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Synthesis of Bis(oxazoline) Ligands Possessing C-5 *gem*-Disubstitution and Their Application in Asymmetric Friedel–Crafts Alkylations

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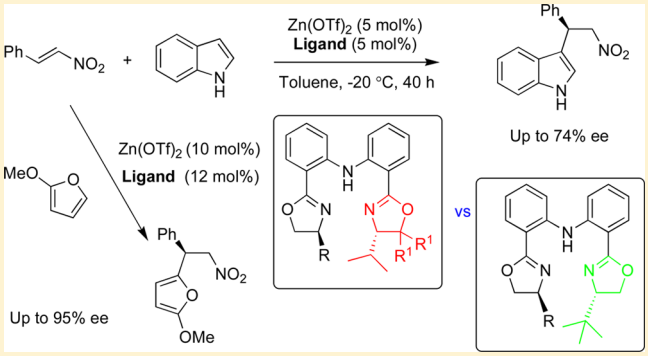
Supporting Information

ABSTRACT: A series of eight novel bis(oxazoline) ligands incorporating *gem*-disubstitution on one of the oxazoline rings were prepared from (*S*)-valine. These ligands are designed as a cost-effective alternative to similar ligands possessing an oxazolinyl C(5)-*tert*-butyl group derived from expensive (*S*)-*tert*-leucine. Four of the ligands possess a C(4)-*gem*-dimethyl group and four a C(4)-*gem*-diphenyl group adjacent to the C(5)-isopropyl substituent. Zinc complexes of ligands **11a–h**, along with non-C(4)-*gem*-disubstituted analogues **1a–g**, were effective in the Friedel–Crafts alkylation of both indole (up to 74% ee) and 2-methoxyfuran (up to 95% ee) with a series of nitroalkenes. Three of the ligands (**11a–c**), an iron dichloride complex of ligand **11d** and two zinc dichloride complexes, were characterized by X-ray crystallography, one with ligand **11d** and the second a bis-*tert*-butyl-substituted *N*-methylamine ligand. A direct comparison of the latter structures clearly illustrates the *gem*-dimethyl effect.



INTRODUCTION

Brunner reported the first example of chiral oxazoline-based ligands in asymmetric catalysis.[1] Subsequently, a diverse range of ligands possessing one, two, or more oxazoline units have been successfully applied in a wide range of metal-catalyzed asymmetric reactions.[2−5] The vast majority of oxazolines used are C_2-symmetric and are derived from naturally occurring chiral amino alcohols. This places the C(5)-substituent α- to the oxazolinyl donor nitrogen atom, thus directly influencing the levels of asymmetric induction of the metal-catalyzed reaction.

As part of our program on the design and application in asymmetric catalysis of metal complexes of bis(oxazoline) ligands, we reported the convergent synthesis of bis(oxazoline) ligands of type **1**, linked by a phenylaniline unit (Figure 1).[6] Our synthetic approach, involving a Buchwald–Hartwig aryl amination as the key step, allowed for the preparation of both C_2- and C_1-symmetric ligands, with varied substitution patterns on each of the oxazoline rings. We subsequently applied these ligands to a range of asymmetric transformations including the Nozaki–Hiyama–Kishi allylation,[7] crotylation,[7] methallylation,[8] and the first regio- and enantioselective homoallenylation of aldehydes.[9]

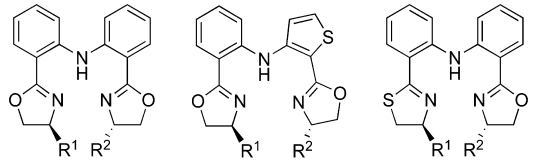


Figure 1. Bis(oxazoline) ligands.

Subsequently, we desymmetrized the ligand biaryl backbone by introducing a thiophene moiety into the structure, making ligands of type **2**, and we also synthesized the first thiazoline–oxazoline hybrid ligands of type **3** (Figure 1). Ligands of type **2** and **3** were then applied in the asymmetric Nozaki–Hiyama–Kishi allylation of benzaldehyde[10] and the asymmetric Friedel–Crafts alkylation of indole,[11] respectively. In many cases, we observed that the C_1-symmetric ligands induced higher levels of enantioselectivity than their C_2-symmetric analogues.[12]

The group of Du has since reported an alternative synthetic approach to **1**.[13] However, this methodology is limited to the synthesis of C_2-symmetric ligands, while our approach can furnish both C_2- and non-C_2-symmetric ligands.[6] Du has subsequently applied metal complexes of **1** in a wide range of asymmetric transformations such as the Henry reaction of α-keto esters,[14] the Friedel–Crafts alkylation of arenes with

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nitroalkenes,[15−18] and the Michael addition of nitroethane to nitroalkenes.[19] Nishiyama has also applied these ligands in the asymmetric hydrosilylation of ketones and enones,[20−22] and Li and Zhang have recently studied their use in the cationic rare-earth metal-catalyzed quasi-living polymerization of isoprene[23] and the Pd-catalyzed polymerization of norbornene.[24]

With the vast majority of the ligands discussed above, it was found that one of the substituents on the oxazoline ring had to be a *tert*-butyl group in order to obtain high levels of enantioselectivity for a range of transformations. However, the high cost of the starting material necessary for the synthesis of these ligands, *tert*-leucine, is a serious drawback and therefore limits the use of such ligands, especially in the case of the (*R*)-enantiomer which would be required to provide the opposite hand of product.[25] A cheaper, alternative ligand that could induce similar levels of enantioselectivity without compromising catalytic activity would therefore be highly desirable.

The first example of a ligand that could achieve similar levels of enantioselectivity to a previously superior *tert*-butyl analogue was reported by Corey.[26] Their bis(oxazoline) ligand replaced the *tert*-butyl substituent at C-4 with an isopropyl group in conjunction with a vicinal *gem*-dimethyl at the C-5 position and provided better enantioselectivity than the analogous *tert*-butyl ligand (85% vs 82%).[27] This *gem*-disubstitution effect[28] was further applied in many other areas of research,[29,30] including chiral auxiliaries,[31−35] phosphinooxazoline (PHOX) ligands,[36,37] and recently by Paquin,[38,39] who explored the *gem*-disubstituent effect, again with the PHOX type ligands,[40,41] as did Stoltz in a very recent report on an electronically modified PHOX ligand.[42]

We have recently exploited this effect in the design of oxazoline-containing N,O ligands **4** and P,N ligands **5** and **6**, which were applied with success in the diethylzinc and ethylphenylzinc addition to aldehydes and the asymmetric intermolecular Heck reaction, respectively (Figure 2).[43,44] In general, metal complexes of C-5 *gem*-disubstituted ligands afforded higher levels of enantioselectivity than those with just an isopropyl group at C-4 and approached that of their *tert*-butyl counterpart.

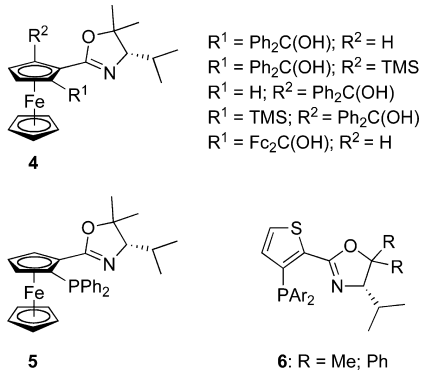


Figure 2. Recent oxazoline-containing ligands possessing *gem*-disubstitution.

RESULTS AND DISCUSSION

Ligand Synthesis. Amino alcohols **7a** and **7b**, prepared according to a procedure by Denmark,[45] were reacted with benzoyl chloride in the presence of Na_2CO_3 with vigorous stirring in a biphasic mixture of H_2O and dichloromethane (3:4 ratio) to afford the corresponding amides **8a** and **8b** in 98% and 93% yields, respectively. Both amides **8a** and **8b** were then cyclized under acidic conditions to form the desired bromoaryloxazolines **9a** and **9b** in 99% and 83% yields, respectively. While the cyclization of amide **8a** proceeded smoothly at 40 °C, microwave irradiation was necessary to promote the cyclization of amide **8b**, where the reaction could be carried out at 60 °C (Scheme 1).

The final step to form the desired ligands **11a−h** utilized a Buchwald−Hartwig aryl amination (Scheme 2).[6,46−48] This allowed us to access non-C_2-symmetric ligands with various combinations of substitution patterns on the oxazoline rings in yields ranging from 40% to 52% (Table 1). The required amino

Scheme 2. Buchwald−Hartwig Aryl Amination of 9a/b and 10a−d Forming Bis(oxazoline) Ligands 11a−h

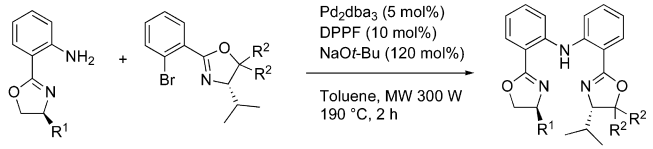
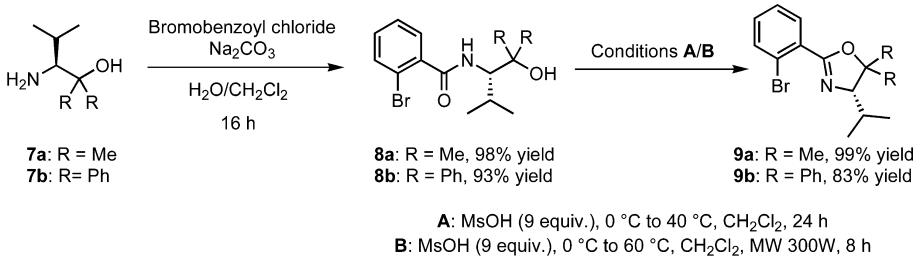


Table 1. Synthesis of Ligands 11a−h under Palladium Catalysis with MW Irradiation

entry	ligand	R^1	R^2	yield[a] (%)
1	**11a**	*i*-Pr	Me	49
2	**11b**	*t*-Bu	Me	47
3	**11c**	Ph	Me	45
4	**11d**	Bn	Me	52
5	**11e**	*i*-Pr	Ph	52
6	**11f**	*t*-Bu	Ph	40
7	**11g**	Ph	Ph	45
8	**11h**	Bn	Ph	45

[a]Yields after column chromatography.

Scheme 1. Synthesis of Bromoaryloxazoline Coupling Partners 9a and 9b



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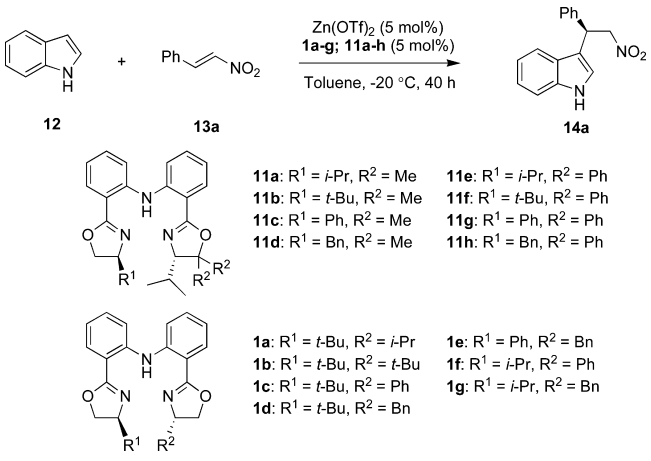
coupling partners **10a–d** were synthesized via a previously reported zinc-catalyzed condensation of aminobenzonitrile and the desired commercially available amino alcohols.[11]

Catalytic Asymmetric Friedel–Crafts Reaction. The Friedel–Crafts (FC) alkylation is a cornerstone reaction in organic chemistry.[49] Extending this reaction to include electron-deficient alkenes as the alkylating agents has only been made possible by the employment of Lewis acid catalysts.[50−52] The two reacting partners most widely studied in the asymmetric Friedel–Crafts variant are indole and nitroalkenes.[11,53−62] The latter possesses one of the strongest electron-withdrawing groups known, a feature that has also been exploited in their use as Michael acceptors.[63−66] This high reactivity, allied to the ease of transformation of the nitro group into a diverse range of functionalities, explains their extensive application to date in organic synthesis.[67−73]

C_2-Symmetrical examples of ligands **1**, first synthesized within our group, were applied by Du in the asymmetric FC alkylation of indole with *trans*-β-nitrostyrene achieving high ee's of up to 83%[15] and in the asymmetric FC alkylation of 2-methoxyfuran with nitroalkenes, again, achieving high ee's of up to 92%.[16] As C_2-symmetric versions of **1** have induced high levels of enantioselectivity in both of these transformations they are ideal reactions to evaluate our novel library of C_1-symmetric ligands **11a–h** along with the analogous C_1-symmetric ligands **1a–g**.[6]

Our initial optimization and ligand screening, in which we applied our full range of C_1-symmetric ligands, was carried out in the reaction of indole (**12**) with *trans*-β-nitrostyrene (**13a**) (Scheme 3). The reactions were carried out using 5 mol % of

Scheme 3. Asymmetric Friedel–Crafts Alkylation of Indole (12) with *trans*-β-Nitrostyrene (13a) Using Ligands 1a–g and 11a–h



$Zn(OTf)_2$ and 5 mol % of ligand at −20 °C in toluene, which were found to be optimal conditions for this type of catalysis in our previous reports and those of both Zhou and Du.[11,15,53,62] However, the reaction time was extended to 40 h in the current study in order to achieve higher conversion levels.

Zinc complexes of the range of ligands tested in the present study gave very good to excellent yields (85–97%) of alkylated product (**14a**) (Table 2). Unsurprisingly, the levels of enantioselectivity were highly dependent upon the ligand substitution pattern, even more so as the ligands are non-C_2-symmetric. The existence of a background reaction due to free zinc compounds or free triflic acid from hydrolysis cannot be

Table 2. Asymmetric Friedel–Crafts Alkylation of Indole Using Zinc Complexes of Ligands 11a–h

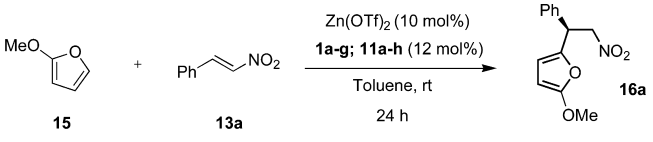
entry	ligand	yield[a] (%)	ee[b] (*R*)[c]	entry	ligand	yield[a] (%)	ee[b] (*R*)[c]
1	**11a**	90	35	9	**1a**	95	27
2	**11b**	95	3	10	**1b**	95	68[d]
3	**11c**	93	61	11	**1c**	89	45
4	**11d**	93	58	12	**1d**	99	67
5	**11e**	94	13	13	**1e**	99	62
6	**11f**	93	Rac	14	**1f**	97	64
7	**11g**	89	44	15	**1g**	97	74
8	**11h**	85	5				

[a]Yields after column chromatography. [b]Determined by chiral HPLC: Chiralcel IB, (heptane/ethanol 70:30, 0.9 mL/min). [c]Absolute configuration determined by comparison to literature $[\alpha]_D$.[51] [d]Literature result included for comparison.[15]

discarded. However, the study does allow a direct comparison to be made between related ligands (**11a–d** vs **1a–d** (*gem*-dimethylisopropyl vs *tert*-butyl), entries 1–4 vs 9–12) and (**11e–f** vs **1a–d** (*gem*-diphenylisopropyl vs *tert*-butyl), entries 5–8 vs 9–12). Complexes of ligands **11a** and **11c** induced higher levels of enantioselectivity of 35% ee and 61% ee versus 27% ee and 45% ee, respectively (entries 1 and 3 vs entries 9 and 11). The optimal *gem*-disubstituted ligand was **11c**, which afforded product (**14a**) in 61% ee, entry 3. Overall, the *gem*-diphenyl-substituted ligands induced poor to moderate levels of enantiodiscrimination (up to 44% ee), which was somewhat surprising as we had envisaged that the more rigid structural motif would have been advantageous for enhanced asymmetric induction. The remaining series of non-C_2-symmetric ligands, **1e–g**, gave more promising results (62–74% ee), although still lower than the best result (83% ee) obtained by Du using this ligand class ($R^1 = R^2 = Ph$).[15]

However, these promising results prompted us to further test the ligands in a similar transformation, replacing indole (**12**) with 2-methoxyfuran (**15**). Although 2-methoxyfuran has not received as much attention as indole (**12**), its inherent reactivity makes it a very interesting substrate for this reaction (Scheme 4), and Du had already reported encouraging levels of enantioselectivities (78–92% ee) with C_2-symmetric ligands of type **1** ($R^1 = R^2$ = *i*-Pr; *t*-Bu; Ph; Bn).[16]

Scheme 4. Asymmetric Friedel–Crafts Alkylation of 2-Methoxyfuran (15) with *trans*-β-Nitrostyrene (13a) Using Ligands 1a–g and 11a–h



Gratifyingly, zinc complexes of ligands **11a–d,g** and **1a–g** gave good to very high enantioselectivities of up to 90% ee in this transformation (Scheme 4 and Table 3). A direct comparison can again be made between related ligands (**11a–d** vs **1a–d** (*gem*-dimethylisopropyl vs *tert*-butyl), entries 1–4 vs 9–12) and (**11e–f** vs **1a–d** (*gem*-diphenylisopropyl vs *tert*-butyl), entries 5–8 vs 9–12). As with indole as substrate, the *gem*-diphenyl-substituted ligands (**11e–h**) gave poor to moderate yields and very low ee's, with the exception of ligand **11g**, which afforded the alkylated furan (**16a**) in 69% yield and

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Table 3. Asymmetric Friedel–Crafts Alkylation of 2-Methoxyfuran Using Zinc Complexes of Ligands 11a–h

entry	ligand	yield (%)[a]	ee[b] (*S*)[c]	entry	ligand	yield (%)[a]	ee[b] (*S*)[c]
1	**11a**	65	69	9	**1a**	80	83
2	**11b**	82	81	10	**1b**	73	92[d]
3	**11c**	65	59	11	**1c**	83	89
4	**11d**	88	89	12	**1d**	85	90
5	**11e**	16	7	13	**1e**	66	88
6	**11f**	20	5	14	**1f**	84	80
7	**11g**	69	70	15	**1g**	90	87
8	**11h**	48	7				

[a]Yields after column chromatography. [b]Determined by chiral HPLC: Chiralcel IB (heptane,ethanol 90:10, 1.0 mL/min). [c]Absolute configuration determined by comparison to literature $[\alpha]_D$.[53] [d]Literature result included for comparison.[16]

70% ee. Complexes of ligands **11b** and **11d** induced high levels of enantioselectivity, although lower than their *tert*-butyloxazoline analogues (**1a** and **1d**), 69% ee and 89% ee versus 83% ee and 90% ee, respectively (entries 1 and 4 vs entries 9 and 12). The remaining series of non-C_2-symmetric ligands, **1e–g**, gave impressive results (80–90% ee), although still lower than the best result (92% ee) obtained by Du using this ligand class (ligand **1b**, entry 10).[16]

It was decided to take the optimal *gem*-disubstituted ligand, **11d**, and investigate a substrate scope in the asymmetric FC reaction between 2-methoxyfuran and a range of nitroalkenes (Scheme 5 and Table 4). The enantioselectivities obtained

Scheme 5. Asymmetric Friedel–Crafts Alkylation of 2-Methoxyfuran (15) with Substituted Nitroalkenes (13a–g) Using Optimal Ligand 11d

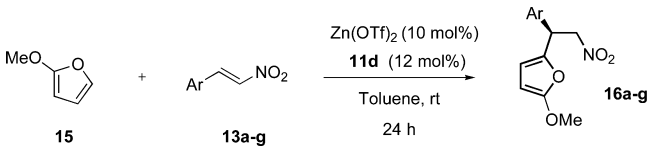

Table 4. Asymmetric Friedel–Crafts Alkylation of 2-Methoxyfuran with Nitroalkenes Using Zinc Complex of Ligand 11d

entry	Ar	product	yield[a] (%)	ee[b] (*S*)[c]
1	Ph	**16a**	88	89
2	4-MeOC$_6$H$_4$	**16b**	84	92
3	4-BrC$_6$H$_4$	**16c**	75	93
4	4-MeC$_6$H$_4$	**16d**	89	92
5	2-furyl	**16e**	70	89[d]
6	2-thienyl	**16f**	68	90[d]
7	3-ClC$_6$H$_4$	**16g**	83	95

[a]Yields after column chromatography. [b]Enantiomeric excess (ee) was determined by chiral HPLC: Chiralcel IB, (heptane:ethanol 90:10, 1 mL/min). [c]Absolute configuration determined by comparison to literature $[\alpha]_D$.[16] [d](*R*)-Enantiomer in excess.

ranged between 89 and 95% ee, with yields of 70–89%, with the optimal substrate being the *m*-chloro-substituted nitrostyrene, entry 7, which gave alkylated furan (**16g**) in 95% ee. Employing heteroaromatic nitroalkenes (**13e–f**) gave rise to slightly lower yields and similar enantioselectivities, entries 5 and 6. The sense of asymmetric induction for these nitroalkene substrates is identical to that of the remaining nitroalkenes studied, and the opposite configuration of the major enantiomer is due to changes in CIP priority assignments.

In the proposed transition states for the FC alkylation of indole (**12**) and 2-methoxyfuran (**15**) (Figure 3), the two

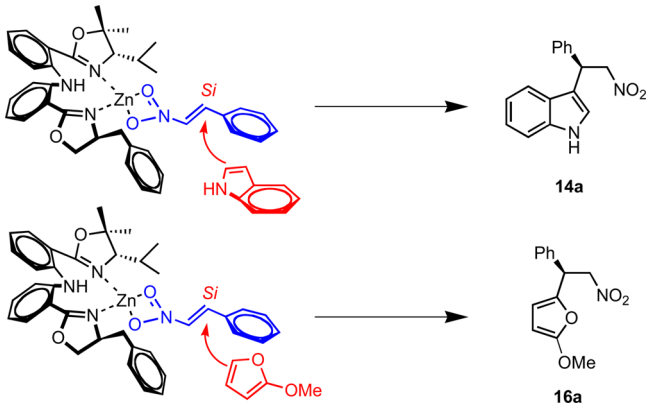

Figure 3. Proposed transition states for the FC alkylation of indole (**12**) and 2-methoxyfuran (**15**).

oxazolinyl nitrogen atoms are coordinated to the zinc center and the nitro group of the nitroalkene coordinates through the two oxygen atoms to the Lewis acid center.[74] This activates the nitroalkene to nucleophilic attack by the electron-rich arene. The attack happens preferentially at the *Si* face due to the influence of the substituents on each of the oxazoline rings, therefore leading to an enantioenriched product with the (*R*)-configuration in the case of indole (**12**) and (*S*)-configuration in the case of 2-methoxyfuran (**15**). There is potential for π-stacking between the benzyl substituent and the electron-deficient alkene, thus promoting *Si*-facial attack. In contrast to proposed transition states proposed by Du,[15,16] we do not propose that the NH is involved as a H-bond donor via an NH$\cdots\pi$ interaction with indole or 2-methoxyfuran.

X-ray Crystal Structural Analysis of the *gem*-Dimethyl Effect. In order to determine the effect of the C(4) *gem*-disubstitution on the orientation of the adjacent isopropyl group, crystal structures for the *gem*-dimethyl-substituted ligands **11a–c** were obtained (Figure 4A–C). As ligand **11d** did not form crystals, we attempted to form a metal complex of this ligand. All initial attempts to synthesize zinc complexes of ligands **11a–d** failed; however, an iron complex of ligand **11d** was amenable to crystallization and its structure was solved by X-ray analysis (Figure 4D). The latter complex possesses a distorted bipyramidal trigonal geometry that would differ considerably from the expected canonical tetracoordination of the Zn complex yet was still of interest as it allowed us to investigate our optimal ligand from the catalytic studies performed.

While these crystal structures clearly illustrate the *gem*-dimethyl effect for three ligands and one metal complex, it is difficult to extrapolate to rationalizing the results in catalysis obtained employing zinc complexes of these ligands. Therefore, we reinvestigated the potential for forming such zinc complexes. We felt that our initial attempts at forming zinc complexes were not facilitated by the presence of the NH group, and hence, we aimed to synthesize the zinc dichloride complex of the related *N*-methyl ligands. As a starting point, we prepared the C_2-symmetric *N*-methyl-bis-*tert*-butyloxazoline zinc dichloride complex (**18**) in 66% yield from the

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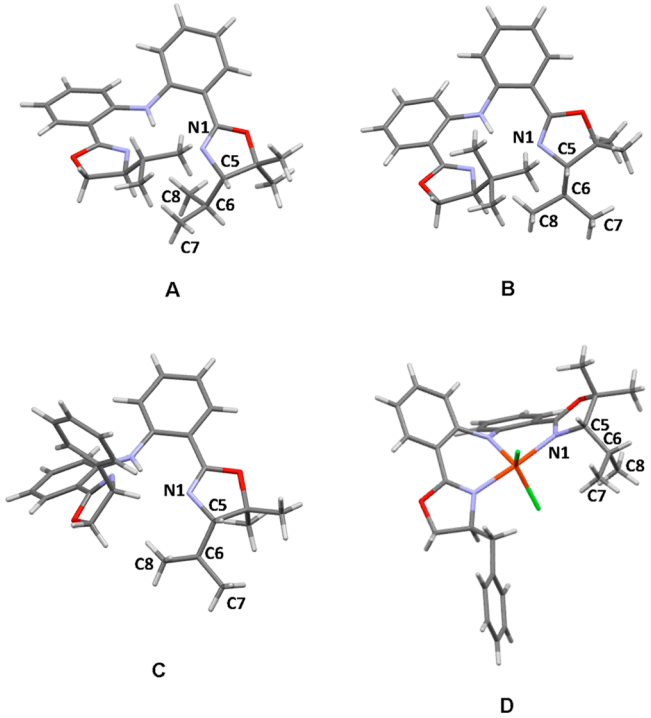
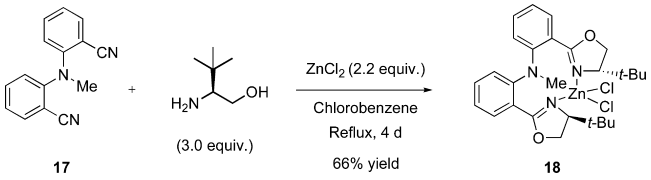


Figure 4. Crystal structures of ligands **11a–c** (A–C) and $FeCl_2$ complex of ligand **11d** (D).

condensation of *N*-methyl-bis(benzonitrile) (**17**) with *tert*-leucinol in the presence of a stoichiometric amount of anhydrous zinc chloride (Scheme 6). This approach employed

Scheme 6. Preparation of C_2-Symmetric *N*-Methyl-bis-*tert*-butyloxazoline Zinc Dichloride Complex (18)



Bolm's zinc dichloride mediated methodology for bisoxazoline synthesis,[75] which used milder reaction conditions than the original report of Witte and Seeliger.[76] Bolm also reported an X-ray crystal structure of a bisoxazoline zinc dichloride complex, which demonstrated the expected tetrahedral coordination about zinc.[75]

To elucidate the structure of **18**, a crystal was grown by isothermal diffusion using dichloromethane/petroleum ether (40–60 °C) as the solvent. X-ray crystallographic analysis showed a distorted tetrahedral complex in which the ligand coordinates to zinc in a bidentate fashion through the two oxazolinyl nitrogen atoms with the central nitrogen atom of the ligand being significantly removed from the metal. Contrary to expectations, the ligand adopts an interesting nonplanar conformation in which the central nitrogen atom has a trigonal planar conformation and the aryl oxazoline units cross over each other (Figure 5A). With this structure in hand, we proceeded to prepare the key comparitor zinc dichloride complex (**19**) derived from ligand **11d** (Scheme 7). Gratifyingly, we were able to obtain crystals of suitable quality for X-ray diffraction by the slow evaporation of an acetonitrile/

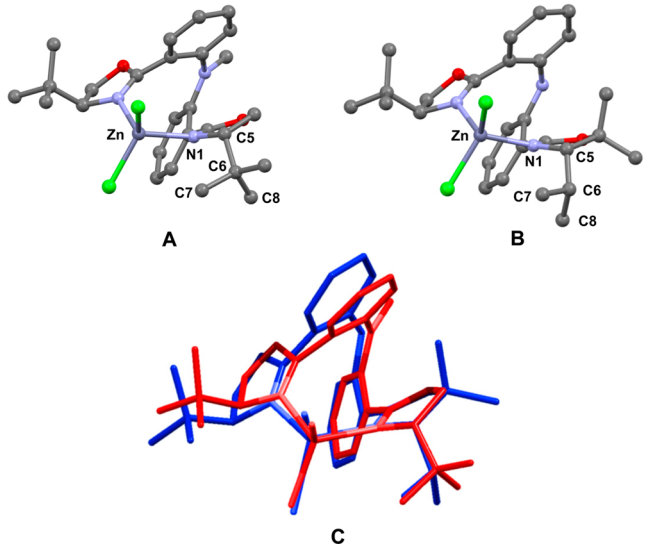
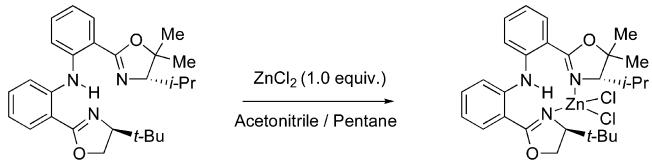


Figure 5. Crystal structures of zinc dichloride complex **18** (A) and zinc dichloride complex **19** (B) and overlay of complexes **18** (red) and **19**(blue) (C).

Scheme 7. Preparation of Zinc Dichloride Complex (19) Derived from Ligand 11d



pentane solution at room temperature. As with complex **18**, the ligand coordinates through both oxazolinyl nitrogen atoms, the aryl oxazoline units cross over each other and the NH points away from the zinc (Figure 5B), which adds weight to our proposed transition-state model (Figure 3) in which we do not invoke NH···π interactions with indole or 2-methoxyfuran. However, the key feature of the *gem*-dimethyl effect and its influence on the conformation of the isopropyl group is clear as there is almost complete overlap between the two structures when overlaid (Figure 5C).

From the torsion angle data, we can determine the orientation of the isopropyl group in each of the three ligands **11a–c**, the iron complex of ligand **11d**, and the zinc complexes **18** and **19** (Table 5). Although ligand **11a** was not analyzed as a metal complex, the dihedral angles obtained (−79° for N_1–C_5–C_6–C_7 and 46° for N_1–C_5–C_6–C_8) closely resemble those obtained for the iron complex of ligand **11d** (−77° for N_1–C_5–C_6–C_7 and 50° for N_1–C_5–C_6–C_8), entries 1 and 4, confirming that the isopropyl methyl groups prefer to take up a region in space away from the vicinal *gem*-dimethyl groups. In contrast, when there is a *tert*-butyl (**11b**) or phenyl substituent (**11c**) on the other oxazoline ring, the isopropyl group positioning is quite different with dihedral angles of N_1–C_5–C_6–C_7 and N_1–C_5–C_6–C_8 of −177°/−177° and −56°/−55°, respectively, entries 2 and 3. This shows that not only do the *gem*-dimethyl substituents have an effect on the adjacent isopropyl unit but so too does the substituent on the other oxazoline ring. With the zinc dichloride complexes **18** and **19** in hand, the direct comparison of the relevant dihedral angles is

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Table 5. Comparison of Dihedral Angles of Novel Ligands 11a–c with Metal Complexes of Ligands 11d, 5, 6a,b, 20, and 21 and Zinc Dichloride Complexes 18 and 19

entry	ligand/complex	dihedral angle (N_1–C_5–C_6–C_7) (deg)	dihedral angle (N_1–C_5–C_6–C_8) (deg)
1	**11a**	−79	46
2	**11b**	−177	−56
3	**11c**	−177	−55
4	$FeCl_2$[**11d**]	−77	50
5	**18**	−58	64
6	**19**	−80	45
7	$PdCl_2$[**6a**][43]	−76	50
8	$PdCl_2$[**6b**][43]	−68	57
9	$PdCl_2$[**5**][43]	−159	−38
10	$PdCl_2$[**20**][39]	−76	51
11	$PdCl_2$[**21**][39]	−80	58

possible with the relevant dihedral angles of N_1–C_5–C_6–C_7 and N_1–C_5–C_6–C_8 being −58°/−80° and 64°/45°, respectively, entries 5 and 6. This shows that there is some distortion of the isopropyl group in **19** with conformation tending toward mimicking the *tert*-butyl group, illustrating the *gem*-dimethyl effect.

In order to further determine the impact of C(4) *gem*-disubstitution, it of interest to compare these X-ray crystal structure data to the metal complex studies reported by Paquin (ligand **20**)[39] and also our palladium complexes of ligands **5** and **6** (Figure 6).[43] In addition, it is useful to compare the dihedral angles with the palladium complex of ligand **21** (*t*-Bu PHOX).[39]

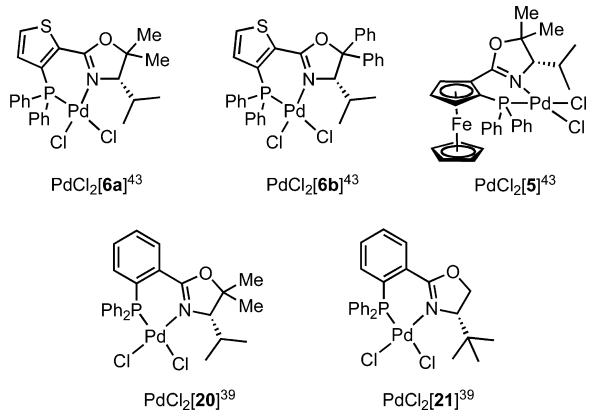

Figure 6. Literature palladium complexes of ligands **5**, **6**, **20**, and **21**.

The corresponding dihedral angles N_1–C_5–C_6–C_7 and N_1–C_5–C_6–C_8 for the palladium complex of ligand **21** are −80° and 58°, entry 11, in line with the dihedral angles observed for ligand **11a** (−79° and 46°), entry 1, and the iron complex of ligand **11d** (−77° and 50°), entry 4. These data are also similar in value to the corresponding dihedral angles of the palladium complexes derived from ligand **20** (−76° and 51°), entry 10, ligands **6a** (−76° and 50°), entry 5, and **6b** (−68° and 57°), entry 6. Palladium complexes of ligands **5** and **6a,b** were applied by us in the intermolecular asymmetric Heck reaction with ee values of up to 97%.[43] Complex **5** did induce high levels of enantioselectivity, even with significantly different dihedral angles of −38° and −159° to ligands of type **6**. In addition, in the present study, the two ligands **11b** and **11c**, which exhibit dihedral angles of −177°/−56° and −177°/−55°, respectively, are not significantly inferior to ligands **11a** and **11d**. A recent meta analysis of the influence of chelate geometry on the roles of P,N chelating ligands highlights the difficulty of extrapolating from solid state data to rationalizing ligand efficacy in asymmetric catalysis.[77]

CONCLUSION

Herein, we have disclosed the synthesis of eight novel bis(oxazoline) ligands (**11a–h**) derived from inexpensive (*S*)-valine as a cost-effective alternative to similar ligands possessing an oxazolinyl C(5)-*tert*-butyl group. Four of the examples possess a C(4)-*gem*-dimethyl group and four a C(4)-*gem*-diphenyl group adjacent to the C(5)-isopropyl substituent. Zinc complexes of ligands (**11a–h**), along with non-C_2-symmetric analogues **1a–g**, were effective in the Friedel–Crafts alkylation of both indole (**12**) and 2-methoxyfuran (**15**) with a series of nitroalkenes, furnishing the alkylation products in high yields and with up to 95% ee in the reaction of 2-methoxyfuran and (*m*-chlorophenyl)nitrostyrene. Three of the ligands (**11a–c**), an iron dichloride complex of ligand **11d**, and two zinc dichloride complexes, one formed from ligand **11d** and the other with a novel *N*-methyl, bis-*tert*-butyl-oxazoline, were characterized by X-ray crystallography. In some cases, the novel ligands induced levels of enantioselectivity comparable to their *tert*-butyl counterparts, suggesting that this type of structural motif can be considered a surrogate *tert*-butyl group. Further investigations to probe the *gem*-disubstitution effect in ligand design and application in asymmetric catalysis are currently underway and will be reported in due course.

EXPERIMENTAL SECTION

General Experimental Methods. All reagents were purchased from commercial sources and used without further purification. Anhydrous dichloromethane, diethyl ether, tetrahydrofuran, and toluene were obtained from a Grubbs solvent system that was checked on a monthly basis for ppm levels of water. Catalytic reactions were repeated at least twice in order to ensure reproducibility. Compounds **7a,b**,[45] **8a,b**,[37] and **10a–d**[11] were prepared according to the literature. All microwave reactions were conducted in a CEM Discover S-class microwave reactor, which utilizes an external infrared temperature sensor.

*(S)-2-Bromo-N-(1-hydroxy-3-methyl-1,1-diphenylbutan-2-yl)-benzamide (**8b**).* (*S*)-2-Amino-3-methyl-1,1-diphenylbutan-1-ol (**7b**) (336 mg, 2.56 mmol, 1 equiv) was dissolved in dichloromethane (10 mL). To this was added a solution of Na_2CO_3 (814 mg, 7.68 mmol, 3 equiv) in H_2O (7.5 mL). The biphasic solution was stirred vigorously, and 2-bromobenzoyl chloride (0.37 mL, 2.82 mmol, 1.1 equiv) was added in a dropwise manner over 5 min. The mixture was allowed to stir for 16 h before the layers were separated. The aqueous layer was then extracted with dichloromethane (2 × 20 mL), and the combined organic layers were treated with a 1 M methanolic solution of KOH (15 mL) for 15 min. The solution was then neutralized to pH 7 by the addition of 3 M HCl. H_2O (25 mL) was then added, and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 20 mL), and the organic layer was dried over Na_2SO_4. The solvent was removed in vacuo, and the resulting residue was purified by flash column chromatography (pentane/EtOAc, 9:1) to yield the title compound as a white solid (1.04 g, 93%): mp 212–215 °C; R_f = 0.31 (pentane/EtOAc, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57–7.47 (m, 5H), 7.36–7.15 (m, 8H), 6.88–6.85 (m, 1H), 6.39 (d, J = 9.9 Hz, 1H), 5.20 (d, J = 9.9 Hz, 1H), 2.76 (br s, 1H), 1.95 (m, 1H), 1.06 (d, J = 6.9 Hz, 3H), 1.01 (d, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 167.8, 146.0, 145.3, 138.5, 133.2, 130.8, 128.9, 128.5, 127.3, 127.1, 127.0, 125.4, 125.2, 119.1, 82.4, 58.4, 29.2, 22.9, 17.9; $[\alpha]_D^{20}$ = −18.2 (c = 0.5, $CHCl_3$); IR (film) ν = 3547, 3347, 3050,

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2953, 2872, 2360, 1626, 1542, 749 cm^{-1}; HRMS (ES^+) calcd for $C_{24}H_{24}NO_2Br$ 437.0990, found 437.0991.

*(S)-2-(2-Bromophenyl)-4-isopropyl-5,5-diphenyl-4,5-dihydrooxazole (**9b**).* (*S*)-2-Bromo-*N*-(1-hydroxy-3-methyl-1,1-diphenylbutan-2-yl)benzamide (**8b**) (1.750 g, 4.0 mmol) was weighed into a large microwave vial. Dichloromethane (10 mL) was added into the vessel, and the contents were cooled to 0 °C. Methanesulfonic acid (2.6 mL, 40 mmol) was then added to the heterogeneous mixture, and the contents were stirred until a clear solution remained (approximately 10 min). The vial was then capped and placed in the microwave and heated to 60 °C at 200 W for 8 h. The reaction was then allowed to cool to room temperature and was quenched with $NaHCO_3$ (20 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (2 × 15 mL), washed with H_2O (15 mL) and brine (15 mL), and dried over Na_2SO_4. The solvent was removed in vacuo, and the resulting residue was purified by flash column chromatography (pentane/EtOAc, 4:1) to yield the title compound as a clear oil (1.40 g, 83%): R_f = 0.56 (pentane/EtOAc, 4:1); ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.67 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 2H), 7.42−7.21 (m, 10H), 4.88 (d, *J* = 4.4 Hz, 1H), 1.90 (m, 1H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.71 (d, *J* = 6.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 160.8, 145.3, 140.5, 134.0, 131.7, 131.6, 129.9, 128.3, 127.8, 127.7, 127.2, 127.1, 126.5, 121.9, 93.2, 79.9, 30.4, 22.0, 17.0; $[\alpha]_D^{20}$ = −304.0 (*c* = 0.5, $CHCl_3$); IR (film) ν = 3552, 3476, 3414, 3240, 2956, 2361, 1658, 701 cm^{-1}; HRMS (ES^+) calcd for $C_{24}H_{23}NOBr$ (M + H) 420.0963, found 420.0976.

General Procedure for the Synthesis of Bis(2-oxazolinylphenyl)amine Ligands 11a−h. 2-(2-Bromophenyl)oxazoline **9a,b** (0.5 mmol), sodium *tert*-butoxide (0.0577 g, 0.6 mmol), 1,1′-bis(diphenylphosphino)ferrocene (DPPF) (0.028 g, 0.05 mmol), Pd_2dba_3 (0.023 g, 0.025 mmol), and 2-(*o*-aminophenyl)oxazoline **10a−d** (0.6 mmol) were added to an oven-dried tube under an atmosphere of nitrogen. Dry, degassed toluene (2 mL) was added via syringe, and the tube was sealed under an atmosphere of nitrogen. The reaction mixture was then heated at 190 °C for 2 h in a microwave. After the reaction mixture was allowed to cool to room temperature, the seal was removed and the contents were concentrated in vacuo to afford a brown oil which was purified by flash column chromatography on silica gel (pentane/EtOAc, 19:1).

*2-((S)-4-Isopropyl-4,5-dihydrooxazol-2-yl)-N-(2-((S)-4-isopropyl-5,5-dimethyl-4,5-dihydrooxazol-2-yl)phenyl)aniline (**11a**):* yellow solid (0.103 g, 49%); mp 88.5−91 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 10.72 (s, 1H), 7.82 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.79 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.41 (dd, *J* = 8.3, 0.7 Hz, 1H), 7.36 (dd, *J* = 8.3, 0.7 Hz, 1H), 7.30−7.22 (m, 2H), 6.93−6.89 (m, 1H), 6.88−6.84 (m, 1H), 4.31 (dd, *J* = 9.1, 7.9 Hz, 1H), 4.09−4.04 (m, 1H), 4.01 (dd, *J* = 16.5, 8.7 Hz, 1H), 3.46 (d, *J* = 8.7 Hz, 1H), 1.87−1.80 (m, 1H), 1.79−1.73 (m, 1H), 1.50 (s, 3H), 1.33 (s, 3H), 1.11 (d, *J* = 6.6 Hz, 3H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 162.5, 161.1, 143.7, 143.1, 131.1, 131.0, 130.5, 130.3, 120.0, 119.5, 119.3, 117.8, 116.9, 116.1, 85.0, 80.9, 73.0, 69.4, 33.1, 29.1, 29.0, 21.2, 21.0, 20.9, 19.2, 18.4; $[\alpha]_D^{20}$ = +11.7 (*c* = 0.53 in $CHCl_3$); IR (film) ν = 2964, 1639, 1579, 1518, 1458, 1315, 1275, 1227, 1053 cm^{-1}; HRMS (ES^+) calcd for $C_{26}H_{34}N_3O_2$ (M + H) 420.2651, found 420.2659.

Crystals suitable for X-ray analysis were grown by dissolving **11a** in Et_2O (3 mL), and the ether layer was carefully layered with heptane (2 mL) with slow evaporation of the solvents at room temperature: $C_{26}H_{33}N_3O_2$, *M* = 419.55, hexagonal, *a* = 9.51079(4) Å, *b* = 9.51079(4) Å, *c* = 44.3094(2) Å, *U* = 3471.04(3) $Å^3$, *T* = 100 K, space group $P3_121$ (no. 152), *Z* = 6, 77335 reflections measured, 4857 unique (R_{int} = 0.0374), which were used in all calculations. The final *wR*(*F2*) was 0.0651 (all data).

*2-((S)-4-tert-Butyl-4,5-dihydrooxazol-2-yl)-N-(2-((S)-4-isopropyl-5,5-dimethyl-4,5-dihydrooxazol-2-yl)phenyl)aniline (**11b**):* colorless solid (0.102 g, 47%); mp 126−129.5 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 10.80 (s, 1H), 7.82 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.79 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.41 (d, *J* = 8.3 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.31−7.19 (m, 2H), 6.93−6.89 (m, 1H), 6.88−6.84 (m, 1H), 4.23 (dd, *J* = 9.9, 8.4 Hz, 1H), 4.11 (t, *J* = 8.0 Hz, 1H), 4.04 (dd, *J* = 9.9, 7.7 Hz, 1H), 3.45 (d, *J* = 8.5 Hz, 1H), 1.85−1.78 (m, 1H), 1.48 (s, 3H), 1.33 (s, 3H), 1.10 (d, *J* = 6.5 Hz, 3H), 0.99 (d, *J* = 6.5 Hz, 3H), 0.90 (s, 9H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 162.4, 161.0, 143.7, 143.2, 131.0 (2C), 130.5, 130.3, 120.0, 119.5, 119.2, 117.7, 116.9, 116.0, 84.9, 80.9, 76.4, 67.6, 34.0, 29.2, 29.0, 25.9, 21.2, 21.0, 20.9; $[\alpha]_D^{20}$ = +18.8 (*c* = 1.0 in $CHCl_3$); IR (film) ν = 2956, 1641, 1579, 1518, 1458, 1318, 1277, 1227, 1053 cm^{-1}; HRMS (ES^+) calcd for $C_{27}H_{35}N_3O_2$ (M + H) 434.2808, found 434.2809.

Crystals suitable for X-ray analysis were grown by dissolving **11b** in Et_2O (3 mL), and the ether layer was carefully layered with heptane (2 mL) followed by slow evaporation of the solvents at room temperature: $C_{27}H_{35}N_3O_2$, *M* = 433.58, orthorhombic, *a* = 9.54492(6) Å, *b* = 12.68954(7) Å, *c* = 19.9983(1) Å, *U* = 2422.21(2) $Å^3$, *T* = 100 K, space group $P2_12_12_1$ (no. 19), *Z* = 4, 25062 reflections measured, 5041 unique (R_{int} = 0.0328) which were used in all calculations. The final *wR*(*F2*) was 0.0686 (all data).

*2-((S)-4-Isopropyl-5,5-dimethyl-4,5-dihydrooxazol-2-yl)-N-(2-((S)-4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)aniline (**11c**):* yellow solid (0.098 g, 45%); mp 100−103.5 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.78 (s, 1H), 7.91 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.79 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.49 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.40 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.37−7.21 (m, 7H), 6.98−6.94 (m, 1H), 6.88−6.84 (m, 1H), 5.41 (dd, *J* = 10.1, 8.3 Hz, 1H), 4.71 (dd, *J* = 10.1, 8.3 Hz, 1H), 4.14 (t, *J* = 8.3 Hz, 1H), 3.25 (d, *J* = 8.7 Hz, 1H), 1.72 (m, 1H), 1.39 (s, 3H), 1.25 (s, 3H), 1.02 (d, *J* = 6.5 Hz, 3H), 0.88 (d, *J* = 6.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 164.0, 161.2, 143.6, 143.1, 142.6, 131.3, 131.04, 130.6, 130.3, 128.5, 127.3, 126.8, 120.3, 120.1, 119.3, 117.2, 116.9, 115.9, 85.1, 80.7, 73.9, 70.3, 29.0, 28.8, 21.06, 20.9, 20.7; $[\alpha]_D^{20}$ = +114.9 (*c* = 0.75 in $CHCl_3$); IR (film) ν = 2968, 1637, 1579, 1518, 1456, 1317, 1271, 1225, 1055 cm^{-1}; HRMS (ES^+) calcd for $C_{29}H_{31}N_3O_2$ (M + Na) 476.2314, found 476.2316.

Crystals suitable for X-ray analysis were grown by dissolving **11c** in Et_2O (3 mL), and the ether layer was carefully layered with heptane (2 mL) followed by slow evaporation of the solvents at room temperature: $C_{29}H_{31}N_3O_2$, *M* = 453.57, triclinic, *a* = 9.86627(6) Å, *b* = 10.19647(8) Å, *c* = 13.1369(1) Å, *U* = 1220.632(17) $Å^3$, *T* = 100 K, space group *P*1 (no. 1), *Z* = 2, 48983 reflections measured, 9742 unique (R_{int} = 0.0269) which were used in all calculations. The final *wR*(*F2*) was 0.0647 (all data).

*2-((S)-4-Benzyl-4,5-dihydrooxazol-2-yl)-N-(2-((S)-4-isopropyl-5,5-dimethyl-4,5-dihydrooxazol-2-yl)phenyl)aniline (**11d**):* sticky yellow solid (0.121 g, 52%); mp unattainable; ^1H NMR (400 MHz, $CDCl_3$) δ 10.71 (s, 1H), 7.81 (m, 2H), 7.44 (d, *J* = 8.3 Hz, 1H), 7.38 (d, *J* = 8.3 Hz, 1H), 7.32−7.16 (m, 7H), 6.90 (m, 2H), 4.57 (m, 1H), 4.25 (t, *J* = 8.8 Hz, 1H), 4.03 (t, *J* = 7.8 Hz, 1H), 3.40 (d, *J* = 8.7 Hz, 1H), 3.17 (dd, *J* = 13.7, 5.3 Hz, 1H), 2.71 (dd, *J* = 13.7, 8.5 Hz, 1H), 1.84 (m, 1H), 1.52 (s, 3H), 1.33 (s, 3H), 1.14 (d, *J* = 6.5 Hz, 3H), 1.00 (d, *J* = 6.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 163.1, 161.2, 143.7, 143.1, 138.1, 131.2, 131.0, 130.5, 130.3, 129.3, 128.4, 126.3, 120.1, 119.7, 119.3, 117.6, 116.9, 116.0, 85.0, 81.0, 70.8, 68.1, 41.8, 29.1, 28.9, 21.2, 21.1, 20.90; $[\alpha]_D^{20}$ = +41.6 (*c* = 0.30 in $CHCl_3$); IR (film) ν = 2955, 1639, 1579, 1518, 1458, 1317, 1275, 1053 cm^{-1}; HRMS (ES^+) calcd for $C_{30}H_{34}N_3O_2$ (M + H) 468.2651, found 468.2648.

*2-((S)-4-Isopropyl-4,5-dihydrooxazol-2-yl)-N-(2-((S)-4-isopropyl-5,5-diphenyl-4,5-dihydrooxazol-2-yl)phenyl)aniline (**11e**):* pale yellow solid (0.141 g, 52%); mp 67−70 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 10.86 (s, 1H), 8.04 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.81 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.58−7.51 (m, 2H), 7.47−7.39 (m, 2H), 7.36−7.34 (m, 2H), 7.33−7.19 (m, 8H), 6.92 (m, 2H), 4.81 (d, *J* = 4.7 Hz, 1H), 4.26 (dd, *J* = 9.2, 7.9 Hz, 1H), 4.03−3.96 (m, 1H), 3.93 (t, *J* = 8.0 Hz, 1H), 1.82 (m, 1H), 1.67 (m, 1H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.83 (d, *J* = 6.7 Hz, 3H), 0.57 (d, *J* = 6.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 162.4, 160.6, 145.8, 144.0, 143.0, 140.9, 131.3, 131.0, 130.5 (2C), 128.2, 127.6 (2C), 127.1, 127.0, 126.3, 120.2, 119.4, 118.1, 117.1, 115.4, 91.1, 80.6, 73.0, 69.4, 33.0, 30.4, 21.9, 19.1, 18.4, 17.2; $[\alpha]_D^{20}$ = −234.4 (*c* = 0.60 in $CHCl_3$); IR (film) ν = 2958, 1647, 1579, 1518, 1458, 1352, 1315, 1273, 1223, 1051 cm^{-1}; HRMS (ES^+) calcd for $C_{36}H_{38}N_3O_2$ (M + H) 544.2964, found 544.2954.

*2-((S)-4-tert-Butyl-4,5-dihydrooxazol-2-yl)-N-(2-((S)-4-isopropyl-5,5-diphenyl-4,5-dihydrooxazol-2-yl)phenyl)aniline (**11f**):* off-white

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solid (0.111 g, 40%); mp 84−86.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.96 (s, 1H), 8.04 (dd, J = 7.9, 1.5 Hz, 1H), 7.81 (dd, J = 7.9, 1.5 Hz, 1H) 7.56−7.54 (m, 2H), 7.46 (d, J = 8.3 Hz, 1H), 7.41 (d, J = 8.3 Hz, 1H), 7.37−7.34 (m, 2H), 7.33−7.19 (m, 8H), 6.93−6.89 (m, 2H), 4.81 (d, J = 4.6 Hz, 1H), 4.19 (dd, J = 9.5, 8.1 Hz, 1H), 4.07−4.03 (m, 1H), 4.01 (dd, J = 9.5, 8.1 Hz, 1H), 1.85−1.76 (m, 1H), 0.99 (d, J = 6.7 Hz, 3H), 0.84 (s, 9H), 0.55 (d, J = 6.7 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 162.2, 160.4, 145.8, 144.1, 143.0, 140.9, 131.3, 131.0, 130.5 (2C), 128.2, 127.6, 127.6 (2C), 127.1, 127.0, 126.3, 120.1, 119.4, 119.3, 118.0, 117.1, 115.3, 91.01, 80.4, 76.4, 67.6, 33.9, 30.4, 25.8, 21.8, 17.1; $[\alpha]_D^{20}$ = −228.4 (c = 0.75 in $CHCl_3$); IR (film) ν = 2956, 1649, 1579, 1518, 1456, 1313, 1275, 1225, 1051 cm^{-1}; HRMS (ES$^+$) calcd for $C_{37}H_{40}N_3O_2$ (M + H) 558.3121, found 558.3123.

*2-((S)-4-Isopropyl-5,5-diphenyl-4,5-dihydrooxazol-2-yl)-N-(2-((S)-4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)aniline (**11g**):* pale yellow solid (0.130 g, 45%); mp 87−89.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.90 (s, 1H), 8.07 (dd, J = 7.9, 1.5 Hz, 1H), 7.90 (dd, J = 7.9, 1.5 Hz, 1H), 7.51−7.46 (m, 3H), 7.43 (d, J = 7.9 Hz, 1H), 7.37−7.15 (m, 15H), 6.98−6.92 (m, 2H), 5.37−5.33 (m, 1H), 4.65 (m, 2H), 4.07 (t, J = 8.4 Hz, 1H), 1.78−1.72 (m, 1H), 0.88 (d, J = 6.7 Hz, 3H), 0.51 (d, J = 6.7 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 162.4, 160.6, 145.8, 144.0, 143.0, 140.9, 131.3, 131.0, 130.5 (2C), 128.2, 127.6 (2C), 127.1, 127.0, 126.3, 120.2, 119.4, 118.1, 117.1, 115.4, 91.1, 80.6, 73.0, 69.4, 33.0, 30.4, 21.9, 19.1, 18.4, 17.2; $[\alpha]_D^{20}$ = −125.3 (c = 0.33 in $CHCl_3$); IR (film) ν = 2922, 1645, 1579, 1516, 1454, 1271, 1051 cm^{-1}; HRMS (ES$^+$) calcd for $C_{39}H_{36}N_3O_2$ (M + H) 578.2809, found 578.2803.

*2-((S)-4-Benzyl-4,5-dihydrooxazol-2-yl)-N-(2-((S)-4-isopropyl-5,5-diphenyl-4,5-dihydrooxazol-2-yl)phenyl)aniline (**11h**):* pale yellow solid (0.133 g, 45%); mp 73−76.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.75 (s, 1H), 8.08 (dd, J = 7.9, 1.6 Hz, 1H), 7.79 (dd, J = 7.9, 1.6 Hz, 1H), 7.57−7.55 (m, 2H), 7.42 (app t, J = 8.6 Hz, 2H), 7.33−7.19 (m, 9H), 7.17−7.14 (m, 4H), 7.10−7.06 (m, 1H), 6.97−6.90 (m, 2H), 6.94−6.90 (m, 1H), 4.75 (d, J = 4.8 Hz, 1H), 4.49 (dtd, J = 8.8, 7.4, 5.4 Hz, 1H), 4.19 (t, J = 8.8 Hz, 1H), 3.97 (dd, J = 8.2, 7.4 Hz, 1H), 3.07 (dd, J = 13.8, 5.4 Hz, 1H), 2.58 (dd, J = 13.8, 8.6 Hz, 1H), 1.88−1.79 (m, 1H), 1.00 (d, J = 6.7 Hz, 3H), 0.58 (d, J = 6.7 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.1, 160.8, 145.7, 143.9, 143.0, 140.9, 138.1, 131.4, 131.3, 130.6, 130.5, 129.2, 128.3, 128.2, 127.6 (2C), 127.1 (2C), 126.3, 120.2, 119.6, 119.5, 118.2, 116.9, 115.6, 91.2, 80.8, 70.9, 68.0, 41.7, 30.4, 22.0, 17.3; $[\alpha]_D^{20}$ = −173.1 (c = 0.65 in $CHCl_3$); IR (film) ν = 2956, 2927, 1643, 1579, 1456, 1352, 1317, 1272, 1221, 1135, 1051 cm^{-1}; HRMS (ES$^+$) calcd for $C_{40}H_{38}N_3O_2$ (M + H) 592.2964, found 592.2969.

Synthesis of $FeCl_2$ Complex of Ligand 11d. Ligand **11d** (72.8 mg, 0.22 mmol) was added under inert conditions to an oven-dried Schlenk tube. Acetonitrile (2.5 mL) was added, and the solution was allowed to stir under nitrogen for 5 min. $FeCl_2$ (25 mg, 0.2 mmol) was then added, and the solution was allowed to stir for 3 h at room temperature, after which time any residual particulate matter was removed by filtration. The filtrate was concentrated in vacuo to yield a green solid residue. This residue was dissolved in Et_2O (3 mL) and the ether layer was carefully layered with heptane (2 mL). Crystals suitable for X-ray analysis were grown by the slow evaporation of the solvents at room temperature: $C_{30}H_{32}Cl_2FeN_3O_2$, M = 593.34, monoclinic, a = 8.4077(1) Å, b = 17.5482(3) Å, c = 9.4560(2) Å, U = 1390.95(4) Å^3, T = 100 K, space group $P21$, Z = 2, 26571 reflections measured, 7971 unique (R_{int} = 0.0300) which were used in all calculations. The final $wR(F2)$ was 0.0575 (all data).

General Procedure for the Catalytic Enantioselective Friedel−Crafts Reaction between Indole (12) and *trans*-β-Nitrostyrene (13a). To an oven-dried Schlenk tube under nitrogen were added $Zn(OTf)_2$ (9.3 mg, 0.025 mmol) and ligand (**1a−g**, **11a−h**) (0.025 mmol) followed by the addition of toluene (2 mL). The solution was stirred at room temperature for 30 min, and the *trans*-β-nitrostyrene (74.5 mg, 0.5 mmol) was added. The mixture was allowed to stir for a further 15 min and cooled to −20 °C before indole (57 mg, 0.5 mmol) was added. After being stirred for 40 h at −20 °C, the mixture was filtered through a pad of silica and concentrated. The resulting yellow oil was purified using flash column chromatography on silica gel (pentane/EtOAc, 5:1).

*(R)-3-(2-Nitro-1-phenylethyl)-1H-indole (**14a**):* R_f = 0.20 (pentane/EtOAc, 5:1); $[\alpha]_D^{20}$ = −18.4 (c = 1.00 in CH_2Cl_2, 61% ee (R)) (lit.[78] $[\alpha]_D^{20}$ = +25.3 (c = 0.9 in CH_2Cl_2, 84% ee (S))); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 ppm (br s, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.35−7.30 (m, 5H), 7.26−7.23 (m, 1H), 7.19 (t, J = 8.0 Hz, 1H), 7.07 (app. t, J = 8.0 Hz, 1H), 6.97 (d, J = 2.0 Hz, 1H), 5.18 (t, J = 8.0 Hz, 1H), 5.05 (dd, J = 12.5, 7.5 Hz, 1H), 4.93 (dd, J = 12.5, 7.5 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 139.2, 136.5, 128.9 (2C), 127.8 (2C), 127.6, 126.1, 122.7, 121.6, 120.0, 118.9, 114.5, 111.4, 79.5, 41.6. The enantioselectivity was determined by HPLC: Chiralcel IB (heptane/EtOH, 70:30, 0.9 mL/min). Retention times: t_{minor} = 10.8 min (S), t_{major} = 12.1 min (R).

General Procedure for the Catalytic Enantioselective Friedel−Crafts Reaction between 2-Methoxyfuran (15) and *trans*-β-Nitrostyrenes 13a−f. To a flame-dried Schlenk tube were added $Zn(OTf)_2$ (9.3 mg, 0.025 mmol) and ligand (**1a−g**, **11a−h**) (0.0275 mmol) under nitrogen, followed by addition of toluene (3.0 mL). The solution was stirred at room temperature for 2 h, and *trans*-β-nitrostyrene (**13a−f**) (37.0 mg, 0.25 mmol) was added. The mixture was stirred for 15 min before the addition of 2-methoxyfuran (24.5 mg, 24.0 μL, 0.25 mmol). After being stirred for 24 h, the mixture was filtered through a pad of silica, concentrated, and purified by flash column chromatography on silica gel (pentane/EtOAc, 9:1) to yield the title compound as a colorless oil.

*(S)-2-Methoxy-5-(1-phenyl-2-nitroethyl)furan (**16a**):* R_f = 0.42 (pentane/EtOAc, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.23 (m, 5H), 5.95 (d, J = 3.2 Hz, 1H), 5.03 (d, J = 3.2 Hz, 1H), 4.94 (dd, J = 16.2, 11.5 Hz, 1H) 4.79−4.71 (m, 2H), 3.78 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 161.5, 141.5, 136.8, 129.0, 128.0, 127.8, 108.8, 79.9, 78.0, 57.7, 43.6; $[\alpha]_D^{20}$ = −50.4 (c = 1.0 in $CHCl_3$, 89% ee) (lit.[16] $[\alpha]_D^{20}$ = −63.2 (c = 1.4 in $CHCl_3$, 94% *ee* (S))); HRMS (ES$^+$) calcd for $C_{13}H_{13}NO_4$ 247.0845, found 247.0857; The enantioselectivity was determined by HPLC: Chiralcel IB, (heptane:/EtOH, 90:10, 1.0 mL/min). Retention times: t_{minor} = 8.5 min (R), t_{major} = 10.0 min (S).

*(S)-2-Methoxy-5-(1-(4-methoxyphenyl)-2-nitroethyl)furan (**16b**):* R_f = 0.24 (pentane/Et_2O, 85:15); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.93 (d, J = 3.2 Hz, 1H), 5.03 (d, J = 3.2 Hz, 1H), 4.92 (dd, J = 15.4, 10.9 Hz, 1H), 4.78−4.67 (m, 2H), 3.80 (s, 3H) 3.78 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.4, 159.2, 141.9, 128.9, 128.7, 114.3, 108.5, 79.9, 78.2, 57.7, 55.2, 42.8; $[\alpha]_D^{20}$ = −65.5.3 (c = 0.32 in $CHCl_3$, 92% ee) (lit.[16] $[\alpha]_D^{20}$ = −40.7 (c = 1.7 in $CHCl_3$, 94% *ee* (S))); HRMS (ES$^+$) calcd for $C_{14}H_{15}NO_5$ 277.0950, found 277.0949. The enantioselectivity was determined by HPLC: Chiralcel IB (heptane/EtOH, 90:10, 1 mL/min). Retention times: t_{minor} = 9.5 min (R), t_{major} = 11.0 min (S).

*(S)-2-(1-(4-Bromophenyl)-2-nitroethyl)-5-methoxyfuran (**16c**):* R_f = 0.39 (pentane/EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 5.97 (d, J = 3.3 Hz, 1H), 5.05 (d, J = 3.3 Hz, 1H), 4.93 (dd, J = 15.8, 10.8 Hz, 1H), 4.80−4.68 (m, 2H), 3.81 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.6, 140.8, 135.8, 132.2, 129.5, 122.1, 109.0, 80.0, 77.7, 57.8, 43.0; $[\alpha]_D^{20}$ = −68.2 (c = 0.37 in $CHCl_3$, 92% ee); HRMS (ES$^+$) calcd for $C_{13}H_{12}NO_4Br$ 324.9950, found 324.9952. The enantioselectivity was determined by HPLC: Chiralcel IB (heptane/EtOH, 90:10, 1 mL/min). Minor retention times: t_{minor} = 9.6 min (R), t_{major} = 10.6 min (S).

*(S)-2-Methoxy-5-(2-nitro-1-(p-tolyl)ethyl)furan (**16d**):* R_f = 0.47 (pentane/EtOAc, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21−7.11 (m, 4H), 5.95 (d, J = 3.2 Hz, 1H), 5.03 (d, J = 3.2 Hz, 1H), 4.94 (dd, J = 15.2, 10.7 Hz, 1H), 4.79−4.69 (m, 2H), 3.80 (s, 3H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.5, 141.8, 137.8, 133.8, 129.7, 127.7, 108.6, 79.9, 78.1, 57.7, 43.2, 21.1; $[\alpha]_D^{20}$ = −28.0 (c = 0.29 in $CHCl_3$, 92% ee) (lit.[16] $[\alpha]_D^{20}$ = −38.4 (c = 1.4 in $CHCl_3$, 94% ee (S))); HRMS (ES$^+$) calcd for $C_{14}H_{15}NO_4$ 261.1001, found 261.0995. The enantioselectivity was determined by HPLC: Chiralcel IB, (heptane/EtOH, 90:10, 1 mL/min). Minor retention times: t_{minor} = 7.4 min (R), t_{major} = 8.7 min (S).

*(R)-2-(1-(Furan-2-yl)-2-nitroethyl)-5-methoxyfuran (**16e**):* R_f = 0.37 (pentane/Et_2O, 85:15); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37

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(d, J = 1.9 Hz, 1H), 6.32 (dd, J = 3.2, 1.9 Hz, 1H), 6.20 (d, J = 3.3 Hz, 1H), 6.05 (d, J = 3.3 Hz, 1H), 5.07 (d, J = 3.3 Hz, 1H), 4.92 (dd, J = 8.7, 6.3 Hz, 1H), 4.85 (dd, J = 7.1, 5.0 Hz, 2H), 3.82 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 161.5, 149.6, 142.5, 139.0, 110.5, 109.4, 107.9, 80.1, 76.1, 57.8, 37.6; $[\alpha]_D^{20}$ = −30.9 (c = 0.75 in $CHCl_3$, 89% ee) (lit.[16] $[\alpha]_D^{20}$ = −24.1 (c = 0.20 in $CHCl_3$, 86% ee (S))); HRMS (ES^+) calcd for $C_{11}H_{11}NO_5$ 237.0637, found 237.0640. The enantioselectivity was determined by HPLC: Chiralcel IB, (heptane:EtOH, 99:1, 1 mL/min). Major retention times: t_{major} = 12.3 min (R), t_{minor} = 13.3 min (S).

*(S)-2-Methoxy-5-(2-nitro-1-(thiophene-2-yl)ethyl)furan (**16f**):* R_f = 0.37 (pentane/Et_2O, 85:15); ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 1.9 Hz, 1H), 6.32 (dd, J = 3.3, 1.9 Hz, 1H), 6.20 (d, J = 3.3 Hz, 1H), 6.05 (d, J = 3.3 Hz, 1H), 5.07 (d, J = 3.3 Hz, 1H), 4.92 (dd, J = 8.7, 6.3 Hz, 1H), 4.85 (dd, J = 7.1, 5.0 Hz, 2H), 3.82 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 161.5, 140.7, 139.2, 127.1, 126.0, 125.3, 109.1, 80.1, 78.5, 57.8, 38.8; $[\alpha]_D^{20}$ = −40.3 (c = 0.85 in $CHCl_3$, 90% ee) (lit.[16] $[\alpha]_D^{20}$ = −33.7 (c = 2.3 in $CHCl_3$, 89% ee (S))); HRMS (ES^+) calcd for $C_{11}H_{11}NO_4S$ 253.0409, found 253.0397. The enantioselectivity was determined by HPLC: Chiralcel OD-H (heptane/EtOH, 95:5, 1 mL/min). Retention times: t_{major} = 11.1 min (R), t_{minor} = 12.3 min (S).

*(S)-2-(1-(3-Chlorophenyl)-2-nitroethyl)-5-methoxyfuran (**16g**):* R_f = 0.39 (pentane/EtOAc, 9:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.22 (m, 4H), 5.96 (d, J = 3.3 Hz, 1H), 5.04 (d, J = 3.3 Hz, 1H), 4.93 (dd, J = 17.0, 12.0 Hz, 1H), 4.80−4.68 (m, 2H), 3.80 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 161.6, 140.9, 135.3, 134.0, 129.2, 129.2 (3C), 109.0, 80.0, 77.8, 57.8, 42.9; $[\alpha]_D^{20}$ = −84.2 (c = 0.28 in $CHCl_3$, 95% ee); HRMS (ES^+) calcd for $C_{13}H_{12}NO_4Cl$ 281.0455, found 281.0455. The enantioselectivity was determined by HPLC: Chiralcel IB (heptane/EtOH, 90:10, 1 mL/min). Minor retention times: t_{minor} = 9.2 min (R), t_{major} = 9.9 min (S).

Dichlorozinc Bis[2-((4*S*)-4-*tert*-butyl-4,5-dihydrooxazol-2-yl)-phenyl]methylamine (18). An oven-dried Schlenk tube was charged with bis(2-cyanophenyl)methylamine (0.500 g, 2.14 mmol), (*S*)-*tert*-leucinol (0.842 g, 6.42 mmol), and anhydrous zinc chloride (0.642 g, 4.71 mmol). Chlorobenzene (anhydrous) (2 mL) was then added, and the resulting suspension was heated at reflux temperature under an atmosphere of nitrogen for 4 d. The reaction mixture was concentrated in vacuo to give a brown oil which was then purified by flash column chromatography on silica gel (3 × 30 cm) using either CH_2Cl_2 or ethyl acetate as the eluent to afford the title compound (0.81 g, 66%) as a yellow/green solid: ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (dd, J = 7.8, 1.5 Hz, 2H), 7.63 (ddd, J = 8.5, 7.8, 1.5 Hz, 2H), 7.24 (dd, J = 8.5, 1.0 Hz, 2H), 7.15 (dt, J = 7.8, 1.0 Hz, 2H), 4.17 (dd, J = 9.1, 3.7 Hz, 2H), 3.89 (dd, J = 9.7, 3.7 Hz, 2H), 3.53 (s, 3H), 3.23 (app t, J = 9.3 Hz, 2H), 0.95 (s, 18H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 172.2, 147.4, 134.3, 133.1, 122.5, 121.2, 116.4, 70.1, 67.2, 42.5, 35.0, 25.7; IR (KBr) ν = 3455, 2964, 1652, 1479, 1254, 945 cm^{-1}; MS-ES^+ m/z 539 (M^+ − Cl, 17), 434 (M^+-$ZnCl_2$ + 1, 100). Anal. Calcd for $C_{27}H_{35}Cl_2N_3O_2Zn$: C, 56.89; H, 6.19; Cl, 12.44; N, 7.40; Zn, 11.47. Found: C, 57.04; H, 6.22; Cl, 11.47; N, 7.33; Zn, 10.36.

Crystals of **18** suitable for X-ray analysis were grown by isothermal diffusion using dichloromethane/petroleum ether (40−60 °C): $C_{27}H_{35}N_3O_2Cl_2Zn$, M = 654.78, monoclinic, a = 9.9185(8) Å, b = 10.6832(9) Å, c = 14.5573(12) Å, U = 1538.1(2) $Å^3$, T = 293 K, space group $P2_1P2_1P2_1$ (#4), Z = 2, 13999 reflections measured, 7493 unique (R_{int} = 0.0171) which were used in all calculations. The final $wR(F2)$ was 0.0962 (all data).

Synthesis of $ZnCl_2$ Complex (19). Ligand **11d** (72.8 mg, 0.22 mmol) was added under inert conditions to an oven-dried Schlenk tube. Acetonitrile (2.5 mL) was added, and the solution was allowed to stir under nitrogen for 5 min. $ZnCl_2$ (0.20 mL, 0.2 mmol) was then added, and the solution was allowed to stir for 5 min at room temperature, after which time pentane (0.30 mL) was added to the solution.

Crystals of **19** suitable for X-ray analysis were grown by the slow evaporation of the solvents at room temperature: $C_{27}H_{35}N_3O_2Cl_2Zn$, M = 569.85, orthorhombic, a = 9.3141(2) Å, b = 11.2722(2) Å, c = 26.2759(4) Å, U = 2758.72 $Å^3$, T = 100 K, space group $P2_12_12_1$, Z = 6, 30100 reflections measured, 6912 unique (R_{int} = 0.0336) which were used in all calculations. The final $wR(F2)$ was 0.0502 (all data).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01767. CCDC 1415749−1415751, 1425893−1425894 contain the supplementary crystallographic data for this paper. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

X-ray data (CIF)

Full analysis of all new compounds including NMR, X-ray, and chromatographic data (PDF)

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Notes

The authors declare no competing financial interest.

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