Salicylaldehyde Based Oxazolidines as Catalysts for the Asymmetric Addition of Diethylzinc to Aldehydes

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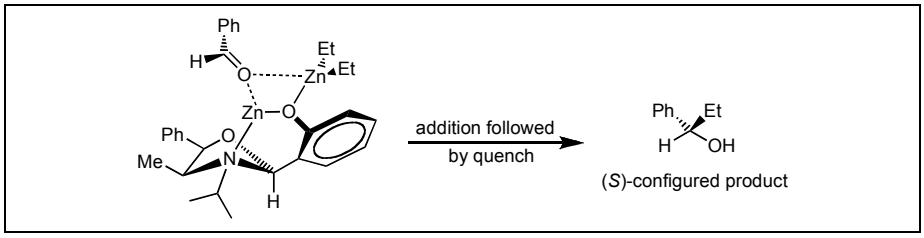
Received December 11, 2007



A series of oxazolidines have been prepared by condensation of *N*-isopropyl norephedrine with a variety of salicylaldehyde derivatives. Despite the stereochemical relationship of (1*R*,2*S*)-norephedrine with (1*R*,2*S*)-ephedrine, the resultant oxazolidines **12-14** were determined to have a stronger stereochemical relationship with (1*S*,2*S*)-pseudoephedrine based oxazolidines. The resultant oxazolidines were used as catalytic ligands in the addition of diethylzinc to several aldehydes. It was determined that the oxazolidine derivative **12** gave the highest yield and a moderate enantioselectivity.

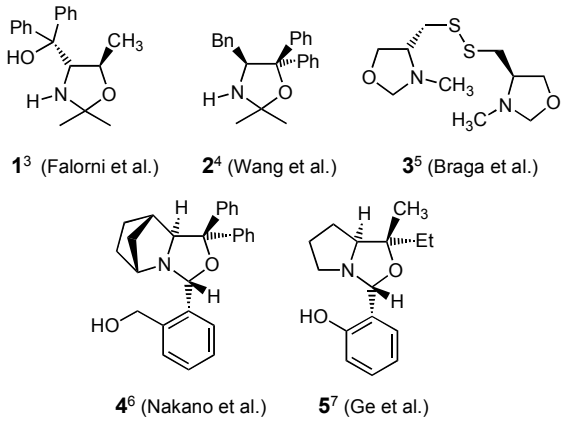
J. Heterocyclic Chem., **45**, 873 (2008).

INTRODUCTION

There have been many different β-aminoalcohol structural motifs that have been employed in the catalytic asymmetric addition of diorganozinc compounds to aldehydes [1,2]. Oxazolidines that contain the β-aminoalcohol moiety have been used to this end. The oxazolidines that have been prepared are structurally diverse and vary in terms of their effectiveness as chiral ligands (Chart 1), [3-7]. Recently, we became interested in the development of new oxazolidine catalysts for asymmetric synthetic applications [8]. In this context, we prepared (1*R*,2*S*)-ephedrine based oxazolidine catalyst **6** and (1*S*,2*S*)-pseudoephedrine based oxazolidine catalyst **7** (Figure 1). These chiral catalysts were employed in the asymmetric 1,2-addition of diethylzinc with aldehydes and gave fair to moderate enantioselectivities (Scheme 1).

The use of the (1*R*,2*S*)-ephedrine based oxazolidine catalyst gave the (*R*)-configured product, while the (1*S*,2*S*)-pseudoephedrine based catalyst gave the (*S*)-configured product. The origin of this enantioselectivity is believed to be based, in part, on the relative stereochemistry of the substituents on the oxazolidine ring. Specifically, the stereochemical positioning of the phenolic unit is potentially the primary controlling mechanism responsible for which enantiomer of the product is formed. In addition to this, it is proposed that the N-methyl group also plays a role in the magnitude of enantioselection that is observed. Thus, we became interested in determining if the magnitude of the asymmetric induction could be influenced further by increasing the steric demand of the alkyl group attached to the nitrogen. This is not directly possible with either ephedrine or pseudoephedrine as the nitrogen substituent is a methyl group. However, the *Ephedra* based β-amino-alcohol norephedrine would be an excellent tool for creating new derivatives. Herein, we report on the synthesis of (1*R*,2*S*)-norephedrine based oxazolidine catalyst with a more sterically demanding nitrogen substituent and its use in the asymmetric addition of diethylzinc to carbonyl compounds.

Chart 1. Oxazolidine catalysts.



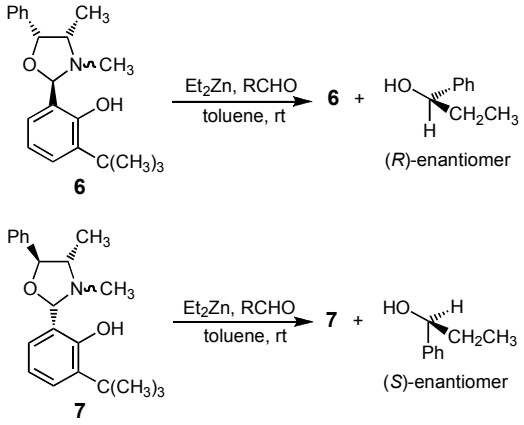
1[3] (Falorni et al.) **2**[4] (Wang et al.) **3**[5] (Braga et al.)

4[6] (Nakano et al.) **5**[7] (Ge et al.)

RESULTS AND DISCUSSION

The oxazolidine catalysts used in this work were prepared by first reductively alkylating enantiomerically pure norephedrine with acetone, benzaldehyde, or cyclohexanone in the presence of sodium borohydride

Scheme 1

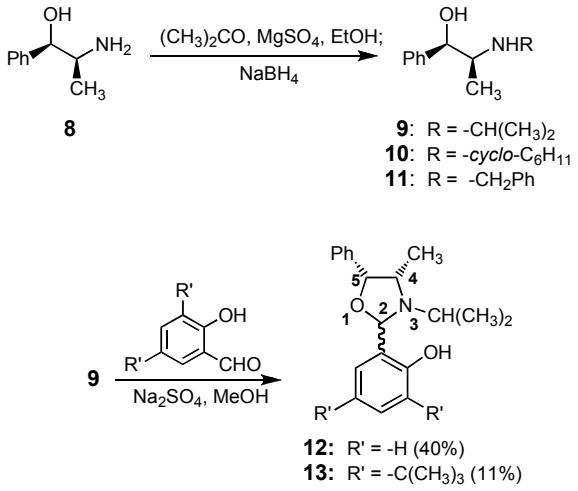


(Scheme 2) [9]. These derivatives were then reacted with a variety of salicylaldehyde derivatives. The *N*-isopropyl-norephedrine derivative **9** was reacted with salicyl-aldehyde and 3,5-di-*tert*-butyl-2-hydroxybenz aldehyde to yield oxazolidines **12** and **13,** respectively (Scheme 1). Oxazolidine **12** was obtained in 40% isolated yield. Unfortunately, oxazolidine **13** could only be obtained in 11% yield and was isolated as a mixture of diastereomers [10]. The preparation of *N*-benzyl- and *N*-cyclohexyl-norephedrine derivatives, **10** and **11**, respectively, proved to be complicated. The crude ^{1}H NMR spectra of these compounds suggested that the target oxazolidines had formed based on the presence of the characteristic C_2-methine proton (~5.1 ppm). However, these compounds were minor components (<5%) of product mixtures that were primarily the corresponding starting materials. The oxazolidines could not be recovered by flash chromatography, presumably due to the hydrolysis of the oxazolidines in the presence of silica. Oxazoldines **10** and **11** were ultimately abandoned in lieu of the other derivatives.

With oxazolidines **12** and **13** in hand, efforts were made to determine the stereochemical orientation of the methine carbon (C_2) bearing the aromatic residue of the salicylaldehyde component. This was accomplished by obtaining an NOE difference spectrum of oxazolidine **12**. The methine proton H_2 was irradiated and the resultant NOE difference spectrum showed positive enhancements for the protons H_4 and H_5.

Oxazolidine **12** was also subjected to X-ray crystal-lographic analysis to determine the absolute configuration of the oxazolidine ring system (Figure 1, Table 1). The ring system (O1/C2/N3/C4/C5) adopts an envelope conformation and all of the bond distances and angles are within normal ranges and are similar to other oxazolidines reported in the chemical literature (Table 2) [11].

Scheme 2



The substituents on C2, C4, and C5 positions share a *cis*-relationship in their orientation as inferred from NOE experiments. Additionally, the crystal structure also suggests that the isopropyl group on the N_3-nitrogen has a *trans*-relationship to the substituents on the ring carbons due to the intermolecular hydrogen bonding interaction between N_3-nitrogen and the hydroxyl group. The relative conformation of the nitrogen substituent in the solid state was determined to be a *trans*-relationship with the C_2, C_4 and C_5-positon. Based on these collected results and the similarity of the ^{1}H NMR spectra of **12** and **13**, it is proposed that oxazolidine **13** also has the same relative configuration about the oxazolidine ring system.

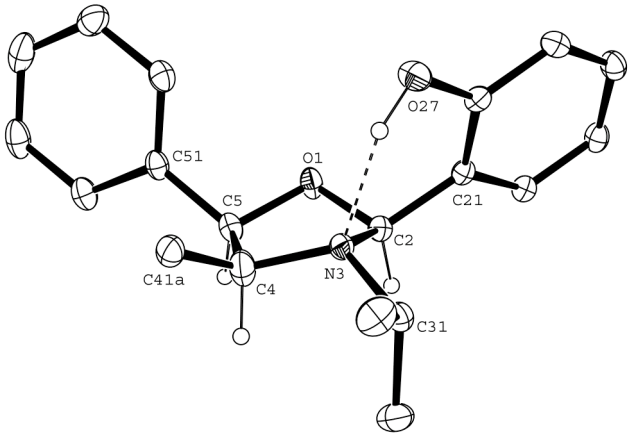


Figure 1. Crystal structure of **12**. Displacement ellipsoids are drawn at the 30% probability level and hydrogen atoms are shown as spheres of arbitrary size. The dashed line indicates the intramolecular hydrogen bond.

Table 1. Crystal data, data collection, and structure refinement data for **12**.

Empirical formula	$C_{19}H_{23}NO_2$
Formula weight	297.38
Crystal dimensions (mm)	0.32 × 0.18 × 0.18
Crystal system	orthorhombic
Space group	$P2_12_12_1$ (No. 19)
Unit cell parameters	
a (Å)	6.2585 (6)
b (Å)	14.8448 (19)
c (Å)	17.2254 (14)
V (Å^3)	1600.3 (3)
Z	4
ρ_{calc} (g cm^{-1})	1.234
μ (mm^{-1})	0.079
R indices ($F^2 > 2\sigma(F^2)$)	$R_1 = 0.0351$, $wR_2 = 0.0726$
R indices (all data)	$R_1 = 0.0746$, $wR_2 = 0.0844$
GOF	1.009
Largest peak and hole (e·Å^{-3})	0.152 and – 0.178

With the stereochemistry about the oxazolidine ring system of **12** established, a structural comparison was made with Ephedra based oxazolidines **6** and **7** that were previously prepared [8]. It was determined that the relative configurations of the C_2- and C_4-positions around the N_3-nitrogen of **12** more closely resembled the configuration of the pseudoephedrine based oxazolidine **7** than the ephedrine based oxazolidine **6** (Figure 2). The stereochemical relationship between **7** and **12** would suggest that the stereochemical outcome in the asymmetric addition of diethylzinc to benzaldehyde would lead to would lead to the same resultant product with the (*S*)-configuration.

Table 2. Selected bond lengths and angles for **12**.

Bond lengths (Å)		Bond angles (°)	
C31-N3	1.492 (3)	C2-N3-C31	112.72 (19)
C4-N3	1.481 (3)	C4-N3-C31	117.9 (2)
C2-N3	1.482 (3)	C4-N3-C2	106.12 (19)
C2-C21	1.509 (3)	N3-C4-C5	102.39 (19)
C2-O1	1.420 (3)	O1-C5-C4	105.28 (19)
C5-O1	1.442 (3)	C2-O1-C5	105.83 (18)
C4-C5	1.565 (4)	O1-C2-N3	102.87 (19)
Torsion angles (°)			
C21-C2-N3-C4	156.8 (2)		
C21-C2-N3-C31	– 72.8 (3)		

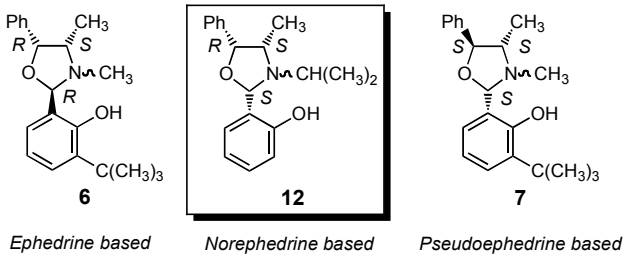
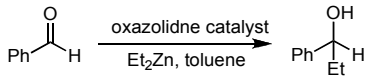


Figure 2

Based on the similarity between the structures of the pseudoephedrine based oxazolidine **7** and the norephedrine oxazolidines **12** and **13**, the expected stereochemical outcome of the catalytic asymmetric addition to benzaldehyde was predicted to give similar results. Thus, the enantioselective diethylzinc process with ligands **12** and **13** was pursued. This was accomplished using 10% mol catalyst loading and three equivalents of diethylzinc. The results of the catalytic addition diethylzinc to benzaldehyde revealed moderate enantioselectivities (Table 3).

As predicted, the norephedrine based catalysts **12** and **13** afforded the same absolute stereochemistry of the alcohol product as the pseudoephedrine based catalyst **7**. This suggested that the stereochemistry in the region of the C2/N3/C4 tandem was the determinant of the stereochemical outcome of the catalysis. In this regard, oxazolidine **13** gave a higher level of enantioselection but proved to be difficult to prepare in sufficient quantities to allow for further testing. In addition to this, the ^{1}H and ^{13}C NMR spectra suggested the presence of the C_2-epimer. Attempts to remove the C_2-epimer by either recrystallization or chromatography were not successful. In contrast oxazolidine **12** could be readily obtained as a single diastereomer by recrystallization as determined by ^{1}H NMR spectroscopy.

Table 3. Enantioselective addition of diethylzinc to benzaldehyde with oxazolidines **7** and **12-13.**



entry	ligand	%completion[a]	er (l*S*-*R*l)[b]	config.[c]
1	**7**[d]	99	74.5:25.5 (49)	*S*
2	**12**	94	69.0:31.0 (38)	*S*
3	**13**	92	77.5:22.5 (55)	*S*

[a]The degree of completion was determined by ^{1}H NMR spectroscopy. [b]The enantiomeric ratios were determined via CSP HPLC using a Chiralcel-OD column. [c]The absolute configuration of the product was determined by comparison of optical activities and retention times in the literature values [12]. dThe enantioselectivity derived from ligand 7 was previously determined [8].

Thus, catalyst **12** was utilized in the asymmetric 1,2-addition of diethylzinc to various aldehydes to test the capabilities of this structural family of catalysts. The addition occurred readily with both aromatic and aliphatic aldehydes and the stereochemical outcome was greater on average for aromatic aldehydes, although the enantioselectivities were modest at best. The result obtained from the use of *n*-hexanal was anomalous as compared to the other entries. The enantiomeric ratio seemed to suggest that the aldehyde could be attacked

from either the *Re*- or *Si*-face with little discrimination for the steric volume of the *n*-hexanal side chain. Nonetheless, there was significant discrimination in the case of the aromatic aldehydes.

Table 4. Enantioselective additions of diethylzinc to aldehydes via oxazolidine **12**.

entry	aldehyde	%completion[a]	er (|*S*:*R*|)[b]	config.[c]
1	C_6H_5-	94	69.0:31.0 (38)	*S*
2	*p*-$CH_3OC_6H_4$-	28	73.5: 26.5 (47)	*S*
3	*p*-ClC_6H_4-	95	71.0:29.0 (42)	*S*
4	*t*-PhCH=CH-	86	65.0:35.0 (30)	*S*
5	C_5H_{11}-	92	45.5:54.5 (9)	*R*

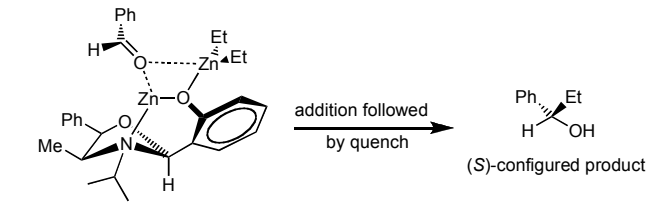
[a]The percent completion was determined by evaluating the ^{1}H NMR spectra. [b]The enantiomeric ratios were determined via CSP HPLC using a Chiralcel-OD column. [c]The configuration was determined by comparison with retention times and optical activities in the chemical literature [12].

The proposed transition state for asymmetric addition of diethylzinc to benzaldehyde catalyzed by oxazolidine **12** is illustrated in Scheme 3. This proposed mechanism is derived from the structure obtained from X-ray crystallography of **12** in conjunction with literature examples of proposed mechanisms [13].

CONCLUSION

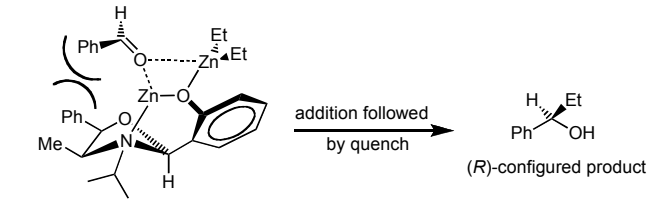
The introduction of a more sterically demanding N_3-isopropyl substituent in oxazolidine **12** had only a limited impact in the catalytic enantioselective addition of diethylzinc to aldehydes. It is apparent that alternate strategies must be applied with oxazolidines in order to exploit their full potential as ligands in this catalytic process. Research is underway to address alternative means of enhancing the efficacy of oxazolidines as asymmetric catalysts.

Scheme 3



Proposed favored transition state for **12**

(*S*)-configured product



unfavored transition state for **12**

(*R*)-configured product

EXPERIMENTAL

General Remarks. Toluene was purchased as an anhydrous reagent and used without further purification. All reactions were run under a nitrogen atmosphere. Unless otherwise noted, all ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using an NMR spectrometer operating at 400 MHz and 100 MHz, respectively. Chemical shifts are reported in parts per million (δ scale), and coupling constants (*J* values) are listed in hertz (Hz). Tetramethylsilane (TMS) was used as the internal standard (δ = 0 ppm). Infrared spectra are reported in reciprocal centimeters (cm-1) and are measured either as a nujol mull, a neat liquid, or in $CHCl_3$. Melting points were recorded on a Mel-Temp apparatus and are uncorrected. 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.

Crystal Structure Determination. Colorless crystals of $C_{19}H_{23}NO_2$ **(12)** were isolated by crystallization from a hexane/ether solution at low temperature. Data for **12** were collected on a Bruker-Nonius CAD4/Mach3 diffractometer equipped with an Oxford Cryostreams Cobra cryostat using Mo Kα radiation at –100 ºC. Data collection and cell refinement was performed using CAD4 express [14]. Data reduction was carried out using XCAD4 [15]. Unit cell parameters were obtained from a least-squares refinement of 25 centered reflections. See Table 1 for a summary of crystal data and X-ray collection information. The structure of **12** was solved using the direct methods program SIR-92 [16] and refinement was completed using the program SHELXL-97 [17]. Carbon C41 was found to be disordered over two positions, with both positions having 50% occupancy. Carbon 41a was modeled anisotropically, while carbon 41b was modeled isotropically. Hydrogen atoms attached to carbon were assigned positions based on the geometries of their attached carbons and were refined as riding with C-H distances between 0.95Å and 1.00 Å and with $U_{iso}(H) = 1.2U_{eq}(C)$ The hydrogen attached to oxygen was assigned its position based on the Fourier difference map.

Crystallographic data for compound **12** have been deposited with the Cambridge Crystallographic Data Centre (CCDC), CCDC No. 662535. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; email: deposit@ccdc.cam.ac.uk.

Procedure for the Reductive Alkylation of Norephedrine. To a flame dried, nitrogen purged flask was added (1*R*,2*S*)-norephedrine 8a (10.1 g, 66.8 mmol), ethanol (100 mL), and acetone (7.4 mL, 100 mmol). The mixture was allowed to stir at room temperature for 24 hours. At that time, the solution was cooled to 0 ºC and sodium borohydride (5.07 g, 134 mmol) was added and allowed to stir for 2 hours. The ethanol was removed under reduced pressure and the reaction quenched with sodium hydroxide (1M, 100 mL). The product was extracted with ethyl acetate (100 mL x 2), washed with brine, dried with magnesium sulfate, gravity filtered, and concentrated under reduced pressure. The amino alcohol was purified via recrystallization with hexanes: ethyl acetate (2:1) to afford **9** as a white solid in 70% yield.

(1*R*,2*S*)-2-Isopropylamino-1-phenyl-1-propanol (9). $[\alpha]_D^{25}$ = -10.3 (*c* 1.28, $CHCl_3$). Mp = 99-101 ºC. ^{1}H NMR: δ 0.80 (d, *J* = 6.6 Hz, 3H), 1.10 (t, *J* = 7.2 Hz, 6H), 2.97 (m, 1H), 3.05 (dq, *J* = 4.0, 6.6 Hz, 1H), 4.70 (d, *J* = 4.0 Hz, 1H), 7.23-7.35 (m, 5H). Characterization data for this compound matched the identical compound found in the literature [9b].

(1*R*,2*S*)-2-(Benzylamino)-1-phenyl-1-propanol (10). [18] Using benzaldehyde, the title compound was obtained in 99% yield as a clear oil. R_f = 0.42 (90:10 hexanes/EtOAc). $[\alpha]_D^{25}$ = -30.0 (*c* 0.86, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.86 (d, *J* = 6.6 Hz, 3H), 3.01 (dq, *J* = 6.6, 3.5 Hz, 1H), 3.89 (s, 2H), 4.80 (d, *J* = 3.5 Hz, 1H), 7.26-7.35 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 14.7, 51.4, 58.1, 73.9, 126.6, 127.4, 127.5, 128.4, 128.5, 128.9, 140.3, 142.2. IR (CHCl3): 3406, 3028, 1603, 1028, 732, 700 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{20}NO$ (M + H)$^+$: 242.1535 Found: 242.1545.

(1*R*,2*S*)-2-Cyclohexylamino-1-phenyl-1-propanol (11). The purified product was isolated via recrystallization (ethyl acetate/hexanes) in 85% yield. Mp: 89-91 °C. $[\alpha]_D^{25}$ = +11.2 (*c* 1.66, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ, 0.78 (d, *J* = 6.6 Hz, 3H), 1.00-1.34 (m, 7H), 1.59-1.64 (m, 1H), 1.71-1.75 (m, 1H), 1.85-1.96 (m, 1H), 2.52-2.59 (m, 1H), 3.05-3.11 (m, 1H), 4.66 (d, *J* = 4.0 Hz, 1H), 7.21-7.34 (m, 5H). ^{13}C NMR ($CDCl_3$): δ, 12.7, 24.8, 24.9, 25.5, 31.8, 32.5, 54.3, 55.8, 72.4, 126.0, 127.0, 128.0, 140.9. IR (nujol mull): 3278, 1102, 738, 701 cm^{-1}. ESI-HRMS calcd for $C_{15}H_{23}NO$ (M + H)$^+$: 234.1858. Found: 234.1858.

General Procedure for Oxazolidine Synthesis with 2-hydroxybenzaldehyde. To a flame dried, nitrogen purged flask was added **9** (2.05 g, 10.6 mmol), methanol (45 mL), 2-hydroxybenzaldehyde (1.12 mL, 10.6 mmol), and sodium sulfate (7.50 g, 53.2 mmol). The mixture was stirred under reflux for 17 hours and filtered through Celite. Excess solvent was removed under reduced pressure and the product was recrystallized with ethyl ether and hexanes (1:2).

2-[(2*S*,4*S*,5*R*)-3-Isopropyl-4-methyl-5-phenyloxazolidin-2-yl] phenol (12). Using 2-hydroxybenzaldehyde and **9**, the title compound was obtained as white crystals (40%). $[\alpha]_D^{25}$ = -133.6 (*c* 0.43, CH_2Cl_2). Mp = 96-98 ºC. ^{1}H NMR ($CDCl_3$): δ 0.88 (d, *J* = 7.2 Hz, 3H), 1.14 (d, *J* = 6.6 Hz, 3H), 1.21 (d, *J* = 6.6 Hz, 3H), 3.09 (septet, *J* = 6.6 Hz, 1H), 3.55 (pentet, *J* = 6.6 Hz, 1H), 5.09 (d, *J* = 7.2 Hz, 1H), 5.38 (s, 1H), 6.81-6.87 (m, 2H), 7.18-7.31 (m, 7H), 12.29 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 18.8, 19.3, 21.6, 50.7, 57.6, 81.1, 81.2, 95.2 (epimer), 95.3 (epimer), 117.0, 118.8, 120.8, 126.4, 127.6, 128.1, 130.2 (epimer), 130.3 (epimer), 136.6, 158.7. IR (nujol mull): 1174, 753, 712, 702 cm^{-1}. ESI-HRMS calcd for $C_{19}H_{24}NO_2$ (M + H)$^+$: 298.1807. Found: 298.1817.

2,4-Di-*tert*-butyl-6-((2*S*,4*S*,5*R*)-3-isopropyl-4-methyl-5-phenyloxazolidin-2-yl)phenol (13). Using 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde and **9**, the title compound was obtained as white crystals (11%). $[\alpha]_D^{25}$ = -72.2 (*c* 0.30, $CHCl_3$). Mp = 94-96 ºC. 1H NMR ($CDCl_3$): δ 0.88 (epimer, d, *J* = 7.2 Hz, 3H), 0.90 (d, *J* = 6,6 Hz, 3H), 1.15 (d, *J* = 6.6 Hz, 3H), 1.20 (d, *J* = 6.6 Hz, 3H), 1.30 (s, 9H), 1.45 (s, 9H), 3.09 (epimer, septet, *J* = 6.6 Hz, 1H), 3.12 (septet, *J* = 6.6 Hz, 1H), 3.58 (pentet, *J* = 6.6 Hz, 1H), 5.09 (d, *J* = 7.2 Hz, 1H), 5.36 (s, 1H), 7.04 (d, *J* = 2.0 Hz, 1H), 7.25-7.37 (m, 5H), 12.15 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 14.8 (epimer), 18.1, 19.3 (epimer), 21.6 (epimer), 23.1 (epimer), 23.3, 29.5, 31.7, 34.1 (epimer), 35.0, 45.9 (epimer), 49.9, 55.4 (epimer), 56.9, 73.2, 81.4, 96.2, 119.4, 124.6, 125.0, 126.1, 126.7 (epimer), 127.0, 127.6, 128.0 (epimer), 128.1, 136.1, 137.2, 139.9, 155.5. IR (nujol mull): 3411, 1607, 1168, 755, 703 cm^{-1}. ESI-HRMS calcd for $C_{27}H_{40}NO_2$ (M + H)$^+$: 410.3059. Found: 410.3060.

General Procedure for the Addition of Diethylzinc to Aldehydes. Oxazolidine **12** (0.088 g, 0.29 mmol) was added with toluene (4 mL) to a flame dried flask in an inert atmosphere. A solution of diethylzinc in hexanes (1M, 8.92 mL) was added and allowed to stir at room temperature for 25 minutes. At that time, benzaldehyde (0.30 mL, 2.97 mmol) was added and allowed to stir at room temperature for 24 hours. The reaction was quenched with a saturated ammonium chloride solution (50 mL) and the corresponding alcohol was extracted using ethyl acetate (50 mL x 2). The alcohol was washed with brine, dried with magnesium sulfate, gravity filtered, and concentrated under reduced pressure.

Chiral Stationary Phase HPLC (CSP HPLC) analysis. The enantioselectivity of the asymmetric addition of diethylzinc to the carbonyl compounds was determined after the reactions were quenched and extracted. The determination was carried out via chiral stationary phase HPLC. A Chiralcel-OD column was employed with a UV detector operating at 254 nm. The solvent system was composed of a mixture of hexanes and isopropanol (99.5:0.5) and the flow rate was 1 mL/min.

1-Phenyl-1-propanol: t_R = 11.8 (*R*) and 14.8 (*S*) min.

1-(4-Methoxyphenyl)propan-1-ol: t_R = 16.3 (*R*) and 19.3 (*S*) min.

1-(4-Chlorophenyl)propan-1-ol: The product of the addition of diethylzinc with 4-chlorobenzaldehyde was derivatized with 2-naphthoyl chloride. Retention time for 1-(4-chlorophenyl)-propan-1-ol (as naphthoate)**:** t_R = 12.8 (*R*) and 10.6 (*S*) min.

1-Phenyl-1-penten-3-ol: t_R =22.8 (*R*) and 43.1 (*S*) min.

3-Octanol: The product of the diethylzinc addition to hexanal was derivatized as the 2-naphthoate derivative: t_R = 20.2 (*R*) and 18.9 (*S*) min.

Acknowledgements. This research was funded in part by a Research Enhancement Award from Illinois State University's College of Arts & Sciences. The authors gratefully acknowledge support for this work, in part, by the National Science Foundation (NSF grant# CHE 644950) and the donors of the Petroleum Research Fund as administered by the American Chemical Society (PRF grant # B 40777-1).

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