Supporting Information

Exploiting \( C_3 \)-Symmetry in the Dynamic Coordination of a Chiral Trisoxazoline to Copper(II): Improved Enantioselectivity, and Catalyst Stability in Asymmetric Lewis Acid Catalysis

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Preparation of the copper(II) complexes

\([\text{Cu}(\text{iPr-trisox})(\beta\text{-ketoester})](\text{ClO}_4)\) (1a)

A mixture of \( \text{Cu(ClO}_4)_2 \cdot 6\text{H}_2\text{O} \) (44mg; 0.119 mmol) and \( \text{iPr-trisox} \) (47 mg; 0.129 mmol) in THF (2 mL) was stirred for 2 hours. A 5.76·10\(^{-2}\) M solution of diethylmalonate / \( \text{t-BuOK} \) (2.3 mL, 0.131 mmol) was subsequently added and the resulting green mixture was stirred overnight. After removal of the volatiles in vacuo, the crude product was washed with cold hexane until a solid was obtained. This solid material was extracted with toluene and the resulting suspension was filtered through a Teflon microfilter (0.2 µm). Slow vapour diffusion of hexane into the solution gave green crystals of compound 1a (51 mg; 64%). Anal. found % (calcd. for \( \text{C}_{27}\text{H}_{44}\text{ClCuN}_3\text{O}_{10} \)): C 48.38 (48.43); H 6.64 (6.62); N 6.16 (6.27). MS (FD\(^{+}\)):

\[ 1239.5 (2\times[M]^+–\text{ClO}_4); 1096.5 (2\times[M]^+–\text{ClO}_4 – \text{C}_7\text{H}_{11}\text{O}_3); 569.3 (100%, [M]^+–\text{ClO}_4). \]

\([\text{Cu}(\text{iPr-trisox})(\beta\text{-ketoester})](\text{BF}_4)\) (1b)

A mixture of \( \text{Cu(BF}_4)_2 \cdot 6\text{H}_2\text{O} \) (44mg; 0.116 mmol) and \( \text{trisoxazoline} \) (46 mg; 0.128 mmol) in THF (2 mL) was stirred for 3 hours. A 5.76·10\(^{-2}\) M solution of diethylmalonate / \( \text{t-BuOK} \) (2.2 mL, 0.131 mmol) was subsequently added and the resulting green mixture was stirred overnight. After removal of the volatiles in vacuo, the crude product was washed with cold hexane until it solidified. The solid was extracted with toluene and the resulting suspension was filtered through a Teflon microfilter (0.2 µm). Removal of the solvent gave the title compound as a dark green solid (69 mg; 91%). Slow vapour diffusion of hexane into a THF solution gave crystals suitable for X-ray analysis. Anal. found % (calcd. for \( \text{C}_{27}\text{H}_{44}\text{BCuF}_4\text{N}_3\text{O}_6 \)): C 48.52 (49.36); H 6.66 (6.75); N 6.76 (6.40). MS (FAB\(^{+}\)):

\[ 426.3 ([M]^+–\text{BF}_4 – \text{C}_7\text{H}_{11}\text{O}_3). \]
General procedures for the Catalyst Testing

Ethyl 2-methylacetoacetate and dibenzylazodicarboxylate are commercially available and were used without further purification. N-tosyl-α-imino ester was prepared from ethyl glyoxylate and p-toluenesulfonyl isocyanate following a literature procedure. The catalyst solutions for the enantioselective Mannich and α-amination reactions of the β-ketoester were obtained by taking the appropriate amount of a stock solution and diluting to 1 mL.

General procedure for the catalytic asymmetric Mannich reaction of ethyl 2-methylacetoacetate.

A stock solution of CuClO₄·6H₂O (8.3 mg, 22.5 µmol) and [iPr-triso] (12.3 mg, 33.8 µmol) in acetone/Et₂O (1.5 mL, 1/3 v/v) was prepared under air. The homogeneous solution was stirred for 30 min and successive aliquots were taken to obtain the desired catalyst loading for each run. To each catalyst solution was added the β-ketoester (22.5 µL, 0.15 mmol) and the solution was cooled down to -28°C. N-tosyl-α-imino ester (360 µL, 0.18 mmol) in solution in toluene (0.5 mol L⁻¹) was then added. After 36 h at -28°C, the solvent was removed in vacuo and the residue was purified by flash chromatography (CH₂Cl₂/MeOH 100/1). The ee-s of the products were determined by HPLC using a Daicel Chiralpak AD-H column.

General procedure for the catalytic asymmetric α-amination reaction of ethyl 2-methylacetoacetate:

A stock solution of Cu(OTf)₂ (8.1 mg, 22.5 µmol) and [Ph-triso] (15.7 mg, 33.8 µmol) in CH₂Cl₂ (1.5 mL) was prepared under air. The homogeneous solution was stirred for 30 min and successive aliquots were taken to obtain the desired catalyst loading for each run. To each catalyst solution was added the β-ketoester (22.5 µL, 0.15 mmol) and the solution was cooled down to 0°C. Pre-cooled dibenzylazodicarboxylate (54.8 mg, 0.18 mmol) in solution in CH₂Cl₂ (0.5 mL) was then added. After 16 h at 0°C, the products were isolated by flash chromatography (Hexane/EtOAc 75/25). The ee-s of the products were determined by HPLC using a Daicel Chiralpak AD-H column.

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