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Synthesis and application of oxadiazines as chiral ligands for the enantioselective addition of diethylzinc to aldehydes

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ABSTRACT

A series of oxadiazines derived from L-phenylalanine bearing phenolic substituents have been synthesized in a multistep, one pot process. This process involves the reaction of a mixed anhydride with a β-hydrazino alcohol, methanesulfonylation of the alcohol moiety, and base induced cyclization. The resultant oxadiazines were employed in the asymmetric addition of diethylzinc to aldehydes.

1. Introduction

Chiral, non-racemic oxadiazines **1** were first prepared by Trepanier et al. in the 1960s (Fig. 1).[1–6] These compounds were of interest because of their central nervous system activity but were not fully pursued to a significant degree after their introduction. These compounds are structurally related to the oxadiazinones **2** that were pioneered by Trepanier et al.[7,8] and later applied in the asymmetric aldol reaction by Hitchcock et al.[9–12] We recently disclosed our efforts in developing syntheses for a series of oxadiazines derived from *Ephedra* alkaloids as well as L-phenylalanine.[13] We became interested in further developing oxadiazines for asymmetric applications. Oxazolines **3** are structurally related to oxadiazines and have been used in the asymmetric addition of diethylzinc to aldehydes.[14–17] Allen and Williams[17] synthesized an oxazoline bearing a phenolic substituent at the 2-position and used this compound as a ligand for the asymmetric addition reaction. This served as a motivation for the synthesis of oxadiazines bearing phenolic positions **4** for application in the diethylzinc addition process with aldehydes.

We opted to create the oxadiazines from L-phenylalanine as we had previously developed a preparative method based on this α-amino acid and had also demonstrated that the related L-phenylalanine based oxadiazinones could serve as effective chiral auxiliaries for the aldol reaction (Fig. 2).[18] We report herein on our efforts to prepare oxadiazines possessing phenolic substituents and their application in the asymmetric addition reaction with diethylzinc and aldehydes.

2. Results and discussion

The preparation of chiral, non-racemic oxadiazines was initiated by the synthesis of the L-phenylalaninol derived β-hydrazinoalcohol **6** using the synthetic route previously established by our research group.[18] The synthesis was effected by reductive alkylation with acetone and sodium borohydride, N-nitrosation, and lithium aluminum hydride reduction (Scheme 1). With the hydrazine in hand, the carboxylic acid component was then pursued. The first carboxylic acid that was employed in the oxadiazine synthesis was acetylsalicylic acid **9** (Scheme 2). Thus, the carboxylic acid was treated with

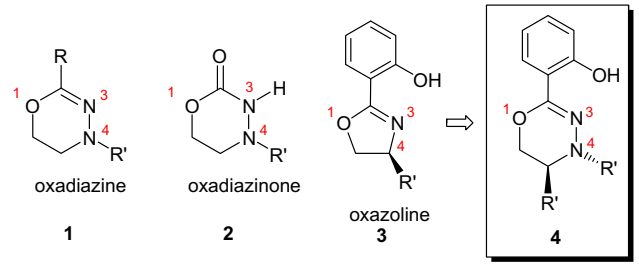

Figure 1. Structural relationship between oxadiazines, oxadiazinones, and oxazolines.

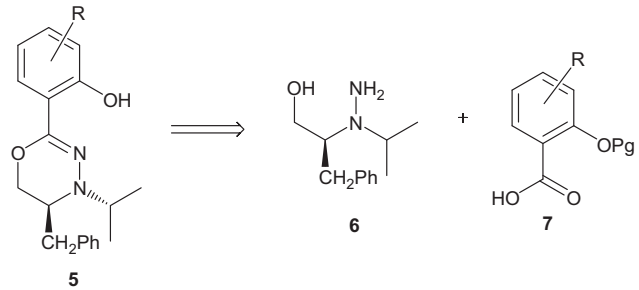

Figure 2. Synthesis plan for the phenolic oxadiazines.

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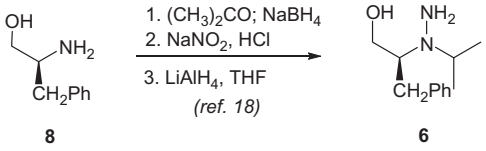


8 6

Scheme 1. Synthesis of β-hydrazinoalcohol **6**.

methanesulfonyl chloride and the resultant mixed anhydride was added dropwise to a solution of β-hydrazinoalcohol **6**.

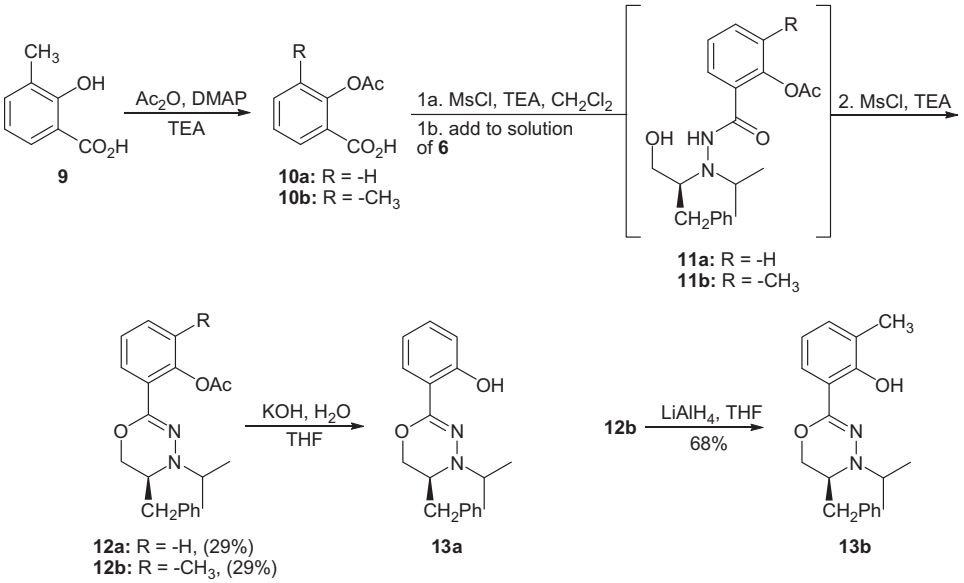
This process created β-hydrazidoalcohol **11a** which proved difficult to isolate in pure form without significant decomposition. In order to obviate this problem, **11a** was not isolated, but was treated directly with a second equivalent of methanesulfonyl chloride and triethylamine leading to the formation of oxadiazine **12a** in 29% yield for the three step process (hydrazide formation, methanesulfonate formation, and cyclization). It should be noted that an excess of methanesulfonyl chloride could not be added at the beginning of the reaction sequence as this might lead into the formation of the sulfonamide of **6** which would not undergo the cyclization process.

There was also an interest in the use of substituted derivatives of salicylic acid. To this end, 3-methylsalicylic acid **13a** was acetylated with acetic anhydride in 75% chemical yield and then employed in the synthesis of β-hydrazidoalcohol **11b** (Scheme 2). Cyclization with methanesulfonyl chloride and triethylamine afforded oxadiazine **12b** in 29% isolated yield after chromatography. With oxadiazines **12a** and **12b** in hand, an effort was made to deprotect the phenolic position. Saponification of **12a** with potassium hydroxide led to the formation of the desired oxadiazine **13a** in 45% yield. Oxadiazine **12b** did not readily undergo saponification perhaps due to steric hindrance inhibiting the formation of the tetrahedral intermediate necessary for the hydrolysis process. Treatment of **12b** with lithium aluminum hydride led to the formation of phenolic oxadiazine **13b** in 68% yield.

An alternate approach was pursued in order to circumvent the use of lithium aluminum hydride. To this end, 3-methylsalicylic acid was esterified with methanol and catalytic sulfuric acid, methylated at the phenolic oxygen with potassium carbonate and iodomethane, and then hydrolyzed under basic conditions to yield functionalized carboxylic acid **17a** (Scheme 3). Other related derivates were sought and so protection of the phenolic oxygen of 1-hydroxy-2-naphthoic acid was also accomplished using this synthetic route, thus providing compound **17b**. The introduction of a *tert*-butyl group onto the aromatic ring was also of interest. Thus, 3-*tert*-butylsalicylaldehyde was used in this process as the corresponding carboxylic acid was not commercially available. The phenolic oxygen was protected by methylation and the aldehyde was oxidized with potassium permanganate to afford carboxylic acid **17c**.

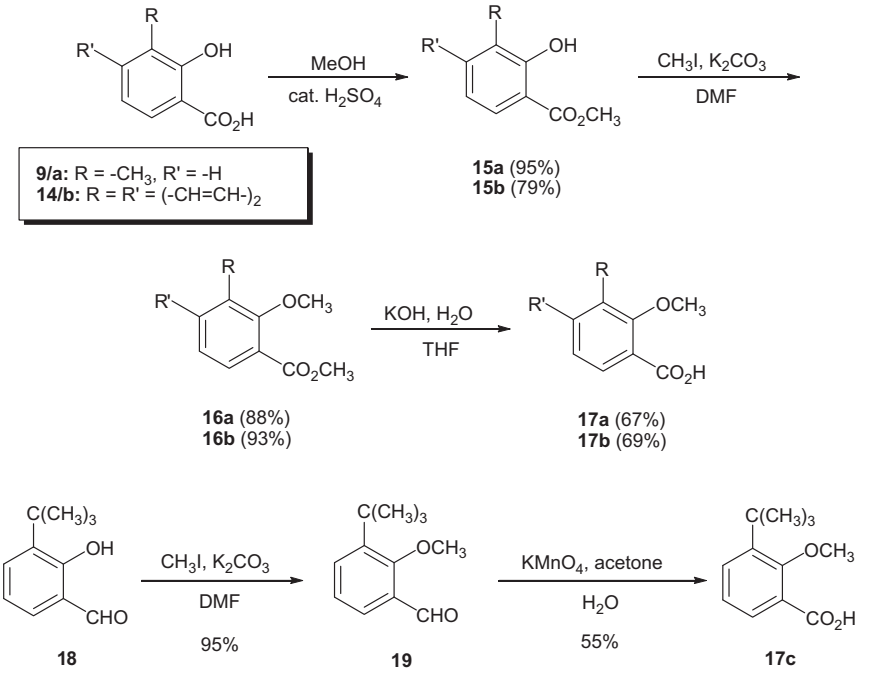
With the carboxylic acids in hand, the synthesis of the phenolic oxadiazine ligands was pursued. The multistep process of hydrazide formation, methanesulfonylation, and cyclization was employed and this led to the formation of oxadiazines **21a–c** in varying yields. The overall yield for the conversion of carboxylic acid **17a** into the desired oxadiazine **21a** through intermediate β-hydrazidoalcohol **20a** was 32% (Scheme 4). In like fashion, carboxylic acid **17b** was reacted with methanesulfonyl chloride to form **20b** which ultimately underwent cyclization to afford **21b** in 68% isolated yield after chromatography. Finally, the *tert*-butylsalicylic acid derivative was taken through the same process. The carboxylic acid was treated with methanesulfonyl chloride to form **20c**. Cyclization of the hydrazide gave a yield of 13% yield. The low yield is attributed to the steric volume of the *tert*-butyl group on the phenolic ring interfering with the cyclization. Finally, the methyl ethers were deprotected using the method of McOmie and West[19] employing boron tribromide (BBr_3) in a dichloromethane solution.

The collected oxadiazines were then employed in the asymmetric addition of diethylzinc to 2-naphthaldehyde to yield 1-(2-naphthyl)-1-propanol (Table 1). The observed enantioselectivities were determined by CSP HPLC to range from 17% to 55% ee with isolated chemical yields ranging from 76% to 93%. Oxadiazines **13a** and **22a** yielded the same level of enantioselection suggesting that the presence of the methyl group on **22a** was not of enough steric volume to make a difference. Changing the number of equivalents of diethylzinc (cf. entries 2 and 3) did not alter the level of enantioselection, but did produce the reduction byproduct 2-naphthylmethanol in addition to the addition product.[20] The oxadiazine bearing the naphthyl group led to a decrease in the enantioselection of the addition process. It is proposed that the naphthyl substituent does

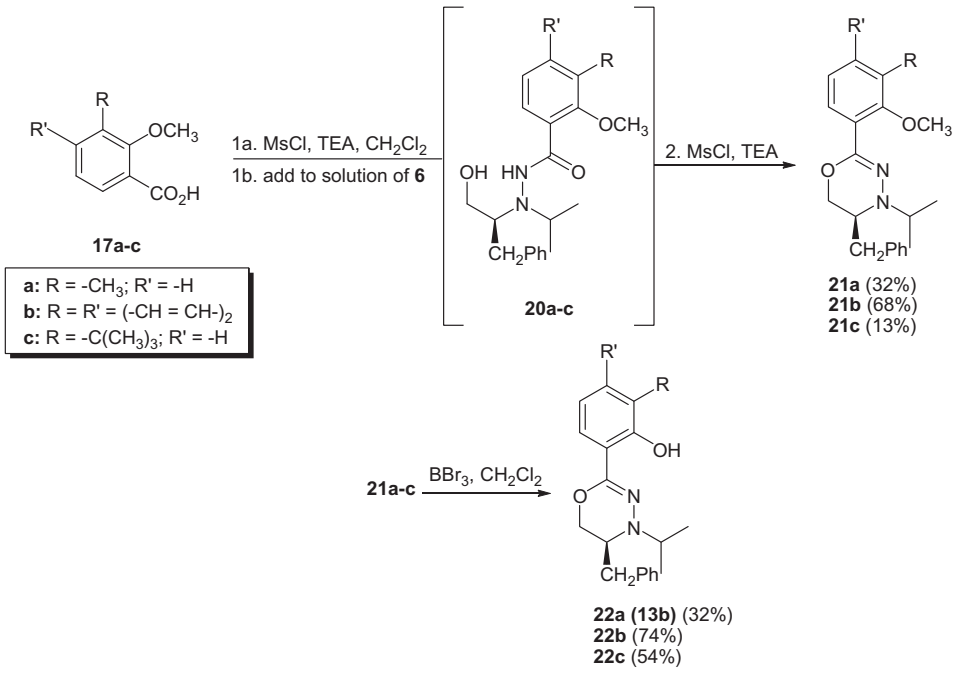


9
10a: R = -H
10b: R = -CH_3
11a: R = -H
11b: R = -CH_3
12a: R = -H, (29%)
12b: R = -CH_3, (29%)
13a
13b

Scheme 2. Synthesis of oxadiazines **13a** and **13b**.



Scheme 3. Preparation of functionalized carboxylic acids.



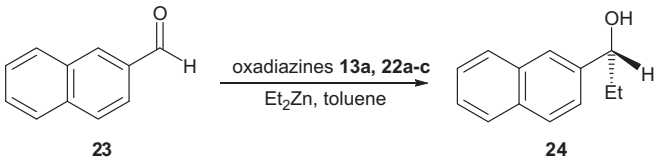
Scheme 4. Synthesis of oxadiazines **22a**–**c**.

not provide a steric environment conducive to the production of high enantioselectivities.

The use of oxadiazine **22c** bearing the *tert*-butyl substituent gave the best enantioselectivity in the formation of the addition product, presumably due to the projection of steric volume of the *tert*-butyl group into the region where the aldehyde potentially resides during the course of the asymmetric induction process (Fig. 3). Overall, the low enantioselectivity may be due to a variety of factors, primary amongst which might be the proximity of the stereocontrol element of the oxadiazine ring, namely, the N_4-position which bears an isopropyl group. Previous research with the related oxadiazinones demonstrated that this position was effective in the asymmetric aldol reaction.[18] However, in this case, the isopropyl group does not provide the same level of stereoselectivity.

The *tert*-butyl containing oxadiazine **22c** yielded the best enantioselectivity but presented a challenge in terms of its synthesis (vide supra). Oxadiazine **22a** was employed in the asymmetric addition of diethylzinc to a variety of aldehydes (Table 2). The observed enantioselectivities ranged from 12% to 36% ee. Again, the argument is made that the stereocontrol element of the N_4-isopropyl group was not sufficient in generating enantioselectivities that would be synthetically useful.

Table 1
Enantioselective addition of diethylzinc with 2-naphthaldehyde with oxadiazine ligands **13a** and **22a–c**



23 **24**

Entry	Oxadiazine	Et_2Zn (equiv)	Yield[a]	er (*R*:*S*), (% ee)[b]	Config.[c]
1	**13a**	2	93	38.1:61.9, (24)	(*R*)
2	**22a**	2	91	37.8:62.2, (24)	(*R*)
3	**22a**	3	76	38.1:61.9, (24)	(*R*)
4	**22b**	2	91	41.5:58.5, (17)	(*R*)
5	**22c**	2	90	22.7:77.3, (55)	(*R*)

[a] The yield was calculated after flash column chromatography.
[b] The enantiomeric ratios were determined via CSP HPLC using a Chiralcel-OD column.
[c] The configuration was determined by comparison of literature values.[21]

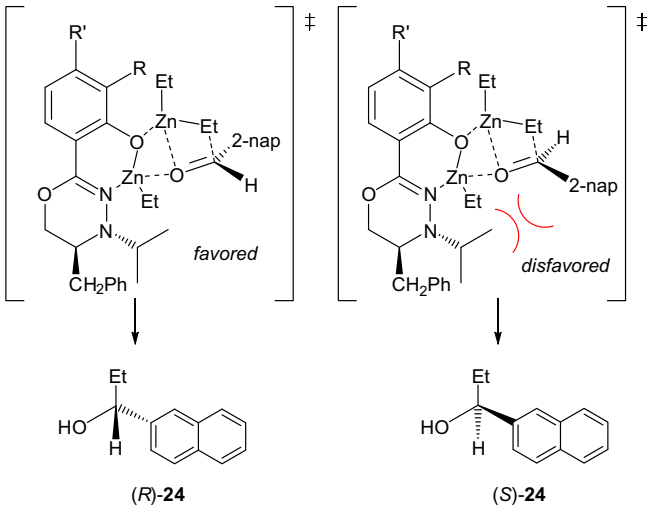


Figure 3. Proposed favored and disfavored transition states.

3. Conclusion

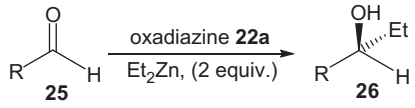
The oxadiazines were used in the asymmetric addition of diethylzinc with aldehydes; the enantiomeric excesses that were observed ranged from 12% to 55% ee. It is believed that the N_4-isopropyl oxadiazines **13a** and **22a-c** did not effectively impose stereoselectivity for the 1,2-addition reactions with diethylzinc and aldehydes. Consequently, we are exploring other applications that may prove to be more amenable to the oxadiazine structure.

4. Experimental

4.1. General remarks

Toluene was purchased as an anhydrous reagent and was used without further purification. Diethylzinc was directly purchased from Aldrich. All reactions were run under a nitrogen atmosphere. Unless otherwise noted, all ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using NMR spectrometer operating at 400 or 100 MHz respectively. Chemical shifts were reported in parts per million (δ scale), and coupling constants (J values) are listed in hertz (Hz). Tetramethylsilane (TMS) was used as internal standard ($\delta = 0$ ppm). Infrared spectra are reported in reciprocal centimeters (cm^{-1}) and

Table 2
Enantioselective additions of diethylzinc with aldehydes with oxadiazine **22a**



25 **26**

Entry	R	Yield[a]	er (*R*:*S*), (% ee)[b]	Config.[c]
1	$1\text{-}C_6H_5$	80	63.4:37.6, (25)	(*R*)
2	$2\text{-}C_{10}H_7$ (-2-naphthyl)	91	38.0:62.0, (24)	(*R*)
3	*-trans*-$CH{=}CHC_6H_5$	74	56.1:43.9, (12)	(*R*)
4	$p\text{-}C_6H_4OCH_3$	63	59.8:40.2, (20)	(*R*)
5	$\text{-}1\text{-}C_{10}H_7$(-1-naphthyl)	84	32.3:67.7, (36)	(*R*)

[a] The yield was calculated after flash column chromatography.
[b] The enantiomeric ratios were determined *via* CSP HPLC using a Chiralcel-OD.
[c] The configuration was determined by comparison of literature values.[21]

are measured either as Nujol mull or a neat liquid. Melting points were recorded on a Mel-Temp apparatus and are uncorrected. Optical activities were measured using at 589 nm using 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. 2-Acetoxy-3-methylbenzoic acid 10b

In a nitrogen purged, flame dried round bottomed flask was placed 3-methylsalicylic acid (10.0 g, 65.7 mmol), CH_2Cl_2 (366 mL), triethylamine (27.5 mL, 197 mmol), acetic anhydride (6.5 mL, 69 mmol), and dimethyaminopyridine (2.00 g, 16.4 mmol). The reaction mixture was stirred overnight before being quenched with 1 M HCl (100 mL). The organic layer was extracted with CH_2Cl_2 (2×100 mL) and washed with brine (75 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The title compound was isolated by recrystallization (EtOAc, hexanes). White solid (75%). Mp = 187–189 °C. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.24 (s, 3H), 2.37 (s, 3H), 7.24 (t, $J = 7.7$ Hz, 1H), 7.48 (d, $J = 6.6$ Hz, 1H) 7.96 (d, $J = 6.6$ Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.1, 20.8, 122.1, 125.8, 130.1, 132.4, 136.4, 169.3, 170.3 ppm. IR (Nujol mull): 3328, 1698, 1592 cm^{-1}. ESI-HRMS calcd for $C_{10}H_{10}O_4Na$ ($M+Na^+$): 217.0477. Found: 217.0473.

4.3. General procedure for formation of β-hydrazido alcohols 11a and 11b

In a 250 mL flamed dried, nitrogen purged round bottomed flask functionalized carboxylic acid (2.00 g, 11.1 mmol), CH_2Cl_2 (110 mL), triethylamine (1.63 mL, 11.7 mmol), and methanesulfonyl chloride (0.85 mL, 11 mmol) were placed and the solution was allowed to stir for 90 min before being transferred to an addition funnel. The solution was added dropwise to a solution made of L-phenyalanine derived β-hydrazino alcohol **3.16** (2.31 g, 11.1 mmol), CH_2Cl_2 (65 mL), and triethylamine (1.63 mL, 11.7 mmol). After the addition, the reaction mixture was allowed to stir overnight before being quenched with a saturated solution of NH_4Cl (75 mL). The organic layer was extracted with CH_2Cl_2 (2×75 mL) and washed with brine (75 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed by rotary evaporation.

4.3.1. (*S*)-2-(2-(1-Hydroxy-3-phenyl-2-propyl)-2-isopropylhydrazinecarbonyl)phenyl acetate 11a

Using acetylsalicylic acid **10a**, the title compound was not isolated and was directly carried out in the cyclization. ESI-HRMS calcd for $C_{21}H_{27}N_2O_4$ ($M+H^+$): 371.1971. Found: 371.1966.

4.3.2. (*S*)-2-(2-(1-Hydroxy-3-phenyl-2-propyl)-2-isopropylhydrazinecarbonyl)-6-methyl phenyl acetate 11b

Using **9**, the title compound was not isolated and was directly carried out in the cyclization. ESI-HRMS calcd for $C_{22}H_{29}N_2O_4$ ($M+H^+$): 385.2127. Found: 385.2116.

4.4. General procedure for one-pot synthesis of oxadiazines 12a and 12b

In a 250 mL flamed dried, nitrogen purged round bottomed flask functionalized carboxylic acid (0.97 g, 4.8 mmol) was placed. CH_2Cl_2 (48 mL), triethylamine (0.80 mL, 5.8 mmol), and methanesulfonyl chloride (0.40 mL, 4.8 mmol) were added and the solution was allowed to stir for 90 min before being transferred to an addition funnel. The solution was added dropwise to a solution composed of L-phenyalanine derived β-hydrazino alcohol **3.16** (1.00 g, 4.80 mmol), CH_2Cl_2 (24 mL), and triethylamine (0.80 mL, 5.8 mmol). After the addition the reaction mixture was allowed to stir overnight before the addition of triethylamine (1.35 mL, 9.60 mmol) and methanesulfonyl chloride (0.40 mL, 5.0 mmol). The reaction mixture was allowed to stir for an additional 48 h before being quenched with a saturated solution of NH_4Cl (75 mL). The organic layer was extracted with CH_2Cl_2 (2 × 75 mL) and washed with brine (75 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed by rotary evaporation.

4.4.1. (*S*)-2-(5-Benzyl-4-isopropyl-5,6-dihydro-4*H*-1,3,4-oxadiazin-2-yl)phenyl acetate 12a

Yellow oil (41%), $[\alpha]_D^{24} = +153.0$ (*c* 1.78, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.12 (d, *J* = 6.4 Hz, 3H), 1.27 (d, *J* = 6.4 Hz, 3H), 2.25 (s, 3H), 2.71 (dd, *J* = 13.5, 9.8 Hz, 1H), 2.95 (dd, *J* = 13.5, 8.4 Hz, 1H), 3.37–3.45 (m, 1H), 3.90 (dd, *J* = 10.2, 2.7 Hz, 1H), 4.06 (dd, *J* = 10.2, 3.5 Hz, 1H), 6.99–7.79 (m, 4H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 18.5, 20.3, 21.0, 34.6, 53.1, 53.6, 65.2, 123.2, 125.6, 125.9, 126.4, 128.4, 128.7, 129.2, 137.8, 141.6, 147.5, 169.4 ppm. IR (neat): 1686, 1622, 1448 cm^{-1}. ESI-HRMS calcd for $C_{21}H_{25}N_2O_3$ ($M+H^+$): 353.1865. Found: 353.1862.

4.4.2. (*S*)-2-(5-Benzyl-4-isopropyl-5,6-dihydro-4*H*-1,3,4-oxadiazin-2-yl)-6-methylphenyl acetate 12b

Yellow oil (68%). $[\alpha]_D^{24} = +124.0$ (*c* 1.31, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.12 (d, *J* = 6.4 Hz, 3H), 1.26 (d, *J* = 6.4 Hz, 3H), 2.18 (s, 3H), 2.28 (s, 3H), 2.71 (dd, *J* = 13.5, 9.9 Hz, 1H), 2.96 (dd, *J* = 13.5, 5.0 Hz, 1H), 3.38–3.46 (m, 1H), 3.90 (dd, *J* = 10.2, 2.6 Hz, 1H), 4.08 (dd, *J* = 10.2, 3.5 Hz, 1H), 7.10–7.34 (m, 7H), 7.58–7.61 (m, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 16.5, 18.7, 20.5, 21.0, 34.7, 53.3, 53.7, 65.5, 125.6, 126.1, 126.6, 126.8, 128.6, 129.4, 131.1, 131.4, 138.1, 142.2, 146.5, 169.0 ppm. IR (neat): 1686, 1622, 1448 cm^{-1}.

4.5. (*S*)-2-(5-Benzyl-4-isopropyl-5,6-dihydro-4*H*-1,3,4-oxadiazin-2-yl)phenol 13a

Oxadiazine **12a** (0.705 g, 2.00 mmol), THF (4 mL), and KOH (1 M, 4 mL) were combined in a 50 mL round bottomed flask. The reaction mixture was stirred for 24 h before the solvent was removed by rotary evaporation. The reaction mixture was diluted with a saturated solution of ammonium chloride (50 mL) and the organic layer was extracted with CH_2Cl_2 (2 × 50 mL) and washed with brine (50 mL). The organic layer was dried over ($MgSO_4$) and the solvent was removed by rotary evaporation. The title compound was isolated by flash column chromatography (hexanes/EtOAc, 95:5). Yellow oil (45%), $[\alpha]_D^{23} = +164.7$ (*c* 0.16, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.07 (d, *J* = 6.4 Hz, 3H), 1.27 (d, *J* = 6.4 Hz, 3H), 2.60 (dd, *J* = 13.6, 9.6 Hz, 1H), 2.99 (dd, *J* = 13.6, 5.0 Hz, 1H), 3.38 (m, 1H), 4.00 (dd, *J* = 10.4, 2.8 Hz, 1H), 4.10 (dd, *J* = 10.4, 5.0 Hz, 1H), 6.74–7.51 (m, 4H), 11.83 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 17.2, 20.9, 34.6, 52.0, 53.9, 66.6, 114.8, 116.4, 118.4, 125.2, 126.8, 128.7, 129.3, 130.4, 137.2, 145.6, 147.2, 157.3 ppm. IR (neat): 3492, 1622, 1448 cm^{-1}.

4.6. (*S*)-2-(5-Benzyl-4-isopropyl-5,6-dihydro-4*H*-1,3,4-oxadiazin-2-yl)-6-methylphenol 13b

Oxadiazine **12b** (0.130 g, 0.350 mmol) was added to a solution of $LiAlH_4$ (0.010 g, 0.17 mmol) in THF (5 mL). The reaction mixture was allowed to stir for 45 min before being quenched with H_2O (50 mL). THF was removed by rotary evaporation and the organic layer was extracted with CH_2Cl_2 (2 × 50 mL) and washed with brine (50 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The title product was isolated by flash column chromatography (hexanes/EtOAc, 98:2). Yellow oil (68%). $[\alpha]_D^{24} = +157.1$ (*c* 1.24, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.13 (d, *J* = 6.4 Hz, 3H), 1.35 (d, *J* = 6.4 Hz, 3H), 2.28 (s, 3H), 2.65 (dd, *J* = 13.6, 9.6 Hz, 1H), 3.04 (dd, *J* = 13.6, 5.0 Hz, 1H), 3.42–3.47 (m, 1H), 4.06 (dd, *J* = 10.4, 2.8 Hz, 1H), 4.16 (dd, *J* = 10.4, 5.0 Hz, 1H), 6.74 (t, *J* = 7.6 Hz, 1H), 7.04–7.45 (m, 8H), 12.11 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.9, 17.2, 21.0, 34.5, 52.1, 53.9, 66.7, 114.2, 117.9, 123.0, 125.2, 126.7, 128.6, 129.2, 131.5, 137.2, 147.5, 155.5 ppm. IR (neat): 3492, 1622, 1448 cm^{-1}. ESI-HRMS calcd for $C_{20}H_{25}N_2O_2$ ($M+H^+$): 325.1916. Found: 325.1907.

4.7. Methyl 2-hydroxy-3-methylbenzoate 15a

In a round bottomed flask were placed 3-methylsalicylic acid **9** (15.0 g, 98.6 mmol), methanol (300 mL), and concentrated H_2SO_4. The reaction mixture was allowed to stir at reflux for 48 h. The solvent was then removed by rotary evaporation. The reaction mixture was then neutralized with $NaHCO_3$. The organic layer was extracted with EtOAc (2 × 100 mL) and washed with brine (100 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The title compound was isolated by flash column chromatography (hexanes/EtOAc, 99:1). Clear liquid (97%). ^1H NMR (400 MHz, $CDCl_3$) δ: 2.27 (s, 3H), 3.94 (s, 3H), 6.78 (t, *J* = 7.6 Hz, 1H), 7.31 (m, 1H), 7.67–7.70 (m, 1H), 11.01 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.6, 52.2, 111.6, 118.5, 126.6, 127.4, 136.4, 160.0, 171.0 ppm. IR (neat): 3483, 1738, 1589 cm^{-1}. ESI-HRMS calcd for $C_9H_{11}O_3$ ($M+H^+$): 167.0618. Found: 167.0619.

4.8. Methyl 1-hydroxy-2-naphthoate 15b

In a round bottomed flask were placed 1-hydroxy-2-naphthoic acid **14b** (10.0 g, 53.1 mmol), methanol (200 mL), and concentrated H_2SO_4 (10 mL). The reaction mixture was allowed to stir at reflux for 48 h. The organic layer was then extracted with EtOAc (2 × 100 mL) and washed with brine (100 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The title compound was isolated by flash column chromatography (hexanes/EtOAc, 99:1). White solid (79%). Mp = 217–220 °C. ^1H NMR (400 MHz, $CDCl_3$) δ: 3.98 (s, 3H), 7.26 (d, *J* = 4.3 Hz, 1H), 7.51 (ddd, *J* = 7.5, 6.9, 1.3, 1H), 7.59 (ddd, *J* = 7.5, 6.9, 1.3 Hz, 1H), 7.74 (d, *J* = 8.8 Hz, 2H), 8.40 (d, *J* = 7.9 Hz, 1H), 11.98 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 52.3, 105.6, 118.6, 123.8, 124.2, 124.7, 125.7, 127.4, 129.4, 137.2, 160.9, 171.4 ppm. IR (Nujol mull): 3483, 1738, 1589 cm^{-1}. ESI-HRMS calcd for $C_{12}H_{11}O_3$ ($M + H^+$): 203.0630. Found: 203.0629.

4.9. Methyl 2-methoxy-3-methylbenzoate 16a

To a flame dried, nitrogen purged flask were added **15a** (15.0 g, 90.3 mmol), DMF (90 mL), and K_2CO_3 (37.40 g, 270.8 mmol). The

reaction mixture was allowed to stir for 45 min before the addition of iodomethane (5.90 mL, 94.8 mmol). The reaction mixture was allowed to stir overnight before being quenched with HCl (1 M, 100 mL). The organic layer was extracted with CH_2Cl_2 (2 × 50 mL) and washed with brine (50 mL). The solvent was removed by rotary evaporation. The title compound was isolated by flash column chromatography (hexanes/EtOAc, 95:5). Clear liquid (72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.31 (s, 3H), 3.82 (s, 3H), 3.90 (s, 3H), 7.03 (t, J = 7.6 Hz, 1H), 7.31–7.33 (m, 1H), 7.61–7.61 (m, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 16.0, 52.1, 61.4, 123.3, 124.4, 128.9, 132.5, 134.9, 158.4, 166.8 ppm. IR (neat): 1729, 1590, 1293. ESI-HRMS calcd for $C_{10}H_{12}O_3Na$ (M+Na$^+$): 203.0684. Found: 203.0683.

4.10. Methyl 1-methoxy-2-naphthoate 16b

To a flame dried, nitrogen purged flask were added **15b** (6.90 g, 40.0 mmol), DMF (40 mL), and K_2CO_3 (16.5 g, 120 mmol). The reaction mixture was allowed to stir for 45 min before the addition of iodomethane (3.75 mL, 60.1 mmol). The reaction mixture was allowed to stir overnight before being quenched with 1 M HCl (100 mL). The organic layer was extracted with CH_2Cl_2 (2 × 75 mL) and washed with brine (75 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The title compound was isolated by flash column chromatography (hexanes/EtOAc, 9:1). Clear liquid (93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.94 (s, 3H), 4.03 (s, 3H), 7.48–7.56 (m, 3H), 7.76–7.83 (m, 2H), 8.23–8.26 (m, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 52.0, 63.1, 118.9, 123.4, 126.3, 126.4, 127.6, 128.1, 128.3, 136.5, 158.1, 166.4 ppm. IR (neat): 1729, 1590, 1293 cm^{-1}. ESI-HRMS calcd for $C_{13}H_{12}O_3$ (M+Na$^+$): 239.0684. Found: 239.0689.

4.11. 2-Methoxy-3-methylbenzoic acid 17a

Ester **16a** (2.63 g, 14.6 mmol), THF (12 mL), and KOH (6 M, 12 mL) were combined in a round bottomed flask and the solution was stirred overnight. The solvents were removed by rotary evaporation. The reaction mixture was acidified by 3 M HCl and the organic layer was extracted with CH_2Cl_2 (2 × 50 mL) and washed with brine (50 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The title compound was recrystallized with EtOAc and hexanes. White solid (77%). Mp = 194–197 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.37 (s, 3H), 3.93 (s, 3H), 7.17 (t, J = 7.6 Hz, 1H), 7.42–7.44 (m, 1H), 7.94–7.96 (m, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 16.0, 62.1, 122.1, 124.9, 130.7, 131.7, 137.0, 158.0, 167.1 ppm. IR (Nujol mull): 3276, 1691, 1281 cm^{-1}. ESI-HRMS calcd for $C_9H_{10}O_3Na$ (M+Na$^+$): 189.0528. Found: 189.0524.

4.12. 1-Methoxy-2-naphthoic acid 17b

Ester **16b** (6.10 g, 32.8 mmol) was dissolved in THF (27 mL) and 6 M KOH (27.0 mL, 164 mmol) was added cautiously. The reaction mixture was stirred at reflux overnight and the solvent was removed by rotary evaporation. The reaction mixture was acidified by 3 M HCl (100 mL) and the organic layer was extracted with CH_2Cl_2 (2 × 50 mL) and washed with brine (50 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The title compound was recrystallized with EtOAc and hexanes. White solid (79%). Mp = 198–199 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.17 (s, 3H), 7.60–7.67 (m, 2H), 7.72 (d, J = 8.6 Hz, 1H), 7.90 (d, J = 7.2 Hz, 1H), 8.10 (d, J = 8.6 Hz, 1H), 8.19–8.21 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 64.3, 117.7, 123.1, 125.1, 126.9, 127.0, 127.1, 128.4, 129.0, 137.6, 157.8, 166.8. IR (Nujol mull): 3276, 1691, 1281 cm^{-1}. ESI-HRMS calcd for $C_{12}H_{10}O_3$ (M+Na$^+$): 225.0528. Found: 225.0525.

4.13. 3-*tert*-Butyl-2-methoxybenzaldehyde 19

In a nitrogen purged, round bottomed flask 3-*tert*-butyl-2-hydroxybenzaldehyde **18** (4.20 mL, 24.5 mmol), DMF (25 mL), and K_2CO_3 (10.2 g, 73.5 mmol) were placed. The reaction mixture was stirred for 45 min before the addition of iodomethane (2.30 mL, 36.8 mmol). The reaction mixture was stirred overnight before being quenched with 1 M HCl (150 mL). The organic layer was extracted with CH_2Cl_2 (2 × 75 mL) and washed with brine (75 mL). The solvent was removed by rotary evaporation. The title compound was isolated by flash column chromatography (hexanes/EtOAc, 95:5). Clear liquid (95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.42 (s, 9H), 3.95 (s, 3H), 7.14 (t, J = 7.8 Hz, 1H), 7.57 (dd, J = 7.8, 1.8 Hz, 1H), 7.70 (dd, J = 7.8, 1.8 Hz, 1H), 10.3 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 30.7, 35.1, 66.0, 123.7, 128.0, 129.7, 133.2, 143.6, 163.3, 190.3 ppm. IR (neat): 2749, 1698, 1596, 1199 cm^{-1}. ESI-HRMS calcd for $C_{12}H_{15}O_2$ (M+H$^+$): 191.1072. Found: 191.1071.

4.14. 3-*tert*-Butyl-2-methoxybenzoic acid 17c

In a flame dried, nitrogen purged flask **19** (4.47 g, 23.3 mmol), acetone (232 mL), H_2O (211 mL), and $KMnO_4$ (9.18 g, 58.1 mmol) dissolved in H_2O (93 mL) were placed. The reaction mixture was allowed to stir overnight before the reaction mixture was filtered through Celite. The filtrate was then removed of solvent by rotary evaporation. The organic layer was made basic with 3 M NaOH (75 mL) and the organic layer was removed with EtOAc (2 × 75 mL). The water layer was acidified with 3 M HCl (100 mL). The organic layer was extracted with EtOAc (2 × 75 mL) and washed with brine (75 mL). The organic layer was then dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The title product was isolated by flash column chromatography (hexanes/EtOAc, 85:15). Yellow solid (55%). Mp = 167–169 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.42 (s, 9H), 3.9 (s, 3H), 7.09 (t, J = 7.8 Hz, 1H), 7.55 (dd, J = 7.8, 1.5 Hz, 1H), 7.83 (dd, J = 7.8, 1.5 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 30.8, 35.3, 63.1, 123.0, 123.2, 130.8, 132.3, 143.9, 160.9, 171.9 ppm. IR (Nujol mull): 3328, 1686, 1293 cm^{-1}. ESI-HRMS calcd for $C_{12}H_{17}O_3$ (M+H$^+$): 209.1178. Found: 209.1173.

4.15. General procedure for one-pot synthesis of oxadiazines

In a 250 mL flamed dried, nitrogen purged round bottomed flask was placed the functionalized carboxylic acid (0.97 g, 4.8 mmol). Then CH_2Cl_2 (48 mL), triethylamine (0.80 mL, 5.8 mmol), and methanesulfonyl chloride (0.40 mL, 4.8 mmol) were added and the solution was allowed to stir for 90 min before being transferred to an addition funnel. The solution was added dropwise to a solution made of the L-phenyalanine derived β-hydrazino alcohol (1.00 g, 4.80 mmol), CH_2Cl_2 (24 mL), and triethylamine (0.80 mL, 5.8 mmol). After the addition the reaction mixture was allowed to stir overnight before the addition of triethylamine (1.35 mL, 9.60 mmol) and methanesulfonyl chloride (0.40 mL, 5.0 mmol). The reaction mixture was allowed to stir for an additional 48 h before being quenched with a saturated solution of NH_4Cl (75 mL). The organic layer was extracted with CH_2Cl_2 (2 × 75 mL) and washed with brine (75 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The target compound was isolated by flash column chromatography (hexanes/EtOAc, 95:5) and contained <5% impurities.

4.15.1. (*S*)-5-Benzyl-4-isopropyl-2-(2-methoxy-3-methylphenyl)-5,6-dihydro-4*H*-1,3,4-oxadiazine 21a

Yellow oil (32%). $[\alpha]_D^{24} = +179.6$ (c 0.98, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.17 (d, J = 6.4 Hz, 3H), 1.32 (d, J = 6.4 Hz, 3H), 2.32 (s, 3H), 2.76 (dd, J = 13.4, 9.9 Hz, 1H), 3.02 (dd, J = 13.4,

4.8 Hz, 1H), 3.42–3.48 (m, 1H), 3.86 (s, 3H), 4.01 (dd, J = 10.4, 2.7 Hz, 1H), 4.14 (dd, J = 10.4, 4.0 Hz, 1H), 6.97–7.43 (m, 7H), 7.80–7.82 (m, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 16.2, 18.3, 20.7, 34.5, 52.6, 53.6, 61.0, 66.0, 123.5, 126.5, 127.1, 127.9, 128.6, 129.3, 131.8, 138.1, 144.1, 156.4 ppm. IR (neat): 1686, 1448, 1213 cm^{-1}. ESI-HRMS calcd for $C_{21}H_{27}N_2O_2$ ($M+H^+$): 339.2073. Found: 339.2072.

4.15.2. (*S*)-5-Benzyl-4-isopropyl-2-(1-methoxynaphthalen-2-yl)-5,6-dihydro-4*H*-1,3,4-oxadiazine 21b

Yellow oil (24%). $[\alpha]_D^{24} = +191.3$ (c 1.21, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.17 (d, J = 6.4 Hz, 3H), 1.36 (d, J = 6.4 Hz, 3H), 2.78 (dd, J = 13.5, 9.8 Hz, 1H), 3.05 (dd, J = 13.5, 4.8 Hz, 1H), 3.45–3.51 (m, 1H), 4.01 (s, 3H), 4.05 (dd, J = 10.3, 2.8 Hz, 1H), 4.20 (dd, J = 10.3, 4.2 Hz, 1H), 7.20–7.33 (m, 1H), 7.42–7.49 (m, 1H), 7.55 (d, J = 8.6 Hz, 1H), 7.72 (d, J = 8.6 Hz, 1H), 7.79–7.87 (m, 1H), 8.20–8.22 (m, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 18.3, 20.9, 34.8, 52.7, 53.8, 62.6, 66.2, 121.8, 122.8, 123.3, 125.9, 126.5, 126.6, 127.6, 128.5, 128.7, 129.3, 135.0, 138.0, 143.8, 154.3 ppm. IR (neat): 1686, 1448, 1213 cm^{-1}. ESI-HRMS calcd for $C_{24}H_{27}N_2O_2$ ($M+H^+$): 375.2073. Found: 375.2066.

4.15.3. (*S*)-5-Benzyl-2-(3-*tert*-butyl-2-methoxyphenyl)-4-isopropyl-5,6-dihydro-4*H*-1,3,4-oxadiazine 21c

Yellow oil (13%). $[\alpha]_D^{24} = +156.1$ (c 1.11, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.13 (d, J = 6.4 Hz, 3H), 1.30 (d, J = 6.4 Hz, 3H), 1.38 (s, 9H), 2.70 (dd, J = 13.5, 9.8 Hz, 1H), 3.05 (dd, J = 13.5, 4.8, 1H), 3.40–3.53 (m, 2H), 3.84 (s, 3H), 4.03 (dd, J = 11.4, 2.8 Hz, 1H), 4.18 (dd, J = 10.4, 4.8 Hz, 1H), 6.98 (t, J = 7.7 Hz, 1H), 7.20–7.41 (m, 7H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 17.9, 20.6, 30.8, 35.1, 35.3, 52.4, 53.5, 60.7, 66.4, 122.5, 126.6, 127.0, 127.8, 128.6, 129.4, 129.5, 137.9, 142.8, 145.1, 158.0 ppm. IR (neat): 1686, 1448, 1213 cm^{-1}. ESI-HRMS calcd for $C_{24}H_{33}N_2O_2$ ($M+H^+$): 381.2542. Found: 381.2537.

4.16. (*S*)-2-(5-Benzyl-4-isopropyl-5,6-dihydro-4*H*-1,3,4-oxadiazin-2-yl)-6-methylphenol 22a

In a flame dried, nitrogen purged flask were placed **21a** (1.10 g, 3.25 mmol) and CH_2Cl_2 (32 mL). The reaction mixture was cooled to 0 °C before the dropwise addition of 1 M BBr_3 in toluene (5.5 mL, 5.5 mmol). The reaction mixture was stirred overnight and then quenched with H_2O (75 mL). The organic layer was extracted with ether (2 × 50 mL) and washed with brine (50 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The title compound was isolated by flash column chromatography (hexanes/EtOAc, 95:5). See **13b** for characterization data.

4.16.1. (*S*)-2-(5-Benzyl-4-isopropyl-5,6-dihydro-4*H*-1,3,4-oxadiazin-2-yl)naphthalen-1-ol 22b

In a flame dried, nitrogen purged flask **21b** (0.147 g, 0.376 mmol) and CH_2Cl_2 (5 mL) were placed. The reaction mixture was cooled to 0 °C before the dropwise addition of 1 M BBr_3 in toluene (0.65 mL, 0.64 mmol). The reaction mixture was stirred overnight and then quenched with H_2O (50 mL). The organic layer was extracted with ether (2 × 50 mL) and washed with brine (50 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The title compound was isolated by flash column chromatography (hexanes/EtOAc, 98:2). Yellow oil (74%). $[\alpha]_D^{24} = +176.6$ (c 0.89, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.22 (d, J = 6.4 Hz, 3H), 1.48 (d, J = 6.4 Hz, 3H), 2.73 (dd, J = 13.6 Hz, 9.6 Hz, 1H), 3.12, (dd, J = 13.6, 5.0 Hz, 1H), 3.49–3.59 (m, 1H), 4.20 (dq, J = 10.4, 5.0 Hz, 1H), 7.26–7.80 (m, 9H), 8.41–8.43 (m, 1H), 13.01 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 17.2, 21.1, 34.5, 52.0, 53.9, 66.9, 107.99, 117.8, 122.0, 123.0, 124.9, 125.1, 126.8, 127.1, 127.3, 128.7, 129.3, 134.7, 137.3, 148.3, 154.6 ppm. IR (neat): 3490, 1618, 1456 cm^{-1}. ESI-HRMS calcd for $C_{23}H_{25}N_2O_2$ ($M+H^+$): 361.1802. Found: 361.1816.

4.16.2. (*S*)-2-(5-Benzyl-4-isopropyl-5,6-dihydro-4*H*-1,3,4-oxadiazin-2-yl)-6-*tert*-butylphenol 22c

In a flame dried, nitrogen purged flask **21c** (0.211 g, 0.555 mmol) and CH_2Cl_2 (5 mL) were placed. The reaction mixture was cooled to 0 °C before the dropwise addition of 1 M BBr_3 in toluene (1.0 mL, 1.0 mmol). The reaction mixture was stirred overnight and then quenched with H_2O (50 mL). The organic layer was extracted with ether (2 × 50 mL) and washed with brine (50 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The title compound was isolated by flash column chromatography (hexanes/EtOAc, 98:2). Yellow oil (54%). $[\alpha]_D^{24} = +146.9$ (c 1.03, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.15 (d, J = 6.4 Hz, 3H), 1.35 (d, J = 6.4 Hz, 3H), 1.44 (s, 3H), 2.69 (dd, J = 13.6, 9.7 Hz, 1H), 3.04 (dd, J = 13.6, 5.0 Hz, 1H), 3.42–3.52 (m. 1H), 4.04 (dd, J = 10.4, 2.8 Hz, 1H), 4.15 (dd, J = 10.4, 4.6 Hz, 1H), 6.77 (t, J = 4.2 Hz, 1H), 7.19–7.29 (m, 7H), 7.49 (dd, J = 7.9, 1.75 Hz, 1H), 12.3 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 17.5, 21.0, 29.5, 34.5, 34.9, 52.3, 53.9, 66.4, 114.8, 117.4, 123.5, 126.7, 127.7, 128.7, 129.3, 136.7, 137.4, 147.8, 156.7. IR (neat): 3489, 1617, 1443 cm^{-1}. ESI-HRMS calcd for $C_{23}H_{31}N_2O_2$ ($M+H^+$): 367.2318. Found: 367.2314.

4.17. General procedure for the diethylzinc addition with aldehydes

A chiral ligand of choice (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. 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 HCl (1 M, 50 mL) and extracted with CH_2Cl_2 (2 × 50 mL). 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 by chiral stationary phase HPLC.

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