Pergamon

Tetrahedron 56 (2000) 5775–5780

TETRAHEDRON

Asymmetric Allylic Oxidation with Biarylbisoxazoline-Copper(I) Catalysis

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Received 26 April 2000; accepted 19 May 2000

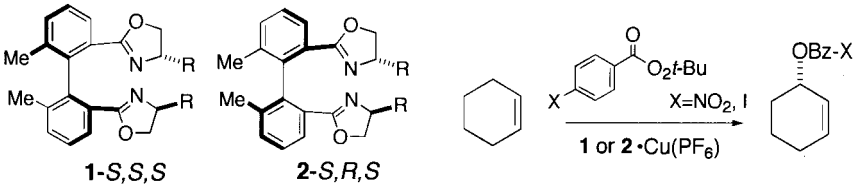
Abstract—Eight new bi-*o*-tolyl bisoxazolines were made and used as ligands in the copper catalyzed asymmetric allylic oxidation reaction. Three benzoyl *tert*-butyl peresters, *p*-nitro, *o*-iodo, and 2,4,6-trichloro were made and used with cyclohexene and cyclopentene with the ligands complexed to copper(I) hexafluorophosphate (10 mol%). High selectivities (73% ee, 78% yield) were obtained with the nitroperester and **1a** (*S*,*S*,*S* R=Ph) and cyclohexene. For the cyclopentene, **1c** (R=Bn) was best at 72% ee, 63% yield.

Introduction

C_2-Symmetric bisoxazolines have become the ligands of choice in numerous catalytic asymmetric processes, including cyclopropanation,[1] aziridination,[2] allylic displacement,[3] imine additions,[4] Diels–Alder,[5] aldol,[6] 1,3-dipolar cycloaddition,[7] reduction,[8] and the ene reaction.[9] We and Pfaltz independently reported[10] that malonyl derived bisoxazoline copper complexes give high selectivities in the Kharasch allylic oxidation reaction.[11] As the utility of this class of ligands expands, efforts to improve reactivity and selectivity will depend on the availability of routes to modified bisoxazolines. While the vast majority of bisoxazoline ligands are methylene and pyridyl linked, Corey recently reported a biaryl bis-*o*-tolyl ligand for a highly selective intramolecular cyclopropanation.[12] We recently reported two asymmetric Ullman coupling routes to the binaphthyl and bitolyl ligands variants as more convenient alternatives not relying on chiral preparative HPLC.[13] We now report efficient routes to the bi-*o*-tolylbisoxazolines **1**, **2** (Scheme 1) that rely on the separation of diastereomeric intermediates, and their use as copper(I) complexes for the catalytic asymmetric allylic olefin oxidation with substituted peresters.

Methylene-linked *S*,*S*-*tert*-butyl bisoxazoline-copper(I) triflate complex produces *S*-allylbenzoate from cyclohexene in 43% yield and 80% ee.[9] While high selectivities were successfully obtained for the first time, the yields and the rate of the reaction were low.[14] Yields and rates of the reaction were recently improved through the use of substituted electron deficient peresters (Scheme 2) and phenylgylcine-derived methylene-linked bisoxazolines.[15] Since the initial investigation, others have reported similar results with bisoxazoline complexes and *tert*-butyl perbenzoate giving low rates and yields.[16] We now report on a systematic investigation of cycloalkene oxidation using the *S*,*S*,*S*-biaryl bisoxazoline ligands.

A wider bite angle between the two nitrogens and the copper in **1** and **2** was anticipated to lead to improved selectivity. A widening would force the reacting allyl and benzoate groups closer together accentuating non-bonded interactions



Scheme 1.

Keywords: allylic oxidation; asymmetric synthesis; cycloalkene; oxidation.

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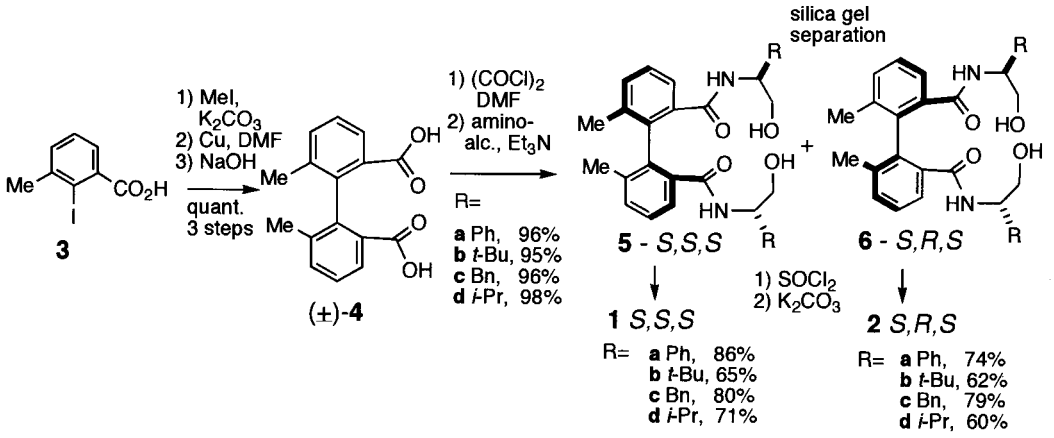


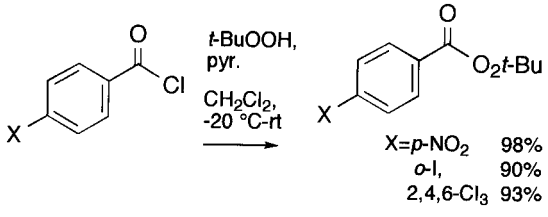
Scheme 2.

resulting in a larger energy difference between the diastereomeric transition states. Related binaphthyl and biphenyl bisoxazoline ligands have been reported by Hayashi[17] and Ikeda for use in other reactions.[18]

Results

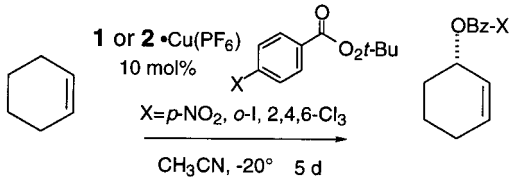
Original routes to the ligands,[12] based on asymmetric Ullmann couplings,[19] were limited by low yields and by a dependence on the use of the *tert*-butyl oxazoline for high selectivities. Subsequently, it was found that the diastereomeric amides, the percursors to the bisoxazoline, or the ligands themselves could easily be separated by chromatography. Racemic Ullmann coupling of the methyl ester of **3**, followed by hydrolysis gave bi-*o*-tolyl diacid **4** in quantitative yield (Scheme 3). Oxalyl chloride produced the diacid chloride that was then treated with four individual *S*-amino alcohols to provide the *S*,*S*,*S* and *S*,*R*,*S* diamides **5a**–**d** and **6a**–**d**. As Hayashi found with a binaphthyl intermediate, the separations of **5** and **6** were readily achieved using flash or radial chromatography. The R_f differences were typically greater than 0.1 in all cases examined. Yields for the two step sequence were very high with the *S*,*S*,*S* diastereomer produced in slight excess (55:45). The identities of the isomers were established by comparisons to NMR and optical rotation values of known intermediates produced previously.[12] The separated diastereomers **5** and **6** were treated with thionyl chloride to provide the dichlorides which were reacted with potassium carbonate to give the bisoxazoline ligands **1a**–**d** and **2a**–**d** in good overall yields. With a wide range of biaryl ligands in hand, the reactivity of three readily prepared peresters was examined.[20]

The allylic oxidation reactions were performed with cyclohexene and cyclopentene. A slight excess of ligand **1** or **2** (12 mol%) was complexed with copper hexafluorophosphate-tetracetonitrile[21] (10 mol%) in degassed acetonitrile for 2 h.[14] Cyclohexene (10 equiv.) and perester (1 equiv.) were added to the solution and the sealed flask was stirred at −20°C for 5 days (Table 1). After work-up and radial chromatography the enantiomeric excess of the isolated ester product was determined by HPLC. The ligands were typically recovered in 80% yield. The *S*,*S*,*S*-phenyl bisoxazoline ligand **1a** gave the highest yield and selectivity, 78 and 73% ee (entry 1) where yields are based on the perester oxidant. In all cases the *S*,*R*,*S* ligands **2** gave very low selectivities, however, as in the case of **2b** the reactivity was high at 76%. With the iodoperester the



Scheme 3.

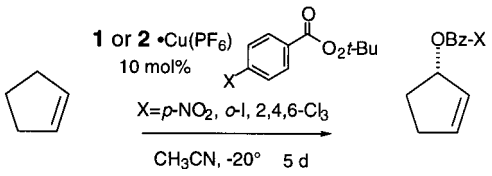
Table 1. Allylic oxidation of cyclohexene with biarylbisoxazoline-copper(I) catalysts



Entry	Catalyst, R[a]	Perester, X	Yield (%)[b]	ee[c]
1	Ph, *S*,*S*,*S*	*p*-NO_2	78	73
2	Ph, *S*,*R*,*S*	*p*-NO_2	76	0
3	Ph, *S*,*S*,*S*	*o*-I	63	71
4	Ph, *S*,*S*,*S*	2,4,6-Cl_3	20	11[d]
5	*t*-Bu, *S*,*S*,*S*	*p*-NO_2	5	18
6	*t*-Bu, *S*,*R*,*S*	*p*-NO_2	0	0
7	Bn, *S*,*S*,*S*	*p*-NO_2	48	52
8	Bn, *S*,*R*,*S*	*p*-NO_2	67	11
9	Bn, *S*,*S*,*S*	*o*-I	68	70
10	Bn, *S*,*R*,*S*	*o*-I	25	13
11	Bn, *S*,*S*,*S*	2,4,6-Cl_3	21	15[d]
12	*i*-Pr, *S*,*S*,*S*	*p*-NO_2	25	66
13	*i*-Pr, *S*,*R*,*S*	*p*-NO_2	29	16
14	*i*-Pr, *S*,*S*,*S*	*o*-I	20	62

[a] Catalysts formed using Cu(I) complexed with indicated bisoxazoline.
[b] Isolated yield based on perester.
[c] Enantiomeric excess determined by chiral HPLC (Chiracel, 0.5% isopropyl alcohol/heptane, 1 mL/min). X=*p*-NO_2, rt 14.3 min *R* isomer, 14.9 min *S*, AD column. X=*o*-I, rt 9.9 min *R*, 10.4 min *S*. X=2,4,6-3Cl, OD.
[d] Column, rt 4.3 min *R*, 6.5 min *S*.

Table 2. Allylic oxidation of cyclopentene



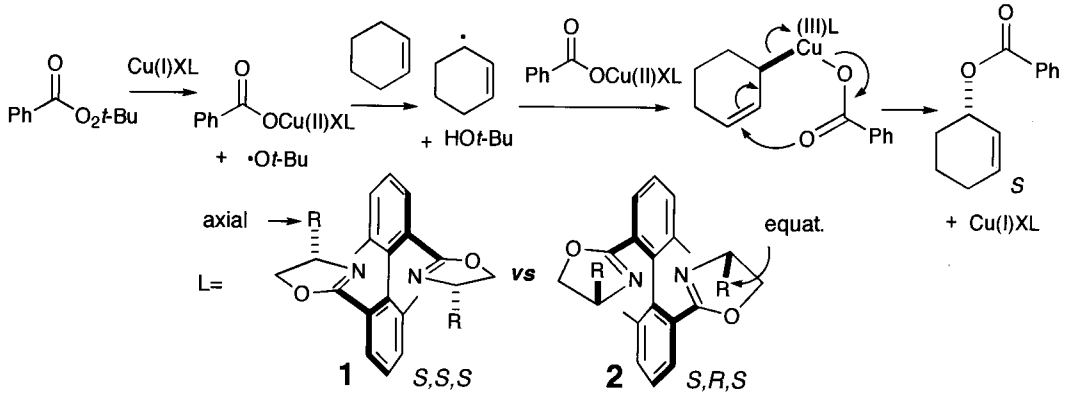
Entry	Catalyst, R[a]	Perester, X	Yield (%)[b]	ee[c]
1	Ph, *S*,*S*,*S*	*p*-NO_2	59	69
2	Ph, *S*,*R*,*S*	*p*-NO_2	51	10
3	Ph, *S*,*S*,*S*	*o*-I	55	65
4	*t*-Bu, *S*,*S*,*S*	*p*-NO_2	2	0
5	*t*-Bu, *S*,*R*,*S*	*p*-NO_2	0	0
6	Bn, *S*,*S*,*S*	*p*-NO_2	63	72
7	Bn, *S*,*R*,*S*	*p*-NO_2	70	22
8	Bn, *S*,*S*,*S*	*o*-I	61	18[d]
9	Bn, *S*,*R*,*S*	*o*-I	61	36[d]
10	*i*-Pr, *S*,*S*,*S*	*p*-NO_2	22	45
11	*i*-Pr, *S*,*S*,*S*	*o*-I	18	54[d]

[a] Catalysts formed using Cu(I) with indicated bisoxazoline.
[b] Isolated yield based on perester.
[c] Enantiomeric excess determined by chiral HPLC (Chiracel, 0.5% isopropyl alcohol/heptane, 1 mL/min). X=*p*-NO_2, rt 11.0 min *R* isomer, 11.5 min *S*, AD column. X=*o*-I, rt 8.6 min *R*, 9.5 min *S*, OD.
[d] Column.

yield was lower but the ee was comparable at 71%. The trichloroperester, bearing two *ortho* substituents, showed poor reactivity and selectivity (entry 4). In contrast to the *tert*-butyl malonyl derived bisoxazoline reported previously,[9] the *tert*-butyl biaryl ligands **1b** and **2b** give either very low or no yield together with very low selectivity (entry 5, 6). This result was also seen using a *tert*-butyl binaphthyl ligand.[22] The benzyl ligands **1c** and **2c** showed similar trends although at lower selectivities. The exception being the iodoperester with ligand **1c** at 70% ee (entry 9), the highest for the series. The isopropyl ligands **1d** and **2d** gave even lower yields with moderate selectivities. Similar trends were found with cyclopentene (Table 2). Good reactivity and selectivity were found using *S*,*S*,*S*-**1a** and **1c**. The diastereomeric *S*,*R*,*S* ligands **2** were again much lower in selectivity. As before, the *tert*-butyl ligands gave very low reactivity and 0% ee. Interestingly, the iodoperester with **1c**, the best conditions for cyclohexene at 70% ee, now with cyclopentene gave only 18% ee. While the trends with *p*-nitroperester are very close between the two olefins, the *o*-iodo perester is sensitive to very small structural changes giving highly variable selectivities.

Discussion

The mechanism of allylic oxidation can be used to provide insight into the factors controlling the selectivity. The initial step is homolysis of the perester oxygen–oxygen bond by copper(I) to give copper(II) benzoate and *t*-butoxy radical (Scheme 4).[23] *t*-Butoxy radical abstracts an allylic hydrogen atom to give *t*-butanol and an allylic radical.[24] Copper(II) then rapidly adds to the allyl radical to generate copper(III) benzoate with an η^1-allyl group.[25] With acyclic internal alkenes, the geometry of the olefin is maintained due to a high barrier to rotation of the allyl radical (~20 kcal/mol).[26] The final step, a postulated rearrangement of the 16e copper(III) intermediate gives both product and regenerates of the copper(I) catalyst. A *d*-8 twisted square planar Cu(III) intermediate leads back to the coordinatively unsaturated Cu(I) intermediate upon product formation. The model assumes a one to one copper–ligand chelate arrangement in accord with established X-ray structures for Diels–Alder, aldol, ene, and Michael intermediates reported by Evans.[4,5,8] Asymmetric induction can be attributed to the steric influence of the flanking R groups that occupy two of the four spatial quadrants available for complexation.[20] The biarylbisoxazoline-copper complexes adopt well defined arrangements with the R groups pseudo axial in the *S*,*S*,*S* isomer and equatorial in the *S*,*R*,*S*. Placement of the allyl and benzoate ligands in the sterically unencumbered positions, in the upper right and the lower left on **1** (Scheme 4), would lead to the observed major *S*-enantiomer.[9] Placement of these groups in the eclipsed positions lead to the minor *R*-ester. Low selectivity of the *S*,*R*,*S* ligands **2** can be attributed to the effective symmetry of the quadrants. When R is *tert*-butyl in *S*,*S*,*S*-**1b**, greater steric congestion due to the wide bite-angle now appears to slow the rate of allylic oxidation. Less hindered Ph and Bn R-groups in **1a** and **1c** show greater reactivity and selectivity. This is in contrast to the malonyl derived ligands, used initially as highly selective catalysts.[9] Ligands **1** and **2**, with a wide range of R groups and *S*/*R* atropisomerism, reacted with various peresters, demonstrate selectivity and reactivity



Scheme 4.

trends that are useful from a design point of view. While the selectivity remains to be improved, important factors determining selectivity and reactivity could be identified that will aid in the design of more efficient catalytic systems for this useful reation.

Experimental

General procedures

THF and ethyl ether were distilled prior to use from sodium benzophenone ketyl. Methylene chloride and amine reagents were distilled from calcium hydride. Column chromatography was performed on silica gel 60 (230–400 mesh) eluting with distilled hexanes and EtOAc. TLC was performed using silica gel 60 F_{254} plates with visualization by UV and standard staining. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR were recorded on an XLR-300 instrument. Optical rotations were measured at 589 nm. Melting points are uncorrected. Mass spectral analyses were performed in the chemistry department at Brigham Young University.

Methyl 2-iodo-3-methylbenzoate. Methyl iodide (49.0 g, 343 mmol) was added to a mixture of 2-iodo-3-methylbenzoic acid 3 (3.0 g, 11.5 mmol) and K_2CO_3 (3.1 g, 23 mmol) in acetone (120 mL). The reaction mixture was stirred at rt for 4 h. The reaction stopped after 4 h, and the solvent was evaporated. Diethyl ether (100 mL) was added to the solid residue, and the organic layer was washed with aqueous K_2CO_3, dried over $MgSO_4$. Evaporation of organic layer under reduced pressure afforded the known light yellow oil product, 3.12 g (100%).[27]

Dimethyl 6,6′-dimethylbiphenyl-2,2′-dicarboxylate. Methyl 2-iodo-3-methylbenzoate (3.1 g, 11.2 mmol) was dissolved in 10 mL of *N*,*N*-dimethylformamide, and activated copper powder (1.65 g) was added to the reaction mixture. The reaction was then gently refluxed for 4 h. The reaction mixture was allowed to cool to rt, and was passed through a silica plug using 20% EtOAc/hexane (200 mL). The filtrate was washed with 14% NH_4OH (50 mL), brine (50 mL), and dried over $MgSO_4$. Evaporation of the solvent afforded a light yellow solid product, 1.68 g (100%). The yellow solid product was then recrystallized from pentane. mp 56–56.5°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87–7.84 (dm, 2H), 7.45–7.42 (dm, 2H), 7.33 (t, 2H, J=12.5 Hz), 3.58 (s, 6H), 1.91 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 167.7, 141.4, 136.7, 133.7, 129.5, 127.9, 127.1, 51.9, 20.2.

6,6′-Dimethylbiphenyl-2,2′-dicarboxylic acid (4). The diester above (1.68 g, 5.63 mmol) was refluxed in a solution of 2.3 g of NaOH in 12 mL of water for 6 h. The mixture was cooled to rt, washed with cold hexane, and then acidified by the addition of 4 M HCl with cooling until pH 3 was achieved. The mixture was extracted with EtOAc (3×80 mL), and the organic layers were collected and washed with cold water (20 mL), and dried over $MgSO_4$. Evaporation of the solvent afforded light yellow solid product 4, 1.50 g (100%). Known compound: mp 233–234°C (lit, 236–237.5°C).[13]

General procedure for synthesis of compounds 5a–d and 6a–d

Diacid **4** (0.8 g, 3.0 mmol) was placed in a flame-dried round bottom flask (100 mL). Methylene chloride (25 mL) was added to the reaction flask. Oxalyl chloride (2.5 mL, 24 mmol) was added followed by three drops of DMF. The reaction mixture was stirred for 8 h at rt under N_2. The solvent was removed under reduced pressure, and a yellow solid diacid chloride was isolated (0.9 g, 99%). Then, a solution of this intermediate (0.9 g, 2.9 mmol) in methylene chloride (15 mL) was cooled to −40°C. In a separate flask, a mixture of (*S*)-phenyl glycinol (0.9 g, 6.5 mmol), triethylamine (1.0 mL), in methylene chloride (15 mL) was cooled to −40°C. The diacid chloride solution was then added dropwise by cannula into the flask containing the (*S*)-phenyl glycinol and triethylamine, and the solution was allowed to warm slowly to rt with stirring overnight under N_2. TLC analysis of the reaction (100% EtOAc) confirmed the formation of two new compounds **5a** and **6a**. The solvent was removed and the solid obtained was dissolved in EtOAc and passed through a silica plug using EtOAc (200 mL). The solvent was evaporated and the two diastereomers **5a** and **6a** were separated by radial chromatography (4 mm rotor, 75–100% EtOAc/hexane) as white solid products **5a** (0.75 g) and **6a** (0.65 g) in 94% total yield. Compounds **5b–d** and **6b–d** were synthesized in the similar fashion. The total yield for compounds **5b/6b**, **5c/6c**, and **5d/6d** were 96, 98, and 95, respectively.

(*S*,*S*,*S*)-6,6′-Dimethyl-biphenyl-2,2′-dicarboxylic acid bis-[(2-hydroxy-1-phenyl-ethyl)-amide] (5a). R_f=0.52 in 100% EtOAc; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64–7.37 (d, 2H, J=8.5 Hz), 7.36–7.07 (m, 16H), 5.00–4.96 (m, 2H), 3.58–3.50 (m, 4H), 2.45 (s, 2H), 1.97 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 138.5, 137.0, 136.7, 136.2, 131.9, 128.6, 128.0, 127.6, 126.7, 124.7, 65.8, 55.5, 20.0; HRMS (FAB^+) calcd for (MH^+) $C_{32}H_{33}N_2O_4$ 509.2440, found 509.2435.

(*S*,*R*,*S*)-6,6′-Dimethyl-biphenyl-2,2′-dicarboxylic acid bis-[(2-hydroxy-1-phenyl-ethyl)-amide] (6a). R_f=0.42 in 100% EtOAc; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, 2H, J=7.0 Hz), 7.33–7.18 (m, 12H), 6.91 (d, 4H, J=7.5 Hz), 4.87–4.83 (m, 2H), 3.66–3.62 (m, 4H), 2.63 (s, 2H), 1.88 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 138.5, 136.5, 136.4, 136.2, 132.2, 128.5, 127.9, 127.5, 126.7, 125.3, 66.3, 56.3, 20.0; HRMS (FAB^+) calcd for (MH^+) $C_{32}H_{33}N_2O_4$ 509.2440, found 509.2442.

(*S*,*S*,*S*)-6,6′-Dimethyl-biphenyl-2,2′-dicarboxylic acid bis-[(2-hydroxy-1-*t*-butyl-ethyl)-amide] (5b). R_f=0.47 in 100% EtOAc; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, 2H,J=10.0 Hz), 7.32–7.25 (m, 6H), 3.81–3.76 (m, 2H), 3.67–3.64 (m, 2H), 3.25–3.21 (m, 2H), 2.15 (s, 2H), 2.05 (s, 6H), 0.86 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 137.5, 137.2, 136.4, 131.3, 127.7, 124.1, 62.2, 59.1, 33.5, 26.7, 20.1; HRMS (FAB^+) calcd for (MH^+) $C_{28}H_{41}N_2O_4$ 469.3066, found 469.3057.

(*S*,*R*,*S*)-6,6′-Dimethyl-biphenyl-2,2′-dicarboxylic acid bis-[(2-hydroxy-1-*t*-butyl-ethyl)-amide] (6b). R_f=0.30 in 100% EtOAc; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (dd,

2H, J=8.0, 7.5 Hz), 7.35–7.30 (m, 4H), 7.11 (d, 2H, J=9.5 Hz), 3.80–3.76 (m, 2H), 3.70–3.67 (m, 2H), 3.42–3.38 (m, 2H), 2.30 (s, 2H), 1.93 (s, 6H), 0.72 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 136.8, 136.5, 136.3, 132.3, 128.1, 125.8, 62.8, 59.9, 33.5, 26.7, 20.1; HRMS (FAB$^+$) calcd for (MH^+) $C_{28}H_{41}N_2O_4$ 469.3066, found 469.3056.

(*S*,*S*,*S*)-6,6′-Dimethyl-biphenyl-2,2′-dicarboxylic acid bis-[(2-hydroxy-1-benzyl-ethyl)-amide] (5c). R_f=0.47 in 100% EtOAc; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, 2H, J=8.5 Hz), 7.21–7.08 (m, 16H), 4.04–4.00 (m, 2H), 3.32–3.20 (m, 4H), 2.67 (dd, 2H, J=14.0, 6.5 Hz), 2.59 (dd, 2H, J=13.5, 6.5 Hz), 2.24 (s, 2H), 1.81 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 137.7, 137.0, 136.9, 136.1, 131.7, 129.1, 128.5, 127.9, 126.5, 124.2, 63.5, 52.9, 36.5, 19.9; HRMS (FAB$^+$) calcd for (MH^+) $C_{34}H_{37}N_2O_4$ 537.2753, found 537.2750.

(*S*,*R*,*S*)-6,6′-Dimethyl-biphenyl-2,2′-dicarboxylic acid bis-[(2-hydroxy-1-benzyl-ethyl)-amide] (6c). R_f=0.35 in 100% EtOAc; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27–7.11 (m, 12H), 7.04 (d, 6H, J=8.0 Hz), 3.99–3.94 (m, 2H), 3.43–3.27 (m, 4H), 2.44 (dd, 2H, J=14.0, 8.5 Hz), 2.40 (dd, 2H, J=14.0, 8.5 Hz), 2.38 (s, 2H), 1.84 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 137.7, 136.6, 136.5, 136.1, 132.1, 129.1, 128.5, 128.1, 126.6, 125.2, 63.6, 53.0, 36.4, 20.0; HRMS (FAB$^+$) calcd for (MH^+) $C_{34}H_{37}N_2O_4$ 537.2753, found 537.2739.

(*S*,*S*,*S*)-6,6′-Dimethyl-biphenyl-2,2′-dicarboxylic acid bis-[(2-hydroxy-1-*i*-propyl-ethyl)-amide] (5d). R_f=0.33 in 100% EtOAc; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.26 (m, 8H), 3.72–3.67 (m, 2H), 3.48–3.44 (m, 2H), 3.37–3.33 (m, 2H), 2.01 (s, 6H), 1.78–1.72 (m, 2H), 1.63 (s, 2H), 0.86 (d, 6H, J=7.0 Hz), 0.83 (d, 6H, J=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 137.1, 136.3, 136.2, 131.6, 127.9, 124.3, 63.7, 56.9, 29.0, 20.1, 19.4, 18.7; HRMS (FAB$^+$) calcd for (MH^+) $C_{26}H_{37}N_2O_4$ 441.2753, found 441.2761.

(*S*,*R*,*S*)-6,6′-Dimethyl-biphenyl-2,2′-dicarboxylic acid bis-[(2-hydroxy-1-*i*-propyl-ethyl)-amide] (6d). R_f=0.22 in 100% EtOAc; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, 2H, J=7.0 Hz), 7.35–7.30 (m, 4H), 7.20 (d, 2H, J=9.0 Hz), 3.64–3.59 (m, 2H), 3.50–3.48 (m, 4H), 2.62 (s, 2H), 1.94 (s, 6H), 1.68–1.61 (m, 2H), 0.75 (d, 6H, J=7.0 Hz), 0.71 (d, 6H, J=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 136.7, 136.5, 136.2, 132.2, 128.1, 125.4, 63.7, 57.4, 28.9, 20.0, 19.2, 18.6; HRMS (FAB$^+$) calcd for (MH^+) $C_{26}H_{37}N_2O_4$ 441.2753, found 441.2767.

General procedure for synthesis of ligands 1a–d and 2a–d

Thionyl chloride (1.51 g, 12.7 mmol) was added to a solution of **5a** (0.43 g, 0.84 mmol) in dichloromethane (8 mL) under N_2. The solution was stirred for 24 h at rt, dichloromethane was added (50 mL) and then water (11 mL). The organic layer was washed with 4 M NaOH (5 mL), brine, and dried over $MgSO_4$. Evaporation of the solvent afforded a dichloro intermediate as a light yellow solid, 0.4 g, 87% yield. To the solution of this intermediate (0.40 g, 0.73 mmol) in acetonitrile (30 mL), were addded K_2CO_3 (7.0 g) and H_2O (2.7 mL). The mixture was then gently refluxed for 8 h, cooled to rt, and the solvent was removed leaving a yellow residue containing K_2CO_3 and the product. The residue was dissolved in EtOAc (150 mL) and water (50 mL). The organic layer was then separated, dried over $MgSO_4$ and evaporation of the solvent afforded a light yellow residue. Purification using radial chromatography (2 mm rotor, 5–35% EtOAc/hexane) produced a white oil product **1a** (0.3 g, 86% yield). Compounds **1b–d** and **2a–d** were synthesized in similar fashion, and the overall yield for the above two reactions were 65, 80, 71, 74, 62, 79 and 60, respectively.

(*S*,*S*,*S*)-2,2′-Bi-*o*-tolyl-1,1′-diphenyl bisoxazoline (1a). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (dd, 2H, J=12.5, 10.0 Hz), 7.30–7.11 (m, 10H), 6.98–6.94 (m, 4H), 5.04 (t, 2H, J=8.0 Hz), 4.29 (overlapt, 2H, J=8.0 Hz), 3.75 (t, 2H, J=8.0 Hz), 1.91 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 165.7, 142.8, 140.1, 137.0, 132.3, 128.5, 127.8, 127.5, 127.3, 127.1, 126.9, 126.8, 74.7, 70.0, 20.5; IR (neat): 3061, 2967, 2895, 1949, 1804, 1643, 1487, 1347 cm^{-1}; HRMS (FAB$^+$) calcd for (MH^+) $C_{32}H_{28}N_2O_2$ 473.2229, found 473.2235. $[\alpha]_D$=+37.8 (c=1.0, $CHCl_3$).

(*S*,*R*,*S*)-2,2′-Bi-*o*-tolyl-1,1′-diphenyl bisoxazoline (2a). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (dd, 2H, J=12.5, 10.0 Hz), 7.42–7.22 (m, 10H), 6.95–6.91 (m, 4H), 5.17 (t, 2H, J=8.0 Hz), 4.43 (overlapt, 2H, J=8.0 Hz), 3.78 (t, 2H, J=8.0 Hz), 2.1 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 165.7, 142.7, 139.6, 137.6, 132.0, 128.5, 128.0, 127.2, 127.1, 127.0, 126.7, 74.8, 70.0, 20.4; IR (neat): 3061, 2967, 2895, 1643, 1487, 1451, 1150 cm^{-1}; HRMS (FAB$^+$) calcd for (MH^+) $C_{32}H_{28}N_2O_2$ 473.2229, found 473.2234. $[\alpha]_D$=−193.5 (c=1.0, $CHCl_3$).

(*S*,*S*,*S*)-2,2′-Bi-*o*-tolyl-1,1′-di *t*-butyl bisoxazoline (1b). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, 2H, J=8.0 Hz), 7.22 (d, 2H, J=7.5 Hz), 7.17 (q, 2H, J=4.0 Hz), 3.88 (t, 2H, J=8.5 Hz), 3.74 (t, 2H, J=9.0 Hz), 3.68 (t, 2H, J=9.0 Hz), 1.84 (s, 3H), 0.63 (s, 18); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5, 140.2, 136.6, 131.6, 127.7, 126.9, 126.6, 76.1, 68.1, 33.7, 25.7, 20.3; IR (neat): 3065, 2950, 2867, 2359, 1731, 1656, 1478, 1207, 1002 cm^{-1}; HRMS (FAB$^+$) calcd for (MH^+) $C_{28}H_{37}N_2O_2$ 433.2855, found 433.2863. $[\alpha]_D$=+85.5 (c=1.0, $CHCl_3$).

(*S*,*R*,*S*)-2,2′-Bi-*o*-tolyl-1,1′-di *t*-butyl bisoxazoline (2b). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, 2H, J=7.0 Hz), 7.20 (t, 2H, J=7.0 Hz), 7.15 (t, 2H, J=7.0 Hz), 3.92 (t, 2H, J=8.5 Hz), 3.70–3.61 (m, 4H), 1.89 (s, 3H), 0.56 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.6, 139.8, 137.4, 131.4, 127.7, 126.7, 126.6, 76.4, 68.1, 33.4, 25.6, 20.3; IR (neat): 3065, 2950, 2867, 1731, 1656, 1478, 1207, 1002 cm^{-1}; HRMS (FAB$^+$) calcd for (MH^+) $C_{28}H_{37}N_2O_2$ 433.2855, found 433.2845. $[\alpha]_D$=−193.5 (c=1.0, $CHCl_3$).

(*S*,*S*,*S*)-2,2′-Bi-*o*-tolyl-1,1′-dibenzyl bisoxazoline (1c). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, 2H, J=8.0 Hz), 7.26–7.08 (m, 10), 7.05 (d, 4H, J=8.0 Hz), 4.22–4.16 (m, 2H), 3.83 (t, 2H), 3.63 (dd, 2H, J=8.0, 7.5 Hz), 2.89 (dd, 2H, J=14.0, 12.5 Hz), 2.36 (dd, 2H, J=14.0, 10.0 Hz), 1.89 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 139.8, 138.4, 136.7, 131.8, 129.1, 128.4, 127.8, 126.9, 126.8, 126.2, 71.7,

67.8, 41.5, 20.2; IR (neat): 3060, 2919, 1648, 1450, 1295, 996 cm^{-1}; HRMS (FAB^+) calcd for (MH^+) $C_{34}H_{33}N_2O_2$ 501.2542, found 501.2528. $[\alpha]_D$=+87.7 (c=1.0, $CHCl_3$).

(*S*,*R*,*S*)-2,2′-Bi-*o*-tolyl-1,1′-dibenzyl bisoxazoline (2c). ^1H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, 2H, J=8.0 Hz), 7.28–7.14 (m, 10), 7.00 (d, 4H, J=8.0 Hz), 4.22–4.16 (m, 2H), 3.87 (t, 2H, J=8.3 Hz), 3.62 (dd, 2H, J=8.5, 7.0 Hz), 2.70 (dd, 2H, J=14.0, 6.0 Hz), 2.25 (dd, 2H, J=13.5, 7.0 Hz), 1.94 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 139.6, 138.4, 137.4, 131.6, 129.2, 128.3, 127.8, 126.9, 126.7, 126.2, 71.6, 67.8, 41.4, 20.2; IR (neat): 3060, 2919, 1648, 1450, 1349, 114, 996 cm^{-1}; HRMS (FAB^+) calcd for (MH^+) $C_{34}H_{33}N_2O_2$ 501.2542, found 501.2528. $[\alpha]_D$=−84.3 (c=1.0, $CHCl_3$).

(*S*,*S*,*S*)-2,2′-Bi-*o*-tolyl-1,1′-di *i*-propyl bisoxazoline (1d). ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, 2H, J=8.0 Hz), 7.30–7.23 (m, 4H), 3.95 (t, 2H, J=8.0 Hz), 3.75 (q, 2H, J=8.0 Hz), 3.70 (t, 2H, J=8.0 Hz), 1.92 (s, 6H), 1.62–1.45 (m, 2H), 0.78 (d, 6H, J=7.0 Hz), 0.73 (d, 6H, J=7.0 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 164.7, 140.2, 136.9, 131.8, 128.1, 127.2, 126.9, 72.7, 70.2, 33.0, 20.5, 19.0, 18.5; IR (neat): 3060, 2919, 2884, 1648, 1460,1302, 996 cm^{-1}; HRMS (FAB^+) calcd for (MH^+) $C_{26}H_{33}N_2O_2$ 405.2542, found 405.2527. $[\alpha]_D$=+13.8 (c=1.0, $CHCl_3$).

(*S*,*R*,*S*)-2,2′-Bi-*o*-tolyl-1,1′-di *i*-propyl bisoxazoline (2d). ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, 2H, J=8.0 Hz), 7.35–7.20 (m, 4H), 4.00 (t, 2H, J=8.0 Hz), 3.80 (q, 2H, J=8.0 Hz), 3.64 (t, 2H, J=8.0 Hz), 1.98 (s, 6H), 1.52–1.40 (m, 2H), 0.70 (d, 6H, J=1.0 Hz), 0.67 (d, 6H, J=1.0 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 164.2, 139.8, 137.4, 131.6, 128.1, 126.9, 126.8, 72.7, 70.1, 32.8, 20.4, 18.8, 18.3; IR (neat): 3060, 2919, 2343, 1648, 1460, 1349, 996 cm^{-1}; HRMS (FAB^+) calcd for (MH^+) $C_{26}H_{33}N_2O_2$ 405.2542, found 405.2527. $[\alpha]_D$=−100.3 (c=1.0, $CHCl_3$).

Acknowledgements

We are grateful for the support provided by the National Science Foundation (Career Award, CHE-9501867), Brigham Young University, and Procter & Gamble (University Exploratory Research Fellow).

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