldehyde were combined to yield compound **6b** as a white solid (54%). Mp = 51–53 °C. $[\alpha]_D^{25} = +140.2$ (*c* 0.71, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.05 (d, $J = 6.6$ Hz, 3H), 2.93 (s, 3H), 3.39 (qd, $J = 2.0$ Hz, $J = 6.6$ Hz, 1H), 5.01 (s, 1H), 5.34 (br s, 1H), 7.23–7.28 (m, 3H), 7.33–7.37 (m, 3H), 7.42–7.44 (m, 2H), 7.52–7.54 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 9.1, 37.3, 67.0, 76.4, 125.1, 125.7, 126.6, 127.2, 127.7, 128.3, 132.4, 135.9, 141.7. IR ($CHCl_3$): 3398, 1051, 912, 754, 700 cm^{-1}. ESI-HRMS calcd for $C_{17}H_{21}N_2O$ ($M + H^+$): 269.1654. Found: 269.1653.

4.2.3. 2-[(*E*)-(2-((1*R*,2*S*)-1-Hydroxy-1-phenyl-2-propyl)-2-methylhydrazono)methyl]-6-methylphenol 6c. (1*R*,2*S*)-Ephedrine **4** and 2-hydroxy-3-methylbenzaldehyde were combined to yield compound **6c** as a clear oil after chromatography (51%). $[\alpha]_D^{25} = +219.7$ (*c* 0.72, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.36 (d, $J = 7.0$ Hz, 3H), 2.02 (d, $J = 3.1$ Hz, 1H), 2.30 (s, 1H), 2.71 (s, 3H), 3.55 (pentet, $J = 6.6$ Hz, 1H), 4.92 (dd, $J = 3.1$, 6.2 Hz, 1H), 6.75–6.79 (m, 1H), 6.94–7.03 (m, 2H), 7.23–7.36 (m, 5H), 11.71 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 13.0, 15.7, 36.2, 67.8, 76.3, 118.6, 119.4, 125.0, 126.2, 126.4, 127.6, 128.3, 129.5, 134.6, 142.5, 154.6. IR (neat): 3426, 1564, 1036, 913, 744, 702 cm^{-1}. ESI-HRMS calcd for $C_{18}H_{23}N_2O_2$ ($M+H^+$): 299.1760. Found: 299.1758.

4.2.4. 2-*tert*-Butyl-6-((*E*)-(2-((1*R*,2*S*)-1-hydroxy-1-phenyl-2-propyl)-2-methylhydrazono)methyl)phenol 6d. (1*R*,2*S*)-Ephedrine **4** and 2-hydroxy-3-*tert*-butylbenzaldehyde were combined to yield compound **6d** as a yellow solid after recrystallization (48%). Mp = 100–101 °C. $[\alpha]_D^{25} = +191.9$ (*c* 0.62, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.36 (d, $J = 6.6$ Hz, 3H), 1.46 (s, 9H), 2.01 (br s, 1H), 2.74 (s, 3H), 3.60 (m, 1H), 4.92 (dd, $J = 3.1$, 5.6 Hz, 1H), 6.77–6.80 (m, 1H), 6.96–6.98 (m, 1H), 7.16–7.18 (m, 1H), 7.26–7.37 (m, 5H), 11.90 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 13.0, 29.4, 34.8, 35.9, 67.7, 76.2, 118.2, 120.0, 125.7, 126.3, 127.2, 127.7, 128.3, 135.7, 136.6, 142.4, 155.8. IR ($CHCl_3$): 3414, 1566, 1038, 910, 748, 702 cm^{-1}. ESI-HRMS calcd for $C_{21}H_{29}N_2O_2$ ($M+H^+$): 341.2229. Found: 341.2232.

4.2.5. 2,4-Di-*tert*-butyl-6-((*E*)-(2-((1*R*,2*S*)-1-hydroxy-1-phenyl-2-propyl)-2-methylhydrazono)methyl)phenol 6e. (1*R*,2*S*)-Ephedrine **4** and 3,5-di-*tert*-butyl-2-hydroxy benzaldehyde were combined and the title compound was obtained as a clear oil after chromatography (28%). $[\alpha]_D^{25} = +111.3$ (*c* 0.80, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.30 (s, 9H), 1.34 (d, $J = 6.6$ Hz, 3H), 1.47 (s, 9H), 2.02 (br s, 1H), 2.73 (s, 3H), 3.57 (pentet, $J = 6.3$ Hz, 1H), 4.92 (dd, $J = 3.5$, 6.3 Hz, 1H), 6.96–6.97 (m, 1H), 7.22–7.37 (m, 6H), 11.72 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 12.9, 29.5, 31.6, 34.1, 35.0, 36.1, 67.8, 76.2, 77.2, 119.1, 123.2, 123.8, 126.3, 127.6, 128.3, 135.9, 136.5, 140.3, 142.6, 153.5. IR (neat): 3419, 909, 738, 701 cm^{-1}. ESI-HRMS calcd for $C_{25}H_{37}N_2O_2$ ($M+H^+$): 397.2855. Found: 397.2864.

4.2.6. 2-((*E*)-(2-((1*R*,2*S*)-1-Hydroxy-1-phenyl-2-propyl)-2-methylhydrazono)methyl)-4-nitrophenol 6f. (1*R*,2*S*)-Ephedrine **4** and 2-hydroxy-5-nitrobenzaldehyde were combined and the title compound was obtained as an orange solid after recrystallization (43%). Mp = 147–149 °C. $[\alpha]_D^{25} = +180.4$ (*c* 0.60, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.39 (d, $J = 7.0$ Hz, 3H), 1.98 (br s, 1H), 2.79 (s, 3H), 3.66 (pentet, $J = 6.3$ Hz, 1H), 4.87 (d, $J = 5.9$ Hz, 1H), 6.95 (d, $J = 8.0$ Hz, 1H), 7.16 (s, 1H), 7.26–7.34 (m, 4H), 8.00–8.02 (m, 2H), 12.37 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 13.3, 36.0, 68.0, 76.7, 116.6, 120.3, 123.7, 124.0, 126.1, 128.0, 128.5, 130.4, 140.3, 142.0, 162.0. IR ($CHCl_3$): 3530, 1092, 900, 751, 702 cm^{-1}. ESI-HRMS calcd for $C_{17}H_{20}N_3O_4$ ($M+H^+$): 330.1454. Found: 330.1463.

4.2.7. 2-((*E*)-(2-((1*R*,2*S*)-1-Hydroxy-1-phenyl-2-propyl)-2-methylhydrazono)methyl)-4-methoxyphenol 6g. (1*R*,2*S*)-Ephedrine **4** and 2-hydroxy-5-methoxybenzaldehyde were reacted to yield the title compound as a clear oil after chromatography (74%). $[\alpha]_D^{25} = +175.8$ (*c* 0.59, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.34 (d, $J = 6.6$ Hz, 3H), 2.08 (br s, 1H), 2.73 (s, 3H), 3.57 (pentet, $J = 6.6$ Hz, 1H), 3.76 (s, 3H), 4.88 (dd, $J = 2.4$, 5.1 Hz, 1H), 6.64 (d, $J = 2.4$ Hz, 1H), 6.71–6.73 (m, 1H), 6.84–6.86 (m, 1H), 7.15 (s, 1H), 7.26–7.33 (m, 4H), 11.08 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 13.0, 36.0, 55.7, 67.8, 76.3, 113.2, 114.0, 116.6, 120.3, 126.2, 127.6, 128.3, 133.4, 142.5, 150.4, 152.3. IR (neat): 3454, 1039, 910, 762, 702 cm^{-1}. ESI-HRMS calcd for $C_{18}H_{23}N_2O_3$ ($M+H^+$): 315.1709. Found: 315.1708.

4.2.8. 1-((*E*)-(2-((1*R*,2*S*)-1-Hydroxy-1-phenyl-2-propyl)-2-methylhydrazono)methyl)naphthalen-2-ol 6h. (1*R*,2*S*)-Ephedrine **4** and 2-hydroxy-1-naphthaldehyde were combined to yield the title compound, which was obtained as a dark yellow solid after recrystallization (46%). Mp = 123–125 °C. $[\alpha]_D^{25} = +192.8$ (*c* 0.63, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.40 (d, $J = 6.6$ Hz, 3H), 2.02 (br s, 1H), 2.87 (s, 3H), 3.65 (septet, $J = 6.6$ Hz, 1H), 4.97 (d, $J = 4.3$ Hz, 1H), 7.19–7.38 (m, 6H), 7.44–7.48 (m, 1H), 7.67 (d, $J = 9.0$ Hz, 1H), 7.77 (d, $J = 7.8$ Hz, 1H), 7.99 (d, $J = 8.6$ Hz, 1H), 8.05 (s, 1H), 12.69 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 12.9, 36.0, 67.9, 76.2, 110.4, 118.9, 120.1, 122.7, 126.1, 126.4, 127.6, 128.2, 128.8, 129.2, 130.6, 131.1, 142.4, 155.5. IR ($CHCl_3$): 3438, 1622, 1047, 952, 745, 702 cm^{-1}. ESI-HRMS calcd for $C_{21}H_{23}N_2O_2$ ($M+H^+$): 335.1760. Found: 335.1758. Anal. Calcd for $C_{21}H_{23}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.10; H, 6.58; N, 8.33.

4.2.9. 2-((*E*)-(2-((1*R*,2*S*)-1-Hydroxy-1-phenyl-2-propyl)-2-isopropylhydrazono)methyl)phenol 6i. (1*R*,2*S*)-Norephedrine based hydrazine **5** and 2-hydroxybenzaldehyde were reacted to form the title compound, which was obtained as a yellow oil after chromatography (49%). $[\alpha]_D^{25} = +314.4$ (*c* 0.70, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.79 (d, $J = 6.6$ Hz, 3H), 1.09 (d, $J = 6.6$ Hz, 3H), 1.35 (d, $J = 6.6$ Hz, 3H), 2.28 (br s, 1H), 3.68 (sextet, $J = 6.6$ Hz, 1H), 3.82 (septet, $J = 6.6$ Hz, 1H), 4.88 (d, $J = 6.6$ Hz, 1H), 6.83–6.94 (m, 2H), 7.07–7.14 (m, 2H), 7.22–7.39 (m, 5H), 11.81 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 14.9, 18.5, 19.6, 47.6, 58.3, 76.6, 116.1, 119.0, 120.5, 126.3, 127.6, 127.8,

128.1, 128.2, 132.5, 142.8, 156.4. IR (neat): 3428, 1591, 1033, 910, 751, 701 cm^{-1}. ESI-HRMS calcd for $C_{19}H_{25}N_2O_2$ ($M+H^+$): 313.1916. Found: 313.1918.

4.2.10. 1-((*E*)-(2-((1*R*,2*S*)-1-Hydroxy-1-phenyl-2-propyl)-2-isopropylhydrazono)methyl)naphthalen-2-ol 6j. (1*R*,2*S*)-Norephedrine based hydrazine **5** and 2-hydroxy-1-naphthaldehyde were reacted to yield the title compound, which was obtained as a yellow oil after chromatography (80%). There was an impurity (ca. 5%) that could not be efficiently removed $[\alpha]_D^{25} = +196.6$ (*c* 0.63, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.92 (d, $J = 6.6$ Hz, 3H), 1.18 (d, $J = 6.6$ Hz, 3H), 1.41 (d, $J = 6.6$ Hz, 3H), 1.55 (br s, 1H), 2.20 (br s, 1H), 3.77 (m, 1H), 3.96 (m, 1H), 4.97 (d, $J = 6.6$ Hz, 1H), 7.20–7.48 (m, 7H), 7.67 (d, $J = 8.6$ Hz, 1H), 7.77 (d, $J = 8.2$ Hz, 1H), 7.99 (d, $J = 8.6$ Hz, 1H), 8.32 (s, 1H), 12.99 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 14.5, 18.5, 19.6, 48.2, 58.7, 76.3, 110.5, 118.9, 120.0, 122.7, 126.2, 126.3, 127.5, 128.1, 128.2, 128.9, 129.1, 130.5, 131.1, 142.8, 155.9. IR (neat): 3434, 1622, 1042, 909, 734, 701 cm^{-1}. ESI-HRMS calcd for $C_{23}H_{27}N_2O_2$ ($M+H^+$): 363.2073. Found: 363.2064.

5. General procedure for the diethylzinc addition to aldehydes

A chiral ligand (0.313 mmol) was added to a flame dried round bottom flask with toluene (4.1 mL) under 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. An aldehyde of choice (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 alcohol. The enantioselectivity of this process was immediately determined via chiral stationary phase HPLC.

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