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Exploiting Threefold Symmetry in Asymmetric Catalysis: The Case of Tris(oxazolinyl)ethanes ("Trisox")

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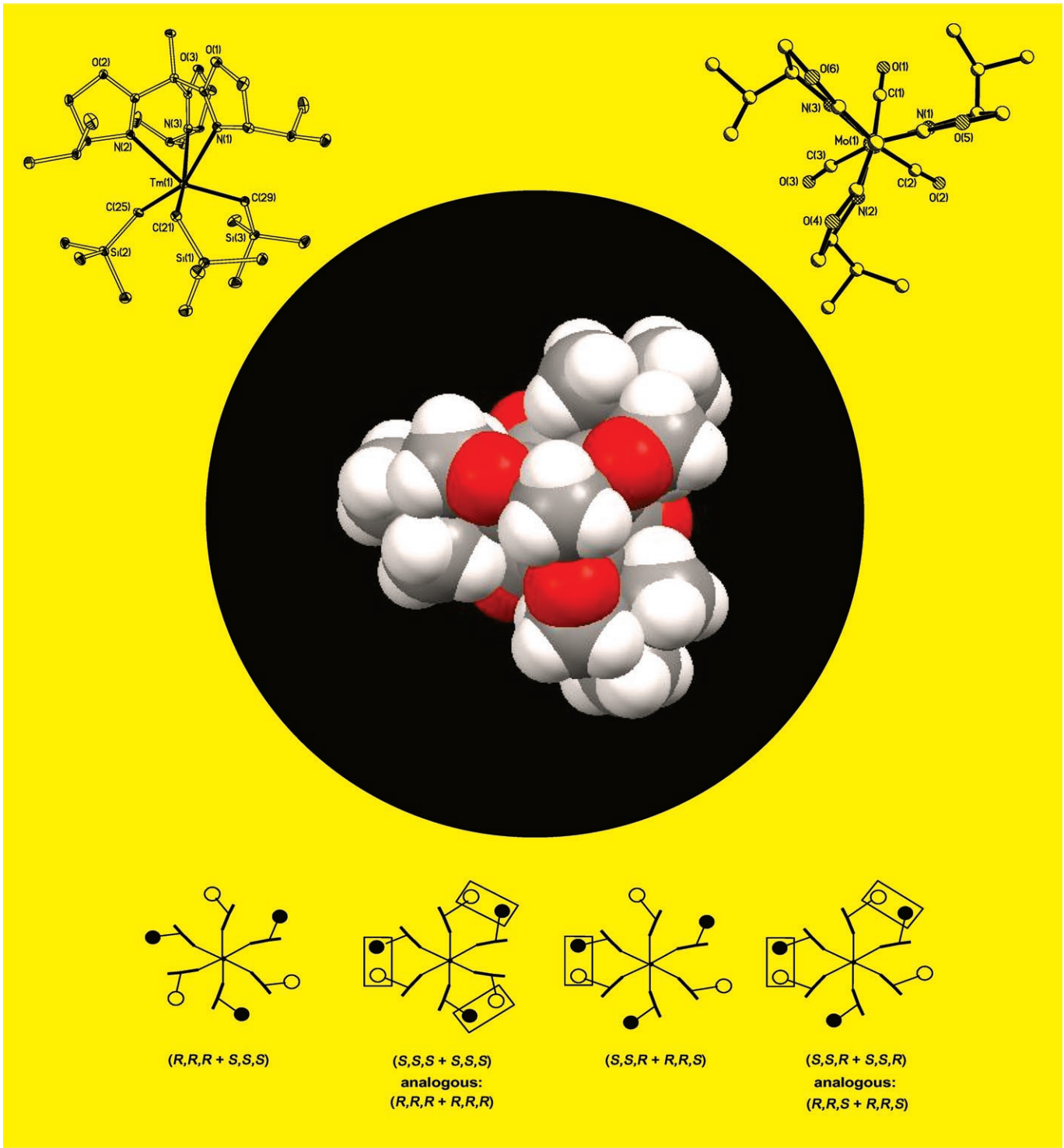

Abstract: Rotational molecular symmetry, modularity and other aspects of ligand design have played a role in the development of a new class of stereodirecting ligands. The use of highly symmetrical, stereodirecting ligands may reduce the number of transition states and diastereomeric reaction intermediates and, in favourable cases, this degeneration of alternative reaction pathways may lead to high stereoselectivity in catalytic reactions and greatly simplifies the analysis of such transformations. In this concept article, we describe the way in which these considerations have played a role in the development of a new class of stereodirecting ligands. Tris(oxazolinyl)ethanes ("trisox") have proved to be versatile ligand systems for the development of enantioselective catalysts of the d- and f-block metals employed in a wide range of catalytic conversions. These include Lewis acid catalysed transesterifications, C–C and C–N coupling reactions, the catalytic polymerisation of α-olefins as well as Pd-catalysed allylic alkylations. An overview of the current state of this field is given and the potential for further development will be highlighted.

Keywords: asymmetric catalysis · chirality · threefold symmetry · transition metals · trisoxazolines

Introduction

The development of catalysts for new chemical transformations or catalytic systems with improved performance for known reactions is one of the key challenges of current chemical research.[1] There is no universal approach to the design and/or discovery of new molecular catalysts with improved performance. Selectivity in catalytic transformations is based on a selection process in a key step of the catalytic cycle, and high selectivity may be obtained by "forcing" the system into one specific reaction pathway. This provides the challenge in the quest for new catalysts.

The exploitation of C_3 chirality in the design of chiral stereodirecting ligands for homogeneous catalytic transformations is currently the focus of considerable research efforts and conceptual debate.[2–6] The use of highly symmetrical stereodirecting ligands may reduce the number of transition states and diastereomeric reaction intermediates and, in favourable cases, this degeneration of alternative reaction pathways may lead to high stereoselectivity in catalytic reactions and greatly simplifies the analysis of such transformations. The most frequently cited line of argument is based on the homotopicity of the "reactive" coordination sites in octahedral complexes representing intermediates in catalytic cycles (Figure 1, top).[2a,4b]

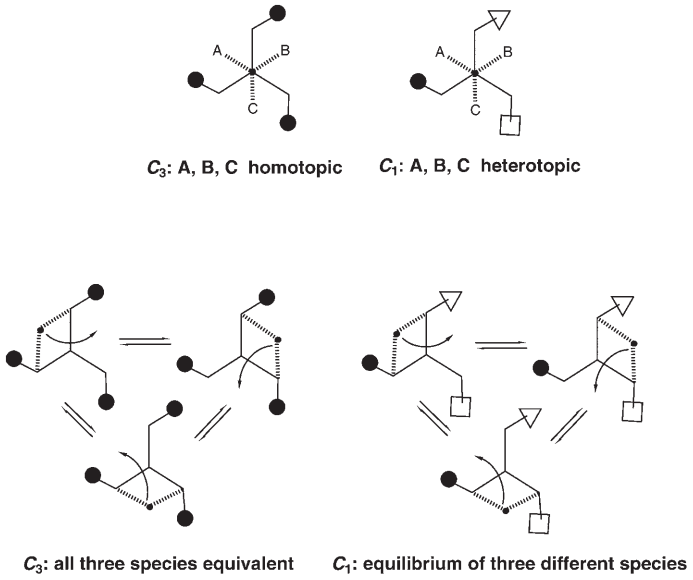

Figure 1. "Static" κ^3-facial coordination of tripod ligands (top) and dynamic exchange of κ^2-chelating tripods coordinated to a complex fragment (●) (bottom).

However, as has recently become apparent, a threefold symmetrical chiral podand may generate a similar simplification in the stereochemistry of key catalytic intermediates for cases in which it only acts a bidentate ligand in the stereoselectivity-determining step. This is the case for systems in which chemical exchange between the different κ^2-coordinated forms takes place and in which the non-coordinated "sidearm" may play a direct or indirect role at some earlier or later stage in the catalytic cycle. As is schematically shown in Figure 1 (bottom), such an exchange represents an equilibrium between identical species for a symmetrical tripod rather than between isomeric complexes, as would be the case for less symmetrical species.

In this concept article, we describe the way in which rotational molecular symmetry, modularity and other aspects of ligand design have played a role in the development of a new class of stereodirecting ligands. Tris(oxazolinyl)ethanes ("trisox") have proved to be versatile ligand systems for the development of enantioselective catalysts of the d- and f-block metals employed in a range of catalytic conversions.

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Designing Chiral Stereodirecting Ligands Based on a Tripod Topology

The majority of stereodirecting ligands are chelates,[7] or sets of monodentate ligands that arrange themselves to generate essentially a similar active space as the chelates.[8] More elaborate ligands include meridionally coordinating polydentate ligands, such as "pincers"[9] or 2,2′-[1,2-ethanediylbis(nitrilomethylidyne)]bisphenol dianion (salen) derivatives.[10] All these are special cases of ligands with "podand" topology[11] and generate active sites that are adapted to a discrimination between two prochiral faces, atom positions, and so forth.

This type of stereodiscrimination is less evident upon going to podands possessing a bridging unit which coordinate as *tripods*. Tripodal ligands are designed to bind facially to a metal centre,[12] and in this case threefold rotational symmetry represents the highly symmetrical reference system adapted to this topology of ligation, in the same way that C_2 symmetry is related to simple chelation.

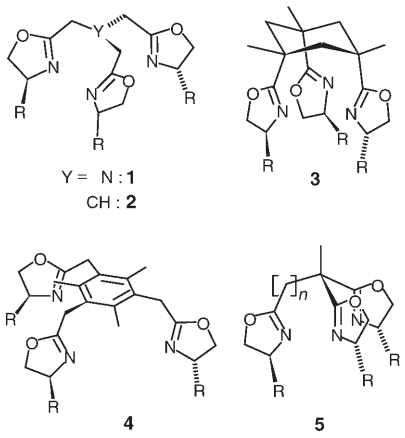
If this aspect of ligand symmetry is not the major focus, tripods may be simply generated by a "sidearm" modification of bidentate ligands: They will then be formally composed of the stereodirecting unit and a modulating additional ligating unit. A notable development is the coupling of such an additional "sidearm" to the bridging carbon atoms of bisoxazolines. Tang and co-workers have found that such potentially tricoordinating ligands may provide Cu-based Lewis acid catalysts that display a significantly improved performance in comparison to the bisoxazoline reference system.[13]

However, the role of the "sidearm" is not always clear,[13,14] and a separation of the influence of the BOX-unit and the third "ligand arm" is only meaningful if the metal–ligand bonding of these components differs significantly. On the other hand, upon going to C_3-chiral tripods, all three possible ligating units become equivalent, effectively giving up the sidearm notion as discussed above. The evident practical implementation of this approach is the use of a symmetrical trisoxazoline.

Trisoxazolines

Oxazolines are nowadays essential ligands in asymmetric catalysis and also important synthons for stereoselective synthesis.[15] The success of the C_2-symmetric bis(oxazolines) (BOX) and pyridine–bis(oxazolines) (pybox) discovered in the early 1990s has established them as a "privileged" class of ligands.[16] In contrast, the development and application of trisoxazolines lagged behind for a long time.

Katsuki and collaborators reported the first example of a chiral trisoxazoline in 1995 (ligands **1** and **2**).[17] The allylic oxidation of alkenes (Karasch–Sosnovsky reaction) as well as the enantioselective addition of diethylzinc to aldehydes[18] was examined giving promising results though ultimately not surpassing the well-established C_2-symmetric systems for these reactions.



Since the beginning of this decade, the trisoxazolines have begun to be systematically employed in asymmetric catalysis, chiral molecular recognition or self-assembly of supramolecular structures.[19] A trisoxazoline based on Kemp's triacid (**3**) was reported by Bolm and co-workers,[20] whilst such systems with a benzene backbone (**4**) were reported by Ahn and collaborators.[21] The latter were found to be very selective for the recognition of α-chiral primary ammonium ions as well as enantioselective catalysts for the Michael reaction between methyl phenylacetate and methyl acrylate in the presence of *t*BuOK.[21c]

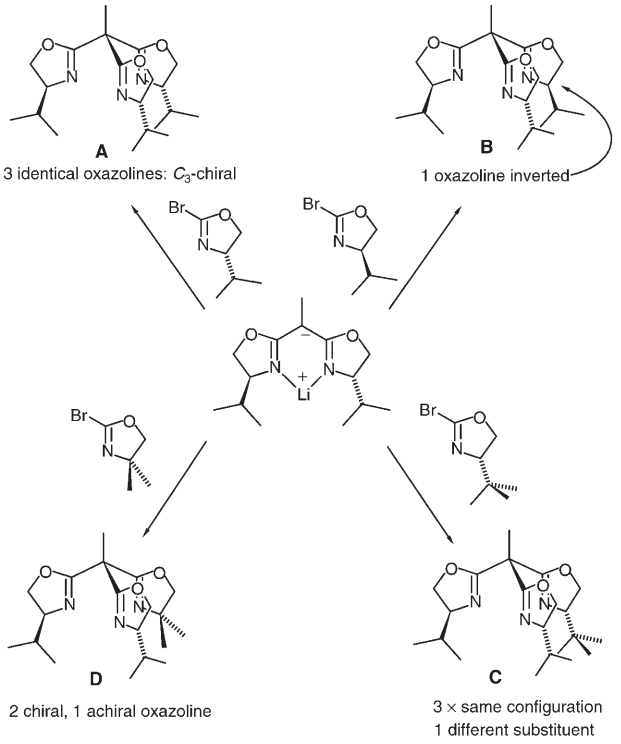
Ligands **1–4** are not adapted to the facial coordination in a deltahedral coordination sphere of a metal, due to the way the oxazoline rings are arranged. However, the class of non-C_3-symmetrical trisoxazolines developed by Tang's group (**5**) do in principle offer the possibility of this type of coordination,[13] although there is to date no crystallographically characterised complex to firmly establish facial binding. These trisoxazoline ligands have been successfully employed in a range of highly enantioselective catalytic transformations.[19]

First Cyclisation and Then Assembly of the Ligand Backbone: A Modular Synthesis of C_3- and C_1-Chiral 1,1,1-Tris(oxazolyl)ethanes ("trisox")

1,1,1-Tris(oxazolyl)methane or -ethane ligands provide a geometry of the metal binding site that is most adapted to facial tripodal coordination of the metal centre. This is thought to lead to a relatively rigid and well-defined coordination geometry. Such trisoxazoline ligands, first proposed in the 1990s, proved to be elusive for a long time.[2] Their attempted synthesis from methane- or ethanetris(carboxylate) or -trinitrile precursors, or from bisoxazoline carboxalates or nitriles led at best to bisoxazoline derivatives due to a kinetically favoured decarboxylation step. Since trisoxazolines of that type, generated by cyclisation at a common carbon atom, were inaccessible, the evident alternative was to cy-

clise first and then to assemble the three oxazoline rings in a final step.

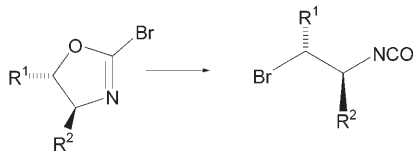
We therefore reverted to a strategy in which a readily accessible bis(oxazoline) derivative was coupled with a preformed activated mono(oxazoline) ring. This was readily achieved by reaction of the lithium salt of 1,1-bis(oxazolinyl)ethane with 2-bromooxazoline[22] and allowed the high yield access to chiral symmetrically substituted derivatives, such as 1,1,1-tris{2-[(*S*)-4-isopropyl]oxazolinyl}ethane (**A**) (Scheme 1). Additionally, the synthesis of tripods with



Scheme 1. Modular assembly of trisoxazoline ligands by reaction of the metallated bisoxazolines with 2-bromooxazoline derivatives. This allows for the synthesis of C_3-chiral ligands (**A**), the inversion of one chiral centre in an otherwise symmetrically substituted tripod (**B**), the combination of different chiral oxazoline rings (**C**) or the combination of chiral and achiral oxazoline rings (**D**).

mixed substitution patterns (**B**–**D**, including the inversion of chiral centres as in **B**) is achieved in excellent yields.[23] This opened up the possibility to approach the synthesis of such polydentate oxazolines in a *modular* way, including tripods with mixed stereochemistry, that is, partially inverted chiral centres as well as achiral oxazoline rings. We have prepared a whole range of derivatives bearing aryl and alkyl substituents at the chiral centres of the oxazoline rings.[24]

A practical limitation of the [2+1] coupling of a lithiated bisoxazoline with a 2-bromooxazoline is the synthesis of the latter, which requires the brominating agent dibromotetrafluoroethane. This reagent is listed among the ozone-depleting freons, which limits its availability, and no truly satisfactory replacement has been found to date. Another limitation is the thermal instability of the bromoozazoline derivatives. Over time, these undergo selective rearrangement to the corresponding α-bromoisocyanates (Scheme 2), which are interesting reagents in their own right.[25]



Scheme 2. Thermal rearrangement of 2-bromooxazolines to the corresponding α-bromoisocyanates.

The Structural Non-Complementarity of Two Homochiral Trisox Ligands in $[M(trisox)_2]^{n+}$ Complexes: A Prerequisite for Potential Catalytic Activity

A key feature of the trisox ligands is the fixed orientation of the substituents at the chiral centre in the 4-position of the oxazoline rings. This favours the formation of catalytically active complexes even for substitutionally labile transition metals that may readily undergo complex redistributions ("dismutations"). The steric demand of the substituent groups, as well as their orientation relative to the molecular axis, render the formation of "homoleptic" $[M(trisox)_2]^{n+}$ species unfavourable and thus stabilises a coordination sphere that combines the stereodirecting tripod with up to three remaining ("active") coordination sites. This is the case, provided that the *enantiomerically pure* C_3-symmetric ligands or the stereochemically "mixed" (C_1-symmetric) derivatives (enantiomerically pure or racemic) are employed.[24]

Possible combinations of trisox ligands representing the different stereochemical possibilities are displayed in Figure 2, specifically emphasizing the consequences of the formation of potentially inactive $[M(trisox)_2]^{n+}$. Only for the racemate (*R*,*R*,*R* + *S*,*S*,*S*) of the C_3-chiral ligands is the formation of such a symmetric hexacoordinate complex expected to be favoured (see bottom, first from the left). In such *meso*-$[M(trisox)_2]^{n+}$ complexes the orientation of the 4-oxazoline substituents is complementary and avoids significant repulsive interactions. In contrast, the combination of a homochiral pair of C_3-trisox ligands at a single metal centre will generate three repulsive interligand interactions (Figure 2, bottom: second from the left) and is thus expected to be disfavoured. This is exactly the situation that would be encountered in the application of the enantiopure C_3-chiral trisoxazolines in catalytic transformations![24] Unfavourable interligand repulsion is also encountered in hetero- or homochiral combinations of the mixed-configuration C_1-trisox derivatives as is indicated in the third and fourth example at the bottom of Figure 2. This phenomenon has been recently discussed by Takacs et al. in relation to C_2-symmetric complexes.[26]

The ability of trisox ligands to coordinate facially to transition metals and lanthanides has been established by X-ray

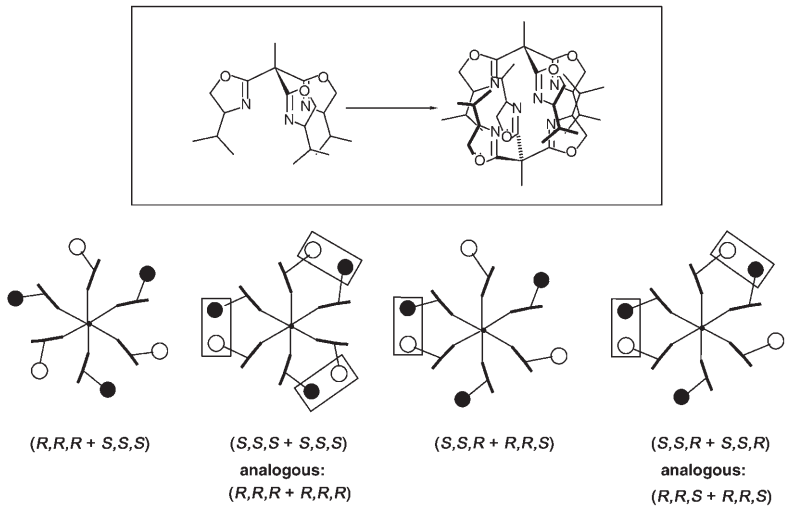
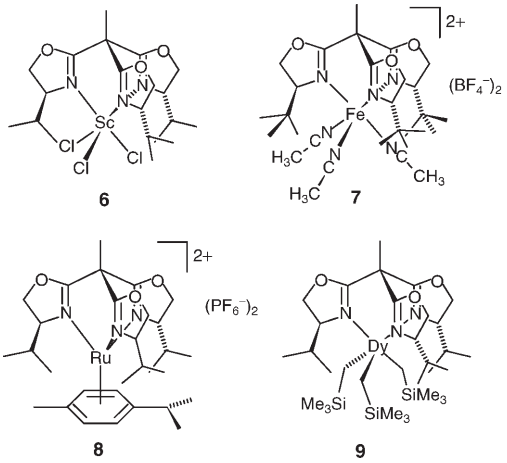


Figure 2. Possible trisox-combinations in $[M(trisox)_2]^{n+}$ complexes, demonstrating the non-complementarity of two homochiral ligands in such species.

diffraction. Provided the stereoelectronic properties of the metal do not strongly favour other coordination geometries, facial binding is observed and several examples (**6**–**9**) are depicted here.[24] Divalent transition metal halides have the



tendency to form halide-bridged face-sharing bisoctahedral complexes, which avoids the unfavourable formation of $[M(trisox)_2]^{n+}$ species. The dinuclear complexes $[M_2(\mu\text{-}Cl_3)(i\text{Pr-trisox})_2](PF_6)$ (M = Fe^{II}: **10**, Co^{II}: **11**, Ni^{II}: **12**), were prepared from the respective metal dihalides (Scheme 3).

The way in which the stereoelectronic properties of the transition metal govern the coordination patterns of these ligands is exemplified by the oxidation of the square-planar $Rh^{I}(d^8)$ complex **13** in Scheme 4, in which the trisox ligand is dicoordinate, to yield the d^6 tribromorhodium(III) complex **14**, in which the podand ligand is symmetrically bound to the metal centre.[24]

Whilst the trisox ligand in derivatives of both Pd^{II} and Pd^0 (**15** and **16**, respectively, in Figure 3) has been found to be dicoordinated both in solution and in the crystalline state, with one dangling "ligand side arm", the presence and nature of the third "ligand arm" appears to exert a strong influence upon their reactivity (vide infra).[27]

A C_3-Chiral Trisoxazoline Zinc Complex as a Functional Model for Zinc Hydrolases

The role of the Zn^{2+} cation in the reactive sites of many metalloenzymes is well established.[28] It is normally found adopting a tetrahedral coordination geometry and is attached to the protein backbone by three amino acid residues, the fourth coordination site being occupied by a water molecule. In many of the zinc-based peptidases a tris(histidine)zinc binding site acts as a "tripodal ligand" for the metal ion.

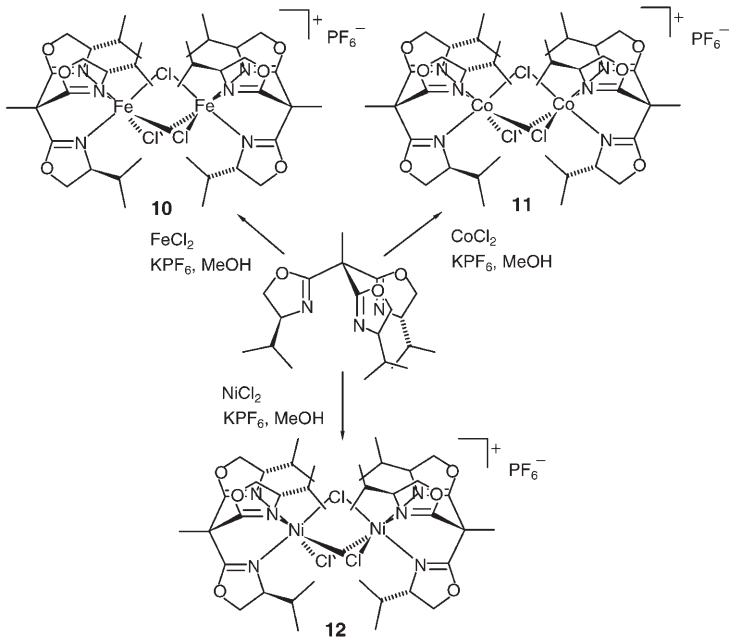
Small molecular models mimicking this enzyme activity have been extensively studied during the past decade. The work on scorpionate and related tripod–Zn complexes, in particular by Vahrenkamp and Parkin, has elucidated key mechanistic features of Zn enzyme activity.[29] The trisox ligands may be viewed as models emulating *both* the tris(histidine) binding sites and the chiral environment of the protein skeletal structure. This provided the opportunity of developing model compounds for hydrolases or transesterases with the potential for *stereoselective* transformations normally only observed for the enzymatic system.

We found that the zinc triflate complex $[Zn_2(\mu\text{-}O_3SCF_3)_3(i\text{Pr-trisox})_2](O_3SCF_3)$ (**17**) (Figure 4) displays catalytic activity in the transesterification of various phenyl esters.[30] It showed modest but significant enantioselectivity in the kinetic resolution of various phenyl ester derivatives of N-protected amino acids by transesterification with methanol (Table 1).

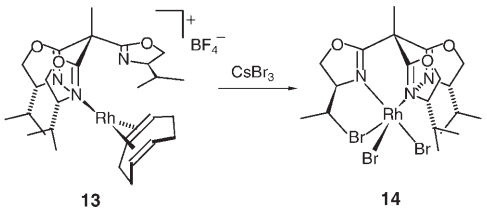
Upon going from the zinc triflato complex **17** to the trifluoroacetate, an increase of the selectivity factor for all the substrates has been observed, notable to 5.1 for entry 3 in the Table 1.[30] A further increase in stereoselectivity has been achieved with the Zn complexes bearing the *tert*-butyl-substituted trisox ligand.

C_3-Chirality in Polymerisation Catalysis with Rare Earth Complexes

The efficient control of the tacticity and molecular weight distribution in polymers by ligand design provides the base for the success of Group 4 metallocene catalysis of α-olefins.[31] Prior to our work, there was no report of the use of



Scheme 3. Synthesis of the dinuclear complexes $[M_2(\mu\text{-}Cl)_3(i\text{Pr-trisox})_2]^+$ (M = Fe: **10**, Co: **11**, Ni: **12**).



Scheme 4. Reaction (oxidative addition) of the square-planar $[Rh(i\text{Pr-trisox})(COD)]^+[BF_4]^-$ (**13**) with $CsBr_3$ giving the octahedral complex $[RhBr_3(i\text{Pr-trisox})]$ (**14**).

C_3-chiral stereodirecting ligands in polymerisation catalysis, although they confer an element of molecular helicity to a complex that is thought to be beneficial for face selection in the key migratory insertion step.

The ubiquitous Group 4 metal catalysts aside, the focus has recently shifted to the use of the Group 3 and lanthanide metals for olefin polymerisation catalysis.[32] The trialkyl complex $[Sc(i\text{Pr-trisox})(CH_2SiMe_3)_3]$ (**18**) was prepared by reaction of the trialkyl precursor $[Sc(CH_2SiMe_3)_3(thf)_2]$ with an equimolar amount of *i*Pr-trisox (Scheme 5).[33] Early attempts to polymerise 1-hexene with in situ generated $[Sc(i\text{Pr-trisox})(CH_2SiMe_3)_2][B(C_6F_5)_4]$ (**19**) suffered from low activity (ca. 30 $kg\,mol^{-1}\,h^{-1}$) and somewhat variable reproducibility as far as tacticity control is concerned as well as bimodal molecular mass distributions. The latter indicated the presence of at least two catalytically active species.

In view of Okuda's previous suggestion that in certain rare-earth polymerisation catalysts a dicationic species may be involved,[34] we investigated the reaction of the trialkyl complex with two equivalents of $[Ph_3C][B(C_6F_5)_4]$, the product of which was tentatively formulated the dicationic complex $[Sc(i\text{Pr-trisox})(CH_2SiMe_3)][B(C_6F_5)_4]_2$ (**20**), although this species has defied isolation and complete characterisation to date. This in situ generated cationic complex was found to be highly active for the polymerisation of 1-hexene and displayed good tacticity control. Polymerisation studies were carried out at various temperatures and the activities and polymer characteristics are provided in Table 2.[33]

The activity of 36200 $kg\,mol^{-1}\,h^{-1}$ (Table 2) is comparable to the extremely high activities reported for zirconium–amine–bis(phenoxide) complexes.[35] Upon reducing the polymerisation temperature to −30 °C, the activity dropped to 2030 $kg\,mol^{-1}\,h^{-1}$; however, at this temperature

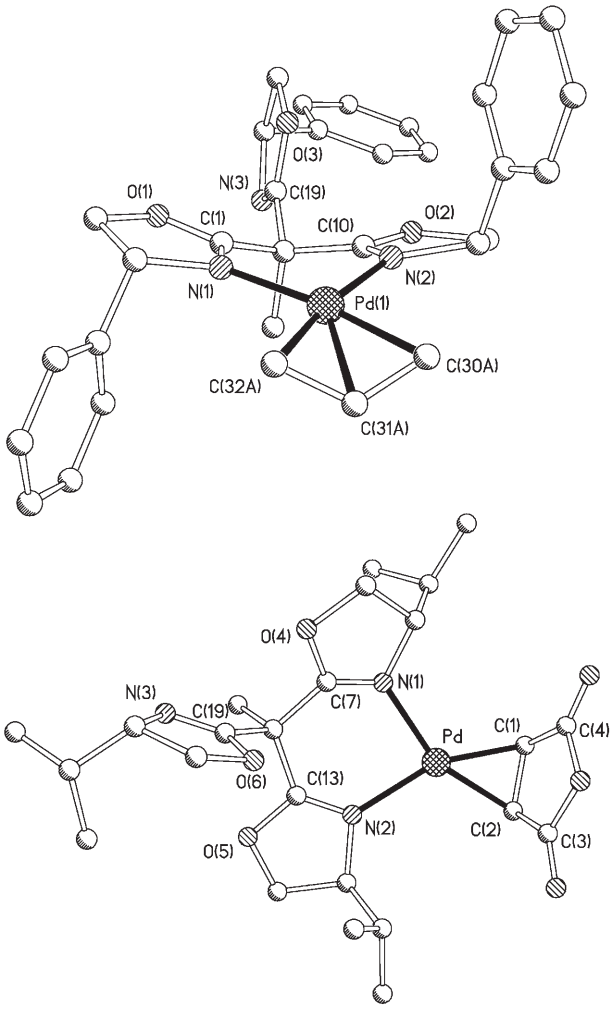


Figure 3. Molecular structures of $[Pd(Ph\text{-trisox})(\eta^3\text{-allyl})]^+$ (**15**; top) and $[Pd(i\text{Pr-trisox})(ma)]$ (**16**, ma = maleic anhydride; bottom).

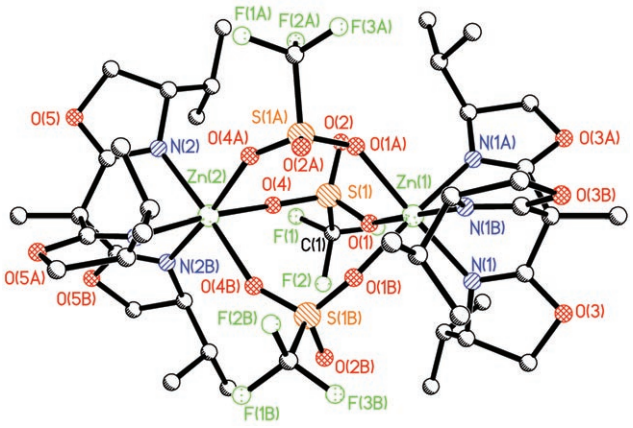
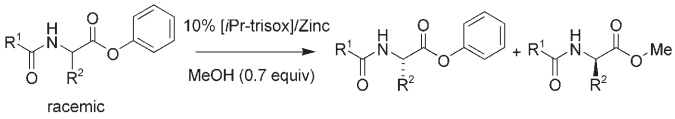
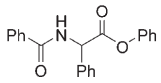
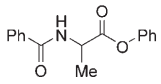
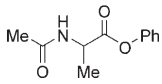
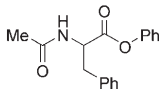


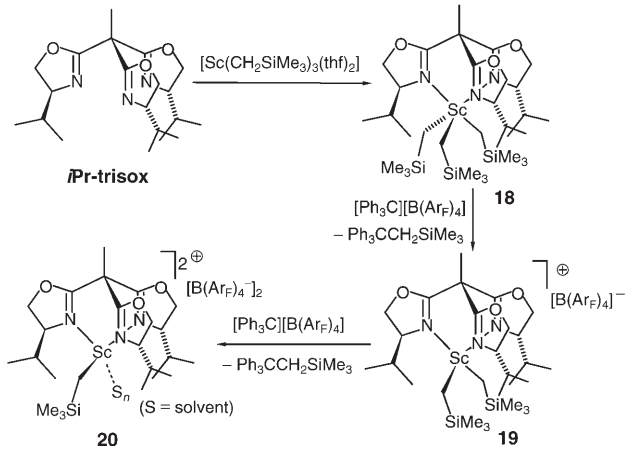
Figure 4. Molecular structure of $[Zn_2(\mu\text{-}O_3SCF_3)_3(i\text{Pr-trisox})_2]^+$ in **17**.

Table 1. Partial kinetic resolution of activated aminoacid esters by stereoselective, trisox–Zn-catalysed transesterification.[a]



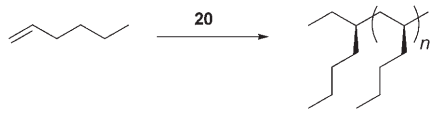
Entry	Substrate	Selectivity factor		
		$Zn(OTf)_2$	$ZnOAc_2$	$Zn(OCOCF_3)_2$
1		1.8	3.5	3.8
2		1.3	2.7	3.0
3		2.0	4.5	5.1
4		1.8	2.6	4.3

[a] All reactions were performed in CH_2Cl_2 at room temperature in the presence of 10 mol% of zinc precursor/*i*Pr-trisox for 2–3 days.



Scheme 5. Synthesis of the Sc complex of $[Sc(i\text{Pr-trisox})(CH_2SiMe_3)_3]$ (**18**) and its conversion to the mono (**19**) and (possibly) dicationic (**20**) catalysts by alkyl abstraction

Table 2. 1-Hexene polymerisation data for the highly active catalyst generated by abstraction of two alkyl groups from $[Sc(i\text{Pr-trisox})(CH_2SiMe_3)_3]$ (**18**) with two molar equivalents of $[Ph_3C][B(C_6F_5)_4]$.



T [°C]	Reaction time [min]	Yield [g]	Activity [kg mol[Sc]$^{-1}$ h^{-1}]	M_w	M_w/M_n
−30	3	1.01	2030	750000	1.18
−20	1.5	1.90	7600	552000	1.87
0	1	2.18	13080	354000	2.36
21	0.5	3.02	36230	227000	2.22

the poly(1-hexene) produced was highly isotactic (*mmmm* = 90% by $^{13}C\{^1H\}$ NMR spectroscopy). GPC analysis of the polymer obtained under these conditions established a very narrow monomodal molecular mass distribution with M_W = 750000 and a PDI of 1.18, indicating that the isoselective catalytic polymerisation carried out at low temperature shows living-type behaviour.

Given these early results obtained with the scandium complex $[Sc(i\text{Pr-trisox})(CH_2SiMe_3)_3]$, we continued our investigations with yttrium and the lanthanides in order of increasing ionic radius. The syntheses of the $[Ln(i\text{Pr-trisox})(CH_2SiMe_3)_3]$ complexes were performed for the metals ranging from lutetium to dysprosium (Figure 5).[36] Although

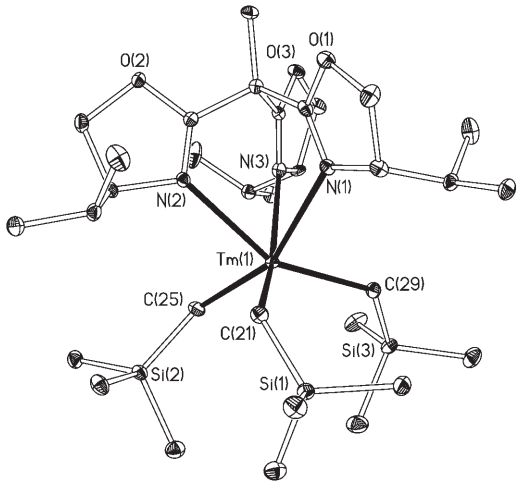


Figure 5. Molecular structure of $[Tm(i\text{Pr-trisox})(CH_2SiMe_3)_3]$.

the *i*Pr-trisox ligand readily adapts to a wide range of ionic radii, we were unable to successfully prepare complexes with the lanthanides preceding dysprosium, possibly owing to the decreased stability of lanthanide alkyl complexes as the ionic radius increases.[36b]

The polymerisation of *n*-hexene, *n*-heptene and *n*-octene was carried out at −5 °C to avoid catalyst decomposition. In all cases polyolefins with M_w/M_n values of between 1.58 and 2.08 were obtained and isotacticities of 80–95% determined by ^{13}C NMR spectroscopy (Figure 6).[36b] Interestingly, the

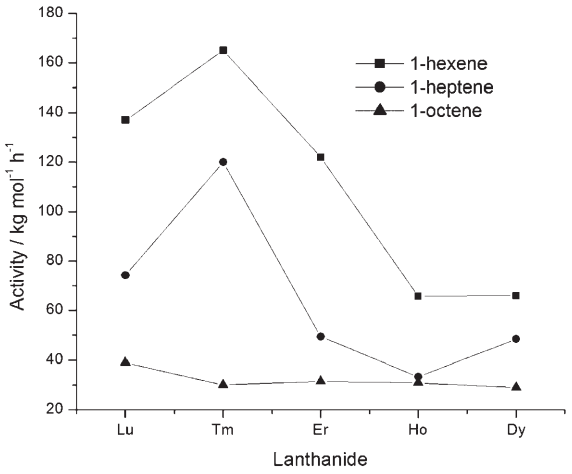


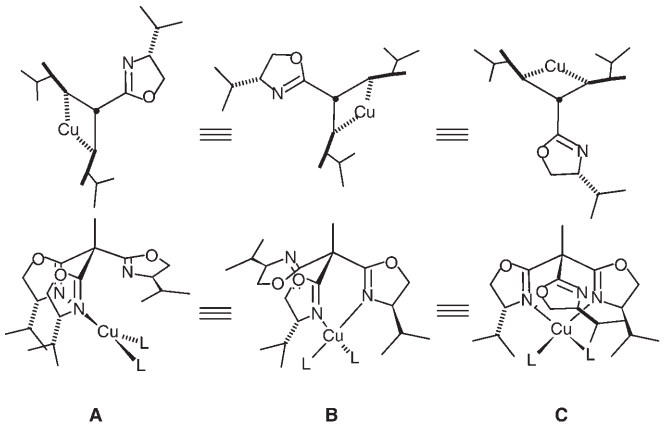
Figure 6. Olefin polymerisation data for [M(*i*Pr-trisox)(CH_2SiMe_3)$_3$] (M = Lu, Tm, Er, Ho and Dy).

polymerisation activity increases from lutetium to thulium, and then subsequently decreases with increasing ionic radius of the metal. However, none of the activities are comparable to those observed with the scandium congener [Sc(*i*Pr-trisox)(CH_2SiMe_3)$_3$] described above.[33]

Trisox as a Bidentate Ligand (Part 1): Exploiting C_3-Symmetry in the Dynamic Coordination of a Chiral Trisoxazoline in Copper(II) Lewis Acid Catalysis

The discussion of catalyst symmetry in connection with stereodirecting podands has mainly focused on static models of the complexes.[2] However, the high rotational symmetry of the chiral tripodal ancillary ligand may render reversible complex transformations into the active catalytic species equivalent. An example of the exploitation of molecular symmetry in this particular context is thought to underlie the highly efficient applications of trisox derivatives in Cu^{II}-based Lewis acid catalysis, the principal domain of the well-established bisoxazoline (BOX) ligands.[15,16] A major practical disadvantage of the latter are the generally high catalyst loadings, which are due to the kinetic lability of copper(II). In this context, the facial coordination by a chiral tridentate ligand was thought to stabilise the *resting state* of the copper complexes.

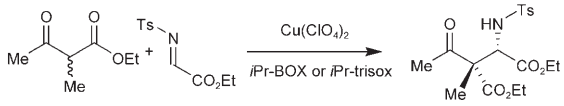
The additional oxazoline ligation is expected to deactivate the complexes in their Lewis acidity as was shown in a recent theoretical study on BOX–Cu catalysts.[37] The transformation of the resting state into the active (17e Cu^{II}) species therefore necessitates the decoordination of an oxazoline unit and the opening up of the system (Scheme 6 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 6, bottom).

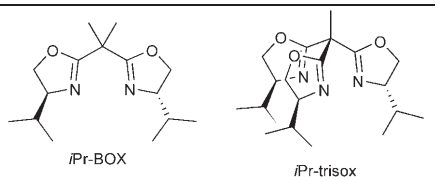


Scheme 6. Coordination/decoordination equilibrium between the proposed resting and active states of the trisox–Cu catalysts giving symmetry-equivalent active species.

To test this concept, we applied [Cu^{II}(trisox)] complexes in the asymmetric Mannich reaction[38] of a β-ketoester with an activated *N*-tosyl-α-imino ester, a reaction that had been previously reported by Jørgensen et al. using chiral copper(II)–bisoxazoline catalysts (10 mol %).[39] After optimisation of the reaction conditions, the reaction product was obtained with an excellent enantiomeric excess (*ee*) of 90% using 10 mol % of the catalyst (Table 3).[40a]

Table 3. Enantioselective Mannich reaction of ethyl 2-methylacetoacetate with *N*-tosyl-α-imino methyl ester catalysed by *i*Pr-trisox/Cu(ClO_4)$_2$ or *i*Pr-BOX/Cu(ClO_4)$_2$.[a]





Entry	Catalyst	Loading [%]	Yield [%]	*ee* [%]	Yield [%]	*ee* [%]
1		10	84	84	84	90
2		1	70	84	75	89
3		1.0	56	80	59	91
4		0.01	35	66	36	90

[a] Experimental conditions: acetone/diethyl ether 1:3, −20 °C, 36 h.

Upon stepwise reduction of the catalyst loading by a factor of 10^3, that is, 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). As a direct comparison, we also investigated the reaction in the presence of 10 mol % of [(*i*Pr-BOX)Cu][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.[40a]

Direct evidence for our assumption of a partially decoordinated trisox ligand in the active state of the catalyst was obtained from an X-ray diffraction study of $[Cu^{II}(i\text{Pr-trisox})(\kappa^2\text{-}O,O'\text{-MeCOCHCOOEt})]^+[BF_4]^-$ (**21**) (Figure 7).

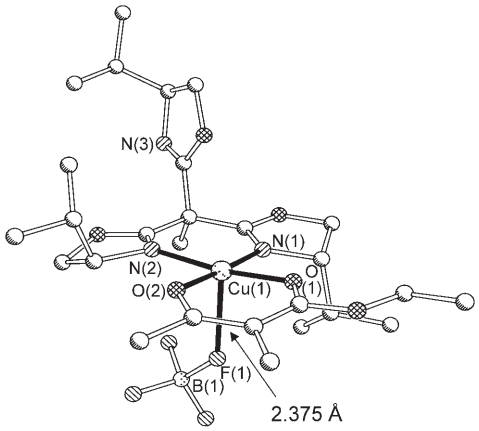


Figure 7. Molecular structure of the copper complex $[Cu^{II}(i\text{Pr-trisox})(\kappa^2\text{-}O,O'\text{-MeCOCHCOOEt})]^+[BF_4]^-$ (**21**).

Given the arrangement of substrate and ancillary ligand in Figure 7 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.[13] This would lead to products having the 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.

As another test reaction we investigated the direct α-amination of α-substituted β-ketoesters with azodicarboxylates,[40] for which an efficient copper(II)–bisoxazoline-catalysed version had previously been reported by Jørgensen and co-workers.[41] Here again, the trisox systems proved to be superior to the corresponding BOX–Cu^{II} catalysts.

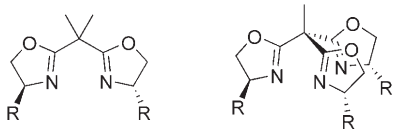
We have found in general that C_3-symmetric trisoxazolines generate highly efficient enantioselective Cu^{II} Lewis acid catalysts which are based on the concept of a *stereoelectronic hemilability* of the divalent copper. Whether or not the third oxazoline unit coordinates to Cu^{II}, appears to depend on the remaining coordination sphere and cannot be unambiguously established in most cases. However, in the direct comparison with the analogous bisoxazoline systems, the trisox-based catalysts have proved to be more efficient in the majority of cases studied in our laboratory to date.

Trisox as a Bidentate Ligand (Part 2): Palladium-Catalysed Asymmetric Allylic Substitutions

It has been argued above, that a threefold symmetrical chiral podand may simplify the stereochemistry of key catalytic intermediates for cases in which it only acts a bidentate ligand in the stereoselectivity-determining step, in other words, for metal complexes with a stereoelectronic preference for non-deltahedral coordination geometries. However, the high substitutional lability of the copper(II) complexes along with their paramagnetism precluded a detailed experimental study into this proposed behaviour. We therefore decided to study a catalytic reaction that also involves an active species with square planar (i.e. non-deltahedral) coordination geometry, which is diamagnetic and less labile than the Cu^{II} complexes. Palladium(II)-catalysed allylic substitutions provide appropriate test reactions along these lines[42] and it was possible to study the dynamic exchange in model systems for both the Pd^{II} and Pd^0 intermediates of this catalytic reaction.

Pfaltz and co-workers had previously investigated the allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate as nucleophile (in the presence of *N,O*-bis(trimethylsilyl)acetamide (BSA)) with the well-established BOX ligands as stereodirecting ligands, and this particular system therefore provided the point of reference for the catalytic study at hand (Table 4, entry 1).[43] Under the reaction conditions displayed in Scheme 7 the trisoxazoline-based catalysts generally induce a better enantioselectivity compared to their bisoxazoline analogues, and this behaviour appears to be independent of the substituent as shown in Table 4

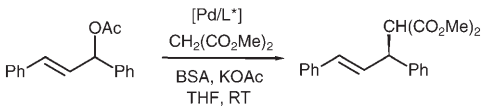
Table 4. Results of asymmetric allylic alkylations with various bisoxazolines and their trisox analogs.[a]



Entry	R	Yield [%]	*ee* [%]	Yield [%]	*ee* [%]
1	(*S*)-*i*Pr	89	89	90	95
2	(*R*)-Ph	7	−72	28	−88
3	(*S*)-Bn	88	83	92	88
4	(4*R*,5*S*)-Ind	13	−93	95	−98

[a] Experimental conditions: catalytic precursor generated in situ from $[\{PdCl(C_3H_5)\}_2]$ and ligand (1 mol%, ratio ligand/Pd = 1.1) in THF at 50 °C for 1.5 h; catalysis carried out at room temperature; yields and *ee* determined after 72 h.

Apart from the effect on the catalyst selectivity, the most notable observation is the rate acceleration with the tripods compared to the BOX ligands for all substitution patterns (Table 5). The rate of the reaction is strongly dependent on the substituent of the respective ligand, with the *i*Pr substituent yielding the most active BOX derivative, whereas



Scheme 7. Allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate (in the presence of *N,O*-bis(trimethylsilyl)acetamide).

Table 5. Turnover frequencies TOF [h^{-1}] of asymmetric allylic alkylations with various bisoxazolines and their trisox analogs (see Table 4).

R	BOX	Trisox	TOF ratio Trisox/BOX
(*S*)-*i*Pr	1.37	5.02	3.7
(*R*)-Ph	0.05	0.2	4
(*S*)-Bn	0.91	3.73	4.1
(4*R*,5*S*)-Ind	0.19	12.2	64.2

the indanyl substituent leads to the highest rate for the trisox-based catalysts.[27] With *i*Pr-, Ph- and Bn-based ligands, the turnover frequencies (TOFs) differ by a factor of four in favour of the tripod, whilst a striking 64-fold acceleration was found for the indanyl derivative!

Since our catalytic systems were prepared in situ from palladium(II) allyl chloride and the trisox ligand, the first step in the formation of the active catalyst involves the reduction of the palladium(II) precursor by a nucleophilic attack by the carbanionic species. The observation of an induction period in the conversion curves is thus not surprising. Introduction of an additional donor function in the stereodirecting ligand generally resulted not only in a rate enhancement, but also the reduction of this induction period. The observed overall rate acceleration might be due to the ability of the additional donating group to induce the formation of the palladium(0) species, both in the initial generation of the active species as well as in the product/substrate exchange step at the end of the catalytic cycle. This mechanistic aspect, as well as the symmetry-related simplification of the reaction network for the catalysts bearing C_3-chiral tripods, may be at the root of the superior performance of the trisox systems.

Perspectives

The adaptability of the trisox ligand to various types of metal centres, coordination geometries and enantioselective catalytic transformations is now well established. Although originally designed to coordinate facially to a metal centre, the potential of C_3-chiral trisox ligands in enantionselective catalytic transformation in which the intermediate in the selectivity-determining step does not adopt deltahedral coordination geometry and thus does not allow tripodal coordination of the stereodirecting ligand has been demonstrated.

The implications which the use of chiral tridentate podands may have in stereoselective catalysis, as compared to the more established bidentate chelates, have recently been clarified.[40b] 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.[40b]

The symmetry-related simplified behaviour with regard to potential catalyst equilibria in solution along with the stereochemical non-ambiguity of the active catalytic species are to be considered in targeted catalyst screening processes.

[1] *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin **1999**.
[2] a) C. Moberg, *Angew. Chem.* **1998**, *110*, 260; *Angew. Chem. Int. Ed.* **1998**, *37*, 248; b) M. C. Keyes, W. B. Tolman, *Adv. Catal.* **1997**, *2*, 189.
[3] a) S. E. Gibson, M. P. Castaldi, *Chem. Commun.* **2006**, 3045; b) S. E. Gibson, M. P. Castaldi, *Angew. Chem.* **2006**, *118*, 4834; *Angew. Chem. Int. Ed.* **2006**, *45*, 4718; c) C. Moberg, *Angew. Chem.* **2006**, *118*, 4838; *Angew. Chem. Int. Ed.* **2006**, *45*, 4721.
[4] Early examples of the use of C_3-chiral ligands in asymmetric catalysis: a) H. Brunner, A. F. M. M. Rahman, *Chem. Ber.* **1984**, *117*, 710; b) M. J. Burk, R. L. Harlow, *Angew. Chem.* **1990**, *102*, 1511; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1467; c) M. J. Burk, J. E. Feaster, R. L. Harlow, *Tetrahedron: Asymmetry* **1991**, *2*, 569; d) T. R. Ward, L. M. Venanzi, A. Albinati, F. Lianza, T. Gerfin, V. Gramlich, G. M. R. Tombo, *Helv. Chim. Acta* **1991**, *74*, 983; e) M. J. Baker, P. J. Pringle, *J. Chem. Soc. Chem. Commun.* **1993**, 314; f) H. Adolfsson, K. Wärnmark, C. Moberg, *J. Chem. Soc. Chem. Commun.* **1992**, 1054; g) H. Adolfsson, K. Nordström, K. Wärnmark, C. Moberg, *Tetrahedron: Asymmetry* **1996**, *7*, 1967; h) D. D. LeCloux, W. B. Tolman, *J. Am. Chem. Soc.* **1993**, *115*, 1153; i) C. J. Tokar, P. B. Kettler, W. B. Tolman, *Organometallics* **1992**, *11*, 2737; j) D. D. Lecloux, C. J. Tokar, M. Osawa, R. P. Houser, M. C. Keyes, W. B. Tolman, *Organometallics* **1994**, *13*, 2855.
[5] Asymmetric catalysis with chiral aminoalcohols as ligands: a) W. A. Nugent, R. L. Harlow, *J. Am. Chem. Soc.* **1994**, *116*, 6142; b) F. DiFuria, G. Licini, G. Modena, R. Motterle, W. A. Nugent, *J. Org. Chem.* **1996**, *61*, 5175; c) H. Lütjens, P. Knochel, *Tetrahedron: Asymmetry* **1994**, *5*, 1161; d) H. Lütjens, G. Wahl, F. Möller, F. Knochel, J. Sundermeyer, *Organometallics* **1997**, *16*, 5869; e) M. Cernerud, H. Adolfsson, C. Moberg, *Tetrahedron: Asymmetry* **1997**, *8*, 2655; f) W. A. Nugent, G. Licini, M. Bonchio, O. Bortolini, M. G. Finn, B. W. McCleland, *Pure Appl. Chem.* **1998**, *70*, 1041; g) M. Bonchio, G. Licini, F. Di Furia, S. Mantovani, G. Modena, W. A. Nugent, *J. Org. Chem.* **1999**, *64*, 1326; h) M. Bonchio, G. Licini, G. Modena, O. Bortolini, S. Moro, W. A. Nugent, *J. Am. Chem. Soc.* **1999**, *121*, 6258; i) M. Bonchio, O. Bortolini, G. Licini, S. Moro, W. A. Nugent, *Eur. J. Org. Chem.* **2003**, 507; j) M. G. Buonomenna, E. Drioli, W. A. Nugent, L. J. Prins, P. Scrimin, G. Licini, *Tetrahedron Lett.* **2004**, *45*, 7515.
[6] Recent advances in the design of C_3-chiral podands: a) G. Bringmann, M. Breuning, R.-M. Pfeifer, P. Schreiber, *Tetrahedron: Asymmetry* **2003**, *14*, 2225; b) G. Bringmann, R.-M. Pfeifer, C. Rummey, K. Hartner, M. Breuning, *J. Org. Chem.* **2003**, *68*, 6859; c) T. Fang, D.-M. Du, S.-F. Lu, J. Xu, *Org. Lett.* **2005**, *7*, 2081; d) M. P. Castaldi, S. E. Gibson, M. Rudd, A. J. P. White, *Angew. Chem.* **2005**, *117*, 3498; *Angew. Chem. Int. Ed.* **2005**, *44*, 3432; e) M. P. Castaldi, S. E. Gibson, M. Rudd, A. J. P. White, *Chem. Eur. J.* **2006**, *12*, 138.
[7] a) *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), Wiley-VCH, Weinheim, **2000**; b) *Asymmetric Catalysis in Organic Synthesis* (Ed.: R. Noyori), Wiley, New-York, **1994**.
[8] a) B. L. Feringa, *Acc. Chem. Res.* **2000**, *33*, 346; b) M. T. Reetz, A. Meiswinkel, G. Mehler, K. Angermund, M. Graf, W. Thiel, R. Mynott, D. G. Blackmond, *J. Am. Chem. Soc.* **2005**, *127*, 10305.
[9] a) M. Albrecht, G. van Koten, *Angew. Chem.* **2001** *113*, 3866; *Angew. Chem. Int. Ed.* **2001**, *40*, 3750; b) M. E. van der Boom, D. Milstein, *Chem. Rev.* **2003**, *103*, 1759; c) M. Q. Slagt, D. A. P. van Zwieten, A. J. C. M. Moerkerk, R. J. M. Klein Gebbink, G. van Koten, *Coord. Chem. Rev.* **2004**, *248*, 2275.
[10] J. F. Larrow, E. N. Jacobsen, *Top. Organomet. Chem.* **2004**, *6*, 123.

[11] L. H. Gade, *Chem. Commun.* **2000**, 173, and references therein.
[12] L. H. Gade, *Acc. Chem. Res.* **2002**, *35*, 575.
[13] a) J. Zhou, Y. Tang, *J. Am. Chem. Soc.* **2002**, *124*, 9030; b) Y. Tang, M.-C. Ye, J. Zhou, *J. Comb. Chem.* **2004**, *6*, 301; c) M.-C. Ye, B. Li, J. Zhou, M.-C. Sun, Y. Tang, *J. Org. Chem.* **2005**, *70*, 6108.
[14] M. Seitz, C. Capacchione, S. Bellemin-Laponnaz, H. Wadepohl, B. D. Ward, L. H. Gade, *Dalton Trans.* **2006**, 193.
[15] Reviews: a) F. Fache, E. Schulz, M. Lorraine Tommasino, M. Lemaire, *Chem. Rev.* **2000**, *100*, 2159; b) H. A. McManus, P. J. Guiry, *Chem. Rev.* **2004**, *104*, 4151.
[16] 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, Y. H. Zhang, *J. Am. Chem. Soc.* **1991**, *113*, 728; d) D. Müller, G. Umbricht, B. Weber, A. Pfaltz, *Helv. Chim. Acta* **1991**, *74*, 232; e) H. Nishiyama, H. Sakaguchi, T. Nakamura, M. Horihata, M. Kondo, K. Itoh, *Organometallics* **1989**, *8*, 846.
[17] a) K. Kawasaki, S. Tsumura, T. Katsuki, *Synlett* **1995**, 1245; b) Y. Kohmura, T. Katsuki, *Tetrahedron Lett.* **2000**, *41*, 3941.
[18] T. H. Chan, G. Z. Zheng, *Can. J. Chem.* **1997**, *75*, 629.
[19] J. Zhou, Y. Tang, Y. *Chem. Soc. Rev.* **2005**, *34*, 664.
[20] T. H. Chuang, J. M. Fang, C. Bolm, *Synth. Commun.* **2000**, *30*, 1627.
[21] a) S. G. Kim, K. H. Kim, J. Jung, S. K. Shin, K. H. Ahn, *J. Am. Chem. Soc.* **2002**, *124*, 591; b) S. G. Kim, K. H. Kim, Y. K. Kim, S. K. Kim, S. K. Shin, K. H. Ahn, *J. Am. Chem. Soc.* **2003**, *125*, 13819; c) S.-G. Kim, K. H. Ahn, *Tetrahedron Lett.* **2001**, *42*, 4175.
[22] S. Bellemin-Laponnaz, L. H. Gade, *Chem. Commun.* **2002**, 1286.
[23] S. Bellemin-Laponnaz, L. H. Gade, *Angew. Chem.* **2002**, *114*, 3623; *Angew. Chem. Int. Ed.* **2002**, *41*, 3473.
[24] L. H. Gade, G. Marconi, C. Dro, B. D. Ward, M. Poyatos, S. Bellemin-Laponnaz, H. Wadepohl, A. Caneschi, G. Poneti, *Chem. Eur. J.* **2007**, *13*, 3058.
[25] C. Foltz, S. Bellemin-Laponnaz, M. Enders, H. Wadepohl, L. H. Gade, *Org. Lett.* **2008**, 10, 305.
[26] J. A. Takacs, P. M. Hrvatin, J. M. Atkins, D. S. Reddy, J. L. Clark, *New J. Chem.* **2005**, *29*, 263.
[27] C. Foltz, M. Enders, S. Bellemin-Laponnaz, H. Wadepohl, L. H. Gade, *Chem. Eur. J.* **2007**, *13*, 5994.
[28] Reviews: a) W. N. Lipscomb, N. Sträter, *Chem. Rev.* **1996**, *96*, 2375; b) D. Auld, *Struct. Bonding* **1997**, *89*, 29; c) J. E. Coleman, *Curr. Opin. Chem. Biol.* **1998**, *2*, 222.
[29] a) H. Vahrenkamp, *Acc. Chem. Res.* **1999**, *32*, 589; b) G. Parkin, *Chem. Commun.* **2000**, 1971; c) G. Parkin, *Chem. Rev.* **2004**, *104*, 699.
[30] C. Dro, S. Bellemin-Laponnaz, R. Welter, L. H. Gade, *Angew. Chem.* **2004**, *116*, 4579; *Angew. Chem. Int. Ed.* **2004**, *43*, 4479.
[31] a) W. Kaminsky, A. Laban, *Appl. Catal. A* **2001**, *222*, 47; b) M. Bochmann, *J. Chem. Soc. Dalton Trans.* **1996**, 255; c) H. H. Brintzinger, D. Fischer, R. Mülhaupt, B. Rieger, R. M. Waymouth, *Angew. Chem.* **1995**, *107*, 1255; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1143.
[32] a) Z. Hou, Y. Wakatsuki, *Coord. Chem. Rev.* **2002**, *231*, 1; b) J. Gromada, J.-F. Carpentier, A. Mortreux, *Coord. Chem. Rev.* **2004**, *248*, 397; c) P. M. Zeimentz, S. Arndt, B. R. Elvidge, J. Okuda, *Chem. Rev.* **2006**, *106*, 2404, and references therein.
[33] B. D. Ward, S. Bellemin-Laponnaz, L. H. Gade, *Angew. Chem.* **2005**, *117*, 1696; *Angew. Chem. Int. Ed.* **2005**, *44*, 1668.
[34] S. Arndt, T. P. Spaniol, J. Okuda, *Angew. Chem.* **2003**, *115*, 5229; *Angew. Chem. Int. Ed.* **2003**, *42*, 5075.
[35] E. Y. Tshuva, I. Goldberg, M. Kol, *J. Am. Chem. Soc.* **2000**, *122*, 10706.
[36] a) L. Lukešová, B. D. Ward, S. Bellemin-Laponnaz, H. Wadepohl, L. H. Gade, *Dalton Trans.* **2007**, 920; b) L. Lukešová, B. D. Ward, S. Bellemin-Laponnaz, H. Wadepohl, L. H. Gade, *Organometallics* **2007**, *26*, 4652.
[37] J. Thorhauge, M. Roberson, R. G. Hazell, K. A. Jørgensen, *Chem. Eur. J.* **2002**, *8*, 1888.
[38] A. Córdova, *Acc. Chem. Res.* **2004**, *37*, 102.
[39] M. Marigo, A. Kjærsgaard, K. Juhl, N. Gathergood, K. A. Jørgensen, *Chem. Eur. J.* **2003**, *9*, 2359.
[40] a) C. Foltz, B. Stecker, G. Marconi, H. Wadepohl, S. Bellemin-Laponnaz, L. H. Gade, *Chem. Commun.* **2005**, 5115; b) C. Foltz, B. Stecker, G. Marconi, S. Bellemin-Laponnaz, H. Wadepohl, L. H. Gade, *Chem. Eur. J.* **2007**, *13*, 9912.
[41] M. Marigo, K. Juhl, K. A. Jørgensen, *Angew. Chem.* **2003**, *115*, 1405; *Angew. Chem. Int. Ed.* **2003**, *42*, 1367.
[42] a) B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395; b) G. Helmchen, *Pure Appl. Chem.* **2004**, *76*, 495; c) T. Graening, H.-G. Schmalz, *Angew. Chem.* **2003**, *115*, 2684–2688; *Angew. Chem. Int. Ed.* **2003**, *42*, 2580.
[43] P. von Matt, G. C. Lloyd-Jones, A. B. E. Minidis, A. Pfaltz, L. Macko, M. Neuburger, M. Zehnder, H. Rüeger, P. S. Pregosin, *Helv. Chim. Acta* **1995**, *78*, 265.

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