An Improved Procedure for the Preparation of 2,2-Bis[2-[4(*S*)-*tert*-butyl-1,3-oxazolinyl]]propane [(*S,S*)-*tert*-Butylbis(oxazoline)] and Derived Copper(II) Complexes

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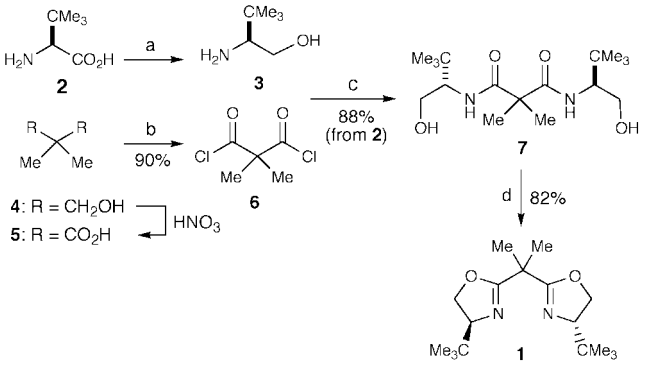
The general utility of C_2-symmetric bis(oxazoline) (box) ligands in copper-catalyzed asymmetric transformations has been demonstrated in a number of processes, including cyclopropanation,[1] olefin aziridination,[2] Diels−Alder,[3] Mukaiyama aldol,[4] and allylic oxidation reactions.[5] Several methods for the synthesis of these ligands have been reported with moderate to good yields.[6] The previously reported synthesis of (*S,S*)-*tert*-butylbis(oxazoline) ((*S,S*)-*t*-Bu-box) (**1**),[1] the optimal ligand for a number of these reactions, proceeded in four steps and 36% overall yield. The purpose of this paper is to describe an improved synthesis of **1** that entails minimal purification and proceeds in three steps and 72% overall yield from (*S*)-*tert*-leucine.

Ligand Synthesis. Our previous method for preparing (*S,S*)-*t*-Bu-box (**1**) involved lithium aluminum hydride reduction of commercially available (*S*)-*tert*-leucine (**2**) to the corresponding amino alcohol **3**, followed by acylation with 0.5 equiv of dimethylmalonyl dichloride (**6**).[1] The dihydroxy malonodiamide **7** was cyclized to the bis(oxazoline) via the bis(alkyl chloride) (PPh_3, Et_3N, CCl_4) and thermal cyclization (62%). Other methods for executing the ring closure of **7** include formation of the bis(mesylate) followed by exposure to aqueous ethanolic or methanolic base[6b,e,f] or treatment with dichlorodimethyltin.[7] Oxazolines[8] have also been prepared from reaction of amino alcohols and nitriles in the presence of Cd(OAc)$_2$[9] or $ZnCl_2$,[10] as well as from threonine derivatives under Mitsunobu conditions[11] or with the Burgess reagent.[12] Our goal in the present study was to reduce the number of synthetic and purification steps and to improve the yield of the oxazoline-forming step, rendering the method more amenable to large-scale preparation.

Scheme 1[a]



[a] Key: (a) $NaBH_4$, I_2, THF, reflux, 19 h; (b) DMF (cat.), oxalyl chloride, CH_2Cl_2, 25 °C, 18 h; (c) 2 equiv of **3**, Et_3N, CH_2Cl_2, 25 °C, 35 min; (d) TsCl, Et_3N, DMAP (cat.), CH_2Cl_2, 25 °C, 27 h.

In our experience, the Meyers procedure[13] ($NaBH_4/I_2$, THF, reflux) was found to be optimal for the reduction of **2** to the derived amino alcohol **3** (Scheme 1). While the (*S*)-*tert*-leucinol may purified by vacuum distillation (79%), the yields of the overall process are improved by employing the unpurified alcohol **3** in the subsequent acylation step with dimethylmalonyl dichloride **6** to form the dihydroxy malonodiamide **7**, mp 163.3−163.7 °C, in 88% overall yield from (*S*)-*tert*-leucine (**2**) after recrystallization. Although dimethylmalonic acid (**5**) is commercially available, nitric acid oxidation of 2,2-dimethyl-1,3-propanediol (**4**)[14] significantly increases the cost-effectiveness of the overall synthesis.

During the course of this investigation, a number of ring-closure methods were evaluated. From this experience, the following oxazoline ring-forming procedure proved to be optimal for large-scale preparation: treatment of dihydroxy malonodiamide **7** with *p*-toluenesulfonyl chloride and triethylamine in the presence of catalytic

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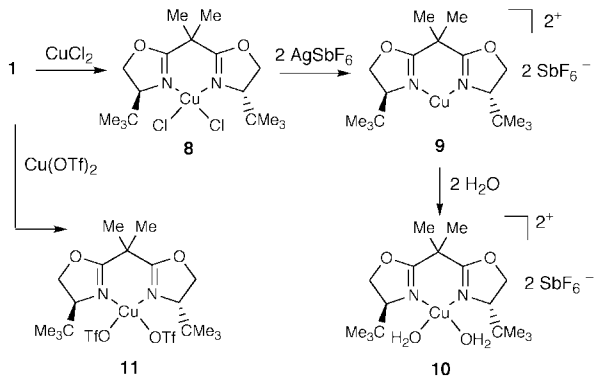
Scheme 2



quantities of 4-(dimethylamino)pyridine (CH_2Cl_2, 25 °C, 27 h) effects in situ formation of the bis(tosylate), which undergoes cyclization to provide bis(oxazoline) **1**. After a conventional extractive isolation, recrystallization from pentane affords bis(oxazoline) **1**, mp 88.9−89.8 °C, in 82% yield. If the mothor liquors from the preceding crystallization are chromatographed, an additional 6% of **1** (88% combined) may be obtained.

Catalyst Preparation. Prior work from our laboratory has demonstrated that the [Cu(*t*-Bu-box)]X_2 complexes **9** and **11** (Scheme 2) are effective catalysts for Diels−Alder reactions of α,β-unsaturated imides.[3] In the early stages of this investigation, the ligand−$Cu(OTf)_2$ complex **11** was employed with the assumption that the highly electronegative triflate ions would readily dissociate as the substrate ligated to the metal center.[3a] Subsequent studies revealed that there is a strong correlation between counterion coordinating ability and catalyst selectivity as well as reactivity.[3c] In all instances, the SbF_6-derived complex **9** is more Lewis acidic than the analogous triflate complex **11**.[3c] Recently, we have found that the bench-stable bis(aquo) complex **10** is a nearly ideal catalyst for Diels−Alder and glyoxylate ene reactions and for most applications is a useful replacement for the anhydro complex **9**.

The SbF_6 complex **9** was produced by treatment of a solution of the CH_2Cl_2-soluble cupric chloride complex **8** with 2 equiv of $AgSbF_6$. Filtration of the deep-green solution of **9** away from the resultant AgCl through a plug of oven-dried Celite afforded the active catalyst. Exposure of **9** to atmospheric moisture affords deep-blue crystals of the bis(aquo) SbF_6 complex **10**, whose crystal structure is illustrated below (Figure 1). The crystallographic data for **10** demonstrate that neither SbF_6 counterion is coordinated to the metal center. Further, the complex exhibits a distorted square-planar geometry, with the coordinated water molecules displaced an average of 33° out of the Cu(II)−ligand plane.

Previous reports from this laboratory have documented the utility of these cationic C_2-symmetric Cu(II)bis(oxazoline) complexes as chiral Lewis acids capable of catalyzing Diels−Alder,[3] aldol,[4] and glyoxylate ene[15] reactions with high enantioselectivities. In these processes, the unifying organizational motif is that the substrate undergoing activation is capable of chelating to the chiral cationic Cu(II) catalyst, a condition that frequently affords high enantioselection. One might infer that the reactants that chelate to **10** adopt a distorted square-planar geometry similar to that illustrated above, where the coordination sites occupied by the coordinated water molecules are replaced by the oxygen heteroatoms in the substrate undergoing activation.

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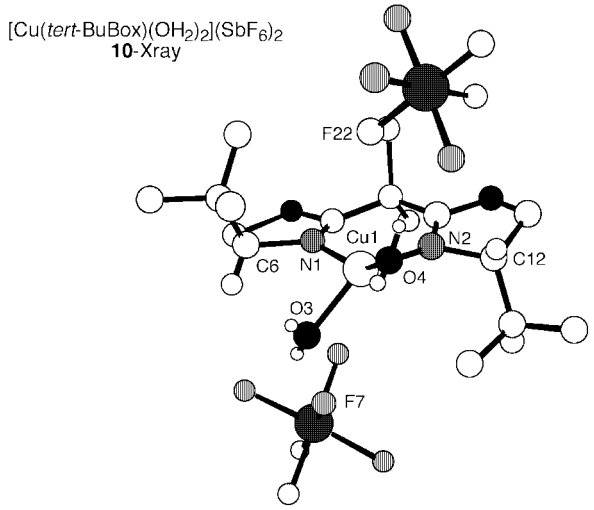

Figure 1. Crystallographic structure of the bis(aquo) complex **10**. Selected bond lengths (Å) and dihedral angles (deg): Cu1−N1 (1.913), Cu1−N2 (1.905), Cu1−O3 (1.994), Cu1−O4 (1.980), Cu1−O10/F22 (3.300), Cu1−O7/F7 (3.500), O3−Cu1−N1−C6 (30.0), O4−Cu1−N2−C12 (36.0).

Experimental Section

General Methods. Unless noted, all reactions were carried out under a nitrogen atmosphere with stirring as indicated. Reagent-grade THF was obtained from EM Science (stored over 4 Å molecular sieves). CH_2Cl_2 was used from an unopened reagent grade bottle or distilled from CaH_2. Triethylamine was distilled from CaH_2. (*S*)-*tert*-Leucine (**2**) was a gift from NSC Technologies. Dimethylmalonic acid (**5**) was prepared according to literature procedures.[14] All other chemicals were obtained from commercial sources and used without further purification, except for *p*-toluenesulfonyl chloride, which was recrystallized prior to use. Flash chromatography was performed using EM Reagent silica gel 60 (230−400 mesh). Analytical thin-layer chromatography was performed on EM Reagent 0.25-mm silica gel 60-F plates. Visualization was accomplished with UV light and potassium iodoplatinate for the *t*-Bu-box product. Melting points are uncorrected. Combustion analyses were performed by Galbraith Microanalytical Laboratory (Knoxville, TN).

(*S*)-*tert*-Leucinol (3). The title compound was prepared according to the procedure of Meyers.[13] A dry 5-L three-necked round-bottom flask equipped with a mechanical stirrer and a 250-mL addition funnel was charged with sodium borohydride (55.6 g, 1.47 mol, 2.41 equiv) and 1.6 L of anhydrous THF. The solution was stirred while (*S*)-*tert*-leucine (**2**) (80.0 g, 610 mmol) was added in one portion. The flask was cooled to 0 °C and fitted with a reflux condenser. The addition funnel was charged with a solution of I_2 (155.0 g, 610 mmol, 1 equiv) in 200 mL of THF, which was added dropwise to the flask over a 1.5-h period with considerable gas evolution. The solution was allowed to warm to room temperature. When the brown color had dissipated to give a cloudy white solution, the reaction was brought to reflux for 19 h. The cloudy white suspension was cooled to room temperature with the aid of a water bath. The addition funnel was charged with 150 mL of MeOH, which was added dropwise with rapid stirring. Vigorous gas evolution was observed. Small aliquots of MeOH were then added until all of the solid white material had dissolved. The solution was concentrated by rotary evaporation to give a white pasty oil that was dissolved in 1.20 L of 20% (w/w) aqueous KOH and mechanically stirred for 6 h at room temperature. The light green solution was extracted with CH_2Cl_2 (3 × 1.50 L, 1 × 600 mL). To minimize the emulsion, 200 mL of brine was added to the aqueous layer after

the first extraction. The combined organic extracts were dried over Na_2SO_4, filtered through glass wool, and concentrated in vacuo to give 74.1 g of a white crystalline solid in a thick, slightly yellow oil. Distillation of (*S*)-*tert*-leucinol (**3**), bp 70−73 °C/2 mm Hg (lit.[16] 117−120 °C/57 mm) from a 30.0 g reduction reaction performed in the above manner yielded 21.3 g of product (79% yield) as a clear oil, which solidified upon cooling to room temperature: $[\alpha]_D^{25}$ +36.5° (*c* 1.22, EtOH); IR ($CHCl_3$) 3420, 2970, 2880, 1585, 1480, 1420, 1400, 1370, 1350, 1135, 1105, 1040, 1020, 985, 940, 920 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.73 (dd, 1H, J = 10.3, 3.8 Hz), 3.21 (t, 1H, J = 10.3 Hz), 2.51 (dd, 1H, J = 10.3, 3.8 Hz), 1.86 (br s, 3H), 0.94 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 62.4, 61.8, 33.2, 26.3. HRMS (CI, ammonia) *m*/*z* 118.1232; exact mass calcd for $C_6H_{16}NO$ $[M + H]^+$ 118.1233.

For maximum overall yield, it is recommended that the unpurified (*S*)-*tert*-leucinol be used in the acylation reaction without distillation.

Dimethylmalonyl Dichloride (6).[17] A dry 2-L round-bottom flask equipped with a 150-mL addition funnel and magnetic stir bar was charged with dimethylmalonic acid (**5**) (57.0 g, 431 mmol, 1 equiv), dimethylformamide (4.2 g, 58.0 mmol, 4.0 mL, 0.13 equiv), and 650 mL of CH_2Cl_2. The solution was cooled to 0 °C, and the addition funnel was charged with oxalyl chloride (164.3 g, 1.30 mol, 113 mL, 3 equiv), which was added dropwise with gas evolution over 1.5 h. The cloudy yellow solution was stirred for 18 h at 25 °C. The solution cleared and turned a deep yellow color as the reaction progressed. The solution was concentrated in vacuo to give a yellow liquid with denser orange oil droplets. The mixture was distilled immediately (150−152 °C, 760 mmHg, N_2) to afford 67.3 g (90%) of a clear, colorless liquid: ^1H NMR (250 MHz, $CDCl_3$) δ 1.65 (s, 6H).

(*S*)-*N*,*N*′-Bis[1-(hydroxymethyl)-2,2-dimethylpropyl]-2,2-dimethyl-1,3-propanediamide (7).[1] A 5-L three-necked flask fitted with a mechanical stirrer was charged with a solution of unpurified (*S*)-*tert*-leucinol (**3**) (74.1 g, 610 mmol (based on a 100% yield of the previous reaction), 2 equiv) in 675 mL of CH_2Cl_2. The solution was cooled in an ice bath, and triethylamine (153.0 g, 1.51 mol, 211 mL, 5 equiv) was added via syringe. A solution of dimethylmalonyl dichloride (51.1 g, 302.5 mmol, 1 equiv) in 235 mL of CH_2Cl_2 was slowly added via cannula to the vigorously stirred reaction over 20 min. The ice bath was removed, and the thick white suspension was stirred at room temperature for 35 min. CH_2Cl_2 (1.78 L) was added, dissolving most of the white solid. The reaction mixture was washed with 445 mL of 1 N HCl, and the aqueous layer was back-extracted with 224 mL of CH_2Cl_2. The combined organic extracts were washed with 445 mL of saturated aqueous $NaHCO_3$, and the aqueous layer was back-extracted with 180 mL of CH_2Cl_2. The combined organic extracts were washed with 445 mL of brine, and the aqueous layer was back-extracted with 180 mL of CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered through glass wool, and concentrated in vacuo to give a white solid, which was recrystallized from ethyl acetate to afford 87.4 g (88%, two steps) of a white crystalline solid: mp 163.3−163.7 °C; TLC R_f = 0.22 (95:5 EtOAc/MeOH); $[\alpha]_D^{25}$ +2.5° (*c* 0.75, MeOH); IR (KBr) 3340, 2970, 2910, 2880, 1645, 1545, 1525, 1480, 1400, 1380, 1370, 1340, 1270, 1240, 1190, 1100, 1050, 1020, 1000 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.39 (br d, 2H, J = 9.6 Hz), 3.87 (m, 4H), 3.44 (m, 2H), 1.52 (s, 6H), 0.93 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 62.2, 59.5, 50.3, 33.4, 26.8, 23.8. Anal. Calcd for $C_{17}H_{34}N_2O_4$: C, 61.79; H, 10.37. Found: C, 61.85; H, 10.27.

2,2-Bis[2-[4(*S*)-*tert*-butyl-1,3-oxazolinyl]]propane [(*S*,*S*)-*tert*-Butyl bis(oxazoline)] (1).[1] A 1-L round-bottom flask with a magnetic stir bar was charged with dihydroxymalonodiamide **7** (20.0 g, 60.6 mmol, 1 equiv), 4-(dimethylamino)pyridine (0.74 g, 6.06 mmol, 0.1 equiv), and 240 mL of CH_2Cl_2. Triethylamine (27.0 g, 267 mmol, 37.1 mL, 4.4 equiv) was added via syringe. The flask was placed in a room temperature water bath, and a solution of *p*-toluenesulfonyl chloride (23.1 g, 121 mmol, 2 equiv) in 50 mL of CH_2Cl_2 was added via cannula, followed by one 10 mL CH_2Cl_2 rinse. The bright yellow solution was stirred at room temperature for 27 h. The solution containing crystalline solid was diluted with 150 mL of CH_2Cl_2, and upon washing with 250 mL of saturated aqueous NH_4Cl, a white solid formed in the aqueous layer. Water (150 mL) was added, the layers were separated, and the aqueous was layer back-extracted with CH_2Cl_2 (3 × 200 mL). The combined organic extracts were washed with 200 mL of saturated aqueous $NaHCO_3$. The aqueous layer was back-extracted with CH_2Cl_2 (3 × 200 mL). The combined organic extracts were dried over Na_2SO_4, filtered through cotton, and concentrated in vacuo to give a yellow-white solid. The resulting solid was triturated with hot pentane (1 × 150 mL, 1 × 50 mL, 2 × 40 mL), followed by hot gravity filtration. The colorless extracts were concentrated in vacuo to give 16.3 g (91% yield) of a white solid that was recrystallized from pentane to give 14.6 g (82%) of a white crystalline solid. The mother liquors were purified by flash chromatography (20% EtOAc/CH_2Cl_2 to 50% EtOAc/CH_2Cl_2) to give an additional 1.2 g (6%) of **1**: mp 88.9−89.8 °C; TLC R_f = 0.18 (3:7 EtOAc/hexanes); $[\alpha]_D^{25}$ +113.2° (*c* 1.22, CH_2Cl_2); IR (CCl_4) 2960, 2930, 2870, 1665, 1480, 1465, 1395, 1385, 1365, 1350, 1335, 1300, 1250, 1210, 1190, 1145, 1115, 980, 920 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.15 (dd, 2H, J = 10.0, 8.7 Hz), 4.11 (dd, 2H, J = 8.7, 7.0 Hz), 3.51 Hz (dd, 2H, J = 10.1, 7.0 Hz), 1.51 (s, 6H), 0.87 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 68.9, 38.5, 33.8, 26.8, 25.6, 24.4. Anal. Calcd for $C_{17}H_{30}N_2O_2$: C, 69.35; H, 10.27; N, 9.51. Found: C, 69.39; H, 10.39; N, 9.57.

[Cu(*S*,*S*)−Bis(*tert*-butyloxazoline)](SbF$_6$)$_2$ (9). To an oven-dried round-bottom flask containing a magnetic stirring bar was added, in an inert atmosphere box, bis(oxazoline) **1** (1.472 g, 5.00 mmol) and $CuCl_2$ (0.672 g, 5.00 mmol). The flask was fitted with a serum cap, removed from the inert atmosphere box and charged with CH_2Cl_2 (20 mL). After being stirred for 3.5 h, no brown $CuCl_2$ was observed, and the clear green solution was transferred via cannula to a syringe fitted with a 0.45 μm PTFE filter and filtered under nitrogen into a Schlenk flask. The solvent was removed in vacuo to deliver Cu(*t*-Bu-box)Cl_2·CH_2Cl_2 (**8**) as a light green powder in 99% yield (2.52 g, 4.95 mmol): mp > 180 °C; $[\alpha]_D$ −251° (*c* 1.06, CH_2Cl_2); IR (CH_2Cl_2) 2968, 1655, 1484, 1371, 1239, 1135, 947 cm^{-1}. Anal. Calcd for $C_{18}H_{32}Cl_4CuN_2O_2$: C, 42.08; H, 6.28; N, 5.45. Found: C, 42.21; H, 6.24; N, 5.51.

To an oven-dried round-bottom flask containing a magnetic stirring bar was added, in an inert atmosphere box, Cu(*t*-Bu-box)Cl_2·CH_2Cl_2 (**8**) (51.2 mg, 0.10 mmol) and $AgSbF_6$ (68.7 mg, 0.20 mmol). The flask was fitted with a serum cap, removed from the inert atmosphere box, and charged with CH_2Cl_2 (2.0 mL). The mixture was stirred for 2−3 h in the absence of light to produce a green solution with a white AgCl precipitate. The mixture was filtered through a plug of oven-dried Celite to provide a solution of **9** as a clear dark green solution. The development of a blue color in room-temperature solutions of this catalyst is indicative of the formation of the bis(aquo) complex **10**.

[Cu(*t*-Bu-box)(H$_2$O)$_2$)](SbF$_6$)$_2$ (10). The CH_2Cl_2 solution of **9** obtained after the Celite filtration step in the preceding experiment was washed through with 4 × 15 mL of CH_2Cl_2 (saturated with H_2O) into a flask. The blue solution containing the aquated complex **10** was concentrated slowly in vacuo to afford 344 mg (99% yield) of **10** as an air-stable light blue solid whose structure was established by X-ray crystallography.

[Cu(*S*,*S*)-bis(*tert*-butyloxazoline)]OTf)$_2$ (11). To an oven-dried round-bottom flask containing a magnetic stirring bar were added, in an inert atmosphere box, bis(oxazoline) **1** (14.7 mg, 0.050 mmol) and $Cu(OTf)_2$ (18.1 mg, 0.050 mmol). The flask was fitted with a serum cap, removed from the inert atmosphere box, and charged with solvent (1.5−3.0 mL of THF or CH_2Cl_2). The resulting suspension was stirred rapidly for 4 h with CH_2Cl_2 to give a slightly cloudy bright green solution or for 1 h with THF to give a clear dark green solution. When the CH_2Cl_2 catalyst solution was cooled to −78 °C, a *clear* blue green solution was obtained. Similarly, cooling the THF catalyst solution to −78 °C yielded a clear blue-green solution. These catalyst solutions must be kept rigorously anhydrous for optimal results in reactions using this catalyst. The development of a blue color in room-temperature solutions of this catalyst is indicative of the formation of the bis(aquo) complex. The use of powdered 3 Å molecular sieves with hydrated catalyst solutions has been

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found to reconstitute the green color characteristic of anhydrous solutions as well as restore the catalytic activity.

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Supporting Information Available: X-ray crystal structure of copper complex **10** (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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