CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200701085

Stereochemical Consequences of Threefold Symmetry in Asymmetric Catalysis: Distorting C_3 Chiral 1,1,1-Tris(oxazolinyl)ethanes ("Trisox") in Cu^{II} Lewis Acid Catalysts

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

Dedicated to Professor Christina Moberg on the occasion of her 60th birthday

Abstract: The underlying conceptual differences in exploiting two- and threefold rotational symmetry in the design of chiral ligands for asymmetric catalysis have been addressed in a comparative study of the catalytic performance of bisoxazoline (BOX) and tris(oxazolinyl)ethanes (trisox) containing copper(II) Lewis acid catalysts. The differences become apparent in constructing new catalysts by systematically "deforming" the stereodirecting ligand by inverting chiral centres or replacing chiral by achiral oxazolines. The catalytic α-amination of ethyl 2-methylacetoacetate with dibenzyl azodicaboxylate, which occurs with high enantioselectivity for both Ph_2-BOX and Ph_3-trisox copper catalysts, has been employed as the test reaction. In the trisox–copper complex $[Cu^{II}(i Pr_3$-trisox)(κ^2-*O*,*O*′-MeCOCHCOOEt)]$^+$ $[BF_4]^-$ (**1**), which was characterised by X-ray diffraction, two of the oxazoline groups are coordinated to the central copper atom, whilst the third oxazoline unit is dangling with the N-donor pointing away from the metal centre. A similar arrangement is found for the stereochemically "mixed" C_1-trisox complex $[Cu^{II}\{(Ph_3$-trisox(*R*,*S*,*S*)$\}$(κ^2-*O*,*O*′-MeCOCHCOOEt)$(H_2O)]^+$ $[ClO_4]^-$ (**2**), in which the phenyl substituents adopt a first coordination sphere *meso* arrangement. The almost identical selectivity of the Ph_3-trisox-(*R*,*R*,*R*)- and Ph_2-BOX(*R*,*R*)-derived catalysts is as expected from the proposed model of the active catalyst based on a partially decoordinated podand. The behaviour of the "desymmetrised" trisox–Cu catalysts may be rationalised in terms of a general steady-state kinetic model for the three possible active bisoxazoline–copper species, which are expected to be in rapid exchange with each other in solution. This applies to both the trisox derivatives with stereochemically inverted and achiral oxazoline rings. The study underscores previous observations of superior performance of the catalysts bearing C_3-chiral stereodirecting ligands as compared to systems of lower symmetry.

Keywords: asymmetric catalysis · chirality · copper · threefold symmetry · trisoxazolines

Introduction

Bisoxazoline (BOX) ligands have been extensively applied in asymmetric Cu^{II} Lewis acid catalysis for a wide variety of C–C and C–heteroatom coupling reactions.[1–3] The key features that render oxazoline units "privileged" structural elements in ligand design for enantioselective catalysis are their rigidity and quasi-planarity as well as facile accessibility by condensation of amino alcohols with carboxylic acid derivatives.[4] Upon coordination of the oxazoline ring through the N atom, the stereodirecting substituents are situated in close proximity to the metal centre and thus directly control the active space available for the substrate(s).

The reduction of the generally high catalyst loadings with BOX–Cu and related systems, which are due to the kinetic

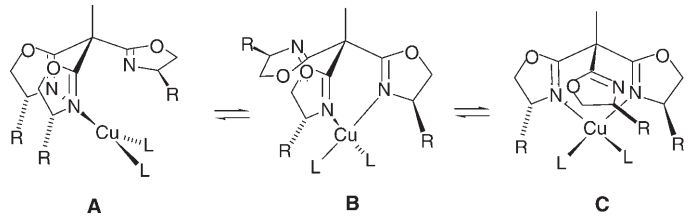
[a] C. Foltz, Dr. B. Stecker, Dr. G. Marconi, Prof. Dr. H. Wadepohl, Prof. Dr. L. H. Gade
Anorganisch-Chemisches Institut
Universität Heidelberg
Im Neuenheimer Feld 270, 69120 Heidelberg (Germany)
Fax.: (+49) 6221-545609
E-mail: lutz.gade@uni-hd.de

[b] Dr. S. Bellemin-Laponnaz
Institut de Chimie, UMR 7177
Institut Le Bel, Université Louis Pasteur
4 rue Blaise Pascal, 67000 Strasbourg (France)
Fax: (+33)
E-mail: bellemin@chimie.u-strasbg.fr

Supporting information for this article is available on the WWW under http://www.chemistry.org or from the author.

WILEY InterScience DISCOVER SOMETHING GREAT
© 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

lability of copper(II), has been attempted through the potential facial coordination of the metal centre by a chiral *tridentate* oxazoline ligand.[5] Using the C_3-chiral 1,1,1-tris(oxazolinyl)ethane ("trisox") ligand system,[6–8] the *resting state* of the copper complexes was expected to be stabilised due to this additional (presumably weak) ligation. This third potential oxazoline coordination reduces the Lewis acidity and thus deactivates the copper complexes as was shown in a theoretical study on BOX–Cu catalysts.[9] The transformation of the stabilised but inactive resting state into the active (17 electron Cu^{II}) species occurs by decoordination of an oxazoline unit induced by the strong dynamic Jahn–Teller effect of the d^9 metal centre. As a consequence of the threefold rotational symmetry of the system, all of the possible dicoordinated catalytically active species (**A**–**C**; Scheme 1)



Scheme 1. Equilibrium between the three symmetry-equivalent trisox isomers with the dicoordinate stereodirecting ligand.

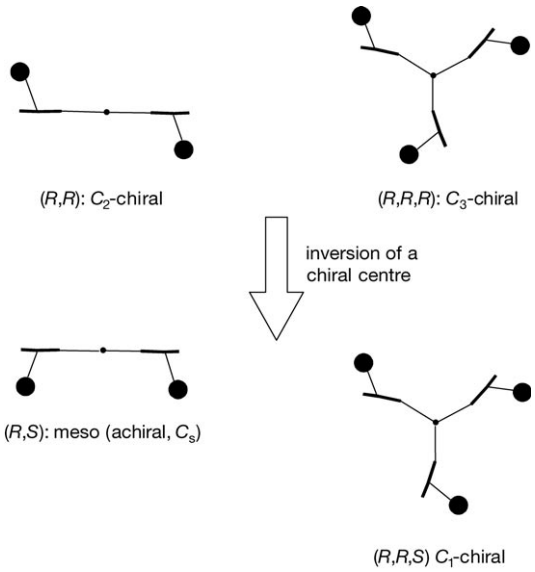
are equivalent.

In a first test of 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 first reported by Jørgensen et al. using chiral copper(II)–bisoxazoline catalysts.[11] Upon stepwise reduction of the catalyst loading by a factor of 10^3, from 10 to 0.01 mol% of catalyst, the enantioselectivity remained unchanged and the selectivity was found to be higher that for the corresponding BOX derivative.[7]

The comparison of the catalytic performance of BOX and trisox containing catalysts aside, there are *underlying conceptual differences* in exploiting two- and threefold rotational symmetry in the design of chiral ligands for asymmetric catalysis that have not been addressed previously. They become apparent in constructing new catalysts by systematically "deforming" the stereodirecting ligand and are delineated in this work. The observed effects are also pertinent to the design of "side-arm"-functionalised bisoxazolines in general.[12,13]

Inverting chiral centres in C_2- and C_3-symmetric stereodirecting tripod ligands: When it comes to the "mechanisms" of stereoselection with reagents or catalysts possessing rotational symmetry there is no specific difference between C_2- and C_3-symmetric systems.[14,15] For both systems the rotational symmetry may reduce the number of diastereomers involved in the sequence of transformation steps, but the mechanism of chiral induction (e.g., the preferential attack of a prochiral face of a substrate molecule) is expected to be based on the same principles.

However, from the point of view of ligand design there is a remarkable difference between C_2- and C_3-chiral podands that becomes apparent when one chiral element (e.g., a chiral centre) out of n ($n=2$, 3 respectively) is inverted, while leaving all other structural features unchanged. The rotational symmetry is thus destroyed. Whereas the inversion of a chiral centre in a C_2-symmetrical chelate ligand will generate a *meso*-structure, that is, an achiral ligand possessing mirror symmetry (C_s), the same process carried out for one of the three "ligand arms" of a C_3-chiral tripod will leave the system chiral and C_1 symmetrical (Scheme 2).

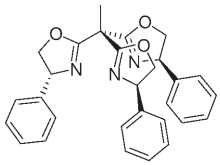


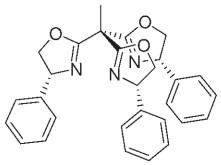
Scheme 2. Transformation of a C_2-chiral chelate (left) and a C_3-chiral podand upon inversion of the configuration at a chiral ligand "arm". Note the mapping of the C_2-symmetric system onto an isomorphic C_s-symmetric derivative.

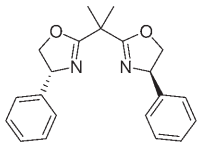
Regarding symmetry considerations alone, for the former, this particular situation is related to the isomorphism between the point groups C_2 and C_s (as well as C_i for non-podand structures), whilst no such isomorphism exists for C_3. It should be noted that the higher rotational symmetry in the C_3-symmetric system will lead to a greater degree of structural degeneracy than achieved for twofold symmetry, whereas deviations from it will necessarily give structures of greater complexity.

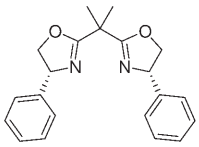
The modular nature of BOX and trisox ligands allows for a systematic investigation of the implications which the considerations put forward in this section have on a given catalytic reaction. The former may be assembled in two subsequent cyclisation steps from a malonic acid derivative, whilst the latter are synthesised by way of 2+1 coupling of a lithiated bisoxazoline with a 2-bromooxazoline derivative. The ligands employed in this work are depicted here.

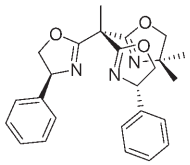
 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

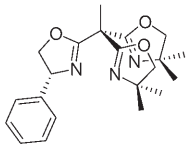

Ph$_3$-trisox(*R*,*R*,*R*) (*C*$_3$)

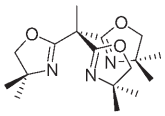

Ph$_3$-trisox(*R*,*S*,*S*) (*C*$_1$)

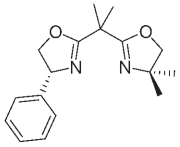

Ph$_2$-BOX(*R*,*R*) (*C*$_2$)

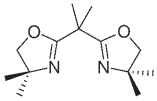

Ph$_2$-BOX(*R*,*S*) (*C*$_s$)

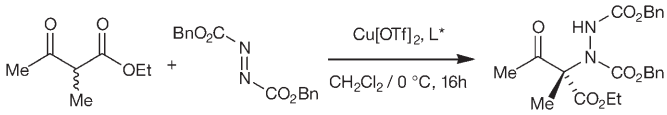

Ph$_2$-dm-trisox


Ph-dm$_2$-trisox


dm$_3$-trisox


Ph-dm-BOX


dm$_2$-BOX



Scheme 3. Direct Cu-catalysed α-amination of an α-substituted β-ketoester using dibenzyl-azodicaboxylate.

The effect of the inversion of a chiral centre, schematically shown in Scheme 2, is investigated by comparison of C_3-chiral Ph$_3$-trisox(*R*,*R*,*R*) with C_1-chiral Ph$_3$-trisox(*R*,*S*,*S*) and the pair of bisoxazoline ligands Ph$_2$-BOX(*R*,*R*) and Ph$_2$-BOX(*R*,*S*). In addition, the combination of chiral and achiral podand "arms" has been investigated in a comparative study of Ph$_2$-dm-trisox and Ph-dm$_2$-trisox with the bidentate Ph-dm-BOX, the latter representing a *minimal structure* in asymmetric oxazoline–copper(II) catalysis.

A test reaction in copper(II) Lewis acid catalysis: An enantioselective catalytic α-amination of carbonyl compounds using azodicaboxylates was first reported by Evans and Nelson who used a chiral bis(sulphonamide)magnesium complex as a catalyst.[16] This reaction is of interest for the synthesis of β-hydroxy-α-amino acids. An efficient copper(II)–bisoxazoline catalysed version, involving the direct α-amination of α-substituted β-ketoesters (Scheme 3), has been subsequently reported by Jørgensen and co-workers.[17]

High yields and excellent enantioselectivities have been observed by using 2,2-bis[(4-phenyl)oxazolinyl]propane ("Ph-BOX") as ancillary ligand. These characteristics were thought to facilitate the analysis of the stereochemical study, which is the objective of this work. We chose ethyl 2-methylacetoacetate as the substrate of the Cu-catalysed transformation.

Results and Discussion

Catalytic α-amination of ethyl 2-methylacetoacetate—the effect of the inversion of one of the chiral centres in BOX and trisox ligands: The test reaction introduced above was carried out using Ph$_3$-trisox(*R*,*R*,*R*) and Ph$_3$-trisox(*R*,*S*,*S*) as stereodirecting podands as well as the bisoxazolines Ph$_2$-BOX(*R*,*R*) and Ph$_2$-BOX(*R*,*S*). The results of the catalytic runs performed with 1 mol% of catalyst are summarised in Table 1.

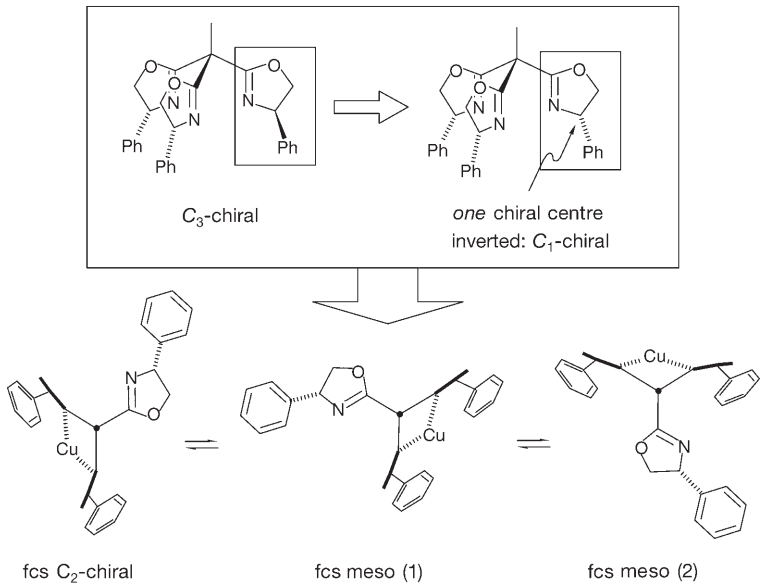
Table 1. α-Amination of ethyl 2-methylacetoacetate with dibenzyl azodicarboxylate with 1 mol% catalyst.

	Ph$_3$-trisox (*R*,*R*,*R*)	Ph$_2$-BOX (*R*,*R*)	Ph$_3$-trisox (*R*,*S*,*S*)	Ph$_2$-BOX (*R*,*S*)
ee [%]	99	98	-41	0
yield [%]	91	93	94	88

The selectivity of the transformation catalysed by Cu^{II} complexes of Ph$_3$-trisox(*R*,*R*,*R*) and the chelating Ph$_2$-BOX-(*R*,*R*) is almost identical. This is as expected from the proposed model of the *active* catalyst based on a partially decoordinated podand. In this model, the dangling oxazoline ring adopts a remote orientation (vide infra), and the trisox system therefore effectively coordinates like the corresponding bisoxazoline. Whereas the use of the *meso*-BOX ligand Ph$_2$-BOX(*R*,*S*) leads to a racemic product, the catalyst formed with the stereochemically mixed C_1-chiral podand Ph$_3$-trisox(*R*,*S*,*S*) gives the reaction product with −41% enantiomeric excess (*ee*). In this case the interplay of three isomeric forms of dicoordinated trisox has to be considered, all three being catalytically active. These three diastereomeric catalysts, which are thought to be involved, are depicted in Scheme 4.

It is instructive to regard the local environment (i.e., the arrangement of the coordinated oxazoline rings) at the metal centre more closely in the discussion of the effect, which the formal inversion of one of the chiral centres in Ph-trisox(*R*,*S*,*S*) has on the catalyst system. As is readily apparent, only one of the three isomers expected to be in equilibrium with each other contains the metal centre in an es-

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 4. Effect of the inversion of a chiral centre in Ph_3-trisox (top) leading to an equilibrium between three inequivalent dicoordinate species in solution (bottom). In two of these the arrangement of the oxazoline substituents at the rings coordinated to the metal centre correspond to a local *meso*-environment.

sentially C_2-chiral BOX-like environment to be found for the three symmetry-equivalent species of the catalyst derived from the C_3-chiral derivative Ph-trisox(*R*,*R*,*R*). This local molecular shape and, specifically, the effective local symmetry of a coordinated ligand at a metal centre will be designated as first-coordination-sphere symmetry (fcs-symmetry) and will play a key role in the following discussions.[18] The other two isomeric forms have a fcs *meso*-arrangement of the oxazoline substituents. Given the orientation and distance of the dangling ligand arm (vide infra), the catalytic behaviour of the latter two forms should be similar to that of the complex bearing the achiral ligand Ph-BOX-(*R*,*S*). It is evident that this line of argument requires support by detailed structural data obtained for suitable models for intermediates of the catalytic cycle with both the C_3- and the C_1-chiral tripods.

Crystal structure analyses of copper(II) acylenolate complexes bearing C_3- and C_1-chiral trisox ligands: The Lewis acid catalytic activity of the Cu^{II} centre is thought to play the key role in the activation of the β-ketoester and the formation of the reactive enolate intermediate. Such metal bonded acylenolates proved to be directly accessible by reaction of trisox–Cu complexes with ethyl 2-acetoacetate. Crystallisation from the reaction mixture using the isopropyl-substituted derivative *i*Pr_3-trisox, gave X-ray quality crystals of $[Cu^{II}(i\mathrm{Pr}_3\text{-trisox})(\kappa^2\text{-}O,O'\text{-MeCOCHCOOEt})]^+[BF_4]^-$ (**1**).[7]

A side-on view of the molecular structure of complex **1** is depicted in Figure 1, and selected bond lengths and angles are listed in Table 2. In the trisox–copper complex, containing the C_3-chiral ligand, two of the oxazoline groups are coordinated to the central copper atom (Cu–N bonds lengths: 1.973(3) and 1.985(3) Å), whilst the third oxazoline unit is dangling with the N-donor pointing away from the metal centre. From the view depicted in Figure 1 it is clear that the third oxazoline ring will have little influence upon the attack of an electrophile on the acylenolate (expected to approach from the left) and that the complex may therefore be effectively treated as a (substituted) bisoxazoline–Cu derivative. The notion will be of importance in the discussion of the catalytic performance of stereochemically different trisox–Cu derivatives in the subsequent sections of this work. The complex geometry of **1** is square pyramidal with a fluorine atom of the (weakly coor-

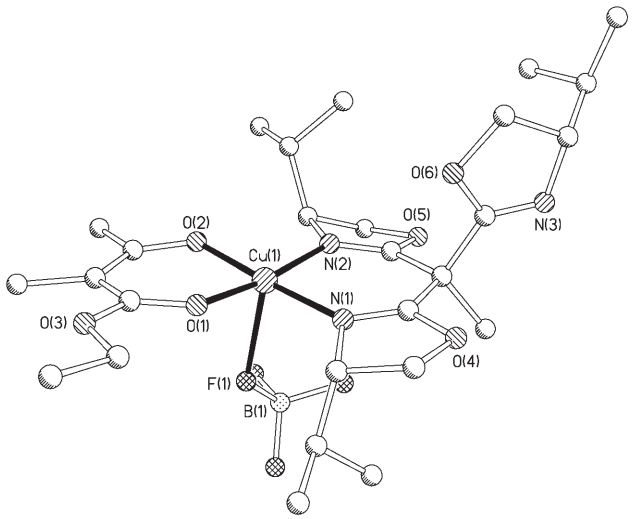


Figure 1. Molecular structure of the copper complex $[Cu^{II}(i\mathrm{Pr}_3\text{-trisox})(\kappa^2\text{-}O,O'\text{-MeCOCHCOOEt})]^+[BF_4]^-$ (**1**). The principal bond lengths and angles are given in Table 2. Hydrogen atoms omitted for clarity.

Table 2. Comparison of selected bond lengths [Å] and angles [°] in complexes **1** and **2**.

	Complex **1**	Complex **2**
Cu(1)–N(1)	1.973(3)	1.973(4)
Cu(1)–N(2)	1.985(3)	1.990(4)
Cu(1)–O(1)	1.939(3)	1.921(4)
Cu(1)–O(2)	1.891(3)	1.886(3)
Cu(1)–X[a]	2.376(2)	2.293(4)
N(1)-Cu(1)-N(2)	89.40(12)	87.42(16)
N(1)-Cu(1)-O(1)	91.05(12)	90.92(16)
N(1)-Cu(1)-O(2)	177.36(13)	177.36(16)
N(2)-Cu(1)-O(1)	171.12(12)	169.48(17)
N(2)-Cu(1)-O(2)	88.51(12)	90.12(16)
O(1)-Cu(1)-O(2)	90.77(12)	91.33(16)

[a] Atom in apical position.

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

dinating) BF_4^- counterion occupying the apical position (Cu(1)–F(1) 2.376(2) Å).

It has also been possible to crystallise the stereochemically "mixed" C_1-trisox complex $[Cu^{II}\{(Ph_3\text{-trisox}(R,S,S)\}(\kappa^2\text{-}O,O'\text{-MeCOCHCOOEt})(H_2O)]^+[ClO_4]^-$ (**2**) by a similar reaction of [Ph_3-trisox(*R*,*S*,*S*)–Cu] with the deprotonated β-ketoester. In complex **2**, as in complex **1**, the trisox ligand adopts bidentate coordination (Cu–N bonds lengths: 1.976(3) and 1.989(3) Å), the third oxazoline unit pointing away from the coordinated oxazoline rings and thus also generating an effective bisoxazoline copper system (Figure 2).

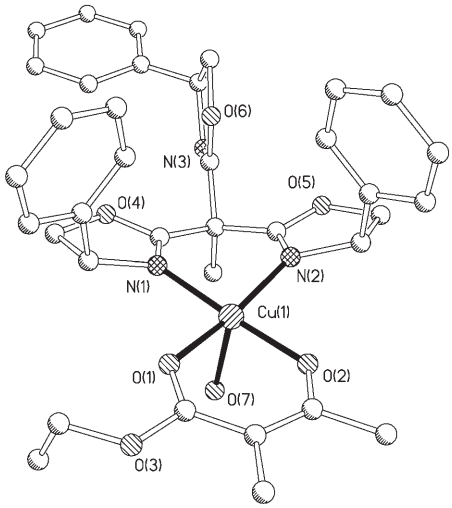


Figure 2. Molecular structure of the copper complex $[Cu^{II}(Ph_3\text{-trisox}(R,S,S))(\kappa^2\text{-}O,O'\text{-MeCOCHCOOEt})(H_2O)]^+[ClO_4]^-$ (**2**). The counterion is omitted for clarity. The principal bond lengths and angles are given in Table 2. Hydrogen atoms omitted for clarity.

As delineated above, three stereochemically distinct ways of coordination of the trisox ligand are to be expected: one leading to an fcs C_2-symmetric species and two representing fcs achiral *meso* species (Scheme 4). One of the two diastereomeric species with an fcs *meso* arrangement of the coordinated bisoxazoline unit crystallised with the phenyl substituents of the coordinated oxazoline units located on the same side (with respect to the CuN_2O_2 plane) as the dangling free oxazoline ring. Similar to complex **1**, the coordination geometry is square pyramidal with an oxygen atom of a water molecule occupying the apical position (Cu(1)–O(7) 2.293(4) Å).

Catalytic α-amination of ethyl 2-methylacetoacetate. A steady-state kinetic model for the behaviour of the stereochemically mixed Ph_3-trisox(*R*,*S*,*S*)–Cu catalyst: As pointed out above, only one of the three isomers of the Ph_3-trisox(*R*,*S*,*S*)–Cu catalyst, which are expected to be in equilibrium with each other, contains the metal centre in the fcs C_2-chiral BOX-like environment, whilst the other two isomeric forms have an fcs *meso*-arrangement of the oxazoline substituents. To understand the observed enantiomeric excess for the catalytic α-amination of ethyl 2-methylacetoacetate of 41%, the ratio of these isomeric species as well as their relative catalytic activity needs to be established. The conversion curves of the Cu-catalysed C–N coupling reaction (under the standard catalytic conditions of 1.0 mol% catalyst loading) for the four catalysts bearing Ph_3-trisox(*R*,*R*,*R*), Ph_3-trisox(*R*,*S*,*S*) as well as Ph_2-BOX(*R*,*R*) and Ph_2-BOX(*R*,*S*) as stereodirecting ligands, are depicted in Figure 3.

Whereas the Ph_2-BOX(*R*,*R*) derivative displays the highest activity (first-order rate constant derived from an exponential fitting analysis of the conversion curve: k_{RR} = 2.484 h^{-1}), the corresponding *meso*-system (Ph_2-BOX(*R*,*S*)) proved to be the least active catalyst (k_{RS} = 0.756 h^{-1}). Since it is thought that the stereodirecting ligand in the *active* trisox–copper catalyst is actually dicoordinate and thus effectively corresponds to the BOX analogues, the behaviour of both the homo and heterochiral systems should be explicable in reasonable approximation in terms of these data. The copper(II) catalyst bearing the C_3-chiral trisox ligand Ph_3-trisox(*R*,*R*,*R*) possesses an activity (k_{RRR} = 1.638 h^{-1}) that is close to that of the C_2-chiral bisoxazoline, whilst the

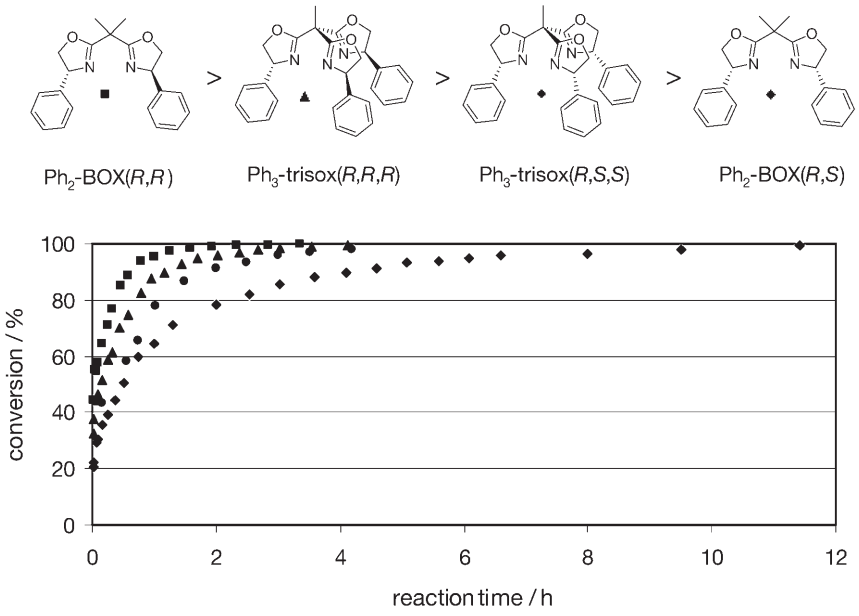


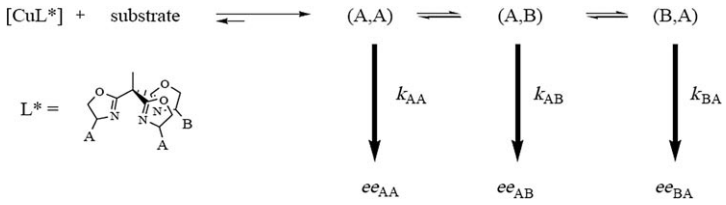
Figure 3. Conversion curves of the Cu-catalysed C-N coupling reaction (1.0 mol% catalyst loading) for the four catalysts bearing Ph_3-trisox(*R*,*R*,*R*), Ph_3-trisox(*R*,*S*,*S*) as well as Ph_2-BOX(*R*,*R*) and Ph_2-BOX(*R*,*S*) as stereodirecting ligands.

© 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

activity of the catalytic system based on the heterochiral tripod lies between this value and the conversion rate of the *meso*-BOX catalyst ($k_{RSS}=1.074\ h^{-1}$). This last observation may indeed be an indication that both the fcs C_2-symmetric chiral isomer as well as the two *meso* forms may play a role in the transformation catalysed by Ph_3-trisox(*R*,*S*,*S*)–Cu.

The behaviour of the "desymmetrised" trisox–Cu catalysts may be rationalised in terms of a general steady-state kinetic model for the three possible active bisoxazoline–copper species that are expected to be in rapid exchange with each other in solution. This assumption is based on the well-established substitutional lability of divalent copper complexes.

Given is a trisoxazoline (trisox-derivative) in which two of the heterocycles bear a substituent A, whilst the third substituent B is assumed to be different. This leads to three dicoordinate species in solution, in which the Cu atom is either coordinated by two equally substituted oxazoline rings (A,A) or by a non-equal combination, (A,B) or (B,A). The two last possibilities are diastereomers; however, since they differ only in terms of the orientation of the third, dangling oxazoline ring which, moreover, is pointing away from the active centre, they may be assumed in reasonable approximation to be equivalent (both in terms of activity and stability). All three catalyst isomers will transform the substrate to a given product P with enantioselectivities of ee_{AA}, ee_{AB} and ee_{BA} ($ee_{AB} \approx ee_{BA}$) as shown in Scheme 5.



Scheme 5.

Designating two enantiomers of the product as P_R and P_S, it is possible to express the rate of formation of these two products as a function of the different rate constants, selectivities and the proportions x_R and x_S of (A,A) that give P_R or P_S, respectively, as well as the proportions $x_{R'}$ and $x_{S'}$ of (A,B) and (B,A) that give P_R or P_S, respectively, with P_R being assumed to be the major product [Eqs. (1) and (2)]:

$$\frac{d[P_R]}{dt} = x_R k_{AA}[(A,A)] + 2\,x_{R'} k_{AB}[A,B] \quad (1)$$

$$\frac{d[P_S]}{dt} = x_S k_{AA}[(A,A)] + 2\,x_{S'} k_{AB}[A,B] \quad (2)$$

In this simplified form, the properties of (A,B) and (B,A) are treated as equal (for details, see Supporting Information). In that case, the ratio of the two rates of formation is given by Equation (3).

$$\frac{d[P_R]}{d[P_S]} = \frac{x_R k_{AA}[(A,A)] + 2\,x_{R'} k_{AB}[(A,B)]}{x_S k_{AA}[(A,A)] + 2\,x_{S'} k_{AB}[(A,B)]} \quad (3)$$

Assuming steady state conditions gives the following expression [Eq. (4)] for the observed *ee* values in which $C_{cat} = [(A,A)]+2[(A,B)]$ represents the total amount of catalyst present.

$$ee = \frac{(k_{AA}\{C_{cat}-2[(A,B)]\}ee_{AA} + 2\,k_{AB}ee_{AB}[(A,B)])}{(k_{AA}\{C_{cat}-2[(A,B)]\} + 2\,k_{AB}[(A,B)])} \quad (4)$$

This general equation, [Eq. (4)], may be directly applied to the case of the Ph_3-trisox(*R*,*S*,*S*)–Cu system presented above. In this case the "hetero-substituent" B is a stereochemically inverted A, that is, B = −A and the two species (A,B) and (B,A) possess the two *meso*-configurations. Consequently $ee_{A,-A} \approx ee_{-A,A} \approx 0$, which gives the simplified expression in Equation (5).

$$ee = \frac{(k_{AA}\{C_{cat}-2[(A,-A)]\}ee_{AA})}{(k_{AA}\{C_{cat}-2[(A,-A)]\} + 2\,k_{A-A}[(A,-A)])} \quad (5)$$

To apply this equation, the pseudo-first-order rate constants derived from the conversion curves discussed above for the different BOX and trisox copper systems may be employed. It is assumed that the (A,−A) and (−A,A) active species from the trisox-based catalyst have approximately the same activity as the *meso*-(A,−A)-BOX/Cu catalyst and that the (A,A) active (trisox-derived) species has the same activity as the (A,A)-BOX/Cu catalyst. Assuming furthermore, that the *meso* and C_2-symmetric active species give the same enantioselectivities as their corresponding BOX/Cu catalysts, as implied by the data reported in the previous section, the relative concentrations and activities of the components of the Ph_3-trisox(*R*,*S*,*S*)-Cu may be estimated.

In a first step the concentration of the *meso*-species, [(A,−A)] is calculated [Eq. (6)] by re-arranging Equation (5).

$$[(A,-A)] = {}^1\!/_2\ \frac{\{k_{AA}(ee_{AA}-ee)}{2\{ee\,k_{A-A} + k_{AA}(ee_{AA}-ee)\}}\,C_{cat} \quad (6)$$

Using the experimental value of $ee = 41 \pm 2\,\%$ and the catalyst concentration C_{cat} of 1.5 μmol in Equation (6) (as well as $k_{A-A} = k_{RS} = 0.756$, $k_{AA} = k_{RR} = 2.484\ h^{-1}$ and $ee_{AA} = ee_{RR} = 0.98$ derived from the two BOX-systems) gives a concentration of 0.615 ± 0.005 μmol for each *meso* diastereomer of the Ph_3-trisox(*R*,*S*,*S*)–Cu catalyst and of 0.270 ± 0.005 μmol for the C_2-symmetric active species. This shows that the amount of each *meso* species is significantly greater than the proportion of the C_2-symmetric species and that the former therefore possesses slightly greater stability ($\Delta G < 1\ kcal\,mol^{-1}$). The greater amount of the *meso* isomers in the equilibrium of exchanging species could explain the observed preferred crystallisation of a catalyst–substrate intermediate with the (*R*,*S*,*S*)-trisox in which the two oxazoline units adopt a *heterochiral* relationship as demonstrated above. The domination

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

of the fcs *meso* active species also explains the magnitude of the pseudo-first order rate constant for the stereoselective α-amination found for the C_1-symmetric tripod. This is closer to that observed for the Ph_2-BOX(*R*,*S*)–Cu than to the one of the C_2-symmetric bisoxazoline ($k_{RSS}=1.074$, $k_{RS}=0.756$ and $k_{RR}=2.484\ h^{-1}$).

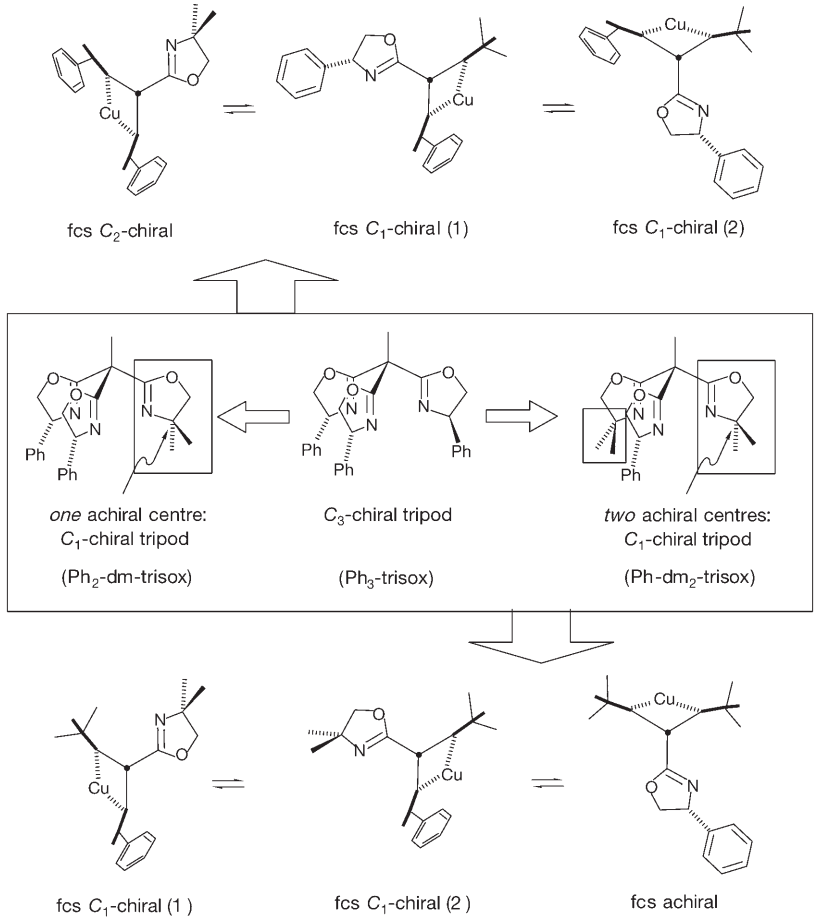
Combination of chiral and achiral oxazolines—synthesis and catalysis with trisox-ligands containing achiral ligating "arms": The inversion of one chiral centre in a C_3-chiral tripod is one way of systematically distorting such a threefold symmetric species with the consequences for Cu^{II} Lewis acid catalysis discussed above. Another such operation is the successive replacement of chirally substituted oxazoline rings in a trisox system by achiral oxazolines. This transformation of the threefold symmetric chiral ligand Ph_3-trisox is represented in Scheme 6. Exchanging one 4-phenyloxazolin-2-yl unit for a 4,4′-dimethyloxazolin-2-yl unit gives the non-symmetrical tripod Ph_2-dm-trisox and upon a similar replacement of a second oxazolinyl ring one arrives at Ph-dm_2-trisox.

Scheme 6 also shows the expected equilibria between the three diastereomeric dicoordinate Cu complexes that have different sets of fcs symmetries[18] for the two nonsymmetrical tripodal ligands. Whilst the Ph_2-dm-trisox–Cu system is composed of one isomer with fcs C_2 symmetry and two which are fcs chiral but unsymmetrical, the proposed equilibrium of the catalytic species derived from Ph-dm_2-trisox comprises one fcs achiral and two unsymmetrical chiral species.

The results of the α-amination of ethyl 2-methylacetoacetate with dibenzyl azodicarboxylate with 1 mol% catalyst using the Cu^{II} complexes of Ph_2-BOX(*R*,*R*), Ph_2-dm-trisox-(*S*,*S*), Ph-dm_2-trisox(*R*) and Ph-dm-BOX(*R*) are summarised in Table 3.

Table 3. α-Amination of ethyl 2-methylacetoacetate with dibenzyl azodicarboxylate with 1.0 mol% catalyst.

	Ph_2-BOX (*R*,*R*)	Ph_2-dm- trisox (*S*,*S*)	Ph-dm_2- trisox (*R*)	Ph-dm-BOX (*R*)
ee [%]	98	-97	82	83
yield [%]	93	90	73	85



Scheme 6. Successive replacement of chirally substituted oxazoline rings in a trisox system by achiral oxazolines: Exchanging one 4-phenyloxazolin-2-yl unit by a 4,4′-dimethyloxazolin-2-yl unit gives the non-symmetrical tripod Ph_2-dm-trisox and upon a similar replacement of a second oxazolinyl ring one arrives at Ph-dm_2-trisox. Both non-symmetrical trisox–Cu systems give rise to three isomeric dicoordinate isomers (not accounting for different orientations of ligands in the "active" coordination sites).

It is notable that the replacement of one 4-phenyloxazolin-2-yl by a 4,4′-dimethyloxazolin-2-yl unit barely affects the catalyst performance (97% *ee*, 90% yield) and even the introduction of the second 4,4′-dimethyloxazolin-2-yl ring within the trisox system only leads to a reduction of the selectivity of this particular transformation to 82% *ee* (1 mol% of catalyst) and a reduced yield due to a decreased catalyst activity. Remarkably, the bisoxazoline–copper catalyst that bears Ph-dm-BOX as the stereodirecting ligand generates the C–N coupling product with an enantiomeric excess of 83% (88% *ee* for 10 mol% of catalyst!). This catalyst with the bidentate ligand, which only contains one chiral centre, may therefore be viewed as possessing the minimal catalyst structure for efficient stereoselective catalysis of this transformation.

The relative activities of the Cu^{II} Lewis acid catalysts bearing the bisoxazolines Ph_2-BOX, Ph-dm-BOX and dm_2-BOX as well as the trisoxazolines Ph_2-

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

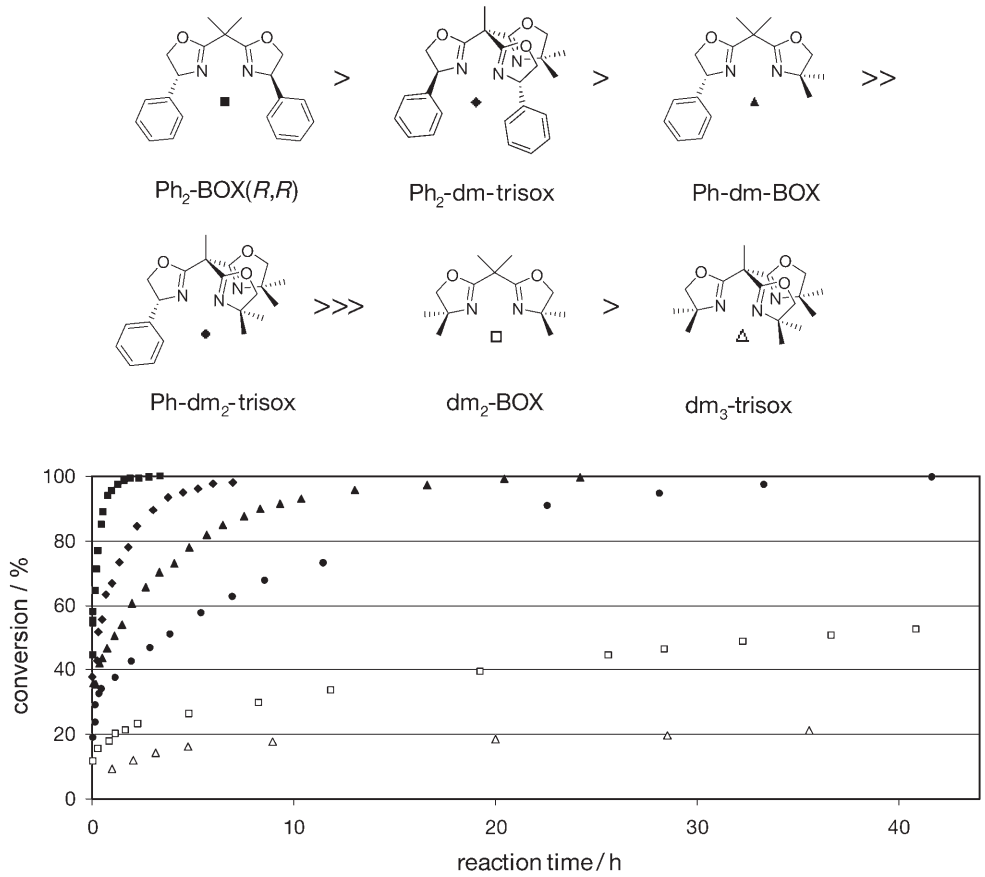


Figure 4. The conversion curves of the asymmetric C-N coupling under pseudo-first order conditions for the stereochemically "mixed" catalysts involving the bisoxazolines Ph_2-BOX, Ph-dm-BOX and dm_2-BOX as well as the trisoxazolines Ph_2-dm-trisox, Ph-dm_2-trisox and dm_3-trisox.

dm-trisox, Ph-dm_2-trisox and dm_3-trisox were established in a kinetic study of the asymmetric C–N coupling under pseudo-first-order conditions for the respective catalyst. The conversion curves are depicted in Figure 4 and display the general trend that the replacement of a 4-phenyloxazolin-2-yl by a 4,4′-dimethyloxazolin-2-yl unit leads to reduced activity.

In general, the ligands with two 4-phenyloxazolin-2-yl rings are more active than the ones with one 4-phenyloxazolin-2-yl unit. The catalysts with the achiral ligands dm_2-BOX and dm_3-trisox possess very low activity and only incomplete conversion of the substrates is observed even after more than 40 h reaction time. An exponential analysis of the conversion curves gives the pseudo-first-order rate constants k_{AA} and k_{AB} in Equation (4) (Table 4) and the relevant data for ee_{AA} and ee_{AB} for both systems are derived from the data listed in Table 3.

Calculation of the quantity of respective non-symmetrical (A,B) isomer from Equation (4) in the following rearranged form [Eqs. (7) and (8)] shows that all three isomers relevant in the exchange equilibrium are present in about equal amount (Table 5):

$$[(A,B)] = \frac{C_{cat} k_{AA} (ee_{AA} - ee)}{(2\,k_{AB}(ee - ee_{AB}) + 2\,k_{AA}(ee_{AA} - ee)} \qquad (7)$$

For Ph-dm_2-trisox–Cu, in which A is achiral and thus $ee_{AA} \approx 0$:

Table 4. Enantiomeric excesses and pseudo-first-order rate constants of the asymmetric amination of ethyl 2-methylacetoacetate with dibenzyl azodicarboxylate with the Cu^{II} Lewis acid catalysts.[a]

	Ph_2-BOX (*R*,*R*)	Ph_2-dm-trisox	Ph-dm-BOX	Ph-dm_2-trisox	dm_2-BOX	dm_3-trisox
ee [%]	98	-97	83	82	0	0
k [h^{-1}]	2.484	0.594	0.222	0.096	0.012	0.060

[a] Experimental conditions: The catalytic runs were carried out at 0 °C using 1 mol % catalyst (C_{cat} = 1.5 μmol) and a ratio of ligand/Cu = 1.2.

Table 5. Estimated composition of the non-symmetrical A_2B-trisox-copper(II) catalysts based on the steady state model of exchange between the diastereomers. The relative amounts of fcs C_2-symmetric species are given in bold and those for fcs achiral (including *meso*) species in italics.

		[(AA)] [%]	[(AB)]+[(BA)] [%]
Ph_3-trisox(*R*,*S*,*S*)	A = Ph(*S*) B = Ph(*R*)	**18 ± 0.5**	*2 × 41 ± 0.5*
Ph_2-dm-trisox	A = Ph B = dm	**56 ± 10**	2 × 22 ± 10
Ph-dm_2-trisox	A = dm B = Ph	*18.4 ± 8*	2 × 40.8 ± 8

© 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

$$[(A,B)] = \frac{C_{cat} k_{AA} ee}{2 k_{AB} ee_{AB} + 2 ee(k_{AA} - k_{AB})} \quad (8)$$

Therefore, the relatively high enantioselectivity of the catalysts bearing the Ph_2-dm-trisox and Ph-dm_2-trisox ligands is a consequence of the significantly greater activity of the species in which 4-phenyloxazolin-2-yl rings are coordinated to the metal centre as compared to for example, the fcs achiral catalytic species in which the Cu atom is coordinated through both dm-oxazolines in Ph-dm_2-trisox.

Conclusion and Outlook

The aim of this study was to shed some light onto the implications which the use of chiral tridentate podands may have in stereoselective catalysis as compared to the more established bidentate chelates. The different order of the rotational axis in symmetrical systems, whilst not affecting the principles of stereoselection by intermolecular interaction between substrate and catalyst, becomes apparent when the symmetry of the stereodirecting ligand is systematically reduced or modified. Here, the twofold rotational symmetry may in principle be mapped onto mirror-/centrosymmetry (as may play a role when chiral molecules adopt a conformation which renders their shape close to achiral), whilst such a scenario is not possible for chiral threefold symmetric systems.

Regarding only the systems bearing ligated tripods, it should be noted, that this study underscores previous observations of superior performance of the catalysts bearing C_3-chiral stereodirecting ligands as compared to systems of lower symmetry.[8] The simplified behaviour with regard to potential catalyst equilibria in solution along with the stereochemical non-ambiguity of the active catalytic species appear to play the principal underlying role in this trend. This may be considered in targeted catalyst screening processes.

Experimental Section

All manipulations, except those indicated, were carried out under an inert atmosphere of dry argon by using standard Schlenk techniques. Solvents were purified and dried by standard methods. Starting compounds monoethyl malonate,[19] (4*R*)-2-bromo-4-phenyloxazoline,[20] 1,1-bis[(4*S*)-4-phenyloxazolin-2-yl]ethane,[21] 2-bromo-4,4-dimethyloxazoline,[6a] 1,1-bis[(4,4-dimethyloxazolin-2-yl]ethane[6a] (dm_2-BOX), 1,1,1-tris[(4*R*)-4-phenyloxazolin-2-yl]ethane[8] (Ph_3-trisox(*R*,*R*,*R*)) and 1,1,1-tris[4,4-dimethyloxazolin-2-yl]ethane[6a] (dm_3-trisox) were synthesised according to literature procedures. Ethyl 2-methylacetoacetate and dodecane were commercially available and were purified by bulb to bulb distillation. All other reagents were commercially available and were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX 200 spectrometer at 200 and 50 MHz, respectively, on a Bruker Avance 300 spectrometer at 300 and 75 MHz, respectively, on a Bruker Avance II 400 spectrometer at 400 and 100 MHz, respectively, and on a Bruker Avance III 600 spectrometer at 600 and 150 MHz, respectively, and were referenced to the residual proton solvent peak. IR spectra were obtained on a Perkin–Elmer 1600 FT-IR spectrometer. Mass spectra and elemental analysis were recorded by the analytical services of Heidelberg University.

Preparation of the trisox ligands and their precursors

2,2-Dimethyl malonic acid ethyl monoester N-(2-hydroxy-1,1-dimethylethyl) monoamide: dicyclohexylcarbodiimide (DCC) (8.3 g, 40.1 mmol) and 1-hydroxy.benzotriazole (HOBt) (5.4 g, 40.1 mmol) were added under argon flow to a solution of monoethyl malonate (5.84 g, 36.5 mmol) in CH_2Cl_2 (250 mL). After 2 h of stirring, 2-amino-2-methylpropan-1-ol (3.6 g, 40.1 mmol) was added and the solution was stirred at room temperature (RT) for 3 days. The reaction mixture was filtered through Celite to remove the dicyclohexylurea (DCU) formed and washed with CH_2Cl_2 (4×80 mL). The organic solution was washed with an aqueous solution of $KHCO_3$ 10% (100 mL), with H_2O (100 mL) and with brine (100 mL) and was then dried over Na_2SO_4. After evaporation of the solvent the crude product was purified by flash chromatography (hexane/EtOAc, 50:50) to give the product as a colourless oil (3.8 g, 45% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ=1.26 (m, 9H; $CH_{3(ethyl)}$, $CH_{3(future\ oxa)}$), 1.41 (s, 6H; $CH_{3(bridge)}$), 3.56 (s, 2H; $CH_{2(future\ oxa)}$), 4.18 (q, J=7.1 Hz, 2H; $CH_{2(ethyl)}$), 4.33 (brs, 1H; O*H*), 6.48 ppm (brs, 1H; N*H*); ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz): δ=14.0 ($CH_{3(ethyl)}$), 23.7 ($CH_{3(bridge)}$), 24.5 (CH_3), 50.0 ($C_{quat(bridge)}$), 56.0 (C_{quat}), 61.7 ($CH_{2(ethyl)}$), 70.3 (CH_2), 172.7 (NCO), 175.1 ppm (OCO); MS (FAB): *m/z* (%): 200.1 (12) [M^+−CH_2OH], 214.1 (6) [M^+−OH], 232.1 (100) [M^++H]; HRMS (FAB): *m/z*: calcd for $C_{11}H_{22}NO_4$ ([M^++H]): 232.1549; found: 232.1559.

N-((R)-2-Hydroxy-1-phenylethyl)-N′-(2-hydroxy-1,1-dimethylethyl)dimethylmalonamide: (*R*)-Phenylglycinol (730 mg, 5.3 mmol) and 2,2-dimethyl malonic acid ethyl monoester *N*-(2-hydroxy-1,1-dimethylethyl) monoamide (1.23 g, 5.3 mmol) were heated at 110°C for 3 h in the presence of catalytic amount of NaH. After evaporation of the ethanol formed the crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 95/5) to give the product as a colourless oil (943 mg, 55% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ=1.22 (s, 3H; $CH_{3(future\ oxa)}$), 1.23 (s, 3H; CH_3), 1.44 (s, 3H; $CH_{3(bridge)}$), 1.46 (s, 3H; $CH_{3(bridge)}$), 3.48 (d, J=11.5 Hz, 1H; $CH_{2(methyl\ side)}$), 3.63 (d, J=11.5 Hz, 1H; $CH_{2(methyl\ side)}$), 3.79 (ddd, J=1.0 Hz, J=4.0 Hz, J=11.5 Hz, 1H; $CH_{2(phenyl\ side)}$), 3.88 (dd, J=6.1 Hz, J=11.5 Hz, 1H; $CH_{2(phenyl\ side)}$), 5.03 (ddd, J=4.1 Hz, J=6.5 Hz, J=7.0 Hz, 1H; $CH_{(phenyl\ side)}$), 6.51 (brs, 1H; $NH_{(methyl\ side)}$), 7.11 (s, J=7.3 Hz, 1H; $NH_{(phenyl\ side)}$) 7.23–7.35 ppm (m, 5H; $CH_{(arom)}$); ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz): δ=23.7, 23.8 ($CH_{3(bridge)}$) 24.0, 24.5 (CH_3), 50.0 ($C_{quat(bridge)}$), 55.7 ($C_{quat(methyl\ side)}$), 55.9 (*C*H), 66.2 ($CH_{2(phenyl\ side)}$), 69.6 ($CH_{2(methyl\ side)}$), 126.4, 128.0, 128.9 ($CH_{(arom)}$), 138.7 ($C_{quat(arom)}$), 173.9, 174.0 ppm (*C*O); MS (FAB): *m/z* (%): 305.1 (36) [M^+−OH], 323.2 (100) [M^++H]; HRMS (FAB): *m/z*: calcd for $C_{17}H_{27}N_2O_4$ ([M^++H]) 323.1971; found: 323.2009

1-{(4R)-4-Phenyloxazolin-2-yl}-1-(4,4-dimethyloxazolin-2-yl)-1-methylethane[22] (Ph-dm-BOX): $SOCl_2$ (0.80 mL, 10.9 mmol) was added dropwise to a cooled solution (0°C) of *N*-{(*R*)-2-hydroxy-1-phenylethyl}-*N′*-(2-hydroxy-1,1-dimethylethyl)-dimethylmalonamide (737 mg, 2.29 mmol) in CH_2Cl_2 (150 mL). The reaction mixture was stirred overnight at ambient temperature, cooled to 0°C and quenched by addition of aqueous $NaHCO_3$ (65 mL). After an additional 5 min of stirring, the aqueous phase was separated and extracted with CH_2Cl_2 (3×70 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was evaporated to give 800 mg of the chlorinated compound. The colourless oil was used directly without further purification. A solution of the chlorinated product (800 mg, 2.23 mmol) and NaOH (223 mg, 5.58 mmol) in ethanol (125 mL) was heated to reflux for 3 h and then cooled to room temperature followed by evaporation of the solvent under reduced pressure. CH_2Cl_2 (50 mL) and a saturated aqueous solution of NH_4Cl (40 mL) was added to the resulting crude product, the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was evaporated to give the oily yellowish crude product. Purification by flash chromatography (hexane/EtOAc, 50:50) gave the product as a colourless oil (391 mg, 60% yield). ^{1}H NMR ($CDCl_3$, 600 MHz): δ=1.30 (s, 6H; $CH_{3(oxa)}$), 1.58 (s, 3H; $CH_{3(bridge)}$), 1.60 (s, 3H; $CH_{3(bridge)}$), 3.97 (s, 2H; $CH_{2(methyl\ oxa)}$), 4.11 (pseudo-t, J=8.0 Hz, 1H; $CH_{2(phenyl\ oxa)}$), 4.62 (dd, J=8.4 Hz, J=10.1 Hz, 1H; $CH_{2(phenyl\ oxa)}$), 5.19 (dd, J=7.6 Hz, J=10.1 Hz, 1H; $CH_{(oxa)}$), 7.23–

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

7.35 ppm (m, 5H; C$H_{(arom)}$); ^{13}C {^{1}H} NMR ($CDCl_3$, 150 MHz): δ = 24.4, 24.5 (C$H_{3(bridge)}$) 28.0, 28.1 (C$H_{3(oxa)}$), 38.5 ($C_{quat(bridge)}$), 67.1 ($C_{quat(methyloxa)}$), 69.4 (CH), 75.5 (C$H_{2(phenyloxa)}$), 79.4 (C$H_{2(methyloxa)}$), 126.6, 127.5, 128.6 (C$H_{(arom)}$), 142.5 ($C_{quat(arom)}$), 167.4 (N$CO_{(methyloxa)}$), 170.5 ppm (N$CO_{(phenyloxa)}$); HRMS (FAB): *m/z*: calcd for $C_{17}H_{23}N_2O_2$ ([M^++H]) 287.1760; found: 287.1757.

2,2-Dimethyl malonic acid ethyl monoester N-((S)-2-hydroxy-1-phenylethyl) monoamide: DCC (9.3 g, 45 mmol) and HOBt (61 g, 45 mmol) were added under argon flow to a solution of monoethyl malonate (6.54 g, 41 mmol) in CH_2Cl_2 (250 mL). After 2 h of stirring, (*S*)-phenylglycinol (6.1 g, 45 mmol) was added and the solution was stirred at room temperature for 3 days. The reaction mixture was filtered through Celite to remove the DCU formed and washed with CH_2Cl_2 (4×100 mL). The organic solution was washed with an aqueous solution of $KHCO_3$ 10% (350 mL), H_2O (300 mL) and brine (300 mL) and was then dried over Na_2SO_4. Evaporation of the solvent gave the product as a white solid (9.8 g, 86% yield). The compound was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.31 (t, J = 7.1 Hz, 3H; C$H_{3(ethyl)}$), 1.52 (s, 3H; C$H_{3(bridge)}$), 1.53 (s, 3H; C$H_{3(bridge)}$), 2.56 (br s, 1H; OH), 3.91 (pseudo-t, J = 3.9 Hz, 2H; CH_2), 4.25 (q, J = 7.1 Hz, 2H; C$H_{2(ethyl)}$), 5.10 (m, 1H; CH), 7.25 (d, J = 6.3 Hz, 1H; NH), 7.31–7.35 (m, 3H; C$H_{(arom)}$), 7.39–7.42 ppm (m, 2H; C$H_{(arom)}$); ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz): δ = 13.9 (C$H_{3(ethyl)}$), 23.6, 23.8 (C$H_{3(bridge)}$), 49.9 ($C_{quat(bridge)}$), 55.9 (CH), 61.7 (C$H_{2(ethyl)}$), 66.5 (CH_2), 126.5, 127.8, 128.8 ($C_{(arom)}$), 138.9 ($C_{quat(arom)}$), 172.3 (OCO), 174.9 ppm (NCO); MS (FAB): *m/z* (%): 262.1 (11) [M^+−OH], 280.1 (100) [M^++H]; HRMS (FAB): *m/z*: calcd for $C_{15}H_{22}NO_4$ ([M^++H]): 280.1549; found: 280.1521.

N-((S)-2-Hydroxy-1-phenylethyl)-N′-((R)-2-hydroxy-1-phenylethyl)dimethylmalonamide: A solution of (*R*)-phenylglycinol (4.5 g, 32.5 mmol) and 2,2-dimethyl malonic acid ethyl monoester *N*-((*S*)-2-hydroxy-1-phenylethyl) monoamide (9.1 g, 32.5 mmol) in toluene (20 mL) was heated at 110°C for 2 days in the presence of a catalytic amount of NaH. The white precipitate obtained was filtered and washed with Et_2O (3× 40 mL). Evaporation of the solvents gave the product as a white solid (5 g, 42% yield). ^{1}H NMR ([D_6]DMSO, 200 MHz) δ 1.37 (s, 3H; C$H_{3(bridge)}$), 1.39 (s, 3H; C$H_{3(bridge)}$), 3.37 (br s, 1H; OH), 3.59 (pseudo-t, J = 5.0 Hz, 4H; CH_2), 4.89 (m, 2H; CH), 7.17–7.31 (m, 10H; C$H_{(arom)}$), 7.25 ppm (d, J = 7.8 Hz, 2H; NH); ^{13}C {^{1}H} NMR ([D_6]DMSO, 50 MHz): δ = 23.1, 24.1 (C$H_{3(bridge)}$), 49.4 ($C_{quat(bridge)}$), 55.4 (CH), 64.4 (CH_2), 126.6, 126.8, 128.0 ($C_{(arom)}$), 141.2 ($C_{quat(arom)}$), 172.7 (OCN); HRMS (FAB): *m/z*: calcd for $C_{21}H_{27}N_2O_4$ ([M^++H]): 371.1971; found: 371.1969.

1-[(4R)-4-Phenyloxazolin-2-yl]-1-((4S)-4-phenyloxazolin-2-yl)-1-methylethane[21] *(Ph$_2$-BOX(R,S))*: A solution of TsCl (5.4 g, 28.5 mmol) in CH_2Cl_2 (30 mL) was slowly added to an ice-cooled solution of *N*-[(*S*)-2-hydroxy-1-phenylethyl]-*N′*-((*R*)-2-hydroxy-1-phenylethyl)dimethylmalonamide (4.8 g, 13 mmol), triethylamine (14.5 mL, 104 mmol) and DMAP (160 mg, 1.3 mmol) in CH_2Cl_2 (200 mL). The mixture was warmed to room temperature, stirred for 10 days and washed with a saturated aqueous solution of NH_4Cl and brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo to give a dark brown oil. Purification by flash chromatography (hexane/EtOAc, 80:20) gave the desired product as a pale yellow oil (3.7 g, 86% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.73 (s, 3H; CH_3), 1.76 (s, 3H; CH_3), 4.22 (pseudo-t, J = 8.1 Hz, 2H; CH_2), 4.72 (dd, J = 8.4 Hz, J = 10.1 Hz, 2H; CH_2), 5.28 (dd, J = 7.7 Hz, J = 10.1 Hz, 2H; CH), 7.25–7.35 ppm (m, 10H; C$H_{(arom)}$); ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz): δ = 24.4, 24.7 (CH_3) 38.9 ($C_{quat(bridge)}$), 69.5 (CH), 75.5 (CH_2), 126.6, 127.6, 128.7 (C$H_{(arom)}$), 142.4 ($C_{quat(arom)}$), 170.3 (N$CO_{(phenyloxa)}$); HRMS (FAB): *m/z*: calcd for $C_{21}H_{23}N_2O_2$ ([M^++H]): 335.1760; found: 335.1771.

1,1-Di[(4S)-4-phenyloxazolin-2-yl]-1-(4,4-dimethyloxazolin-2-yl)ethane (Ph$_2$-dm-trisox): *t*BuLi (4.4 mL, 1.5 M in pentane, 6.6 mmol) was added dropwise to a solution of 1,1-bis[(4*S*)-4-phenyloxazolin-2-yl]ethane (1.8 g, 5.5 mmol) in THF (100 mL) at −78°C. The resulting red solution was stirred for an additional 30 min prior to the addition of 1.2 equiv of 2-bromo-4,4-dimethyloxazoline (1.17 mg, 6.6 mmol). The solution was allowed to warm slowly to room temperature for 12 h and then concentrated to remove the pentane and finally the Schlenk tube was sealed. The stirred solution was heated at 70°C for 4 days. The resulting orange solution was evaporated to dryness. The residue was redissolved in dichloromethane (100 mL) and washed with water (10 mL). The organic extract was dried over Na_2SO_4 and concentrated in vacuo to give an orange oil. Purification by flash chromatography (hexane/EtOAc, 95:5 to 50:50) gave the desired product as a white solid (906 mg, 39% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.13 (s, 3H; CH_3), 4.27–4.34 (m, 3H; CH_2), 4.79–4.85 (m, 3H; CH_2), 5.33–5.41 (m, 3H; CH), 7.25–7.42 ppm (m, 15H; C$H_{(arom)}$); ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz): δ = 21.7 (CH_3), 45.1 ((CH$_3$)C(oxa)$_3$), 69.6, 69.6, 69.6 (CH), 75.9, 75.9, 76.0 (CH_2), 126.8, 126.8, 126.9, 127.6, 127.6, 127.6, 128.6, 128.7, 128.7 (C$H_{(arom)}$), 142.0, 142.1 ($C_{quat(arom)}$), 165.9, 166.0, 166.1 ppm (NCO); elemental analysis calcd (%) $C_{25}H_{27}N_3O_3$: C 71.92, H 6.52, N 10.06; found: C 71.85, H 6.50, N 10.10; HRMS (FAB): *m/z*: calcd for $C_{25}H_{28}N_3O_3$ ([M^++H]) 418.2131; found: 418.2118.

1-[(4R)-4-phenyloxazolin-2-yl]-1,1-di[(4S)-4-phenyloxazolin-2-yl]ethane [Ph$_3$-trisox (R,S,S)]: *t*BuLi (2 mL, 1.5 M in pentane, 3 mmol) was added dropwise to a solution of 1,1-bis[(4*S*)-4-phenyloxazolin-2-yl]ethane (794 mg, 2.5 mmol) in THF (80 mL) at −78°C. The resulting orange solution was stirred for an additional 30 min prior to the addition of 1.2 equiv of (4*R*)-2-bromo-4-phenyloxazoline (673 mg, 3 mmol). The solution was allowed to warm slowly to room temperature for 12 h and then concentrated to remove the pentane and finally the Schlenk tube was sealed. The stirred solution was heated at 70°C for 5 days. The resulting orange solution was evaporated to dryness. The residue was redissolved in dichloromethane (100 mL) and washed with water (10 mL). The organic extract was dried over Na_2SO_4 and concentrated in vacuo to give an orange oil. Purification by flash chromatography (hexane/EtOAc, 50:50) gave the desired product as a pale orange solid (350 mg, 30% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.38 (s, 3H; C$H_{3(oxa)}$), 1.39 (s, 3H; C$H_{3(oxa)}$), 2.04 (s, 3H; C$H_{3(apical)}$), 4.11 (d, J = 8.0 Hz, 1H; C$H_{2(methyloxa)}$), 4.13 (d, J = 8.0 Hz, 1H; C$H_{2(methyloxa)}$), 4.26 (dd, J = 2.5 Hz, J = 8.0 Hz, 1H; C$H_{2(phenyloxa)}$), 4.28 (dd, J = 2.4 Hz, J = 7.9 Hz, 1H; C$H_{2(phenyloxa)}$), 4.78 (m, 2H; C$H_{2(phenyloxa)}$), 5.32 (dd, J = 7.7 Hz, J = 9.8 Hz, 1H; C$H_{(oxa)}$), 5.35 (dd, J = 7.6 Hz, J = 10.0 Hz, 1H; C$H_{(oxa)}$), 7.25–7.38 ppm (m, 5H; C$H_{(arom)}$); ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz): δ = 21.6 (C$H_{3(apical)}$) 27.9 (C$H_{3(oxa)}$), 44.8 ((CH$_3$)C(oxa)$_3$), 67.5 ($C_{quat(methyloxa)}$), 69.5 (CH), 75.8, 75.9 (C$H_{2(phenyloxa)}$), 79.8 (C$H_{2(methyloxa)}$), 126.8, 126.9, 127.4, 127.5, 128.5, 128.6 (C$H_{(arom)}$), 142.2 ($C_{quat(arom)}$), 163.0 (N$CO_{(methyloxa)}$), 166.2, 166.3 ppm (N$CO_{(phenyloxa)}$); HRMS (FAB): *m/z* (%): 466.2137 (100) [M^++H]; elemental analysis calcd (%) $C_{29}H_{27}N_3O_3$: C 74.82, H 5.85, N 9.03; found: C 74.80, H 5.81, N 9.10; HRMS (FAB): *m/z*: calcd for $C_{29}H_{28}N_3O_3$ ([M^++H)]): 466.2131; found: 466.2137.

1-[(4R)-4-phenyloxazolin-2-yl]-1,1-di(4,4-dimethyloxazolin-2-yl)ethane (Ph-dm$_2$-trisox): *t*BuLi (1.7 mL, 1.5 M in pentane, 2.6 mmol) was added dropwise to a solution of 1,1-bis[(4,4-dimethyloxazolin-2-yl]ethane (485 mg, 2.2 mmol) in THF (80 mL) at −78°C. The resulting bright yellow solution was stirred for an additional 30 min prior to the addition of 1.2 equiv of (4*R*)-2-bromo-4-phenyloxazoline (588 mg, 2.6 mmol). The solution was allowed to warm slowly to room temperature for 12 h and then concentrated to remove the pentane and finally the Schlenk tube was sealed. The stirred solution was heated at 75°C for 5 days. The resulting orange solution was evaporated to dryness. The residue was redissolved in dichloromethane (100 mL) and washed with water (10 mL). The organic extract was dried over Na_2SO_4 and concentrated in vacuo to give an orange oil. Purification by flash chromatography (hexane/EtOAc, 50:50) gave the desired product as an orange oil (360 mg, 45% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.30 (s, 3H; C$H_{3(oxa)}$), 1.31 (s, 9H; C$H_{3(oxa)}$), 1.91 (s, 3H; C$H_{3(apical)}$), 4.00 (d, J = 8.0 Hz, 1H; C$H_{2(methyloxa)}$), 4.01 (d, J = 8.0 Hz, 1H; C$H_{2(methyloxa)}$), 4.04 (d, J = 8.0 Hz, 1H; C$H_{2(methyloxa)}$), 4.05 (d, J = 8.0 Hz, 1H; C$H_{2(methyloxa)}$), 4.17 (pseudo-t, J = 8.1 Hz, 1H; C$H_{2(phenyloxa)}$), 4.69 (dd, J = 8.4 Hz, J = 10.1 Hz, 1H; C$H_{2(phenyloxa)}$), 5.24 (dd, J = 8.4 Hz, J = 10.1 Hz, 1H; C$H_{(oxa)}$), 7.23–7.34 ppm (m, 5H; C$H_{(arom)}$); ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz): δ = 21.8 (C$H_{3(apical)}$) 27.8 (C$H_{3(oxa)}$), 44.4 ((CH$_3$)C(oxa)$_3$), 67.3, 67.4 ($C_{quat(methyloxa)}$), 69.4 (CH), 75.8 (C$H_{2(phenyloxa)}$), 79.6, 79.7 (C$H_{2(methyloxa)}$), 126.8, 127.5, 128.5 (C$H_{(arom)}$), 142.4 ($C_{quat(arom)}$), 163.1, 163.2 (N$CO_{(methyloxa)}$), 166.4 (N$CO_{(phenyloxa)}$); HRMS (FAB): *m/z*: calcd for $C_{21}H_{28}N_3O_3$ ([M^++H]): 370.2131; found: 370.2135.

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Preparation of the copper complexes

[Cu^{II}(iPr$_3$-trisox)(κ^2-O,O′-MeCOCHCOOEt)]$^+$[BF$_4$]$^-$ (***1***): A mixture of $Cu[BF_4]_2{\cdot}6H_2O$ (44 mg; 0.116 mmol) and trisoxazoline (46 mg; 0.128 mmol) in THF (2 mL) was stirred for 3 h. 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 **1** as a dark green solid (69 mg; 91 %). Slow vapour diffusion of hexane into a solution of **1** in THF gave crystals suitable for X-ray analysis. Elemental analysis calcd (%) $C_{27}H_{44}BCuF_4N_3O_6$: C 49.36, H 6.75, N 6.40; found: C 48.52, H 6.66, N 6.76; MS (FAB+): 426.3 [$M^+-BF_4-C_7H_{11}O_3$].

[Cu(Ph$_3$-trisox(R,S,S))(κ^2-O,O′-MeCOCHCOOEt)][ClO$_4$] (***2***): A mixture of $Cu[ClO_4]_2{\cdot}6H_2O$ (54 mg; 0.143 mmol) and Ph$_3$-trisox(*R*,*S*,*S*) (70 mg; 0.150 mmol) in THF (2 mL) was stirred for 1.5 h. A $5.8{\cdot}10^{-2}$ M solution of diethylmethylmalonate/*t*BuOK (2.7 mL, 0.157 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 hexane (3×5 mL) and the green solid was dried under vacuum. 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 at −4 °C gave green crystals of compound **2** (57 mg; 52 %). Elemental analysis calcd (%) $C_{36}H_{40}ClCuN_3O_{11}$: C 54.75, H 5.11, N 5.32; found: C 54.39, H 5.09, N 5.36.

Procedure for the asymmetric α-amination reaction of ethyl 2-methylacetoacetate: A stock solution of $Cu[OTf]_2$ (8.1 mg, 22.5 μmol) and the ligand (27 μmol) in distilled CH_2Cl_2 (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. The β-ketoester (21.4 μL, 0.15 mmol) was added to each catalyst solution and the resulting mixture 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 product was isolated by flash chromatography (hexane/EtOAc 75:25). The *ee* of the product was determined by HPLC using a Daicel Chiralpak AD-H column. Yields and *ee* values are the average of at least two corroborating runs.

The comparative studies of the catalytic activities were conducted for each experiment using copper catalysts prepared in situ by reacting the respective ligand with the $Cu[OTf]_2$ salt at room temperature for 0.5 h in CH_2Cl_2. The catalytic α-amination reactions were carried out at 0 °C with 1.0 mol % catalyst loading. The progress of the reaction was monitored by measuring the disappearance of the ethyl 2-methylacetoacetate by GC, with dodecane as internal standard.

Crystal structure determinations: Crystal data and details of the structure determinations are listed in Table 6. Intensity data were collected at 100(2) K with a Bruker AXS Smart 1000 CCD diffractometer ($Mo_{K\alpha}$ radiation, graphite monochromator, $\lambda = 0.71073$ Å). Data were corrected for Lorentz, polarisation and absorption effects (semiempirical, SADABS).[23] The structures were solved by the heavy-atom method combined with structure expansion by direct methods applied to difference structure factors and refined by full-matrix least squares methods based on F^2 with all measured unique reflections. All non-hydrogen atoms were given anisotropic displacement parameters. Hydrogen atoms were input at calculated positions and refined with a riding model. The calculations were performed using the programs DIRDIF[24] and SHELXL-97.[25]

The crystals of **2** were found to contain 16 molecules of toluene per unit cell as a solvent of crystallisation. Evident disorder of the perchlorate anion was modeled with two partially occupied molecules (refined fractional populations 0.53 and 0.47), which were restricted to have similar Cl−O and O···O distances. The coordinated water molecule was refined as a rigid group, allowing rotation around the Cu−O bond. The starting positions of its hydrogen atoms were calculated based on the principle of maximum hydrogen bonding.[26] The atomic charges used were estimated by partial equalisation of orbital electronegativity.[27]

Table 6. Details of the X-ray structure determinations of complexes **1** and **2**.

	1[7]	**2**
formula	$C_{27}H_{44}BCuF_4N_3O_6$	$C_{50}H_{56}ClCuN_3O_{11}$
M_r	657.00	973.97
crystal size [mm]	0.2·0.1·0.05	0.2·0.2·0.1
crystal system	orthorhombic	tetragonal
space group	$P2_12_12_1$	$P4_12_12$
a [Å]	9.5673(5)	15.9231(8)
b [Å]	11.3995(7)	
c [Å]	28.6673(16)	36.637(3)
V [Å^3]	3126.5(3)	9289.2(9)
Z	4	8
ρ_{calcd} [M gm^{-3}]	1.396	1.393
μ [mm^{-1}]	0.766	0.593
max/min transmission	0.963/0.862	0.926/0.890
index ranges	$-11 \le h \le 11$	$-13 \le h \le 13$
	$0 \le k \le 13$	$0 \le k \le 19$
	$0 \le l \le 34$	$0 \le l \le 44$
θ range [°]	1.4–25.0	1.4–25.7
F_{000}	1380	4088
reflns collected	18621	117733 [0.0729]
independent reflns [R_{int}]	5535 [0.0633]	8663
data/restraints/parameters	5535/0/389	8663/94/615
goodness-of-fit on F^2	1.058	1.064
R indices [$I > 2\sigma(I)$]	$R1 = 0.0415$, $wR2 = 0.0847$	$R1 = 0.0529$, $wR2 = 0.1395$
R indices (all data)	$R1 = 0.0593$, $wR2 = 0.0918$	$R1 = 0.0657$, $wR2 = 0.1485$
absolute structure parameter	-0.002(14)	0.002(17)
largest residual peaks [e Å^{-3}]	0.396/−0.396	0.522/−0.754

CCDC 277609 (**1**) and 653021 (**2**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

We thank the Deutsche Forschungsgemeinschaft (SFB 623, Project B6), the European Union (RTN Network AC3S), the Deutsch-Französische Hochschule (DFH) and the CNRS (France) for funding. We thank Dr. Vincent César for helpful comments and critical suggestions. Support by BASF (Ludwigshafen) and Degussa (Hanau) is gratefully acknowledged.

[1] a) R. E. Lowenthal, A. Abiko, S. Masamune, *Tetrahedron Lett.* **1990**, *31*, 6005; b) D. A. Evans, K. A. Woerpel, M. M. Hinman, M. M. Faul, *J. Am. Chem. Soc.* **1991**, *113*, 726; c) E. J. Corey, N. Imai, H. Y. Zhang, *J. Am. Chem. Soc.* **1991**, *113*, 728; d) D. Müller, G. Umbricht, B. Weber, A. Pfaltz, *Helv. Chim. Acta* **1991**, *74*, 232.

[2] For reviews of nitrogen-containing ligands for asymmetric catalysis, see: a) F. Fache, E. Schulz, M. Lorraine Tommasino, M. Lemaire, *Chem. Rev.* **2000**, *100*, 2159; b) A. Togni, L. M. Venanzi, *Angew. Chem.* **1994**, *106*, 517; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 497; for reviews of applications of oxazoline-containing ligands in asymmetric catalysis, see: c) A. K. Ghosh, P. Mathivanan, J. Cappiello, *Tetrahedron: Asymmetry* **1998**, *9*, 1; d) J. S. Johnson, D. A. Evans, *Acc. Chem. Res.* **2000**, *33*, 325; e) G. Desimoni, G. Faita, P. Quadrelli, *Chem. Rev.* **2003**, *103*, 3119; f) H. A. McManus, P. J. Guiry, *Chem. Rev.* **2004**, *104*, 4151; g) G. Desimoni, G. Faita, K.-A. Jørgensen,

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Chem. Rev. **2006**, *106*, 3561; h) L. H. Gade, S. Bellemin-Laponnaz, *Coord. Chem. Rev.* **2007**, *251*, 718.

[3] Selected examples: a) J. Thorhauge, M. Johannsen, K.-A. Jørgensen, *Angew. Chem.* **1998**, *110*, 2543; *Angew. Chem. Int. Ed.* **1998**, *37*, 2404; b) D. A. Evans, C. S. Burgey, M. C. Kozlowski, S. W. Tregay, *J. Am. Chem. Soc.* **1999**, *121*, 686; c) D. A. Evans, K. A. Scheidt, J. N. Johnston, M. C. Willis, *J. Am. Chem. Soc.* **2001**, *123*, 4480; d) N. Nishiwaki, K. R. Knudsen, K. V. Gothelf, K.-A. Jørgensen, *Angew. Chem.* **2001**, *113*, 3080; *Angew. Chem. Int. Ed.* **2001**, *40*, 2992; e) K. R. Knudsen, T. Risgaard, N. Nishiwaki, K. V. Gothelf, K.-A. Jørgensen, *J. Am. Chem. Soc.* **2001**, *123*, 5843; f) D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw, C. W. Downey, *J. Am. Chem. Soc.* **2003**, *125*, 12692; g) D. A. Evans, C. W. Downey, J. L. Hubbs, *J. Am. Chem. Soc.* **2003**, *125*, 8706; h) J. Cong-Dung Le, B. Pagenkopf, *Org. Lett.* **2004**, *6*, 4097; i) C. Palomo, M. Oiarbide, R. Halder, M. Kelso, E. Gómez-Bengoa, J. M. García, *J. Am. Chem. Soc.* **2004**, *126*, 9188; j) L. Bernardi, W. Zhuang, K.-A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 5772; k) S. Rajaram, M. S. Sigman, *Org. Lett.* **2005**, *7*, 5473; l) K. Matsumoto, K. Jitsukawa, H. Masuda, *Tetrahedron Lett.* **2005**, *46*, 5687; m) D. A. Evans, Y. Aye, J. Wu, *Org. Lett.* **2006**, *8*, 2071; n) A. Landa, A. Minkkilä, G. Blay, K.-A. Jørgensen, *Chem. Eur. J.* **2006**, *12*, 3472.

[4] T. P. Yoon, E. N. Jacobsen, *Science* **2003**, *299*, 1691.

[5] Copper(II) complexes with facial coordination of C_{3v}-symmetrical ligands have been characterised by X-ray diffraction. For the tris(2-pyridyl)methane ligand, see: a) M. Kodera, Y. Tachi, T. Kita, H. Kobushi, Y. Sumi, K. Kano, M. Shiro, M. Koikawa, T. Tokii, M. Ohba, H. Okawa, *Inorg. Chem.* **2000**, *39*, 226; b) M. Kodera, Y. Kajita, Y. Tachi, K. Kano, *Inorg. Chem.* **2003**, *42*, 1193; c) P. J. Arnold, S. C. Davies, J. R. Dilworth, M. C. Durrant, D. V. Griffiths, D. L. Hughes, R. L. Richards, P. C. Sharpe, *J. Chem. Soc. Dalton Trans.* **2001**, 736; d) T. Astley, P. J. Ellis, H. C. Freeman, M. A. Hitchman, F. R. Keene, E. R. T. Tiekink, *J. Chem. Soc. Dalton Trans.* **1995**, 595; for the tris(-pyrazolyl)methane ligand, see: e) K. Fujisawa, T. Ono, H. Aoki, Y. Ishikawa, Y. Miyashita, K. Okamoto, H. Nakazawa, H. Higashimura, *Inorg. Chem. Commun.* **2004**, *7*, 330; f) D. L. Reger, C. A. Little, M. D. Smith, G. J. Long, *Inorg. Chem.* **2002**, *41*, 4453; g) D. Martini, M. Pellei, C. Pettinari, B. W. Skelton, A. H. White, *Inorg. Chim. Acta* **2002**, *333*, 72.

[6] a) S. Bellemin-Laponnaz, L. H. Gade, *Chem. Commun.* **2002**, 1286; b) S. Bellemin-Laponnaz, L. H. Gade, *Angew. Chem.* **2002**, *114*, 3623; *Angew. Chem. Int. Ed.* **2002**, *41*, 3473; c) C. Dro, S. Bellemin-Laponnaz, R. Welter, L. H. Gade, *Angew. Chem.* **2004**, *116*, 4579; *Angew. Chem. Int. Ed.* **2004**, *43*, 4479; d) B. D. Ward, S. Bellemin-Laponnaz, L. H. Gade, *Angew. Chem.* **2005**, *117*, 1696; *Angew. Chem. Int. Ed.* **2005**, *44*, 1668; e) L. Lukešová, B. D. Ward, S. Bellemin-Laponnaz, H. Wadepohl, L. H. Gade, *Dalton Trans.* **2007**, 920; f) L. H. Gade, G. Marconi, C. Dro, B. D. Ward, M. Poyatos, S. Bellemin-Laponnaz, H. Wadepohl, L. Sorace, G. Poneti, *Chem. Eur. J.* **2007**, *13*, 3058.

[7] C. Foltz, B. Stecker, G. Marconi, H. Wadepohl, S. Bellemin-Laponnaz, L. H. Gade, *Chem. Commun.* **2005**, 5115.

[8] C. Foltz, M. Enders, S. Bellemin-Laponnaz, H. Wadepohl, L. H. Gade, *Chem. Eur. J.* **2007**, *13*, 5994.

[9] J. Thorhauge, M. Roberson, R. G. Hazell, K.-A. Jørgensen, *Chem. Eur. J.* **2002**, *8*, 1888.

[10] For an overview of the direct catalytic asymmetric Mannich reaction, see: A. Córdova, *Acc. Chem. Res.* **2004**, *37*, 102.

[11] M. Marigo, A. Kjærsgaard, K. Juhl, N. Gathergood, K.-A. Jørgensen, *Chem. Eur. J.* **2003**, *9*, 2359.

[12] A "sidearm" strategy has been succesfully employed for the development of efficient ligands for a range of copper-catalysed enantioselective reactions: a) J. Zhou, Y. Tang, *J. Am. Chem. Soc.* **2002**, *124*, 9030; b) J. Zhou, M. C. Ye, Y. Tang, *J. Comb. Chem.* **2004**, *6*, 301; c) Z.-Z. Huang, Y.-B. Kang, J. Zhou, M.-C. Ye, Y. Tang, *Org. Lett.* **2004**, *6*, 1677; d) M.-C. Ye, J. Zhou, Y. Tang, *J. Org. Chem.* **2006**, *71*, 3576; e) R. Rasappan, M. Hager, A. Gissible, O. Reiser, *Org. Lett.* **2006**, *8*, 6099.

[13] For a review see: J. Zhou, Y. Tang, *Chem. Soc. Rev.* **2005**, *34*, 664.

[14] The exploitation of C_2-symmetry in enantioselective catalysis was first reported (and explicitely formulated) by Kagan: a) H. B. Kagan, T. P. Dang, *J. Am. Chem. Soc.* **1972**, *94*, 6429; Reviews: b) J. K. Whitesell, *Chem. Rev.* **1989**, *89*, 1581; c) H. Brunner, *Top. Stereochem.* **1988**, *18*, 129.

[15] Reviews on C_3-chiral systems in asymmetric catalysis and molecular recognition: a) C. Moberg, *Angew. Chem.* **1998**, *110*, 260; *Angew. Chem. Int. Ed.* **1998**, *37*, 248; b) M. C. Keyes, W. B. Tolman, *Adv. Catal. Processes* **1997**, *2*, 189; c) S. E. Gibson, M. P. Castaldi, *Chem. Commun.* **2006**, 3045; d) S. E. Gibson, M. P. Castaldi, *Angew. Chem.* **2006**, *118*, 4834; *Angew. Chem. Int. Ed.* **2006**, *45*, 4718; e) C. Moberg, *Angew. Chem.* **2006**, *118*, 4838; *Angew. Chem. Int. Ed.* **2006**, *45*, 4721.

[16] D. A. Evans, S. G. Nelson, *J. Am. Chem. Soc.* **1997**, *119*, 6452.

[17] M. Marigo, K. Juhl, K.-A. Jørgensen, *Angew. Chem.* **2003**, *115*, 1405; *Angew. Chem. Int. Ed.* **2003**, *42*, 1367.

[18] The term first coordination sphere (fcs) symmetry is introduced to designate the effective local symmetry of a coordinated ligand at a metal centre. This is meant to avoid confusion with the stereochemical term "local symmetry", for which Mislow and Siegel have given a strict definition with reference to the symmetry of the whole molecule: K. Mislow, J. Siegel, *J. Am. Chem. Soc.* **1984**, *106*, 3319.

[19] R. E. Strube, *Org. Synth.* **1963**, *4*, 417.

[20] a) A. I. Meyers, K. A. Novachek, *Tetrahedron Lett.* **1996**, *37*, 1747; b) C. Foltz, S. Bellemin-Laponnaz, L. H. Gade, unpublished results.

[21] J. Bourguignon, U. Bremberg, G. Dupas, K. Hallman, L. Hagberg, L. Hortala, V. Levacher, S. Lutsenko, E. Macedo, C. Moberg, G. Quéguiner, F. Rahm, *Tetrahedron* **2003**, *59*, 9583.

[22] P. Västilä, I. M. Pastor, H. Adolfsson, *J. Org. Chem.* **2005**, *70*, 2921.

[23] G. M. Sheldrick, SADABS-2004/1, Bruker AXS, **2004**.

[24] P. T. Beurskens, G. Beurskens, R. de Gelder, S. Garcia-Granda, R. O. Gould, R. Israel, J. M. M. Smits, DIRDIF-99, University of Nijmegen (The Netherlands), **1999**.

[25] G. M. Sheldrick, SHELXL-97, University of Göttingen, Göttingen, **1997**.

[26] M. Nardelli, *Comput. Chem. Eng.* **1999**, *32*, 563.

[27] C. J. Cramer, *Essentials of Computational Chemistry, 2nd ed.*, Wiley, New York, **2004**, Chapter 9.1.3.

Received: July 16, 2007
Published online: October 23, 2007

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim