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Synthesis of highly modular bis(oxazoline) ligands by Suzuki cross-coupling and evaluation as catalytic ligands

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ABSTRACT

New bis(oxazoline) ligands (BOXs) containing biaryl substitutents at the C-4 position and H or CH_2OR substituents at the C-5 position have been synthesized using Suzuki cross-coupling as the main tool for structural diversity. Copper, zinc, and palladium complexes of the prepared BOXs have been evaluated in the following catalytic asymmetric processes: Acylation with kinetic resolution of *trans*-1,2-cyclohexanediol (Cu), enantioselective Friedel–Crafts alkylation of indole (Zn), and enantioselective alkylation of 3-acetoxy-1,3-diphenylpropene (Pd).

1. Introduction

C_2-Symmetric bis(oxazolines) (BOXs) are among the most widely studied ligands in asymmetric catalysis.[1] Since their introduction,[2,3] numerous BOX ligands with different backbones have been reported, indicating that the fine tuning of these structures can dramatically improve the enantioselectivity of many asymmetric reactions.

Structural variation in these compounds can be performed either on the spacer connecting the two oxazoline rings (methylene, isopropylidene, cyclopropylidene…), or at the C-4 and C-5 positions of the oxazoline units (Fig. 1). Given the ready availability of 2-amino-1-alcohols, BOXs of type I have been more extensively studied.[1–6] Bis(oxazolines) involving 4,5-disubstituted oxazoline moieties (i.e., deriving from internal amino alcohols) have also been reported, thus covering both cis (Type II)[7] and trans derivatives (Type III).[8]

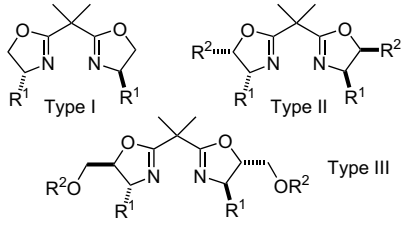

Figure 1. Common bis(oxazoline) ligands.

Over the last years, we have shown[9] that a wide variety of modular, enantiopure amino alcohol ligands for asymmetric catalysis can be easily synthesized in either enantiomeric form via ring-opening of enantiomerically pure synthetic epoxides[10] with nitrogen nucleophiles.[11] More recently, we have extended the range of chiral amino alcohols available through this approach by using Suzuki reactions of enantiopure epoxides bearing halogen-substituted aryl substituents (Fig. 2).[12] Some characteristics of this approach deserve further consideration: (a) there are few precedents of productive cross-coupling reactions in the presence of activated epoxides,[13] and (b) new biaryl and teraryl substituted amino alcohols, hardly available through a direct procedure due to limitations of the epoxidation step, could be easily prepared.

Herein, we report our studies on the development of a new family of BOX ligands of types I and III containing biaryl fragments at the C-4 position of the oxazoline moieties, using the Suzuki cross-coupling as the key synthetic tool for molecular diversity. The increased length and the larger effective volume of the aryl substituents in these molecules can give rise to deeper cavities in their metal chelates, and in fact can translate into an increased steric discrimination between the two enantiotopic faces of reacting substrates in catalytic processes.

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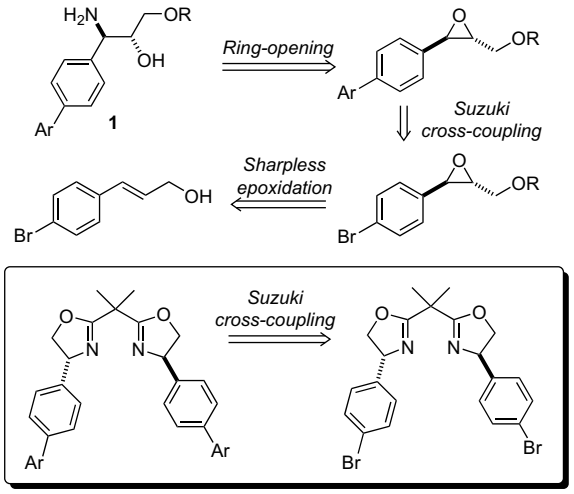
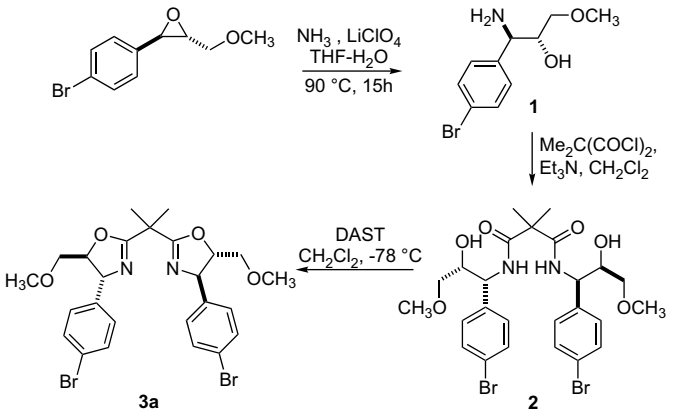


Figure 2. Suzuki strategy for the synthesis of biaryl containing amino alcohols and bis(oxazolines).

2. Results and discussion

Bis(oxazoline) **3a**, depicting two 4-bromophenyl groups ready for Suzuki cross-coupling was identified as the key intermediate in our approach. It is to be noted that the alkoxy groups in this molecule represent an additional source of diversity, since a variety of 4-bromophenylglycidyl ethers are readily available in enantiomerically pure form from the corresponding arylglycidol precursor.[14] For the preparation of **3a** (Scheme 1), (2*R*,3*R*)-(4-bromophenyl)glycidyl methyl ether (>99% ee) was submitted to stereospecific and regioselective ring-opening with ammonia[15] in the presence of $LiClO_4$[16] in aqueous THF in an autoclave at 90 °C, amino alcohol **1** being obtained in 81% yield. This amino alcohol could be readily converted into **3a** can via bis(hydroxyamide) **2**,[12] the final cyclization step being best achieved (87% overall yield) with diethylaminosulfur trifluoride (DAST).[17]



Scheme 1. Synthesis of bis(oxazoline) **3a**.

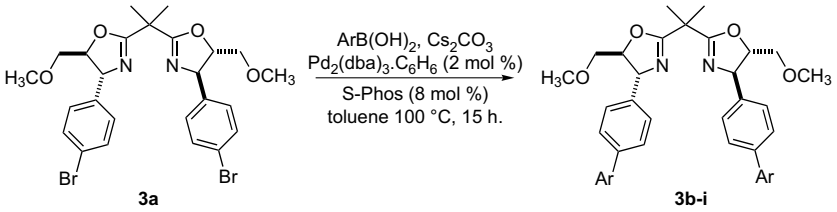
From a chemical perspective, the introduction of diversity in the final stages of syntheses is a most powerful strategy for the preparation of molecular libraries, because a single key intermediate can be converted to the target compounds in a parallel manner. When a family of BOXs **3**, with diversity arising exclusively from the aryl substituent on the oxazoline is considered (for instance, in view of ligand optimization for a particular application in catalysis), the use of such a strategy becomes an appealing alternative, and bis(oxazoline) **3a** appears as a most convenient relay. According to these ideas we planned to access BOXs of type III by double Suzuki cross-coupling reactions performed on **3a** (Table 1). Quite gratifyingly, the double Suzuki cross-couplings on **3a** under Buchwald's conditions[18] took place with complete conversion after 15 h and afforded the biaryl-substituted bis(oxazolines) **3b**–**3i** in good to excellent yields. This method appears to be quite general since both arylboronic acids containing electron withdrawing or electron donating groups can be incorporated in the BOX backbone. It is noteworthy that the more bulky and electron rich 2,6-dimethoxyphenyl boronic acid provided the best results (**3i**, entry 8). Notably, since the oxazoline rings are much less prone to undesired side reactions than the epoxides from which they ultimately arise,[12] it is much more convenient to perform the Suzuki cross-coupling reaction on the preformed BOX derivatives.

In a closely related approach, BOXs of Type I involving complex aryl groups in their skeletons could also be accessed from 4-bromophenyl substituted bis(oxazoline) **8** via Suzuki cross-coupling reactions. The viability of this possibility is illustrated by the preparation of the 4,4′-bis(biphenyl) substituted BOX ligand **9** (Scheme 2). In this particular case, the synthesis of the precursor was initiated by Corey–Chaykovsky reaction on 4-bromobenzaldehyde **4**, followed by hydrolytic kinetic resolution of the resulting (4-bromophenyl)oxirane **5** using Jacobseńs procedure (ee≥99%).[19] After some experimentation, we found that ring-opening of epoxide **5** could be best effected by a two-step sequence involving ammonium chloride catalyzed azidolysis of the epoxide[20] and reduction of the azido group by the Staudinger protocol. Although a 1:1 regioisomeric mixture of amino alcohols was obtained, the desired isomer **7** could be easily separated by flash chromatography. It is worth mentioning that the ring-opening of an epoxide at the benzylic position can occur both via S_N1 and S_N2 mechanisms; in our case, although the optical purity of the obtained azido alcohol **6** only reached 92%, an additional recrystallization resulted in an enantiomeric enrichment up to 99% ee. Finally, the synthetic precursor 4-bromophenyl substituted bis(oxazoline) **8** was obtained via condensation of **6** with dimethylmalonyl dichloride followed by cyclization with DAST. In accordance with our expectations, the Suzuki cross-coupling reaction of **8** with phenylboronic acid took place smoothly, yielding the desired BOX **9** in 65% yield.

With bis(oxazolines) **3a**–**3i** and **9** in hand, effort was devoted to the preparation of their metal complexes in view of synthetic application. In the case of **9**, after reaction with 1 equiv of $CuCl_2$, the BOX complex **9**·$CuCl_2$ could be isolated as single crystals grown from CH_2Cl_2 and the crystal structure could be determined by X-ray diffraction (Fig. 3).[21] As expected, the structure of **9**·$CuCl_2$ is related to the other $CuCl_2$ complexes of bis(oxazolines): the copper atom is in a distorted square planar environment, the sum of the angles around the copper atom being 374° (379–383° for the other related structures) and the angle between the ClCuCl and NCN planes is only 40.4° (45.7–51.5° for the related complexes).[5,22] The main structural characteristic of the complex lies on the length of the aryl substituents (8.63 Å for the distance between the C4 atom of the oxazoline ring and the distal carbon in the biphenyl moieties), which enhances the C_2-symmetric nature of the ligand. In the biphenyl moieties, the two aromatic rings show the usual twisting (43.7°) due to steric repulsions between the ortho hydrogen atoms. For comparison, the 1-naphthyl and 2-naphthyl BOXs have substituents of similar lenghts than those of Ph-BOX but that are wider and can rotate toward the metallic center; the Inda-BOX (II) has a constrained structure, with one of the *ortho* hydrogen forced to look toward the copper atom. Of all these ligands, **9** is the one where the steric bulk of the aryl substituents is projected the farthest away from the oxazoline rings.

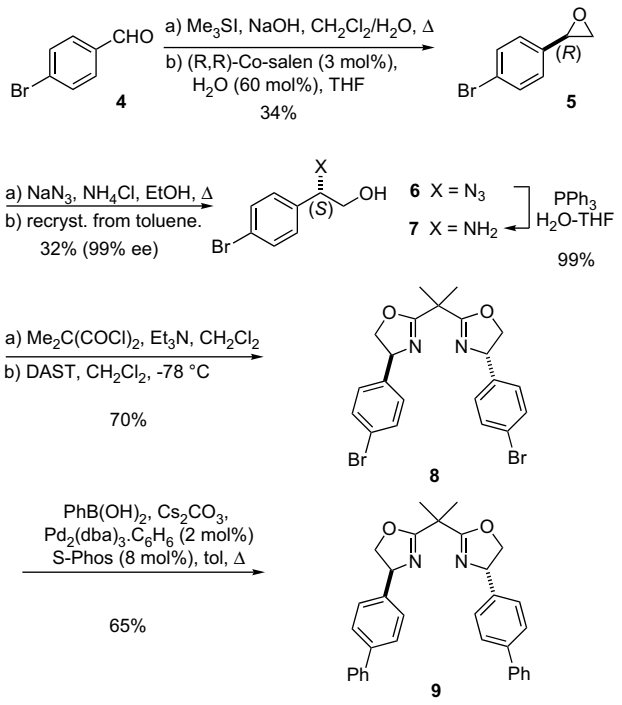
The catalytic properties of **9**·$CuCl_2$ and **3b**·$CuCl_2$ were investigated in the deracemization of *trans*-1,2-cyclohexanediol with benzoyl chloride (Table 2), a reaction where copper(II) complexes of

Table 1
Formation of structurally complex bis(oxazolines) **3aa–aj** by Suzuki cross-coupling on BOX **3ac**



Entry	Aryl	Product	Yield[a] (%)
1	Phenyl	**3b**	77
2	4-Trifluoromethylphenyl	**3c**	52
3	3,5-Bis(trifluoromethyl)phenyl	**3d**	76
4	3,5-Dimethylphenyl	**3e**	71
5	4-Methoxyphenyl	**3f**	69
6	2-Tolyl	**3g**	61
7	2,6-Dimethylphenyl	**3h**	67
8	2,6-Dimethoxyphenyl	**3i**	94

[a] Isolated yield after flash chromatography.



Scheme 2. Synthesis of bis(oxazoline) **9**.

BOXs have been previously employed as catalysts.[23] When **9**·$CuCl_2$ was used (entry 1), the observed enantioselectivity exactly replicated that recorded with (*R*,*R*)-Ph–BOX·$CuCl_2$ on the same substrate, **9**·$CuCl_2$ behaving as a slightly more active catalyst.[20] On the other hand, the results obtained with the $CuCl_2$ complex of **3b** (entry 2) show that increasing the steric bulk of the bis(oxazoline) ligand through the introduction of a substituent on the C-5 position in the oxazoline ring and keeping constant the size of the aryl substituent at C-4 provokes a drop in the enantioselectivity of the reaction, while the catalytic activity depicted by the complexes is maintained. When the use of **10**, a bulkier analogue of **3b**, was studied (entry 3; see Experimental part for the synthesis of this ligand)[12] an even more important decrease in enantioselectivity was observed.

The new BOXs **3b** and **9** were also tested in the zinc-mediated Friedel–Crafts alkylation of indole with *trans*-β-nitrostyrene,

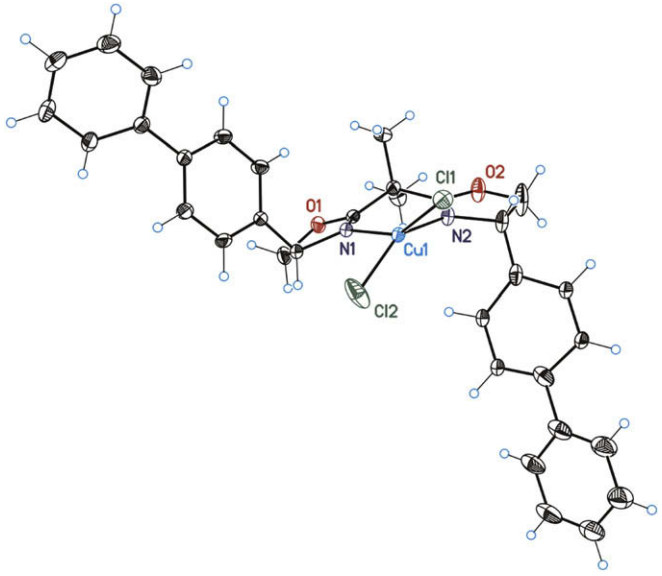
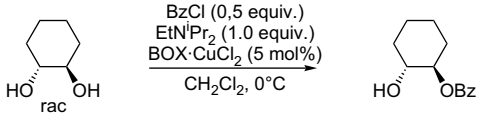


Figure 3. Crystal structure of **9**·$CuCl_2$.

Table 2
Desymmetrization via benzoylation of *rac-trans*-1,2-cyclohexanediol with benzoyl chloride catalyzed by BOX·$CuCl_2$

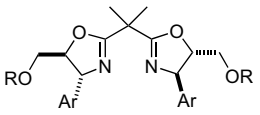


Entry	Ligand	Yield[a] (%)	ee[b] (%)
1	**9**	45	80
2	**3b**	39	60
3	**10**	38	33

[a] Isolated yield after flash chromatography.
[b] Determined by chiral HPLC.

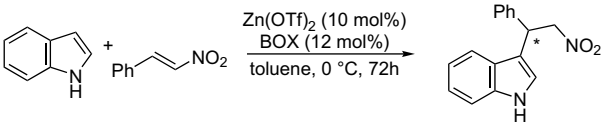
a process where zinc complexes of structurally more simple BOXs have been studied as catalysts.[24] For a better understanding of the influence of the different molecular fragments on the catalytic activity and enantioselectivity in this particular process, the zinc chloride complexes of the known BOX **11**[8] and of **10** and **12**, prepared in turn from structurally complex amino alcohols (see Experimental part),[12] were also tested in the reaction The results of

this study have been summarized in Table 3, where the following general trends in catalytic behavior can be observed. With respect to catalytic activity, the volume of the tunable substituent at C-4 appears to play a fundamental role. Thus, while **11** behaves as a not very active catalyst (entry 3), the presence of a C-4 substituent (biphenyl) whose steric influence reaches space regions farthest away from the reaction center (**3b**, entry 2) leads to faster reactions. This effect is even more pronounced when the C-5 position is unsubstituted (**9**, entry 1). According to our results, the best compromise between catalytic activity and enantioselectivity is attained when a very bulky teraryl substituent is present at C-4 and a rather bulky benzyloxymethyl group is present at C-5 (**12**, entry 4).



BOX	Ar	R
10	3,5-diphenylphenyl	methyl
11	phenyl	methyl
12	3,5-diphenylphenyl	benzyl

Table 3
Enantioselective Friedel–Crafts alkylation of indole

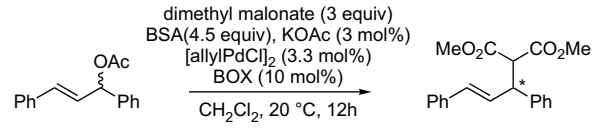


Entry	Ligand	Yield[a] (%)	ee[b] (%)
1	**9**	90	50
2	**3b**	70	44
3	**11**	47	56
4	**12**	96	59
5	**10**	80	20

[a] solated yield after flash chromatography.
[b] Dermined by chiral HPLC.

As a third test on the effect of the nature of the aryl substituents in the modular BOXs on the catalytic behavior, we decided to test the performance of the palladium complexes of these ligands in the asymmetric allylic alkylation[8,25] of *rac*-3-acetoxy-1,3-diphenylpropene with dimethyl malonate using Trost's conditions.[26] Also in this case, BOX ligands of different typologies were included in the screening in an attempt to understand the role exerted by the different molecular fragments on the catalytic behavior. The results of this screening have been collected in Table 4.

Table 4
Enantioselective allylic alkylation of 3-acetoxy-1,3-diphenylpropene catalyzed by BOX π-allylpalladium complexes



Entry	Ligand	Yield[a] (%)	ee[b] (%)
1	**9**	30	96
2	**10**	70	96
3	**11**	>95	96
4	**12**	>95	94
5	**3a**	41	95
6	**3b**	58	94
7	**3c**	>95	95
8	**3d**	43	91
9	**3e**	60	95
10	**3h**	63	94
11	**3i**	59	94

[a] Isolated yield after flash chromatography.
[b] Determined by chiral HPLC.

First of all, it is interesting to note that all the studied ligands lead to very high enantioselectivity in the alkylation process with the relative exception of **3d** (entry 8). This ligand contains in its structure very electron-poor 3′,5′-bis(trifluoromethyl)-4,4′-biphenyl substituents that can be responsible for this diminished enantiodiscrimination. With respect to catalytic activity, it seems clear that the presence of a substituent at C-5 on the oxazoline ring plays an important role (see entry 1). When substituents at C-4 and C-5 are simultaneously present, no correlation can be easily established between the C-4 or C-5 substituent size or electronic character and the catalytic activity exhibited by the corresponding palladium complexes. However, it is clear that some privileged combinations exist (entries 3, 4, and 7). It is worth noting that in two of these privileged combinations (**3c** and **12**), the synthetic methodology based on Suzuki cross-coupling, either at the stage of a precursor enantiopure epoxide (for **12**)[12] or at the stage of the relay BOX ligand **3a** (for **3c**) is key to the availability of the BOX ligands.

3. Conclusion

In conclusion, a new family of enantiopure bis(oxazolines) that contain biaryl substituents on the key C-4 position of the oxazoline rings has been synthesized by Suzuki cross-coupling on a single precursor. For comparison purposes, a reduced set of BOX ligands containing teraryl substituents at the same C-4 position has been prepared from amino alcohols already containing the bulky aryl substituent (installed also by Suzuki cross-coupling at the level of an epoxide precursor). The new BOX ligands containing extended aromatic substituents have been evaluated in a variety of metal catalyzed (Cu, Zn, Pd) processes with promising results. The synthetic strategy employed here, that overcomes limitations in the supply of enantiopure precursors (of either natural or synthetic origin), might also be applied to any other oxazoline containing ligands (pyridine-bisoxazolines or phosphinoxazolines)[27] in order to increase their structural complexity through parallel approaches.

4. Experimental section

4.1. General

NMR spectra were recorded in $CDCl_3$ at 298 K. ^1H and ^{13}C chemical shifts are reported in parts per million relative to Me_4Si, and ^{19}F chemical shifts are reported in parts per million relative to $CFCl_3$. Dry, oxygen-free solvents (SPS) were employed. Compounds **10** and **11** were prepared by known procedures.[8,12]

4.2. (2*R*,3*R*)-3-(4-Bromophenyl)-3-amino-1-methoxypropan-2-ol (1)

A 100 mL autoclave was filled with >99% ee (2*S*,3*S*)-(4-bromophenyl)glycidyl methyl ether[12] (2.2 g, 9.0 mmol), lithium perchlorate (1.9 g, 18 mmol), THF (30 mL), and ammonia (30% solution in water, 40 mL). The sealed reactor was heated to 90 °C for 15 h. After cooling, the mixture was extracted with ether (3×30 mL), the organic phase was sequentially washed with water (50 mL) and brine, and dried over magnesium sulfate. Solvent evaporation and purification by flash chromatography on silicagel (CH_2Cl_2/EtOAc 9/1 then CH_2Cl_2/MeOH 9/1) yielded amino alcohol **1** (81%) as a white crystalline solid: mp 115–116 °C; $[\alpha]_D^{20}$ −25.8 (*c* 2.82, $CHCl_3$); ^1H NMR (400 MHz): δ=2.05 (br, 3H), 3.32 (m, 5H), 3.91 (m, 1H), 4.12 (d, 5.2 Hz, 1H), 7.26 (d, 8.4 Hz, 2H), 7.48 (d, 8.4 Hz, 2H); ^{13}C NMR (100 MHz): δ=57.3, 59.2, 73.3, 73.4, 121.2, 128.9, 131.5, 141.6; HRMS (ES^+): calcd for $C_{10}H_{14}BrNO_2Na$ (M+Na): 282.0106; found: 282.0100.

4.3. (4*R*,4′*R*,5*S*,5′*S*)-2,2′-(Propane-2,2-diyl)bis(4-(4-bromophenyl)-5-(methoxymethyl)-4,5-dihydrooxazole) (3a)

To a stirred solution of amino alcohol **1** (8.0 mmol) and triethylamine (1.4 mL, 9.7 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added dimethylmalonyl dichloride (0.52 mL, 3.9 mmol). The solution was allowed to slowly warm up to room temperature, and stirred for 15 additional hours. After dilution with CH_2Cl_2, the mixture was washed with 10% aqueous HCl (10 mL), saturated $NaHCO_3$ (10 mL), water (10 mL) then brine. The bis(hydroxyamide) **2** was obtained after drying over magnesium sulfate and concentration of the solution, and used in the next step without purification. Crude **2** (4 mmol) was diluted in anhydrous CH_2Cl_2 (40 mL) and the solution was cooled to −78 °C. Diethylaminosulfur trifluoride (DAST) (1.24 mL, 10.1 mmol) was added. The mixture was allowed to warm up to room temperature, and then a saturated aqueous solution of $NaHCO_3$ was slowly added (10 mL). After addition of water (20 mL) and CH_2Cl_2 (40 mL), the phases were separated. The organic phase was washed with water (40 mL) and brine, dried over magnesium sulfate then concentrated. Purification by flash chromatography on silicagel (hexane/EtOAc 1/1) yielded the pure BOX **3a** in 87% yield: ^{1}H NMR (400 MHz): δ=1.69 (s, 6H), 3.44 (s, 6H), 3.57 (dd, 4.9 and 10.4 Hz, 2H), 3.63 (dd, 5.7 and 10.4 Hz, 2H), 4.47 (m, 2H), 4.92 (d, 6.5 Hz, 2H), 7.16 (d, 8.5 Hz, 4H), 7.46 (d, 8.5 Hz, 4H). ^{13}C NMR (100 MHz): δ=24.3 (CH_3), 39.1 (C), 59.5 (CH_3), 71.3 (CH), 73.4 (CH_2), 86.0 (CH), 121.5 (C), 128.3 (CH), 131.8 (CH), 141.1 (C), 170.0 (C). $[\alpha]_D^{20}$ 141.1 (*c* 0.55, $CHCl_3$). HRMS (ES^+): calcd for $C_{25}H_{29}Br_2N_2O_4$ (M+H): 579.0494; found: 579.0506.

4.4. General procedure for the Suzuki reaction on bis(oxazoline) 3a

A solution of the substrate (1 mmol), the arylboronic acid (2.2 mmol), cesium carbonate (4 mmol), *S*-Phos (0.08 mmol), and $Pd_2(dba)_3\cdot C_6H_6$ (1 mmol) in dry, degassed toluene (5 mL) was heated to 100 °C for 16 h. After cooling, the mixture was filtered over Celite and concentrated. Purification by flash chromatography yielded the corresponding BOX **3b**–**3i**.

Compound **3b**: yield 77%. ^{1}H NMR (400 MHz): δ=1.75 (s, 6H), 3.47 (s, 6H), 3.66 (m, 4H), 4.61 (m, 2H), 5.01 (d, 6.6 Hz, 2H), 7.37 (m, 6H), 7.44 (m, 4H), 7.58 (m, 8H). ^{13}C NMR (100 MHz): δ=24.4 (CH_3), 39.1 (C), 59.5 (CH_3), 71.6 (CH), 73.7 (CH_2), 86.2 (CH), 127.08 (CH), 127.14 (CH), 127.3 (CH), 127.5 (CH), 128.8 (CH), 140.6 (C), 140.9 (C), 141.1 (C), 169.8 (C). $[\alpha]_D^{20}$ 206 (*c* 0.33, $CHCl_3$). HRMS (ES^+): calcd for $C_{37}H_{39}N_2O_4$ (M+H): 575.2990; found: 575.2896.

Compound **3c**: yield 52%. ^{1}H NMR (400 MHz): δ=1.75 (s, 6H), 3.47 (s, 6H), 3.66 (m, 4H), 4.60 (m, 2H), 5.03 (d, 6.4 Hz, 2H), 7.41 (d, 8.0 Hz, 4H), 7.56 (d, 8.0 Hz, 4H), 7.67 (m, 8H). ^{13}C NMR (100 MHz): δ=24.3 (CH_3), 39.2 (C), 59.5 (CH_3), 71.6 (CH), 73.6 (CH_2), 86.1 (CH), 124.3 (q, 272 Hz, CF_3), 125.7 (q, 3.7 Hz, CH), 127.3 (CH), 127.4 (CH), 127.6 (CH), 129.4 (q, 33 Hz, C), 139.0 (C), 142.2 (C), 144.3 (C), 170.0 (C). ^{19}F NMR (471 MHz): δ=−62.6. $[\alpha]_D^{20}$ 166.4 (*c* 0.67, $CHCl_3$). HRMS (ES^+): calcd for $C_{39}H_{36}F_6N_2O_4Na$ (M+Na): 579.0494; found: 579.0506.

Compound **3d**: yield 76%. ^{1}H NMR (400 MHz): δ=1.75 (s, 6H), 3.48 (s, 6H), 3.67 (m, 4H), 4.57 (m, 2H), 5.06 (d, 6.4 Hz, 2H), 7.44 (d, 8.0 Hz, 4H), 7.59 (d, 8.0 Hz, 4H), 7.86 (br, 2H), 7.98 (br, 4H). ^{13}C NMR (100 MHz): δ=24.3 (CH_3), 39.2 (C), 59.5 (CH_3), 71.5 (CH), 73.5 (CH_2), 86.1 (CH), 120.9 (sept, 3.7 Hz, CH), 123.3 (q, 273 Hz, C), 127.1 (m, CH), 127.57 (CH), 127.59 (CH), 132.1 (q, 33 Hz, C), 137.5 (C), 142.9 (C), 143.0 (C), 170.1 (C). ^{19}F NMR (471 MHz): δ=−63.0. $[\alpha]_D^{20}$ 134.6 (*c* 0.72, $CHCl_3$). HRMS (ES^+): calcd for $C_{41}H_{34}F_{12}N_2O_4Na$ (M+Na): 869.2225; found: 869.2222.

Compound **3e**: yield 71%. ^{1}H NMR (400 MHz): δ=1.76 (s, 6H), 2.38 (s, 12H), 3.46 (s, 6H), 3.64 (dd, 4.7 and 10.7 Hz, 2H), 3.68 (dd, 6.0 and 10.7 Hz, 2H), 4.59 (m, 2H), 5.00 (d, 6.5 Hz, 2H), 7.00 (br, 2H), 7.19 (br, 4H), 7.35 (d, 8.2 Hz, 4H), 7.55 (d, 8.2 Hz, 4H). ^{13}C NMR (100 MHz): δ=21.4 (CH_3), 24.4 (CH_3), 39.1 (C), 59.5 (CH_3), 71.7 (CH), 73.7 (CH_2), 86.3 (CH), 125.0 (CH), 127.0 (CH), 127.5 (CH), 128.9 (CH), 138.3 (C), 140.8 (C), 140.9 (C), 141.0 (C), 169.8 (C). $[\alpha]_D^{20}$ 189.7 (*c* 0.68, $CHCl_3$). HRMS (ES^+): calcd for $C_{41}H_{47}N_2O_4$ (M+H): 631.3536; found: 631.3530.

Compound **3f**: yield 69%. ^{1}H NMR (400 MHz): δ=1.74 (s, 6H), 3.46 (s, 6H), 3.65 (m, 4H), 3.87 (s, 6H), 4.61 (m, 2H), 5.00 (d, 6.5 Hz, 2H), 6.97 (d, 8.7 Hz, 4H), 7.35 (d, 8.2 Hz, 4H), 7.50 (m, 8H). ^{13}C NMR (100 MHz): δ=24.4 (CH_3), 39.1 (C), 55.3 (CH_3), 59.5 (CH_3), 71.7 (CH), 73.7 (CH_2), 86.2 (CH), 114.2 (CH), 127.0 (CH), 127.1 (CH), 128.1 (CH), 133.4 (C), 140.1 (C), 140.5 (C), 159.1 (C), 169.8 (C). $[\alpha]_D^{20}$ 197.4 (*c* 0.65, $CHCl_3$). HRMS (ES^+): calcd for $C_{39}H_{42}N_2O_6Na$ (M+Na): 657.2941; found: 657.2919.

Compound **3g**: yield 61%. ^{1}H NMR (400 MHz): δ=1.76 (s, 6H), 2.27 (s, 6H), 3.48 (s, 6H), 3.66 (m, 4H), 4.63 (m, 2H), 5.01 (d, 6.6 Hz, 2H), 7.2–7.4 (m, 16H). ^{13}C NMR (100 MHz): δ=20.5 (CH_3), 24.4 (CH_3), 39.1 (C), 59.5 (CH_3), 71.7 (CH), 73.6 (CH_2), 86.3 (CH), 125.6 (CH), 126.4 (CH), 127.3 (CH), 129.5 (CH), 129.8 (CH), 130.3 (CH), 135.4 (C), 140.5 (C), 141.3 (C), 141.6 (C), 169.8 (C). $[\alpha]_D^{20}$ 147 (*c* 0.70, $CHCl_3$). HRMS (ES^+): calcd for $C_{41}H_{42}N_2O_4Na$ (M+Na): 625.3042; found: 625.3055.

Compound **3h**: yield 67%. ^{1}H NMR (400 MHz): δ=1.77 (s, 6H), 2.02 (s, 12H), 3.47 (s, 6H), 3.68 (m, 4H), 4.60 (m, 2H), 4.99 (d, 6.6 Hz, 2H), 7.1–7.2 (m, 10H), 7.3–7.4 (m, 4H). ^{13}C NMR (100 MHz): δ=20.9 (CH_3), 24.5 (CH_3), 39.1 (C), 59.5 (CH_3), 71.8 (CH), 73.7 (CH_2), 86.4 (CH), 126.7 (CH), 127.0 (CH), 127.3 (CH), 129.4 (CH), 136.1 (C), 140.3 (C), 140.4 (C), 141.5 (C), 169.9 (C). $[\alpha]_D^{20}$ 141.1 (*c* 0.88, $CHCl_3$). HRMS (ES^+): calcd for $C_{41}H_{47}N_2O_4$ (M+H): 631.3536; found: 631.3558.

Compound **3i**: yield 94%. ^{1}H NMR (400 MHz): δ=1.73 (s, 6H), 3.46 (s, 6H), 3.61–3.74 (m, 4H), 3.72 (s, 12H), 4.68 (m, 2H), 4.96 (d, 6.5 Hz, 2H), 6.65 (d, 8.2 Hz, 4H), 7.28 (d, 8.2 Hz, 2H), 7.31 (m, 8H). ^{13}C NMR (100 MHz): δ=24.4 (CH_3), 39.0 (C), 55.9 (CH_3), 59.4 (CH_3), 71.8 (CH), 73.9 (CH_2), 86.1 (CH), 104.2 (CH), 119.4 (C), 126.0 (CH), 128.6 (CH), 131.2 (CH), 133.4 (C), 140.2 (C), 157.7 (C), 169.6 (C). $[\alpha]_D^{20}$ 120.9 (*c* 0.70, $CHCl_3$). HRMS (ES^+): calcd for $C_{41}H_{46}N_2O_6Na$ (M+Na): 717.3152; found: 717.3159.

4.5. 4-Bromostyrene oxide (5)

To a solution of 4-bromobenzaldehyde **4** (7.4 g, 40 mmol), Me_3SI (8.1 g, 40 mmol), and tetrabutylammonium bromide (0.19 g, 0.6 mmol) in CH_2Cl_2 (40 mL), was added a 50% aqueous sodium hydroxide solution (40 mL). After 60 h heating at reflux, the mixture was cooled, poured onto ice, and extracted with CH_2Cl_2 (2×20 mL) The combined organic extracts were sequentially washed with water (40 mL), saturated aqueous sodium metabisulfite (30 mL), water (40 mL), and brine, then dried over magnesium sulfate, yielding 7.6 g (96%) of **5** as an oil that crystallized upon standing.

4.6. Hydrolytic kinetic resolution of 4-bromostyrene oxide (5)

To a solution of the (*R*,*R*)-Co(salen) catalyst (1.7 g, 2.8 mmol) in toluene (20 mL), acetic acid (4.6 mL, 80 mmol) was added. The mixture was stirred for 30 min under a gentle stream of air, then concentrated in vacuo. A solution of *rac*-4-bromostyrene oxide **5** (18.7 g, 94 mmol) in THF (10 mL) was then added; the mixture was cooled to 0 °C, and water (0.93 mL, 52 mmol) was added slowly. The reaction mixture was stirred for 2 days at room temperature and then passed through a pad of silica, eluting with an hexanes/AcOEt mixture (9/1). After concentration, the red residue was distilled under reduced pressure (90 °C, 1 mbar), to yield optically pure (*R*)-4-bromostyrene oxide as a white solid (6.5 g, 35%). The enantiomeric excess was determined by HPLC: Chiralcel AD-H

column, hexane, 0.7 mL/min, detection at 230 nm, t_R (major)=23.4 min (*R*), t_R (minor)=27.5 min (*S*).

4.7. (*S*)-2-Azido-2-(4-bromophenyl) ethan-1-ol (6)

A mixture of ammonium chloride (6.8 g, 64 mmol), sodium azide (20.9 g, 321 mmol), (*R*)-4-bromostyrene oxide **5** (6.4 g, 32 mmol) in ethanol (80 mL) was heated at reflux for 12 h. After cooling, it was partitioned between ether (100 mL) and water (100 mL). The aqueous phase was extracted with ether (2×30 mL); the combined organic phases were washed with water (2×30 mL), brine, and dried over magnesium sulfate. Separation of both regioisomers was achieved by flash chromatography on silicagel (hexanes/ethyl acetate 9:1) The ee of crude **6** was 92–95%. Recrystallization from hot toluene (30 mL) afforded white needles (2.5 g, 32% yield, 99% ee): mp 110–111 °C. $[\alpha]_D^{20}$ 188.8 (*c* 3.6, $CHCl_3$). ^1H NMR (400 MHz): δ=2.00 (t, 6.4 Hz, 1H), 3.75 (m, 2H), 4.66 (dd, 5.0 and 7.6 Hz, 1H), 7.24 (d, 8.5 Hz, 2H), 7.55 (d, 8.5 Hz, 2H). ^{13}C NMR (100 MHz): δ=66.4, 67.2, 122.8, 128.8, 132.1, 135.4. HRMS (ES^+): calcd for $C_8H_7BrON_3$ (M+H): 239.9772; found: 239.9771. The enantiomeric excess was determined by HPLC: Chiralcel AD-H column, hexane/IPA 95/5, 1 mL/min, detection at 230 nm, t_R (minor)=12.7 min (*R*), t_R (major)=15.4 min (*S*).

4.8. (S)-2-Amino-2-(4-bromophenyl)ethan-1-ol (7)

A mixture of (*S*)-2-azido-2-(4-bromophenyl)ethan-1-ol **6** (2.50 g, 10.3 mmol), triphenylphosphine (4.06 g, 15.5 mmol), and water (1.2 mL, 62 mmol) in THF (20 mL) was stirred at room temperature for 15 h. After addition of ether (20 mL) and 10% hydrochloric acid (20 mL), the phases were separated. The aqueous phase was washed with ether (2×20 mL), then basified by addition of a 10% NaOH solution (40 mL). The mixture was then extracted with CH_2Cl_2 (3×30 mL) and the combined organic phases were washed with brine, dried over sodium sulfate, and concentrated, yielding the amino alcohol **7** as a white hygroscopic solid (2.21 g, 99%): $[\alpha]_D^{20}$ 16.7 (*c* 2.0, MeOH). ^1H NMR (400 MHz, CD_3OD): δ=3.61 (dd, 8.2 and 10.8 Hz, 1H). 3.72 (dd, 4.2 and 10.8 Hz, 1H), 4.00 (dd, 4.2 and 8.2 Hz, 1H), 7.37 (d, 8.2 Hz, 2H), 7.56 (d, 8.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=56.8, 67.9, 121.3, 128.3, 131.7, 141.8. HRMS (ES^+): calcd for $C_8H_{11}BrON$ (M+H): 216.0024; found: 216.0034.

4.9. (4*S*,4′*S*)-2,2′-(Propane-2,2-diyl)bis[4-(4-bromophenyl)-4,5-dihydrooxazole] (8)

Prepared according to the general procedure described in Section 4.3. Oil, 70% yield: $[\alpha]_D^{20}$ −141.2 (*c* 0.7, $CHCl_3$). ^1H NMR (400 MHz): δ=1.68 (s, 6H), 4.13 (dd, 7.6 and 8.4 Hz, 2H), 4.68 (dd, 8.4 and 10.1 Hz, 2H), 5.22 (dd, 7.6 and 10.1 Hz, 2H), 7.16 (d, 8.4 Hz, 4H), 7.47 (d, 8.4 Hz, 4H). ^{13}C NMR (100 MHz): δ=24.4, 39.0, 68.9, 75.3, 121.5, 128.4, 131.8, 141.4, 170.6. HRMS (ES^+): calcd for $C_{21}H_{20}Br_2N_2NaO_2$ (M+Na): 512.9789; found: 512.9807.

4.10. (4*S*,4′*S*)-2,2′-(Propane-2,2-diyl)bis(4-(biphenyl-4-yl)-4,5-dihydrooxazole) (9)

Prepared according to the general procedure described in Section 4.4 for the double Suzuki reaction on bis(oxazolines), was obtained as a yellowish solid that was recrystallized from hot toluene (5 mL), giving white crystals (65%). $[\alpha]_D^{20}$ −234.8 (*c* 1.4, $CHCl_3$). ^1H NMR (400 MHz): δ=1.75 (s, 6H), 4.27 (dd, 7.6 and 8.3 Hz, 2H), 4.75 (dd, 8.3 and 10.1 Hz, 2H), 5.32 (dd, 7.6 and 10.1 Hz, 2H), 7.30–7.47 (m, 10H), 7.55–7.62 (m, 8H). ^{13}C NMR (100 MHz): δ=24.5, 39.0, 69.3, 75.5, 127.1, 127.2, 127.3, 127.5, 128.8, 140.6, 140.8, 141.5, 170.5. HRMS (ES^+): calcd for $C_{33}H_{30}N_2NaO_2$ (M+Na): 509.2205; found: 509.2213.

4.11. (4*R*,4′*R*,5*S*,5′*S*)-2,2′-(Propane-2,2-diyl)bis(4-(3,5-diphenylphenyl)-5-(benzyloxymethyl)-4,5-dihydrooxazole) (12)

To a stirred solution of (1*R*,2*S*)-1-amino-3-(benzyloxy)-1-(3,5-dimethylphenyl)propan-2-ol[12] (0.38 g, 1.1 mmol) and triethylamine (0.18 mL, 1.2 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added dimethylmalonyl dichloride (0.075 mL, 0.56 mmol) in CH_2Cl_2 (2 mL). The solution was allowed to slowly warm up to room temperature, and stirred for 15 additional hours. After dilution with CH_2Cl_2, the mixture was washed with 10% aqueous HCl (10 mL), saturated $NaHCO_3$ (10 mL), water (10 mL), then brine. Drying the solution over magnesium sulfate and evaporation under vacuum afforded the crude bis(hydroxyamide) as an oil. To a stirred solution of the crude bis(hydroxyamide) (1.1 mmol) and triethylamine (0.35 mL, 2.5 mmol) in CH_2Cl_2 (5 mL) at 0 °C, methanesulfonyle chloride (0.10 mL, 1.2 mmol) was added dropwise. The solution was stirred for 2 h at room temperature, diluted with CH_2Cl_2 (10 mL), and sequentially washed with aqueous NH_4Cl (10 mL), water (10 mL), and brine. After concentration, the crude mesylate was treated with a 5% solution of KOH in methanol (6 mL), and the solution was stirred at room temperature for 2 days. CH_2Cl_2 (10 mL) and water (5 mL) were added, and the phases were separated. After extracting the aqueous phase with CH_2Cl_2 (2×10 mL), the combined organic extracts were washed with water (20 mL), brine, and dried over magnesium sulfate. After concentration, the bis(oxazoline) **12** was purified by flash chromatography on silicagel (hexane/AcOEt 100% to 7/3). Yield 53%. ^1H NMR (400 MHz): δ=1.75 (s, 6H), 3.74 (m, 4H), 4.63 (m, 6H), 5.07 (d, 6.4 Hz, 2H), 7.25–7.40 (m, 16H), 7.40–7.46 (m, 4H), 7.50–7.60 (m, 8H). ^{13}C NMR (100 MHz): δ=24.4 (CH_3), 39.1 (C), 71.0 (CH_2), 71.7 (CH), 73.4 (CH_2), 86.3 (CH), 127.1 (CH), 127.16 (CH), 127.25 (CH), 127.5 (CH), 127.6 (CH), 127.8 (CH), 128.5 (CH), 128.8 (CH), 137.9 (C), 140.5 (C), 140.9 (C), 141.2 (C), 169.8 (C). $[\alpha]_D^{20}$ 200 (*c* 0.87, $CHCl_3$). HRMS (ES^+): calcd for $C_{45}H_{46}N_2O_4Na$ (M+Na): 749.3355; found: 749.3372.

4.12. General procedure for the copper-catalyzed acylation with desymmetrization of *trans*-1,2-cyclohexanediol

To a solution of *trans*-1,2-cyclohexanediol (116 mg, 1 mmol), diisopropylethylamine (129 mg, 1 mmol) and BOX·$CuCl_2$ (0.05 mmol) in CH_2Cl_2 at 0 °C was added benzoyl chloride (70 mg, 0.5 mmol). After 3 h, the solution was poured in water, and the mixture was extracted with three portions of CH_2Cl_2. The combined organic extracts were dried on $MgSO_4$, then concentrated. The products were separated by flash chromatography on silicagel (hexane/ethyl acetate 3/1). The enantiomeric excess of the product was determined by HPLC: Chiralcel OJ column, hexane/isopropanol 97/3, 1 mL/min, detection at 230 nm, t_R=13.3 min (*S*,*S*), t_R=15.9 min (*R*,*R*).

4.13. General procedure for the zinc-catalyzed, asymmetric Friedel–Crafts alkylation of indole

To a dried Schlenk tube under Ar, $Zn(OTf)_2$ (18 mg, 0.05 mmol), BOX (0.06 mmol), and toluene (5 mL) were added. The solution was stirred at room temperature for 2 h, and *trans*-β-nitrostyrene (149 mg, 1 mmol) was added. The mixture was cooled to 0 °C, and stirred for 10 min before indole (59 mg, 0.5 mmol) was added. After the reaction was complete, the solvent was removed under vacuum and the residue was chromatographed on silicagel (hexane/ethyl acetate 3/1) to afford the pure product. The enantiomeric excess was determined by chiral HPLC: Chiralcel OD-H column, hexane/isopropanol 70/30, 0.7 mL/min, detection at 254 nm, t_R=33.0 min (*S*), t_R=39.4 min (*R*).

4.14. General procedure for the palladium-catalyzed, asymmetric allylic alkylation of 3-acetoxy-1,3-diphenylpropene

To a dried Schlenk tube, allylpalladium chloride dimer (4.8 mg, 0.013 mmol) and the corresponding BOX ligand (0.04 mmol) were added. The mixture was dried under vacuum, then dry CH_2Cl_2 (1 mL) was added. After stirring for 1 h, 3-acetoxy-1,3-diphenylpropene (100 mg, 0.4 mmol), BSA (366 mg; 1.8 mmol), and KOAc (2 mg, 0.02 mmol) were added and the mixture was stirred overnight. Diethyl ether was added, and the mixture was washed with saturated NH_4Cl, water, and brine. The organic fraction was dried over $MgSO_4$ and concentrated. The resulting mixture was separated by flash chromatography on silicagel (hexane/ethyl acetate 20/1). The enantiomeric excess was determined by chiral HPLC: Chiralcel AD-H column, hexane/isopropanol 95/5, 1 mL/min, detection at 254 nm, t_R=16.8 min (*R*), t_R=24.4 min (*S*).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.07.053.

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21. Crystals of **9**·$CuCl_2$ could be obtained by slow evaporation of a solution of the compound in dichloromethane. Crystal data for **9**·$CuCl_2$ at 100 K: ($C_{33}H_{30}C_{12}Cu_1N_2O_2$), 621.03 g mol^{-1}, monoclinic, $P2_1$, a=6.0864(2) Å, b=13.7198(4) Å, c=17.6188(10) Å, β=98.887(1)°, V=1453.58(7) Å^3, Z=2, ρ_{calcd}=1.419 Mg/m^3, R_1=0.0322 (0.0344), $wR2$=0.0836 (0.0824), Flack×parameter=0.0130(5), for 10,532 reflections with $I>2\sigma(I)$ (for 11,186 reflections [R_{int}: 0.0222] with a total measured of 27,208 reflections), goodness-of-fit on F^2=1.049, largest diff. peak (hole)=1.32 (−1.49) e Å^{-3}. CCDC 696288 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk).
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