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

Carole Foltz, Björn Stecker, Guido Marconi, Stéphane Bellemin-Laponnaz,* Hubert Wadepohl, and Lutz H. Gade*

Preparation of the copper(II) complexes

[Cu(^{i}Pr-trisox)(β-ketoester)](ClO$_4$) (1a)

A mixture of $Cu(ClO_4)_2 \cdot 6H_2O$ (44mg; 0.119 mmol) and ^{i}Pr-trisox (47 mg; 0.129 mmol) in THF (2 mL) was stirred for 2 hours. A $5.76 \cdot 10^{-2}$ M solution of diethylmethylmalonate / *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 $C_{27}H_{44}ClCuN_3O_{10}$): C 48.38 (48.43); H 6.64 (6.62); N 6.16 (6.27). MS (FD+): 1239.5 ($2\times[M]^+ - ClO_4$); 1096.5 ($2\times[M]^+ - ClO_4 - C_7H_{11}O_3$); 569.3 (100%, $[M]^+ - ClO_4$).

[Cu(^{i}Pr-trisox)(β-ketoester)](BF$_4$) (1b)

A mixture of $Cu(BF_4)_2 \cdot 6H_2O$ (44mg; 0.116 mmol) and trisoxazoline (46 mg; 0.128 mmol) in THF (2 mL) was stirred for 3 hours. A $5.76 \cdot 10^{-2}$ M solution of diethylmethylmalonate / *t*-BuOK (2.2 mL, 0.128 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 $C_{27}H_{44}BCuF_4N_3O_6$): C 48.52 (49.36); H 6.66 (6.75); N 6.76 (6.40). MS (FAB+): 426.3 ($[M]^+ - BF_4 - C_7H_{11}O_3$).

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.[1] 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 $CuClO_4.6H_2O$ (8.3 mg, 22.5 μmol) and [^{i}Pr-trisox] (12.3mg, 33.8 μmol) in acetone/Et_2O (1.5mL, 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 (CH_2Cl_2/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-trisox] (15.7mg, 33.8 μmol) in CH_2Cl_2 (1.5mL) 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 CH_2Cl_2 (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.

[1] G. R. Heintzelman, S. M. Weinreb, M. Parvez, *J. Org. Chem.* 1996, **61**, 4594.