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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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Received (in Cambridge, UK) 6th July 2005, Accepted 24th August 2005
First published as an Advance Article on the web 16th September 2005
DOI: 10.1039/b509571a

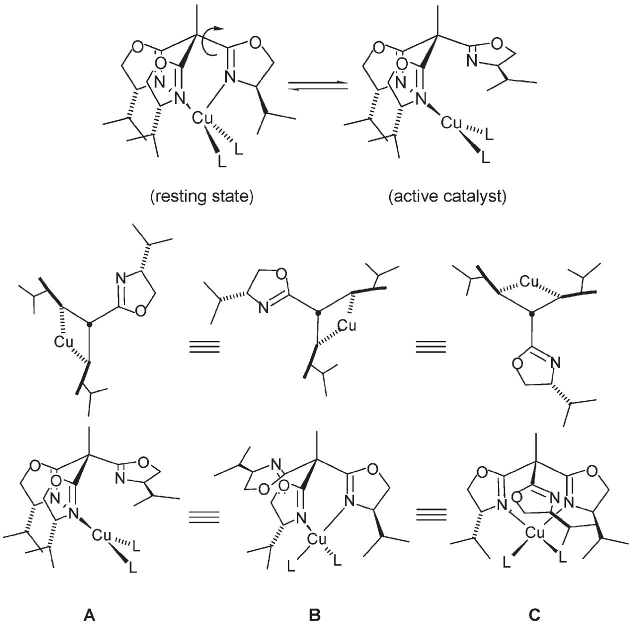
Chiral C_3-symmetric trisoxazolines are highly efficient stereodirecting ligands in enantioselective Cu^{II} Lewis acid catalysis which is based on the concept of a *stereoelectronic hemilability* of the divalent copper; in direct comparison with the analogous bisoxazoline systems they are more efficient in the enantioselective α-amination as well as the enantioselective Mannich reaction of prochiral β-ketoesters.

Molecular symmetry has been one of the guiding principles in catalyst design for enantioselective transformations. The symmetry-related reduction of the number of diastereomeric intermediates and transition states in a catalytic cycle simplifies the analysis of the enantioselection process and may be beneficial for the selectivity of the catalyst.[1] The discussion of catalyst symmetry has mainly focused on static models of the complex fragments bearing the stereodirecting ancillary ligand.[2] In this work we present a conceptual approach in which the high rotational symmetry of the chiral tripodal ancillary ligand renders the reversible pathways leading to the active catalyst, containing the partially decoordinated podand, equivalent and thus leading to a single catalytic species.

Whereas C_2-symmetric bisoxazoline ligands have found widespread use in asymmetric catalysis,[3,4] and have thus been the focus of extensive efforts in ligand design, C_3-symmetric trisoxazoline ligands are only now beginning to be studied.[5] Recently, we reported an efficient modular synthesis of 1,1,1-tris(oxazolinyl)-ethane ("trisox") derivatives which are ideally suited to facial coordination to transition metals.[6] First studies into their application in catalysis have established them as effective chiral ligands for several catalytic transformations in which their facial coordination to the metal centre was found to be a key feature.[7]

Bisoxazoline (BOX) ligands have been extensively applied in asymmetric Cu^{II} Lewis acid catalysis,[3,4,8] however, the generally high catalyst loadings, which are due to the kinetic lability of copper(II), remain a problem and thus a challenge for further research. In this context, facial coordination by a chiral tridentate ligand was thought to stabilize the *resting state* of the copper complexes. The additional oxazoline ligation is expected to deactivate the complexes in their Lewis acidity as was shown in a recent theoretical study on (BOX)Cu-catalysts.[9] The transformation of the resting state into the active (17e Cu^{II}) species therefore necessitates the decoordination of an oxazoline unit and the opening up of the system (Scheme 1, top). This required "hemilability" is provided *stereoelectronically* by the strong dynamic Jahn–Teller-effect of the d^9-Cu^{II} centre. As a consequence of the threefold rotational symmetry of the system, all of the possible dicoordinated catalytically active species (**A**–**C**) are equivalent (Scheme 1, bottom)

To test this concept, we applied [Cu^{II}(trisox)] complexes in the asymmetric Mannich reaction[10] of a β-ketoester with an activated *N*-tosyl-α-imino ester, a reaction which has been previously reported by Jørgensen *et al.* using chiral copper(II)-bisoxazoline catalysts (10 mol%).[11] These workers showed that the size of the alkoxy moiety of the β-ketoesters is critical. In order to obtain high enantioselectivities, the *tert*-butyl ester was required, while the corresponding ethyl esters gave only moderate selectivities of 22–42% ee. We therefore chose the latter for the Mannich reaction



Scheme 1 Coordination/decoordination equilibrium between the proposed resting and active states of the trisox-Cu catalysts giving symmetry-equivalent active species.

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† Electronic supplementary information (ESI) available: Experimental details. See http://dx.doi.org/10.1039/b509571a

catalyzed by $[(^{i}\text{Pr-trisox})\text{Cu}](\text{ClO}_4)_2$ and, after optimization of the conditions, gave the reaction product with an excellent ee of 90% using 10 mol% of the catalyst (Table 1).

Upon stepwise reduction of the catalyst loading by a factor of 10^3, *i.e.* in the presence of only 0.01 mol% of catalyst, the enantioselectivity remained unchanged (90% ee, the diastereoselectivity being throughout the dilution series at *ca. syn*/*anti* = 13/87). The reactions did not require any special precautions and were carried out in the air, thus illustrating the practical applicability of the process. As a direct comparison, we also investigated the reaction in the presence of 10 mol% of $[(^{i}\text{Pr-BOX})\text{Cu}](\text{ClO}_4)_2$ for which 84% ee (84% yield) were observed. Reducing the catalyst loading for these systems led to a decrease of the stereoselectivity, with enantiomeric excesses of 80% and 66% ee being observed at catalyst concentrations of 0.1 and 0.01 mol%, respectively.

A considerable number of copper complexes bearing facially coordinated tripodal N_3-ligands have been structurally characterized whereas the opening up of these systems, as postulated here, is rarely observed.[12] Direct evidence for our assumption of a partially decoordinated trisox-ligand in the active state of the catalyst was obtained by crystallization of the reaction intermediate which results from the reaction of the {trisox-Cu} complex system with ethyl-2-acetylpropionate. This gave single crystals of $[\text{Cu}^{\text{II}}(^{i}\text{Pr-trisox})(\kappa^2\text{-}O,O'\text{-MeCOCHCOOEt})]^{+}(\text{BF}_4^{-})$ (**1a**) as well as of the analogous and isomorphous ClO_4^{-}-salt (**1b**) which were studied by X-ray diffraction.‡ The structure of the complex cation in both salts is depicted in Fig. 1. Two of the oxazoline groups of the ^{i}Pr-trisox ligand are coordinated to the central copper atom [Cu–N bonds lengths: **1a**: 1.973(3) and 1.985(3) Å; **1b**: 1.966(4), 1.986(3) Å], whilst the third oxazoline unit is dangling with the N-donor pointing away from the metal centre. The complex geometry is square pyramidal with a fluorine atom of the BF_4-counterion (an oxygen atom of ClO_4^{-} in **1b**) occupying the apical position [**1a**: Cu(1)–F(1) 2.376(2) Å; **1b**: Cu(1)–O(7) 2.403(3) Å]. The six-membered metallacycles formed by the Cu-centre and the deprotonated β-ketoester and by the metal and the bisoxazoline unit lie within one molecular plane.[13] Given this arrangement of substrate and ancillary ligand as well as the coordination of the counterion, it appears likely that electrophilic attack on the metallated β-ketoester occurs on the *re*-face which is liberated by the decoordination of the hemilabile third oxazoline.[11] This would lead to products having the correct absolute stereochemistry, as observed in the Mannich addition. However, the substitutional lability of the copper(II) complexes, and thus the possibility of rapid equilibria, sets limits to interpretations based on X-ray structural data.

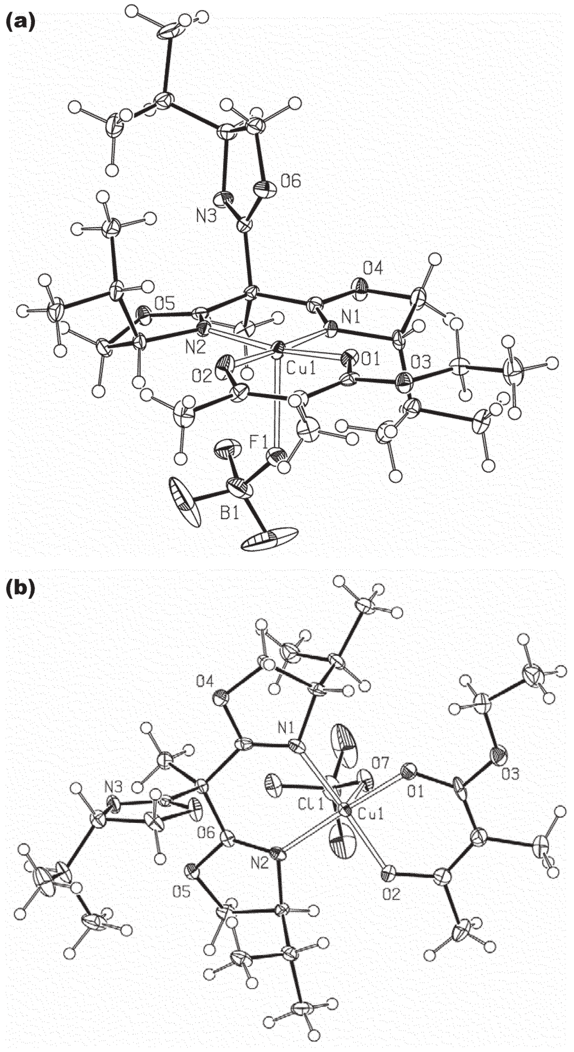
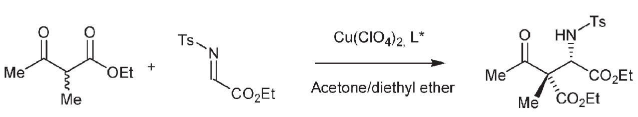
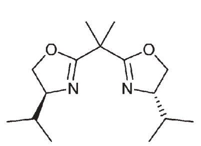
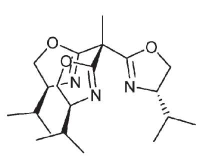


Fig. 1 a) Molecular structure of the copper complex $[\text{Cu}^{\text{II}}(^{i}\text{Pr-trisox})(\kappa^2\text{-}O,O'\text{-MeCOCHCOOEt})]^{+}(\text{BF}_4^{-})$ (**1a**): Principal bond lengths [Å] and angles [°]: Cu(1)–N(1)/N(2) 1.973(3)/1.985(3), Cu(1)–O(1)/O(2) 1.939(3)/1.891(3); N(1)–Cu(1)–N(2), 89.40(12), N(1)–Cu(1)–O(1)/O(2) 91.05(12)/177.36(13), N(2)–Cu(1)–O(2)/O(1) 88.51(12)/171.12(12), O(1)–Cu(1)–O(2) 90.77(12). b) Orthogonal view of the molecular structure of $[\text{Cu}^{\text{II}}(^{i}\text{Pr-trisox})(\kappa^2\text{-}O,O'\text{-MeCOCHCOOEt})]^{+}(\text{ClO}_4^{-})$ (**1b**): Cu(1)–N(1)/N(2) 1.966(4)/1.986(3), Cu(1)–O(1)/O(2) 1.939(3)/1.897(3); N(1)–Cu(1)–N(2) 89.41(15), N(1)–Cu(1)–O(1)/O(2) 90.98(14)/176.71(15), N(2)–Cu(1)–O(2)/O(1) 88.64(15)/171.17(15), O(1)–Cu(1)–O(2) 90.54(14).

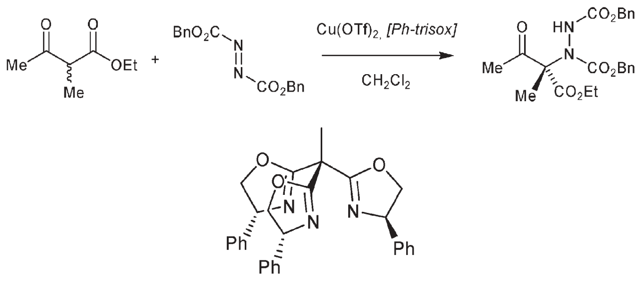
Table 1 Enantioselective Mannich reaction of ethyl 2-methylacetoacetate with *N*-tosyl-α-imino methyl ester catalyzed by $[(^{i}\text{Pr-trisox})\text{Cu}](\text{ClO}_4)_2$ or $[(^{i}\text{Pr-BOX})\text{Cu}](\text{ClO}_4)_2$



Entry	Catalyst loading (%)	Ligand			
		[^{i}Pr-BOX]		[^{i}Pr-trisox]	
					
		Yield (%)	ee (%)	Yield (%)	ee (%)
1	10	84	84	84	90
2	1	70	84	75	89
3	0.1	56	80	59	91
4	0.01	35	66	36	90

[a] Experimental conditions: acetone/diethyl ether 1/3, −28 °C, 36 h. The product was isolated by chromatography. Chiral HPLC was used to determine the ee values.

Table 2 Enantioselective α-amination of ethyl 2-methylacetoacetate with dibenzylazodicarboxylate catalyzed by [(Ph-trisox)Cu(OTf)$_2$]



Entry	Catalyst loading (%)	Yield (%)	ee (%)
1	10	91	99
2	1	91	99
3	0.1	72	99
4	0.01	49	48

[a] Experimental conditions: CH_2Cl_2, 0 °C, 16 h. The product was isolated by chromatography. Chiral HPLC was used to determine the ee values.

As a second test reaction we investigated the direct α-amination of α-substituted β-ketoesters with azodicarboxylates. This reaction is of interest for the synthesis of β-hydroxy-α-amino acids, and an efficient copper(II)-bisoxazoline catalyzed version has been reported very recently by Jørgensen and co-workers.[14] High yields and excellent enantioselectivities were observed using 2,2-bis[(4-phenyl)oxazolinyl]propane [Ph-BOX] as ancillary ligand. Originally performed in the presence of 10 mol% of catalyst, the reaction proceeds with catalyst loadings of 0.2–0.5 mol% without loss in selectivity. Only further reduction of the catalyst loading leads to a significant drop in the stereoselectivity of the transformation.

Using 10 mol% of the tripodal system [(Ph-trisox)Cu(OTf)$_2$], an enantiomeric excess of 99% (91% yield) was observed for the reaction of ethyl-2-acetylpropionate with dibenzylazodicarboxylate performed at 0 °C in the air (Table 2). Decreasing the amount of catalyst to 0.1 mol% did not affect yield and enantioselectivity (99% ee). However, further reduction of the catalyst loading by a factor of 10 led to a significant decrease in enantioselectivity for this reaction (entry 4, Table 2) and therefore the influence of the third oxazoline donor is less pronounced than for the Mannich reaction.

In conclusion, we have shown that C_3-symmetric trisoxazolines form highly efficient enantioselective Cu^{II} Lewis acid catalysts which are based on the concept of a *stereoelectronic hemilability* of the divalent copper. In direct comparison with the analogous bisoxazoline systems they have proved to be more efficient in the enantioselective α-amination as well as the enantioselective Mannich reaction of prochiral *β*-ketoesters.

We thank the Deutsche Forschungsgemeinschaft (SFB 623), the CNRS (France) and the EU (RTN-Network AC3S, PDF-grant for B.S.) for financial support.

Notes and references

‡ *Crystal data* for [Cu^{II}(^{i}Pr-trisox)(κ^2-*O,O′*-MeCOCHCOOEt)]$^+$(BF_4^-) (**1a**): $C_{27}H_{44}BCuF_4N_3O_6$, M = 657.00, orthorhombic, a = 9.5673(5), b = 11.3995(7), c = 28.6673(16) Å, V = 3126.5(3) Å^3, T = 100(2) K, space group $P2_12_12_1$ (no. 19), Z = 4, μ(Mo-Kα) = 1.396 mm^{-1}, 18621 reflections measured, 5535 unique (Rint = 0.063), $wR2$ (all data) = 0.092, R_1 = 0.041 [4634 reflections with $I > 2\sigma(I)$]. *Crystal data* for [Cu^{II}(^{i}Pr-trisox)(κ^2-*O,O′*-MeCOCHCOOEt)]$^+$(ClO_4^-) (**1b**): $C_{27}H_{44}ClCuN_3O_{10}$, M = 669.64, orthorhombic, a = 9.5398(8), b = 11.5517(9), c = 28.674(2), V = 3159.9(4) Å^3, T = 100(2) K, space group $P2_12_12_1$ (no. 19), Z = 4, μ(Mo-Kα) = 0.833 mm^{-1}, 18461 reflections measured, 5589 unique (Rint = 0.070), $wR2$ (all data) = 0.113, R_1 = 0.050 [4503 reflections with $I > 2\sigma(I)$]. CCDC 277609 and 277610. See http://dx.doi.org/10.1039/b509571a for crystallographic data in CIF or other electronic format.

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