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Intramolecular chiral relay at stereogenic nitrogen: oxazolidine catalysts derived from *Ephedra* alkaloids

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Abstract—A series of oxazolidines have been prepared by reaction of either (1*R*,2*S*)-ephedrine or (1*S*,2*S*)-pseudoephedrine with salicylaldehyde derivatives. The resultant oxazolidines were used as catalytic ligands in the addition of diethylzinc to a variety of aromatic and aliphatic aldehydes. It was determined that the (1*R*,2*S*)-ephedrine based oxazolidine derivative **9** gave the highest enantioselectivities.

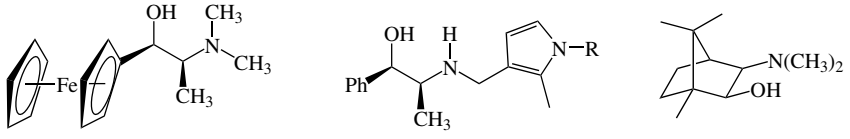
1. Introduction

The stereoselective formation of carbon–carbon bonds represents one of the most important processes in synthetic organic chemistry.[1] Much research has been devoted to developing a great variety of asymmetric methods for addressing this central transformation.[2] Of these methods, the use of diorganozinc reagents in conjunction with chiral, nonracemic β-amino alcohol ligands has proven to be very successful.[3] The ligands that have been employed (e.g., α-amino acid derived,[4] *Ephedra* derived,[5] and terpene derived[6]) in the catalytic process vary greatly in their structural motifs (Chart 1).[7] However, to the best our knowledge, there are only a few reports involving oxazolidines as chiral templates for conducting catalytic asymmetric syntheses with diorganozinc reagents.[8]

Oxazolidines have perhaps received less attention due to the success of the related oxazolidinones developed by Evans.[9] Nonetheless, oxazolidines have shown significant promise as chiral synthons and auxiliaries.[10] Based on these observations, we became interested in the development of oxazolidine ligands for use as catalysts in catalytic asymmetric diorganozinc reactions. In particular, we sought to explore oxazolidines derived from (1*R*,2*S*)-ephedrine and (1*S*,2*S*)-pseudoephedrine and salicylaldehyde derivatives. Herein, we report on the synthesis of these compounds and their application in asymmetric 1,2-addition of diethylzinc to aldehydes.

2. Results and discussion

We began our investigation by preparing a series of oxazolidines by reacting either (1*R*,2*S*)-ephedrine or (1*S*,2*S*)-pseudoephedrine with salicylaldehyde in methanol at reflux temperatures. After recrystallization of the products, this process yielded the ephedrine and pseudoephedrine oxazolidines **6** and **7**, respectively (Scheme 1). The stereochemistry of these oxazolidines was assigned based on the previous, independent, works of Watson et al. (X-ray crystallography)[11] and Agami and Rizk (^{1}H NMR



1[4] (Pelinski et al.) **2**[5] (Unaleroglu, Aydin, and Demir) **3**[6] (Jiang et al.)

Chart 1. β-Amino alcohol catalysts.

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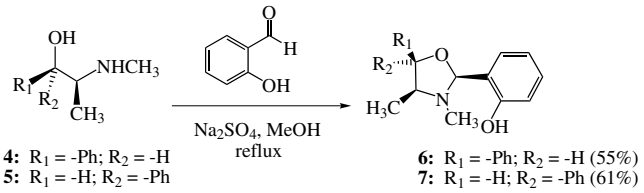


Scheme 1. Synthesis of oxazolidine ligands **6** and **7**.

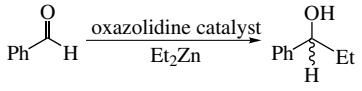
spectroscopy).[12,13] The selective formation of a predominant diastereomer in each case is believed to be the result of a thermodynamic equilibration process.[11,12]

With oxazolidine **6** in hand, we pursued its application in the catalytic asymmetric addition of diethylzinc to benzaldehyde (Table 1).[14] In the course of our initial optimization studies, it was determined that 10 mol % of catalyst loading of **6** in toluene at room temperature was ideal in addition to 30 equiv of diethylzinc relative to the catalyst. The final reaction conditions and stoichiometry provided the best compromise in terms of the reaction completion and enantiomeric excess of the end product, 1-phenyl-1-propanol. Nonetheless, we were disappointed to learn that the optimized enantiomeric excess for the product was 15%, based on chiral stationary phase HPLC. Thus, pseudoephedrine based oxazolidine **7** was used as a catalyst in the process using the optimized reaction conditions developed with **6** to determine if there would be enhanced enantiomeric excess of the product. Ultimately, this catalytic process went to completion, but the enantiomeric excess improved to only 23% ee.

Interestingly, the absolute stereochemistry of the addition product was the same for ephedrine based catalyst **6** as it was for pseudoephedrine based catalyst **7**, namely the (*S*)-configuration. It is proposed that the diastereomeric transition states involved in the carbon–carbon bond formation directly rely on the stereochemical orientation of the phenolic unit and the N_3-methyl substituent, and only indirectly on the stereochemical configuration of the C_5-position (Fig. 1).

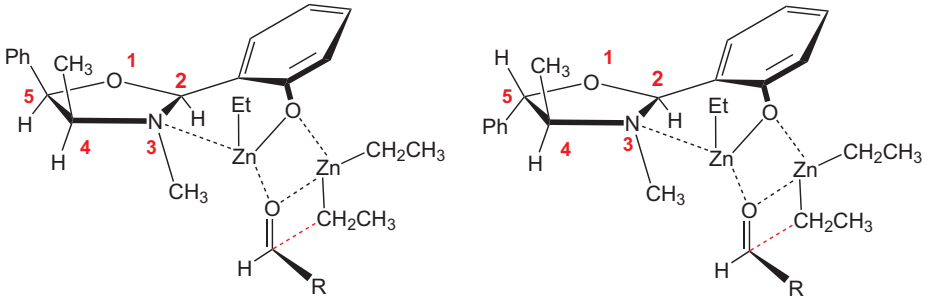
In order to improve the observed enantiomeric excesses for this catalytic process, new oxazolidines were prepared. These derivatives would involve the use of mono- and disubstituted salicylaldehydes rather than unsubstituted salicylaldehyde. The rationale for using these aldehydes was driven by the successes of the chiral, nonracemic salen catalysts pioneered by Jacobsen[15] and Katsuki.[16] Consequently, (1*R*,2*S*)-ephedrine and (1*S*,2*S*)-pseudoephedrine were reacted with either 3-*tert*-butyl-2-hydroxybenzaldehyde or 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde to afford oxazolidines **8**–**11** (Scheme 2). We were gratified

Table 1. Enantioselective addition of diethylzinc to benzaldehyde with oxazolidines **6** and **7**



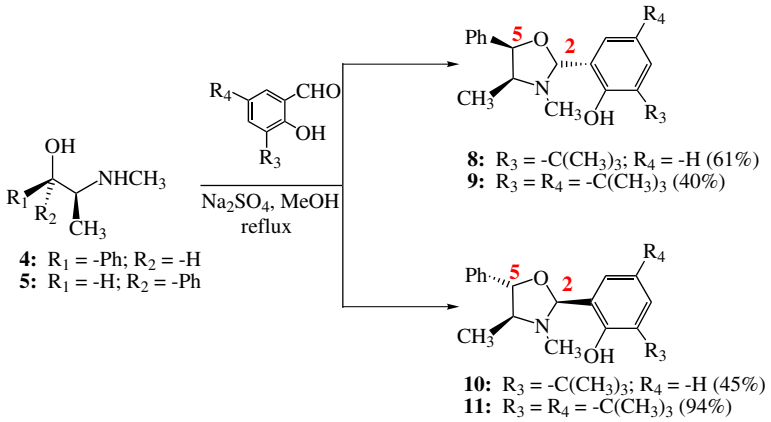
Entry	Catalyst (mol %)	Et_2Zn (equiv)	Temperature (°C)	Completion[a] (%)	ee[b] (%)	Configuration[c]
1	**6** (10)	15	−30	0	—	—
2	**6** (10)	20	0	11	19	*S*
3	**6** (10)	5	rt	14	17	*S*
4	**6** (10)	10	rt	41	19	*S*
5	**6** (20)	20	0	49	20	*S*
6	**6** (10)	30	rt	99	15	*S*
7	**7** (10)	30	rt	99	23	*S*

[a] A completed reaction did not reveal remaining aldehyde signals in ^1H NMR spectra.
[b] The % ee values were determined via HPLC using a Chiralcel-OD column. 2% 2-propanol in hexane, flow rate: 1 mL/min, UV detector (254 nm). $t_R = 11.8$ (*R*) and 14.8 (*S*) min.
[c] The configuration was determined by comparison of the literature values.[14]



TS(1): catalyst **6**-Et_2Zn-PhCHO TS(2): catalyst **7**-Et_2Zn-PhCHO

Figure 1. Proposed transition states for catalysts **6** and **7**.



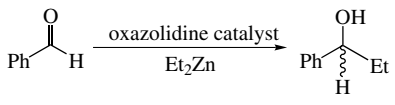
Scheme 2. Synthesis of oxazolidine ligands **8**–**11**.

to learn that the products of these reactions were crystalline, with the exception of **11**. It was not possible to purify oxazolidine **11** as it reverted to starting materials when exposed to chromatographic conditions with silica gel. Nonetheless, this material was deemed pure enough (~92%) for application in the catalytic asymmetric addition process. The stereochemical configuration of oxazolidines **8**–**11** was tentatively assigned based on ^{1}H NMR spectroscopic methods involving NOESY and are as depicted in Scheme 2. There was no significant NOE enhancement observed for protons at the C_2- and C_5-positions in derivatives **8**–**11**, suggesting that the ephedrine and pseudoephedrine oxazolidines all have a *trans* relationship between the two positions.

Using the optimized conditions developed in Table 1, oxazolidine ligands **8**–**11** were employed in the asymmetric addition of diethylzinc to benzaldehyde (Table 2). It was discovered that ligand **9** resulted in the highest enantioselective addition. The increase of enantioselectivity in ligands **8**–**11** is attributed to the presence of the *tert*-butyl groups (Fig. 2).

However, the absolute stereochemistry of the end product of the catalysis is not necessarily the result of direct steric interactions with the *tert*-butyl substituents of the phenol ring. Rather, the N_3-methyl group is proposed to be the stereocontrol element via an intramolecular chiral relay.[17] When comparing ephedrine based oxazolidine **6** with **8** and **9**, oxazolidine **6** has a *cis* relationship between the C_2 and C_5 position, whereas **8** and **9** have a *trans* relationship between the C_2 and C_5 positions. The *cis* relationship in **6** is attributed to the equilibration that occurs during the formation of the oxazolidine.[11,12] In contrast, **8** and **9** have larger aryl substituents at the C_2 position making the *cis* orientation less favorable, thus leading to the predominance of the *trans*-isomer that is isolated by recrystallization. As a consequence, the *trans* geometry C_2–C_5 tandem of **8** and **9** change the conformational position of the N_3-methyl group. It is most likely that this methyl group undergoes some degree of pyramidal inversion in the free ligand. However, when the catalysis process is underway, it is likely that the N_3-methyl group is held rigidly in place by the zinc chelate (Fig. 2). This would ultimately suggest that the N_3-methyl group is the stereocontrol element in terms of the absolute stereochemistry of the product. Thus, the ephedrine based oxazolidines **8** and **9** affords the (*R*)-enantiomer of the product, while the ephedrine based oxazolidine **6** yields the (*S*)-enantiomer.

Table 2. Enantioselective additions of diethylzinc to benzaldehyde[a]



Entry	Catalyst	ee[b] (%)	Configuration[c]
1	**8**	51	*R*
2	**9**	59	*R*
3	**10**	49	*S*
4	**11**	55	*S*

[a] All reactions went to completion as determined by ^{1}H NMR spectroscopy and CSP HPLC.

[b] The % ee values were determined via HPLC using a Chiralcel-OD column. 2% 2-propanol in hexane, flow rate: 1 mL/min, UV detector (254 nm).

[c] The configuration was determined by comparison of the literature values.[14]

With regard to the pseudoephedrine based oxazolidines **10** and **11**, they also generate the same absolute stereochemistry in the end product as oxazolidine **7**. All of these derivatives are believed to share the *trans* relationship between the C_2 and C_5 positions and, therefore, would all give rise to the same absolute configuration of the end product. Again, it is proposed that N_3-methyl group is responsible for the asymmetric induction during the transition state of the addition reaction.

The ephedrine based oxazolidine **9** gave the highest enantioselectivity in trial studies in Table 2. Accordingly, this catalyst was employed in a series of reactions with a variety of aromatic and aliphatic aldehydes (Table 3). The observed enantioselectivities were moderate and ranged from 26% to 59% ee. Aromatic aldehydes gave better isolated chemical yields and better enantiomeric excesses over the aliphatic examples that were employed.

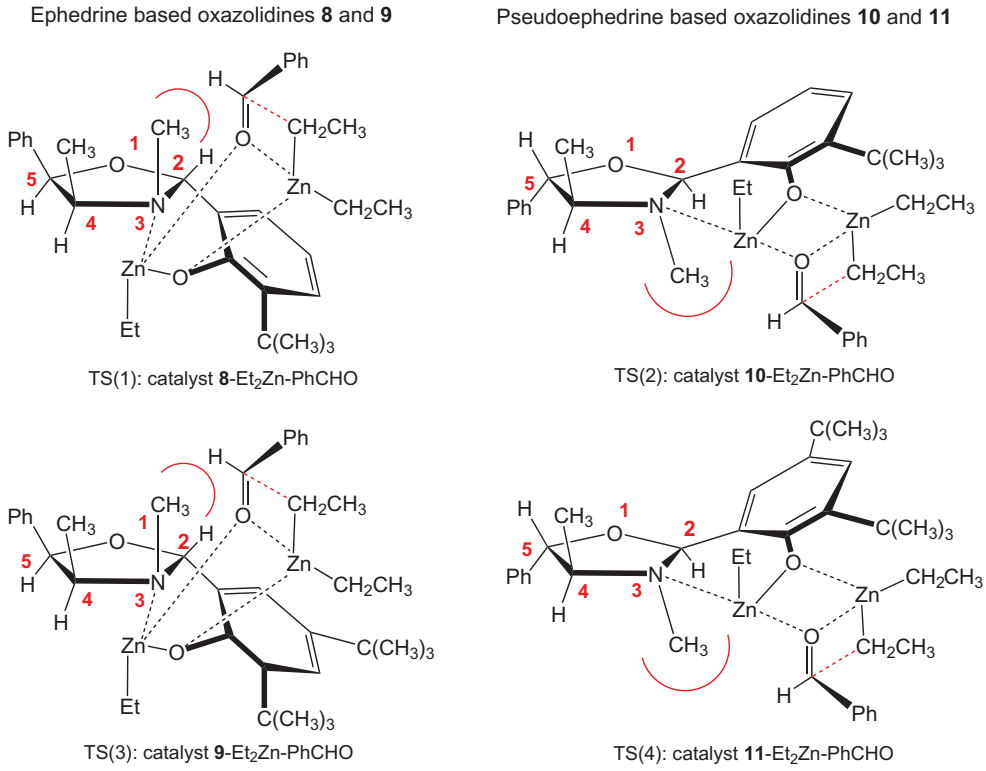
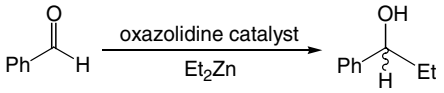


Figure 2. Proposed transition states for oxazolidines **8**–**11**.

Table 3. Enantioselective additions of diethylzinc to aldehydes via catalyst **9**



Entry	Aldehyde	Isolated yield (%)	ee (%)	Configuration[d]
1	Benzaldehyde	83	59[a]	*R*
2	4-Chlorobenzaldehyde	62	46[b]	*R*
3	*p*-Anisaldehyde	77	51[a]	*R*
4	2-Naphthaldehyde	80	54[a]	*R*
5	*trans*-Cinnamaldehyde	64	35[a]	*R*
6	Hexanal	30[c]	26[b]	*R*

[a] The % ee values were determined via CSP HPLC using a Chiralcel-OD column. 2% 2-propanol in hexane, flow rate: 1 mL/min, UV detector (254 nm). For 1-(4-methoxyphenyl)propan-1-ol, $t_R = 16.3$ (*R*) and 19.3 (*S*) min; for 1-(2′-Naphthyl)propan-1-ol, $t_R = 31.9$ (*R*) and 28.0 (*S*) min; for 1-phenyl-1-penten-3-ol, $t_R = 22.8$ (*R*), and 43.1 (*S*) min.

[b] The % ee values were determined via HPLC using a Chiralcel-OD column. 0.5% 2-propanol in hexane, flow rate: 1 mL/min, UV detector (254 nm) after naphthoylation. For 1-(4-chlorophenyl)propan-1-ol (as naphthoate), $t_R = 12.8$ (*R*), and 10.6 (*S*) min.; for 3-octanol (as naphthoate), $t_R = 20.2$ (*R*), and 18.9 (*S*) min.

[c] Yield determined after purification of the naphthyl ester.

[d] The configuration was determined by comparison of the literature values.[14]

3. Conclusion

We have prepared a family of chiral oxazolidine ligands derived from *Ephedra* alkaloids as templates for conducting asymmetric synthesis. These ligands can be synthesized easily and have been successfully used in the asymmetric addition of diethylzinc to aldehydes affording fair to moderate enantioselectivities and good yields. It is proposed that the N_3-methyl group is the stereocontrol element whose conformation is established by the substituents of the oxazolidine ring and by coordination with the zinc reagent.

4. Experimentals

4.1. General remarks

Toluene was purchased as an anhydrous reagent and used without further purification. All reactions were run under a nitrogen atmosphere. Unless otherwise noted, all ^1H and ^{13}C $\{^1H\}$ 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 ($\delta = 0$ ppm). Infrared spectra are reported in reciprocal centimeters (cm^{-1}) and are measured either as a Nujol mull or as a neat liquid. Melting points were recorded on a Mel-Temp apparatus and are uncorrected. Observed rotations were measured using a JASCO Model DIP-360 digital polarimeter. Measurements of the observed rotation were made at 589, 577, 546, 435, and 405 nm to ensure the accuracy of the observed rotation at 589 nm.

4.2. General procedure for oxazolidine synthesis with 2-hydroxybenzaldehyde

(1*R*,2*S*)-Ephedrine (10.02 g, 60.61 mmol) was dissolved in methanol (255 mL). To this solution was added 2-hydroxybenzaldehyde (6.38 mL, 60.6 mmol) via syringe and sodium sulfate (43.10 g, 303.1 mmol). The solution was allowed to reflux for 2 h. At that time, the solution was cooled to room temperature and filtered through Celite. Excess solvent was removed under reduced pressure and the oxazolidine was recrystallized using ethyl ether and hexanes (1:2).

4.2.1. (2′*S*,4′*S*,5′*R*)-2-(3′,4′-Dimethyl-5′-phenyl-oxazolidin-2′-yl)-phenol 6. White solid (55%), $[\alpha]_D = -32.3$ (*c* 0.62, $CHCl_3$), mp = 112–114 °C (760 torr). ^1H NMR ($CDCl_3$): δ 0.82 (d, $J = 6.6$ Hz, 3H), 2.38 (s, 3H), 3.08 (dq, $J = 2.0$, 6.2 Hz, 1H), 4.91 (s, 1H), 5.25 (d, $J = 9.0$ Hz, 1H), 6.86 (t, $J = 7.4$ Hz, 1H), 6.93 (d, $J = 8.2$ Hz, 1H), 7.21 (d, $J = 7.4$ Hz, 1H), 7.25–7.38 (m, 6H), 11.37 (br s, 1H). ^{13}C {^1H} NMR ($CDCl_3$): δ 15.63, 35.74, 63.45, 81.35, 98.95, 116.92, 119.02, 126.99, 127.81, 128.09, 128.13, 130.85, 131.01, 138.24, 158.19. IR (Nujol mull): 1616, 1594, 1168, 764, 716, 702 cm^{-1}. ESI-HRMS calcd for $C_{17}H_{20}NO_2$: 270.1494. Found: 270.1498. Anal. Cacld for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.43; H, 7.15; N, 5.33.

4.2.2. (2′*S*,4′*S*,5′*S*)-2-(3′,4′-Dimethyl-5′-phenyl-oxazolidin-2′-yl)-phenol 7. White solid (67%), $[\alpha]_D = +71.6$ (*c* 0.64, $CHCl_3$), mp = 76–78 °C (760 torr). ^1H NMR ($CDCl_3$): δ 1.22 (d, $J = 6.3$ Hz, 3H), 2.29 (s, 3H), 2.59 (m, $J = 2.7$ Hz and $J = 6.3$ Hz, 1H), 4.74 (d, $J = 8.6$ Hz, 1H), 5.10 (s, 1H), 6.81 (t, $J = 7.4$ Hz, 1H), 6.87 (d, $J = 8.2$ Hz, 1H), 7.16–7.36 (m, 7H), 11.21 (br s, 1H). ^{13}C {^1H} NMR ($CDCl_3$): δ 14.38, 34.87, 68.01, 86.21, 99.69, 116.73, 118.90, 120.18, 126.30, 128.00, 128.33, 130.63, 130.66, 139.34, 157.77. IR (Nujol mull): 1622, 1596, 1177, 756, 742, 705 cm^{-1}. ESI-HRMS calcd for $C_{17}H_{20}NO_2$: 270.1494. Found: 270.1490. Anal. Cacld for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.44; H, 7.03; N, 5.39.

4.3. General procedure for oxazolidine synthesis with 3-*tert*-butyl-2-hydroxybenzaldehyde and 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde

(1*R*,2*S*)-Ephedrine (1.09 g, 6.58 mmol) was dissolved in methanol (28 mL). To this solution was added 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (1.54 g, 6.58 mmol) and sodium sulfate (4.67 g, 32.9 mmol). The solution was allowed to reflux for 24 h. At that time, the solution was cooled to room temperature and filtered through Celite. Excess solvent was removed under reduced pressure and the oxazolidine was recrystallized using ethyl ether and hexanes (1:2). There are a series of companion peaks that are observed in the ^{13}C NMR spectra of compounds **8**–**11**. These peaks are attributed to potential atropisomers. This phenomenon has been observed in oxazolidine systems before.[10c]

4.3.1. (2′*R*,4′*S*,5′*R*)-2-*tert*-Butyl-6-(3′,4′-dimethyl-5′-phenyl-oxazolidin-2′-yl)-phenol 8. White solid (61%), $[\alpha]_D = +12.0$ (*c* 0.64, $CHCl_3$), mp = 129–131 °C (760 torr). ^1H NMR ($CDCl_3$): δ 0.84 (d, $J = 6.6$ Hz, 3H), 1.46 (s, 9H), 2.36 (s, 3H), 3.07 (dq, $J = 2.4$, 6.2 Hz, 1H), 4.90 (s, 1H), 5.24 (d, $J = 9.0$ Hz, 1H), 6.79 (t, $J = 7.8$ Hz, 1H), 7.05 (d, $J = 1.6$ Hz, 1H), 7.07 (d, $J = 2.0$ Hz, 1H), 7.24–7.41 (m, 5H), 11.74 (br s, 1H). ^{13}C {^1H} NMR ($CDCl_3$): δ 15.47, 29.39, 34.82, 35.47, 63.48, 81.27 (atropisomer), 81.29 (atropisomer), 99.70 (atropisomer), 99.75 (atropisomer), 118.12, 118.87, 127.12, 127.76, 127.96, 128.02, 129.08, 137.02, 138.48, 157.40. IR (Nujol mull): 1593, 1143, 751, 722, 703 cm^{-1}. ESI-HRMS calcd for $C_{21}H_{28}NO_2$: 326.2120. Found: 326.2128. Anal. Calcd for $C_{21}H_{27}NO_2$: C, 77.50; H, 8.36; N, 4.30. Found: C, 77.10; H, 8.45; N, 4.48.

4.3.2. (2′*R*,4′*S*,5′*R*)-2,4-Di-*tert*-butyl-6-(3′,4′-dimethyl-5′-phenyl-oxazolidin-2′-yl)-phenol 9. White solid (40%), $[\alpha]_D = -22.6$ (*c* 0.60, $CHCl_3$), mp = 136–139 °C (760 torr). ^1H NMR ($CDCl_3$): δ 0.83 (d, $J = 6.6$ Hz, 3H), 1.30 (s, 9H), 1.47 (s, 9H), 2.36 (s, 3H), 3.05 (dq, $J = 2.0$, 6.6 Hz, 1H), 4.89 (s, 1H), 5.23 (d, $J = 9.0$ Hz, 1H), 7.04 (d, $J = 2.3$ Hz, 1H), 7.22–7.42 (m, 6H), 11.52 (br s, 1H). ^{13}C {^1H} NMR ($CDCl_3$): δ 15.48, 29.53, 31.62, 34.10, 35.04, 35.57, 63.58, 81.34, 100.20 (atropisomers), 100.24 (atropisomers), 117.86, 125.19, 125.56, 127.21, 127.76, 128.02, 136.12, 138.57, 140.23, 154.78. IR (Nujol mull): 1608, 1176, 751, 722, 704 cm^{-1}. ESI-HRMS calcd for $C_{25}H_{36}NO_2$: 382.2746. Found: 382.2754. Anal. Calcd for $C_{25}H_{35}NO_2$: C, 78.70; H, 9.25; N, 3.67. Found: C, 77.87; H, 9.12; N, 3.82.

4.3.3. (2′*S*,4′*S*,5′*S*)-2-*tert*-Butyl-6-(3′,4′-dimethyl-5′-phenyl-oxazolidin-2′-yl)-phenol 10. White solid (45%), $[\alpha]_D = -188.6$ (*c* 0.64, $CHCl_3$), mp = 95–97 °C (760 torr). ^1H NMR ($CDCl_3$): δ 1.33 (d, $J = 5.9$ Hz, 3H), 1.42 (s, 9H), 2.36 (s, 3H), 2.64 (m, $J = 2.7$, 6.3 Hz, 1H), 4.81 (d, $J = 8.6$ Hz, 1H), 5.12 (s, 1H), 6.77 (t, $J = 7.8$ Hz, 1H), 7.06 (dd, $J = 1.6$, 7.4 Hz, 2H), 7.24–7.41 (m, 5H), 11.41 (br s, 1H). ^{13}C {^1H} NMR ($CDCl_3$): δ 14.69, 29.54, 34.82, 34.99, 68.36, 86.21 (atropisomers), 86.26 (atropisomers), 100.65 (atropisomers), 100.69 (atropisomers), 118.21, 119.99, 126.43, 128.06, 128.10, 128.50, 128.94, 137.09, 139.84, 157.12. IR (Nujol mull): 1595, 754, 748, 700 cm^{-1}. ESI-HRMS calcd for $C_{21}H_{28}NO_2$: 326.2120. Found: 326.2122. Anal. Calcd for $C_{21}H_{27}NO_2$: C, 77.50; H, 8.36; N, 4.30. Found: C, 76.63; H, 7.99; N, 4.83.

4.3.4. (2′*S*,4′*S*,5′*S*)-2,4-Di-*tert*-butyl-6-(3,4-dimethyl-5-phenyl-oxazolidin-2-yl)-phenol 11. Yellow oil (94% crude recovery). $[\alpha]_D = +40.0$ (*c* 0.65, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.29 (s, 9H), 1.32 (d, $J = 6.3$ Hz, 3H), 1.43 (s, 9H), 2.37 (s, 3H), 2.64 (m, $J = 2.8$, 6.1 Hz, 1H), 4.81 (d, $J = 9.0$ Hz, 1H), 5.13 (s, 1H), 7.03 (d, $J = 2.5$ Hz, 1H),

7.23–7.43 (m, 6H), 11.26 (br s, 1H). ^{13}C {^{1}H} NMR ($CDCl_3$): δ 14.57, 29.65, 31.60, 34.10, 34.99, 68.31, 86.20 (atropisomers), 86.24 (atropisomers), 101.08, 101.13, 199.02, 125.20, 125.40, 126.49, 128.06, 128.45, 136.15, 139.82, 140.278, 154.50. IR (Neat): 1608, 1189, 756, 724, 700 cm^{-1}. ESI-HRMS calcd for $C_{25}H_{36}NO_2$: 382.2746. Found: 382.2750.

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