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Second generation Trisoxazolines – New polydentate and recyclable dendritic ligands for asymmetric catalysis

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"Obstacles cannot crush me. Every obstacle yields to stern resolve."

Leonardo da Vinci
(English translation by Jean Paul Richter, 1888)

Abstract

In this work, directed towards more efficient and broadened applications of tris(oxazolinyl)ethanes (trisoxazolines) in asymmetric Lewis acid catalysis, a library of new stereodirecting polydentate and linker-functionalised ligands was designed.

On the basis of a multigramm-scale access to appropriately functionalised α-amino alcohol precursors, three C_1-chiral pentadentate and two C_3-symmetric hexadentate trisoxazoline derivatives, incorporating peripheral (thio)ether functions, were synthesised. Conferring greater kinetic persistence to labile metals such as lanthanides, they are assumed to allow efficient applications in stereoselective transformations.

Bis- and trisoxazolines containing an alkynyl unit have been covalently attached to carbosilane dendrimers and the general catalytic potential of their Cu^{II}-complexes was assessed by studying two benchmark reactions. For both of them, the bisoxazoline-based multisite catalysts displayed superior selectivity and, in particular, catalyst activity. The latter was interpreted as being due to the hindered decoordination of the third oxazoline unit, the key step in the generation of the active catalyst, in the immobilised trisoxazoline-copper complexes.

Second generation dendrimer catalysts were immobilised in dialysis membrane bags, allowing to effect catalytic conversions by dipping them into substrate-filled reaction vessels. The bisoxazoline-based catalysts gave good and reproducible results after several recyclings, whereas the performance of the trisoxazoline dendrimers decreased monotonically due to their low activity, which necessitated an increased reaction time for each cycle. This resulted in higher levels of catalyst leaching.

Abstract

Le présent travail, axé sur un élargissement et une optimisation des applications des ligands de type tris(oxazolinyl)ethane (trisoxazolines) en catalyse asymétrique « acide de Lewis », présente une panoplie de nouveaux ligands stéréodirecteurs multidentates et porteurs de fonctions capables de permettre d'ultérieurs connexions ou autre greffage (« linkers »).

Basé sur la préparation (à l'échelle du gramme) de précurseurs fonctionnalisés de la classe des alcools aminés appropriés, trois dérivés chiraux pentadentates de symétrie C_1 et deux dérivés hexadentates de symétrie C_3 de la famille des trisoxazolines, incorporant des fonctions (thio)ether, ont pu être synthétisés. Conférant de meilleures stabilités cinétiques envers les métaux labiles comme les lanthanides, ces nouveaux ligands sont alors supposés fournir des applications plus efficaces dans les transformations stéréosélectives.

Les bis- et trisoxazolines contenant une fonction alkynyl ont pu être greffées de façon covalente à des supports dendritiques de type carbosilane et le potentiel catalytique des complexes de cuivre(II) de ces nouveaux ligands polydispersés a pu être examiné au travers de l'étude de deux réactions de référence. Pour chacune de ces réactions, les catalyseurs multisites de type bisoxazoline montrent une meilleure sélectivité et plus particulièrement, une activité catalytique supérieure. Cette observation peut être interprétée comme étant due à une gêne dans la décoordination de la troisième unité oxazoline, représentant l'étape clé pour la génération de l'espèce catalytiquement active pour les complexes de cuivre porteurs de ligands trisoxazoline immobilisés.

Les catalyseurs dendritiques de seconde génération ont été encapsulés dans des sachets à membranes de dialyse. Ainsi, les réactions catalytiques ont pu être effectuées en immergent ces « sachets catalytiques » dans un récipient contenant une solution de substrat. Les

catalyseurs contenant les unités bisoxazoline ont ainsi conduits à de bons résultats reproductibles après plusieurs recyclages, alors que la performance des dendrimères contenant les ligands trisoxazoline diminue de manière monotone au fil des tours catalytiques en raison de leur faible activité, nécessitant alors une augmentation du temps de réaction après chaque cycle. Par conséquence, ceci engendre une perte plus importante du catalyseur.

Zusammenfassung

Im Rahmen dieser Arbeit wurde, mit dem Ziel Tris(oxazolinyl)ethanderivate (Trisoxazoline) in der asymmetrischen Lewissäure-Katalyse effizienter und breiter anzuwenden, eine Serie neuer polydentater und Linker-funktionalisierter Steuerliganden synthetisiert.

Basierend auf einem Zugang zu entsprechend funktionalisierten α-Aminoalkoholvorstufen im Multigramm-Maßstab wurden drei C_1-chirale pentadentate und zwei C_3-symmetrische hexadentate Trisoxazolinderivate mit peripheren (Thio)etherfunktionen synthetisiert. Diese tragen im Prinzip zur kinetischen Stabilisierung labiler Metalle, z.B. der Lanthanoiden, bei und ermöglichen so deren effiziente Anwendung in stereoselektiven Reaktionen.

Nach der kovalenten Trägerung Alkinyl-funktionalisierter Bis- und Trisoxazoline an Carbosilandenrimeren wurde das katalytische Potential ihrer Cu^{II}-Komplexe in zwei Benchmarkreaktionen abgeschätzt. Bisoxazolin-basierte Vielzentrenkatalysatoren erzielten mit beiden Systemen höhere Selektivitäten und insbesondere Aktivitäten als ihre Trisoxazolinanaloga. Dies wurde auf die gehinderte Dekoordination des dritten Oxazolins, dem Schlüsselschritt bei der Ausbildung des aktiven Katalysators im Falle der immobilisierten Trisoxazolin-Kupferkomplexe, zurückgeführt.

Dendritische Katalysatoren der zweiten Generation wurden in einer Dialysemembran immobilisiert, um durch Eintauchen der resultierenden Beutel in mit Substrat befüllte Reaktionsgefäße katalytische Umsetzungen durchzuführen. Dabei erzielten die Bisoxazolin-basierten Katalysatoren über mehrere Läufe gute, reproduzierbare Werte, während jene der Trisoxazolindendrimere monoton abnahmen. Dies ließ sich auf ihre geringe Aktivität, die damit verbundenen längeren Reaktionszeiten und die erhöhten Katalysatorverluste durch Leaching zurückführen.

Contents

CHAPTER 1

Introduction: The Economic Relevance of Catalysis

Since the first report of a catalytic process almost 200 years ago,[1] the field has undergone a tremendous development, making catalysts indispensable nowadays. Since it combines economic and ecological aspects like no other scientific or technical principle, catalytic transformations play a role in virtually every industrial process. According to recent estimates, 15-20% of the economies of the industrially developed western nations rely directly or indirectly on applications of catalyses.[2] This is reflected in the impressive volume of catalyst world production (1 million tons/year), corresponding to an estimated global market of about 10 billion euros.[3] Therefore, by providing us with a wide range of products for our health, nutrition, and environment, catalysis has an impact on our life as few other technologies do.

A replacement of the predominant stoichiometric processes by catalytic procedures has started in the 1990s. In particular, homogeneous catalysts proved reliable tools, offering a broad range of advantages over heterogeneous systems such as milder reaction conditions, excellent selectivities, and analytic accessibility of reaction intermediates.[2,4] Latest developments in this field concentrate on the establishment of a renewable chemicals industry, featuring renewable crop-based feedstocks rather than fossil resources.[5] The use of improved and recyclable olefin metathesis catalysts,[6] for example, is thought to be a promising approach to access sunflower-based feedstocks as raw materials for the chemical industry.[7]

The most important advantage of homogeneous catalysts, however, is their potential to perform asymmetric catalysis. Recent trends in the Food and Drug Administration approval of new drug applications show that the percentage of chiral drugs has increased

significantly from 58% in 1992 to 75% in 2006. Furthermore, the proportion of single enantiomer drugs manufactured, using purely synthetic methodology, has increased from 20% in 1992 to over 50% in 2006.[8] The reason is the generally superior performance of the pure enantiomers as ingredients, especially for pharmaceuticals, flavours, fragrances and agrochemicals.[9]

Among the approaches for producing enantiopure compounds, enantioselective catalysis is one of the most attractive.[10] Its significance was acknowledged by the award of the Nobel prize to *Knowles*, *Noyori* and *Sharpless* in 2001 for their work in this field.[11] Today, a large number of catalysts are known which deliver products with more than 95% *ee*; some are applied in highly selective processes on an industrial scale.[9,12] Using the rhodium complex of *Noyori*'s (*S*)-BINAP, for example, (*R*)-citronellal-enamine is produced with 96-99% *ee* by the Japanese company Takasago (1500 tons/year).[4] Enantioselective hydrogenation processes represent the most important industrial application of asymmetric catalysis, because of their atom economy, scalability and robustness.[8b] Consequently, the iridium-catalysed enantioselective hydrogenation yielding (*S*)-metolachlor – active ingredient of one of the most important grass herbicides – is today's largest application of asymmetric catalysis, providing more than 10 000 tons/year of the compound in a full-scale plant.[12a,13]

These examples demonstrate that catalysis, asymmetric catalysis namely, is of real importance beyond academic laboratories. Recent trends such as the approach to establish a sustainable industry, however, indicate a constant need for new tools. Therefore, catalysis has to continually pass through a cycle of innovation, optimisation, and implementation to supply scalable, industrially viable processes for the needs of today's society.[3]

CHAPTER 2

State of the Field

2.1 The need for new metal-based asymmetric catalysts

Asymmetric catalysis is an elegant approach to selectively access chiral enantiopure compounds.[10] The controlled assembly of three-dimensional molecular structures is still the most challenging problem during the synthesis of biologically active natural products, because of the limited number of available catalytic transformations. Although new asymmetric catalytic methods contribute to a greater fundamental understanding of the leading principles that govern the construction of stereocentres, only a relatively small number of them are useful for large-scale industrial applications. Viable commercial operations must account for more than effective asymmetric induction: high catalyst activity, easy availability, stability and reusability as well as low toxicity must be guaranteed besides feasible large-scale handling and low costs. Additionally, nowaday's synthetic chemical industry requires catalysts showing increased functional group tolerance while being able to generate multiple stereocentres: properties which are needed to shorten synthetic routes and to avoid protecting and masking strategies.[14]

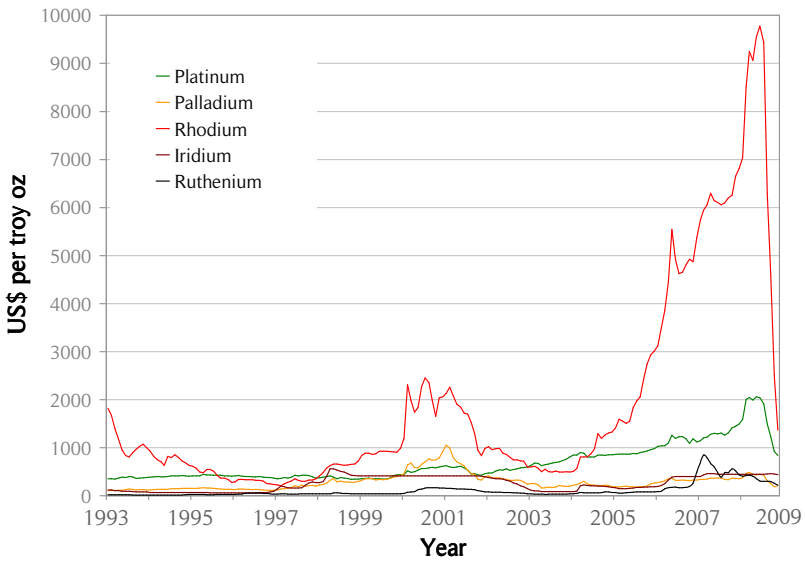
In principle, there are three ways to promote asymmetric catalysis: biocatalysis, metal catalysis, and organocatalysis. Metal-based catalysts have long proven their versatility and efficiency[15] whereas organocatalysts have undergone a tremendous development in academia since 1998 and are on the brink of being established in industry.[16] The reasons for the increasing interest in organocatalysts as complementary tools for asymmetric catalysis originate from the drawbacks connected to the application of chiral metal complexes. They concern, among others, high preparation costs, the use of toxic metals, which could

contaminate the final product, and sometimes the need to operate under rigorously anhydrous or anaerobic conditions.[17] Organocatalysts, on the other hand, usually require high catalyst loadings due to low activities,[18] while displaying a high level of substrate dependency, and only a relatively narrow scope of transformations.[19] By contrast, metal-based catalysts access a wealth of oxidations, reductions, σ-bond insertions, π-bond activations, Lewis acid-promoted reactions and most importantly CH-activation. These arguments reflect the need for new metal-based tools in molecular catalysis.

2.2 Latest trends in metal-based catalysis

The latest trends in catalyst design, particularly in industry, are directed towards creating a sustainable, more efficient, "green" chemistry that allows the use of less material and energy. Robust, atom economical technologies based on the use of safer materials (e.g. "green" solvents) are to minimise the generation of waste and pollutants.[20] Waste minimisation, therefore, is a key concern and can be achieved by replacing stoichiometric by catalytic processes, batch reactions by continuous processes, and by focussing the recycling and reuse of materials.[21]

CHART 2.1 **Development of selected precious metal prices**[22]



In this context, the area of catalysis is referred to as a "foundational pillar" of green chemistry, a notion that is justified best by an example: non-catalytic processes generate over 30 kg of waste per kg of the pain relief drug Ibuprofen whereas the catalytic method produces less than 1 kg of waste.[20c] Moreover, the catalytic step almost halved the number of steps needed to manufacture this drug while helping to eliminate the toxic solvent CCl_4 from the process.[20a] During the last decades, many transition metals, especially precious metals such as palladium, rhodium, iridium and ruthenium, have proven efficient catalysts for a large number of similar applications. The limited availability of these metals, however, as well as their high and inconstant prices[22] (Chart 2.1) make more economical alternatives desirable. On the one hand, this problem can be addressed by increasing the use of cheaper transition metals such as iron,[23] copper, zinc, and manganese or by applying rare earths. On the other hand, recycling technologies (supplementary to metal substitution or if a replacement proves difficult) allowing the reuse of catalysts are focussed.

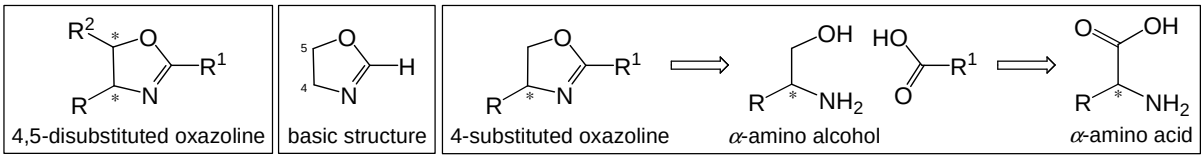
2.3 The oxazoline motif in ligand design

Metal-based chiral catalysts derive from a combination of a metal atom or ion, being the actual promoter of the reaction, and a chiral ligand which tunes the molecule's electronic and steric properties. In this way, the activity and selectivity – including the stereoselectivity – of a reaction catalysed by a metal-complex are determined by the ligand. This is why an almost unlimited number of lead structures are to be found in literature. Ligands incorporating different donoratoms, motifs and skeletons based on symmetric and non-symmetric entities have been created.[24] Among them, nitrogen donors have proven versatile ligands for asymmetric catalysis.[25]

Out of this group, oxazolines (4,5-dihydro-1,3-oxazoles, Scheme 2.1) and their derivatives are ideally suited for broad application. The impressive number of publications[26] since the first application of an oxazoline ligand in asymmetric catalysis in 1986 underlines their potential.[27] Today, these compounds belong to one of the most efficient classes of ligands, offering a broad range of transformations.[28]

Oxazolines and their derivatives are particularly suited for broad application in asymmetric catalysis for a number of reasons: on the one hand, these heterocyclic units are easily rendered chiral by introduction of substituents in the 4- or 5-position (Scheme 2.1).

SCHEME 2.1 The basic oxazoline, its derivatives, and the common disconnection approach



On the other hand, their synthesis can be conveniently conducted by the use of carboxylic acid derivatives and optically active α-amino alcohols as starting materials.[29] The latter are easily accessible *via* α-amino acids from the chiral pool. This renders the resulting ligands relatively inexpensive compared to other types of ligands. Moreover, the stereodirecting substituents are located close to the metal centre upon coordination through the nitrogen atom. This property in unison with their rigid, quasi-planar structure and their versatile coordination behaviour[30] allows for optimal transfer of the chiral information to the substrate. Finally, oxazolines tend to be relatively stable towards hydrolysis, radicals and oxidation, allowing their application in different types of transformations with different reagents and substrates under various conditions. Therefore, their inherent properties such as accessibility, structure and stability helped establishing their success story.

Diverse ligand structures incorporating the oxazoline motif have been developed to enable optimal coordination and stabilisation of the chosen metal and (therefore) have improved stereoselectivity (Figure 2.1).[31]

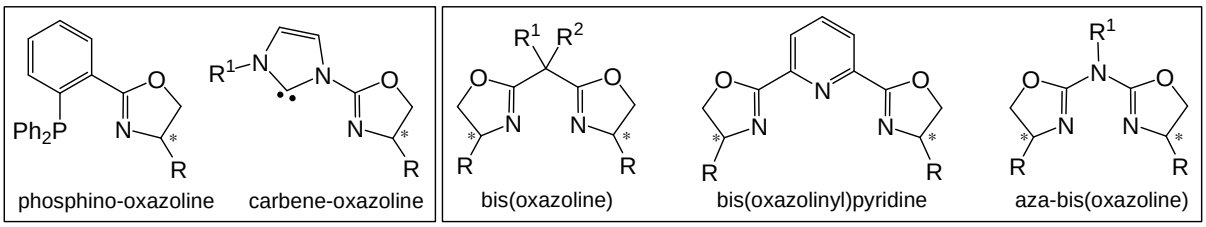


FIGURE 2.1 Some ligands incorporating the oxazoline motif.

Oxazoline ligands can be classified according to denticity (mono- to polydentate), the number of incorporated heterocycles (mono-, bis- and trisoxazolines) and their symmetry (non-symmetric, pseudo-symmetric and C_2-/C_3-symmetric). Their structures vary in the

backbones, the connecting units between the cycles, and the combination with other structural units. Moreover, diverse ligands incorporating combinations of the oxazoline nitrogen donor(s) and other donor atoms have been reported (P/N, C/N, N/N, O/N, S/N).[28c,31b,32] The most interesting of these compounds are multidentate bisoxazolines,[33-35] although only few conceptual studies based on the use of these ligands are known (Figure 2.2).[36]

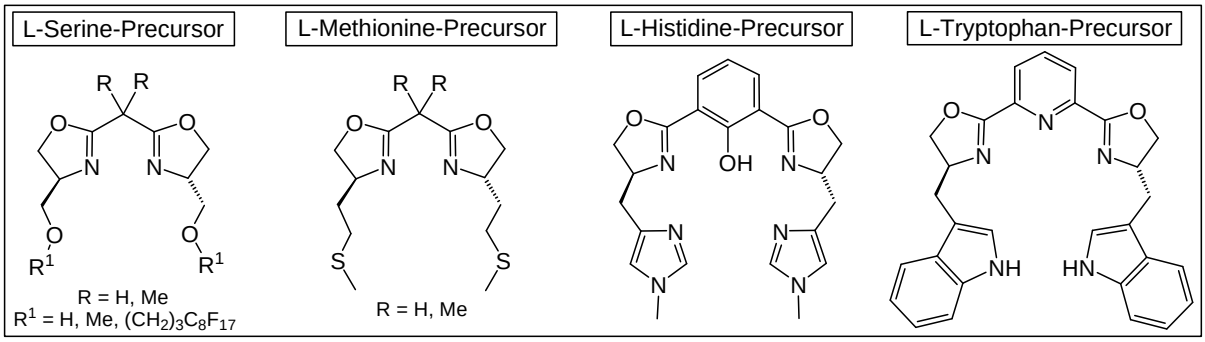


FIGURE 2.2 Peripherally heteroatom-functionalised bisoxazolines.

Overall, bisoxazolines ("Box") constitute the most efficient class of oxazoline ligands:[37] they are widely applied in catalysis; even a considerable number of immobilised species are common (Chapter 2.6).[38] These bidentate ligands, which possess the advantages of the whole class of oxazolines (such as versatility of ligand design and straightforward synthesis),[39] exhibit a symmetry element: a twofold rotational axes that positively affects stereoselectivity (Chapter 2.4.2). A drawback of bisoxazolines, however, are the relatively high catalyst loadings of around 10 mol%, required to obtain satisfying activity and selectivity. Compared to metal-catalysed reactions in general, this is a large amount resembling the conditions of organocatalysis. A new type of oxazoline ligands – tridentate trisoxazolines – has been developed to circumvent this handicap. Moreover, these (pseudo)-C_3-symmetric ligands are adapted to metals which prefer octahedral coordination geometries whereas C_2-symmetric bisoxazolines favour tetrahedral or square-planar geometries.[40]

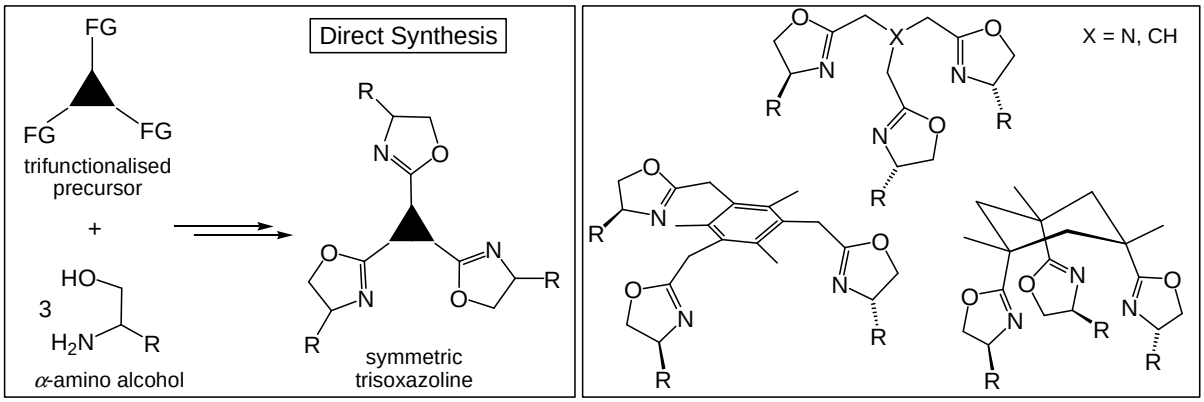
2.4 Trisoxazolines – an emerging class of ligands

The role of the additional donor atom is to increase the stability of metal complexes and to induce greater air- and (possibly) moisture stability. As many metal-catalysed reactions require an irreversible complexation of the metal to avoid formation of racemic product *via* an achiral catalyst,[41] trisoxazolines are expected to provide higher stereo-selectivities for certain reactions. Moreover, the third heterocycle creates a sterically strained situation, allowing the use of sterically less hindered chiral sources. These features combined with the aforementioned accessibility of octahedral metal centres provide an impetus for the design of trisoxazolines as stereodirecting ligands for asymmetric catalysis. This family represents the most recent group of oxazoline ligands.[42]

2.4.1 Synthetic approaches to trisoxazolines

An achiral trisoxazoline incorporating a central nitrogen atom was reported by *Sorrell et al.* as early as 1993.[43] The first chiral compound, exhibiting the same skeleton, was reported independantly by *Katsuki* and *Chan* in 1995.[44] Subsequently, a whole range of trisoxazolines featuring other cores and backbones were synthesised (Scheme 2.2).[45]

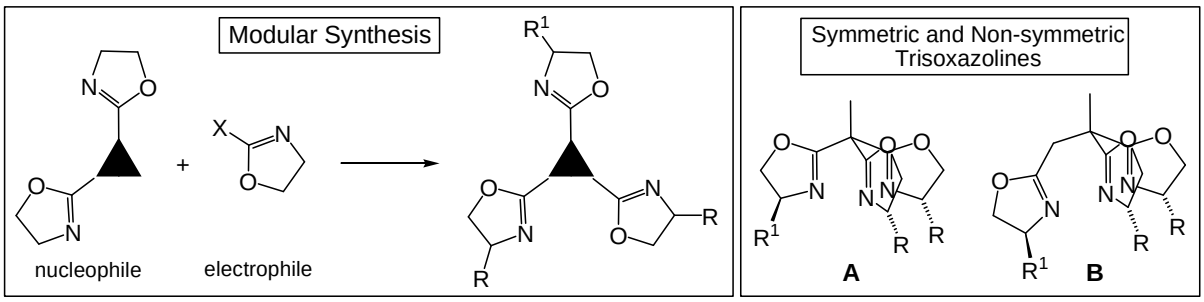
SCHEME 2.2 Direct approach to symmetric trisoxazolines



All these species, however, shared the same way of preparation. They were obtained by means of a direct synthesis forming the three cycles simultaneously. Although a range of highly symmetrical ligands could be created by this route, two major drawbacks favour another approach: first, the final step of the synthesis in which the heterocycles are formed

suffers from low yields. Second, only C_3-symmetric (or pseudo-C_3-symmetric) trisoxazolines are accessible, non-symmetric trisoxazolines being ignored. The latter, however, are additionally required to understand the effect of symmetrical ligands on stereoselectivity. Moreover, the synthesis of the structurally distinguished tris(oxazolinyl)ethane ("Trisox") derivatives failed *via* this route, as the precursors were decarboxylated and decomposed during the formation of the third oxazoline ring.[40] Finally, none of the systems depicted in Scheme 2.2 may act as a facially binding ligand.

SCHEME 2.3 Modular approach to symmetric and non-symmetric trisoxazolines



A modular synthetic strategy for Trisox ligands was proposed by *Gade* in 2002 (Scheme 2.3).[46] This approach was based on the coupling of a lithiated bisoxazoline and an electrophilic bromooxazoline *via* nucleophilic substitution. By combining modules which incorporate identical (or different) substituents at the chiral centres, C_3-symmetric (or non-symmetric) analogues were obtained. Most importantly, however, the synthesis of C_3-symmetric tris(oxazolinyl)ethane derivatives (**A**) was achieved (Scheme 2.3). These tripodal ligands exhibit a rigid structure, being most adapted to facially coordinate metal centres[47] in polyhedral coordination spheres (Chapter 2.4.3). Application of the high-yielding, modular approach by *Tang et al*., furthermore, yielded numerous non-symmetric trisoxazolines (**B**).[48]

2.4.2 Symmetric ligands in asymmetric catalysis

Using highly symmetrical, stereodirecting ligands in asymmetric catalysis may reduce the number of transition states and diastereomeric reaction intermediates, leading in favourable cases to increased stereoselectivity. This concept was applied successfully in the case of C_2-symmetrical molecules,[49] involving phosphines[50] and bisoxazolines.[37] In contrast, little is known about the behaviour of systems which are based on higher-symmetrical,

notably C_3-symmetric ligands, although their potential advantages in the design of chiral stereodirecting ligands have already been demonstrated.[51] These species mainly contribute to fewer competing reaction pathways when being coordinated to octahedral metal centres. Upon facial coordination, C_3-symmetric ligands render the residual free coordination sites of an octahedral coordination sphere homotopic. The same effect is observed with C_2-symmetric ligands, namely bisoxazolines, in tetrahedral or square-planar spheres (Figure 2.3).

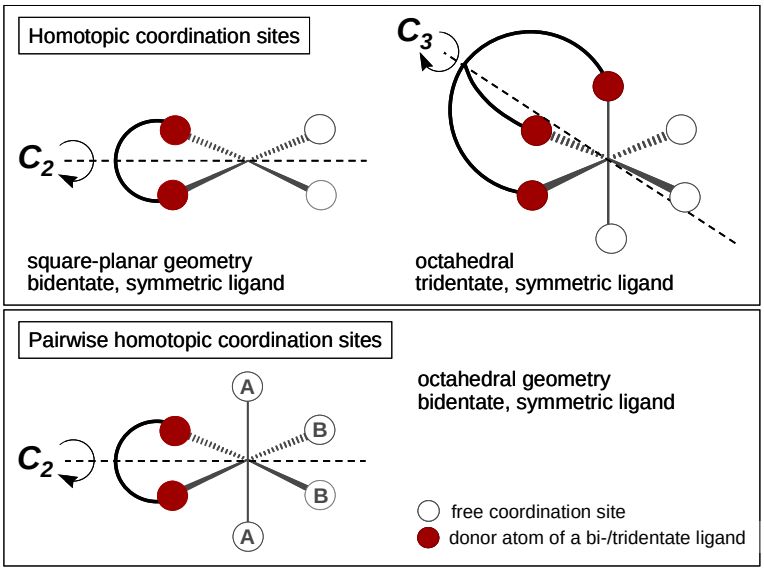


FIGURE 2.3 Effect of symmetric ligands on the free coordination sites of a metal.

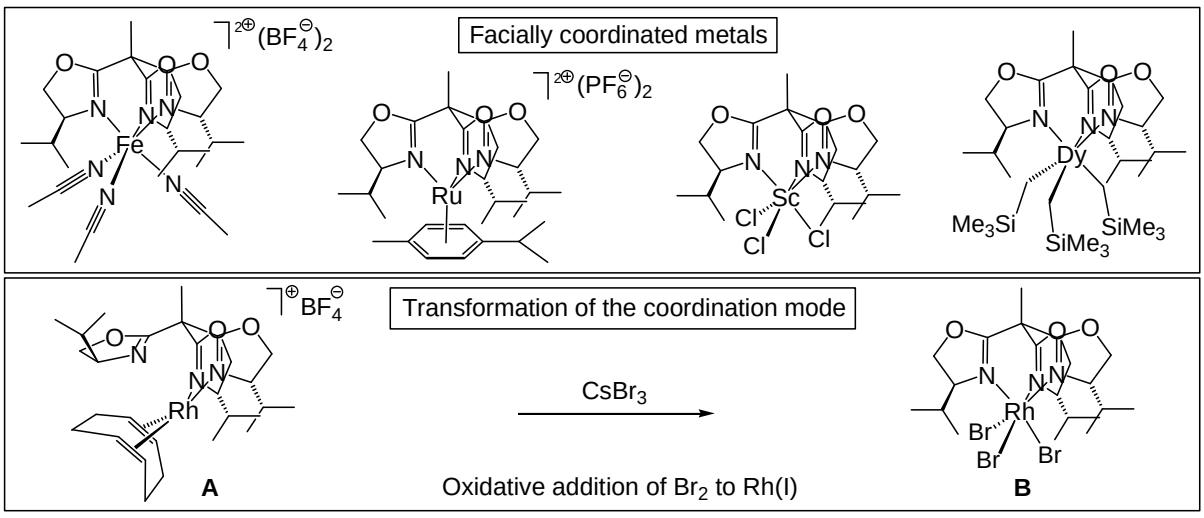
This phenomenon has been studied for around two decades.[52] The implications, however, that the use of chiral tridentate podands may have in stereoselective catalysis, have only recently been clarified. Although designed to coordinate facially to a metal centre, the potential of C_3-symmetric trisoxazolines has been demonstrated in transformations in which the intermediates do *not* adopt deltahedral coordination geometry, and thus do *not* allow tripodal coordination of the stereodirecting ligand. If the stereoselectivity determining step involves an octahedral species, the facial coordination of the trisoxazoline ligand, and consequently the threefold symmetry of the trisoxazoline-metal-fragment, will indeed simplify the stereoselection by rendering the free coordination sites homotopic. The symmetry of the ligand, however, will act "dynamically" (in fluxional processes) in species in which it is bidentate (Chapter 2.4.4).

2.4.3 Coordination chemistry of tris(oxazolinyl)ethanes

Investigating the general coordination behaviour of trisoxazolines provides the basis for understanding their behaviour in asymmetric catalysis. As extensive coordination studies have been mainly conducted with tris(oxazolinyl)ethanes, they are the only trisoxazolines to be considered in this section.

Tris(oxazolinyl)ethane ligands are generally able to facially coordinate to transition metals and lanthanides. This has been established by a series of X-ray structures (Scheme 2.4).[53] Provided that the stereoelectronic properties of the metal do not strongly favour other coordination geometries than octahedral, facial binding was indeed observed. These ligands, however, readily adapt to various coordination geometries and metal radii, depending on the given stereoelectronic situation. Their flexibility was demonstrated by the oxidation of the dicoordinate square-planar $Rh^{I}(d^{8})$-complex **A** to the d^{6} tribromo-rhodium(III) complex **B**, in which the podand ligand is symmetrically bound to the metal centre (Scheme 2.4). In both $Pd^{II}(d^{8})$- and $Pd^{0}(d^{10})$-complexes, by contrast, the third arm of the trisoxazoline ligand was found to be decoordinated in solution as well as in the crystalline state.

SCHEME 2.4 Facially coordinated trisoxazoline-metal-complexes[53]



Moreover, it was shown that the sterically demanding substituents at the chiral centres of the trisoxazoline hinder the formation of *catalytically inactive*, *homoleptic* $[M(Trisox)_2]^{n\oplus}$ species. This is the case for enantiopure ligands that are applied in asymmetric catalysis. Therefore, a coordination sphere offering up to three free

coordination sites for a substrate is generated. Stereochemically "mixed" (C_1-symmetric) derivatives (enantiopure and racemic) behave similarly. Only the application of racemic Trisox – composed of (*R*,*R*,*R*)-Trisox and (*S*,*S*,*S*)-Trisox – allows the formation of *meso*-$[M(Trisox)_2]^{n\oplus}$.[53] For bisoxazolines, similar considerations and observations were published by *Takacs et al.*[54]

In general, tris(oxazolinyl)ethanes serve as versatile stereodirecting ligands for a broad range of metals, as they readily adapt to various types of metal centres and coordination geometries. They were shown to efficiently coordinate early and late transition metals as well as lanthanides.

2.4.4 Application of trisoxazolines in asymmetric catalysis

Katsuki et al. reported the first application of trisoxazoline ligands in the asymmetric Kharash-Sosnovsky reaction in 1995 and later an allylic amination as well as the addition of diethylzinc to aldehydes. Already these first experiments indicated a promising catalytic behaviour of trisoxazolines compared to the well-established group of bisoxazolines, although the results of the latter have not been surpassed, yet.[44,55] Later, the various trisoxazolines described above (Chapter 2.4.1) – particularly *Tang*'s derivatives – were applied to a range of other reactions and to molecular recognition.[56,57] Excellent results were achieved in numerous examples, indicating a superiority of trisoxazolines to bisoxazolines in several cases.

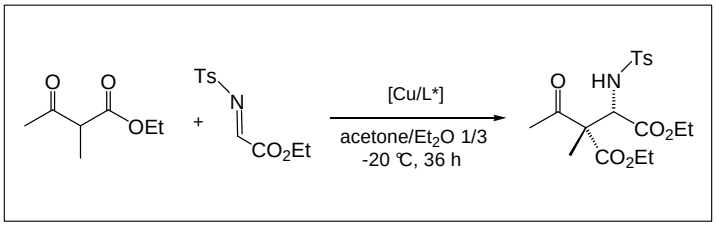
All these examples, however, were based on conformationally flexible ligands, only little being known about their coordination mode. Especially, the metal binding in the active catalyst species is not unambiguously established, still raising the question about facial coordination. Tris(oxazolinyl)ethane derivatives exhibit a rigid structure and a known coordination behaviour that can address this issue. In the following paragraphs only the main achievements using this type of ligand are reviewed, highlighting the role of C_3-symmetric ligands in asymmetric catalysis.

A Zn^{II}-trisoxazoline-complex, being a functional model for zinc-based peptidases, was successfully applied to the kinetic resolution of racemic esters, being the first example

of a non-enzymatic Zn-catalysed asymmetric transesterification.[58] The new trisoxazolines were moreover the first C_3-symmetric ligands applied to polymerisation catalysis: a Sc^{III}-complex was highly active in the polymerisation of a range of α-olefins exerting remarkable tacticity control.[59] Similar results were observed in polymerising different olefins with trisoxazoline-lanthanide-complexes, the metal centres ranging from lutetium to dysprosium.[60]

The processes that occur during catalysis were the object of detailed studies of two Cu^{II}-promoted Lewis acid catalyses:[61] the asymmetric Mannich reaction[62] of a β-ketoester with an activated N-tosyl-α-imino ester,[63] and the direct α-amination of α-substituted β-ketoesters with azodicarboxylates.[64] Using Cu^{II}-trisoxazoline-complexes, the catalyst loading required for the tosylation was reduced by a factor of 1000 (up to 0.01 mol%!) while achieving excellent and stable enantioselectivities around 90% (Scheme 2.5).

SCHEME 2.5 **Cu^{II}-promoted asymmetric Mannich reaction**[61]



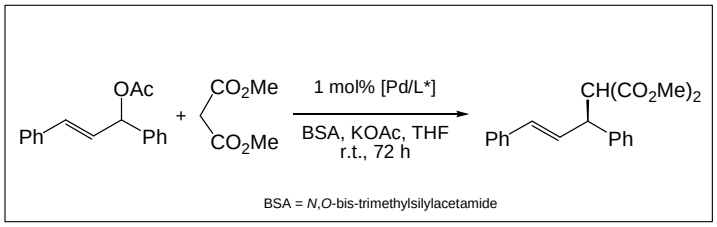
Loading [%]	Yield [%]	*ee* [%]	Yield [%]	*ee* [%]
10	84	84	84	90
1	70	84	75	89
0.01	35	66	36	90

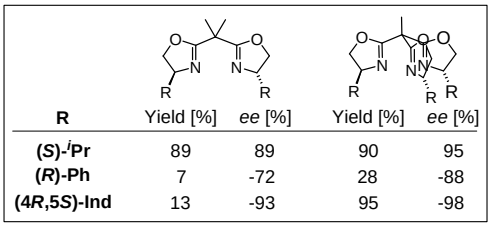
The corresponding bisoxazoline catalysts, on the other hand, suffered a drop in enantioselectivity from 84% to 66%. Similar differences, though somewhat less pronounced, were observed in the α-aminations. The kinetic lability of copper explains the different behaviour of both catalysts: in the resting state, trisoxazolines additionally stabilise the Cu^{II}-centre by weak coordination of the third nitrogen. Therefore, catalyst leaching is reduced compared to bisoxazolines, leading to better results.

Generation of an active species, however, requires decoordination of the third oxazoline, increasing the Lewis-acidity of Cu^{II} while offering a free coordination site to the substrate.[65] Indeed, the decoordination of one arm was evidenced by the X-ray structures of Cu^{II}-trisoxazoline-complexes which additionally contained coordinated ethyl 2-methylaceto-acetate. Nevertheless, rapid equilibria in solution may occur which limit interpretations based on X-ray structural data. To gain more reliable insight into the processes in solution,

non-deltahedral, less labile, diamagnetic palladium was chosen as active metal for complementary studies on allylic substitution (Scheme 2.6).[66]

SCHEME 2.6 **Pd^{II}-promoted allylic alkylation**[68]





R	Yield [%]	*ee* [%]	Yield [%]	*ee* [%]
(*S*)-^{i}Pr	89	89	90	95
(*R*)-Ph	7	-72	28	-88
(4*R*,5*S*)-Ind	13	-93	95	-98

The Pd^{II}-bisoxazoline-catalysed allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate served as reference system.[67] Trisoxazoline catalysts achieved better enantioselectivities in this reaction than their bisoxazoline analogues as well as remarkable rate enhancement (dependending on the substituents) along with a reduced induction period.[68] In solution, dynamic equilibria of Pd^{II}- and Pd^{0}-model-complexes were detected, indicating chemical exchange between the three different κ^2-coordinated forms of the trisoxazoline ligand (Figure 2.4).

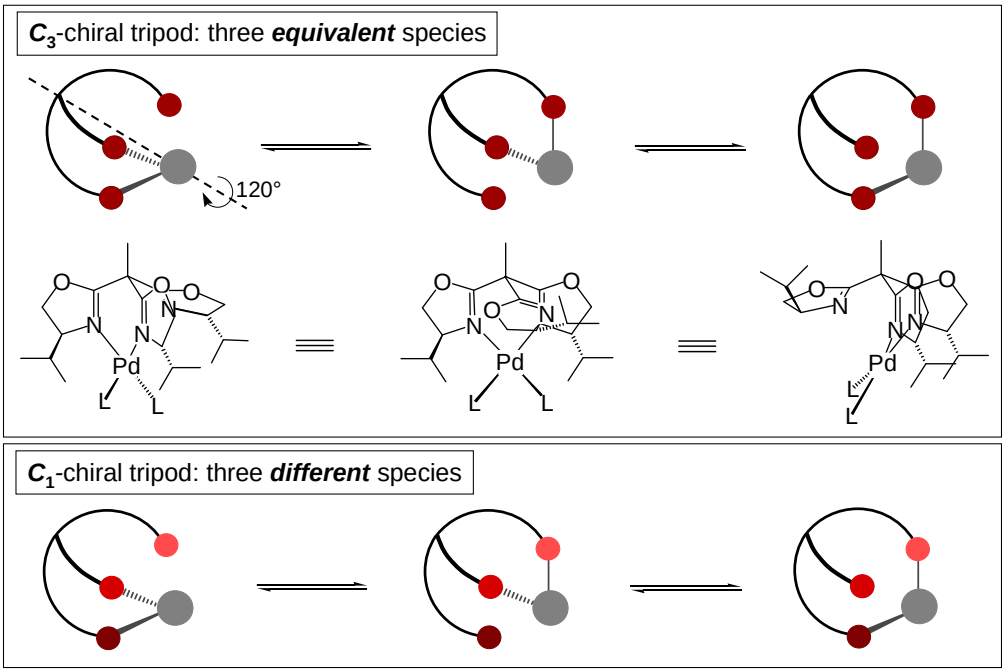


FIGURE 2.4 **Dynamic exchange of κ^2-chelating tripods coordinated to a complex fragment**; example: square-planar Pd^{II}-complexes.

For a symmetric tripod, such an exchange represents an equilibrium between *identical* rather than between *isomeric* species, as would be the case for less symmetrical complexes.

Therefore, these studies showed that a C_3-symmetrical podand may simplify the stereochemistry of the key catalytic intermediates even when acting as a bidentate ligand (apparently contradicting the most frequently cited line of arguments in favour of highly symmetric stereodirecting ligands, Chapter 2.4.2) in non-deltahedral metal complexes.

All these examples underline that C_3-symmetric, tripodal ligands – tris(oxazolinyl) ethanes – indeed influence the mechanism of a catalytic reaction: they may additionally stabilise the metal centres, shorten induction periods and increase reaction rates. Consequently, lower catalyst loadings were required and higher stereoselectivities were achieved. In every transformation, the chiral information of the ligand was efficiently transmitted to the substrates. Therefore, tris(oxazolinyl)ethanes have proven to be versatile ligand systems for enantioselective catalysts of the d- and f-block metals, applicable to a wide range of catalytic transformations.

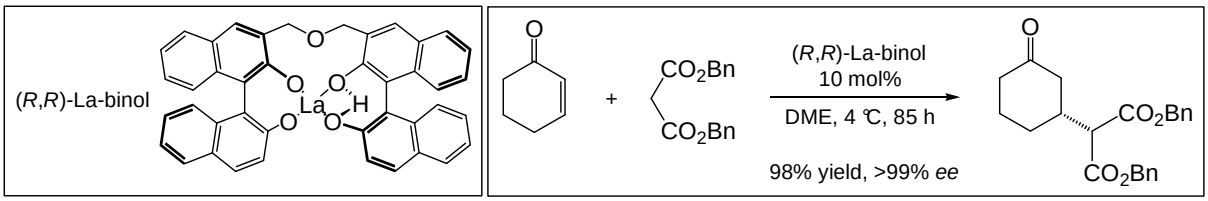
2.5 Rare earth-promoted asymmetric Lewis acid catalysis

Rare earths[69] are relatively abundant in the Earth's crust, although their name suggests the contrary. The occurrence of scandium in crustal rocks, for example, is greater than that of lead, mercury and the precious metals. In 1900, rare earths were produced only to supply materials for lighting applications. Over the past hundred years their consumption grew from hundreds of tons in 1900 to tens of thousands of tons. Applications diversified to the same degree. Nowadays rare earths serve as petroleum refining catalysts, metallurgical additives, components in alloys, permanent magnets, phosphors for colour monitors, and energy-efficient fluorescent lighting due to their remarkable electronic and magnetic properties.[70]

Lewis acid promoted reactions have emerged an important tool in organic synthesis over the past decades. Many different Lewis acid catalysts were elaborated, covering almost all the metals in the periodic table.[71] The development of achiral[72] and chiral Ln^{III}-catalysts[73,74] for "green chemistry" has gained importance due to the unique properties of

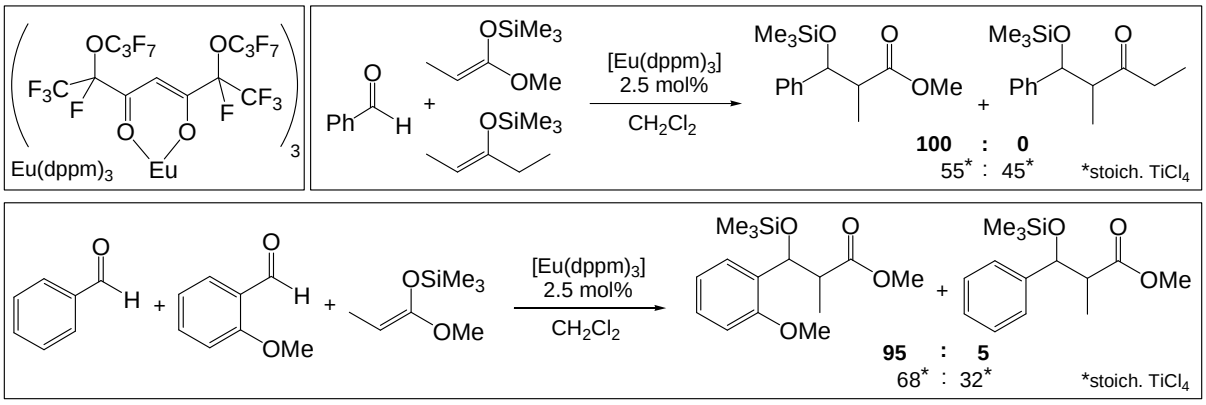
lanthanides.[75] In contrast to traditional Lewis acids ($AlCl_3$, BF_3, $TiCl_4$, and $SnCl_4$) which are applied stoichiometrically, lanthanides allow catalytic applications while being relatively stable towards deactivation *via* hydrolysis and oxidation. Moreover, rare earths exhibit only minor toxic potential, are recoverable, and reusable.[76] *Shibasaki*'s La^{III}-binol complex represents an example for the convenient application of lanthanide catalysts.[77] Being applied to asymmetric Michael reaction with a broad scope (Scheme 2.7), high *ee*-values (>99%) were obtained up to the fourth recovery cycle.

SCHEME 2.7 **La-promoted asymmetric Michael reaction**[77]



Applied in the Mukaiyama aldol reaction, [Eu(dppm)$_3$] (dppm = bis(perfluoro-2-propoxy-propionyl)methane) constitutes an example for the remarkable chemo- and stereoselectivity that can be achieved with lanthanide systems in comparison to stoichiometrically applied $TiCl_4$. Although containing achiral ligands, this catalyst demonstrates strikingly the advantages to traditional Lewis acids.[73c]

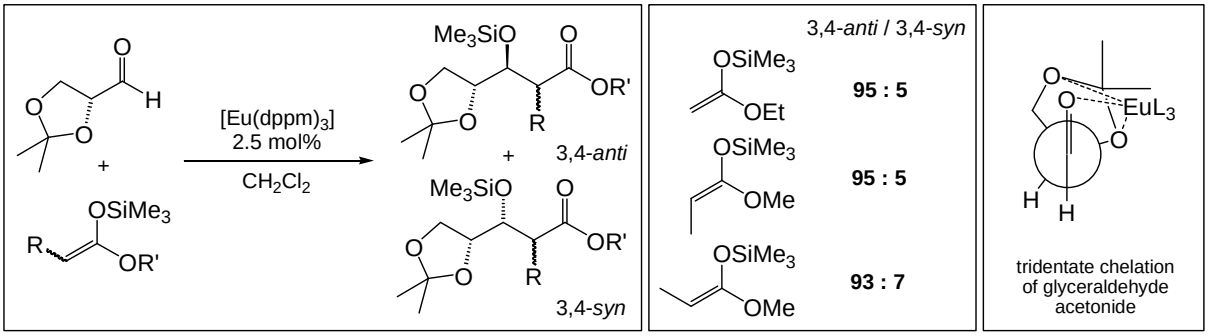
SCHEME 2.8 **Eu-promoted Mukaiyama adol reaction**: chemoselective conversion of silyl enol ethers (upper equation) and aldehydes (below).[73c]



[Eu^{III}(dppm)$_3$] chemoselectively converts the electrophile as well as the nucleophile, discriminating both between the different aldehydes and silyl enol ethers in competitive aldol reactions (Scheme 2.8): the substrates exhibit different reactivities depending on their substituents, protecting groups, and steric demand. These selections are due to the coordinating potential of the substrates (not their electrophilicity!) and are determined by

their ability to act as chelates. Moreover, the Eu^{III}-catalyst induces excellent and unusual diastereoselectivities which reflect anew the mode of complexation of the aldehydes, namely chelation or nonchelation: the unique stereoselectivity observed with glyceraldehyde acetonide, for example, can only be explained by a tridentate chelation of the aldehyde (Scheme 2.9).

SCHEME 2.9 **Eu-promoted Mukaiyama adol reaction**: unusual diastereoselectivity observed with glyceraldehyde acetonide.[73c]



As lanthanides provide a continuous range of ionic radii, fine-tuning of the Lewis acidity required for a certain transformation can be achieved by choosing an appropriate lanthanide ion. According to the HSAB classification of *Pearson*,[78] rare earth cations are considered to be hard acids ranking between Sr^{II} and Ti^{IV}. As hardness increases with decreasing ionic radius, $Sc^{3\oplus}$ is the most Lewis acidic rare earth ion whereas the large $Ln^{3\oplus}$-ions constitute rather mild Lewis acidic catalysts. Therefore, a broad range of reactions – (hetero) Diels-Alder, Michael addition, aldol and hydrogenation – are accessed as well as yet challenging transformations such as metal-catalysed *direct* aldol reactions of aldehydes with unmodified ketones.[79] The latter represent one of the most important and promising applications of chiral lanthanide catalysts,[80] besides catalyses in water.[81]

$Ln^{3\oplus}$-ions are hard oxophilic metal ions that lack orbital restrictions and do *not* maximize orbital overlap as do d-block transition-metals. Consequently, electrostatic factors determine their interaction with ligands. This is why lanthanides generally attain varying and high coordinating numbers, 6 to 9 being common and extendable up to 12. On the one hand, these features render lanthanides attractive metals for catalysis: high activity in ligand-substitution reactions, for example, accelerates association with substrates and dissociation of products causing catalyst efficiency. On the other hand, exactly these

properties give rise to problems: $Ln^{3\oplus}$-ions allow for construction of structurally sophisticated and often oligomeric complexes. Therefore, control of their molecular structures is a key issue in the design of Ln-catalysts, requiring a precise topological and electronic control of the metal sites to create well-defined, stable species.[82,73d] Similar to the supramolecular chemistry of lanthanides, developed among others by *Piguet* and *Bünzli*,[83] polydentate podand ligands derived from known and established podands represent a convenient way to generate defined chiral-helical complexes (Figure 2.5).

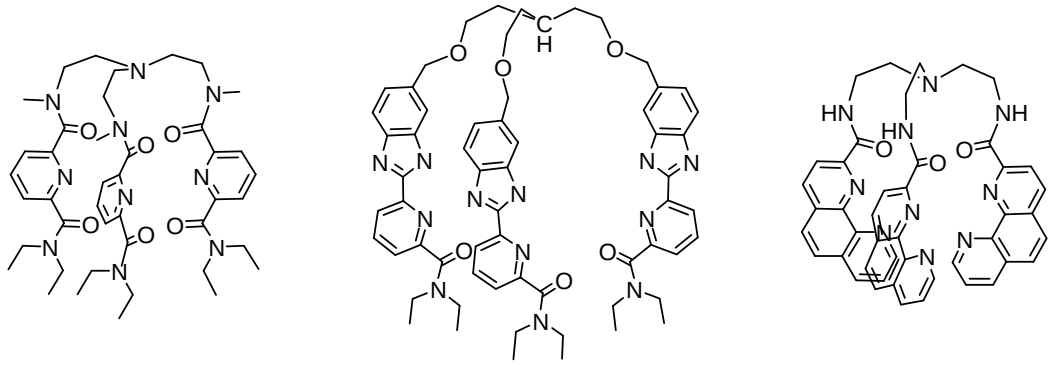


FIGURE 2.5 Multidentate podands.[84]

Enantioselective catalytic tools based on rare earths have developed from their first applications in the 1980s[85] to a stage at which many reactions can be catalysed with high enantioselectivities (>90%) under convenient experimental conditions. The factors enhancing catalytic activity in Ln-complexes (e.g., labile Ln-ligand bonds and flexible coordination chemistry), however, make it difficult to define an effective chiral binding site for the substrate. Besides, the required catalyst loadings are generally quite high (from 5 to 20 mol%). Consequently, the number of truly effective catalysts, including the binaphtol- and pybox-stabilised systems, is still limited.

2.6 Immobilisation – heterogenation of homogeneous catalysts

Immobilised homogeneous catalysts are promising tools, potentially satisfying both commercial and ecological demands by combining the advantages of molecular and heterogeneous catalysts. These species allow for easy separation from the product and reapplication in further catalyses, leading to decreased processing costs. Research in this field has gained increasing interest in academia and industry since first attempts of catalyst immobilisation were made in the late 1960s.[86] Nowadays, a wide range of powerful catalysts, for example, for olefin metathesis,[87] based on phosphines,[88] and bisoxazolines[38] have been immobilised by various approaches. Two basic methods are to be distinguished: fixation on solid supports and immobilisation in liquid/liquid-systems.[89] Common solid supports are organic polymers[90] and inorganic materials[91] such as silica gels. They can be connected to the catalyst *via* various possible types of bonding,[92] although covalent binding through a linking unit is preferred.

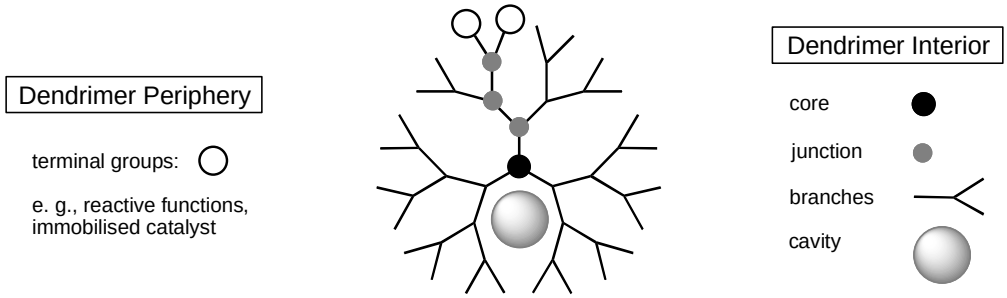


FIGURE 2.6 General structure of a dendrimer and its different entities.

The appropriate choice of support exerts a critical influence on the immobilised catalyst, requiring certain modifications of the latter. Therefore, the support's type and number of functional groups, its solubility, possible interference in the catalytic reaction, and of course its commercial availability have to be considered. Moreover, negative effects on activity, selectivity, and catalyst lifetime are to be avoided. Soluble supporting materials are favourable, because "purely" homogeneous reactions proceed during catalysis and during immobilisation. These systems additionally allow for convenient characterisation, because analytical procedures for low-weight molecules (NMR, mass spectrometry) can be used.

Dendrimers represent a well-established class of soluble supporting materials for catalysts. These highly-aesthetical molecules, first described by *Vögtle et al.* in 1978,[93] have emerged as a powerful platform for various applications:[94] light- and energy-harvesting materials, optoelectronic devices,[95] drug carriers,[96] host-guest-aggregations,[97] and catalyst supports.[98] Dendrimers exhibit regularly branched, uniform macromolecular structures[99] which are highly flexible and more or less globular in solution (Figure 2.6).[100] Nowadays, divergent[101] and convergent[102] synthetic approaches are well-established for many types of dendrimers,[103] several of them being commercially available. Among those, poly(amine)[104] and carbosilane dendrimers[105] are of particular interest for catalyst immobilisation which can be performed at different positions of their skeleton (Figure 2.7).

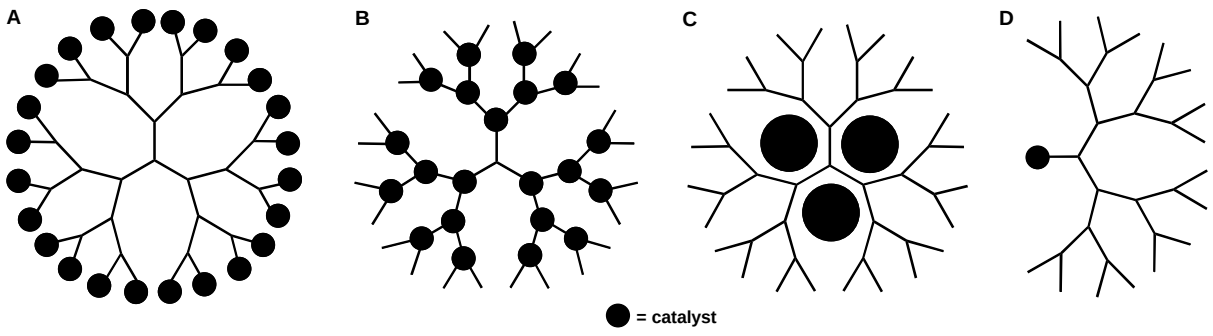


FIGURE 2.7 **Different types of catalyst immobilisation to dendrimers:** at the periphery **A**, at the junctions **B**, metal nanocomposites in the cavities **C**, at the focal position of dendrons **D**.

Nevertheless, peripheral functionalisation is preferred, as the dendrimer's terminal groups are most accessible and can readily interact with substrates. Therefore, less activity is lost compared to mononuclear reference systems.[106] Dendritic catalysts allow, moreover, for convenient recycling procedures:[107] filtration,[108] extraction[108] and phase separation.[109] Ultra- and nanofiltration techniques based on dialysis (that originate from enzymatic catalysis in biotechnology)[110] have been established by *van Koten* and *van Leeuwen* more recently.[111]

These techniques require the use of membranes, being adapted to the reaction conditions to achieve good catalytic performance.[112] First, the pore size of the membrane should guarantee retention of the catalyst, and smooth transport of the reactants and products. Nanofiltration, for example, includes a nominal MWCO (molecular weight cut-off: the molecular weight at which 90% of the solutes are retained by the membrane) in the range of 200-1000 Da, retaining molecules that average 0.5 to 8 nm in diameter. On

the other hand, possible interactions of the various compounds/intermediates with the membrane surface have to be considered. Finally, a mechanically, thermally, and chemically stable membrane in the chosen solvent and at the chosen temperature is required. This is a major issue with polymeric membranes that may swell, change their structure and therefore their pore size, leading to increased catalyst leaching. Catalyst leaching is a general problem of membrane-based recyclings: leaching of the dendritic catalyst through the membrane as well as metal leaching from the dendrimer into the exterior solution occur.

The functional principle of the technique is as follows: driven by a force (gradient), the substrates/reactants are transported through the membrane whereas the catalyst is retained mainly due to its size (Figure 2.8).

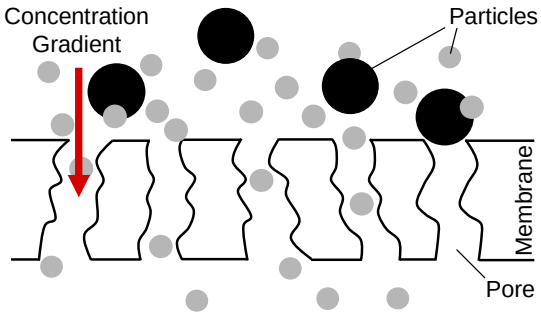


FIGURE 2.8 **Functional principle of membrane separation techniques:** driven by a force, e. g., a concentration gradient, the materials are separated according to their size.

The force can be generated by a pressure, concentration or temperature gradient as well as an electrical potential. Depending on the set-up, several types of membrane-based recyclings are known.[112] Probably the most advantageous approach is catalyst inclusion in the membrane. It is easy to perform, allows for good dispersion of the catalyst and guarantees minimal interaction between the catalyst and the polymer (only Van-der-Waals interactions and some steric constraints). Additionally, higher selectivities and activities than in other approaches can be obtained. A major problem, however, is leaching of the catalyst into the reaction phase.

The application of ultra- and nanofiltration techniques in aqueous phase has been growing rapidly, but the nonaqueous application is still an emerging field, facing a number of problems. Nevertheless, it is a promising approach to increase the use of asymmetric catalysts in industrial processes, especially by profiting from well-defined dendritic supports.

A large number of immobilised bisoxazolines are known today: this type of ligand has been linked to polymers and silica gels, and recycled in ionic liquids.[38] Few examples, however, are reported which include the use of dendrimers.[113]

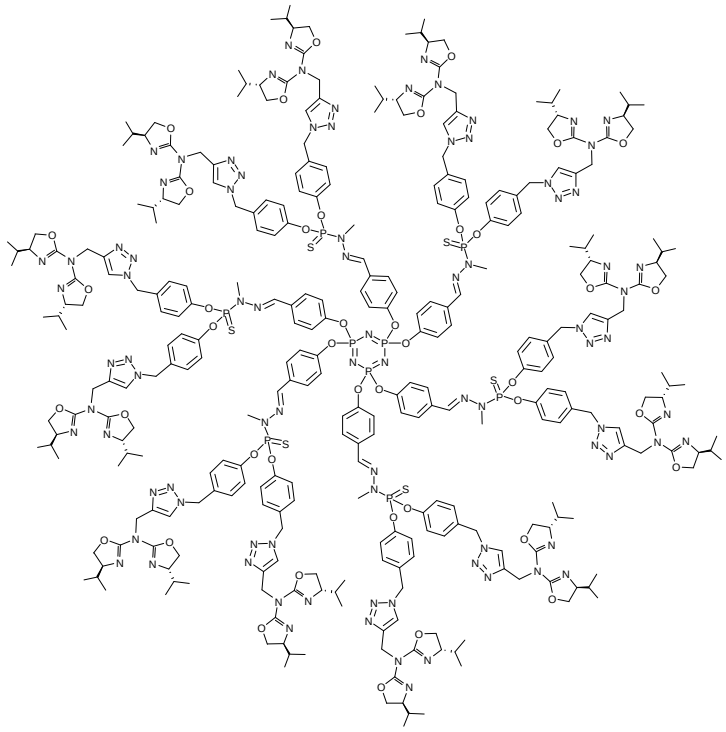
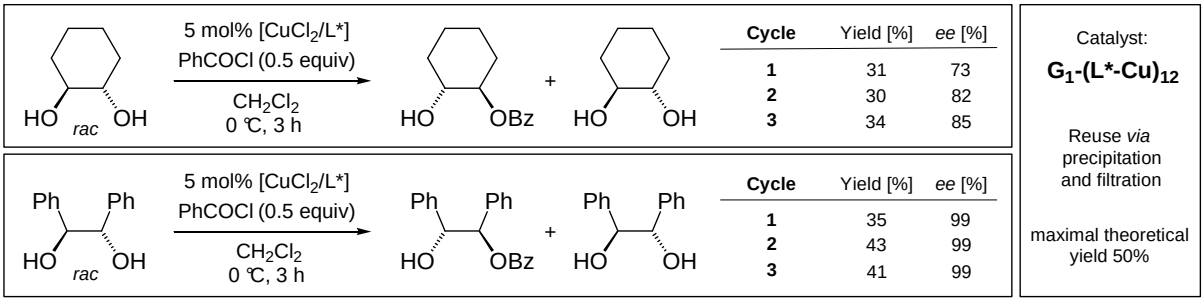


FIGURE 2.9 **Dendritic aza-bis(oxazoline):** The ligand was grafted to a first generation phosphorus dendrimer using Click chemistry.[113d]

In all of these studies moderate results were obtained, concerning both activity and selectivity. Only *Majoral*'s and *Reiser*'s dendritic aza-bis(oxazolines) (Figure 2.9) were recycled (up to three times).[113e] They also performed best, achieving good yields, and good to excellent enantioselectivities at 5 mol% catalyst loading. The results proved remarkably stable throughout all three recyclings (Scheme 2.10).

SCHEME 2.10 **Asymmetric benzoylation of diols applying a dendritic Cu-aza-bis(oxazoline)-catalyst**[113e]



Overall, aza-bis(oxazolines) constitute the most versatile bisoxazoline ligands for immobilisation.[114,115] Among the enormous number of attempts to support and recycle this class of ligands, just a few approaches have given as good, consistent results at low catalyst loadings as the aza-bisoxazolines.[116] They were grafted to Tentagel™,[117,114d] polystyrene,[114d] poly(ethylene glycol),[114a,c] and used in an ionic liquid.[114b] Mostly, 1 mol% of the catalyst was used in the Cu^{II}-promoted cyclopropanation with different substrates, yielding the products in good to excellent yields and enantioselectivities (more than 90% in many cases). Even better results than with homogeneous Cu^{II}-catalysts were obtained. Facile catalyst separation *via* precipitation/filtration and extraction allowed stable reuse between 4 to 13 times (depending on the catalyst support). From cycle to cycle, different substrates were applied smoothly. The same catalyst, furthermore, promoted a Mukaiyama-aldol reaction in one cycle and a cyclopropanation in the next with still excellent results!

CHAPTER 3

Research Project

Based on the modular synthesis of tris(oxazolinyl)ethanes, the aim of this project has been the design of new stereodirecting ligands for asymmetric Lewis acid catalysis. Two approaches were followed to create additionally functionalised trisoxazolines for more efficient, and broader catalytic applications: first, generation of penta- and hexadentate derivatives by introducing supplementary peripheral donors, and, second, generation of immobilised trisoxazolines *via* an apical linking unit (Figure 3.1).

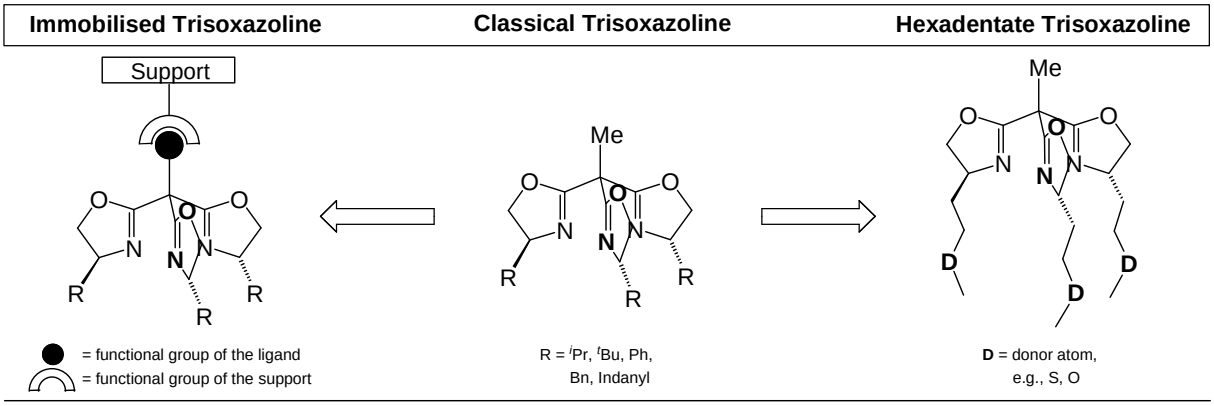


FIGURE 3.1 Basic structures of the differently functionalised trisoxazolines.

Polydentate trisoxazolines are to confer greater kinetic persistence to labile metals such as Fe, Co, Ni and the lanthanides. Moreover, they are supposed to create a helical-chiral environment by arranging their identically orientated arms around the metal centre. Therefore, they are to efficiently induce stereoinformation to prochiral substrates and allow the coordination of lanthanides (Chapter 2.5) for enantioselective catalyses. This project has focussed the synthesis of appropriately functionalised, chiral α-amino alcohol precursors and the design of a ligand library, including C_3-symmetric hexa- and C_1-symmetric pentadentate trisoxazolines.

The immobilisation approach comprised the development of dendritic bis- and trisoxazolines, concentrating, on the one hand, on practical aspects such as catalyst recycling with simple membrane reactors (Chapter 2.6), on the other hand, on the analysis of dendritic effects. The high density of catalysts being immobilised at a dendrimer's periphery (in contrast to conventional polymers) affects their characteristic behaviour, frequently resulting in modified activities and selectivities. This phenomenon, generally referred to as dendritic effect, is influenced by diverse factors such as the linker, the building blocks of the dendritic skeleton, and even small conformational changes of the support. Bis- and trisoxazolines are ideal systems to study these phenomena: both ligands exhibit symmetrical structures that simplify catalytic processes (Chapter 2.4.2 and 2.4.4), their behaviour is well understood and fairly similar while not identical. The differences may be enhanced by dendritic effects and, therefore, are expected to become apparent.

Polydentate Trisoxazolines

Asymmetric catalysis has been mainly developed and optimised by intuitive research. In order to define universally valid mechanisms of enantioselection, however, more conceptual studies are required.[118]

4.1 Design concept

By introducing additional donor functions to trisoxazolines' skeleton, their application may be extended to labile metal centres, namely lanthanides, the coordination behaviour of which differs from that of transition metals (Chapter 2.4.1). To achieve efficient transfer of the chiral information to these multivalent metals and to guarantee optimal coordination, the new donors must be easily accessible and located near the chiral centres of the oxazolines. Therefore, they were introduced into the substituents at the stereocentres, being connected to them *via* sterically non-demanding alkyl chains (Figure 4.1).

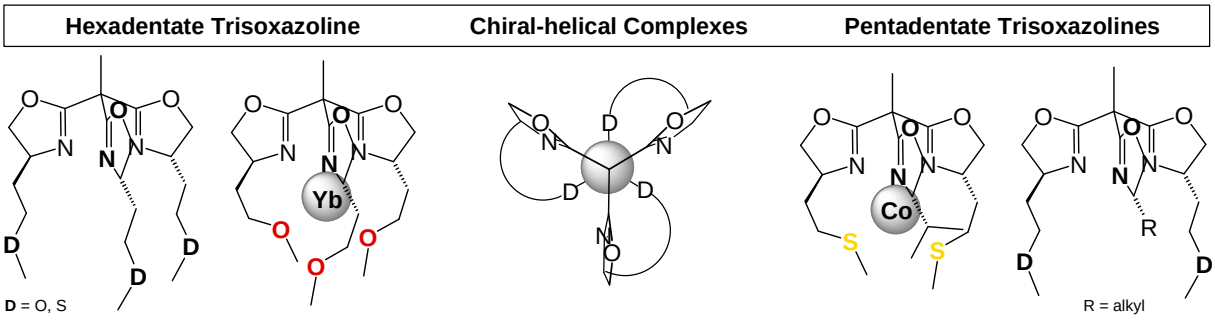


FIGURE 4.1 Target molecules and a schematic view of a chiral-helical metal complex.

These unidirectional chains (bound to stereocentres of identical configuration) may form a spiral shape, being fixed through coordination of the supplementary donors. In this way, a chiral-helical environment will be created around the metal centre (Figure 4.1). As lanthanides capture up to 12 ligands while trisoxazolines create a hemilabile coordination sphere, there will be enough space for substrates and reagents to coordinate, and to benefit from the chiral environment for efficient stereoinduction.

Ethylene chains where chosen as linking units between the chiral centres of the oxazolines and the donor functions. This principle had already been applied by *Chisholm et al.* to create a tris-pyrazolylborate bearing hemilabile ether appendages.[119] In contrast to shorter methylene groups, requiring steric strain to coordinate to a metal, ethylene groups are sufficiently flexible to orientate the donors and thus capture a metal. Alkyl chains longer than ethylene units would imply a non-negligible loss of entropy when re-oriented upon coordination which renders the process unfavourable.

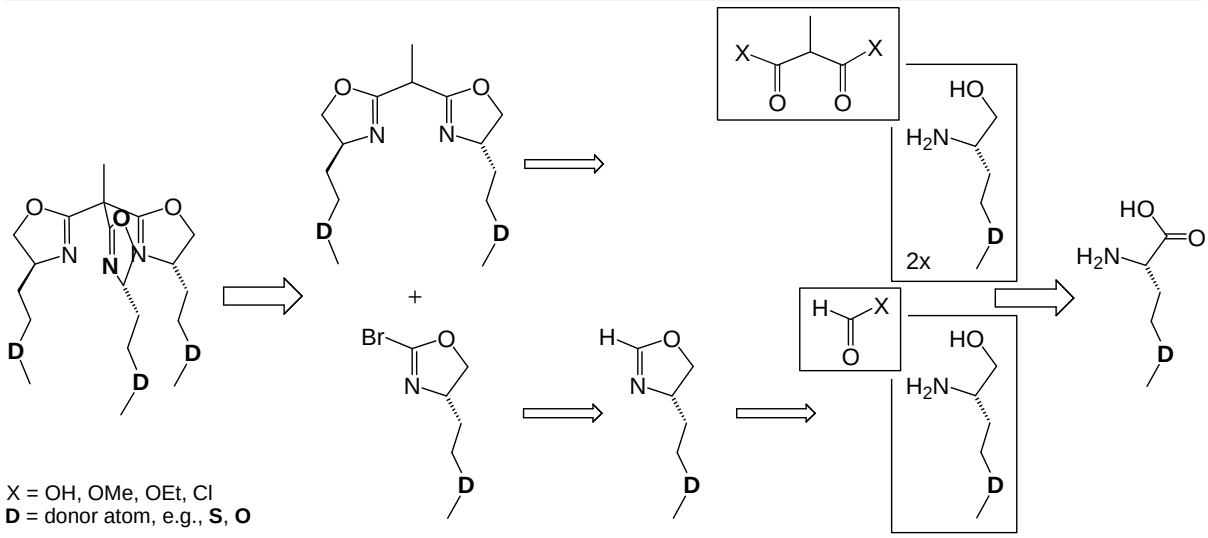
As to the character of the donors, according to the HSAB classification of *Pearson*,[78] a range from hard to soft Lewis bases – oxygen, nitrogen, and sulfur functions – should be introduced to optimally adapt the ligands to the requirements of different metals: oxygen-containing ligands, for example, are especially prone to coordinate multivalent, relatively small, highly charged (hard) metal ions like the lanthanides. Soft sulfur is more adapted to group 8, 9 and 10 metals such as Fe, Co, Ni whereas nitrogen bridges the gap between oxygen and sulfur. Although the nucleophile nitrogen was likely to interfere with trisoxazoline synthesis, attempts were made to introduce this element and complete the library of ligands.

Hexa- and pentadentate ligands were supposed to be created to adapt the ligand's denticity to the metals as well. As hexadentate ligands are C_3-symmetric whereas pentadentate derivatives bearing one "classical" arm would be C_1-chiral, these features would extend our analyses of the symmetry effect in enantioselective catalysis to coordinatively distinguished lanthanide ions.

4.2 Disconnection approach

The strategy developed to generate the new trisoxazolines is best understood by retrosynthetically analysing the target molecules (Scheme 4.1). As the principal approach to both tris(oxazolinyl)ethane types is identical, only C_3-symmetric ligands are considered.

SCHEME 4.1 Retrosynthesis of a hexadentate trisoxazoline



The key step is a [2+1]-strategy consisting of a C-C-coupling of a bisoxazoline with a monooxazoline.[46] This was achieved by reacting a lithiated bisoxazoline and a 2-bromooxazoline. If the 2-bromooxazoline contains the same substituent as the bis-oxazoline, C_3-symmetric ligands are obtained. Mixed substitution leads to C_1-chiral species.

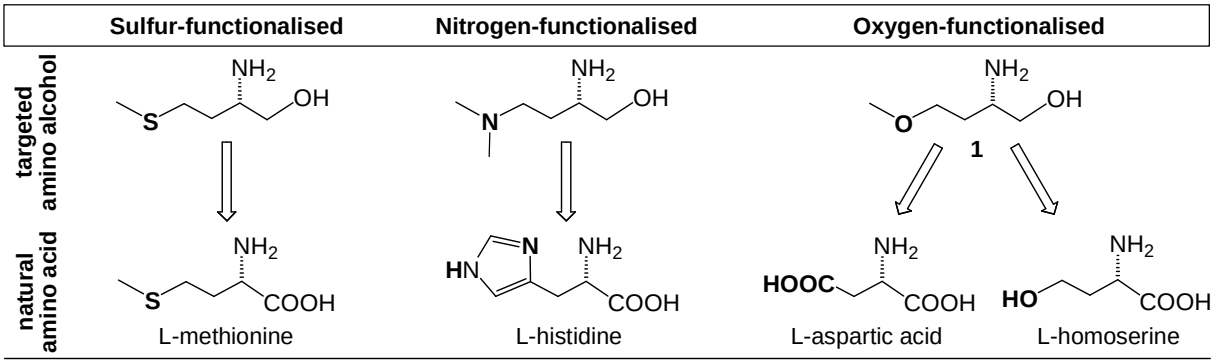
Analysis of the two oxazoline building blocks traces them back to carboxylic acid derivatives and α-amino alcohols.[29] As a broad selection of differently functionalised, relatively inexpensive carboxylic acid derivatives is commercially available, the synthesis concentrated initially on the formation of functionalised α-amino alcohols. Later, generation of heteroatom-functionalised oxazoline building blocks required adaptation of the synthetic approach and the purification methodology to the properties of the hydrophile polar precursors compared to classical unpolar derivatives.

4.3 Accessing heteroatom-functionalised *α*-amino alcohols

Generally, *α*-amino alcohols are accessible *via* proteinogenic *α*-amino acids, their most important precursors from the chiral pool. Being on the one hand, commercially available and inexpensive, on the other hand, structurally diverse amino acids represent ideal building blocks for large scale syntheses of molecules with defined stereochemistry. Based on several efficient methods,[120] they are reduced to the corresponding amino alcohol in a single step. Today, various *α*-amino alcohols are directly commercially available (e.g., L-valinol, L-alaninol, L-phenylalaninol). As building blocks for organic syntheses, particularly for oxazolines, mainly alkyl- and aryl-substituted derivatives are applied. Only serine is a popular heteroatom-functionalised precursor.[33]

Considering the chiral precursors for our polydentate trisoxazolines (*vide supra*), requiring separation of the heteroatom and the stereocentre by two carbon entities, three proteinogenic amino acids are appropriate: L-methionine, L-histidine, and L-aspartic acid (Scheme 4.2). Although a number of methods are known to synthetically generate chiral amino acids,[121] it remains more convenient to apply proteinogenic compounds.

SCHEME 4.2 Targeted amino alcohols and their natural counterpart(s)



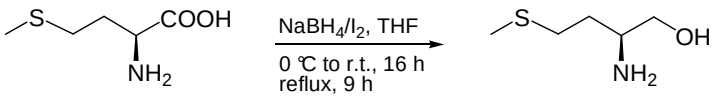
The oxygen-functionalised amino alcohol (labelled as **1**, Scheme 4.2) can be accessed basically *via* two precursors: L-aspartic acid and L-homoserine. Aspartic acid is an inexpensive proteinogenic *α*-amino acid, exhibiting two identical oxygen-functions which need to be distinguished during the synthesis. Non-proteinogenic homoserine bears two different oxygen-functions, seemingly allowing for straightforward synthesis. However, as this amino acid only occurs as by-product in the methionine metabolism and as an

intermediate in the biosynthesis of several amino acids, it is produced *via* fermentative processes and therefore too expensive for large scale syntheses.

4.3.1 Sulfur-functionalised *α*-amino alcohol – L-methioninol

The sulfur-functionalised amino alcohol, L-methioninol, was directly obtained from L-methionine by reduction of the carboxyl function. A system of $NaBH_4/I_2$ published by *Meyers et al.* yielded the amino alcohol in excellent purity and reproducible yields of about 70% (Scheme 4.3).[120b] The method based on a $NaBH_4/H_2SO_4$-system that has been generally applied in our group to reduce aliphatic and aromatic amino acids failed[120a] as well as reduction using highly reactive $LiAlH_4$.[122]

SCHEME 4.3 Reduction of L-methionine to L-methioninol[120b]



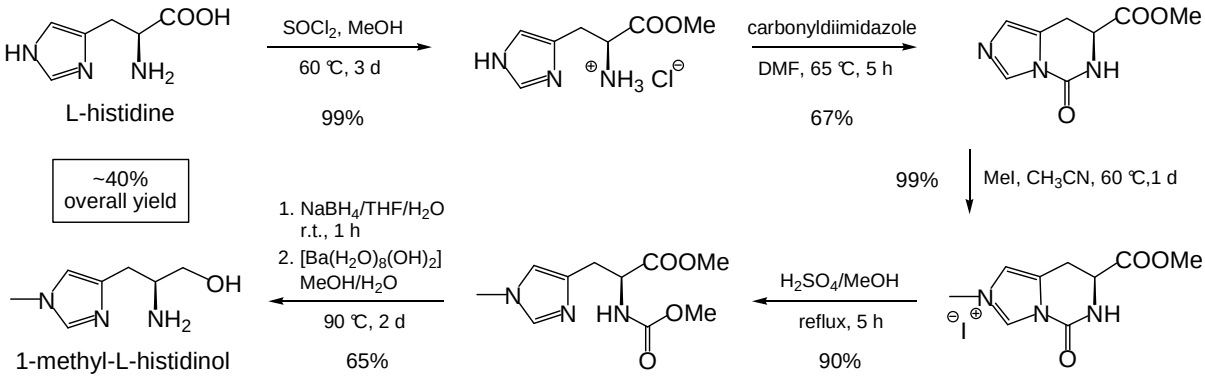
L-methionine — 70% — L-methioninol

A threefold quantity of methionine (30 g instead of 10 g) compared to the original procedure could be reduced while achieving identical yields and obtaining pure amino alcohol. As methioninol is *very* hygroscopic, however, it should be handled under argon to avoid binding of water that would interfere with subsequent transformations.

4.3.2 Nitrogen-functionalised *α*-amino alcohol – 1-methyl-L-histidinol

The nitrogen-functionalised amino alcohol was derived from histidine, requiring protection of the acidic imidazole proton (that might later interfere in the trisoxazoline synthesis) and reduction of the carboxyl function, following a strategy developed by *Pfaltz et al.* (Scheme 4.4).[35a,123] The robust, reproducible 6-step route yielded 1-methyl-L-histidinol in stable overall yields of about 40%.

SCHEME 4.4 Synthesis of 1-methyl-L-histidinol from L-histidine *via* a 6-step route[35a,123]



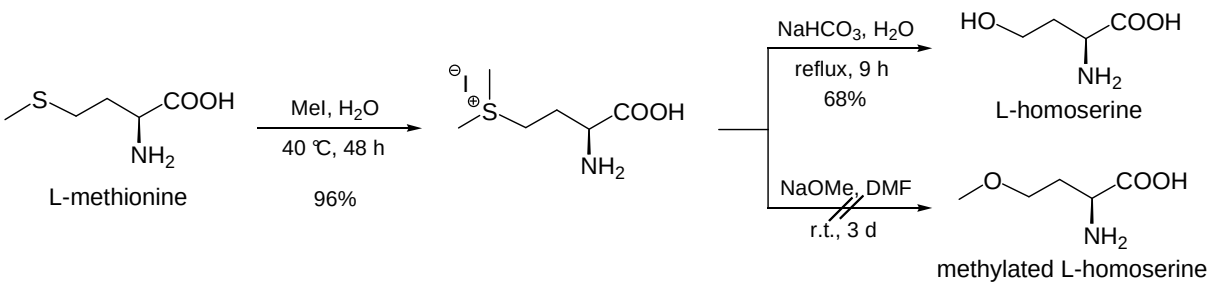
4.3.3 Oxygen-functionalised *α*-amino alcohol 1

Synthesising the oxygen-functionalised enantiopure amino alcohol **1** (Scheme 4.2) in sufficient amounts for a multistep ligand synthesis proved to be a challenging task. The main problems in generating this compound originated from its constitution and, therefore, from the nature of its precursors: bound to a skeleton of only four carbons, the three polar functional groups may interact in almost every reaction. Furthermore, they rendered the molecules very polar and hydrophilic, compared to common organic compounds, making their separation from polar side products, excess reagents, and salts difficult. Both approaches based on one of the oxygen-containing amino acids – homoserine or aspartic acid – therefore, required elaborate reaction sequences, including protecting group strategy to generate the target molecule.

Consequently, attempts were made to develop synthetic routes to access the amino alcohol in only 3-4 steps. Homoserine seemed more appropriate for such approaches, as it apparently required simple transformation of the two already distinct carbon-oxygen-functions to other functions: etherification of the alcohol (to abolish the acidic proton) and reduction of the acid. These approaches were chosen inspite of the high price of homoserine which is also conveniently accessed from methionine (Scheme 4.5).[124] Two selected examples are depicted below to demonstrate the attempts that were made to develop short synthetic routes to amino alcohol **1**.

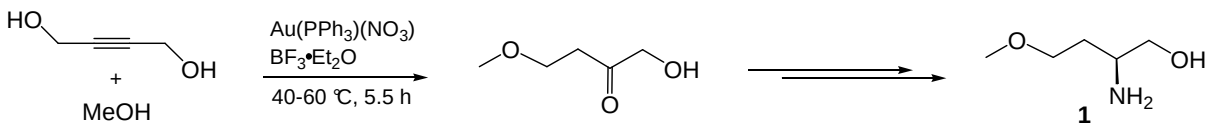
Modifying the synthesis of homoserine (Scheme 4.5), an attempt was made to directly access methylated homoserine. Similar to the generation of the latter, methionine was methylated under standard conditions, forming the corresponding methylsulfonium iodide cleanly and quantitatively. The resulting dimethyl sulfonium was meant to act as leaving group and undergo substitution as in the synthesis of homoserine. Therein, hydroxide ions buffered by $NaHCO_3$ were sufficiently nucleophilic to introduce the desired alcohol function by substituting the sulfonium function. This strategy worked relatively reliable at a 20 g scale, yielding homoserine of satisfying quality. To generate the methylated derivative, methoxide ions served as nucleophiles. Conversion, however, was low and unspecific. Attempts to isolate a product gave a mixture of the starting material containing a small percentage of the desired target compounds besides diverse side and decomposition products.

SCHEME 4.5 Synthesis of L-homoserine from L-methionine[124]



Gold-catalysed conversion of an alkyne had previously been reported to form a methoxybutanone in one step only (Scheme 4.6).[125] Transformation of its carbonyl function *via* reductive amination or an imine formation–hydrogenation sequence would have yielded amino alcohol **1** in 2-3 steps. The synthesis of the methoxybutanone derivative, however, was unreliable, yielding a mixture with other compounds. Being thermodynamically unstable, its purification and subsequent reactions proved difficult.

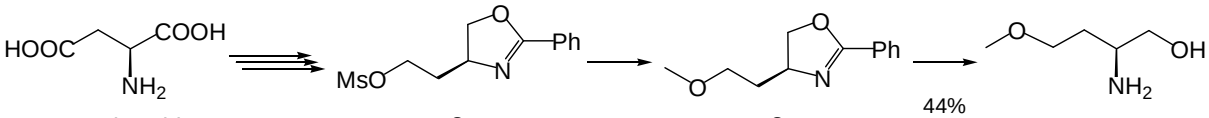
SCHEME 4.6 Gold-catalysed formation of 1-hydroxy-4-methoxybutan-2-one[125]



These attempts indicated that a straightforward access to **1** was difficult to establish. Consequently, a longer synthetic route was unavoidable, rendering inexpensive,

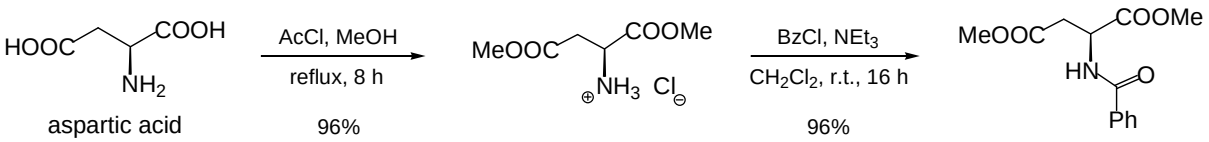
natural aspartic acid the preferred starting material. As mentioned before, the major problem in applying aspartic acid was to develop a route that allowed for chemical discrimination of the two carboxyl functions. Based on a protocol published by *Burgess et al.*,[126] we developed a 6-step route to access the desired amino alcohol (Scheme 4.7).

SCHEME 4.7 Compact overview of the 6-step conversion from aspartic acid to amino alcohol 1



In a preliminary reaction, the carboxyl functions of aspartic acid were converted to the corresponding methyl esters, using a standard procedure: the amino acid was reacted in a methanol/HCl-solution that was generated by adding acetyl chloride to methanol (Scheme 4.8).[126] Unlike the original procedure, *undried* methanol was used to convert the acid cleanly and quantitatively to the diester, allowing for multigram-scale reactions. With this transformation, the carboxyl functions were activated for subsequent reduction. In the following reaction, the amine function was transformed into an amide by benzoyl-protection – a procedure being likewise easy to conduct under standard conditions.[126]

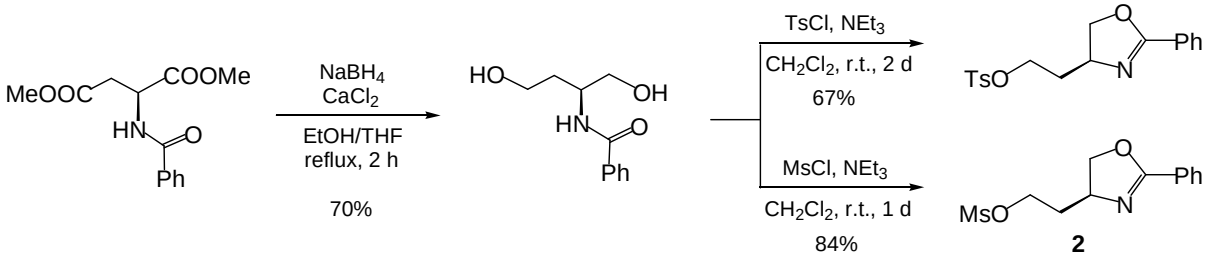
SCHEME 4.8 Esterification and amine protection of aspartic acid[126]



One of the critical steps during this synthesis was the subsequent reduction of both methyl esters to generate the corresponding diol. Although several protocols of this conversion have been published, it proved difficult to find the conditions that cleanly yielded the diol (avoiding the monoalcohol as byproduct), e.g., no conversion was observed with $NaBH_4$ in wet ethanol.[127] Reduction with $LiAlH_4$[128] yielded a mixture of both possible alcohols. Only *Burgess*'s protocol proved effective and reproducible, giving the pure diol at constant yields of about 60%. The procedure was based on the use of $NaBH_4$ in wet EtOH/THF and $CaCl_2$ as additive (Scheme 4.9). $CaCl_2$ apparently acted as Lewis acid, therefore, activating the carbon for the nucleophilic attack of the hydride by coordinating to the carbonyl oxygen.

The following step was the key of the strategy. After *in situ* conversion of the hydroxyl functions into better leaving groups, one of them underwent cyclisation with the benzoyl amine to form a heterocycle – either an oxazoline or a dihydro oxazine, depending on the function. Meanwhile, the second leaving group stayed intact, being accessible for nucleophilic substitution. According to the Baldwin rules,[129] both cyclisations (5-exo-tet and 6-exo-tet) were kinetically favoured. In reality, the oxazoline – the entropically favoured of both heterocycles – preferentially formed. This cyclisation, in fact, provided the chemical discrimination of the two hydroxyl groups: one of the oxygen-functions was protected *via* an oxazoline unit that acted here in its classical function as a protecting group for both amine and alcohol. The other oxygen-function was activated for substitution by the desired methoxy group.

SCHEME 4.9 **Butanediol formation and chemical discrimination of the hydroxyl functions *via* a cyclisation reaction**[126]



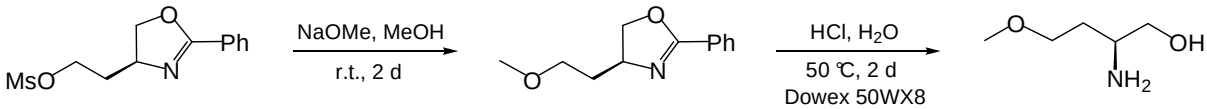
The published protocol was based on tosylation of the alcohol functions to activate them. This procedure, however, proved to give varying results, with yields ranging from 0 to 50% (67% were published). The quality of the reagent TsCl and the amount of starting material (up to 10 g gave good results) proved to be limiting factors. Moreover, dry dichloromethane had to be used and the separation of excess TsCl, required to obtain good conversions, was laborious. These factors rendered up-scaling of the reaction difficult. Therefore, tosylation was replaced by mesylation in undried dichloromethane. Clean conversion was achieved, completely avoiding purification procedures when applying up to 15 g of the diol, because excess MsCl could be removed *in vacuo*. Consequently, up-scaling was achieved, around 30 g being normally converted.

Nucleophilic substitution of the mesylate by a methoxy function proceeded cleanly in undried methanol or DMF, using NaOMe as reagent (Scheme 4.10). Methanol, however,

was preferred, as it could be easier removed after the reaction. Provided that the starting material was of good quality, the methoxy-substituted compound was always pure enough to be used in further steps *without* purification (after neutralising NaOMe).

Finally, deprotection of the alcohol and amine function was achieved in acidic aqueous solution in analogy to *Meyers*'s protocol for an oxazoline-protected serine derivative.[130] Amino alcohol **1** was initially obtained as its hydrochloride. Liberation *via* basic extraction gave only poor yields, as the product is very hydrophilic and partly decomposed if the pH of the mixture was not carefully controlled. In several cases the smell of ammonia indicated an elimination reaction. Alternatively, amino alcohol **1** was obtained by treatment of the hydrochloride with an acidic ion exchanger. This approach also involved separation of eventually occuring side products and more importantly benzoic acid that was formed as byproduct during the deprotection.

SCHEME 4.10 Introduction of the methoxy group and liberation of amino alcohol 1



2 96% **3** 87% **1**

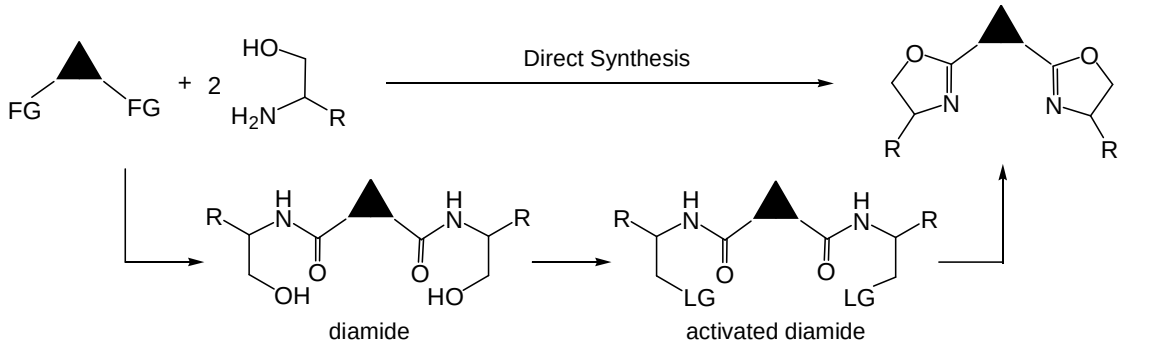
Using basic organic reaction methodology, amino alcohol **1** was reliably generated in a 6-step strategy, achieving an overall yield of 44%. The approach principally provides a basis for the introduction of other donors/donor functions, therefore, allowing the generation of diverse other amino alcohol precursors. Phenolates or thiophenolates, for example, should be readily introduced. Such sterically more demanding groups will be important counterparts to –SMe and –OMe in future asymmetric catalytic applications.

4.4 Oxazoline building blocks

4.4.1 Heteroatom-functionalised bisoxazolines

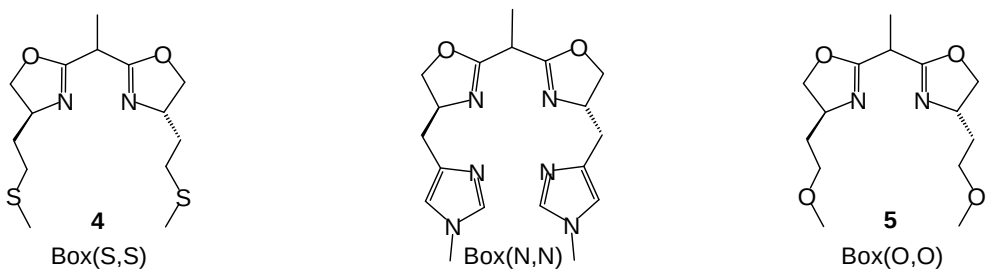
A large number of synthetic strategies to access bisoxazolines have been reported, based on different precursor combinations and a multitude of reagents.[37] A closer look reveals that they may be divided into two classes: synthesis *via* a diamide-formation–cyclisation sequence and direct synthesis, combining both transformations in one reaction (Scheme 4.11).

SCHEME 4.11 Synthetic strategies to bisoxazolines



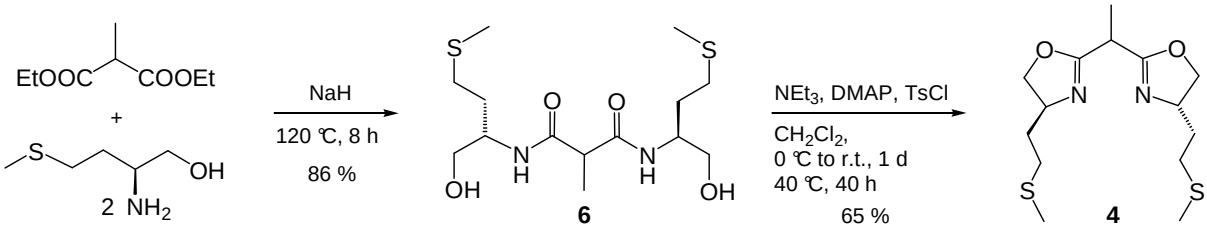
Reagents range from classical chemicals (e.g., NaH, $SOCl_2$, TsCl, NaOH) to more recently developed tools like molybdenum oxides,[131] a tetranuclear zinc carboxylate complex,[132] DAST,[133] and Deoxo-Fluor.[134] Many of these approaches apply successfully to certain cases only, depending on the substituent of the amino alcohol to introduce. Several approaches, however, are rather generally effective.[135,136] The syntheses of the donor-functionalised 1,1-bis(oxazolinyl)ethanes (Scheme 4.12) described in the following are based on this established set of tools.

SCHEME 4.12 Targeted bisoxazolines



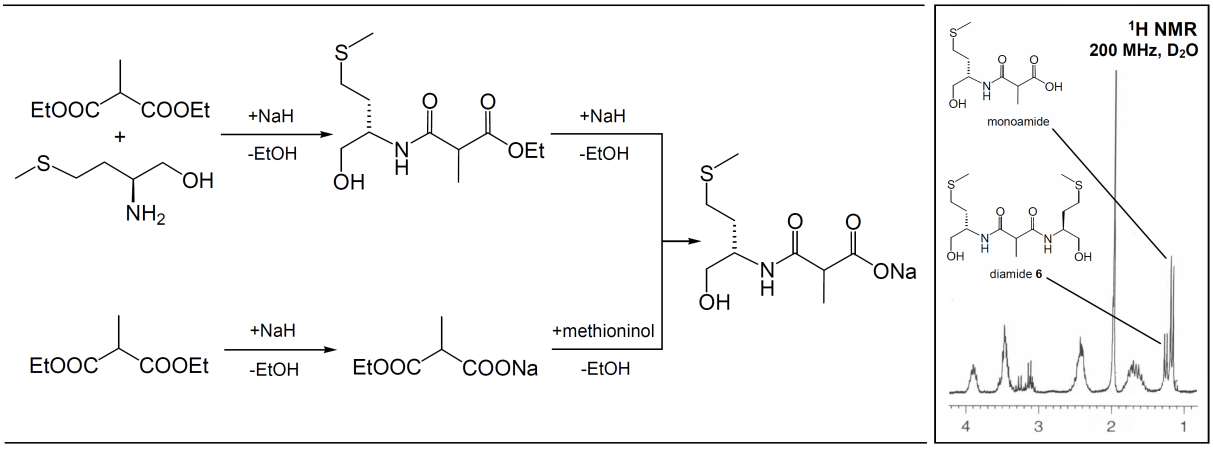
Diamid **6** was synthesised classically by reacting the corresponding amino alcohol with a malonate precursor, in the presence of catalytic amounts of NaH. It was cyclised in the following step *via in situ*-tosylation to form Box(S,S) **4** (Scheme 4.13).[136]

SCHEME 4.13 Synthesis of sulfur-functionalised bisoxazoline 4



Using very pure amino alcohol, both compounds were obtained in good yields and excellent purities. However, methioninol that contained a considerable amount of water led to an inseparable mixture of the corresponding mono- and diamide (Scheme 4.14). The ratio of both compounds could be readily established by analysis of the ^{1}H NMR spectrum of the mixture, as the doublets deriving from the central methyl groups of both amides exhibit different chemical shifts whereas all other signals overlap.

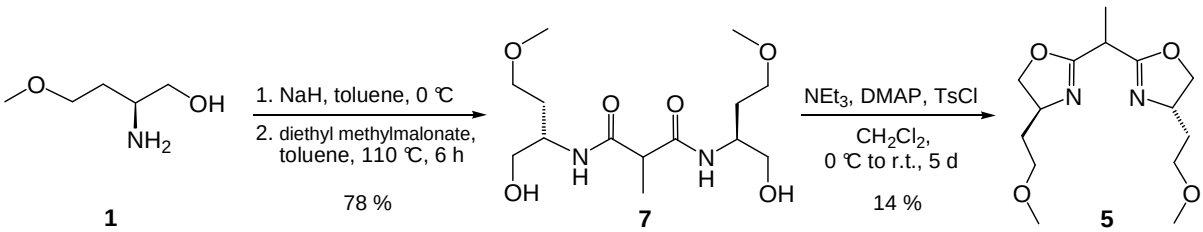
SCHEME 4.14 Generation of monoamide as byproduct during diamide formation: reaction and ^{1}H NMR.



Several ways of cyclisation were tested: the most robust and efficient proceeded *via* tosylation of the hydroxyl functions (65% yield). Cyclisation by mesylation and subsequent treatment with NaOH gave only about 10% yield of compound **4**. Molybdenum oxide[131] and DAST[133] gave complex mixtures and even lower conversions (5-10%).

As bisoxazolines **4** and **5** (Scheme 4.15) are almost identical, the sole difference being homologous atoms as supplementary donor functions, Box(O,O) was initially synthesised like Box(S,S). The amino alcohol **1** was reacted with a malonate precursor (diethyl- or more reactive dimethylmalonate), using catalytic amounts of NaH. A mixture of mainly mono-, some diamid **7**, and other compounds was formed. Obviously, the same problem occurred as when applying "wet" methioninol to prepare diamide **6**, because amino alcohol **1** is hygroscopic. To optimise diamide formation, the alcoholate of **1** was generated *quantitatively* by applying stoichiometric amounts of NaH prior to reaction with the malonate (Scheme 4.15).

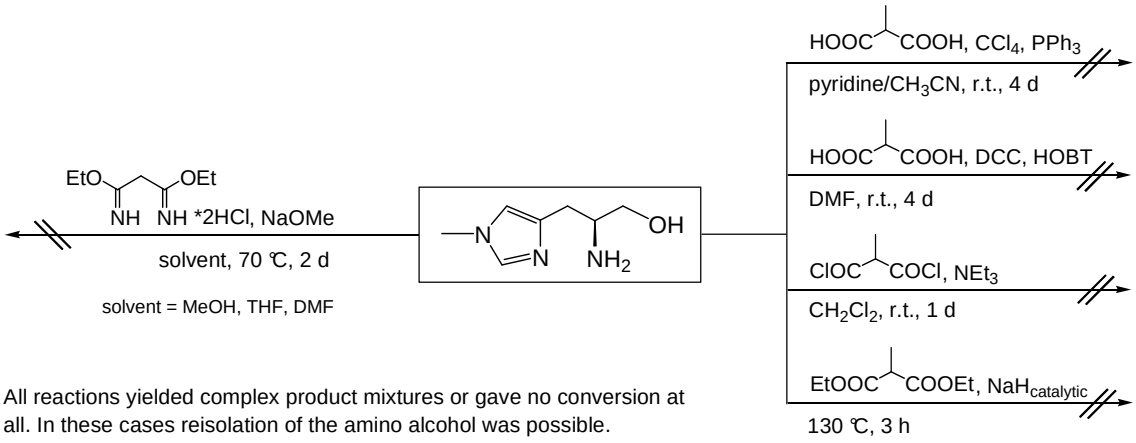
SCHEME 4.15 Synthesis of oxygen-functionalised bisoxazoline 5



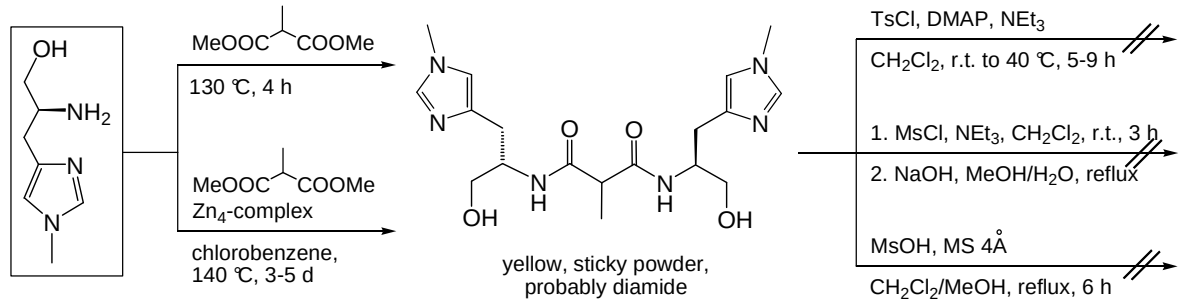
Although an excess of alcoholate (with respect to each ester function) was used, at best a mixture of mono- and diamide was obtained, containing 85% of the latter. Again, this was caused by the competitive reaction of NaOH (*in situ*-generated out of H_2O when stoichiometrically deprotonating amino alcohol **1**) and the alcoholate. Consequently, cyclisation to **5** proceeded with moderate conversions, yielding 14% of the product due to decomposition during purification.

Most of the approaches to Box(N,N) resulted in uninterpretable product mixtures (Scheme 4.16). Even when applying optimised strategies[137] for histidinol-based bis-oxazolines, no product was obtained. Only two reactions gave products of identical properties: reaction of dimethylmalonate and methyl-histidinol that was meant to form diamid(N,N) and reaction of the same starting materials in the presence of the tetranuclear zinc-complex to directly form Box(N,N).[132] Cyclisation attempts of the assumed diamide (Scheme 4.17), however, gave inseparable mixtures, containing up to ten compounds of about the same amount each.

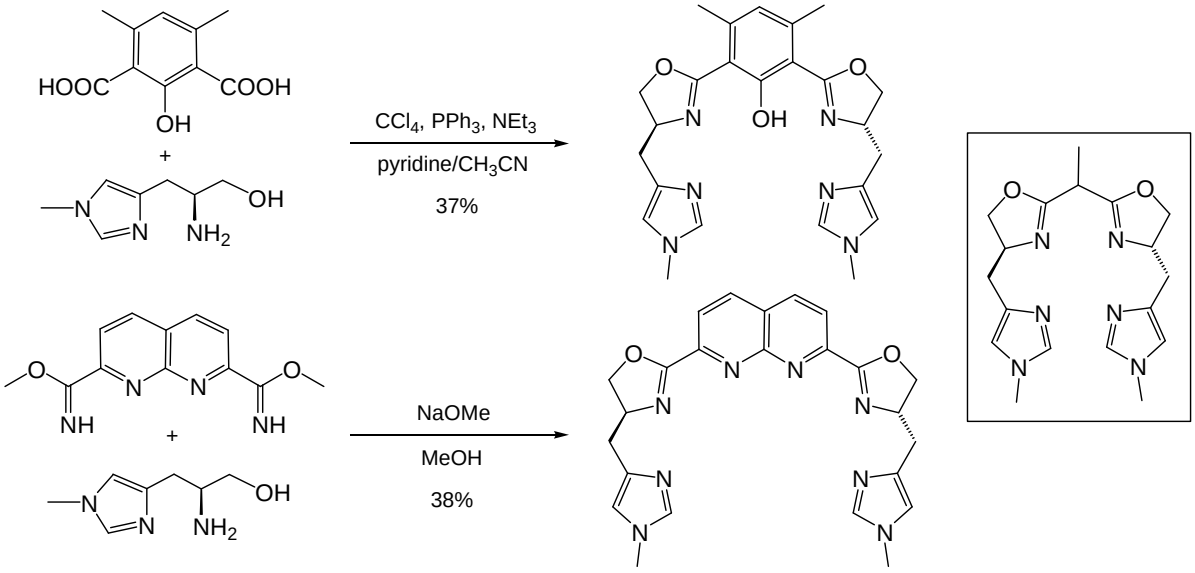
SCHEME 4.16 Synthetic approaches to access Box(N,N)



SCHEME 4.17 Attempts to cyclise diamide(N,N)



SCHEME 4.18 Syntheses of histidinol-based bisoxazolines by *Pfaltz et al.*[35a]



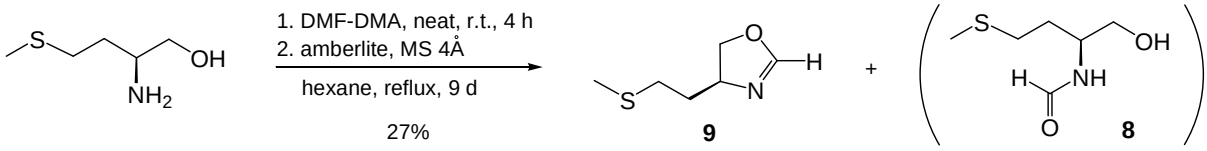
Steric effects probably hindered the formation of Box(N,N). The only published examples of histidinol-based bisoxazolines from *Pfaltz et al.*[35a] exhibit large central phenol- or 1,8-naphthyridine units (Scheme 4.18). In these derivatives, the imidazole cycles are, therefore, more distant from each other during the formation of the oxazoline rings and in the resulting bisoxazoline, consequently facilitating their synthesis. *Pfaltz* and coworkers obtained these derivatives in low yields (37% and 38%), even after having optimised reaction conditions. This seems to additionally indicate the general difficulty to form histidinol-based bisoxazolines. As a result, no further attempts were made to synthesise nitrogen-functionalised oxazoline building blocks.

4.4.2 (Thio)ether-functionalised monooxazolines

2*H*-oxazolines are preferred intermediates for the further functionalisation in the 2-position.[29] They are generally prepared by condensation of an α-amino alcohol and an activated ester.[138]

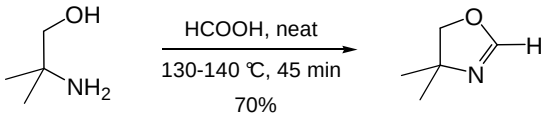
To synthesise sulfur-functionalised monooxazoline **9**, *Meyers*'s efficient method based on dimethylformamide dimethylacetal (DMF-DMA) was used (Scheme 4.19).[138a] Therein, DMF-DMA formed a formamidine with methioninol prior to acid-catalysed cyclisation while releasing dimethylamine. Using amberlite resin as the catalyst, the reaction proceeded cleanly and quantitatively whereas toluene sulfonic acid gave considerably lower conversions. The isolated yield, however, was low (27%) due to decomposition during the purification: oxazoline **9** was hydrolised on silica gel, resulting in the formation of formylated methioninol **8**. Storing **9** in the air at room temperature, the same process occurred: 50% of the heterocycle were ring-opened after a few weeks, giving the thermodynamically more stable amide. When applying "wet" amino alcohol as starting material for the reaction, likewise formylated methioninol formed in variable yields. Amino alcohol **1** yielded *predominantly* formylated amino alcohol **11**, under identical conditions. Up to 70% of this compound were isolated.

SCHEME 4.19 Formation of sulfur-functionalised monooxazoline 9



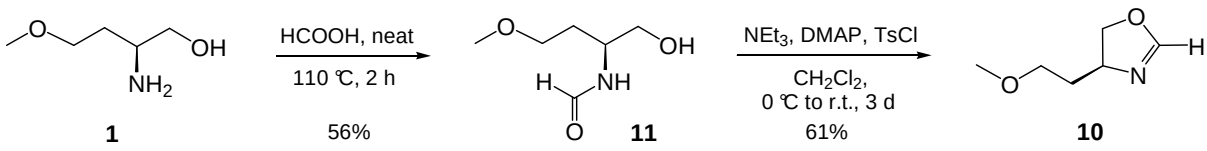
Meyers had described the direct formation of a 2*H*-oxazoline by reacting the corresponding amino alcohol and formic acid (Scheme 4.20).[139]

SCHEME 4.20 Direct 2*H*-oxazoline formation by condensing formic acid and an amino alcohol[139]



According to general observations, application of these conditions to **1**, gave formylated **11** (instead of oxazoline **10**) in good yields and excellent purity, making purification unnecessary. Being heated with carboxylic acids, 3-unsubstituted and 3-monosubstituted amino alcohols generally form amides rather than heterocycles whereas disubstituted amino alcohols readily cyclise to 2-oxazolines.[28a] Therefore, systematic formylation of **1** with formic acid and subsequent cyclisation to monooxazoline **10** were targeted (Scheme 4.21). Two approaches were tested: first, a chlorination–base-induced cyclisation sequence,[35c] and second, *in situ* tosylation of amide **11**, having been successfully applied to bisoxazolines.[136] Again, the latter gave better conversions. Those, however, were *not* reflected in the isolated yield (61%), as some of the volatile monooxazoline **10** was lost during purification.

SCHEME 4.21 Formation of oxygen-functionalised monooxazoline 10

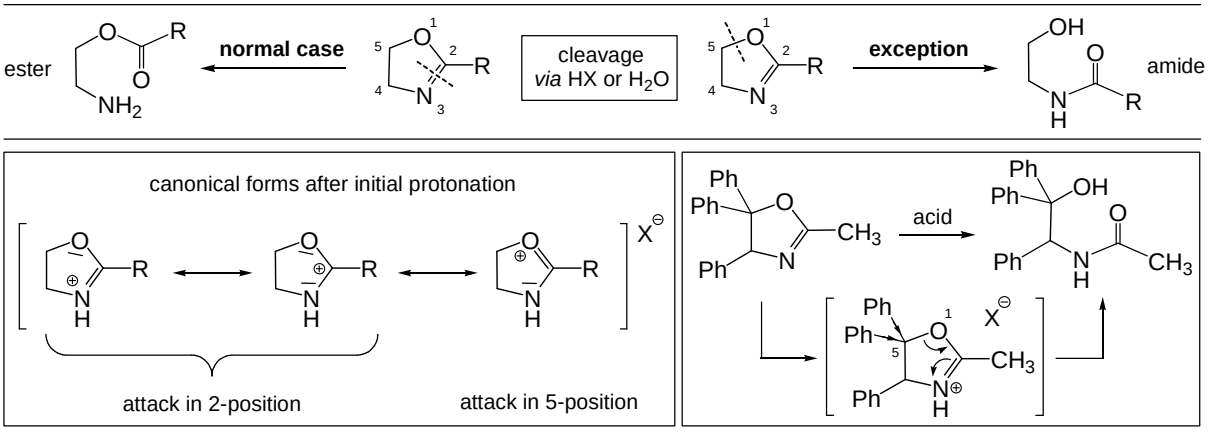


All in all, both 2*H*-oxazolines **9** and **10** were efficiently generated. Their isolated yields, though, were only moderate. However, both compounds proved less stable than the known 2*H*-oxazolines, bearing aromatic and aliphatic substituents.

It is generally known that oxazolines, depending on their structure, are more or less prone to hydrolysis. Especially strained cycles such as (4*R*,5*S*)-4,5-indanediyloxazoline readily undergo ring opening,[140] initiated by electrophilic attacks,[28a] particularly acidolysis,[141] and rearrangement in organometallic compounds.[142] Ring-opening polymerisation of oxazolines is based on this reactivity,[143] the driving force being isomerisation to the thermodynamically more stable amide rather than relief of ring strain, as it is for most ring-opening polymerisations.

Acids or water normally cleave the bond between C2 and nitrogen, resulting in the formation of an amino ester.[28a,141b] In several cases, however, cleavage of the bond between C5 and oxygen was observed, resulting in the formation of amides. Which of these reactions occurs, depends mainly on the stabilisation of the positive charge, deriving from initial protonation of the oxazoline (Scheme 4.22).[141b]

SCHEME 4.22 **Acid- and water-promoted oxazoline cleavage**: canonical forms of the protonated species and ring-opening of a 5-diphenyl-substituted oxazoline.[144,141b]

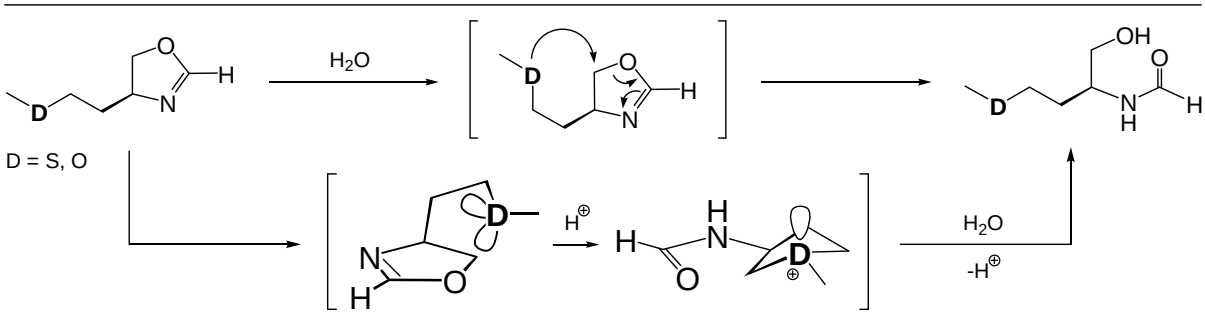


The canonical resonance form that contributes most to the real situation directs the position of cleavage. A triphenyl-substituted oxazoline, for example, was transformed to the corresponding amide due to stabilisation of the charge at C5 by the phenyl groups.[144,141b]

The reduced thermal stability of heteroatom-functionalised oxazolines **9** and **10** (compared to their aliphatic/aromatic-substituted analogues) probably derives from a similar effect: activation of C5 *via* a neighbour group effect might lead to increased reactivity of this carbon and, therefore, promote hydrolysis of the oxazolines to the corresponding

amides. Neighbour group effects may occur during unimolecular nucleophilic substitutions, if a potential donor is located in the surrounding of the electrophile's leaving group. This donor intramolecularly displaces the leaving group by forming a cyclic intermediate and is successively substituted by the nucleophile. Such reactions generally proceed faster than their non-assisted counterparts, because of the active participation of the neighbour group. The latter, however, is only guaranteed, if a three- or five-membered cyclic intermediate participates. All other cycles form too slowly.[145] Considering the ethylene appendages of compounds **9** and **10**, these monooxazolines comply with this requirement (Scheme 4.23). Therefore, their cleavage could indeed proceed *via* participation of the ether[146] or thioether, forming a cyclic intermediate rather than a common carbocation, and thus explain their elevated instability.

SCHEME 4.23 Proposed oxazoline cleavage with anchimeric assistance by the (thio)ether appendages



Comparative kinetic studies, hydrolysing both traditional 2*H*-monooxazolines and derivatives **9** and **10**, may provide experimental evidence to this hypothesis. If indeed an anchimeric effect occurs during the ring opening of (thio)ether-functionalised **9** and **10**, the rate of their cleavage should exceed those of the traditional derivatives, because of the active participation of the "side group". Furthermore, the orders of the rate laws should differ.

4.5 Trisoxazoline synthesis

Synthesis of the multidentate trisoxazolines proceeded *via* the established coupling of lithiated bisoxazolines and 2-bromooxazolines.[46] The latter, were generated prior to coupling and directly applied in the reaction, as they are generally prone to rearrange to the corresponding 2-bromoisocyanates.[140]

Meyers's methodology[147] was used to form bromooxazolines **12** and **13**. It had proved a versatile tool, allowing the generation of a series of differently functionalised bromooxazolines (Figure 4.2). This method is based on the deprotonation of the 2*H*-oxazoline and electrophilic bromination of the resulting anion with 1,2-dibromotetrafluoroethane. To date no adequate alternative has been found for this non-oxidising $Br^{\oplus}$-source that provides smooth bromination and has found application to various other substrates.[148]

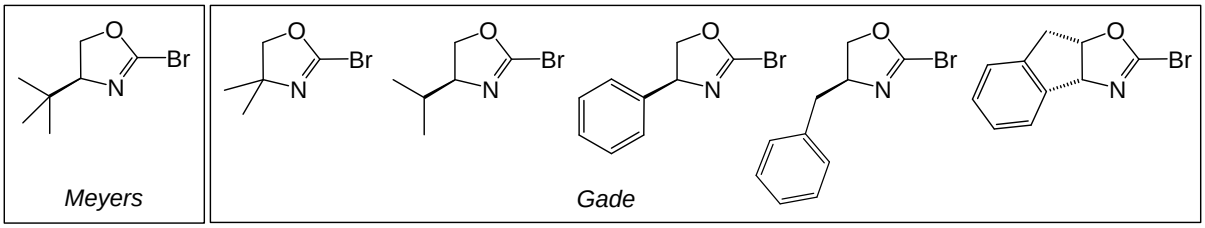


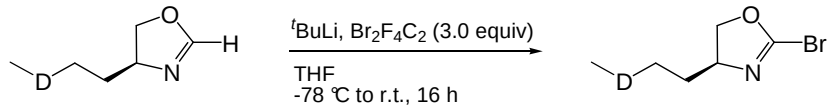
FIGURE 4.2 Substituted 2-bromooxazolines synthesised by *Meyers* and in our group.[140,147]

As oxazolines are known to open under a variety of conditions[28a,140-143] – monooxazolines **9** and **10** being particularly susceptible (Chapter 4.4) –, deuterating experiments at their 2-position had been performed to test the stability of their anions prior to bromination. They were deprotonated particularly carefully (very slow addition of the base at -90 °C) with ^{t}BuLi and reacted with D_2O, forming 2*D*-oxazolines. Clean ^{1}H NMR spectra indicated selective substitution at C2.

First test reactions applying brominating conditions, however, gave mixtures of the monooxazolines, two to three sideproducts, and the bromooxazoline. This was due to the reduced thermal stability and decreased reactivity of the lithiated compounds. A higher stoichiometric excess of 1,2-dibromotetrafluoroethane was necessary to convert monooxazolines **9** and **10**: 3.0 equivalents of the brominating agent had to be used compared to

generally applied 1.2 equivalents (Scheme 4.24). In addition, the reagent had to be added *very* slowly to avoid decomposition of the lithiated compounds by a local increase of the temperature (compensation *via* the cooling bath being too slow). Proceeding as described, both monooxazolines **9** and **10** were converted cleanly and quantitatively to the corresponding bromooxazolines.

SCHEME 4.24 Generation of heteroatom-functionalised 2-bromooxazolines 12 and 13



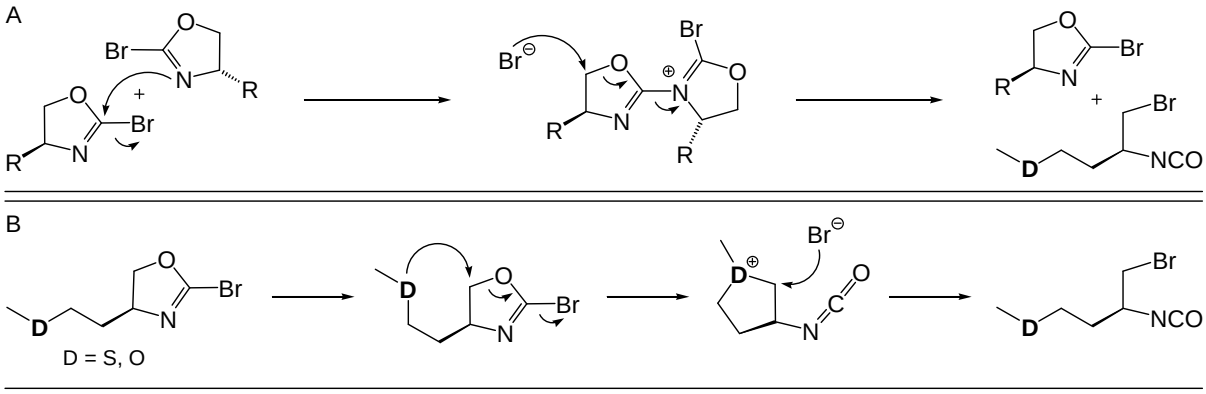
D = S: **9**
D = O: **10**

D = S: **12** 84%
D = O: **13** 26%

Additional problems arose during the purification of **12** and **13**, necessitating a modified approach compared to their unpolar analogues. In view of their sensitivity, chromatography was avoided, distillation as well, as both species thermally decomposed. Furthermore, oxygen-functionalised **13** proved as volatile as its precursor, complicating the removal of the solvent. Consequently, the crude mixtures were concentrated after the reaction to enable purification *via* precipitation of the polymeric side product (formed of dibromo-tetrafluoroethane). For the volatile bromooxazoline **13** this was done *very* slowly with additional cooling. Successive extraction–filtration cycles, yielded pure bromo-oxazolines **12** and **13**, containing only minor amounts of the side product. Therefore, thioether-functionalised **12** was obtained in excellent yield of 84% compared to other bromo-oxazolines whereas only 26% of the ether-functionalised volatile derivative **13** were yielded.

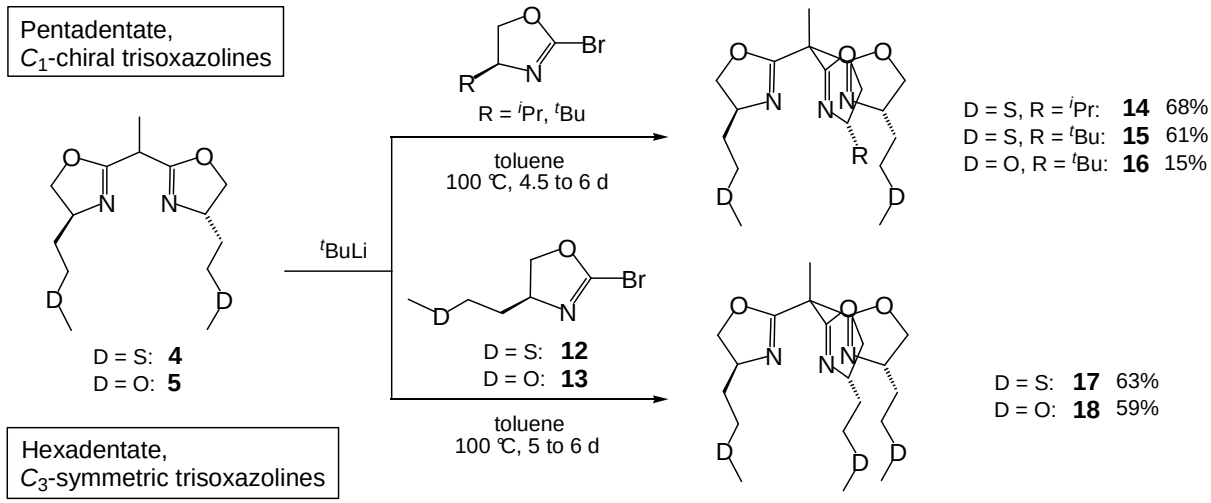
The reduced stability of bromooxazolines **12** and **13** is probably due to the (thio)ether appendages, promoting their rearrangement to the corresponding isocycanates *via* an anchimeric effect and, therefore, accelerating their decomposition (similar to monooxazolines, Chapter 4.4). A comparison of the proposed mechanisms for the rearrangement of classical bromooxazolines[140,149] and the new derivatives can account for this (Scheme 4.25). The first path proceeds *via* a bimolecular reaction whereas the second path proceeds *via* a generally faster unimolecular reaction.

SCHEME 4.25 Possible mechanisms for the rearrangement of traditional 2-bromooxazolines (**A**)[149] and for (thio)ether-functionalised 2-bromooxazolines 12 and 13 (**B**)



Trisoxazolines **14**-**18** were synthesised by lithiating Box(S,S) **4** or Box(O,O) **5** and reacting them with 1.4 to 2.7 equivalents of a 2-bromooxazoline: ^{i}Pr- or ^{t}Bu-substituted bromooxazolines yielded mixed C_1-chiral ligands. Ether- or thioether-functionalised bromooxazolines yielded C_3-symmetric trisoxazolines (Scheme 4.26).

SCHEME 4.26 Synthesis of C_1- and C_3-chiral multidentate trisoxazolines



The relatively high stoichiometric excess of the electrophiles was chosen to guarantee complete conversion and to compensate losses due to their decomposition. In this way, separation of residual bisoxazoline and generated trisoxazoline was avoided. As both compounds generally exhibit similar R_f-values on silica gel, their separation is difficult. Being reacted in toluene at 100 °C, indeed, all couplings proceeded cleanly and

quantitatively (according to ^{1}H NMR spectra of the crude products). Isolated yields of the ligands averaged at 60%, an excellent result for this class of compounds. The difference between converted and isolated material derives, as mentioned before, from the decomposition of a certain amount of the product when being chromatographed. Even by applying coarse grained heated silica gel, this could not be avoided. This is why trisoxazoline **16**, which is particularly prone to decomposition like its precursor Box(O,O), was obtained in a very low yield (15%). Trisox(O,O,O) (**18**), in contrast, was obtained in "normal" yield. This compound is rendered sufficiently polar by its three ether-functions so that its purification could be achieved by simple washings and extractions with rather unpolar solvents, avoiding chromatography.

The composition of the new ligands is clearly distinguished in their ^{1}H NMR spectra (Figure 4.3). A comparison of Trisox(S,S,S), its symmetric ether-functionalised counterpart Trisox(O,O,O), and non-symmetric Trisox(O,O,^{t}Bu) reveals the characteristics of each ligand.

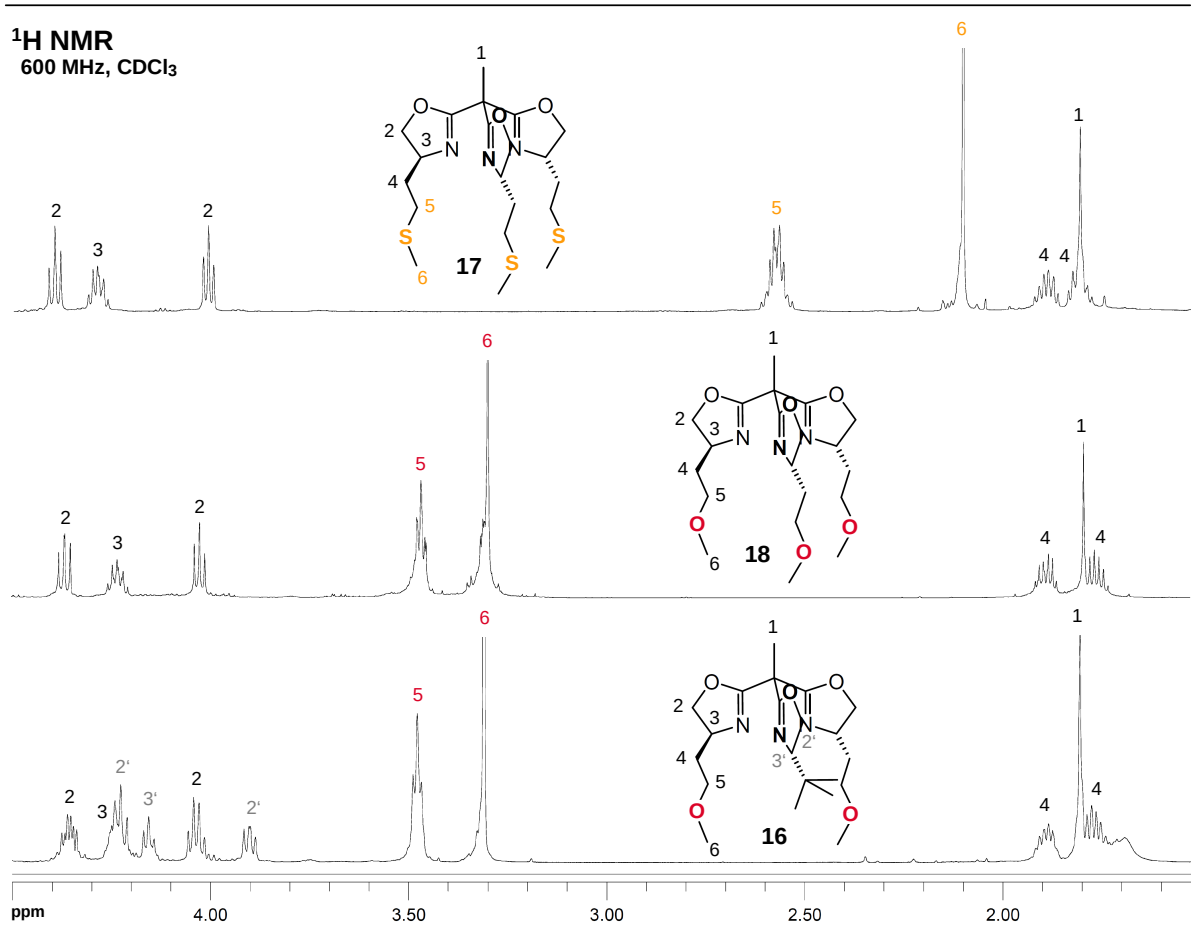


FIGURE 4.3 **^{1}H NMR spectra of Trisox(S,S,S)** (17), **Trisox(O,O,O)** (18), **and Trisox(O,O,^{t}Bu)** (16).

Protons remote from the (thio)ether-appendages exhibit identical chemical shifts in every trisoxazoline: e.g., the apical methyl protons and the oxazolines' protons, except those belonging to a differently substituted oxazoline. The protons adjacent to oxygen and sulfur exhibit different shifts according to the electronegativity of the heteroatom: SCH_3-protons, for instance, are located at 2.10 ppm whereas OCH_3-protons are low-field shifted to 3.28 ppm, as are the adjacent methylene atoms (H5). These proton sets will be ideal sensors to detect the heteroatoms' interaction with metal centres, provided that the latter are diamagnetic.

4.6 Coordination chemistry – First attempts

Although this project concentrated on synthetic aspects of ligand design, first attempts to coordination chemistry were made. NMR and mass spectra of Sc^{III}-, Fe^{II}-, and Co^{II}-complexes suggest that, similar to first generation ligands, the new trisoxazolines flexibly respond to the demands of the corresponding metal ion.

Reaction of Trisox(S,S,^{i}Pr) (**14**) with $[Sc(THF)_3Cl_3]$ in THF yielded a white powder, giving the ^{1}H NMR spectrum depicted below (Figure 4.4). In complex **19**, the proton signals close to coordinating nitrogen (H2-4 and H7-9) are dramatically shifted whereas the signals close to sulfur (H5 and H6) are almost unchanged. The signals of the ^{i}Pr-substituted oxazoline (H7-9), moreover, are identical to those of the well-characterised Sc-complex of C_3-symmetric Trisox(^{i}Pr).[53] These correlations signify complex formation *via* coordination of the three nitrogen donors. Proton sets H5 and H6, being (almost) unaffected by scandium's presence, indicate that the thioether functions do not coordinate.

An *in situ* formed complex of $FeCl_2$ and Trisox(S,S,^{i}Pr) was reacted with 2.0 equivalents of $AgBF_4$ to abstract the chlorides and generate free coordination sites for the thioether-functions. In the mass spectrum, an ion corresponding to $[Fe(Trisox(S,S,^iPr)Cl]^+$ (**20**) was detected, suggesting that at least one chloride was exchanged to yield complex $[Fe(Trisox(S,S,^iPr)Cl]BF_4$.

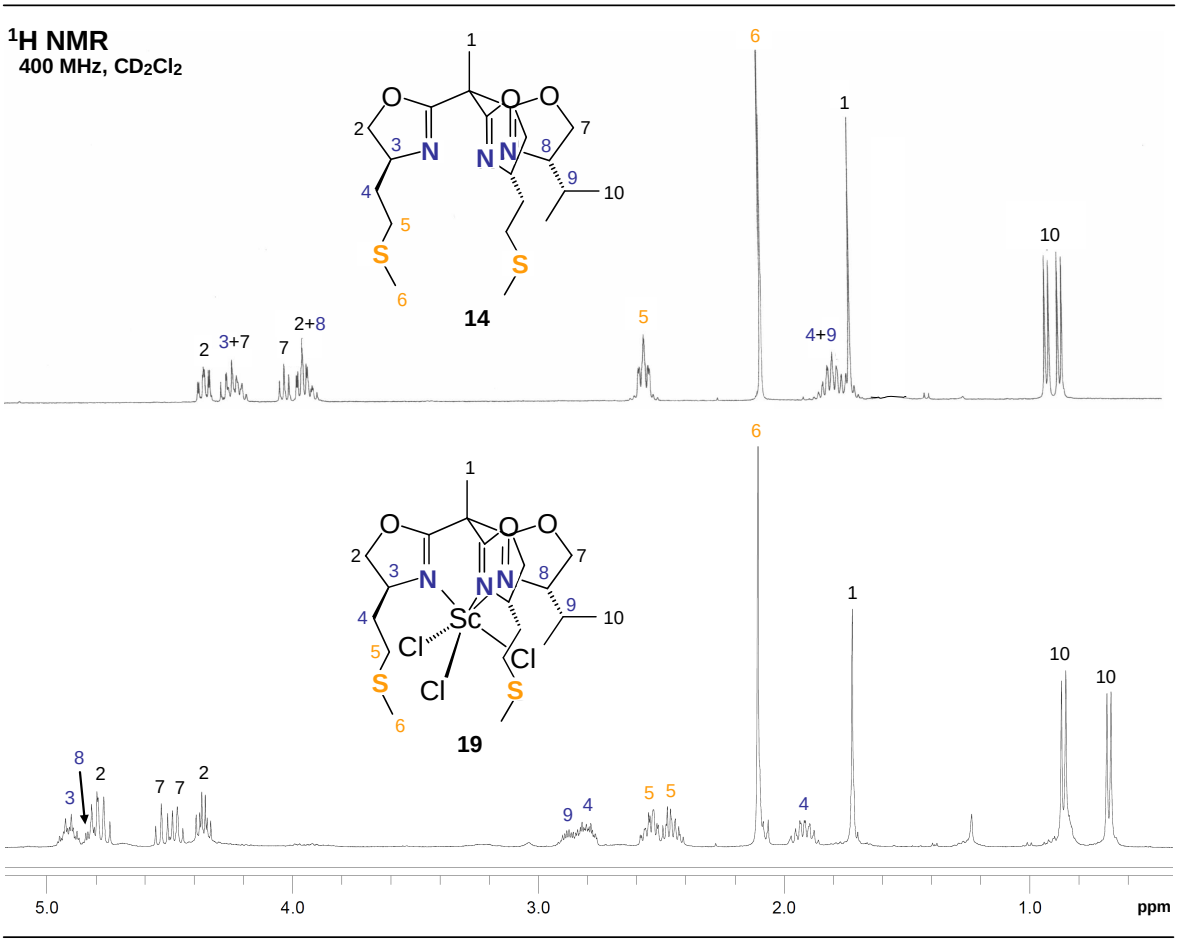


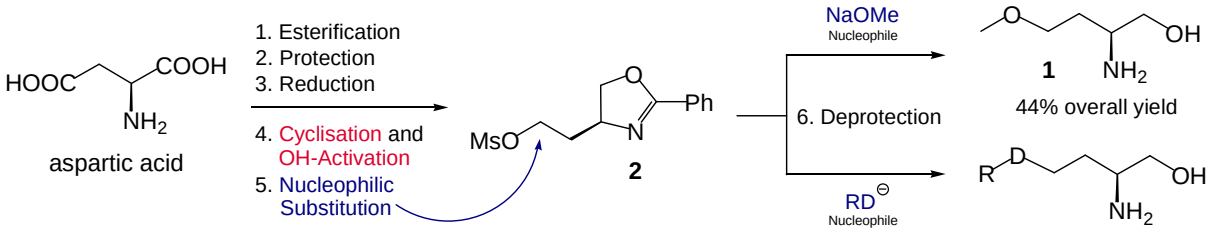
FIGURE 4.4 **^{1}H NMR spectrum of Trisox(S,S,^{i}Pr) (14) and [Sc(Trisox(S,S,^{i}Pr)Cl$_3$] (19).**

Another study targeted on Co^{II}-complexes of ligands **14** and **15**. They were coordinated to $[Co(H_2O)_6](BF_4)_2$ and $[Co(H_2O)_6](ClO_4)_2$, using solvents of different donor capability: methanol, acetonitrile, and dichloromethane. The principle difference of the two complex series lay in their colour: BF_4-counterions gave pink complexes in every solvent whereas ClO_4-counterions yielded orange-coloured powders in every case. In accordance with reported expamples,[53,36b,150] these observations indicate that by changing tetrafluoroborate to less coordinating perchlorate the thioether appendages of **14** become involved in coordination. The corresponding mass spectra and paramagnetic ^{1}H NMR of the $Co(ClO_4)_2$-complexes prepared in the aforementioned solvents (and also measured in those) suggested, furthermore, that complex formation depended on the solvent's donor capability. Switching from methanol to acetonitrile and further to dichloromethane increasing amounts of the product were detected. Altogether, complexation depended strongly on the donor character of both solvent and counter ion.

4.7 Conclusions and perspectives

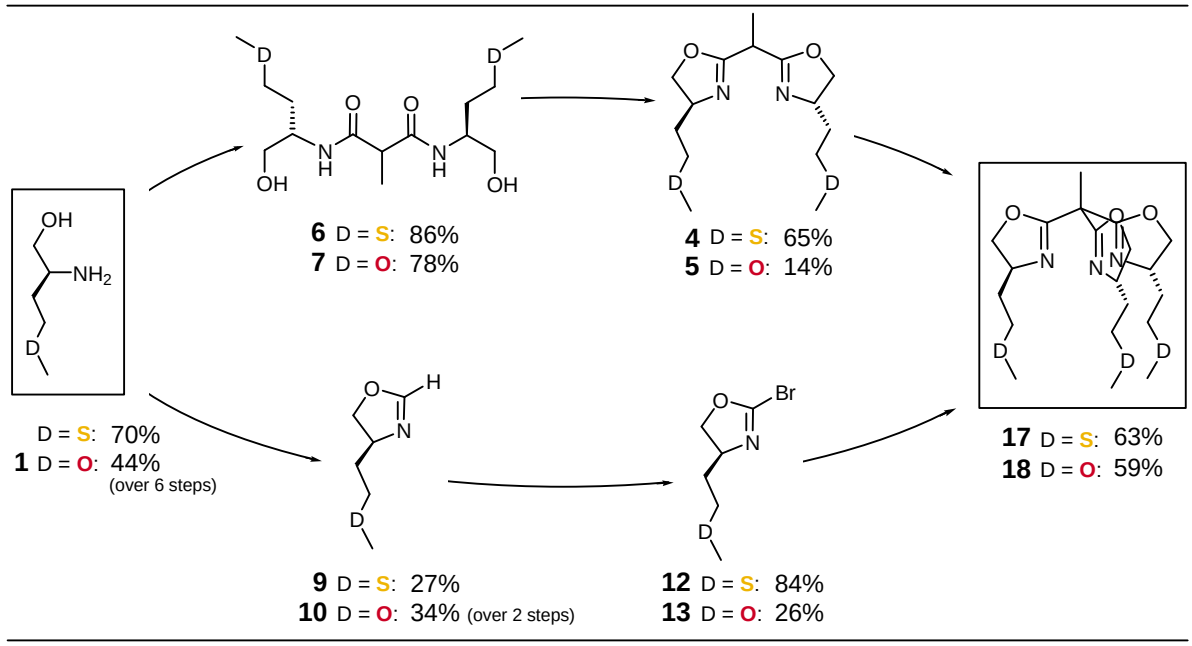
Based on aspartic acid, a multigram-scale synthesis of ether-functionalised amino alcohol **1** was developed (Scheme 4.27). By introducing other nucleophiles than methoxide into mesylated key compound **2**, this strategy leads to various donor-functionalised precursors.

SCHEME 4.27 Synthesis of donor-functionalised amino alcohols based on aspartic acid



(Thio)ether-functionalised bisoxazoline and monooxazoline building blocks were generated on the basis of amino alcohol **1** and methioninol (Scheme 4.28). By coupling these bisoxazolines with 2-bromooxazolines **12** and **13**, hexadentate trisoxazolines were synthesised. By coupling them with traditional bromooxazolines, three pentadentate ligands were obtained (Figure 4.5).

SCHEME 4.28 Synthesis of hexadentate C_3-symmetric trisoxazolines 17 and 18



The strategy based on thioether derivatives proceeded smoothly, giving about the same yields and purities for the different intermediates as those based on aliphatic and aromatic amino alcohols. Generation of the ether-functionalised building blocks, on the contrary, proved problematic due to the polarity and water-affinity of **1**. Consequently, the isolated yields of **5**, **10** and **6** were low due to losses during purification, although optimised reaction conditions assured high conversions.

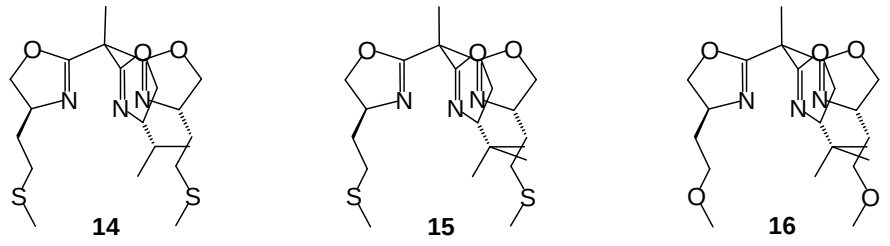


FIGURE 4.5 **Pentadentate C_1-chiral trisoxazolines 14, 15, 16.**

Unfortunately, no crystal structures of these trisoxazolines' metal complexes have been obtained to date, raising the question if the supplementary donors actually coordinate. After the coordination chemistry of these multidentate ligands will have been clarified, these ligands will be tested in asymmetric catalysis. Among others, the Mukaiyama-aldol reaction will be an ideal benchmark reaction to detect their potential, as it has been studied using a broad range of ligands and metals, including rare earths.[151] A lot of different variants are known, allowing for further development, e.g. catalysis in aqueous media.[152,151] Furthermore, in an Fe^{II}-catalysed Mukaiyama-aldol reaction, pybox ligands with serine-based appendages yielded products of considerably increased *ee*-values compared to aliphatic-functionalised derivatives,[153] the reason, however, still being an open question.

CHAPTER 5

Dendritic Bis- and Trisoxazolines

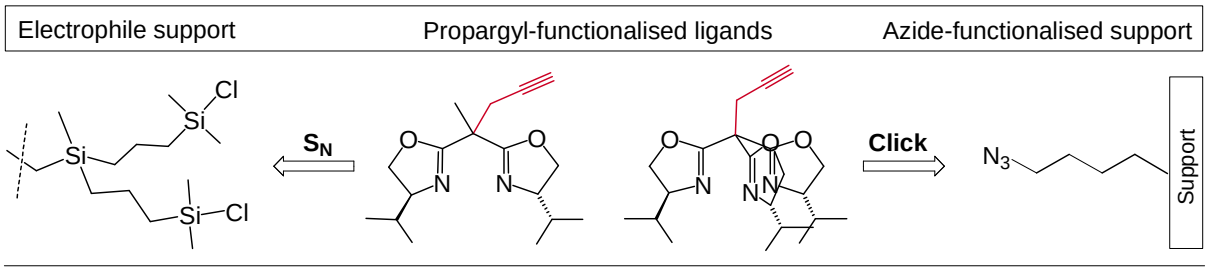
5.1 Immobilisation concept

Depending on the immobilisation strategy and the nature of the supporting material, leaching of the metal is a major problem in the application of immobilised catalysts. It may be suppressed, to various degrees, by polydentate ligands which form thermally and kinetically more stable complexes. Indeed, a number of bidentate[38,88] and tridentate ligands[154] have been immobilised and reused successfully. For example, aza-bis(oxazolines) immobilised on dendrimers yielded satisfactory results and were reused efficiently in copper-promoted catalysis (Chapter 2.4.2).[114,115] In view of these results, the catalytic behaviour of immobilised trisoxazolines compared to analogous bisoxazolines has been investigated.

Dendrimers were chosen as macromolecular supports, as they generally allow the introduction of a controlled number of catalytic sites on defined molecular frameworks. Since they exhibit a high level of branching, higher catalyst loadings may be achieved compared to linear polymers. Peripherally fixed catalysts profit or suffer from this steric crowding which may lead to cooperative effects.[155,156] Carbosilane dendrimers[157] guarantee a minimum interaction of the catalytic centres with the dendritic core and allow for reliable and flexible synthetic access, this being a prerequisite to establish structure–property relations required for the evaluation of dendritic effects.

The choice of the appropriate linker is based on two principal requirements: a relatively inert binding to the supporting macromolecule and minimised interference with the catalytic sites.[90a,90f,92a] A propargyl-function at the bridging position of the Box ligand or the apical position of the Trisox ligand appeared to meet these requirements (Scheme 5.1). Moreover, the terminal alkyne subsequently allowed facile linkage to the dendrimers *via* deprotonation and reaction with the chlorosilane termini.[154b,158] Furthermore, the oxazolines could also be attached to other supports *via* addition to the alkyne triple bond, using the Click reaction, for instance.[114c,159,160]

SCHEME 5.1 **Immobilisation concept for bisoxazoline- and trisoxazoline-functionalised carbosilane dendrimers**



Finally, the Cu^{II}-complexes of the polyfunctional dendritic ligands were designed for immobilisation in membrane bags, serving as semipermeable containers which allow the recycling of the catalysts. By dipping these recyclable "tea bags" into reactant solutions, the catalytic conversion of the substrates which penetrate the membrane (as does the product in the reverse direction) should be achieved.

5.2 Construction of oxazoline-functionalised dendrimers

The synthesis of bis- and trisoxazolines, containing a linker unit in the backbone, and their covalent attachment to carbosilane dendrimers will be described. The systems of reference are the bisoxazolines (Box) **A** and **B** as well as the trisoxazoline (Trisox) **C** depicted in Figure 5.1.

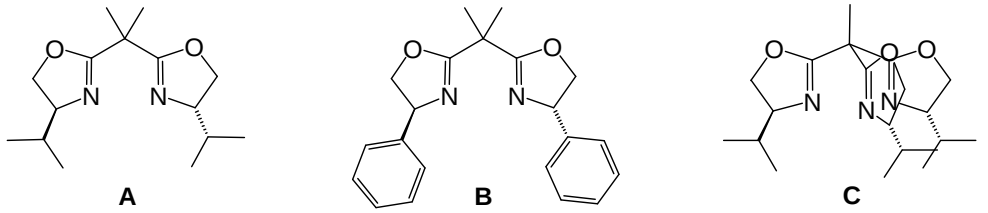
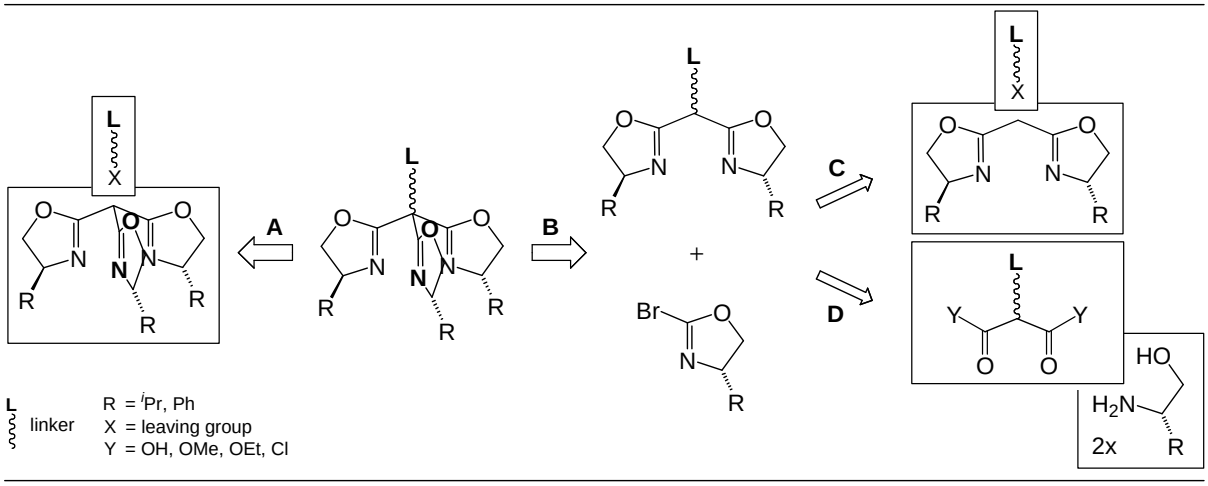


FIGURE 5.1 **Reference ligands Box A, B and Trisox C bearing methyl groups at the bridgehead or apical position.**

5.2.1 Disconnection approach

Although the substituents at the chiral centres of the heterocycles have been widely varied (isopropyl, *tert*-butyl, phenyl, benzyl and indanyl), only trisoxazolines with apical methyl groups have been synthesised to date. In principle, other substituents can be introduced in that position.

SCHEME 5.2 **Disconnection approach to apically functionalised tris(oxazolinyl)ethanes**



In principle, two strategies may lead to apically functionalised trisoxazolines (Scheme 5.2): deprotonation of a trisoxazoline derivative that contains an apical proton

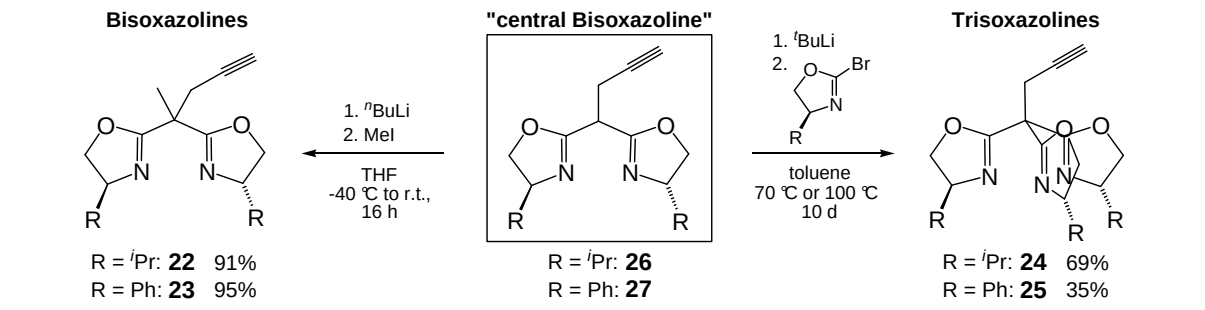
and subsequent reaction with an electrophile (Strategy **A**) or application of a linker-functionalised bisoxazoline that is coupled with a traditional 2-bromooxazoline (Strategy **B**). Strategy **A** would allow for flexible introduction of any linker after the critical [2+1]-coupling. As the required trisoxazoline, however, is (presumably) unstable and could not be synthesised in preliminary experiments (only starting material was reisolated), this route was abandoned early on.

Therefore, we initially focussed on the generation of a monofunctionalised bisoxazoline building block (Strategy **B**) which can be generated using two approaches: synthesis of an unsubstituted bisoxazoline and its subsequent monofunctionalisation *via* nucleophilic substitution (Method **C**), or direct synthesis, applying an appropriately functionalised derivative of malonic acid (Method **D**). The [2+1]-coupling to generate the trisoxazoline would later require adaptation of the reaction conditions to allow the conversion of the bisoxazoline in the presence of the linker appendage.

5.2.2 Linker-functionalised bis- and trisoxazolines

The synthesis of the new propargyl-functionalised bisoxazoline (**22**, **23**) and trisoxazoline ligands (**24**, **25**) for dendrimer fixation was based on a modular and convergent strategy. As mentioned above, this derived from appropriate "central bisoxazolines" (**26**, **27**, Scheme 5.3).

SCHEME 5.3 Modular access to propargyl-functionalised bisoxazoline and trisoxazoline ligands, based on a central monosubstituted bisoxazoline

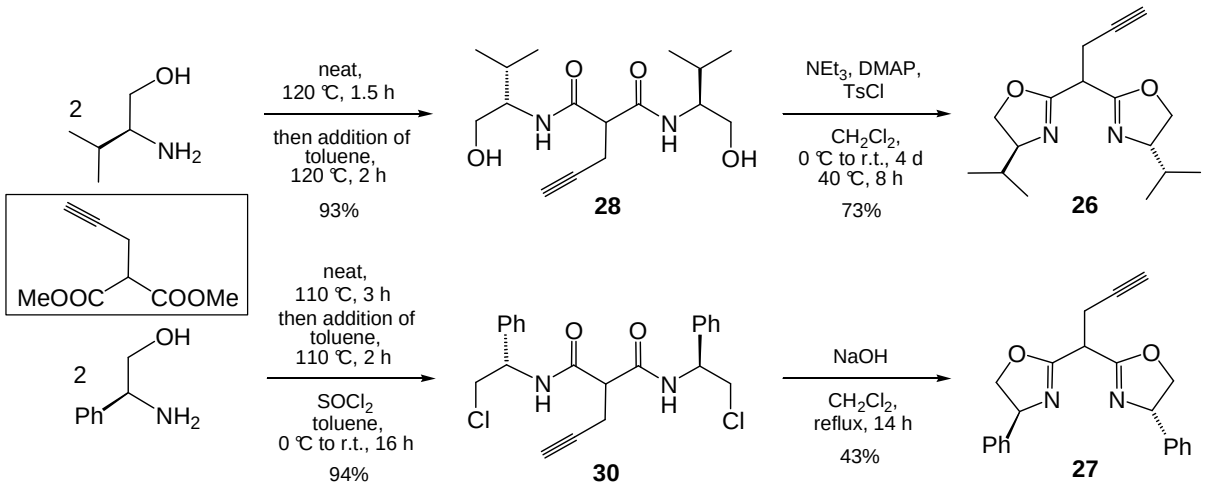


In preliminary studies, method **C** (Scheme 5.2) proved unsuccessful for the synthesis of these monosubstituted Box derivatives, since disubstituted products formed preferably, resulting in low yields and a complicated purification of the desired species.

Method **D**, on the other hand, turned out to be efficient, as many functionalised malonates were commercially available, therefore, reducing the number of synthetic steps. The tethered ligands **22**-**24** were, therefore, synthesised from purchased dimethyl propargyl-malonate and (*S*)-valinol or (*S*)-*α*-phenylglycinol.

Based on established procedures, the synthesis of bisoxazolines **26** and **27** proceeded *via* initial formation of diamides and subsequent cyclisation (Scheme 5.4). Contrary to the strategy used for diamides **6** and **7** (Chapter 4.4.1), application of catalytic sodium hydride was avoided to prevent deprotonation of the propargylic function and accompanying side reactions. Therefore, the formation of both diamide intermediates **28** and **29** proceeded cleanly and almost quantitatively, by directly reacting the amino alcohols with the malonate at 100-120 °C.

SCHEME 5.4 Synthesis of propargyl-functionalised bisoxazoline intermediates 26 and 27



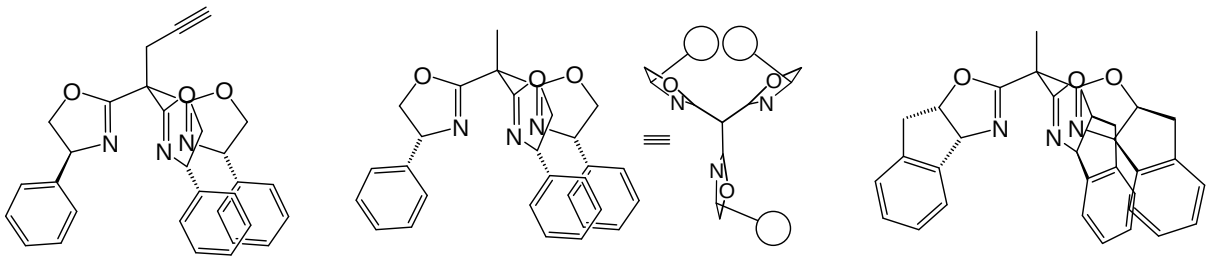
For the (*S*)-valinol-substituted diamide **28**, cyclisation was achieved using tosyl chloride[136] to give propargyl-functionalised bisoxazoline **26** in 68% yield (after 2 steps). Application of this method to (*S*)-*α*-phenylglycinol-derived compound **29**, proceeded less cleanly. However, treatment with $SOCl_2$ and subsequent cyclisation with NaOH,[35c] generated Box **27** in a reasonable yield (41%, after 3 steps).

After lithiation of bisoxazolines **26** and **27**, they were reacted with MeI to give propargyl-Box(^{i}Pr) **22** and propargyl-Box(Ph) **23** in excellent yields of over 90% (Scheme 5.3): The replacement of the acidic atom at the bridgehead in **26** and **27** was required to

avoid competitive side reactions in the following immobilisation reaction.

The syntheses of C_3-symmetric propargyl-Trisox(^{i}Pr) **24** and propargyl-Trisox(Ph) **25** were achieved by the established coupling[46] of a lithiated bisoxazoline with a 2-bromo-oxazoline[147] (compare ligands **14**-**18**, Chapter 4.5). The presence of the propargyl-moiety necessitated more vigorous conditions and longer reaction times as well as a higher stoichiometric excess of the bromooxazolines than previously reported for the parent Trisox derivatives. The solvent THF, for example, was replaced by toluene to increase the reaction temperature from 70 °C to 100 °C. Under these conditions, propargyl-Trisox(^{i}Pr) **24** was obtained in 69% yield. In the case of propargyl-Trisox(Ph) **25** high temperatures had to be avoided because 2-bromophenyloxazoline is far more unstable than 2-bromoisopropyl-oxazoline. It is especially prone to rearrange and form a 2-bromoisocyanate.[140] Accordingly, propargyl-Trisox(Ph) **25** could only be isolated in 35% yield. This value, however, is comparable to yields obtained for other trisoxazoline derivatives which were based on particularly unstable bromooxazolines[68] or suffered from steric hindrance[61b] during the [2+1]-coupling (Scheme 5.5).

SCHEME 5.5 The yield of Trisox(Ph) 25 compared to other trisoxazoline derivatives

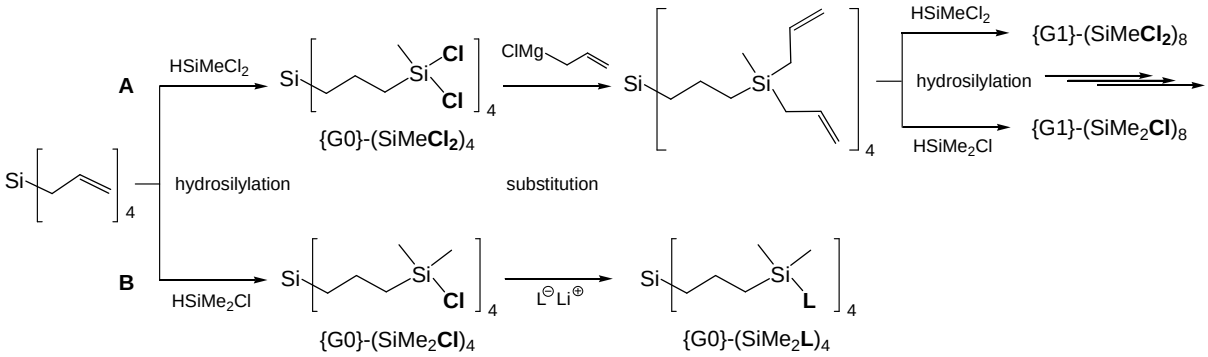


With reference to the starting material dimethyl propargylmalonate and based on reliable synthetic routes, the desired ligands **22**-**24** were obtained in good overall yields compared to analogous compounds. In general, isopropyl-functionalised derivatives reacted more cleanly and proved to be more robust than phenyl-substituted species.

5.2.3 Dendrimer fixation

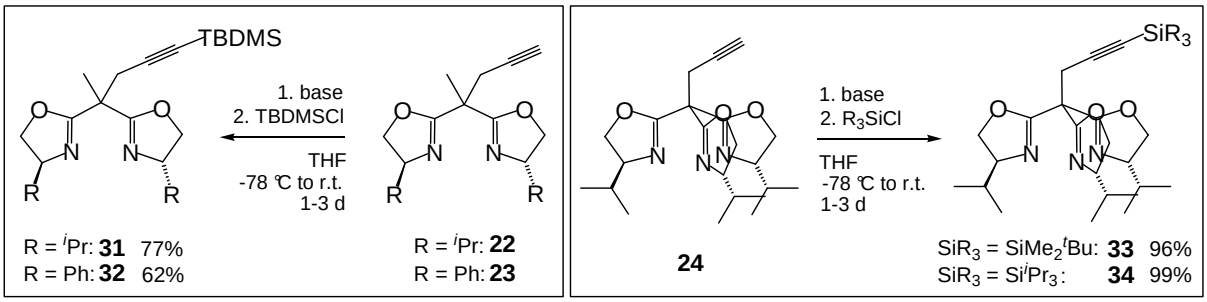
Oxazoline ligands **22-25** were attached to three different generations of carbosilane dendrimers containing chlorosilane termini *via* nucleophilic substitution. These parent dendrimers {G0}-$(SiMe_2Cl)_4$, {G1}-$(SiMe_2Cl)_8$ and {G2}-$(SiMe_2Cl)_{16}$ were synthesised from tetraallylsilane according to literature procedures, using alternating hydrosilylations and reactions with Grignard reagents (Scheme 5.6).[105,161]

SCHEME 5.6 **Synthetic strategy to access carbosilane dendrimers of different generations**: Hydrosilylation using dichlorosilanes allowed for dendrimer growth (pathway **A**) whereas chlorosilanes provided the dendrimers for ligand immobilisation (pathway **B**).



To test the potential of ligands **22-25** for nucleophilic substitution at chlorosilyl functions, $^{t}BuMe_2SiCl$ (TBDMSCl) and more bulky $^{i}Pr_3SiCl$ (TIPSCl) were chosen as model systems, their branched substituents mimicking the dendrimer framework. After deprotonation of oxazolines **22-24** by LDA or BuLi and reaction with the chlorosilane, clean and complete product formation (**31-34**) was observed (Scheme 5.7).

SCHEME 5.7 **Synthesis of TBDMS- and TIPS-functionalised models as counterpart to the functionalised carbosilane dendrimers**; Trisox(Ph) **25** reacted as smoothly as its anlogues, but decomposed during purification.



However, employing the same reaction conditions with {G0}-$(SiMe_2Cl)_4$, {G1}-$(SiMe_2Cl)_8$ and {G2}-$(SiMe_2Cl)_{16}$, only led to low or moderate conversion and inseparable

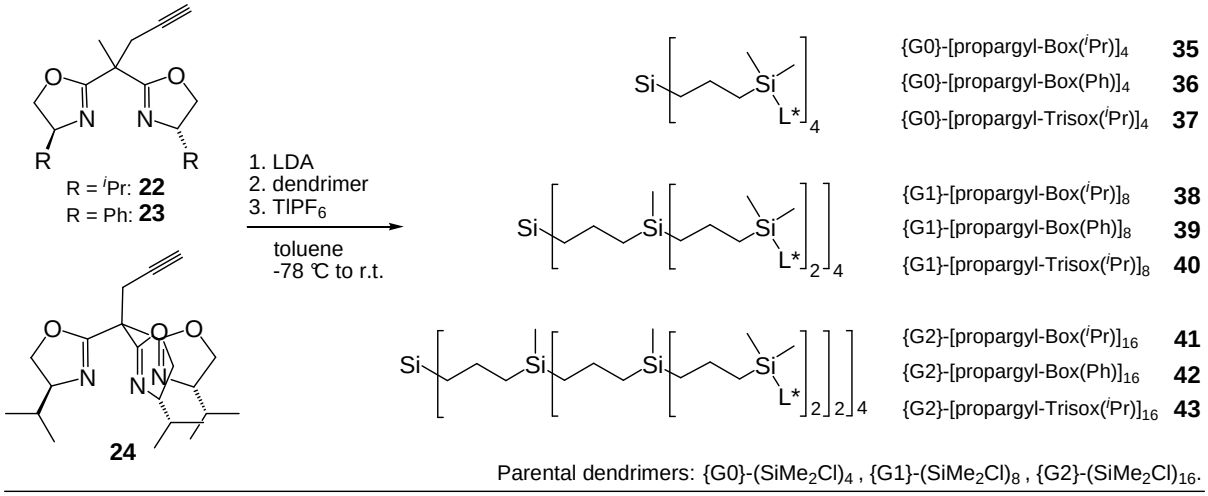
product mixtures of in part defective dendritic systems. Using {G0}-$(SiMe_2Cl)_4$, for example, all possible products containing one up to four immobilised ligands were detected (by ^1H NMR and mass spectrometry), their separation being almost impossible. As the increasing bulk of the dendrimers obviously hindered the reaction with the lithiated ligands, especially the trisoxazoline, the reactivity of the reactants had to be increased by changing general reaction parameters (Table 5.1). However, most of these variations promoted decomposition and side reactions rather than conversion.

TABLE 5.1 **Different reaction parameters adopted for the immobilisation of Trisox(^{i}Pr) 24 to {G0}-$(SiMe_2Cl)_4$;** conversions refer to the amount of applied ligand that reacted with the dendrimer. They were determined *via* ^1H NMR spectroscopy of the crude products.

Entry	***Reaction Parameters***					***Conversion***	***Remarks***
	Time	*Temperature*	*Solvent*	*Base*	*Additive*	*%*	
1	1 d	r.t.	toluene	LDA	$TlPF_6$	65	
2	4 d					68	
3	6 d	70 °C	THF	LDA		52	side reactions
4		100 °C				68	side reactions
5	1 d	r.t.	THF	LDA	$TlPF_6$	-	many side reactions
6			DME			no reaction	
7			toluene			65	
8	6 d	110 °C	THF	LiHMDS	DMAP	no reaction	
9		70 °C		NaH		no reaction	
10		70 °C		LDA		52	
11	6 d	110 °C	toluene	LDA	DMAP	67	clean reaction
12	6 d	r.t.	THF		$AgPF_6$	-	many side reactions
13	1 d	r.t.	toluene		$BiCl_3$	62	side reactions
14	1 d	r.t.	toluene		$TlPF_6$	65	satisfactorily clean

Supplementary activators such as DMAP and inorganic salts (Table 5.1, entries 11 and 14) enhanced the reactivity of the electrophile and compensated the moderate nucleophilic properties of the propargylic anions. Therefore, the sluggish and incomplete conversion could be overcome by addition of one equivalent of $TlPF_6$ (Table 5.1, entries 1 and 2) per acetylide unit and the use of an excess of the linker-ligand reagent (up to 1.8 equivalents per chlorosilyl function, Scheme 5.8). Applying this strategy, high conversions for all dendrimer and ligand combinations were achieved. However, the immobilisation of Trisox(Ph) **25** was unsuccessful, as many side reactions were observed.

SCHEME 5.8 **Synthesis of the oxazoline-functionalised carbosilane dendrimers {G0}-L*$_4$, {G1}-L*$_8$, {G2}-L*$_{16}$**: Depending on the dendrimer's size, 1.4 to 1.8 equivalents of the corresponding oxazoline per reactive chlorosilyl function were applied.



Parental dendrimers: {G0}-$(SiMe_2Cl)_4$, {G1}-$(SiMe_2Cl)_8$, {G2}-$(SiMe_2Cl)_{16}$.

The purification of the dendritic compounds **35**-**43** was carried out by applying *van Koten*'s strategy of dendrimer isolation *via* dialysis,[162] particularly to remove excess ligand. Thus, the zeroth generation trisoxazoline derivative **37** as well as all first and second generation dendrimers {G1}-L*$_8$ and {G2}-L*$_{16}$ **38**-**43** could be purified efficiently and were obtained in pure form in moderate to good yields (49% - 77%, Figure 5.2).

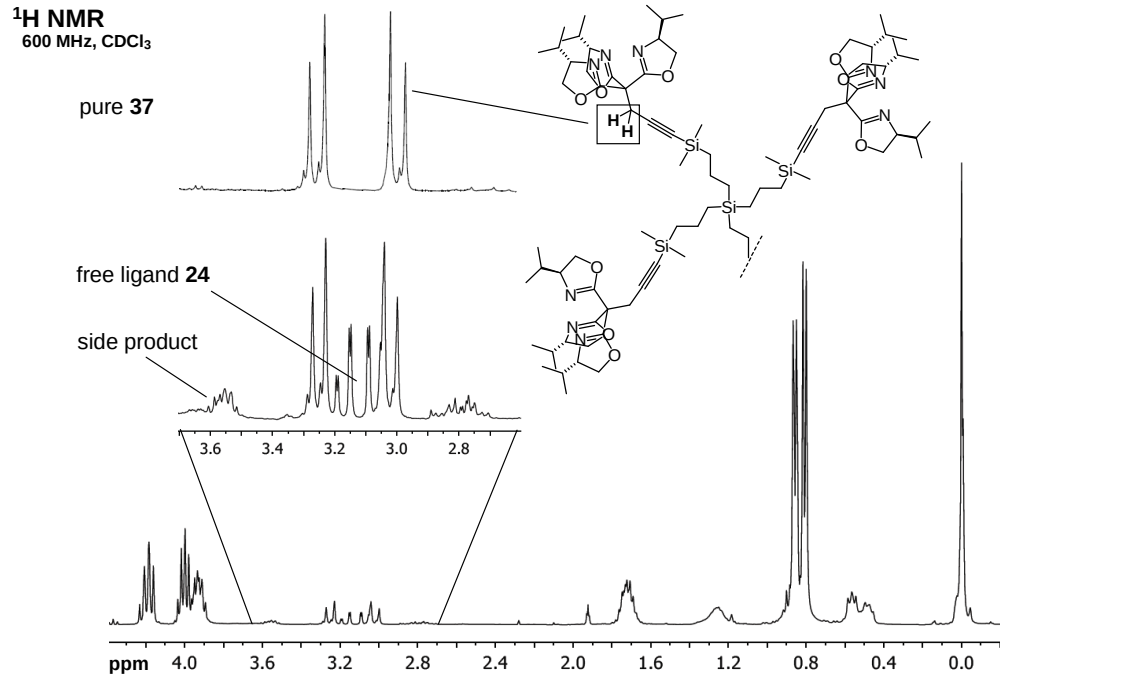


FIGURE 5.2 **^{1}H NMR spectrum of crude {G0}-[propargyl-Trisox(^{i}Pr)]$_4$ 37.** A comparison of the characteristic region – the propargylic protons – before and after dialysis shows the efficiency of this purification method.

The zeroth generation {G0}-L^*_4 derivatives (L^* = Box) were too small to be efficiently retained by the membrane pores and therefore had to be purified by column chromatography. As they tend to decompose on silica, they were isolated in low yields (28% and 22%). Characterisation (and assessment of purity) of the oxazoline-functionalised dendrimers was provided by ^{13}C and ^{29}Si NMR spectroscopy, elemental analysis as well as by mass spectrometry for the lower generations. Figure 5.3 depicts {G2}-$Trisox_{16}$ **43** as an example of the polyfunctional dendritic ligands.

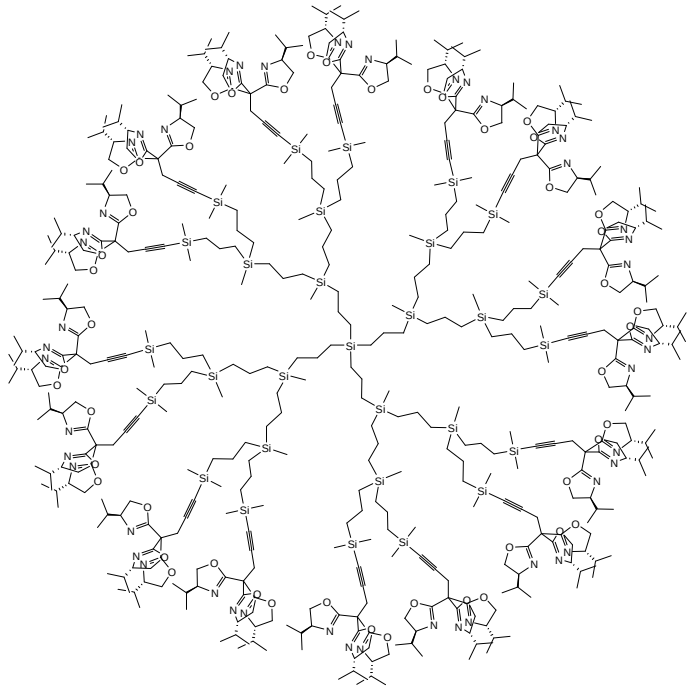


FIGURE 5.3 Schematic view of {G2}-[propargyl-Trisox(^{i}Pr)]$_{16}$ 43.

Figures 5.4 and 5.5 display the ^1H NMR spectra of {G0}- and {G2}-dendrimers of Box **22** and Trisox **24**. With growing dendrimer size the signals tend to broaden, the extent depending on the immobilised ligand. When switching from bisoxazoline-functionalised species **35** to **41**, this broadening is clearly visible, whereas there is no difference between trisoxazoline-functionalised **37** and **43**. This is due to the different local symmetry of both ligands, derivatives of C_3-symmetric trisoxazolines exhibiting simpler spectra compared to the derivatives of C_2-symmetric bisoxazolines.

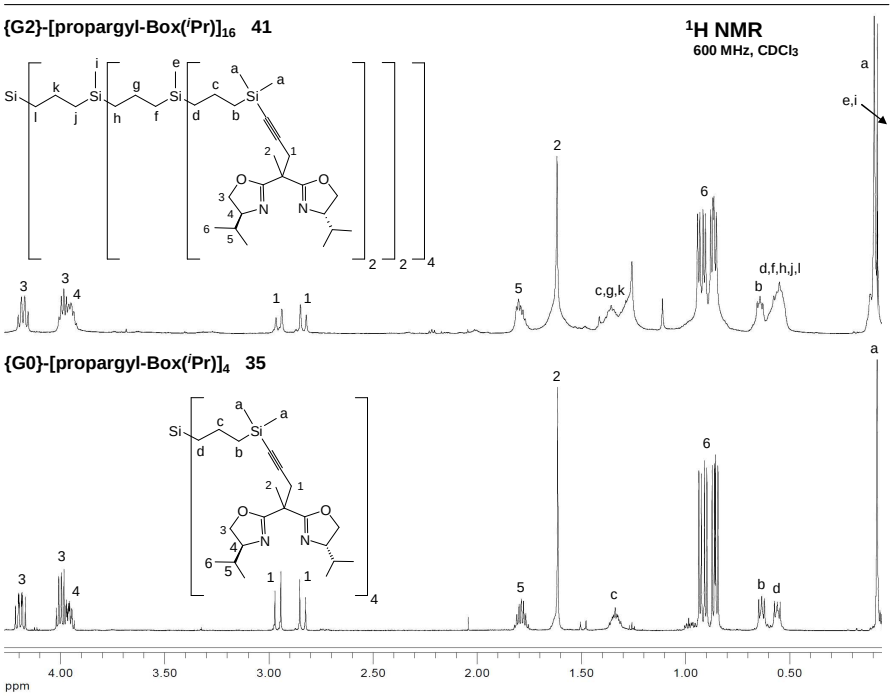


FIGURE 5.4 ^{1}H NMR spectra of {G0}-[propargyl-Box(^{i}Pr)]$_4$ 35 and {G2}-[propargyl-Box(^{i}Pr)]$_{16}$ 41.

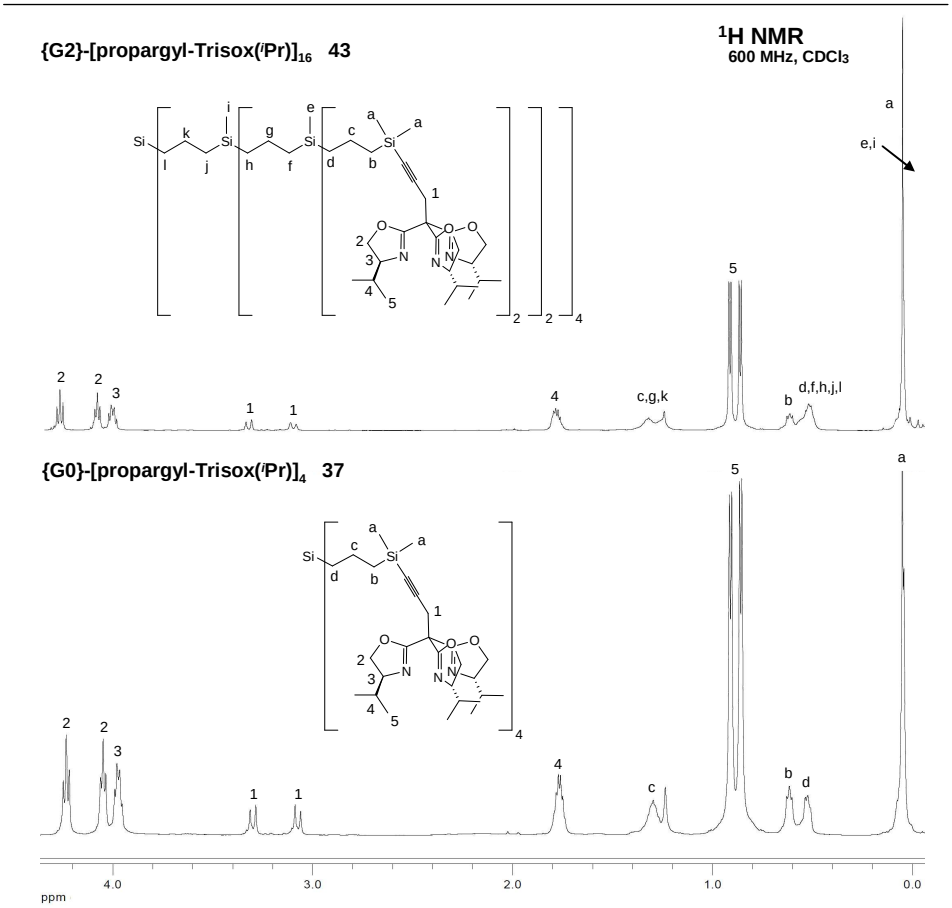


FIGURE 5.5 ^{1}H NMR spectra of {G0}-[propargyl-Trisox(^{i}Pr)]$_4$ 37 and {G2}-[propargyl-Trisox(^{i}Pr)]$_{16}$ 43.

5.3 Probing of multisite chiral copper(II) catalysts

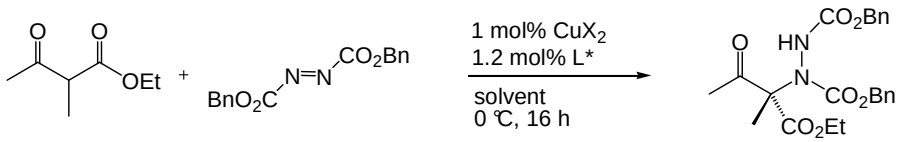
The general catalytic potential of compounds {G0}-L^*_4, {G1}-L^*_8 and {G2}-L^*_{16} as polyfunctional chiral ligand systems for asymmetric copper(II) Lewis acid catalysis was assessed by studying two benchmark reactions: the α-hydrazination of a β-ketoester[61,64] (Chapter 2.4.4) as well as the Henry reaction of 2-nitrobenzaldehyde with nitromethane.[163] Both reactions had previously been studied using various bisoxazoline derivatives as stereodirecting ligands.[61,64,163]

Box **A**, **B** and Trisox **C** (Figure 5.1, *vide supra*, p.55), bearing only a methyl group at the bridgehead or the apical position, were employed as reference systems as well as the propargyl-functionalised ligands **22-24** and the model systems **33-34**. This work focussed on two issues: a comparison of the polyfunctional dendritic ligands with the corresponding mononuclear systems and of bisoxazoline and trisoxazoline derivatives.

5.3.1 α-Hydrazination of ethyl 2-methylacetoacetate

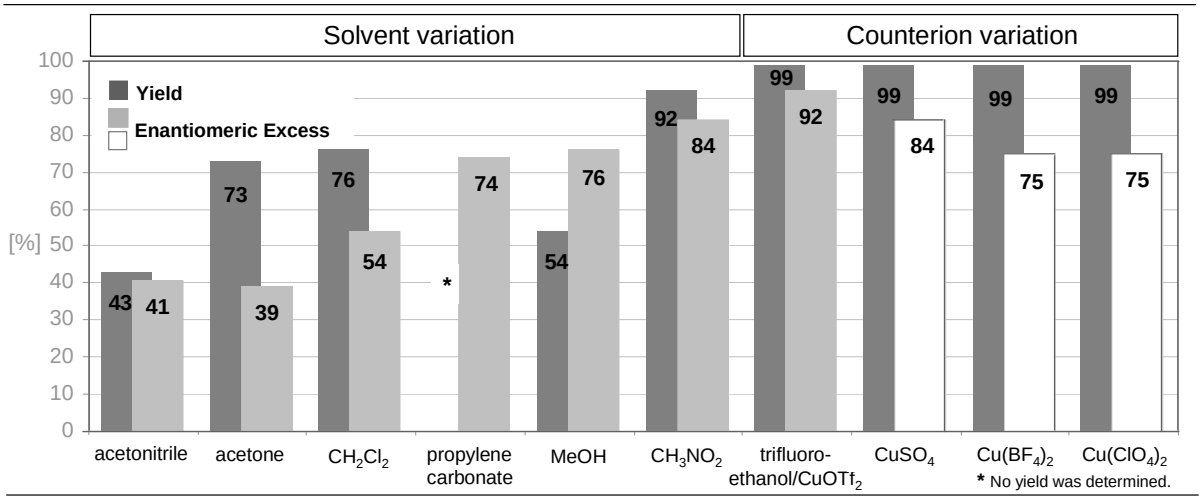
The α-hydrazination of ethyl 2-methylacetoacetate (Scheme 5.9) has been studied extensively[61,64] and therefore lent itself to assess the influence of the dendritic support (and subsequently the recycling in a membrane bag, Chapter 5.5) on the catalytic system.

SCHEME 5.9 α-Hydrazination of ethyl 2-methylacetoacetate



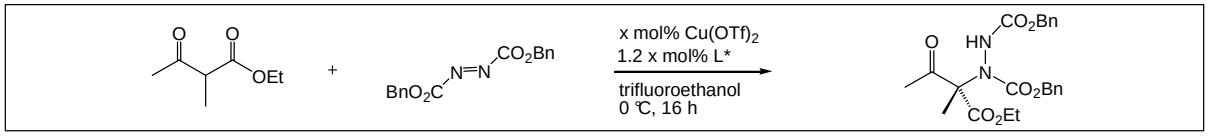
A preliminary screening of the reaction conditions (the solvent and the copper salt, Scheme 5.9 and Chart 5.1) allowed for a basic evaluation of the performance of the polyfunctional dendritic ligands and helped to find the optimal conditions for their use. Whereas the solvents were observed to exert quite a strong influence on conversion as well as enantiomeric excess, the counter ions influenced only the latter (Chart 5.1). The best results where obtained by using a combination of strongly dipolar trifluoroethanol[164] and copper triflate (which were employed as the standard parameters in all subsequent studies).

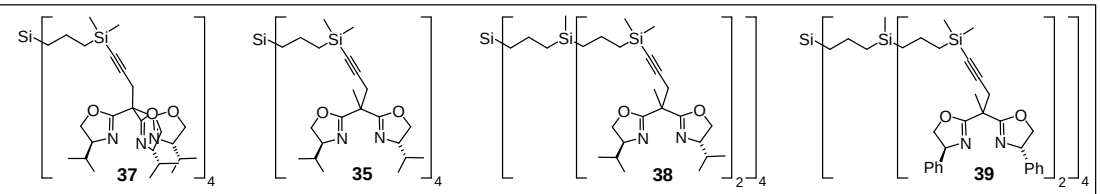
CHART 5.1 **Variation of the solvent and counterion in the *α*-hydrazination of ethyl 2-methylacetoacetate with {G0}-[propargyl-Trisox(^{i}Pr)]$_4$ 37**; All reactions were run with 1 mol% catalyst loading at 0 °C for 16 h. $Cu(OTf)_2$ was used as metal source for all solvent screening experiments. Trifluoroethanol served as solvent for counterion screening.



Variation of the temperature, on the contrary, did not affect the outcome of the reactions significantly: at -28 °C and 0 °C, identical *ee*-values (92% at 1 mol% catalyst loading) and similar yields were obtained. At reduced catalyst loadings (0.1 mol% and 0.01 mol%, Table 5.2) moderate *ee*-values to almost racemic products were obtained. At this extremely low catalyst loading, however, results were difficult to reproduce due to the susceptibility of the labile Cu^{II}-complexes. Thus, 1 mol% was applied for further studies and all values were determined as averages of at least three experimental runs. The results are displayed in Table 5.3.

TABLE 5.2 ***α*-Hydrazination of ethyl 2-methylacetoacetate at different catalyst loadings**



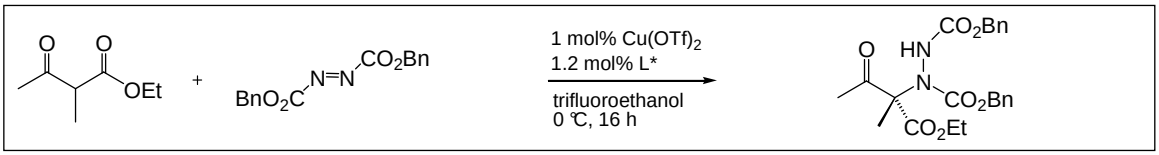


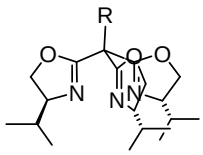
Loading [mol%]	37 Yield [%]	37 *ee* [%]	35 Yield [%]	35 *ee* [%]	38 Yield [%]	38 *ee* [%]	39 Yield [%]	39 *ee* [%]
1	99	92	99	93	99	95	99	97
0.1	99	30	99	54	99	41	99	51
0.01	93	4	99	8	-	-	99	5

The remarkably low catalyst loading of 1 mol% was found to be sufficient and generally high yields and selectivities were obtained. The highest enantioselectivities were

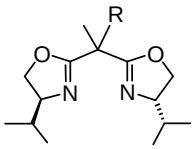
observed for the Box(Ph) derivatives – a trend which had already been noted earlier.[61,64] Enantiomeric excesses of between 97% and 99% were obtained with these catalysts, whereas those obtained with Box(*i*Pr) and Trisox(*i*Pr) ranged betwen 90% and 97%.

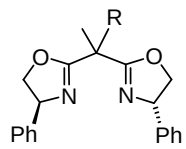
TABLE 5.3 **Catalytic asymmetric *α*-hydrazination of ethyl 2-methylacetoacetate with free and immobilised Box and Trisox species bearing an increasing steric bulk**; Quantitative yields were obtained throughout all catalyses.





Substituent at the apical position or the carbon bridge **R**





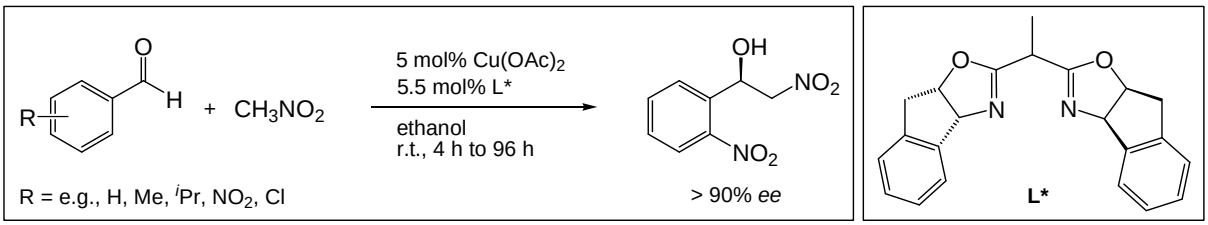
Ligand	*ee* [%]	R	*ee* [%]	Ligand	*ee* [%]	Ligand
C	94	Me	94	**A**	98	**B**
24	96	propargyl	97	**22**	99	**23**
33	93	propargyl-TBDMS	96	**31**	99	**32**
34	93	propargyl-TIPS	-		-	
37	92	{G0}-L*$_3$	93	**35**	97	**36**
40	95	{G1}-L*$_7$	95	**38**	97	**39**
43	90	{G2}-L*$_{15}$	94	**41**	98	**42**

There are some notable aspects concerning the results obtained with Box(*i*Pr) and Trisox(*i*Pr) derivatives, namely an increase of *ee*-values from 94% for the catalysts with the parent ligand systems **A** and **C** to 97% and 96% with propargyl-substituted ligands **22** and **24**, respectively. Similar observations were made for the smaller dendritic species {G0}-L*$_4$ **35/37** as well as {G1}-L*$_8$ **38/40**. In general, enantioselectivities were slightly higher (3% - 4%) for the bisoxazolines compared with the Trisox-systems. These distinctions suggested that trisoxazoline and bisoxazoline ligands indeed experienced varying dendritic effects which was supported by their different reaction rates, roughly indicated by the vanishing of the substrate colour, a point which will be surveyed in Chapter 5.4.

5.3.2 Henry reaction of nitromethane and 2-nitrobenzaldehyde

The Henry reaction was chosen as a complementary test reaction to assess the trend observed in the α-hydrazination. Reacting carbonyl compounds with CH-acidic nitroalkanes (mostly nitromethane), this transformation is a powerful tool to form C-C bonds and to access functionalised structural motifs such as amino alcohols and amino acids.[165] This is mainly due to the versatile reactivity of the nitro group which can be converted to ketones, aldehydes or carboxylic acids *via* Nef oxidation,[166] to amines *via* reduction,[167] and to other heteroatom-functionalised compounds *via* nucleophilic substitution.[168] As a consequence of practical issues, however, first stereocontrolled versions of the nitroaldol reaction have emerged relatively late in 1992 (particularly, compared to related aldol reactions). Although there are promising approaches to asymmetric Henry reactions using preformed nitronates,[169] direct versions (generating the nitronate *in situ*) have been less studied. Moreover, the use of a broad range of substrates, including ketones, diverse nitroalkanes and functionalised carbonyl compounds is desired.

SCHEME 5.10 Direct Henry reaction reported by *Evans et al* [163]

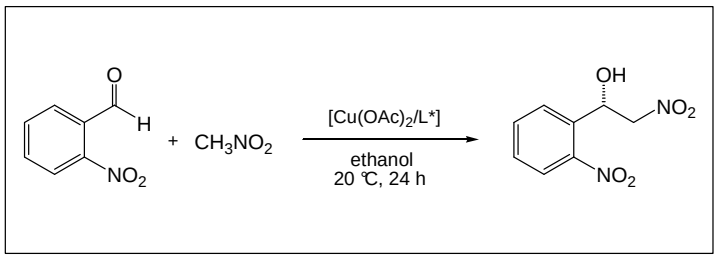


An efficient approach to direct Henry reactions has been reported by *Evans et al*.[163] In this mild version (Scheme 5.10), Box ligands were applied successfully in the reaction of various benzaldehyde derivatives with nitromethane at 5 mol% catalyst loading, yielding products with good enantioselectivities of around 90%.

To assess the effect of the varying environments on the catalyst performance, a reference system was chosen that only gave moderate enantiomeric excesses, allowing both increase and decrease in enantioselectivities. This was verified by preliminary experiments, applying Cu^{II}-catalysts derived from methyl-substituted ligands **A** and **C** under *Evans*'s conditions (Table 5.4). 2-Nitrobenzaldehyde was chosen as a carbonyl reagent, because it is particularly reactive. Using different catalyst loadings, both ligands yielded identical results

of up to 80% *ee*. This suggested, furthermore, that if different behaviour was detected when applying the dendritic catalysts, this would indeed originate from the environment of the ligands.

TABLE 5.4 **Comparison of the performance of methyl-substituted bisoxazoline A and trisoxazoline C in the nitro aldol reaction**; At 5 mol% and 1 mol% catalyst loading, 10 equivalents of nitromethane were applied. At 0,1 mol% and 0,01 mol%, 50 equivalents were used.



Loading [mol%]	A Yield [%]	A *ee* [%]	C Yield [%]	C *ee* [%]
5	99	82	99	79
1	98	73	97	73
0.1	52	16	50	16
0.01	28	0	33	0

Since reactions using the dendritic ligands proceeded slowly under these conditions, the parameters were optimised to achieve reasonable reaction times at a catalyst loading of 1 mol% (Chart 5.2, left). Whereas classical alcohols and chlorinated solvents favoured either activity or selectivity, trifluoroethanol bridged the gap between these two criteria. Similar observations had been made for asymmetric hydrogenation with self-assembling rhodium complexes, as only fluorinated alcohols allowed the formation of hydrogen bonds which are the basis for those catalyst assemblies.[170] This suggests that the performance of the dendritic oxazolines is likewise determined by an arrangement of their framework.[171]

CHART 5.2 **Variation of the solvent in the Henry reaction of 2-nitrobenzaldehyde and nitromethane with {G0}-[propargyl-Box(^{i}Pr)-Cu(OTf)$_2$]$_4$ 35-Cu**

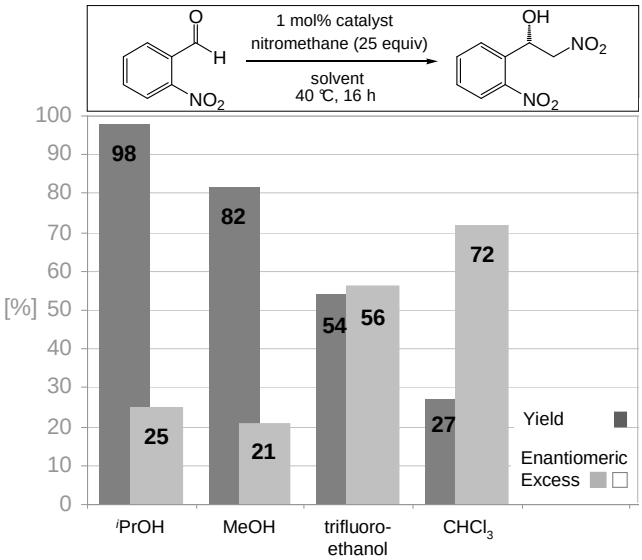


Table 5.5 summarises the definite reaction conditions as well as the results of catalytic runs with the different Cu^{II}-catalysts (determined as averages of at least two experimental runs). All catalyses proceeded smoothly and gave the products cleanly, only traces of the elimination products being detected (Scheme 5.11). Furthermore, it should be noted that the methyl-substituted reference system Box **A** gave identical values with respect to Trisox **C** at these reaction parameters, supporting the results from the preliminary study (Table 5.4, *vide supra*).

SCHEME 5.11 Elimination products that may occur in the Henry reaction

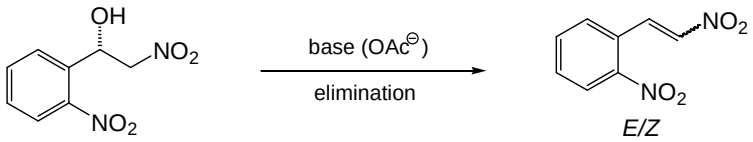
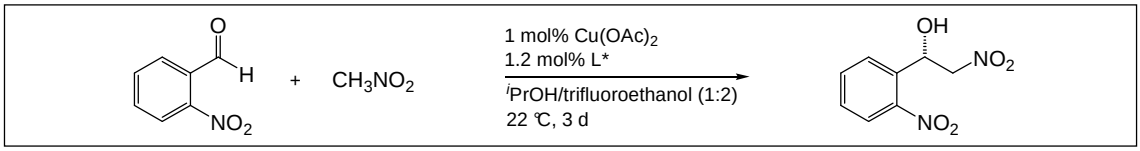
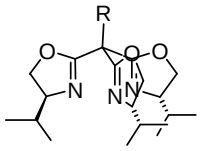
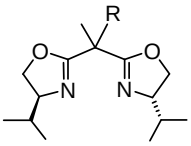


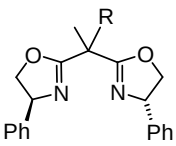
TABLE 5.5 Catalytic asymmetric Henry reaction of 2-nitrobenzaldehyde and nitromethane with free and immobilised Box and Trisox species bearing an increasing steric bulk





Substituent at the apical position or the carbon bridge **R**





Ligand	Yield [%]	*ee* [%]	**R**	*ee* [%]	Yield [%]	**Ligand**	*ee* [%]	Yield [%]	**Ligand**
C	93	75	Me	74	95	**A**	71	89	**B**
24	32	67	propargyl	77	45	**22**	74	74	**23**
33	24	50	propargyl-TBDMS	77	36	**31**	74	65	**32**
34	18	51	propargyl-TIPS	-	-		-	-	
37	42	52	{G0}-L*$_3$	84	86	**35**	84	83	**36**
40	58	53	{G1}-L*$_7$	87	87	**38**	83	85	**39**
43	54	53	{G2}-L*$_{15}$	83	87	**41**	81	82	**42**

First of all, a significant difference between the Box- and Trisox-based catalysts was observed. Box(Ph) and Box(^{i}Pr) gave similar *ee*-values (71% up to 77%, respectively) and yields for all mononuclear catalysts. On the other hand, the dendritic Box-derivatives all gave reaction products with significantly higher enantiomeric excesses (81% up to 87%). In contrast, the performance of all the Trisox-based catalysts proved to be inferior, both in terms of the activities and enantioselectivities (51% up to 75%). The negative trend, with respect to them, observed for the α-hydrazination is thus enhanced for the Henry reaction.

5.4 Comparison of the Box- and Trisox-copper catalysts

To gain some insight into the different behaviour of immobilised Box and Trisox for both types of reactions, the rates of conversion were monitored. For this purpose, the α-hydrazination of ethyl 2-methylacetoacetate was chosen because it had already been the object of a detailed kinetic study[61b] and proceeded very cleanly. The corresponding conversion curves are shown in Chart 5.3. To allow for a better comparison Chart 5.4 depicts the time each catalyst required to achieve 90% conversion.

Both the Box-based catalysts and their TBDMS-functionalised derivatives displayed similar rates of conversion, whereas the G2-supported catalysts were markedly less active (Charts 5.3, top and middle). In contrast, the conversion curves recorded for the three Trisox species revealed different behaviour. Whereas the parent catalyst containing ligand **C** displayed an activity similar to the Box-based catalysts, the TBDMS-substituted Trisox catalyst **33** was significantly less active, and the conversion was even slower for the dendritic catalyst **43** (Charts 5.3, bottom and Charts 5.4). In summary, whilst the attachment of a linker at the ligand backbone and the immobilisation only moderately affected the Box-based catalysts for the two reactions studied in this work, the effect on the Trisox-based catalysts was dramatic. Attachment of trisox to a second generation carbosilane dendrimer increased the reaction times by an order of magnitude!

This observation may be understood on the basis of the previously proposed role of the third ligand arm in Trisox-copper(II) Lewis acid catalysts.[61] In solution, an equilibrium between κ^3- and κ^2-Trisox coordinated complexes is thought to exist for which the coordination of the third ligand arm stabilises the resting state, but leads to a deactivation of the copper complexes by reduction of the Lewis acidity as was shown in a theoretical study on (Box)Cu catalysts.[65] The transformation of the stabilised but inactive resting state into the active (17 electron Cu^{II}) species therefore requires the decoordination of an oxazoline unit which then adopts a remote position from the centre as is depicted in Scheme 5.12 (*vide supra*).[61] The resulting vacant coordination site can only then be occupied by the enolate form of ethyl 2-methylacetoacetate. Enantiodescrimination is thus effected by similar copper species in the Box and Trisox systems.

CHART 5.3 Conversion curves for the α-hydrazination of ethyl 2-methylacetoacetate using catalysts with different steric bulk.

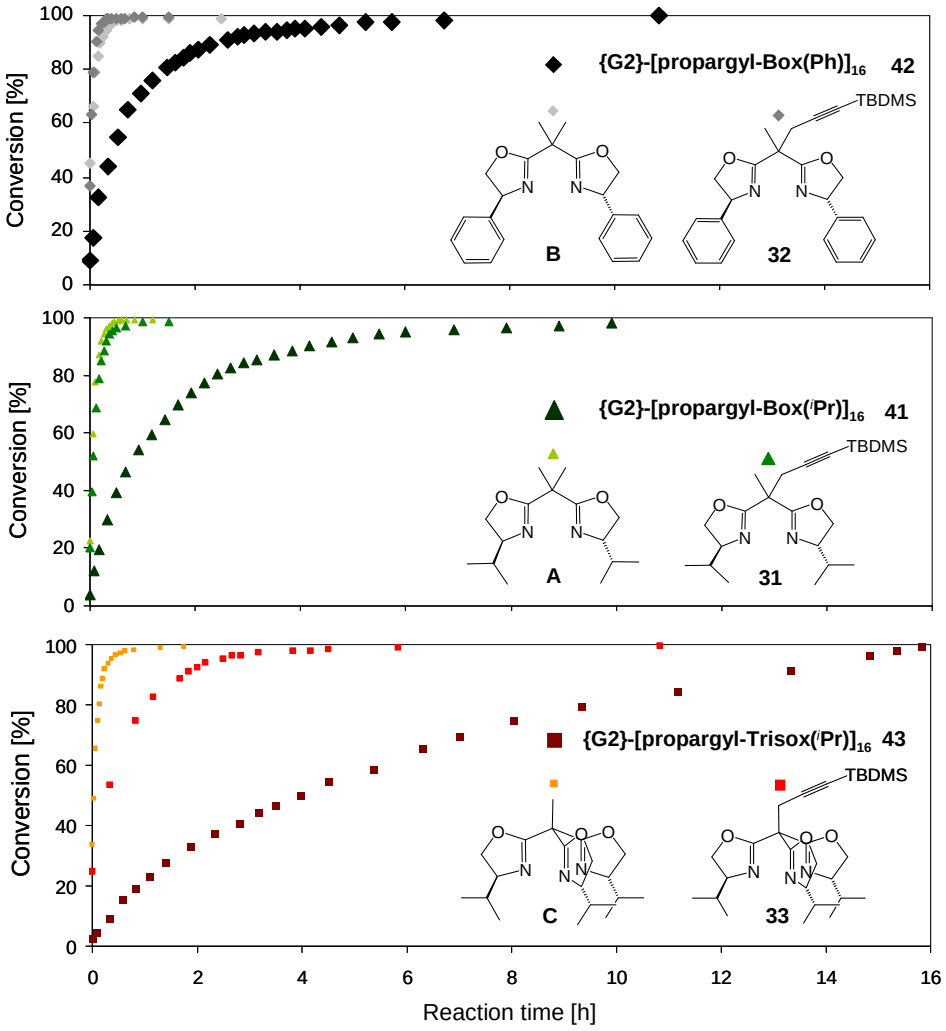
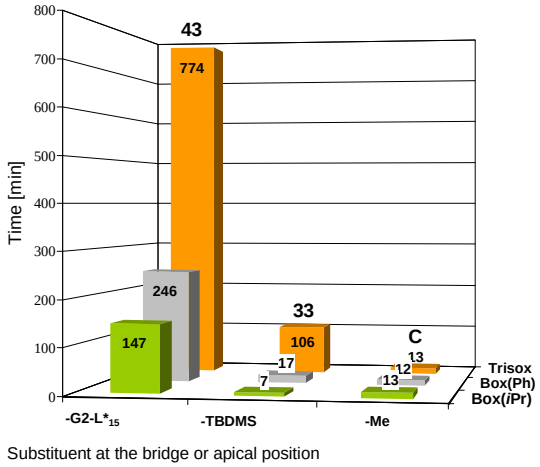
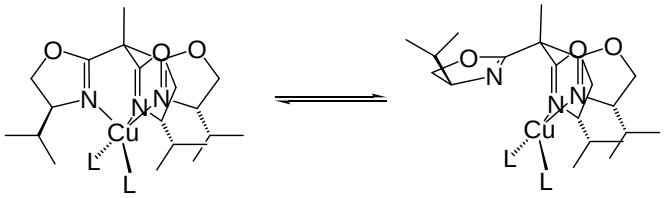


CHART 5.4 Comparison of the time needed to achieve 90% conversion with the different catalysts.



SCHEME 5.12 **Coordination–decoordination equilibrium of Cu^{II}-trisoxazoline-catalysts**; required to generate a vacant site for binding of the substrate.



However, decoordination of the third arm and a fast equilibration of the κ^3- and κ^2-Trisox coordinated complexes require sufficient space for the intramolecular movement of one of the oxazoline rings. Introduction of a bulky substituent (in the form of the linker or even more so of the dendrimer!) to the apical position hinders this process sterically and therefore only a fraction of the actually employed (Trisox)Cu catalyst will be catalytically active. For immobilised Trisox the catalyst loading is thus effectively reduced and the background reaction leading to a racemic product gains in importance. In summary, increasing steric bulk in the periphery of the immobilised Trisox ligands is thought to result in the negative observed effect on both the catalyst activity and selectivity. On the other hand, increasing steric bulk may be beneficial for the enantiodiscrimination in the case of the more "open" Box as manifested in an increase of the *ee*-values by ca 10%!

5.5 "Catalysis in a tea bag" – Recycling *via* dialysis

The exploitation of ultra- and nanofiltration techniques based on dialysis in the reaction engineering of catalytic processes was originally developed for biotechnological applications.[172] *Kula*, *Wandrey* and others used continuous flow membrane reactors for enzymatic transformations since the early 1980s,[173] and a simple, practical variation of this approach for batch reactions was put forward by *Whitesides* and coworkers in 1987 who employed membrane bags to recycle the enzymatic catalyst.[174]

The application of this technique to organometallic homogeneous catalysis has been a more recent development. *Kragl* and others made key contributions to the development of continuously operating membrane reactors for this type of catalytic systems,[175] using

amongst others a polymer-supported proline-derivative as chiral catalyst.[176] Finally, it were *van Koten*, *van Leeuwen* and their coworkers who first reported the application of this technique to dendrimer catalysis and led to its establishment in dendrimer chemistry.[177,178] These techniques, based on adapted membranes, combine simple and convenient use with the advantages of solid phase immobilisation, allowing for high total turnover numbers and easy recovery for repeated use.

Several types of membrane-based reactors have been reported, some of which require sophisticated engineering.[172e,g,h] The simplest approach is based on catalyst enclosure within a membrane "bag".[179] It provides adequate dispersion of the catalyst and guarantees minimal interaction between the catalyst and the polymer, thus allowing the use of relatively labile catalyst systems. This is certainly the case for the Cu^{II}-based Lewis acid catalysts employed in this work.

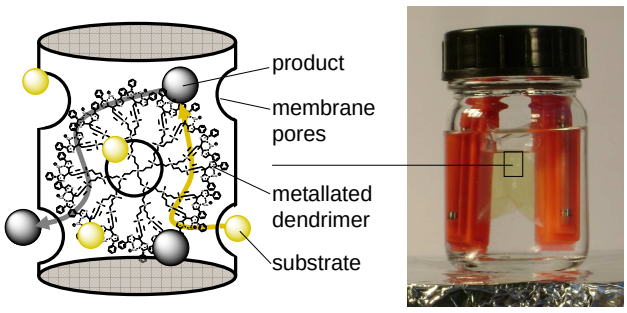


FIGURE 5.6 **General setup for the recycling using "catalysts in a tea bag";** An enlarged schematic view clarifies the functional principle.

As indicated above (Chapter 5.1), the dendrimer catalysts were developed with the purpose of catalyst recycling based on dialysis, using membrane bags fabricated from commercially available dialysis membranes (Sigma-Aldrich: dialysis tubing, benzoylated, avg. flat width 32 mm, MWCO 2000), which may be "dipped" like a "tea bag"[180] into a reactant solution and recycled several times. As reactors we chose simple screw cap vials which are depicted in Figure 5.6.

Two of the highest generation dendrimers – {G2}-Box(Ph)$_{16}$ **42** and {G2}-Trisox(^{i}Pr)$_{16}$ **43** – were applied to compare the behaviour of Box and Trisox in the recycling study of the α-hydrazination. The metallated analogues {G2}-propargyl-Box(Ph)-Cu$_{16}$ **42-Cu** and {G2}-propargyl-Trisox(^{i}Pr)-Cu$_{16}$ **43-Cu** of these dendritic ligands possess molecular

weights of around 14 500 g/mol, whereas the membrane allows only the migration of molecules up to 2 000 g/mol. On the other hand, the transport of the substrates and the product in and out of the membrane bag occurs by diffusion which was accelerated by operating at an elevated temperature of 40 °C (no reaction occurred at 0 °C whereas slow reaction was observed at room temperature), consequently resulting in somewhat lower enantioselectivity. The substrates migrate into the membrane bag where they interact with the catalytically active terminal groups of the dendrimer and are converted to the product. Consequently, the latter is enriched in the interior and then passes through the membrane to the exterior part of the reactor following the concentration gradient. The practical handling of such a catalyst tea bag is illustrated in Figure 5.7.

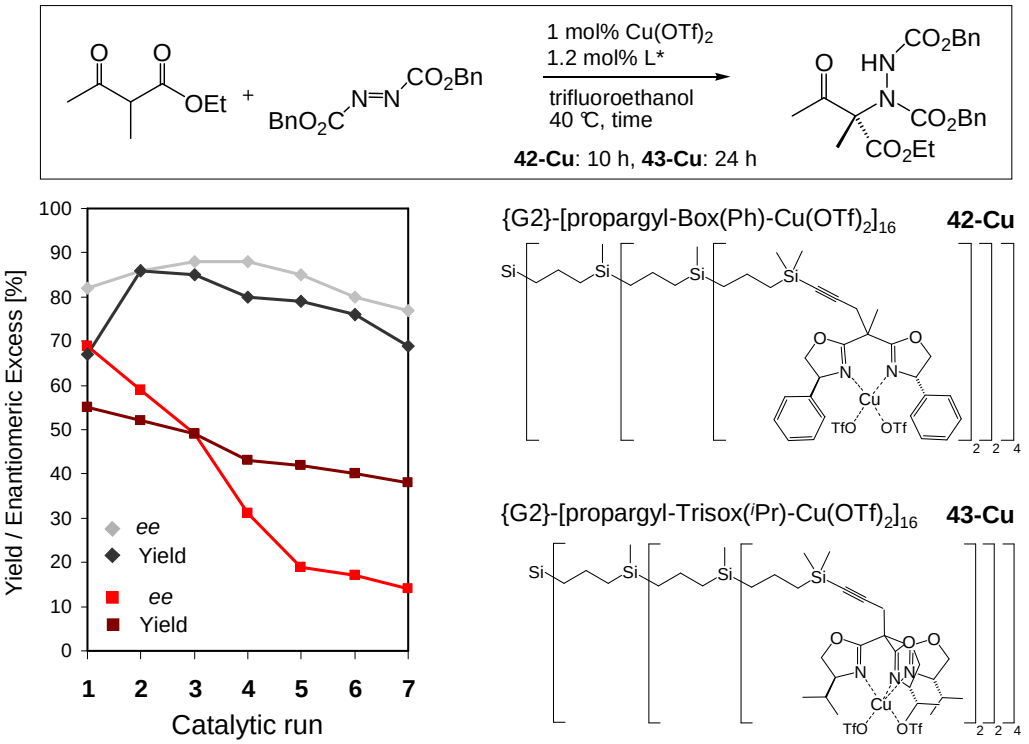
Figure 5.7 **A photo series showing the course of one recycling.** a) Dendrimer-filled membrane bag in the yellow solution of the substrates; magnetic clips attached to it allow for stirring; b) Colourless solution after complete conversion; c) Transfer of the bag into another vial; d) Successive reaction.

Initially the dendrimer-filled membrane bag is placed into the vial containing the yellow solution of the substrates, the colour being due to the diazodicarboxylate (Figure 5.7 a). After their complete conversion to the product, which is accompanied by a decoloration of the solution (Figure 5.7 b), the bag is transferred into another vial containing fresh substrates (Figure 5.7 c). Monitoring the rate of decolouration, 10 hours were chosen as reaction time for one cycle with {G2}-Box(Ph)-Cu_{16} **42-Cu** and 24 hours with {G2}-Trisox(^{i}Pr)-Cu_{16} **43-Cu** in order to achieve complete conversions. The results obtained for 7 successive runs are summarised in Chart 5.5.

The values given for each recycling were determined as average of at least five catalytic runs. Provided that the solvent volumes and the size of the membrane bag were

constant, the results proved to be reproducible. Yields and *ee*-values generally varied by about 2%. When modifying the parameters, however, stronger divergence of the values for the yields was noted due to a different diffusion rate.

CHART 5.5 **Catalytic results of the recycling study.** 7 successive runs of the *α*-hydrazination with {G2}-Box(Ph)$_{16}$ and {G2}-Trisox(^{i}Pr) are presented.



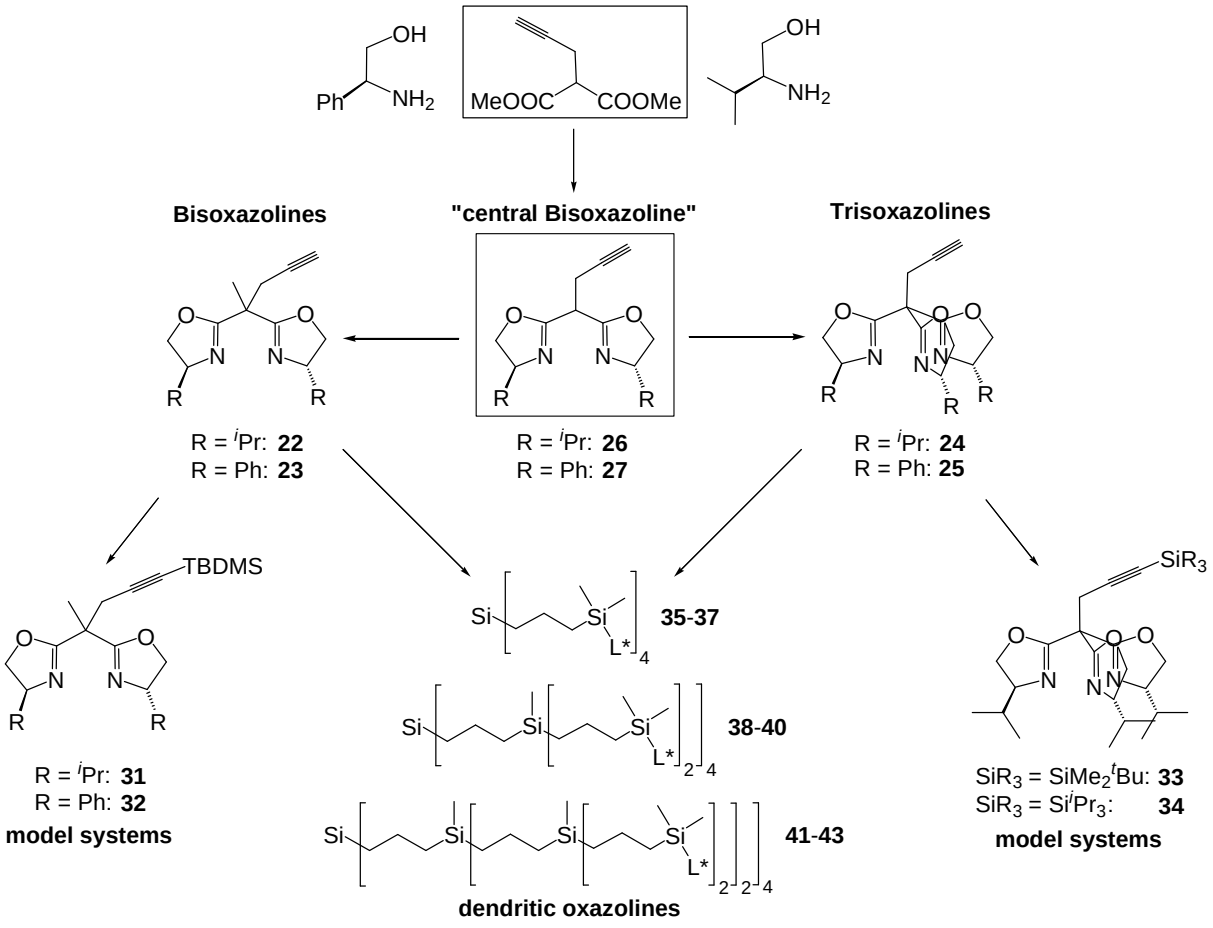
It is notable that the enantioselectivities obtained with {G2}-Box(Ph)-Cu$_{16}$ **42-Cu** vary only slightly from 82% in the first to 77% in the last run. A maximum *ee* of 88% was reached during the third and fourth cycle. The corresponding yields reflect the classical behaviour of membrane systems, showing increase between the first (67%) and the second run (86%) which reflects the establishment of a stationary state. Then, the values drop gradually to 69% again in the seventh cycle. Overall, the supported Box catalyst {G2}-Box(Ph)-Cu$_{16}$ **42-Cu** gave good and highly reproducible results throughout the study. The Trisox dendrimer system {G2}-Trisox(^{i}Pr)-Cu$_{16}$ **43-Cu**, on the other hand, started out with a moderate performance (69% *ee*, 55% yield) which decreased monotonically to 14% *ee* and 38% yield for the final run. The reason for the different behaviour of the two dendrimer catalysts is the markedly lower activity of **43-Cu** compared to {G2}-Box(Ph)-Cu$_{16}$ **42-Cu** (compare Chapter 5.4). This necessitated the increased reaction time for each cycle, leading

to higher levels of catalyst leaching which were assessed by AAS measurements. After one recycling with **42-Cu** (10 h) about 2.5% (of the initially applied amount) of copper had leached into the exterior solution, whereas 5% were found in the case of **43-Cu** (24 h). This indicated that the level of leaching is proportional to the reaction time which is believed to result from the modification of the membrane structure by its exposure to trifluoroethanol at 40 °C.

5.6 Conclusions and perspectives

Based on dimethyl propargylmalonate, a modular and convergent strategy was developed to access propargyl-functionalised bis- and trisoxazoline ligands in good overall yields *via* a monosubstituted bisoxazoline intermediate. In this way, four linker-containing ligands **22**-**25** were generated (Scheme 5.13).

SCHEME 5.13 Synthesis of free and immobilised propargyl-substituted oxazoline-systems

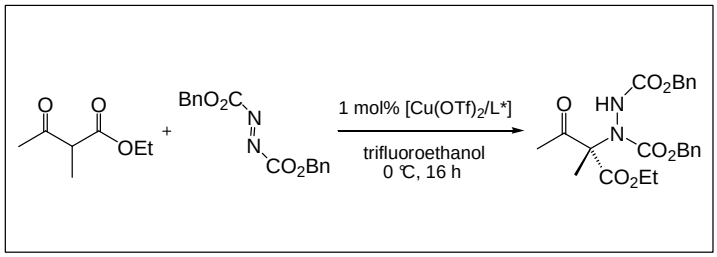


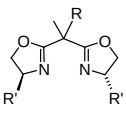
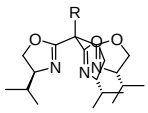
Via deprotonation and nucleophilic substitution, three of these derivatives were converted to TBDMS-/TIPS-functionalised model systems **31**-**34**, incorporating minimal dendritic structures. Using a similar approach, the same ligands were immobilised to carbosilane dendrimers {G0}-$(SiMe_2Cl)_4$, {G1}-$(SiMe_2Cl)_8$ and {G2}-$(SiMe_2Cl)_{16}$ with chlorosilyl termini. Therefore, nine oxazoline-functionalised dendrimers were synthesised, containing 4 (**35**-**37**), 8 (**38**-**40**) and 16 (**41**-**43**) ligands in their periphery.

The general catalytic potential of compounds {G0}-L^*_4, {G1}-L^*_8, {G2}-L^*_{16} as polyfunctional chiral ligand systems for asymmetric copper(II) Lewis acid catalysis was assessed by studying two benchmark reactions, the α-hydrazination of β-ketoesters (Scheme 5.14) as well as the Henry reaction of 2-nitrobenzaldehyde with nitromethane (Scheme 5.15). Mononuclear systems with different steric environment were employed as reference systems.

For the α-hydrazination, a remarkably low catalyst loading of 1 mol% was found to be sufficient and generally high yields and selectivities were obtained. In general, enantioselectivities were slightly higher (3% - 4%) for the bisoxazoline-based catalysts compared with the Trisox-systems.

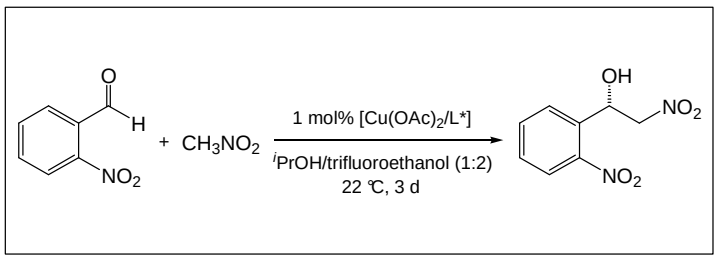
SCHEME 5.14 **α-Hydrazination of ethyl 2-methylacetoacetate**: summary of the results.

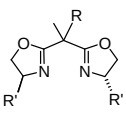
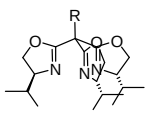


Catalyst	 Yield [%]	*ee* [%]	 Yield [%]	*ee* [%]
mononuclear systems	99	94 to 99	99	93 to 96
dendritic systems	99	93 to 98	99	90 to 95

The Henry reaction was chosen as a complementary reference system that only gave moderate enantiomeric excesses, this allowing both increase and decrease in enantioselectivities. Generally, the dendritic Box-derivatives all gave reaction products with significantly higher enantiomeric excesses (81% up to 87%) compared to their mononuclear analogues (71% up to 77%). The negative trend with respect to trisoxazoline-based catalysts observed for the α-hydrazination was enhanced.

SCHEME 5.15 **Henry reaction of 2-nitrobenzyladehyde with nitromethane**: summary of the results.



Catalyst	 Yield [%]	*ee* [%]	 Yield [%]	*ee* [%]
mononuclear systems	36 to 95	71 to 77	18 to 93	51 to 75
dendritic systems	82 to 87	81 to 87	42 to 54	53

To gain some insight into the different behaviour of immobilised Box and Trisox for both types of reactions, the rates of conversion were monitored. Whilst the attachment of a

linker at the ligand backbone and the immobilisation only moderately affected the activity of the Box-based catalysts, the effect on the Trisox-based catalysts was dramatic. This was interpreted as being due to the hindered decoordination of the third oxazoline unit, the key step in the generation of the active catalyst, in the immobilised Trisox-copper complexes.

To highlight the practical aspect of dendritic catalysts, an approach to their recycling has been developed. The copper(II) complexes of two dendritic oxazolines, {G2}-Box(Ph)$_{16}$ **42-Cu** and {G2}-Trisox(^{i}Pr)$_{16}$ **43-Cu**, were immobilised in dialysis membrane bags and catalytic conversions were effected by dipping the catalyst-filled dialysis bags into reaction vessels containing the substrates (similar to previously reported enzymatic systems). During seven successive cycles, only {G2}-Box(Ph)$_{16}$ gave good and stable results (~80% yield and *ee*) due to the sufficient reactivity of its copper complexes.

Overall, it has been shown that bis- and trisoxazolines due to their different skeleton respond differently to dendritic supports which is mainly manifested in their catalytic activities.

CHAPTER 6

General Conclusion

On the basis of established tris(oxazolinyl)ethanes ("trisoxazolines"), the aim of this project was the design of new stereodirecting ligands. By introducing functionalities into the periphery of the basic framework, a library of polydentate and linker-functionalised trisoxazolines was obtained for more efficient and broadened application in asymmetric Lewis acid catalysis. These supplementary functionalities were introduced at the chiral centres of the oxazoline cycles and in the apical position of the ligands. By variation of both the malonate and amino alcohol precursors and adaptation of all synthetic stages to the properties of the new starting materials, seven new derivatives were synthesised.

Using aspartic acid as a starting material, appropriately functionalised α-amino alcohol precursors were accessed in multigramm-scale quantities. Three C_1-chiral pentadentate and two C_3-symmetric hexadentate trisoxazolines, incorporating peripheral (thio)ether functions, were synthesised to confer greater kinetic robustness to complexes of labile metals such as lanthanides. Ongoing research focusses on elucidation of the coordination chemistry of these polydentate ligands and their application to stereoselective catalytic transformations.

Bis- and trisoxazolines containing an alkynyl linker unit in the ligand backbone have been covalently attached to carbosilane dendrimers of zeroth, first and second generation. The general catalytic potential of their copper(II) complexes was assessed by studying two benchmark reactions, the α-hydrazination of β-ketoesters as well as the Henry reaction of 2-nitrobenzaldehyde with nitromethane. For both reactions the bisoxazoline-based multisite catalysts displayed superior selectivity and, in particular, catalyst activity. The latter was interpreted as being due to the hindered decoordination of the third oxazoline unit, the key step in the generation of the active catalyst, in the immobilised Trisox-copper complexes.

Solutions of the second generation dendrimer catalysts were placed in membrane bags, fabricated from commercially available dialysis membranes, with the purpose of catalyst recycling based on dialysis. Only the bisoxazoline-based catalysts displayed sufficient activity to allow recycling without significant decrease in activity and selectivity. This has enabled us to perform catalytic conversions by dipping the catalyst-filled dialysis bags into reaction vessels containing the substrate. Similar to previously reported enzymatic systems, the dendrimers provided the basis of a catalytic "tea bag" which may be easily recycled several times. Ongoing research addresses the problems associated with the transport phenomena which govern the properties of this type of system along with the issue of membrane stability in organic solvents.

CHAPTER 7

Experimental Section

7.1 General procedures

7.1.1 Preparative techniques

All manipulations were carried out using standard Schlenk line or drybox techniques, unless stated otherwise. An atmosphere of Argon was applied for these experiments, being dried with P_4O_{10}-granula (Granusic, T. J. Baker).

Solvents were dried according to standard procedures: they were pre-dried over activated molecular sieves, refluxed over the drying agent, and saturated with argon. Metal complexes were synthesised using degassed solvents. The latter were prepared by exposing them to three successive freeze-pump-thaw-cycles.

7.1.2 Analytical methods

Optical rotations were measured applying a Perkin Elmer 341 Polarimeter in a 1 dm thermostated cuvette, using a mercury lamp. Optical rotation at the sodium D-line was calculated according to the Drude-equation:

$$[\alpha]_{\lambda}^{T} = \frac{\alpha \cdot 100}{c \cdot d} \qquad [\alpha]_{D}^{T} = \frac{A \cdot [\alpha]_{546}}{A + 1.3727} \qquad A = \frac{[\alpha]_{578}}{[\alpha]_{546} - [\alpha]_{578}}$$

T = temperature [°C], d = path length [dm], α = measured rotation [°], c = concentration [g/100mL], λ = wavelength [nm].

^{1}H, ^{13}C{^{1}H}, ^{29}Si{^{1}H} nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance II 400 or a Bruker Avance III 600 spectrometer. ^{1}H and ^{13}C assignments were

confirmed when necessary with the use of DEPT-135 and twodimensional ^{1}H-^{1}H as well as ^{13}C-^{1}H NMR experiments. ^{1}H and ^{13}C NMR spectra were referenced internally to residual protio-solvent (^{1}H) or solvent (^{13}C) resonances and are reported relative to tetramethylsilane. ^{29}Si NMR spectra were referenced externally to tetramethylsilane. Chemical shifts δ are given in ppm whereas coupling constants *J* are stated in Hertz (Hz). The following abbreviations are used to classify the multiplicity of the observed signals: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, dd = doublet from doublet, dt = doublet from triplet, ddd = doublet from doublet from doublet, ddt = doublet from doublet from triplet, m = complex multiplet.

Infrared spectra (IR) were recorded on a Varian Excalibur 3100 series FTIR spectrometer. Samples were prepared as KBr pellets, sandwiched directly between NaCl plates or levigated in nujol, and then applied onto NaCl plates. Band maxima are given in wave numbers [cm^{-1}]. Their intensity is described using the following abbreviations: s = strong, m = medium, w = weak, ν = valence vibration, δ = deformation vibration.

Mass spectra (MS) and **High resolution mass spectra (HRMS)** were recorded by the mass spectrometry service of the Chemical Institutes of the University of Heidelberg using a JEOL JMS-700 or a Bruker ApexQe FT-ICR instrument. Molpeaks and a selection of characteristic fragmentation peaks are specified.

Elemental analyses were recorded by the analytical service of the Chemical Institutes of the University of Heidelberg.

Analytical separation of enantiomers was carried out by high pressure liquid chromatography on a Finnigan Surveyor machine. Daicel Chiralcel columns AD-H and OD-H (250 x 4.6 mm, 5 µm) and the corresponding guard cartridge (10 x 4 mm, 5 µm) were used.

Monitoring of conversion curves was achieved by gas chromatography on a Finnigan Focus GC apparatus equipped with a capillary column (BPX5, 5% phenyl, polysilphenylene-siloxane, nonpolar, 30 m x 0.25 mm x 0.5 µm): T_{inj} = 200 °C, T_{det} = 220 °C (Flame Ionization Detector), carrier gas: He.

7.1.3 Starting material

Reagents were purchased from commercial chemical suppliers (mainly Acros, Aldrich and Strem) and used without further purification. L-*tert*-Leucine was provided by the BASF AG (Ludwigshafen, Germany).

Dimethyl L-aspartate hydrochloride,[126] (*S*)-*N*-benzoyl-aspartic acid dimethyl ester,[126] (*S*)-2-(benzoylamino)-1,4-butanediol,[126] (*S*)-valinol,[120a] (*S*)-α-phenylglycinol,[120a] (*S*)-*tert*-leucinol,[120a] (*S*)-methioninol,[120b] (*S*)-4-*tert*-butyloxazoline,[138] (*S*)-4-isopropyloxazoline,[138] (*S*)-4-phenyl-oxazoline,[138] (*S*)-2-bromo-4-*tert*-butyloxazoline,[147] (*S*)-2-bromo-4-isopropyloxazoline,[147] (*S*)-2-bromo-phenyloxazoline,[147] and the chlorosilyl functionalised carbosilane dendrimers[105] were prepared according to published procedures.

7.1.4 Purification

Column chromatography was carried out using silica gel from Merck (0.063-0.200 mm) or Macherey-Nagel (0.032-0.062 μm). Prior to application to sensitive compounds it was dehydrated in a vacuum oven.

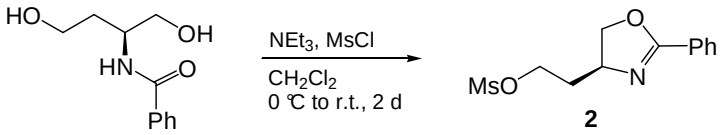
Ion exchange was performed using the commercially available resin Dowex 50WX8 (p.a., H^+-form, strongly acidic, 200-400 mesh).

Dialysis membranes for dendrimer purification and the recycling study were purchased from Sigma-Aldrich (dialysis tubing, benzoylated, avg. flat width 32 mm).

7.2 Polydentate trisoxazolines

7.2.1 Methoxy-functionalised aminoalcohol

7.2.1.1 (*S*)-2-Phenyl-4-(2-methylsulfonylethyl)oxazoline (2)[181]



2

Dry NEt_3 (12.43 mL, 89.4 mmol) was added to a suspension of (*S*)-2-(benzoylamino)-1,4-butanediol (3.74 g, 17.9 mmol) in dry dichloromethane (100 mL). The resulting pale yellow solution was cooled to 0 °C and MsCl (3.60 mL, 44.7 mmol) was added over a period of 3.5 h. A turbid, orange mixture was obtained which was stirred at room temperature for 2 days. After dilution *via* addition of dichloromethane, the organic phase was washed with NH_4Cl_{aq} as well as brine, and dried over Na_2SO_4. Filtration and removal of the solvent *in vacuo* afforded an orange oil that was pure enough to be used in the next step. If needed, the product can be further purified by column chromatography (pentane/EtOAc 70:30, then EtOAc) giving **2** as a yellow oil (4.05 g, 84%).

^{1}H NMR (600.13 MHz, $CDCl_3$, 293 K):

δ 7.93 (dd, ^3J = 8.38 Hz, ^4J = 1.31 Hz, 2H, $^{ortho}CH_{aryl}$), 7.51-7.47 (m, 1H, $^{para}CH_{aryl}$), 7.43-7.39 (m, 2H, $^{meta}CH_{aryl}$), 4.56 (dd, ^2J = 9.57 Hz, ^3J = 8.34 Hz, 1H, CH_2O), 4.53-4.41 (m, 3H, NC***H***, CH_2OMs), 4.10 (m, 1H, CH_2O), 3.05 (s, 3H, CH_3), 2.13 (m, 1H, CH_2CH_2OMs), 2.04 (m, 1H, CH_2CH_2OMs).

^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 293 K):

δ 164.27 (N***C***O), 131.54 ($^{para}CH_{aryl}$), 128.36/128.27 ($^{ortho}CH_{aryl}$, $^{meta}CH_{aryl}$), 127.43 ($C_{q,\ aryl}$), 72.40 (CH_2O), 67.51 (CH_2OMs), 63.17 (N***C***H), 37.32 (CH_3), 35.42 (CH_2CH_2OMs).

IR (KBr):

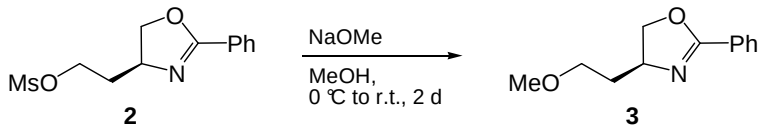
$\tilde{\nu}$ [cm^{-1}] = 3062 (m, $\nu_{C\text{-}H(aryl)}$), 3029 (m, $\nu_{C\text{-}H(aryl)}$), 2967-2905 (m, $\nu_{C\text{-}H(aliphat)}$), 1648 (s, $\nu_{C=N}$), 1351 (s, $CH_2OSO_2CH_3$), 1172 (s, $CH_2OSO_2CH_3$).

MS (ESI):

m/z = 270.1 (100%) $[M+H]^+$, 292.1 (27%) $[M+Na]^+$, 308.0 (21%) $[M+K]^+$; **HRMS (ESI):**

m/z = 270.0795, calcd. for $C_{12}H_{16}NO_4S$ $[M+H]^+$: 270.0795; m/z = 292.0615, calcd. for $C_{12}H_{15}NO_4SNa$ $[M+Na]^+$: 292.0620; m/z = 308.0354, calcd. for $C_{12}H_{15}NO_4SK$ $[M+K]^+$: 308.0359.

7.2.1.2 (*S*)-2-Phenyl-4-(2-methoxyethyl)oxazoline (3)



A solution of oxazoline **2** (10.23 g, 38.0 mmol) in MeOH (70 mL) was cooled to 0 °C and solid NaOMe (20.53 g, 0.38 mol) was added. The resulting suspension was stirred at room temperature for 2 days. After removal of MeOH *in vacuo*, the residue was redissolved in dichloromethane, washed with NH_4Cl_{aq} as well as brine, and dried over Na_2SO_4. Filtration and removal of the solvent afforded compound **3** as an orange oil of excellent purity. If needed, it can be further purified by column chromatography (7.52 g, 96%).

^{1}H NMR (600.13 MHz, $CDCl_3$, 293 K):

δ 7.94 (d, ^3J = 7.14 Hz, 2H, $^{ortho}C\boldsymbol{H}_{aryl}$), 7.46 (t, ^3J = 7.40 Hz, 1H, $^{para}C\boldsymbol{H}_{aryl}$), 7.40 (t, ^3J = 7.53 Hz, 2H, $^{meta}C\boldsymbol{H}_{aryl}$), 4.51 (dd, ^2J = 9.40 Hz, ^3J = 8.35 Hz, 1H, $C\boldsymbol{H}_2O$), 4.38 (m, 1H, NC***H***), 4.09 (m, 1H, $C\boldsymbol{H}_2O$), 3.60-3.54 (m, 2H, $C\boldsymbol{H}_2OCH_3$), 3.35 (s, 3H, $C\boldsymbol{H}_3$), 2.02 (m, 1H, $C\boldsymbol{H}_2CH_2OCH_3$), 1.85 (m, 1H, $C\boldsymbol{H}_2CH_2OCH_3$).

^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 293 K):

δ 163.70 (N***C***O), 131.24 ($^{para}\boldsymbol{C}H_{aryl}$), 128.26/128.20 ($^{ortho}\boldsymbol{C}H_{aryl}$, $^{meta}\boldsymbol{C}H_{aryl}$), 127.79 ($\boldsymbol{C}_{q,\,aryl}$), 72.86 ($\boldsymbol{C}H_2O$), 70.00 ($\boldsymbol{C}H_2OCH_3$), 64.47 (N***C***H), 58.74 ($\boldsymbol{C}H_3$), 35.96 ($\boldsymbol{C}H_2CH_2OCH_3$).

IR (KBr):

$\tilde{\nu}$ [cm^{-1}] = 3086 (w, $\nu_{C\text{-}H(aryl)}$), 3063 (w, $\nu_{C\text{-}H(aryl)}$), 3033 (w, $\nu_{C\text{-}H(aryl)}$), 2975-2877 (m, $\nu_{C\text{-}H(aliphat)}$), 2831 (m, OCH_3), 1648 (s, $\nu_{C=N}$).

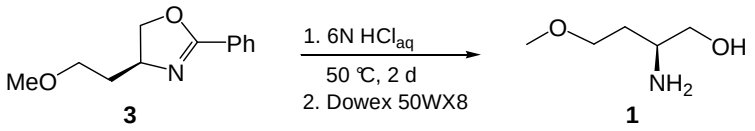
MS (FAB):

m/z = 206.1 (100%) $[M+H]^+$, 174.1 (2%) $[M\text{-}OCH_3]^+$, 146.1 (7%) $[M\text{-}C_3H_7O]^+$; **HRMS (FAB):** m/z = 206.1178, calcd. for $C_{12}H_{16}NO_2$ $[M+H]^+$: 206.1181.

Elemental Analysis:

anal. calcd. for $C_{12}H_{15}NO_2$ (205.25) • 0.05 CH_2Cl_2: C 69.08, H 7.26, N 6.69; found C 68.95, H 7.38, N 6.74.

7.2.1.3 (*S*)-2-Amino-4-methoxybutan-1-ol (1)[182]



A solution of oxazoline **3** (14.03 g, 68.0 mmol) in 6N HCl_{aq} (415 mL) was stirred at 50 °C for 2 days. The resulting suspension was cooled to 0 °C prior to filtration and extraction with Et_2O (4x). Removal of H_2O *in vacuo* gave **1** as the corresponding ammonium salt. Treatment with an ion exchanger (Dowex 50WX8) yielded the free amino alcohol **1** as a hygroscopic, yellow oil (7.09 g, 87%).

Optical Rotation (MeOH):

$[\alpha]_D^{23}$ = laevorotatory (Only the direction of rotation is given, because the compound is hygroscopic and no absolute concentration can be assigned.)

^{1}H NMR (600.13 MHz, $CDCl_3$, 293 K):

δ 3.55 (dd, ^2J = 10.79 Hz, ^3J = 4.28 Hz, 1H, C***H***$_2$OH), 3.50 (t, ^3J = 5.91 Hz, 2H, C***H***$_2$OCH$_3$), 3.37 (dd, ^2J = 10.80 Hz, ^3J = 6.69 Hz, 1H, C***H***$_2$OH), 3.34 (s, 3H, C***H***$_3$), 3.00 (m, 1H, NC***H***), 1.70 (ddd, ^2J = 14.20 Hz, ^3J = 11.63 Hz, ^3J = 5.61 Hz, 1H, C***H***$_2$CH$_2$OCH$_3$), 1.60 (ddd, ^2J = 14.18 Hz, ^3J = 9.85 Hz, ^3J = 5.72 Hz, 1H, C***H***$_2$CH$_2$OCH$_3$).

^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 293 K):

δ 70.10 (***C***H$_2$OCH$_3$), 66.94 (***C***H$_2$OH), 58.70 (***C***H$_3$), 51.04 (N***C***H), 34.33 (***C***H$_2$CH$_2$OCH$_3$).

IR (KBr):

$\tilde{\nu}$ [cm^{-1}] = 3360 (s_{broad}, $\nu_{O\text{-}H}$), 2961-2876 (m, $\nu_{C\text{-}H(aliphat)}$).

MS (FAB):

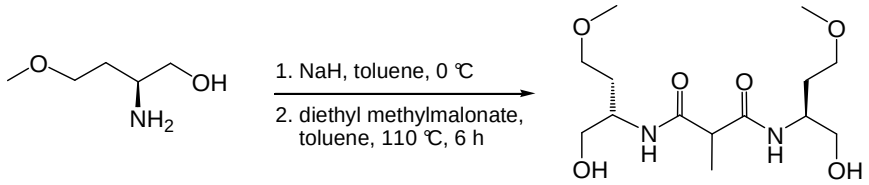
m/z = 120.1 (39%) $[M+H]^+$, 88.1 (26%) $[M\text{-}OCH_3]^+$; **HRMS (FAB):** m/z = 120.0990, calcd. for $C_5H_{14}NO_2$ $[M+H]^+$: 120.1024; **HRMS (EI):** m/z = 119.0924, calcd. for $C_5H_{13}NO_2$ $[M]^+$: 119.0946.

Elemental Analysis:

anal. calcd. for $C_5H_{18}NO_4$ (119.16) • 2.6 H_2O: C 36.18, H 11.05, N 8.44; found C 36.27, H 11.02, N 8.49.

7.2.2 Heteroatom-functionalised bisoxazolines

7.2.2.1 *N,N'*-Bis[(*S*)-1-(hydroxymethyl)-3-methoxypropyl]-2-methylmalonamide (7)



1 **7**

A solution of aminoalcohol **1** (3.08 g, 25.8 mmol) in dry toluene (5 mL) was cooled to 0 °C and solid NaH (0.65 g, 26.9 mmol, 60% w/w dispersion in mineral oil) was added in small portions. After hydrogen formation had ceased, all volatile components were removed *in vacuo*. The residue was washed with dry pentane and the resulting powder was dried *in vacuo*. Diethyl methylmalonate (1.78 mL, 10.3 mmol) and dry toluene (10 mL) were added to generate a suspension which was heated at 110 °C for 6 h. The solvent and other volatiles were removed *in vacuo*, H_2O (470 µL) and CH_3CN (70 mL) were added, and the mixture was stirred until a pale yellow suspension was obtained. Complete precipitation of the product was caused by addition of hexane/Et_2O (1:1). Subsequent filtration and removal of the residual solvent yielded a mixture of the desired product **7** and the corresponding monoamide as a pale yellow, hygroscopic powder (3.04 g, 85% w/w; 2.58 g, 78%).

^{1}H NMR (600.13 MHz, D_2O, 293 K):

δ 3.98 (m, 2H, NC***H***), 3.64-3.56 (m, 2H, C***H***$_2$OH), 3.56-3.39 (m, 6H, C***H***$_2$OH, C***H***$_2$OCH$_3$), 3.30 (s, 6H, OC***H***$_3$), 3.22 (m, 1H, C***H***CH$_3$), 1.87-1.78 (m, 2H, C***H***$_2$CH$_2$OCH$_3$), 1.69-1.59 (m, 2H, C***H***$_2$CH$_2$OCH$_3$), 1.27 (d, ^3J = 7.17 Hz, 3H, CHC***H***$_3$).

^{13}C{^{1}H} NMR (150.90 MHz, D_2O, 293 K):

δ 173.10/172.60 (N***C***O), 68.96/68.89 (***C***H$_2$OCH$_3$), 63.37 (***C***H$_2$OH), 57.87/57.85 (O***C***H$_3$), 49.84 (***C***HCH$_3$), 48.65/48.61 (N***C***H), 29.94/29.92 (***C***H$_2$CH$_2$OCH$_3$), 14.61 (CH***C***H$_3$).

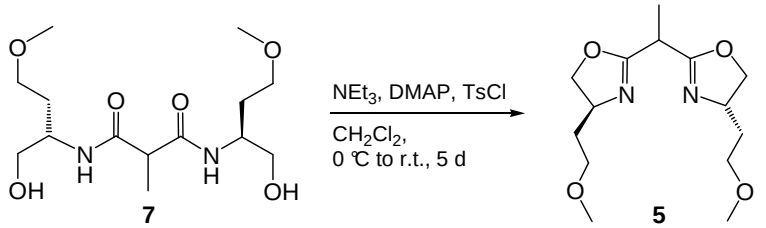
IR (KBr):

$\tilde{\nu}$ [cm^{-1}] = 3389 (s$_{broad}$, ν_{O-H}), 2939-2883 (m, $\nu_{C-H(aliphat)}$), 1647 (s, $\nu_{C=O}$), 1577 (s, $\nu_{C=O}$).

MS (ESI):

m/z = 319.2 (100%) [M-H]$^-$, 305.2 (69%) [M-CH$_3$]$^-$; **HRMS (ESI):** m/z = 319.1876, calcd. for $C_{14}H_{27}N_2O_6$ [M-H]$^-$: 319.1875.

7.2.2.2 1,1-Bis[(*S*)-4-(2-methoxyethyl)oxazolin-2-yl]ethane (Box(O,O), 5)



Dry NEt_3 (5.80 mL, 41.8 mmol) and DMAP (326 mg, 2.7 mmol) were added to a suspension of dihydroxy diamide **7** (3.04g, 85% w/w mixture with the monoamide; 2.58 g diamide, 8.1 mmol) in dry dichloromethane (80 mL). The mixture was cooled to -20 °C, solid TsCl (3.99 g, 20.9 mmol) was added in small portions over a period of 3 h and then stirred at room temperature for 5 days. The resulting brownish yellow suspension was diluted by addition of dichloromethane, washed with NH_4Cl_{aq}, and dried over Na_2SO_4. Filtration and removal of the solvent gave an oily crude product which was purified by column chromatography (EtOAc/MeOH 85/15) to yield **5** as a yellow, viscous oil (315 mg, 14%).

Optical Rotation (c = 0.52, MeOH):

$[\alpha]_D^{23}$ = -71.2.

^{1}H NMR (600.13 MHz, $CDCl_3$, 293 K):

δ 4.30 (m, 2H, C***H***$_2$O), 4.15 (m, 2H, NC***H***), 3.92 (pseudo-t, $^{2,3}J$ = 8.05 Hz, 2H, C***H***$_2$O), 3.49-3.42 (m, 5H, C***H***CH$_3$, C***H***$_2$OCH$_3$), 3.27 (s, 6H, OC***H***$_3$), 1.86 (m, 2H, C***H***$_2$CH$_2$OCH$_3$), 1.71 (m, 2H, C***H***$_2$CH$_2$OCH$_3$), 1.42 (d, ^3J = 7.22 Hz, 3H, CHC***H***$_3$).

^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 293 K):

δ 165.79/165.74 (N***C***O), 73.00 (***C***H$_2$O), 69.71/69.68 (***C***H$_2$OCH$_3$), 63.80/63.78 (N***C***H), 58.58 (O***C***H$_3$), 35.58/35.54 (***C***H$_2$CH$_2$OCH$_3$), 33.84 (***C***HCH$_3$), 15.11 (CH***C***H$_3$).

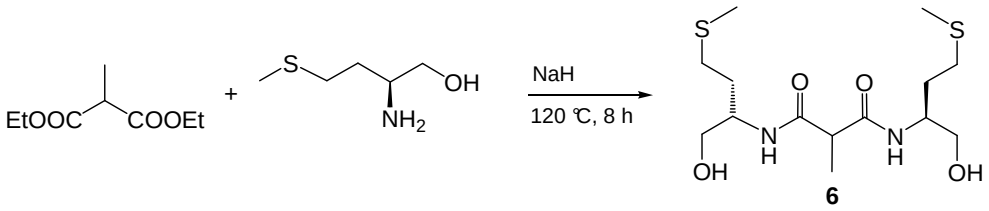
IR (KBr):

$\tilde{\nu}$ [cm^{-1}] = 2929-2877 (m, $\nu_{C\text{-}H(aliphat)}$), 2834 (m, OCH$_3$), 1656 (s, $\nu_{C=N}$).

HRMS (ESI):

m/z = 285.1808, calcd. for $C_{14}H_{25}N_2O_4$ $[M+H]^+$: 285.1809.

7.2.2.3 *N,N'*-Bis[(*S*)-1-(hydroxymethyl)-3-(methylthio)propyl]-2-methylmalonamide (6)



6

In a sealed Schlenk tube, L-methioninol (5.92 g, 43.8 mmol), a catalytic amount of NaH (60% w/w dispersion in mineral oil) and diethyl methylmalonate (3.60 mL, 20.9 mmol) were heated at 120 °C for 8 h. All volatile components were removed *in vacuo* and the residual viscous oil was redissolved in CH_3CN (20 mL). Precipitation of the product was achieved by addition of hexane/Et_2O (1:1). After filtration, washing with hexane, and removal of the residual solvent, **6** was obtained as a white, hygroscopic powder (6.35 g, 86%).

^{1}H NMR (600.13 MHz, D_2O, 293 K):

δ 4.02 (m, 2H, NC***H***), 3.60 (m, 2H, C***H***$_2$OH), 3.53 (m, 2H, C***H***$_2$OH), 3.37 (q, ^3J = 7.10 Hz, 1H, C***H***CH_3), 2.55 (ddd, ^2J = 13.19 Hz, ^3J = 8.87 Hz, ^3J = 4.89 Hz, 2H, C***H***$_2$S), 2.48 (ddd, ^2J = 13.17 Hz, ^3J = 7.60 Hz, ^3J = 3.73 Hz, 2H, C***H***$_2$S), 2.08 (s, 3H, SC***H***$_3$), 2.07 (s, 3H, SC***H***$_3$), 1.90-1.81 (m, 2H, C***H***$_2$CH$_2$S), 1.75-1.65 (m, 2H, C***H***$_2$CH$_2$S), 1.36 (d, ^3J = 7.17 Hz, 3H, CC***H***$_3$); **^{1}H NMR (600.13 MHz, DMSO-d_6, 293 K):** δ 7.63 (m, 2H, N***H***), 4.78 (s, 2H, O***H***).

^{13}C{^{1}H} NMR (150.90 MHz, D_2O, 293 K):

δ 173.19/172.70 (N***C***O), 63.28/63.25 (***C***H$_2$OH), 50.46 (N***C***H), 47.97 (***C***HCH$_3$), 29.65/29.61/ 29.57/29.55 (***C***H$_2$***C***H$_2$S), 14.18 (CH***C***H$_3$), 14.13/14.11 (S***C***H$_3$).

IR (KBr):

$\tilde{\nu}$ [cm^{-1}] = 3301 (s_{broad}, ν_{O-H}), 2946-2852 (m, $\nu_{C-H(aliphat)}$), 1646 (s, $\nu_{C=O}$), 1540 (s, $\nu_{C=O}$).

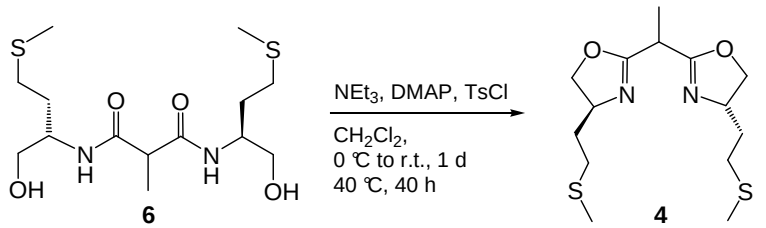
MS (ESI):

m/z = 353.2 (4%) [M+H]$^+$, 335.1 (4%) [M-OH]$^+$; **HRMS (ESI):** m/z = 353.1564, calcd. for $C_{14}H_{29}N_2O_4S_2$ [M+H]$^+$: 353.1563; m/z = 375.1383, calcd. for $C_{14}H_{28}N_2O_4S_2Na$ [M+Na]$^+$: 375.1383.

Elemental Analysis:

anal. calcd. for $C_{14}H_{28}N_2O_4S_2$ (352.51) • 0.4 H_2O: C 46.74, H 8.07, N 7.79; found C 46.65, H 8.01, N 7.63.

7.2.2.4 1,1-Bis[(*S*)-4-[2-(methylthio)ethyl]oxazolin-2-yl]ethane (Box(S,S), 4)



Dry NEt_3 (6.16 mL, 44.3 mmol) and DMAP (350 mg, 2.9 mmol) were added to a suspension of dihydroxy diamide **6** (3.51 g, 10.0 mmol) in dry dichloromethane (100 mL). The mixture was cooled to 0 °C, solid TsCl (4.22 g, 22.1 mmol) was added over a period of 2 h and, after warming to room temperature, it was stirred for another 24 h. Completion of conversion was achieved by subsequent heating at 40 °C for another 40 h. The resulting mixture was diluted by addition of dichloromethane, washed with NH_4Cl_{aq} as well as brine, and dried over Na_2SO_4. Filtration and removal of the solvent afforded a yellowish oil which was purified by column chromatography (EtOAc/MeOH 10:1) yielding **4** as a pale yellow oil (2.07 g, 65%).

Optical Rotation (c = 0.53, MeOH):

$[\alpha]_D^{23}$ = -127.5.

^{1}H NMR (600.13 MHz, $CDCl_3$, 293 K):

δ 4.36 (m, 2H, C***H***$_2$O), 4.23 (m, 2H, NC***H***), 3.92 (pseudo-t, $^{2,3}J$ = 7.88 Hz, 2H, C***H***$_2$O), 3.50 (q, ^3J = 7.19 Hz, 1H, C***H***CH_3), 2.63-2.54 (m, 4H, C***H***$_2$S), 2.10 (s, 6H, SC***H***$_3$), 1.93-1.86 (m, 2H, C***H***$_2$CH$_2$S), 1.84-1.75 (m, 2H, C***H***$_2$CH$_2$S), 1.47 (d, ^3J = 7.23 Hz, 3H, CHC***H***$_3$).

^{13}C{^{1}H} NMR (150.92 MHz, $CDCl_3$, 293 K):

δ 165.93/165.86 (N***C***O), 72.62/72.60 (***C***H$_2$O), 65.18/65.16 (N***C***H), 35.48/35.17 (***C***H$_2$CH$_2$S), 33.94 (***C***HCH$_3$), 30.42/30.36 (***C***H$_2$S), 15.53 (S***C***H$_3$), 15.23 (CH***C***H$_3$).

IR (KBr):

$\tilde{\nu}$ [cm^{-1}] = 2936-2854 (m, $\nu_{C\text{-}H(aliphat)}$), 1662 (s, $\nu_{C=N}$).

MS (FAB):

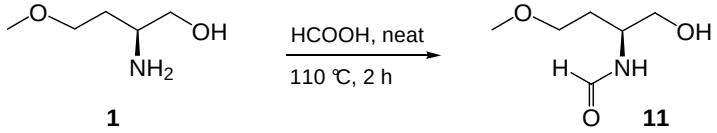
m/z = 317.3 (62%) $[M+H]^+$, 242.4 (8%) $[(M+H)\text{-}C_3H_7S]^+$; **HRMS (ESI):** m/z = 317.1352, calcd. for $C_{14}H_{25}N_2O_2S_2$ $[M+H]^+$: 317.1352; m/z = 339.1171, calcd. for $C_{14}H_{24}N_2O_2S_2Na$ $[M+Na]^+$: 339.1171.

Elemental Analysis:

anal. calcd. for $C_{17}H_{26}N_2O_2$ (316.48): C 53.13, H 7.64, N 8.85; found C 52.61, H 7.62, N 8.75.

7.2.3 Heteroatom-functionalised 2-bromooxazolines

7.2.3.1 (*S*)-2-(Formylamino)-4-methoxybutan-1-ol (11)



1 **11**

Formic acid (783 mg, 17.0 mmol) was added to amino alcohol **1** (2.03 g, 17.0 mmol). The resulting viscous mixture was stirred for 10 min prior to the removal of volatile components *in vacuo*. The residual oil was heated at 110 °C for 2 h. Again, volatiles were removed *in vacuo*. Purification of the product was provided by column chromatography (EtOAc, then EtOAc/MeOH 9:1) yielding **11** as a pale yellow, slightly hygroscopic, viscous oil (1.40 g, 56%).

Optical Rotation (c = 0.52, MeOH):

$[\alpha]_D^{23}$ = -24.9.

^{1}H NMR (600.13 MHz, $CDCl_3$, 293 K):

δ 8.18 (s, 1H, O=C***H***), 6.40 (s_{broad}, 1H, N***H***), 4.12 (m, 1H, NC***H***), 3.70 (dd, ^2J = 11.51 Hz, ^3J = 4.20 Hz, 1H, C***H***$_2$OH), 3.65 (dd, ^2J = 11.46 Hz, ^3J = 3.60 Hz, 1H, C***H***$_2$OH), 3.53-3.45 (m, 2H, C***H***$_2$OCH$_3$), 3.36 (s, 3H, C***H***$_3$), 1.98-1.91 (m, 1H, C***H***$_2$CH$_2$OCH$_3$), 1.89-1.82 (m, 1H, C***H***$_2$CH$_2$OCH$_3$).

^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 293 K):

δ 161.38 (***C***=O), 69.30 (***C***H$_2$OCH$_3$), 64.87 (***C***H$_2$OH), 58.85 (***C***H$_3$), 49.67 (N***C***H), 30.97 (***C***H$_2$CH$_2$OCH$_3$).

IR (KBr):

$\tilde{\nu}$ [cm^{-1}] = 3389, 3300 (s_{broad}, $\nu_{(OH)+(NH)}$), 3063 (w, $\nu+\delta_{(CO+NH)}$), 2936, 2879 (m, $\nu_{C\text{-}H(aliphat)}$), 1664 (s, $\nu_{C=O}$), 1541 (m, $\nu_{N\text{-}H}$).

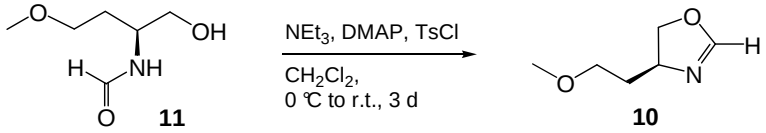
MS (CI):

m/z = 148.2 (100%) $[M+H]^+$, 116.1 (12%) $[M-CH_3O]^+$, 88.1 (10%) $[116.1-CHO]^+$; **HRMS (EI):** m/z = 117.0792, calcd. for $C_5H_{11}NO_2$ $[(M+H)-OCH_3]^+$: 117.0790; m/z = 116.0727, calcd. for $C_5H_{10}NO_2$ $[M-OCH_3]^+$: 116.0711; m/z = 88.0768, calcd. for $C_4H_{10}NO$ $[M-OCH_3-CHO]^+$: 88.0763.

Elemental Analysis:

anal. calcd. for $C_6H_{13}NO_3$ (147.17) • 0.9 H_2O: C 44.11, H 9.13, N 8.57; found C 44.12, H 9.06, N 8.55.

7.2.3.2 (*S*)-4-(2-Methoxyethyl)oxazoline (10)



To an ice-cooled solution of formylamino alcohol **11** (632 mg, 4.3 mmol) in dichloromethane (50 mL), dry NEt_3 (1.20 mL, 8.6 mmol) and DMAP (73 mg, 0.6 mmol) were added. Solid TsCl (820 mg, 4.3 mmol) was added in small portions over a period of 2 h whilst keeping the temperature at 0 °C. After slow warming to room temperature, the pale yellow solution was stirred for 3 days. Dichloromethane was removed by distillation through a vigreux column at atmospheric pressure. The residue was redissolved in hexane (5 mL), filtered and subjected to bulb-to-bulb-distillation. The resulting liquid was kept at -78 °C and stirred vigorously while removing residual solvent and impurities *in vacuo*. Therefore **10** was yielded as a colourless, volatile oil (337 mg, 61%).

^{1}H NMR (600.13 MHz, $CDCl_3$, 293 K):

δ 6.80 (d, ^4J = 1.75 Hz, 1H, N=C***H***), 4.29 (dd, ^2J = 9.67 Hz, ^3J = 8.47 Hz, 1H, C***H***$_2$O), 4.17 (m, 1H, NC***H***), 3.87 (m, 1H, C***H***$_2$O), 3.51 (m, 2H, C***H***$_2$$OCH_3$), 3.33 (s, 3H, C***H***$_3$), 1.88 (ddt, ^2J = 13.75 Hz, ^3J = 6.77 Hz, ^3J = 5.57 Hz, 1H, C***H***$_2$$CH_2OCH_3$), 1.76 (m, 1H, C***H***$_2$$CH_2OCH_3$).

^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 293 K):

δ 154.54 (N=***C***H), 71.48 (***C***H_2O), 69.80 (***C***H_2S), 63.07 (N***C***H), 58.76 (***C***H_3), 35.89 (***C***H_2CH_2S).

IR (NaCl, Nujol):

$\tilde{\nu}$ [cm^{-1}] = 2978-2813 (s, $\nu_{C\text{-}H(aliphat)}$), 1628 (s, $\nu_{C=N}$).

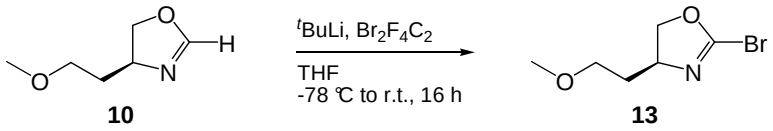
MS (EI):

m/z = 130.1 (1%) $[M+H]^+$, 129.1 (1%) $[M]^+$, 98.1 (9%) $[M\text{-}OCH_3]^+$, 84.1 (42%) $[M\text{-}C_2H_5O]^+$, 70.0 (79%) $[M\text{-}C_3H_7O]^+$.

Elemental Analysis:

anal. calcd. for $C_6H_{11}NO_2$ (129.16): C 55.80, H 8.58, N 10.84; found C 55.19, H 8.52, N 10.74.

7.2.3.3 (*S*)-2-Bromo-4-(2-methoxyethyl)oxazoline (13)



A solution of oxazoline **10** (311 mg, 2.4 mmol) in dry THF (125 mL) was cooled to -78 °C and ^{t}BuLi (1.77 mL, 1.5 M in pentane) was added over a period of 2 h. It was stirred for 20 min prior to the slow addition of 1,2-dibromotetrafluoroethane (0.86 mL, 7.2 mmol) over 40 min. The bright yellow mixture was warmed to room temperature *very* slowly over night. The resulting yellowish orange solution was cooled to ca. -20 °C and concentrated *in vacuo* over 4 h. Dry hexane was added to precipitate the side product. After filtration the solution was concentrated slowly while being cooled. The volatile, residual oil was redissolved in dry toluene (3 mL) and filtered. The resulting solution contained bromo-oxazoline **13** as a pale yellow, volatile oil (130 mg, 26%).

^{1}H NMR (600.13 MHz, $CDCl_3$, 293 K):

δ 4.56 (m, 1H, C***H***$_2$O), 4.32 (m, 1H, NC***H***), 4.13 (m, 1H, C***H***$_2$O), 3.60-3.51 (m, 2H, C***H***$_2$OCH$_3$), 3.36 (s, 3H, C***H***$_3$), 1.96 (dt, ^2J = 12.70 Hz, ^3J = 6.06 Hz, 1H, C***H***$_2$CH$_2$O), 1.91-1.79 (m, 1H, C***H***$_2$CH$_2$O).

^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 293 K):

δ 142.98 (N***C***O), 75.86 (***C***H$_2$O), 65.29 (N***C***H), 69.93 (***C***H$_2$OCH$_3$), 58.99 (***C***H$_3$), 35.57 (***C***H$_2$CH$_2$O).

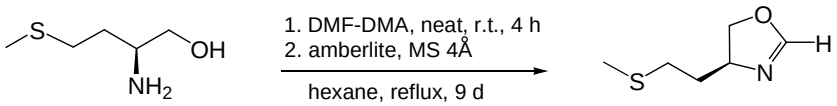
IR (NaCl, Nujol):

$\tilde{\nu}$ [cm^{-1}] = 2965-2868 (m, $\nu_{C\text{-}H(aliphat)}$), 1626 (s, $\nu_{C=N}$).

MS (EI):

m/z = 150.0 (16%) [(M-$C_3H_7O)_{^{81}Br}$]$^+$, 148.0 (16%) [(M-$C_3H_7O)_{^{79}Br}$]$^+$.

7.2.3.4 (*S*)-4-[2-(Methylthio)ethyl]oxazoline (9)



9

L-Methioninol (5.42 g, 40.1 mmol) and DMF-DMA (6.44 mL, 48.1 mmol) were stirred at room temperature for 4 h. The mixture was dissolved in dry hexane and all volatile components were removed *in vacuo*. Hexane (150 mL) and a catalytic amount of amberlite IR120 (strongly acidic) were added, the flask was connected to a liquid/solid extraction apparatus containing 4Å molecular sieve, and the mixture was refluxed for 9 days. After dilution with dichloromethane, the resin was filtered off, the solvent was removed *in vacuo*, and the residual yellow oil was purified by column chromatography (EtOAc) yielding **9** as a pale yellow oil (1.59 g, 27%).

Optical Rotation (c = 0.60, MeOH):

$[\alpha]_D^{23}$ = -140.9.

^{1}H NMR (600.13 MHz, $CDCl_3$, 293 K):

δ 6.81 (s, 1H, N=C***H***), 4.31 (pseudo-t, $^{2,3}J$ = 9.04 Hz, 1H, C***H***$_2$O), 4.21 (m, 1H, NC***H***), 3.83 (m, 1H, C***H***$_2$O), 2.67-2.57 (m, 2H, C***H***$_2$S), 2.12 (s, 3H, C***H***$_3$), 1.88 (m, 1H, C***H***$_2$CH$_2$S), 1.79 (m, 1H, C***H***$_2$CH$_2$S).

^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 293 K):

δ 154.60 (N=***C***H), 71.06 (***C***H$_2$O), 64.39 (N***C***H), 35.34 (***C***H$_2$CH$_2$S), 30.64 (***C***H$_2$S), 15.59 (***C***H$_3$).

IR (KBr):

$\tilde{\nu}$ [cm^{-1}] = 2959-2854 (m, $\nu_{C\text{-}H(aliphat)}$), 1628 (s, $\nu_{C=N}$).

MS (FAB):

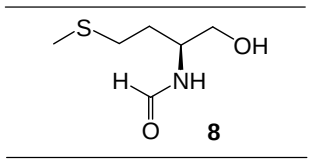
m/z = 145.0 (44%) [M]$^+$, 130.0 (4%) [M-CH$_3$]$^+$; **HRMS (ESI):** m/z = 281.1352, calcd. for

$C_{11}H_{25}N_2O_2S_2$ $[M+C_5H_{14}NOS]^+$: 281.1352.

Elemental Analysis:

anal. calcd. for $C_6H_{11}NOS$ (145.22): C 49.62, H 7.63, N 9.64; found C 49.23, H 7.64, N 9.78.

(*S*)-2-(Formylamino)-4-(methylthio)butan-1-ol (side product)



8

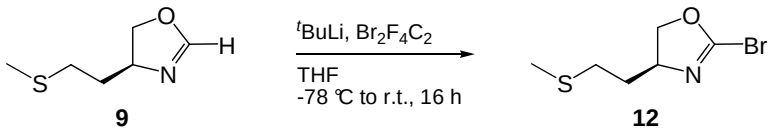
^{1}H NMR (600.13 MHz, $CDCl_3$, 293 K):

δ 8.18 (s, 1H, O=C***H***), 6.41 (s_{broad}, 1H, N***H***), 4.11 (tt, ^3J = 8.90 Hz, ^3J = 4.36 Hz, 1H, NC***H***), 3.68 (dd, ^2J = 11.36 Hz, ^3J = 3.75 Hz, 1H, C***H***$_2$O), 3.62 (dd, ^2J = 11.33 Hz, ^3J = 4.88 Hz, 1H, C***H***$_2$O), 2.54 (ddd, ^2J = 7.83 Hz, ^3J = 6.70 Hz, ^3J = 5.09 Hz, 2H, C***H***$_2$S), 2.09 (s, 3H, C***H***$_3$), 1.91-1.78 (m, 2H, C***H***$_2$CH$_2$S).

^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 293 K):

δ 161.71 (***C***O), 64.19 (***C***H$_2$OH), 49.78 (N***C***H), 30.57 (***C***H$_2$S), 30.42 (***C***H$_2$CH$_2$S), 15.47 (***C***H$_3$).

7.2.3.5 (*S*)-2-Bromo-4-[2-(methylthio)ethyl]oxazoline (12)



9 **12**

A solution of oxazoline **9** (355 mg, 2.4 mmol) in dry THF (100 mL) was cooled to -78 °C, ^{t}BuLi (1.79 mL, 1.5 M in pentane) was added over a period of 2.5 h and then stirred 15 min prior to the slow addition of 1,2-dibromotetrafluoroethane (0.86 mL, 7.2 mmol) over 20 min. The mixture was warmed to room temperature *very* slowly over night. The resulting bright orange solution was concentrated *in vacuo*. After redissolving the brownish residue in dry toluene, hexane was added to precipitate the side product which was filtered off. Removal of the solvent *in vacuo* yielded bromooxazoline **12** as a yellow oil (457 mg, 84%).

^{1}H NMR (600.13 MHz, $CDCl_3$, 293 K):

δ 4.56 (m, 1H, C***H***$_2$O), 4.31 (m, 1H, NC***H***), 4.08 (m, 1H, C***H***$_2$O), 2.64 (m, 2H, C***H***$_2$S), 2.12 (s, 3H, C***H***$_3$), 1.95 (dt, ^2J = 14.20 Hz, ^3J = 7.13 Hz, 1H, C***H***$_2$CH$_2$S), 1.88-1.80 (m, 1H, C***H***$_2$CH$_2$S).

$^{13}C\{^1H\}$ NMR (150.90 MHz, $CDCl_3$, 293 K):

δ 142.42 (N***C***O), 75.20 (***C***H_2O), 66.07 (N***C***H), 34.99 (***C***H_2CH_2S), 30.42 (***C***H_2S), 15.60 (***C***H_3).

IR (KBr):

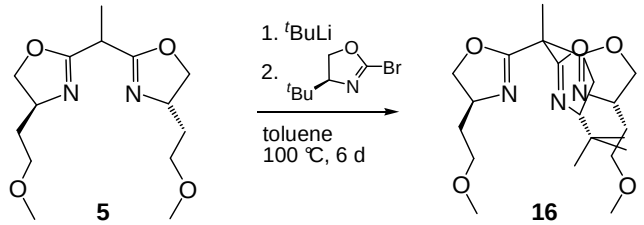
$\tilde{\nu}$ [cm^{-1}] = 2959-2865 (m, $\nu_{C\text{-}H(aliphat)}$), 1626 (s, $\nu_{C=N}$).

MS (EI):

m/z = 225.0 (23%) $[M_{^{81}Br}]^+$, 223.0 (23%) $[M_{^{79}Br}]^+$, 150.9 (70%) $[(M+H)_{^{81}Br} - C_3H_7S]^+$, 148.9 (69%) $[(M+H)_{^{79}Br}\text{-}C_3H_7S]^+$; **HRMS (ESI):** m/z = 229.9821, calcd. for $C_6H_{10}NOS^{79}BrLi$ $[M+Li]^+$: 229.9821; m/z = 247.9544, calcd. for $C_6H_{10}NOS^{81}BrNa$ $[M+Na]^+$: 247.9544.

7.2.4 Pentadentate trisoxazolines

7.2.4.1 1,1-Bis[(*S*)-4-(2-methoxyethyl)oxazolin-2-yl]-1-[(*S*)-4-*tert*-butyloxazolin-2-yl]ethane (Trisox(O,O,^{t}Bu), 16)



A solution of bisoxazoline **5** (520 mg, 1.8 mmol) in dry toluene (100 mL) was cooled to -78 °C and ^{t}BuLi (1.34 mL, 1.5 M in pentane) added. 15 min after completion of the addition, (*S*)-2-bromo-4-*tert*-butyloxazoline (989 mg, 4.8 mmol, 42% w/w in THF) was transferred to the yellow solution, giving rise to an orange colour. The mixture was warmed to room temperature, concentrated to eliminate the pentane originating from ^{t}BuLi, and heated at 100 °C for 6 days. The therefore resulting greyish, turbid mixture was evaporated to dryness. Its residue was purified by column chromatography (EtOAc/MeOH 95:5, then EtOAc/MeOH 90:10) yielding **16** as a slightly yellow, viscous oil (114 mg, 15%).

Optical Rotation (c = 0.53, MeOH):

$[\alpha]_D^{23}$ = -70.3.

^1H NMR (600.13 MHz, $CDCl_3$, 293 K):

δ 4.38-4.33 (m, 2H, C***H***$_2O_{Oxazoline(OMe)}$), 4.27-4.20 (m, 3H, NC***H***$_{Oxazoline(OMe)}$, C***H***$_2O_{Oxazoline(^tBu)}$), 4.16 (pseudo-t, $^{2,3}J$ = 7.91 Hz, 1H, C***H***$_2O_{Oxazoline(^tBu)}$), 4.04 (dd, ^2J = 16.31 Hz, ^3J = 8.19 Hz,

2H, C***H***$_2$O$_{Oxazoline(OMe)}$), 3.90 (dd, ^3J = 9.65 Hz, ^3J = 7.69 Hz, 1H, NC***H***$_{Oxazoline(^tBu)}$), 3.48 (t, ^3J = 6.25 Hz, 4H, C***H***$_2$OCH$_3$), 3.31 (s, 6H, OC***H***$_3$), 1.89 (m, 2H, C***H***$_2$CH$_2$O), 1.81 (s, 3H, CC***H***$_3$), 1.79-1.72 (m, 2H, C***H***$_2$CH$_2$OCH$_3$), 0.87 (s, 9H, C(C***H***$_3$)$_3$).

^{13}C{^{1}H} NMR (150.90 MHz, CDCl$_3$, 293 K):

δ 165.03/164.88 (N***C***O$_{Oxazoline(OMe)}$), 164.23 (N***C***O$_{Oxazoline(^tBu)}$), 75.28 (N***C***H$_{Oxazoline(^tBu)}$), 73.39/ 73.32 (***C***H$_2$O$_{Oxazoline(OMe)}$), 69.72 (***C***H$_2$OCH$_3$), 69.46 (***C***H$_2$O$_{Oxazoline(^tBu)}$), 63.91/63.80 (N***C***H $_{Oxazoline(OMe)}$), 58.66 (O***C***H$_3$), 44.58 (***C***CH$_3$), 35.40/35.37 (***C***H$_2$CH$_2$OCH$_3$), 33.95 (***C***(CH$_3$)$_3$), 25.68 (C(***C***H$_3$)$_3$), 21.07 (C***C***H$_3$).

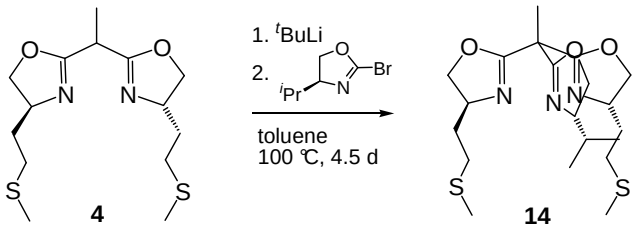
IR (KBr):

$\tilde{\nu}$ [cm^{-1}] = 2953-2872 (m, $\nu_{C\text{-}H(aliphat)}$), 1668 (s, $\nu_{C=N}$), 1663 (s, $\nu_{C=N}$), 1655 (s, $\nu_{C=N}$).

MS (ESI):

m/z = 448.2 (42%) [M+K]$^+$, 432.2 (76%) [M+Na]$^+$, 416.3 (61%) [M+Li]$^+$, 410.3 (100%) [M+H]$^+$; **HRMS (ESI):** m/z = 410.2652, calcd. for $C_{21}H_{36}N_3O_5$ [M+H]$^+$: 410.2650; m/z = 432.2470, calcd. for $C_{21}H_{35}N_3O_5Na$ [M+Na]$^+$: 432.2469; m/z = 448.2212, calcd. for $C_{21}H_{35}N_3O_5K$ [M+K]$^+$: 448.2208.

7.2.4.2 1,1-Bis{(*S*)-4-[2-(methylthio)ethyl]oxazolin-2-yl}-1-[(*S*)-4-isopropyloxazolin-2-yl] ethane (Trisox(S,S,^{i}Pr), 14)



A solution of bisoxazoline **4** (845 mg, 2.7 mmol) in dry toluene (60 mL) was cooled to -78 °C and ^{t}BuLi (1.73 mL, 1.7 M in hexane) was added. 15 min after completion of the addition, (*S*)-2-bromo-4-isopropyloxazoline (718 mg, 3.7 mmol, 58% w/w in THF) was transferred to the mixture, giving rise to a slightly yellow colour. The mixture was warmed to room temperature, concentrated to eliminate the hexane originating from ^{t}BuLi, and heated at 100 °C for 4.5 days. The therefore resulting greyish, turbid mixture was evaporated to dryness, its residue was redissolved in dichloromethane (100 mL), washed with H_2O (20 mL), and dried over Na_2SO_4. Filtration and removal of the solvent yielded the crude product which was purified by column chromatography (EtOAc/MeOH 20:1) yielding

14 as an almost colourless oil (783 mg, 68%).

Optical Rotation (c = 0.53, MeOH):

$[\alpha]_D^{23}$ = -126.0.

^{1}H NMR (399.89 MHz, $CDCl_3$, 293 K):

δ 4.39 (dd, ^2J = 9.44 Hz, ^3J = 2.79 Hz, 1H, C***H***$_2O_{Oxazoline(SMe)}$), 4.37 (dd, ^2J = 9.41 Hz, ^3J = 2.75 Hz, 1H, C***H***$_2O_{Oxazoline(SMe)}$), 4.32-4.23 (m, 3H, NC***H***$_{Oxazoline(SMe)}$, C***H***$_2O_{Oxazoline(^iPr)}$), 4.07 (dd, ^2J = 8.08 Hz, ^3J = 7.42 Hz, 1H, C***H***$_2O_{Oxazoline(^iPr)}$), 4.04-3.97 (m, 3H, NC***H***$_{Oxazoline(^iPr)}$, C***H***$_2O_{Oxazoline(SMe)}$), 2.63-2.51 (m, 4H, C***H***$_2$S), 2.10 (s, 6H, SC***H***$_3$), 1.94-1.84 (m, 2H, C***H***$_2CH_2$S), 1.84-1.73 (m, 3H, C***H***$_2CH_2$S, C***H***$(CH_3)_2$), 1.81 (s, 3H, CC***H***$_3$), 0.92 (d, ^3J = 6.79 Hz, 3H, CH(C***H***$_3)_2$), 0.87 (d, ^3J = 6.77 Hz, 3H, CH(C***H***$_3)_2$).

^{13}C{^{1}H} NMR (100.56 MHz, $CDCl_3$, 293 K):

δ 165.01/164.92 (N***C***$O_{Oxazoline(SMe)}$), 164.23 (N***C***$O_{Oxazoline(^iPr)}$), 72.89/72.85 (***C***$H_2O_{Oxazoline(SMe)}$), 71.70 (N***C***$H_{Oxazoline(^iPr)}$), 70.60 (***C***$H_2O_{Oxazoline(^iPr)}$), 65.20/65.15 (N***C***$H_{Oxazoline(SMe)}$), 44.62 (***C***CH_3), 34.96 (***C***H_2CH_2S), 32.28 (***C***$H(CH_3)_2$), 30.21 (***C***H_2S), 21.16 (C***C***H_3), 18.53 (CH(***C***$H_3)_2$), 17.76 (CH(***C***$H_3)_2$), 15.51 (S***C***H_3).

IR (KBr):

$\tilde{\nu}$ [cm^{-1}] = 2958-2874 (m, $\nu_{C\text{-}H(aliphat)}$), 1662 (s, $\nu_{C=N}$), 1655 (s, $\nu_{C=N}$).

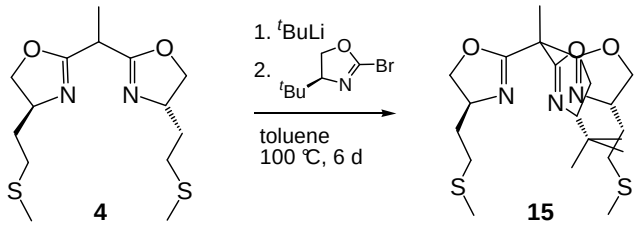
MS (FAB):

m/z = 428.3 (59%) $[M+H]^+$; **HRMS (ESI):** m/z = 428.2042, calcd. for $C_{20}H_{34}N_3O_3S_2$ $[M+H]^+$: 428.2036; m/z = 450.1861, calcd. for $C_{20}H_{33}N_3O_3S_2Na$ $[M+Na]^+$: 450.1856; m/z = 466.1601, calcd. for $C_{20}H_{33}N_3O_3S_2K$ $[M+K]^+$: 466.1595.

Elemental Analysis:

anal. calcd. for $C_{20}H_{33}N_3O_3S_2$ (427.62): C 56.17, H 7.78, N 9.83; found C 56.18, H 7.91, N 9.84.

7.2.4.3 1,1-Bis{(*S*)-4-[2-(methylthio)ethyl]oxazolin-2-yl}-1-[(*S*)-4-*tert*-butyloxazolin-2-yl] ethane (Trisox(S,S,^{t}Bu), 15)



A solution of bisoxazoline **4** (800 mg, 2.5 mmol) in dry toluene (60 mL) was cooled to -78 °C and ^{t}BuLi (1.64 mL, 1.7 M in hexane) was added. 15 min after completion of the addition, (*S*)-2-bromo-4-*tert*-butyloxazoline (729 mg, 3.5 mmol, 55% w/w in THF) was transferred to the yellow solution. The mixture was warmed to room temperature, concentrated to eliminate the hexane originating from ^{t}BuLi, and heated at 100 °C for 6 days. The therefore resulting yellow, turbid solution was evaporated to dryness. Its residue was purified by column chromatography (EtOAc/MeOH 95:5) yielding **15** as a colourless, viscous oil (670 mg, 61%).

Optical Rotation (c = 0.51, MeOH):

$[\alpha]_D^{23}$ = -123.8.

^{1}H NMR (600.13 MHz, $CDCl_3$, 293 K):

δ 4.37 (m, 2H, C***H***$_2$O$_{Oxazoline(SMe)}$), 4.28 (m, 2H, NC***H***$_{Oxazoline(SMe)}$), 4.23 (dd, ^2J = 9.87 Hz, ^3J = 8.88 Hz, 1H, C***H***$_2$O$_{Oxazoline(^tBu)}$), 4.16 (m, 1H, C***H***$_2$O$_{Oxazoline(^tBu)}$), 4.00 (m, 2H, C***H***$_2$O$_{Oxazoline(SMe)}$), 3.91 (dd, ^3J = 10.04 Hz, ^3J = 7.29 Hz, 1H, NC***H***$_{Oxazoline(^tBu)}$), 2.60-2.54 (m, 4H, C***H***$_2$S), 2.10 (s, 6H, SC***H***$_3$), 1.92-1.84 (m, 2H, C***H***$_2$CH$_2$S), 1.84-1.75 (m, 2H, C***H***$_2$CH$_2$S), 1.80 (s, 3H, CC***H***$_3$), 0.87 (s, 9H, C(C***H***$_3$)$_3$).

^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 293 K):

δ 165.07/164.92 (N***C***O$_{Oxazoline(SMe)}$), 164.10 (N***C***O$_{Oxazoline(^tBu)}$), 75.33 (N***C***H$_{Oxazoline(^tBu)}$), 72.90/ 72.81 (***C***H$_2$O$_{Oxazoline(SMe)}$), 69.48 (***C***H$_2$O$_{Oxazoline(^tBu)}$), 65.20/65.12 (N***C***H$_{Oxazoline(SMe)}$), 44.62 (***C***CH$_3$), 34.99/34.95 (***C***H$_2$CH$_2$S), 33.95 (***C***(CH$_3$)$_3$), 30.24/30.18 (***C***H$_2$S), 25.70 (C(***C***H$_3$)$_3$), 21.01 (C***C***H$_3$), 15.51 (S***C***H$_3$).

IR (KBr):

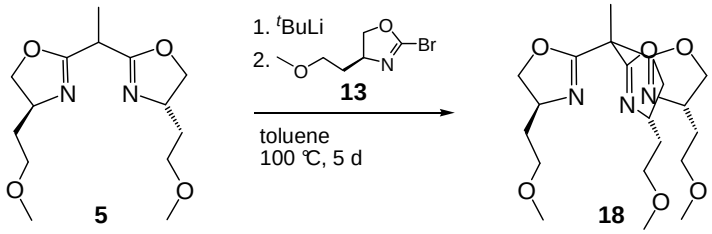
$\tilde{\nu}$ [cm^{-1}] = 2955-2870 (m, $\nu_{C\text{-}H(aliphat)}$), 1662 (s, $\nu_{C=N}$), 1655 (s, $\nu_{C=N}$).

MS (FAB):

m/z = 442.2 (23%) $[M+H]^+$, 394.2 (4%) $[M-SCH_3]^+$; **HRMS (FAB):** m/z = 442.2191, calcd. for $C_{21}H_{36}N_3O_3S_2$ $[M+H]^+$: 442.2198.

7.2.5 Hexadentate trisoxazolines

7.2.5.1 1,1,1-Tris[(*S*)-4-(2-methoxyethyl)oxazolin-2-yl]ethane (Trisox(O,O,O), 18)



A solution of bisoxazoline **5** (75 mg, 0.26 mmol) in dry toluene (20 mL) was cooled to -78 °C and ^{t}BuLi (0.19 mL, 1.5 M in pentane) was added. 15 min after completion of the addition, a precooled solution of bromooxazoline **13** (110 mg, 0.53 mmol) in dry toluene (3 mL) was transferred to the yellow solution. The mixture was warmed to room temperature, concentrated to eliminate the pentane originating from ^{t}BuLi, and heated at 100 °C for 5 days. The resulting yellow, turbid mixture was evaporated to dryness. Its residue was washed with pentane (3x) and redissolved in dichloromethane. Addition of pentane caused precipitation of the impurities. After filtration and removal of the solvent *in vacuo*, trisoxazoline **18** was obtained as a yellow, viscous oil (63 mg, 59%).

Optical Rotation (c = 0.51, MeOH):

$[\alpha]_D^{23}$ = -66.5.

^{1}H NMR (600.13 MHz, $CDCl_3$, 293 K):

δ 4.35 (dd, ^2J = 9.36 Hz, ^3J = 8.36 Hz, 3H, C***H***$_2$O), 4.22 (m, 3H, NC***H***), 4.01 (m, 3H, C***H***$_2$O), 3.45 (m, 6H, C***H***$_2$OCH$_3$), 3.28 (s, 9H, OC***H***$_3$), 1.90-1.84 (m, 3H, C***H***$_2$CH$_2$OCH$_3$), 1.78 (s, 3H, CC***H***$_3$), 1.78-1.71 (m, 3H, C***H***$_2$CH$_2$OCH$_3$).

^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 293 K):

δ 164.83 (N***C***O), 73.43 (***C***H$_2$O), 69.77 (***C***H$_2$OCH$_3$), 63.97 (N***C***H), 58.69 (O***C***H$_3$), 44.50 (***C***CH$_3$), 35.34 (***C***H$_2$CH$_2$OCH$_3$), 21.27 (C***C***H$_3$).

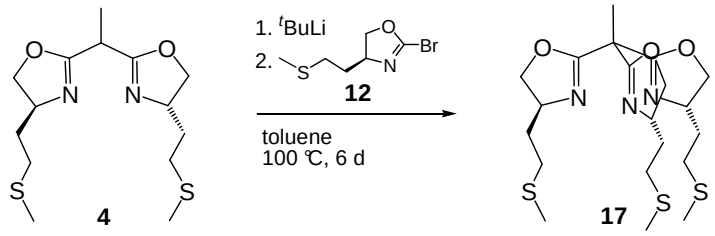
IR (KBr):

$\tilde{\nu}$ [cm^{-1}] = 2927-2879 (m, $\nu_{C\text{-}H(aliphat)}$), 2831 (m, OCH_3), 1662(s, $\nu_{C=N}$).

MS (ESI):

m/z = 450.2 (50%) $[M+K]^+$, 434.2 (100%) $[M+Na]^+$, 418.3 (46%) $[M+Li]^+$, 412.2 (33%) $[M+H]^+$; **HRMS (ESI):** m/z = 412.2458, calcd. for $C_{20}H_{34}N_3O_6$ $[M+H]^+$: 412.2442; m/z = 434.2278, calcd. for $C_{20}H_{33}N_3O_6Na$ $[M+Na]^+$: 434.2262; m/z = 450.2019, calcd. for $C_{20}H_{33}N_3O_6K$ $[M+K]^+$: 450.2001.

7.2.5.2 1,1,1-Tris{(*S*)-4-[2-(methylthio)ethyl]oxazolin-2-yl}ethane (Trisox(S,S,S), 17)



A solution of bisoxazoline **4** (323 mg, 1.02 mmol) in dry toluene (100 mL) was cooled to -78 °C and ^{t}BuLi (0.75 mL, 1.5 M in pentane) was added. 30 min after completion of the addition, a solution of bromooxazoline **12** (457 mg, 2.04 mmol) in dry toluene/THF 90:10 (5 mL) was transferred to the yellow solution, giving rise to an orange colour. The mixture was warmed to room temperature, concentrated to eliminate the pentane originating from ^{t}BuLi, and heated at 100 °C for 6 days. The resulting yellow, turbid mixture was evaporated to dryness. Its residue was purified by column chromatography (EtOAc, then EtOAc/MeOH 95:5 and EtOAc/MeOH 90:10) yielding trisoxazoline **17** as a yellow, viscous oil (297 mg, 63%).

Optical Rotation (c = 0.54, MeOH):

$[\alpha]_D^{23}$ = -112.9.

^{1}H NMR (600.13 MHz, $CDCl_3$, 293 K):

δ 4.39 (m, 3H, C***H***$_2$O), 4.28 (m, 3H, NC***H***), 4.00 (m, 3H, C***H***$_2$O), 2.57 (m, 6H, C***H***$_2$S), 2.10 (s, 9H, SC***H***$_3$), 1.89 (td, ^2J = 14.74 Hz, ^3J = 6.65 Hz, 3H, C***H***$_2$CH$_2$S), 1.84-1.77 (m, 3H, C***H***$_2$CH$_2$S), 1.80 (s, 3H, CC***H***$_3$).

^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 293 K):

δ 164.81 (N***C***O), 72.93 (***C***H$_2$O), 65.16 (N***C***H), 44.60 (***C***CH$_3$), 34.91 (***C***H$_2$CH$_2$S), 30.21

($\boldsymbol{C}H_2S$), 21.10 ($C\boldsymbol{C}H_3$), 15.51 ($S\boldsymbol{C}H_3$).

IR (KBr):

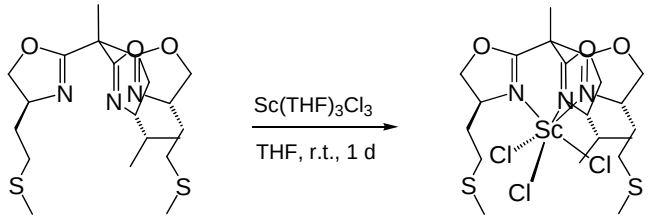
$\tilde{\nu}$ [cm^{-1}] = 2958-2872 (m, $\nu_{C\text{-}H(aliphat)}$), 1655 (s, $\nu_{C=N}$).

MS (ESI):

m/z = 498.1 (39%) $[M+K]^+$, 482.2 (100%) $[M+Na]^+$, 478.2 (9%) $[M+H_3O]^+$, 460.2 (64%) $[M+H]^+$; **HRMS (ESI):** m/z = 460.1761, calcd. for $C_{20}H_{34}N_3O_3S_3$ $[M+H]^+$: 460.1757; m/z = 478.1866, calcd. for $C_{20}H_{36}N_3O_4S_3$ $[M+H_3O]^+$: 478.1863; m/z = 482.1579, calcd. for $C_{20}H_{33}N_3O_3S_3Na$ $[M+Na]^+$: 482.1576; m/z = 498.1319, calcd. for $C_{20}H_{33}N_3O_3S_3K$ $[M+K]^+$: 498.1316.

7.2.6 Coordination chemistry

7.2.6.1 [Sc(Trisox(S,S,^{i}Pr)Cl_3] (19)



14 **19**

A solution of trisoxazoline **14** (197 mg, 0.46 mmol) in THF (25 mL) was added to a suspension of $Sc(THF)_3Cl_3$ (169 mg, 0.46 mmol) in THF (25 mL). The resulting solution was stirred over night. After filtration, the solvent was removed *in vacuo*, yielding a white powder (297 mg, 49%).

^{1}H NMR (399.89 MHz, CD_2Cl_2, 293 K):

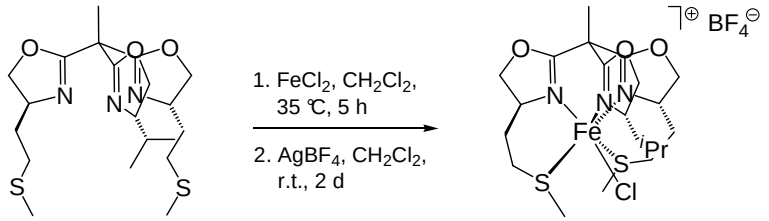
δ 4.91 (m, 2H, $NC\boldsymbol{H}_{Oxazoline(SMe)}$), 4.85-4.74 (m, 3H, $NC\boldsymbol{H}_{Oxazoline(^iPr)}$, $C\boldsymbol{H}_2O_{Oxazoline(SMe)}$), 4.50 (m, 2H, $C\boldsymbol{H}_2O_{Oxazoline(^iPr)}$), 4.36 (m, 2H, $C\boldsymbol{H}_2O_{Oxazoline(SMe)}$), 2.93-2.75 (m, 3H, $C\boldsymbol{H}(CH_3)_2$, $C\boldsymbol{H}_2CH_2S$), 2.59-2.50 (m, 2H, $C\boldsymbol{H}_2S$), 2.50-2.40 (m, 2H, $C\boldsymbol{H}_2S$), 2.11 (s, 6H, $SC\boldsymbol{H}_3$), 1.92 (m, 2H, $C\boldsymbol{H}_2CH_2S$), 1.72 (s, 3H, $CC\boldsymbol{H}_3$), 0.86 (d, ^3J = 7.13 Hz, 3H, $CH(C\boldsymbol{H}_3)_2$), 0.68 (d, ^3J = 6.73 Hz, 3H, $CH(C\boldsymbol{H}_3)_2$).

^{13}C{^{1}H} NMR (100.56 MHz, $CDCl_3$, 293 K):

δ 77.64/77.50 ($\boldsymbol{C}H_2O_{Oxazoline(SMe)}$), 72.21 ($N\boldsymbol{C}H_{Oxazoline(^iPr)}$), 72.75 ($\boldsymbol{C}H_2O_{Oxazoline(^iPr)}$), 67.35

(N***C***H$_{Oxazoline(SMe)}$), 44.74 (***C***CH$_3$), 33.05/33.02 (***C***H$_2$CH$_2$S), 30.29/30.25 (***C***H$_2$S), 28.62 (***C***H(CH$_3$)$_2$), 19.04 (CH(***C***H$_3$)$_2$), 15.46 (S***C***H$_3$), 14.50 (CH(***C***H$_3$)$_2$), 12.83 (C***C***H$_3$).

7.2.6.2 [Fe(Trisox(S,S,^{i}Pr)Cl](BF$_4$) (20)



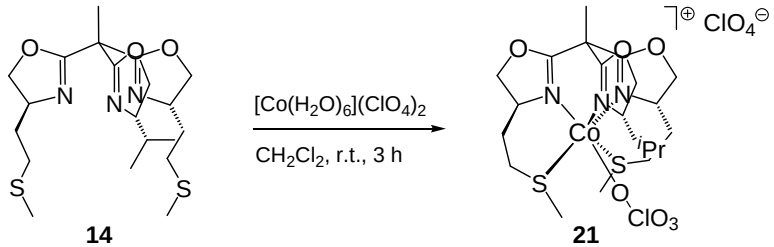
14 **20**

A suspension of trisoxazoline **14** (96 mg, 0.22 mmol) and $FeCl_2$ (28 mg, 0.22 mmol) in dichloromethane (2.5 mL) was stirred at 35 °C for about 5 h until the metal salt dissolved. At room temperature, $AgBF_4$ (86 mg, 0.44 mmol) was added to this solution, forming a suspension which was stirred in the dark for 2 days. The brownish grey precipitate was filtered off, giving a pale orange-pink solution. Dichloromethane was removed *in vacuo*, yielding a pale orange powder (42 mg, 31%).

MS (FAB):

m/z = 518.2 (28%) [Fe(Trisox(S,S,^{i}Pr)Cl]$^+$.

7.2.6.3 [Co(Trisox(S,S,^{i}Pr)](ClO$_4$)$_2$ (21)



14 **21**

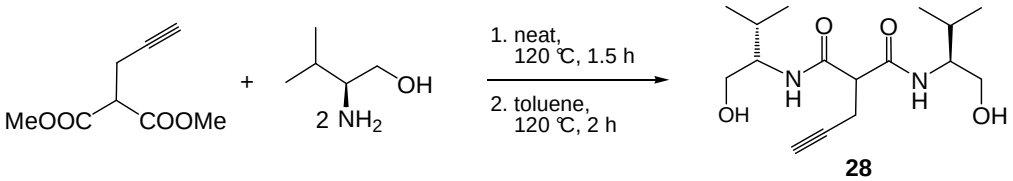
A suspension of trisoxazoline **14** (40 mg, 0.094 mmol) and $[Co(H_2O)_6](ClO_4)_2$ (34 mg, 0.094 mmol) in dichloromethane (4.0 mL) was stirred for about 3 h until the metal salt dissolved. After filtration, the solvent was removed *in vacuo*, yielding a brownish orange powder (61 mg, 93%).

HRMS (ESI): m/z = 585.0787, calcd. for $C_{20}H_{33}N_3O_7S_2ClCo$ [Co(Trisox(S,S,^{i}Pr)(ClO$_4$)]$^+$: 585.0775.

7.3 Dendritic bis- and trisoxazolines

7.3.1 Propargyl-functionalised bisoxazolines

7.3.1.1 *N,N'*-Bis[(*S*)-1-(hydroxymethyl)-2-methylpropyl]-2-prop-2-yn-1-ylmalonamide (28)



28

In a sealed Schlenk tube, L-valinol (7.57 g, 73.4 mmol) and dimethyl propargylmalonate (5.58 mL, 36.7 mmol) were heated at 120 °C until a light solid formed (about 1.5 h). To the warm mixture, dry toluene was added to generate a suspension which was heated at 120 °C for another 2 h. The product was precipitated *via* addition of hexane at room temperature. Subsequent filtration, another washing with hexane, and removal of the residual solvent *in vacuo* yielded diamide **28** as an off-white powder (10.62 g, 93%).

^{1}H NMR (600.13 MHz, DMSO-d_6, 293 K):

δ 7.59 (d, ^3J = 9.26 Hz, 1H, N***H***), 7.52 (d, ^3J = 9.19 Hz, 1H, N***H***), 4.64 (dd_{broad}, ^3J = 9.03 Hz, ^3J = 5.30 Hz, 2H, O***H***), 3.61 (m, 1H, NC***H***), 3.54 (m, 1H, NC***H***), 3.44-3.26 (m, 5H, C***H***$_2$OH, C***H***CH$_2$C≡CH), 2.73 (t, ^4J = 2.59 Hz, 1H, CH$_2$C≡C***H***), 2.56 (ddd, ^2J = 16.66 Hz, ^3J = 8.62 Hz, ^4J = 2.62 Hz, 1H, C***H***$_2$C≡CH), 2.46 (ddd, ^2J = 16.67 Hz, ^3J = 6.21 Hz, ^4J = 2.63 Hz, 1H, C***H***$_2$C≡CH), 1.86 (m, 1H, C***H***(CH$_3$)$_2$), 1.80 (m, 1H, C***H***(CH$_3$)$_2$), 0.86 (d, ^3J = 6.83 Hz, 3H, CH(C***H***$_3$)$_2$), 0.82 (d, ^3J = 6.66 Hz, 3H, CH(C***H***$_3$)$_2$), 0.81 (d, ^3J = 6.59 Hz, 3H, CH(C***H***$_3$)$_2$), 0.78 (d, ^3J = 6.83 Hz, 3H, CH(C***H***$_3$)$_2$).

^{13}C{^{1}H} NMR (150.90 MHz, DMSO-d_6, 293 K):

δ 167.65/167.30 (N***C***O), 82.22 (***C***≡CH), 71.79 (C≡***C***H), 61.16/61.07 (***C***H$_2$OH), 55.53/ 55.24 (N***C***H), 51.70 (***C***HCH$_2$C≡CH), 28.22/27.57 (***C***H(CH$_3$)$_2$), 19.65/19.55 (CH(***C***H$_3$)$_2$), 18.28 (***C***H$_2$C≡CH), 17.92/17.38 (CH(***C***H$_3$)$_2$).

IR (KBr):

$\tilde{\nu}$ [cm^{-1}] = 3520-3320 (s_{broad}, ν_{O-H}), 3320-3200 (m, ν_{N-H}), 2980-2870 (m, $\nu_{C-H(aliphat)}$), 2121 (w, $\nu_{C\equiv C}$), 1634 (s, $\nu_{C=O}$), 1559 (s, $\nu_{C=O}$).

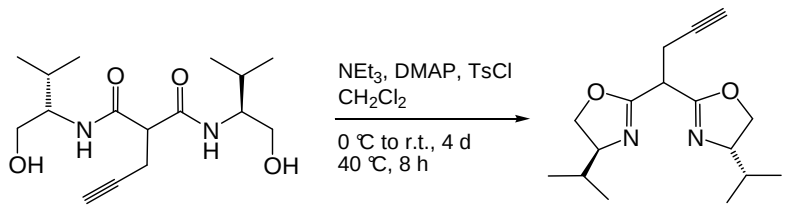
MS (FAB):

m/z = 625.5 (3%) $[2M+H]^+$, 313.3 (100%) $[M+H]^+$, 295.3 (95%) $[M-OH]^+$.

Elemental Analysis:

anal. calcd. for $C_{16}H_{28}N_2O_4$ (312.41): C 61.51, H 9.03, N 8.97; found C 61.25, H 8.92, N 8.95.

7.3.1.2 4,4-Bis[(*S*)-4-isopropyloxazolin-2-yl]but-1-yne (26)



28 **26**

Dry NEt_3 (12.17 mL, 87.6 mmol) and DMAP (241 mg, 2.0 mmol) were added to a suspension of dihydroxy diamide **28** (6.15 g, 19.7 mmol) in dry dichloromethane (250 mL). The mixture was cooled to 0 °C and solid TsCl (7.50 g, 39.3 mmol) was added over a period of 3 h. After warming the resulting off-white suspension to room temperature, a yellow solution formed which was stirred for another 4 days. Completion of conversion was achieved by subsequent heating at 40 °C for 8 h. The resulting mixture was diluted by addition of dichloromethane, washed with NH_4Cl_{aq} as well as brine, and dried over Na_2SO_4. Filtration and removal of the solvent *in vacuo* afforded an oily crude product which was purified by column chromatography (pentane/EtOAc 60:40) yielding **26** as a pale yellow oil (3.97 g, 73%).

Optical Rotation (c = 2.00, MeOH):

$[\alpha]_D^{23}$ = -111.0.

^{1}H NMR (600.13 MHz, $CDCl_3$, 293 K):

δ 4.27-4.22 (m, 2H, C***H***$_2$O), 4.03-3.94 (m, 4H, C***H***$_2$O, NC***H***), 3.65 (t, ^3J = 7.74 Hz, 1H, C***H***CH_2C≡CH), 2.86 (ddd, ^2J = 16.89 Hz, ^3J = 7.71 Hz, ^4J = 2.65 Hz, 1H, C***H***$_2$C≡CH), 2.81 (ddd, ^2J = 16.88 Hz, ^3J = 7.80 Hz, ^4J = 2.66 Hz, 1H, C***H***$_2$C≡CH), 1.98 (t, ^4J = 2.65 Hz, 1H, CH_2C≡C***H***), 1.78 (m, 2H, C***H***$(CH_3)_2$), 0.92 (d, ^3J = 6.80 Hz, 6H, CH(C***H***$_3)_2$), 0.86 (d, ^3J = 6.78 Hz, 6H, CH(C***H***$_3)_2$).

$^{13}C\{^1H\}$ NMR (150.90 MHz, $CDCl_3$, 293 K):

δ 163.14/163.08 (N***C***O), 80.69 (***C***≡CH), 71.88/71.82 (N***C***H), 70.30 (***C***H_2O), 70.05 (C≡***C***H), 39.08 (***C***HCH$_2$C≡CH), 32.28/32.21 (***C***H(CH$_3$)$_2$), 19.78 (***C***H_2C≡CH), 18.56/18.51 (CH(***C***H_3)$_2$), 17.72 (CH(***C***H_3)$_2$).

IR (KBr):

$\tilde{\nu}$ [cm^{-1}] = 2960-2874 (m, $\nu_{C\text{-}H(aliphat)}$), 2108 (w, $\nu_{C\equiv C}$), 1665 (s, $\nu_{C=N}$).

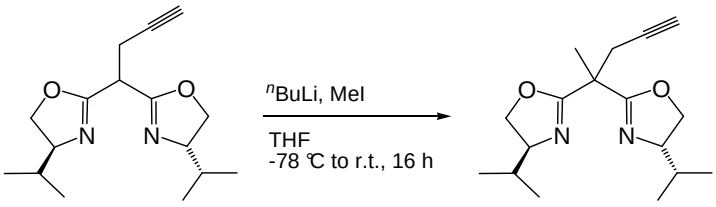
MS (FAB):

m/z = 277.2 (100%) $[M+H]^+$, 191.1 (4%) $[(M+H)\text{-}C_5H_{10}O]^+$; **HRMS (FAB):** m/z = 277.1944, calcd. for $C_{16}H_{25}N_2O_2$ $[M+H]^+$: 277.1916.

Elemental Analysis:

anal. calcd. for $C_{16}H_{24}N_2O_2$ (276.37) • 0.05 CH_2Cl_2: C 68.69, H 8.66, N 9.98; found C 68.57, H 8.75, N 9.96.

7.3.1.3 4,4-Bis[(*S*)-4-isopropyloxazolin-2-yl]pent-1-yne (propargyl-Box(^{i}Pr), 22)



26 **22**

A solution of bisoxazoline **26** (2.40 g, 8.7 mmol) in THF (50 mL) was cooled to -78 °C and ^{n}BuLi (5.97 mL, 1.6 M in hexane) was added. The resulting bright yellow mixture was stirred at -40 °C for 30 min prior to the addition of MeI (1.62 mL, 26.0 mmol). The mixture was slowly warmed to room temperature over night. After removal of the solvent *in vacuo*, the residue was redissolved in dichloromethane, washed with NH_4Cl_{aq}, and dried over Na_2SO_4. Filtration and removal of the solvent gave the crude product which was purified by column chromatography (pentane/EtOAc 60:40) yielding **22** as a pale yellow oil (2.30 g, 91%).

Optical Rotation (c = 2.00, MeOH):

$[\alpha]_D^{23}$ = -107.2.

^{1}H NMR (600.13 MHz, $CDCl_3$, 293 K):

δ 4.23-4.19 (m, 2H, C***H***$_2$O), 4.03-3.95 (m, 4H, C***H***$_2$O, NC***H***), 2.90 (dd, ^2J = 16.80 Hz, ^4J =

2.64 Hz , 1H, C***H***$_2$C≡CH), 2.85 (dd, ^2J = 16.79 Hz, ^4J = 2.63 Hz , 1H, C***H***$_2$C≡CH), 1.98 (t, ^4J = 2.60 Hz, 1H, CH$_2$C≡C***H***), 1.80 (m, 2H, C***H***(CH$_3$)$_2$), 1.63 (s, 3H, CC***H***$_3$), 0.91 (m, 6H, CH(C***H***$_3$)$_2$), 0.86 (m, 6H, CH(C***H***$_3$)$_2$).

^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 293 K):

δ 166.67/166.54 (N***C***O), 80.02 (***C***≡CH), 71.79/71.54 (N***C***H), 70.79 (C≡***C***H), 70.12/70.09 (***C***H$_2$O), 41.72 (***C***CH$_2$C≡CH), 32.18/32.13 (***C***H(CH$_3$)$_2$), 26.95 (***C***H$_2$C≡CH), 21.25 (C***C***H$_3$), 18.64/18.47 (CH(***C***H$_3$)$_2$), 17.55/17.39 (CH(***C***H$_3$)$_2$).

IR (KBr):

$\tilde{\nu}$ [cm^{-1}] = 2960-2874 (m, $\nu_{C\text{-}H(aliphat)}$), 2121 (w, $\nu_{C\equiv C}$), 1661 (s, $\nu_{C=N}$).

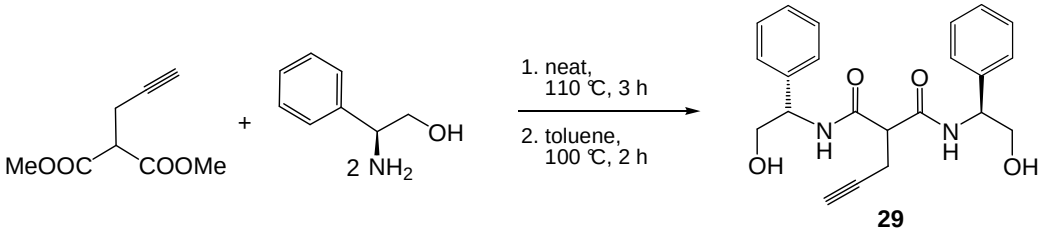
MS (FAB):

m/z = 291.2 (100%) [M+H]$^+$, 289.1 (4%) [M-H]$^+$, 247.1 (2%) [M-C$_3$H$_7$]$^+$, 205.1 (4%) [(M+H)-C$_5$H$_{10}$O]$^+$; **HRMS (FAB):** m/z = 291.2066, calcd. for C$_{17}$H$_{27}$N$_2$O$_2$ [M+H]$^+$: 291.2072.

Elemental Analysis:

anal. calcd. for C$_{17}$H$_{26}$N$_2$O$_2$ (290.40) • 0.09 CH$_2$Cl$_2$: C 68.87, H 8.85, N 9.40; found C 69.13, H 8.95, N 9.08.

7.3.1.4 *N,N'*-Bis[(*S*)-2-hydroxy-1-phenylethyl]-2-prop-2-yn-1-ylmalonamide (29)



29

In a sealed Schlenk tube, L-*α*-phenylglycinol (13.77 g, 100.4 mmol) and dimethyl propargylmalonate (7.63 mL, 50.2 mmol) were heated at 110 °C until a light solid formed (about 3 h). Then, dry toluene was added to the warm mixture to generate a suspension which was heated at 100 °C for another 2 h. The product was precipitated *via* addition of pentane at room temperature. Subsequent filtration, another washing with pentane, and removal of the residual solvent *in vacuo* yielded diamide **29** as a white powder (18.20 g, 95%).

^{1}H NMR (600.13 MHz, DMSO-d_6, 293 K):

δ 8.51 (d, ^3J = 7.93 Hz, 1H, N***H***), 8.45 (d, ^3J = 7.87 Hz, 1H, N***H***), 7.36-7.21 (m, 10H, C***H***$_{aryl}$), 5.04 (s, 2H, O***H***), 4.84 (m, 2H, NC***H***), 3.64-3.59 (m, 4H, C***H***$_2$OH), 3.57 (t, ^3J = 7.38 Hz, 1H,

C***H***CH_2C≡CH), 2.76 (t, ^4J = 2.35 Hz, 1H, CH_2C≡C***H***), 2.53 (d, ^3J = 5.76 Hz, 2H, C***H***$_2$C≡CH).

^{13}C{^{1}H} NMR (150.90 MHz, DMSO-d$_6$, 293 K):

δ 166.99/166.88 (N***C***O), 140.90/140.68 (***C***$_{q, aryl}$), 127.98/126.69/126.66/126.62 (***C***$_{aryl}$), 82.18 (***C***≡CH), 71.95 (C≡***C***H), 64.73/64.42 (***C***H_2OH), 54.94/54.89 (N***C***H), 51.48 (***C***HCH_2C≡CH), 17.91 (***C***H_2C≡CH).

IR (KBr):

$\tilde{\nu}$ [cm^{-1}] = 3520-3340 (s_{broad}, ν_{O-H}), 3340-3240 (m, ν_{N-H}), 3100-3040 (m, $\nu_{C-H(aryl)}$), 2990-2860 (m, $\nu_{C-H(aliphat)}$), 1665 (s, $\nu_{C=O}$), 1541 (s, $\nu_{C=O}$).

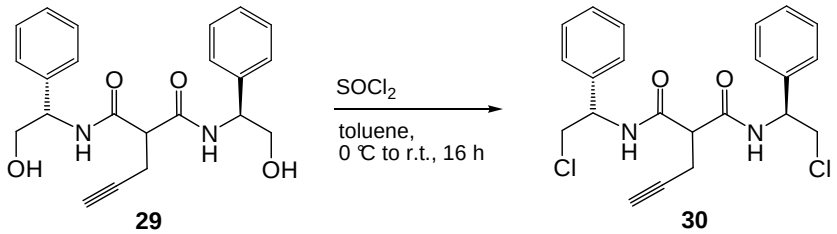
MS (FAB):

m/z = 381.2 (100%) [M+H]$^+$; **HRMS (FAB):** m/z = 381.1808, calcd. for $C_{22}H_{25}N_2O_4$ [M+H]$^+$: 381.1814.

Elemental Analysis:

anal. calcd. for $C_{22}H_{24}N_2O_4$ (380.44): C 69.46, H 6.36, N 7.36; found C 69.03, H 6.43, N 7.28.

7.3.1.5 *N,N'*-Bis[(*S*)-2-chloro-1-phenylethyl]-2-prop-2-yn-1-ylmalonamide (30)



29 **30**

A suspension of dihydroxy diamide **29** (6.75 g, 17.7 mmol) in dry toluene (140 mL) was cooled to 0 °C and $SOCl_2$ (7.77 mL, 107.1 mmol) was added slowly. The reaction proceeded at room temperature over night, yielding a greyish green solution. Removal of the solvent *in vacuo* gave a yellow glass which was redissolved in dichloromethane, washed with $KHCO_3$ (10% w/w in H_2O), and dried over Na_2SO_4. Subsequent filtration and removal of the residual solvent *in vacuo* yielded **30** as a reddish orange powder of sufficient purity for direct use in the next step (7.39 g, 99%).

^{1}H NMR (600.13 MHz, MeOH-d$_4$, 293 K):

δ 7.34-7.25 (m, 10H, C***H***$_{aryl}$), 5.18 (m, 2H, NC***H***), 3.86-3.71 (m, 4H, C***H***$_2$Cl), 3.49 (t, ^3J = 7.59 Hz, 1H, C***H***CH_2C≡CH), 2.76-2.68 (m, 2H, C***H***$_2$C≡CH), 2.31 (t, ^4J = 2.63 Hz, 1H,

$CH_2C{\equiv}C\boldsymbol{H}$).

$^{13}C\{^1H\}$ NMR (150.90 MHz, MeOH-d_4, 293K):

δ 170.20/170.19 (N***C***O), 140.03/139.93 (***C***$_{q, aryl}$), 129.80/129.72/129.12/129.04/128.00/127.92 (***C***$_{aryl}$), 82.29 (***C***≡CH), 72.14 (C≡***C***H), 56.39/56.25 (N***C***H), 54.11 (***C***HCH$_2$C≡CH), 47.84/47.65 (***C***H$_2$Cl), 20.78 (***C***H$_2$C≡CH).

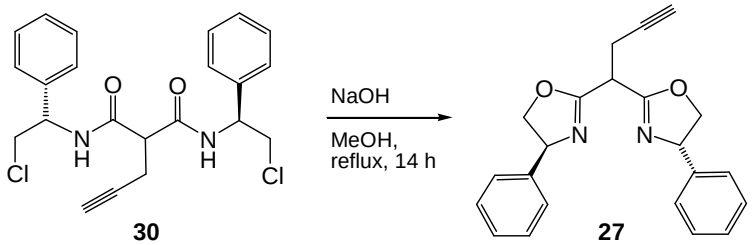
IR (KBr):

$\tilde{\nu}$ [cm^{-1}] = 3295 (m, $\nu_{N\text{-}H}$), 3120-3000 (m, $\nu_{C\text{-}H(aryl)}$), 3000-2850 (w, $\nu_{C\text{-}H(aliphat)}$), 2121 (w, $\nu_{C\equiv C}$), 1670 (s, $\nu_{C=O}$), 1558 (s, $\nu_{C=O}$).

MS (FAB):

m/z = 417.2 (50%) [M+H]$^+$, 367.2 (6%) [M-CH$_2$Cl]$^+$; **HRMS (FAB):** m/z = 417.1163, calcd. for $C_{22}H_{23}N_2O_2{}^{35}Cl_2$ [M+H]$^+$: 417.1136; m/z = 419.1143, calcd. for $C_{22}H_{23}N_2O_2{}^{35}Cl^{37}Cl$ [M+H]$^+$: 419.1108; m/z = 421.1134, calcd. for $C_{22}H_{23}N_2O_2{}^{37}Cl_2$ [M+H]$^+$: 421.1078.

7.3.1.6 4,4-Bis[(*S*)-4-phenyloxazolin-2-yl]but-1-yne (27)



30 **27**

In air, dichloride **30** (7.39 g, 17.7 mmol) was dissolved in methanolic NaOH (2.13 g, 53.3 mmol in 260 mL) and heated to reflux for 14 h during which NaCl precipitated. The solvent was removed *in vacuo*, the residue was redissolved in dichloromethane, washed with NH_4Cl_{aq}, and dried over Na_2SO_4. Filtration and removal of the solvent *in vacuo* afforded an orange foam which was purified by column chromatography (pentane/EtOAc 70:30) yielding **27** as an orange, viscous oil (2.61 g, 43%).

Optical Rotation (c = 2.00, MeOH):

$[\alpha]_D^{23}$ = -108.9.

^{1}H NMR (600.13 MHz, $CDCl_3$, 293 K):

δ 7.35-7.26 (m, 10H, C***H***$_{aryl}$), 5.28 (m, 2H, NC***H***), 4.71 (m, 2H, C***H***$_2$O), 4.19 (m, 2H, C***H***$_2$O), 3.90 (t, ^3J = 7.71 Hz, 1H, C***H***CH$_2$C≡CH), 3.02 (m, 2H, C***H***$_2$C≡CH), 2.10 (dt, ^4J = 2.50 Hz,

^5J = 1.18 Hz, 1H, $CH_2C{\equiv}C\boldsymbol{H}$).

$^{13}C\{^1H\}$ NMR (150.90 MHz, $CDCl_3$, 293 K):

δ 164.75/164.67 (N***C***O), 141.94/141.87 (***C***$_{q, aryl}$), 128.69/128.68/127.65/126.75/126.65 (***C***$_{aryl}$), 80.58 (***C***≡CH), 75.55/75.47 (***C***H_2O), 70.49 (C≡***C***H), 69.69/69.60 (N***C***H), 39.14 (***C***$HCH_2C{\equiv}CH$), 19.97 (***C***$H_2C{\equiv}CH$).

IR (KBr):

$\tilde{\nu}$ [cm^{-1}] = 3295 (m, C≡CH), 3070-3005 (w, $\nu_{C\text{-}H(aryl)}$), 2980-2860 (m, $\nu_{C\text{-}H(aliphat)}$), 2121 (w, $\nu_{C{\equiv}C}$), 1664 (s, $\nu_{C=N}$).

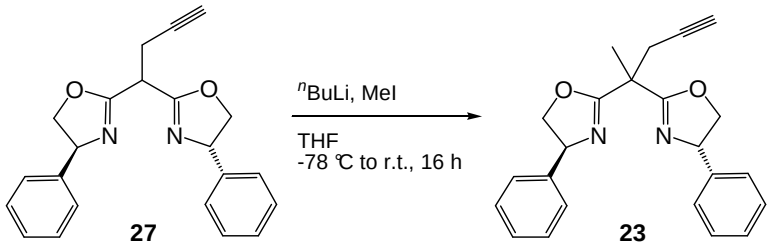
MS (FAB):

m/z = 345.1 (100%) $[M+H]^+$, 225.1 (2%) $[(M+H)\text{-}C_8H_8O]^+$; **HRMS (FAB):** m/z = 345.1600, calcd. for $C_{22}H_{21}N_2O_2$ $[M+H]^+$: 345.1603.

Elemental Analysis:

anal. calcd. for $C_{22}H_{20}N_2O_2$ (344.41) • 0.05 CH_2Cl_2: C 75.96, H 5.81, N 8.03; found C 75.85, H 5.90, N 7.99.

7.3.1.7 4,4-Bis[(*S*)-4-phenyloxazolin-2-yl]pent-1-yne (propargyl-Box(Ph), 23)



27 **23**

A solution of bisoxazoline **27** (858 mg, 2.5 mmol) in THF (10 mL) was cooled to -78 °C and ^{n}BuLi (1.70 mL, 1.6 M in hexane) was added. The resulting bright yellow mixture was stirred at -40 °C for 30 min prior to adding MeI (0.47 mL, 7.5 mmol). The solution was warmed to room temperature over night. After removal of the solvent *in vacuo*, the residue was redissolved in dichloromethane, washed with NH_4Cl_{aq}, and dried over Na_2SO_4. Filtration and removal of the solvent yielded the crude product which was purified by column chromatography (pentane/EtOAc 60:40) yielding **23** as a colourless, extremely viscous oil (847 mg, 95%).

Optical Rotation (c = 2.00, MeOH):

$[\alpha]_D^{23}$ = -125.7.

^{1}H NMR (600.13 MHz, $CDCl_3$, 293 K):

δ 7.35-7.26 (m, 10H, C***H***$_{aryl}$), 5.26 (m, 2H, NC***H***), 4.70 (m, 2H, C***H***$_2$O), 4.18 (m, 2H, C***H***$_2$O), 3.05 (d, ^4J = 2.48 Hz, 2H, C***H***$_2$C≡CH), 2.10 (t, ^4J = 2.39 Hz, 1H, CH$_2$C≡C***H***), 1.81 (s, 3H, CC***H***$_3$).

^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 293 K):

δ 168.29/168.20 (N***C***O), 142.13/142.05 (***C***$_{q,\ aryl}$), 128.69/128.62/127.61/126.84/126.63 (***C***$_{aryl}$), 79.85 (***C***≡CH), 75.71/75.63 (***C***H$_2$O), 71.28 (C≡***C***H), 69.74/69.52 (N***C***H), 42.08 (***C***CH$_3$), 27.12 (***C***H$_2$C≡CH), 21.41 (C***C***H$_3$).

IR (KBr):

$\tilde{\nu}$ [cm^{-1}] = 3291 (m, C≡CH), 3070-3000 (w, $\nu_{C\text{-}H(aryl)}$), 3000-2840 (m, $\nu_{C\text{-}H(aliphat)}$), 2121 (w, $\nu_{C\equiv C}$), 1654 (s, $\nu_{C=N}$).

MS (FAB):

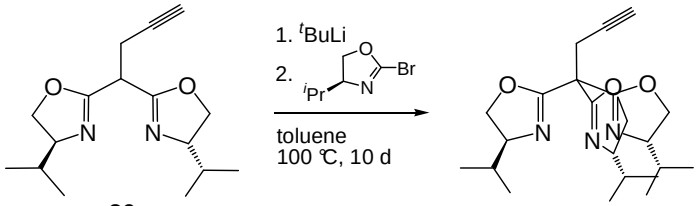
m/z = 359.1 (100%) [M+H]$^+$, 357.1 (6%) [M-H]$^+$, 239.0 (5%) [(M+H)-C$_8$H$_8$O]$^+$; **HRMS (FAB):** m/z = 359.1771, calcd. for C$_{23}$H$_{23}$N$_2$O$_2$ [M+H]$^+$: 359.1760.

Elemental Analysis:

anal. calcd. for C$_{23}$H$_{22}$N$_2$O$_2$ (358.43) • 0.08 CH$_2$Cl$_2$: C 75.90, H 6.12, N 7.67; found C 75.85, H 6.25, N 7.48.

7.3.2 Propargyl-functionalised trisoxazolines

7.3.2.1 4,4,4-Tris[(*S*)-4-isopropyloxazolin-2-yl]but-1-yne (propargyl-Trisox(^{i}Pr), 24)



26 **24**

A solution of bisoxazoline **26** (970 mg, 3.5 mmol) in dry toluene (100 mL) was cooled to -78 °C and ^{t}BuLi (2.27 mL, 1.7 M in hexane) was added. 15 min after completion of the addition, (*S*)-2-bromo-4-isopropyloxazoline (943 mg, 4.9 mmol, 62% w/w in THF) was transferred to the yellow solution, giving rise to an orange-brown colour. The mixture was warmed to room temperature, concentrated to eliminate the hexane originating from ^{t}BuLi, and heated at 100 °C for 10 days. The resulting deep brown solution was evaporated to dryness, its residue was redissolved in dichloromethane (100 mL), washed with H_2O (20 mL), and dried over Na_2SO_4. Filtration and removal of the solvent *in vacuo* yielded a brown oil which was purified by column chromatography (EtOAc/MeOH 97.5:2.5) yielding **24** as a yellow, viscous oil (934 mg, 69%).

^{1}H NMR (399.89 MHz, $CDCl_3$, 293 K):

δ 4.27 (dd, ^{2}J = 9.48 Hz, ^{3}J = 8.07 Hz, 3H, C***H***$_2$O), 4.07 (m, 3H, C***H***$_2$O), 4.03-3.98 (m, 3H, NC***H***), 3.24 (dd, ^{2}J = 16.69 Hz, ^{4}J = 2.64 Hz, 1H, C***H***$_2$C≡CH), 3.14 (dd, ^{2}J = 16.70 Hz, ^{4}J = 2.66 Hz, 1H, C***H***$_2$C≡CH), 1.99 (t, ^{4}J = 2.64 Hz, 1H, CH$_2$C≡C***H***), 1.80 (m, 3H, C***H***(CH$_3$)$_2$), 0.92 (d, ^{3}J = 6.80 Hz, 9H, CH(C***H***$_3$)$_2$), 0.87 (d, ^{3}J = 6.77 Hz, 9H, CH(C***H***$_3$)$_2$).

^{13}C{^{1}H} NMR (100.56 MHz, $CDCl_3$, 293 K):

δ 162.44 (N***C***O), 80.00 (***C***≡CH), 71.66 (N***C***H), 70.28 (***C***H$_2$O), 70.22 (C≡***C***H), 47.92 (***C***CH$_2$C≡CH), 32.21 (***C***H(CH$_3$)$_2$), 25.44 (***C***H$_2$C≡CH), 18.64/18.46 (CH(***C***H$_3$)$_2$), 17.87/17.71 (CH(***C***H$_3$)$_2$).

IR (KBr):

$\tilde{\nu}$ [cm^{-1}] = 2960-2874 (m, $\nu_{C\text{-}H(aliphat)}$), 2108 (w, $\nu_{C\equiv C}$), 1665 (s, $\nu_{C=N}$).

MS (EI):

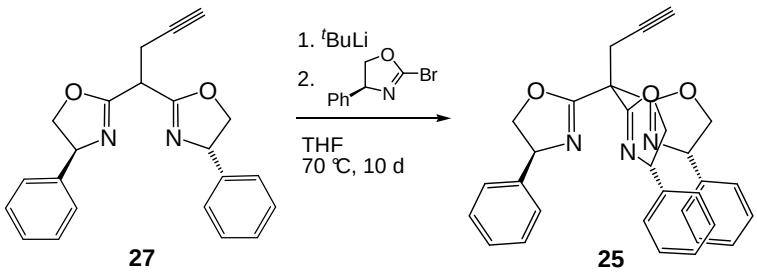
m/z = 387.2 (4%) [M]$^{+}$, 344.1 (100%) [M-C$_3$H$_7$]$^{+}$, 275.1 (30%) [M-C$_6$H$_{10}$NO]$^{+}$; **HRMS**

(FAB): m/z = 388.2597, calcd. for $C_{22}H_{34}N_3O_3$ $[M+H]^+$: 388.2600.

Elemental Analysis:

anal. calcd. for $C_{22}H_{33}N_3O_3$ (387.52) • 0.3 MeOH: C 67.44, H 8.68, N 10.58; found C 67.39, H 8.56, N 10.29.

7.3.2.2 4,4,4-Tris[(*S*)-4-phenyloxazolin-2-yl]but-1-yne (propargyl-Trisox(Ph), 25)



27 **25**

A solution of bisoxazoline **27** (442 mg, 1.3 mmol) in dry toluene (70 mL) was cooled to -78 °C and ^{t}BuLi (0.94 mL, 1.7 M in hexane) was added. 15 min after completion of the addition, (*S*)-2-bromo-4-phenyloxazoline (406 mg, 1.8 mmol, 54% w/w in THF) was transferred to the yellow solution, giving rise to an orange-brown colour. The mixture was warmed to room temperature, concentrated to eliminate the hexane originating from ^{t}BuLi, and heated at 70 °C for 10 days. The resulting pale brown solution was evaporated to dryness, its residue was redissolved in dichloromethane (50 mL), washed with H_2O (10 mL), and dried over Na_2SO_4. Filtration and removal of the solvent *in vacuo* yielded a brown oil which was purified by column chromatography (pentane/EtOAc 40:60, then EtOAc and EtOAc/MeOH 99:1) yielding **25** as a light brown, extremely viscous oil which turned into a glass upon standing (220 mg, 35%).

^{1}H NMR (600.13 MHz, $CDCl_3$, 293 K):

δ 7.36-7.26 (m, 15H, C***H***$_{aryl}$), 5.35 (dd, ^3J = 10.09 Hz, ^3J = 7.88 Hz, 3H, NC***H***), 4.78 (dd, ^2J = 10.13 Hz, ^3J = 8.35 Hz, 3H, C***H***$_2$O), 4.26 (m, 3H, C***H***$_2$O), 3.45 (dd, ^2J = 16.81 Hz, ^4J = 2.62 Hz, 1H, C***H***$_2$C≡CH), 3.39 (dd, ^2J = 16.80 Hz, ^4J = 2.65 Hz, 1H, C***H***$_2$C≡CH), 2.11 (t, ^4J = 2.62 Hz, 1H, CH$_2$C≡C***H***).

^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 293 K):

δ 164.25 (N***C***O), 141.90 (***C***$_{q, aryl}$), 128.58/127.57/126.93 (***C***$_{aryl}$), 79.77 (***C***≡CH), 76.04 (***C***H$_2$O), 71.03 (C≡***C***H), 69.64 (N***C***H), 48.47 (***C***CH$_2$C≡CH), 25.68 (***C***H$_2$C≡CH).

IR (KBr):

$\tilde{\nu}$ [cm^{-1}] = 3291 (m, C≡CH), 3070-3005 (w, $\nu_{C\text{-}H(aryl)}$), 2980-2850 (m, $\nu_{C\text{-}H(aliphat)}$), 2108 (w, $\nu_{C\equiv C}$), 1663 (s, $\nu_{C=N}$).

MS (FAB):

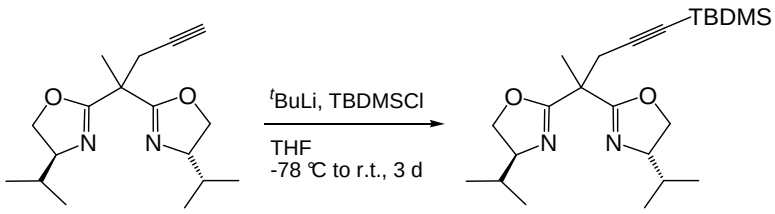
m/z = 490.1 (100%) $[M+H]^+$, 464.1 (5%) $[M\text{-}C_2H]^+$, 345.0 (10%) $[464.1\text{-}C_8H_8O]^+$; **HRMS (FAB):** m/z = 490.2145, calcd. for $C_{31}H_{28}N_3O_3$ $[M+H]^+$: 490.2130.

Elemental Analysis:

anal. calcd. for $C_{31}H_{27}N_3O_3$ (489.56) • 0.9 MeOH: C 73.91, H 5.95, N 8.11; found C 73.96, H 6.00, N 7.85.

7.3.3 TBDMS/TIPS-functionalised model systems

7.3.3.1 1-[*tert*-Butyl(dimethyl)silyl]-4,4-bis[(*S*)-4-isopropyloxazolin-2-yl]pent-1-yne (TBDMS-propargyl-Box(ⁱPr), 31)



A solution of bisoxazoline **22** (376 mg, 1.3 mmol) in THF (20 mL) was cooled to -78 °C and ^{t}BuLi (0.84 mL, 1.7 M in hexane) was added slowly. The bright yellow mixture was stirred for 30 min prior to the addition of TBDMSCl (253 mg, 1.7 mmol in 2 mL THF). The resulting red mixture was warmed to room temperature and stirred for 3 days. After removal of the solvent *in vacuo*, the residue was redissolved in dichloromethane, washed with NH_4Cl_{aq}, and dried over Na_2SO_4. Filtration and removal of the solvent gave an oily crude product which was purified *via* column chromatography (pentane/EtOAc 60:40). Therefore, **31** was obtained as a yellow oil (406 mg, 77%).

^{1}H NMR (600.13 MHz, $CDCl_3$, 293 K):

δ 4.21 (m, 2H, C***H***$_2$O), 4.02-3.91 (m, 4H, C***H***$_2$O, NC***H***), 3.00 (d, ^2J = 16.93 Hz, 1H, C***H***$_2$C≡C), 2.84 (d, ^2J = 16.93 Hz, 1H, C***H***$_2$C≡C), 1.83-1.73 (m, 2H, C***H***$(CH_3)_2$), 1.63 (s, 3H,

CC***H***$_3$), 0.93 (d, ^3J = 6.82 Hz, 3H, CH(C***H***$_3$)$_2$), 0.91-0.89 (m, 12H, C(C***H***$_3$)$_3$, CH(C***H***$_3$)$_2$), 0.85 (m, 6H, CH(C***H***$_3$)$_2$), 0.05 (s, 6H, Si(C***H***$_3$)$_2$).

^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 293 K):

δ 166.73 (N***C***O), 102.99 (***C***≡C-TBDMS), 85.27 (C≡***C***-TBDMS), 71.88/71.55 (N***C***H), 70.23/69.99 (***C***H$_2$O), 41.88 (***C***CH$_2$C≡C), 32.37/32.13 (***C***H(CH$_3$)$_2$), 28.32 (***C***H$_2$C≡C), 26.05 (C(***C***H$_3$)$_3$), 21.29 (C***C***H$_3$), 18.74/18.54 (CH(***C***H$_3$)$_2$), 17.71/17.33 (CH(***C***H$_3$)$_2$), 16.49 (***C***(CH$_3$)$_3$), -4.57 (Si(***C***H$_3$)$_2$).

^{29}Si{^{1}H} NMR (79.44 MHz, $CDCl_3$, 293 K):

δ -8.86.

IR (KBr):

$\tilde{\nu}$ [cm^{-1}] = 2958-2858 (m, $\nu_{C\text{-}H(aliphat)}$), 2177 (w, $\nu_{C\equiv C}$), 1662 (s, $\nu_{C=N}$).

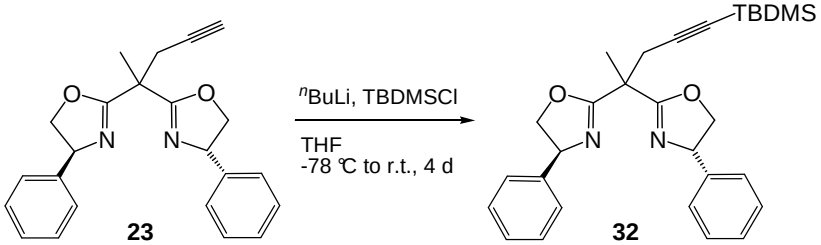
MS (FAB):

m/z = 405.2 (100%) [M+H]$^+$, 361.2 (2%) [M-C$_3$H$_7$]$^+$; **HRMS (FAB):** m/z = 405.2925, calcd. for $C_{23}H_{41}N_2O_2Si$ [M+H]$^+$: 405.2937.

Elemental Analysis:

anal. calcd. for $C_{23}H_{40}N_2O_2Si$ (404.66): C 68.27, H 9.96, N 6.92; found C 68.10, H 9.86, N 6.84.

7.3.3.2 1-[*tert*-Butyl(dimethyl)silyl]-4,4-bis[(*S*)-4-phenyloxazolin-2-yl]pent-1-yne (TBDMS-propargyl-Box(Ph), 32)



A solution of bisoxazoline **23** (543 mg, 1.5 mmol) in THF (10 mL) was cooled to -78 °C and ^{n}BuLi (1.14 mL, 1.6 M in hexane) was added slowly. The resulting light orange mixture was stirred for 30 min prior to adding TBDMSCl (296 mg, 2.0 mmol, in 2 mL THF). The mixture was warmed to room temperature and stirred for 4 days. After removal of the solvent *in vacuo*, the residue was redissolved in dichloromethane, washed with NH_4Cl_{aq}, and dried over Na_2SO_4. Filtration and removal of the solvent gave a gold-coloured foam which was

purified by column chromatography (pentane/EtOAc 60:40). Therefore, bisoxazoline **32** was obtained as an off-white, waxy solid (440 mg, 62%).

Optical Rotation (c = 2.00, MeOH):

$[\alpha]_D^{23}$ = -113.2.

^{1}H NMR (600.13 MHz, $CDCl_3$, 293 K):

δ 7.34-7.26 (m, 10H, C***H***$_{aryl}$), 5.24 (m, 2H, NC***H***), 4.68 (m, 2H, C***H***$_2$O), 4.19-4.11 (m, 2H, C***H***$_2$O), 3.17 (d, ^2J = 16.91 Hz, 1H, C***H***$_2$C≡C), 3.01 (d, ^2J = 16.90 Hz, 1H, C***H***$_2$C≡C), 1.80 (s, 3H, CC***H***$_3$), 0.94 (s, 9H, C(C***H***$_3$)$_3$), 0.10 (s, 6H, Si(C***H***$_3$)$_2$).

^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 293 K):

δ 168.56/168.33 (N***C***O), 142.26/142.07 (***C***$_{q, aryl}$), 128.66/127.55/126.72/126.67 (***C***$_{aryl}$), 102.64 (***C***≡C-TBDMS), 85.81 (C≡***C***-TBDMS), 75.63/75.58 (***C***H$_2$O), 69.71/69.57 (N***C***H), 42.32 (***C***CH$_3$), 28.53 (***C***H$_2$C≡C), 26.04 (C(***C***H$_3$)$_3$), 21.42 (C***C***H$_3$), 16.51 (***C***(CH$_3$)$_3$), -4.52 (Si(***C***H$_3$)$_2$).

^{29}Si{^{1}H} NMR (79.44 MHz, $CDCl_3$, 293 K):

δ -8.61.

IR (KBr):

$\tilde{\nu}$ [cm^{-1}] = 3090-3004 (w, $\nu_{C\text{-}H(aryl)}$), 3000-2854 (m, $\nu_{C\text{-}H(aliphat)}$), 2175 (w, $\nu_{C\equiv C}$), 1668 (s, $\nu_{C=N}$), 1664 (s, $\nu_{C=N}$).

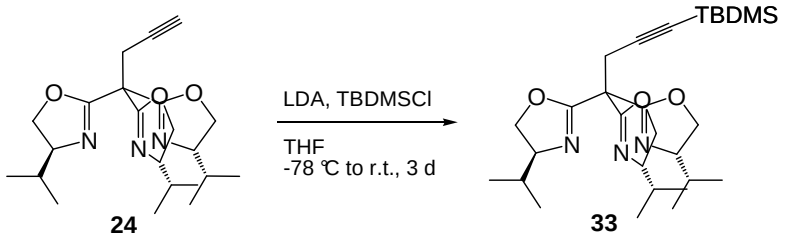
MS (FAB):

m/z = 473.2 (100%) $[M+H]^+$, 471.2 (3%) $[M-H]^+$, 353.1 (1%) $[(M+H)-C_8H_8O]^+$, 319.1 (4%) $[M-C_9H_{17}Si]^+$; **HRMS (FAB):** m/z = 473.2693, calcd. for $C_{29}H_{37}N_2O_2Si$ $[M+H]^+$: 473.2624.

Elemental Aanalysis:

anal. calcd. for $C_{29}H_{36}N_2O_2Si$ (472.69): C 73.69, H 7.68, N 5.93; found C 73.28, H 7.61, N 5.92.

7.3.3.3 1-[*tert*-Butyl(dimethyl)silyl]-4,4,4-tris[(*S*)-4-isopropyloxazolin-2-yl]but-1-yne (TBDMS-propargyl-Trisox(^{i}Pr), 33)



A solution of trisoxazoline **24** (111 mg, 0.29 mmol) in THF (10 mL) was cooled to -78 °C and LDA (0.16 mL, 2 M in THF/hexane) was added slowly. The resulting dark brown mixture was stirred at -40 °C for 30 min. After recooling to -78 °C, a solution of TBDMSCl (52 mg, 0.35 mmol) in THF (0.15 mL) was added. The mixture was warmed to room temperature, giving a pale orange solution which was stirred for 3 days. After removal of the solvent *in vacuo*, the residue was redissolved in dichloromethane, washed with NH_4Cl_{aq}, and dried over Na_2SO_4. Filtration and removal of the solvent *in vacuo* gave an orange oil which was purified by filtration through a pad of silica gel, using hexane, and later EtOAc/MeOH 9:1 as eluent. Trisoxazoline **33** was therefore yielded as an almost colourless, viscous oil (140 mg, 96%).

^{1}H NMR (399.89 MHz, $CDCl_3$, 293 K):

δ 4.25 (dd, ^2J = 9.37, ^3J = 8.39 Hz, 3H, C***H***$_2$O), 4.05 (m, 3H, C***H***$_2$O), 3.97 (ddd, ^3J = 9.60 Hz, ^3J = 7.34 Hz, ^3J = 6.10 Hz, 3H, NC***H***), 3.31 (d, ^2J = 16.88 Hz, 1H, C***H***$_2$C≡C), 3.15 (d, ^2J = 16.81 Hz, 1H, C***H***$_2$C≡C), 1.78 (m, 3H, C***H***$(CH_3)_2$), 0.92 (d, ^3J = 6.87 Hz, 9H, CH(C***H***$_3)_2$), 0.90 (s, 9H, C(C***H***$_3)_3$), 0.87 (d, ^3J = 6.77 Hz, 9H, CH(C***H***$_3)_2$), 0.04 (s, 3H, Si(C***H***$_3)_2$), 0.03 (s, 3H, Si(C***H***$_3)_2$).

^{13}C{^{1}H} NMR (100.56 MHz, $CDCl_3$, 293 K):

δ 162.56 (N***C***O), 102.84 (***C***≡C-TBDMS), 84.29 (C≡***C***-TBDMS), 71.88 (N***C***H), 70.60 (***C***H_2O), 48.05 (***C***CH_2C≡C), 32.43 (***C***$H(CH_3)_2$), 26.88 (***C***H_2C≡C), 26.07 C(***C***$H_3)_3$), 18.69 (CH(***C***$H_3)_2$), 17.91 (CH(***C***$H_3)_2$), 16.57 (***C***$(CH_3)_3$), -4.55 (Si(***C***$H_3)_2$).

^{29}Si{^{1}H} NMR (79.44 MHz, $CDCl_3$, 293 K):

δ -9.09.

IR (KBr):

$\tilde{\nu}$ [cm^{-1}] = 2961-2858 (m, $\nu_{C\text{-}H(aliphat)}$), 2180 (w, $\nu_{C\equiv C}$), 1677 (s, $\nu_{C=N}$).

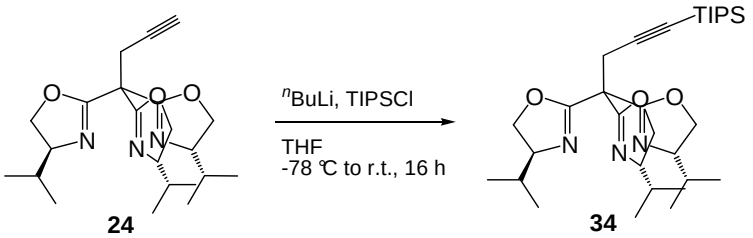
MS (FAB):

m/z = 502.3 (100%) $[M+H]^+$, 348.3 (4%) $[M-C_9H_{17}Si]^+$; **HRMS (FAB):** m/z = 502.3445, calcd. for $C_{28}H_{48}N_3O_3Si$ $[M+H]^+$: 502.3465.

Elemental Analysis:

anal. calcd. for $C_{28}H_{47}N_3O_3Si$ (501.78) • 0.5 MeOH: C 66.11, H 9.54, N 8.12; found C 66.01, H 9.26, N 8.19.

7.3.3.4 1-[Tris(isopropyl)silyl]-4,4,4-tris[(*S*)-4-isopropyloxazolin-2-yl]but-1-yne (TIPS-propargyl-Trisox(*i*Pr), 34)



A solution of trisoxazoline **24** (20 mg, 0.052 mmol) in THF (2 mL) was cooled to -78 °C and *n*BuLi (25 µL, 2.5 M in hexane) was added slowly. The resulting orange mixture was stirred at -40 °C for 30 min. After recooling to -78 °C, TIPSCl (50 µL, 0.23 mmol) was added. The mixture was warmed to room temperature over night, giving a brownish orange solution which was evaporated to dryness. The residue was redissolved in dichloromethane, washed with NH_4Cl_{aq}, and dried over Na_2SO_4. Filtration and removal of the solvent *in vacuo* gave an orange oil which was purified by column chromatography (EtOAc/MeOH 95:5). Trisoxazoline **34** was therefore yielded as an almost colourless oil (28 mg, 99%).

^{1}H NMR (600.13 MHz, $CDCl_3$, 293 K):

δ 4.24 (m, 3H, C***H***$_2$O), 4.03 (m, 3H, C***H***$_2$O), 3.95 (td, ^3J = 9.17 Hz, ^3J = 7.26 Hz, 3H, NC***H***), 3.29 (d, ^2J = 16.81 Hz, 1H, C***H***$_2$C≡C), 3.21 (d, ^2J = 16.80 Hz, 1H, C***H***$_2$C≡C), 1.76 (m, 3H, C***H***$(CH_3)_2$), 1.03 (d, ^3J = 6.40 Hz, 18H, SiCH(C***H***$_3)_2$), 1.00 (m, 3H, SiC***H***$(CH_3)_2$), 0.92 (d, ^3J = 6.65 Hz, 9H, CH(C***H***$_3)_2$), 0.85 (d, ^3J = 6.66 Hz, 9H, CH(C***H***$_3)_2$).

^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 293 K):

δ 162.68 (N***C***O), 103.83 (***C***≡C-TIPS), 82.02 (C≡***C***-TIPS), 71.91 (N***C***H), 70.56 (***C***H_2O), 48.08 (***C***CH_2C≡C), 32.41 (***C***$H(CH_3)_2$), 27.01 (***C***H_2C≡C), 18.77 CH(***C***$H_3)_2$), 18.57 (SiCH(***C***$H_3)_2$), 17.87 (CH(***C***$H_3)_2$), 11.25 (Si***C***$H(CH_3)_2$).

$^{29}Si\{^1H\}$ NMR (79.44 MHz, $CDCl_3$, 293 K):

δ -21.89.

IR (KBr):

$\tilde{\nu}$ [cm^{-1}] = 2958-2867 (m, $\nu_{C\text{-}H(aliphat)}$), 2180 (w, $\nu_{C\equiv C}$), 1664 (s, $\nu_{C=N}$).

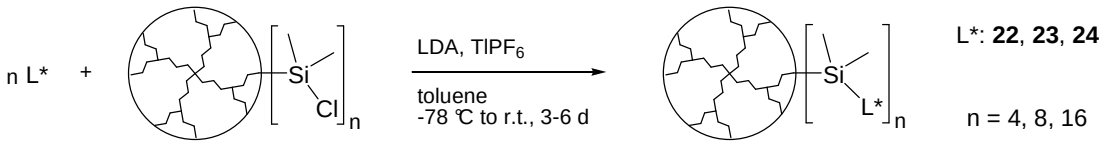
MS (FAB):

m/z = 544.3 (100%) $[M+H]^+$, 501.3 (39%) $[(M+H)\text{-}C_3H_7]^+$, 348.3 (22%) $[M\text{-}C_{12}H_{23}Si]^+$;

HRMS (FAB): m/z = 544.3896, calcd. for $C_{31}H_{54}N_3O_3Si$ $[M+H]^+$: 544.3935.

7.3.4 Bis- and trisoxazoline-functionalised carbosilane dendrimers

General procedure for the synthesis of the functionalised dendrimers



The appropriate amount of ligand (1.1-1.8 equiv with respect to each chlorosilyl function of the carbosilane dendrimer) was dissolved in dry toluene (3 mL), cooled to -78 °C and LDA (1.0 equiv with respect to the amount of ligand, 1.8 M in THF/heptane/ethylbenzene) was added slowly. The resulting solution was stirred at -40 °C for 30 min. A solution of the corresponding chlorosilyl functionalised dendrimer (10-70 μmol) in dry toluene (2 mL) and solid $TlPF_6$ (1.1-1.6 equiv per chlorosilyl function) were added. The mixture was warmed to room temperature over night and stirred for several days. After removal of the solvent *in vacuo*, the residue was redissolved in dichloromethane, washed with H_2O (1-2 mL), and dried over Na_2SO_4. The solvent was removed again, the residue redissolved in MeOH, and filtered using a biochemical filtre (0.45 μm pore size). This step was repeated once or twice. {G0}-[propargyl-Box(^{i}Pr)]$_4$ and {G0}-[propargyl-Box(Ph)]$_4$ were then purified *via* flash filtration through silica gel (pentane/EtOAc 60:40, later EtOAc/MeOH 97.5:2.5 and EtOAc/MeOH 95:5). All other derivatives were purified *via* dialysis: the membrane was washed with dichloromethane (3x) and filled with a concentrated solution of the crude product in dichloromethane. The resulting bag was put into pure dichloromethane (200 mL)

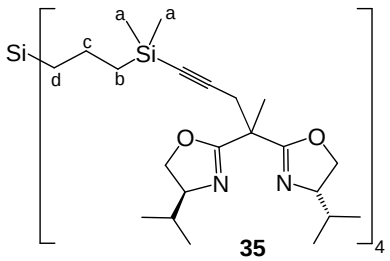
and gently stirred for 8-16 h. Then the exterior solvent was replaced. This was repeated up to four times, depending on the amount of residual free ligand and other impurities in the sample.

7.3.4.1 {G0}-[propargyl-Box(^{i}Pr)]$_4$ (35)

Reagents:

262 mg	(0.90 mmol)	bisoxazoline **22**
0.50 mL	(0.90 mmol)	LDA (1.8 M)
107 mg	(0.19 mmol)	{G0}-($SiMe_2Cl$)$_4$
314 mg	(0.90 mmol)	$TlPF_6$

Product: yellow, viscous oil (83 mg, 28%)



35

^{1}H NMR (600.13 MHz, $CDCl_3$, 293 K):

δ 4.20 (dd, ^2J = 9.47 Hz, ^3J = 8.12 Hz, 4H, C***H***$_2$O), 4.18 (dd, ^2J = 9.47 Hz, ^3J = 8.17 Hz, 4H, C***H***$_2$O), 4.02-3.98 (m, 8H, C***H***$_2$O), 3.98-3.93 (m, 8H, NC***H***), 2.96 (d, ^2J = 16.92 Hz, 4H, C***H***$_2$C≡C), 2.84 (d, ^2J = 16.92 Hz, 4H, C***H***$_2$C≡C), 1.79 (m, 8H, C***H***$(CH_3)_2$), 1.61 (s, 12H, CC***H***$_3$), 1.34 (m, 8H, ***H***$_c$), 0.93 (d, ^3J = 6.81 Hz, 12H, CH(C***H***$_3)_2$), 0.90 (d, ^3J = 6.82 Hz, 12H, CH(C***H***$_3)_2$), 0.87 (d, ^3J = 6.78 Hz, 12H, CH(C***H***$_3)_2$), 0.85 (d, ^3J = 6.79 Hz, 12H, CH(C***H***$_3)_2$), 0.64 (m, 8H, ***H***$_b$), 0.56 (m, 8H, ***H***$_d$), 0.081 (s, 12H, ***H***$_a$), 0.080 (s, 12H, ***H***$_a$).

^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 293 K):

δ 166.75/166.60 (N***C***O), 102.67 (***C***≡C-Si), 86.56 (C≡***C***-Si), 71.75/71.44 (N***C***H), 70.11/69.96 (***C***H$_2$O), 41.79 (***C***CH_3), 32.27/32.10 (***C***H$(CH_3)_2$), 28.23 (***C***H$_2$C≡C), 21.25 (C***C***H_3), 21.06 (***C***$_b$), 18.70/18.43 (CH(***C***H$_3)_2$), 18.31 (***C***$_c$), 17.69/17.36 (CH(***C***H$_3)_2$), 17.02 (***C***$_d$), -1.63/-1.65 (***C***$_a$).

^{29}Si{^{1}H} NMR (79.44 MHz, $CDCl_3$, 293 K):

δ 0.73 (***Si***$(CH_2)_4$), -17.93 (***Si***$(CH_3)_2$).

IR (KBr):

$\tilde{\nu}$ [cm^{-1}] = 2960-2875 (s, $\nu_{C\text{-}H(aliphat)}$), 2177 (w, $\nu_{C\equiv C}$), 1662 (s, $\nu_{C=N}$).

MS (FAB):

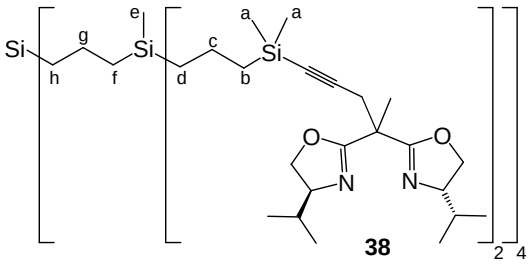
m/z = 1856 (17%) $[M+H]^+$, 1196 (5%) $[M\text{-}C_{22}H_{37}N_2O_2Si]^+$, 807 (2%) $[M\text{-}C_{44}H_{74}N_4O_4Si_2]^+$, 389 (24%) $[C_{22}H_{37}N_2O_2Si]^+$; **HRMS (Maldi):** m/z = 1586.0330, calcd. for $C_{88}H_{149}N_8O_8Si_5$ $[M+H]^+$: 1586.0339.

7.3.4.2 {G1}-[propargyl-Box(^{i}Pr)]$_8$ (38)

Reagents:

65 mg	(0.22 mmol)	bisoxazoline **22**
0.12 mL	(0.22 mmol)	LDA (1.8 M)
27 mg	(0.019 mmol)	{G1}-($SiMe_2Cl$)$_8$
77 mg	(0.22 mmol)	$TlPF_6$

Product: pale yellow, viscous oil (51 mg, 77%)



^{1}H NMR (600.13 MHz, $CDCl_3$, 293 K):

δ 4.19 (dd, ^2J = 18.97 Hz, ^3J = 9.27 Hz, 16H, C***H***$_2$O), 4.04-3.92 (m, 32H, C***H***$_2$O, NC***H***), 2.95 (d, ^2J = 17.06 Hz, 8H, C***H***$_2$C≡C), 2.84 (d, ^2J = 17.00 Hz, 8H, C***H***$_2$C≡C), 1.83-1.75 (m, 16H, C***H***$(CH_3)_2$), 1.61 (s, 24H, CC***H***$_3$), 1.39-1.31 (m, 24H, ***H***$_c$, ***H***$_g$), 0.93 (d, ^3J = 6.68 Hz, 24H, CH(C***H***$_3)_2$), 0.90 (d, ^3J = 6.74 Hz, 24H, CH(C***H***$_3)_2$), 0.86 (d, ^3J = 6.79 Hz, 24H, CH(C***H***$_3)_2$), 0.85 (d, ^3J = 7.71 Hz, 24H, CH(C***H***$_3)_2$), 0.66-0.60 (m, 16H, ***H***$_b$), 0.58-0.51 (m, 32H, ***H***$_d$, ***H***$_f$, ***H***$_h$), 0.08 (s, 48H, ***H***$_a$), -0.08 (s, 12H, ***H***$_e$).

^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 293 K):

δ 166.69/166.64 (N***C***O), 102.73 (***C***≡C-Si), 86.59 (C≡***C***-Si), 71.77/71.48 (N***C***H), 70.16/70.01 (***C***H_2O), 41.83 (***C***CH_3), 32.15/32.12 (***C***$H(CH_3)_2$), 28.29 (***C***H_2C≡C), 21.30 (C***C***H_3), 20.98 (***C***$_b$), 18.75/18.48 (CH(***C***$H_3)_2$), 18.44 (***C***$_d$, ***C***$_f$, ***C***$_h$), 18.31 (***C***$_c$, ***C***$_g$), 17.74/17.38 (CH(***C***$H_3)_2$), -1.53 (***C***$_a$), -5.07 (***C***$_e$).

^{29}Si{^{1}H} NMR (79.44 MHz, $CDCl_3$, 293 K):

δ 1.04 (***Si***$(CH_2)_3CH_3$), 0.42 (***Si***$(CH_2)_4$), -17.85 (***Si***$(CH_3)_2$).

IR (KBr):

$\tilde{\nu}$ [cm^{-1}] = 2960-2875 (s, $\nu_{C\text{-}H(aliphat)}$), 2177 (w, $\nu_{C\equiv C}$), 1655 (s, $\nu_{C=N}$).

MS (Maldi):

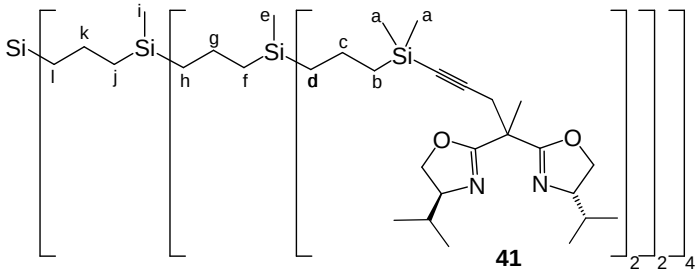
m/z = 3485 (76%) $[M+H]^+$, 3231 (24%) $[(M+H)\text{-}C_{14}H_{24}N_2O_2]^+$, 3136 (31%) $[(M+H)\text{-}C_{19}H_{31}N_2O_2Si]^+$; **HRMS (Maldi):** m/z = 3483.2798, calcd. for $C_{192}H_{333}N_{16}O_{16}Si_{13}$ $[M+H]^+$: 3483.2731.

7.3.4.3 {G2}-[propargyl-Box(^{i}Pr)]$_{16}$ (41)

Reagents:

82 mg	(0.28 mmol)	bisoxazoline **22**
0.16 mL	(0.28 mmol)	LDA (1.8 M)
32 mg	(0.010 mmol)	{G2}-($SiMe_2Cl$)$_{16}$
60 mg	(0.17 mmol)	$TlPF_6$

Product: pale yellow, viscous oil (48 mg, 66%)



41

^{1}H NMR (600.13 MHz, $CDCl_3$, 293 K):

δ 4.19 (m, 32H, C***H***$_2$O), 4.03-3.92 (m, 64H, C***H***$_2$O, NC***H***), 2.96 (d, ^2J = 16.92 Hz, 16H, C***H***$_2$C≡C), 2.84 (d, ^2J = 16.87 Hz, 16H, C***H***$_2$C≡C), 1.84-1.74 (m, 32H, C***H***$(CH_3)_2$), 1.61 (s, 48H, CC***H***$_3$), 1.40-1.31 (m, 56H, ***H***$_c$, ***H***$_g$, ***H***$_k$), 0.93 (d, ^3J = 6.79 Hz, 48H, CH(C***H***$_3$)$_2$), 0.90 (d, ^3J = 6.79 Hz, 48H, CH(C***H***$_3$)$_2$), 0.87 (d, ^3J = 6.83 Hz, 48H, CH(C***H***$_3$)$_2$), 0.85 (d, ^3J = 6.85 Hz, 48H, CH(C***H***$_3$)$_2$), 0.67-0.60 (m, 32H, ***H***$_b$), 0.59-0.49 (m, 80H, ***H***$_d$, ***H***$_f$, ***H***$_h$, ***H***$_j$, ***H***$_l$), 0.08 (s, 96H, ***H***$_a$), -0.08 (s, 24H, ***H***$_e$), -0.09 (s, 12H, ***H***$_i$).

^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 293 K):

δ 166.78/166.63 (N***C***O), 102.70 (***C***≡C-Si), 86.57 (C≡***C***-Si), 71.77/71.46 (N***C***H), 70.14/69.98 (***C***H$_2$O), 41.81 (***C***CH$_3$), 32.25/32.13 (***C***H$(CH_3)_2$), 28.27 (***C***H$_2$C≡C), 21.28 (C***C***H$_3$), 20.96 (***C***$_b$), 18.74/18.47 (CH(***C***H$_3$)$_2$), 18.41 (***C***$_d$, ***C***$_f$, ***C***$_h$, ***C***$_j$, ***C***$_l$), 18.31 (***C***$_c$, ***C***$_g$, ***C***$_k$), 17.73/17.39 (CH(***C***H$_3$)$_2$), -1.55 (***C***$_a$), -5.05 (***C***$_e$, ***C***$_i$).

^{29}Si{^{1}H} NMR (79.44 MHz, $CDCl_3$, 293 K):

δ 1.09/0.85 (***Si***$(CH_2)_3CH_3$), 0.46 (***Si***$(CH_2)_4$), -17.88 (***Si***$(CH_3)_2$).

IR (KBr):

$\tilde{\nu}$ [cm^{-1}] = 2959-2874 (s, $\nu_{C\text{-}H(aliphat)}$), 2177 (w, $\nu_{C\equiv C}$), 1662 (s, $\nu_{C=N}$).

Elemental Analysis:

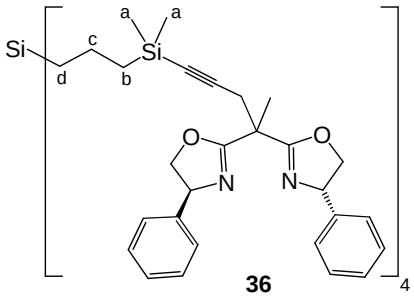
anal. calcd. for $C_{400}H_{700}N_{32}O_{32}Si_{29}$ (7284.51) • 0.9 $TlPF_6$: C 63.22, H 9.28, N 5.90; found C 63.26, H 9.25, N 5.85.

7.3.4.4 {G0}-[propargyl-Box(Ph)]$_4$ (36)

Reagents:

111 mg	(0.31 mmol)	bisoxazoline **23**
0.17 mL	(0.31 mmol)	LDA (1.8 M)
40 mg	(0.070 mmol)	{G0}-($SiMe_2Cl$)$_4$
108 mg	(0.31 mmol)	$TlPF_6$

Product: pale yellow, viscous oil (29 mg, 22%)



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^{1}H NMR (600.13 MHz, $CDCl_3$, 293 K):

δ 7.36-7.26 (m, 40H, C***H***$_{aryl}$), 5.25 (m, 8H, NC***H***), 4.68 (m, 8H, C***H***$_2$O), 4.14 (m, 8H, C***H***$_2$O), 3.13 (d, ^2J = 16.90 Hz, 4H, C***H***$_2$C≡C), 3.03 (d, ^2J = 16.90 Hz, 4H, C***H***$_2$C≡C), 1.80 (s, 12H, CC***H***$_3$), 1.38 (m, 8H, ***H***$_c$), 0.69 (m, 8H, ***H***$_b$), 0.59 (m, 8H, ***H***$_d$), 0.14 (s, 24H, ***H***$_a$).

^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 293 K):

δ 168.44/168.38 (N***C***O), 142.23/142.07 (***C***$_{q,\ aryl}$), 128.65/127.54/126.75/126.62 (***C***$_{aryl}$), 102.44 (***C***≡C-Si), 87.15 (C≡***C***-Si), 75.63/75.58 (***C***H_2O), 69.72/69.50 (N***C***H), 42.26 (***C***CH_3), 28.50 (***C***H_2C≡C), 21.43 (C***C***H_3), 21.09 (***C***$_b$), 18.38 (***C***$_c$), 17.06 (***C***$_d$), -1.52 (***C***$_a$).

^{29}Si{^{1}H} NMR (79.44 MHz, $CDCl_3$, 293 K):

δ 0.89 (***Si***$(CH_2)_4$), -17.68 (***Si***$(CH_3)_2$).

IR (KBr):

$\tilde{\nu}$ [cm^{-1}] = 3086-3030 (w, $\nu_{C\text{-}H(aryl)}$), 2960-2875 (s, $\nu_{C\text{-}H(aliphat)}$), 2177 (w, $\nu_{C\equiv C}$), 1662 (s, $\nu_{C=N}$).

MS (Maldi):

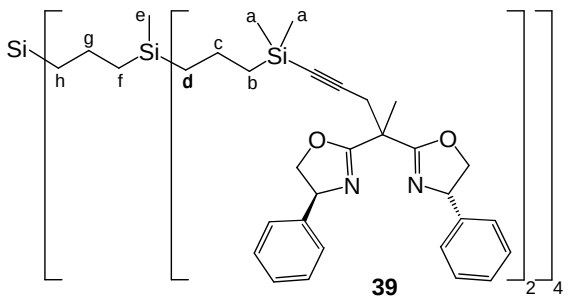
m/z = 1858 (73%) $[M+H]^+$, 1618 (5%) $[(M+H)\text{-}C_{16}H_{16}O_2]^+$; **HRMS (Maldi):** m/z = 1857.9106, calcd. for $C_{112}H_{133}N_8O_8Si_5$ $[M+H]^+$: 1857.9087.

7.3.4.5 {G1}-[propargyl-Box(Ph)]$_8$ (39)

Reagents:

82 mg	(0.23 mmol)	bisoxazoline **23**
0.13 mL	(0.23 mmol)	LDA (1.8 M)
28 mg	(0.019 mmol)	{G1}-($SiMe_2Cl$)$_8$
80 mg	(0.23 mmol)	$TlPF_6$

Product: pale yellow, viscous oil (40 mg, 52%)



39

^{1}H NMR (600.13 MHz, $CDCl_3$, 293 K):

δ 7.35-7.25 (m, 80H, C***H***$_{aryl}$), 5.23 (m, 16H, NC***H***), 4.67 (m, 16H, C***H***$_2$O), 4.13 (m, 16H, C***H***$_2$O), 3.12 (d, ^2J = 16.88 Hz, 8H, C***H***$_2$C≡C), 3.02 (d, ^2J = 16.85 Hz, 8H, C***H***$_2$C≡C), 1.79 (s, 24H, CC***H***$_3$), 1.38 (m, 24H, ***H***$_c$, ***H***$_g$), 0.68 (m, 16H, ***H***$_b$), 0.63-0.49 (m, 32H, ***H***$_d$, ***H***$_f$, ***H***$_h$), 0.13 (s, 48H, ***H***$_a$), -0.07 (s, 12H, ***H***$_e$).

^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 293 K):

δ 168.33 (N***C***O), 142.33/142.11 (***C***$_{q, aryl}$), 128.66/127.55/126.76/126.63 (***C***$_{aryl}$), 102.36 (***C***≡C-Si), 87.12 (C≡***C***-Si), 75.63 (***C***H$_2$O), 70.41 (N***C***H), 42.41 (***C***CH$_3$), 28.47 (***C***H$_2$C≡C), 21.44 (C***C***H$_3$), 21.09 (***C***$_b$), 18.63 (***C***$_d$, ***C***$_f$, ***C***$_h$), 18.28 (***C***$_c$, ***C***$_g$), -1.46 (***C***$_a$), -4.93 (***C***$_e$).

^{29}Si{^{1}H} NMR (79.44 MHz, $CDCl_3$, 293 K):

δ 1.05 (***Si***(CH$_2$)$_3$CH$_3$), 0.44 (***Si***(CH$_2$)$_4$), -17.64 (***Si***(CH$_3$)$_2$).

IR (KBr):

$\tilde{\nu}$ [cm^{-1}] = 3086-3030 (w, $\nu_{C\text{-}H(aryl)}$), 2956-2874 (s, $\nu_{C\text{-}H(aliphat)}$), 2177 (w, $\nu_{C\equiv C}$), 1655 (s, $\nu_{C=N}$).

MS (Maldi-TOF):

m/z = 4051 (100%) [M+Na]$^+$, 4029 (71%) [M+H]$^+$, 3707 (37%) [M-$C_{20}H_{19}N_2O_2$]$^+$, 3028 (28%) [(M+H)-$C_{60}H_{75}N_4O_4Si_3$]$^+$; **MS (Maldi-TOF):** m/z = 2038 (98%) [M+2Na]$^{2+}$.

Elemental Analysis:

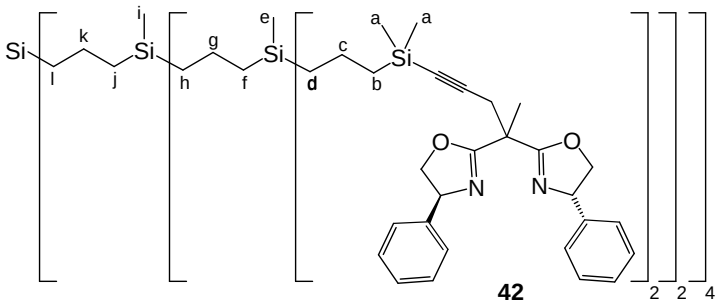
anal. calcd. for $C_{240}H_{300}N_{16}O_{16}Si_{13}$ (4030.16) • 0.8 $TlPF_6$: C 66.83, H 6.99, N 5.22; found C 66.81, H 6.75, N 4.90.

7.3.4.6 {G2}-[propargyl-Box(Ph)]$_{16}$ (42)

Reagents:

101 mg	(0.28 mmol)	bisoxazoline **23**
0.16 mL	(0.28 mmol)	LDA (1.8 M)
32 mg	(0.010 mmol)	{G2}-($SiMe_2Cl$)$_{16}$
60 mg	(0.17 mmol)	$TlPF_6$

Product: pale yellow, viscous oil (41 mg, 49%)



42

^{1}H NMR (600.13 MHz, $CDCl_3$, 293 K):

δ 7.36-7.18 (m, 160H, C***H***$_{aryl}$), 5.22 (m, 32H, NC***H***), 4.65 (m, 32H, C***H***$_2$O), 4.11 (m, 32H, C***H***$_2$O), 3.11 (d, ^2J = 16.73 Hz, 16H, C***H***$_2$C≡C), 3.00 (d, ^2J = 16.69 Hz, 16H, C***H***$_2$C≡C), 1.77

(s, 48H, CC$\boldsymbol{H}_3$), 1.44-1.31 (m, 56H, $\boldsymbol{H}_c$, $\boldsymbol{H}_g$, $\boldsymbol{H}_k$), 0.71-0.63 (m, 32H, $\boldsymbol{H}_b$), 0.63-0.44 (m, 80H, $\boldsymbol{H}_d$, $\boldsymbol{H}_f$, $\boldsymbol{H}_h$, $\boldsymbol{H}_j$, $\boldsymbol{H}_l$), 0.12 (s, 96H, $\boldsymbol{H}_a$), -0.09 (s, 36H, $\boldsymbol{H}_e$, $\boldsymbol{H}_i$).

^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 293 K):

δ 168.40 (N$\boldsymbol{C}$O), 142.22/142.06 ($\boldsymbol{C}_{q,\ aryl}$), 128.65/127.55/126.75/126.62 ($\boldsymbol{C}_{aryl}$), 102.45 ($\boldsymbol{C}$≡C-Si), 87.13 (C≡$\boldsymbol{C}$-Si), 75.64/75.59 ($\boldsymbol{C}H_2O$), 69.71/69.50 (N$\boldsymbol{C}$H), 42.26 ($\boldsymbol{C}CH_3$), 28.50 ($\boldsymbol{C}H_2C{\equiv}C$), 21.45 (C$\boldsymbol{C}H_3$), 20.96 ($\boldsymbol{C}_b$), 19.03 ($\boldsymbol{C}_d$, $\boldsymbol{C}_f$, $\boldsymbol{C}_h$, $\boldsymbol{C}_j$, $\boldsymbol{C}_l$), 18.35 ($\boldsymbol{C}_c$, $\boldsymbol{C}_g$, $\boldsymbol{C}_k$), -1.46 ($\boldsymbol{C}_a$), -5.03 ($\boldsymbol{C}_e$, $\boldsymbol{C}_i$).

^{29}Si{^{1}H} NMR (79.44 MHz, $CDCl_3$, 293 K):

δ 1.03/0.82 ($\boldsymbol{Si}(CH_2)_3CH_3$), 0.40 ($\boldsymbol{Si}(CH_2)_4$), -17.65 ($\boldsymbol{Si}(CH_3)_2$).

IR (KBr):

$\tilde{\nu}$ [cm^{-1}] = 3086-3031 (w, $\nu_{C\text{-}H(aryl)}$), 2956-2877 (s, $\nu_{C\text{-}H(aliphat)}$), 2177 (w, $\nu_{C\equiv C}$), 1655 (s, $\nu_{C=N}$).

Elemental Analysis:

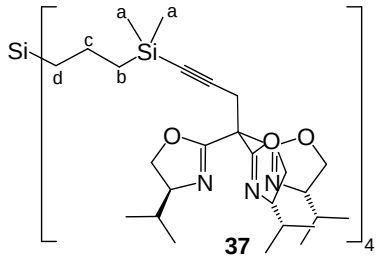
anal. calcd. for $C_{496}H_{636}N_{32}O_{32}Si_{29}$ (8373.03) • 1.4 $TlPF_6$: C 67.22, H 7.23, N 5.06; found C 67.06, H 7.21, N 5.19.

7.3.4.7 {G0}-[propargyl-Trisox(^{i}Pr)]$_4$ (37)

Reagents:

140 mg	(0.36 mmol)	trisoxazoline **24**
0.20 mL	(0.36 mmol)	LDA (1.8 M)
43 mg	(0.075 mmol)	{G0}-$(SiMe_2Cl)_4$
126 mg	(0.36 mmol)	$TlPF_6$

Product: brownish orange, viscous oil (49 mg, 33%)



37

^{1}H NMR (600.13 MHz, $CDCl_3$, 293 K):

δ 4.23 (m, 12H, C$\boldsymbol{H}_2$O), 4.05 (m, 12H, C$\boldsymbol{H}_2$O), 3.99 (td, ^3J = 9.10 Hz, ^3J = 6.95 Hz, 12H, NC$\boldsymbol{H}$), 3.30 (d, ^2J = 16.72 Hz, 4H, C$\boldsymbol{H}_2$C≡C), 3.07 (d, ^2J = 16.77 Hz, 4H, C$\boldsymbol{H}_2$C≡C), 1.79 (m, 12H, C$\boldsymbol{H}(CH_3)_2$), 1.30 (m, 8H, $\boldsymbol{H}_c$), 0.91 (d, ^3J = 6.62 Hz, 36H, CH(C$\boldsymbol{H}_3)_2$), 0.86 (d, ^3J = 6.61 Hz, 36H, CH(C$\boldsymbol{H}_3)_2$), 0.62 (m, 8H, $\boldsymbol{H}_b$), 0.52 (m, 8H, $\boldsymbol{H}_d$), 0.05 (s, 12H, $\boldsymbol{H}_a$), 0.04 (s, 12H, $\boldsymbol{H}_a$).

^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 293 K):

δ 162.44 (N$\boldsymbol{C}$O), 102.50 ($\boldsymbol{C}$≡C-Si), 85.57 (C≡$\boldsymbol{C}$-Si), 71.80 (N$\boldsymbol{C}$H), 70.55 ($\boldsymbol{C}H_2O$), 47.98 ($\boldsymbol{C}CH_2C{\equiv}C$), 32.40 ($\boldsymbol{C}H(CH_3)_2$), 26.73 ($\boldsymbol{C}H_2C{\equiv}C$), 21.14 ($\boldsymbol{C}_b$), 18.58 (CH($\boldsymbol{C}H_3)_2$), 18.24 ($\boldsymbol{C}_c$), 17.93 (CH($\boldsymbol{C}H_3)_2$), 17.17 ($\boldsymbol{C}_d$), -1.70 ($\boldsymbol{C}_a$).

^{29}Si{^{1}H} NMR (79.44 MHz, $CDCl_3$, 293 K):

δ 0.73 (***Si***$(CH_2)_4$), -18.29 (***Si***$(CH_3)_2$).

IR (KBr):

$\tilde{\nu}$ [cm^{-1}] = 2961-2877 (s, $\nu_{C\text{-}H(aliphat)}$), 2181 (w, $\nu_{C\equiv C}$), 1669 (s, $\nu_{C=N}$), 1666 (s, $\nu_{C=N}$).

MS (Maldi):

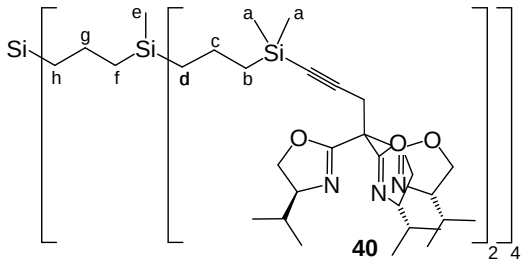
m/z = 1974 (39%) $[M+H]^+$, 1863 (75%) $[(M+H)\text{-}C_6H_{10}NO]^+$; **HRMS (Maldi):** m/z = 1974.2461, calcd. for $C_{108}H_{177}N_{12}O_{12}Si_5$ $[M+H]^+$: 1974.2450.

7.3.4.8 {G1}-[propargyl-Trisox(^{i}Pr)]$_8$ (40)

Reagents:

68 mg	(0.18 mmol)	trisoxazoline **24**
0.10 mL	(0.18 mmol)	LDA (1.8 M)
21 mg	(0.014 mmol)	{G1}-$(SiMe_2Cl)_8$
63 mg	(0.18 mmol)	$TlPF_6$

Product: brownish orange, viscous oil (32 mg, 54%)



^{1}H NMR (600.13 MHz, $CDCl_3$, 293 K):

δ 4.21 (m, 24H, C***H***$_2$O), 4.02 (m, 24H, C***H***$_2$O), 3.95 (td, ^3J = 9.37 Hz, ^3J = 6.85 Hz, 24H, NC***H***), 3.28 (d, ^2J = 16.73 Hz, 8H, C***H***$_2$C≡C), 3.05 (d, ^2J = 16.72 Hz, 8H, C***H***$_2$C≡C), 1.74 (m, 24H, C***H***$(CH_3)_2$), 1.29 (m, 24H, ***H***$_c$, ***H***$_g$), 0.88 (d, ^3J = 6.73 Hz, 72H, CH(C***H***$_3)_2$), 0.83 (d, ^3J = 6.72 Hz, 72H, CH(C***H***$_3)_2$), 0.59 (m, 16H, ***H***$_b$), 0.49 (m, 32H, ***H***$_d$, ***H***$_f$, ***H***$_h$), 0.03 (s, 48H, ***H***$_a$), 0.01 (s, 12H, ***H***$_e$).

^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 293 K):

δ 162.48 (N***C***O), 102.54 (***C***≡C-Si), 85.58 (C≡***C***-Si), 71.82 (N***C***H), 70.58 (***C***H_2O), 48.01 (***C***CH_2C≡C), 32.43 (***C***$H(CH_3)_2$), 26.78 (***C***H_2C≡C), 21.03 (***C***$_b$), 18.61 (CH(***C***$H_3)_2$), 18.54 (***C***$_d$, ***C***$_f$, ***C***$_h$), 18.24 (***C***$_c$, ***C***$_g$), 17.96 (CH(***C***$H_3)_2$), -1.60 (***C***$_a$), -5.00 (***C***$_e$).

^{29}Si{^{1}H} NMR (79.44 MHz, $CDCl_3$, 293 K):

δ 1.05 (***Si***$(CH_2)_3CH_3$), 0.53 (***Si***$(CH_2)_4$), -18.22 (***Si***$(CH_3)_2$).

IR (KBr):

$\tilde{\nu}$ [cm^{-1}] = 2961-2876 (s, $\nu_{C\text{-}H(aliphat)}$), 2182 (w, $\nu_{C\equiv C}$), 1665 (s, $\nu_{C=N}$), 1660 (s, $\nu_{C=N}$).

MS (Maldi-TOF):

m/z = 4327 (<1%) $[M+C_2H_8O_2]^+$, 3201 (<1%) $[M\text{-}C_{58}H_{97}N_6O_6Si_3]^+$.

Elemental Analysis:

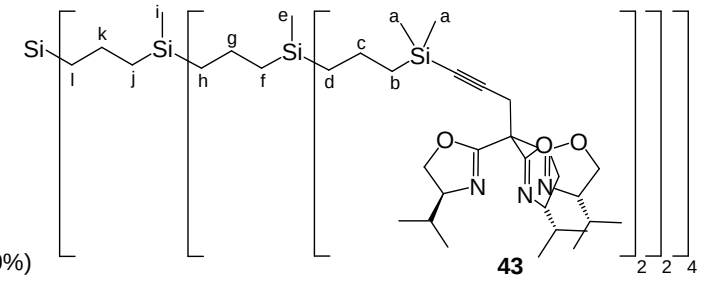
anal. calcd. for $C_{232}H_{388}N_{24}O_{24}Si_{13}$ (4262.82) • 0.7 $TlPF_6$: C 62.30, H 8.74, N 7.52; found C 62.04, H 8.82, N 7.34.

7.3.4.9 {G2}-[propargyl-Trisox(^{i}Pr)]$_{16}$ (43)

Reagents:

91 mg	(0.23 mmol)	trisoxazoline **24**
0.13 mL	(0.23 mmol)	LDA (1.8 M)
32 mg	(0.010 mmol)	{G2}-$(SiMe_2Cl)_{16}$
60 mg	(0.17 mmol)	$TlPF_6$

Product: brownish orange, viscous oil (44 mg, 50%)



43

^{1}H NMR (600.13 MHz, $CDCl_3$, 293 K):

δ 4.25 (m, 48H, C***H***$_2$O), 4.06 (m, 48H, C***H***$_2$O), 3.98 (td, ^3J = 9.09 Hz, ^3J = 6.86 Hz, 48H, NC***H***), 3.31 (d, ^2J = 16.76 Hz, 16H, C***H***$_2$C≡C), 3.09 (d, ^2J = 16.83 Hz, 16H, C***H***$_2$C≡C), 1.82-1.74 (m, 48H, C***H***$(CH_3)_2$), 1.38-1.28 (m, 56H, ***H***$_c$, ***H***$_g$, ***H***$_k$), 0.92 (d, ^3J = 6.74 Hz, 144H, CH(C***H***$_3)_2$), 0.87 (d, ^3J = 6.71 Hz, 144H, CH(C***H***$_3)_2$), 0.65-0.59 (m, 32H, ***H***$_b$), 0.57-0.46 (m, 80H, ***H***$_d$, ***H***$_f$, ***H***$_h$, ***H***$_j$, ***H***$_l$), 0.06 (s, 96H, ***H***$_a$), -0.09 (s, 24H, ***H***$_e$), -0.10 (s, 12H, ***H***$_i$).

^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 293 K):

δ 162.45 (N***C***O), 102.51 (***C***≡C-Si), 85.54 (C≡***C***-Si), 71.81 (N***C***H), 70.56 (***C***H_2O), 47.97 (***C***CH_2C≡C), 32.43 (***C***$H(CH_3)_2$), 26.74 (***C***H_2C≡C), 21.02 (***C***$_b$), 18.62 (CH(***C***$H_3)_2$), 18.51 (***C***$_d$, ***C***$_f$, ***C***$_h$, ***C***$_j$, ***C***$_l$), 18.24 (***C***$_c$, ***C***$_g$, ***C***$_k$), 17.98 (CH(***C***$H_3)_2$), -1.59 (***C***$_a$), -5.03 (***C***$_e$), -5.04 (***C***$_i$).

^{29}Si{^{1}H} NMR (79.44 MHz, $CDCl_3$, 293 K):

δ 1.03/0.82 (***Si***$(CH_2)_3CH_3$), 0.40 (***Si***$(CH_2)_4$), -17.65 (***Si***$(CH_3)_2$).

IR (KBr):

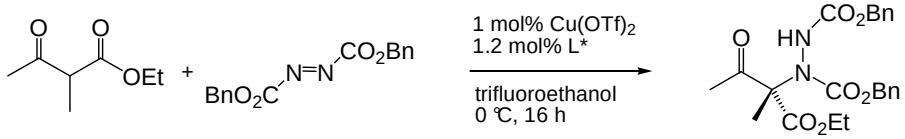
$\tilde{\nu}$ [cm^{-1}] = 2961-2877 (s, $\nu_{C\text{-}H(aliphat)}$), 2182 (w, $\nu_{C\equiv C}$), 1669 (s, $\nu_{C=N}$), 1665 (s, $\nu_{C=N}$).

Elemental Analysis:

anal. calcd. for $C_{480}H_{812}N_{48}O_{48}Si_{29}$ (8838.36) • 0.7 $TlPF_6$: C 63.47, H 9.01, N 7.40; found C 63.26, H 9.02, N 7.65.

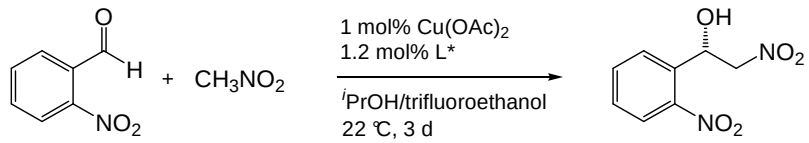
7.3.5 Comparative catalytic studies

7.3.5.1 α-Hydrazination of ethyl 2-methylacetoacetate – General procedure



Stock solutions of $Cu(OTf)_2$ (10.9 mg) and of the corresponding ligand or functionalised dendrimer (respective amount) in MeOH (1.00 mL) were prepared under air. Successive aliquots of both homogeneous solutions (containing 1.5 µmol of $Cu(OTf)_2$ and 1.8 µmol of the corresponding ligand species) were taken and reacted for 1 h to obtain the catalyst for each run. The resulting turquoise to light green solution was evaporated to dryness (30 min) and the complex redissolved in trifluoroethanol (1.00 mL). Ethyl 2-methylacetoacetate (21.5 µL, 0.15 mmol) was added to the solution prior to cooling to 0 °C followed by addition of a precooled solution of dibenzylazodicarboxylate (54.7 mg, 0.18 mmol) in trifluoroethanol (0.50 mL). After 16 h at 0 °C, the products were isolated by flash column chromatography (pentane/EtOAc 80:20). The enantioselectivity of the product was determined by HPLC, using a Daicel Chiralpak AD-H column (hexane/^{i}PrOH 90:10, 82 bar, 10 µL, 0.95 mL/min, detection 213 nm, 225 nm, 254 nm, t_R(maj) = 33.0 min, t_R(min) = 36.3 min). All given values were determined as average of three catalytic runs.

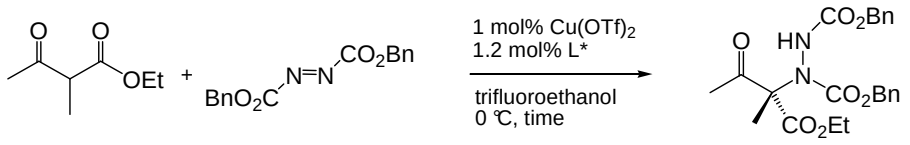
7.3.5.2 Henry reaction of nitromethane and 2-nitrobenzaldehyde – General procedure



Stock solutions of $Cu(OAc)_2$ hydrate (9 mg) in MeOH (1.50 mL) and of the corresponding ligand or functionalised dendrimer (respective amount) in MeOH (1.00 mL) were prepared under air. Successive aliquots of both homogeneous solutions (containing 1.5 µmol of $Cu(OAc)_2$ hydrate and 1.8 µmol of the corresponding ligand species) were taken and reacted for 1 h to obtain the catalyst for each run. The resulting green solution was evaporated to dryness (30 min) and the complex redissolved in trifluoroethanol/^{i}PrOH 2:1

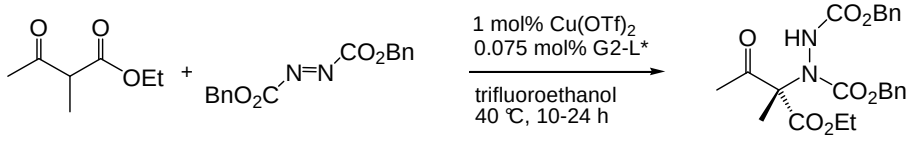
(1.00 mL) prior to the addition of nitromethane (410 µL) and a solution of 2-nitro-benzaldehyde (22.7 mg, 0.15 mmol) in trifluoroethanol/^{i}PrOH 2:1 (0.50 mL). The resulting brownish solution was stirred at 23 °C for 3 days. Then, the mixture was filtered through a small pad of silica gel to remove the catalyst. The solvent was removed *in vacuo* and the product was isolated *via* flash column chromatography (pentane/EtOAc 80:20). The enantioselectivity of the product was determined by HPLC, using a Daicel Chiralpak OD-H column (hexane/^{i}PrOH 90:10, 64 bar, 10 µL, 0.8 mL/min, detection 225 nm, 254 nm, t_R(min) = 17.8 min, t_R(maj) = 19.6 min). All given values were determined as average of at least two catalytic runs.

7.3.5.3 Monitoring of conversion curves – General procedure for the α-hydrazination



Catalyses were conducted like mentioned above. The progress of the reaction was monitored by measuring the disappearance of ethyl 2-methylacetoacetate *via* GC, using methyl hexanoate as internal standard. The following GC method was applied: T_{inj} = 200 °C, T_{det} = 250 °C, 20 mL/min He flow, splitless, temperature program: 40 °C, 1 min, 25 °C/min up to 270 °C, 270 °C, 2 min; t_R (methyl hexanoate) = 4.3 min, t_R (substrate) = 4.9 min.

7.3.5.4 Recycling study – General procedure for the α-hydrazination



Membrane pieces of identical length (6.5 cm) were washed with trifluoroethanol (4x). In the meantime, stock solutions of $Cu(OTf)_2$ (10.9 mg) and {G2}-[propargyl-Box(Ph)]$_{16}$ or {G2}-[propargyl-Trisox(^{i}Pr)]$_{16}$ (respective amount) in MeOH (1.00 mL) were prepared under air. Successive aliquots of both homogeneous solutions (containing 1.5 µmol of $Cu(OTf)_2$ and 0.11 µmol of the corresponding dendrimer) were taken and reacted for 1 h to obtain

the catalyst for each run. The solvent was removed *in vacuo* (30 min). Then, the residue was redissolved in trifluoroethanol (5 mL) and transferred into the membrane. The resulting bag was put into a screw cap vial and gently stirred in pure trifluoroethanol (10 mL) at 40 °C for 10 h. It was transferred into a screw cap vial containing a solution of ethyl 2-methylacetoacetate (21.5 μL, 0.15 mmol) and dibenzylazodicarboxylate (54.7 mg, 0.18 mmol) in trifluoroethanol (10 mL). The reaction was allowed to proceed for the appropriate time (10 h with ({G2}-[propargyl-Box(Ph)]$_{16}$, 24 h with {G2}-[propargyl-Trisox(^{i}Pr)]$_{16}$) at 40 °C. Then, the bag was directly transferred into another vial containing a fresh solution of substrates for the next run whereas the solution from the preceding run was concentrated *in vacuo*. Isolation of the product was provided by flash column chromatography (pentane/EtOAc 80:20). The enantioselectivity of the product was determined by HPLC, using a Daicel Chiralpak AD-H column (hexane/^{i}PrOH 90:10, 82 bar, 10 μL, 0.95 mL/min, detection 213 nm, 225 nm, 254 nm, t_R(maj) = 33.0 min, t_R(min) = 36.3 min). Values given for each run were determined as average of at least five catalytic runs.

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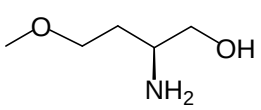
Appendix

Molecular structures



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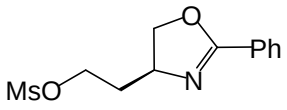

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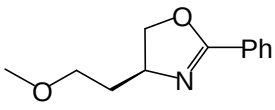

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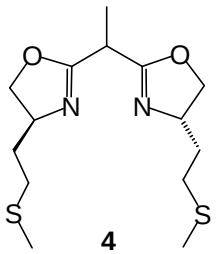

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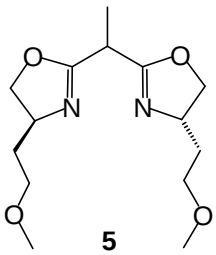

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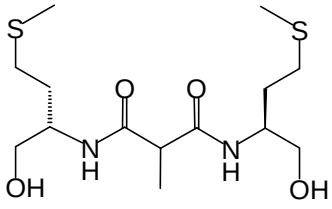

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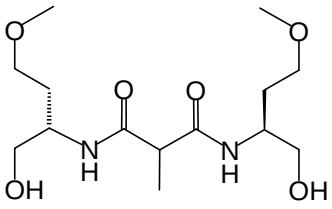

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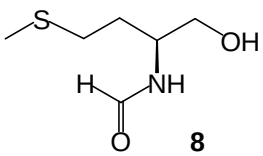

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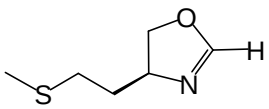

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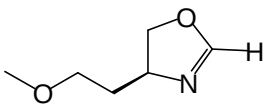

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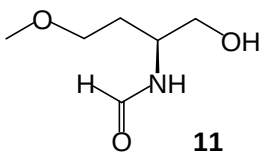

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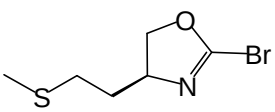

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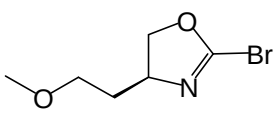

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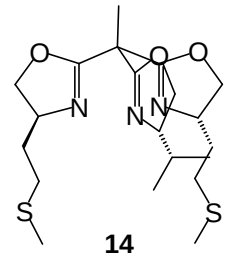

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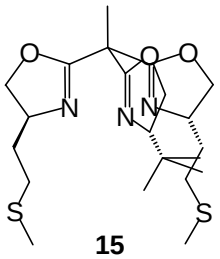

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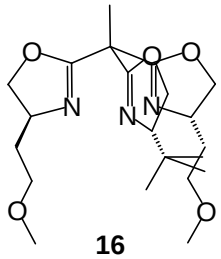

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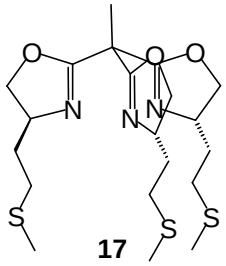

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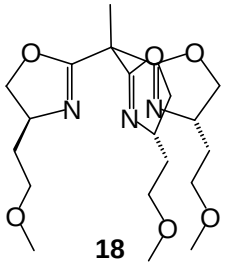

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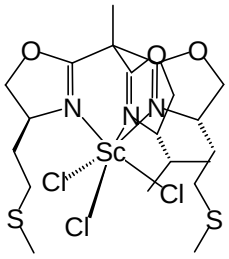

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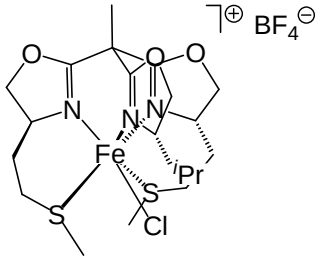

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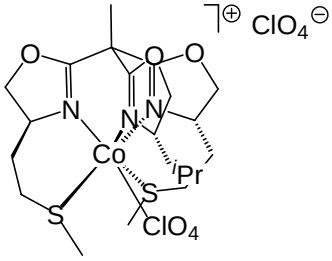

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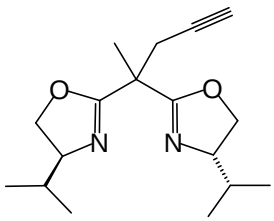

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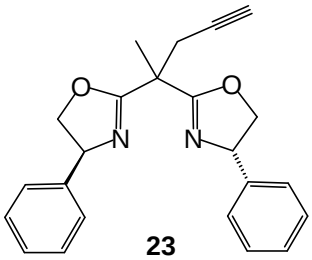

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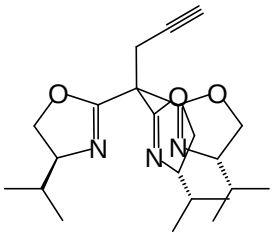

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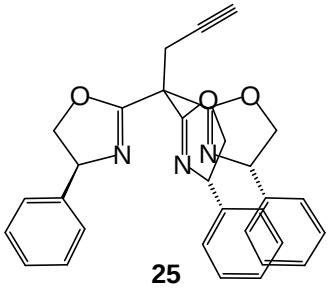

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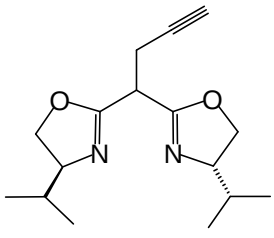

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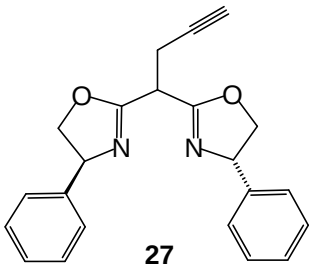

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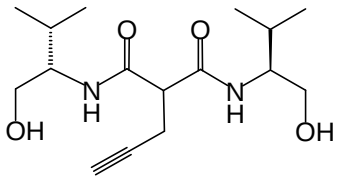

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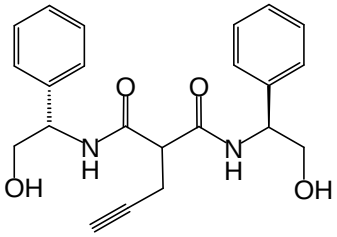

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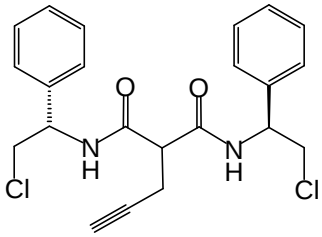

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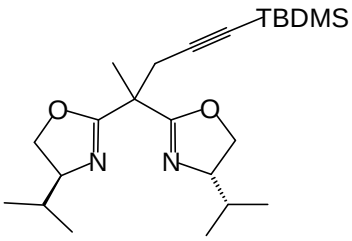

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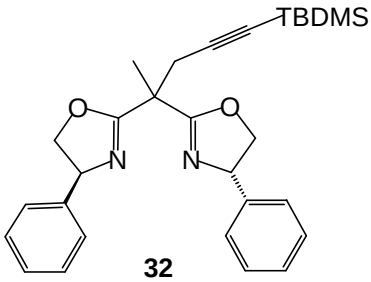

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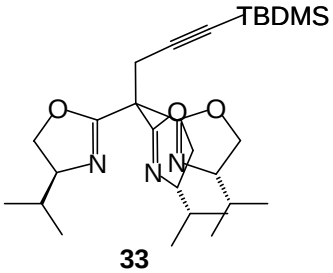

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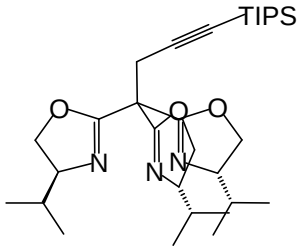

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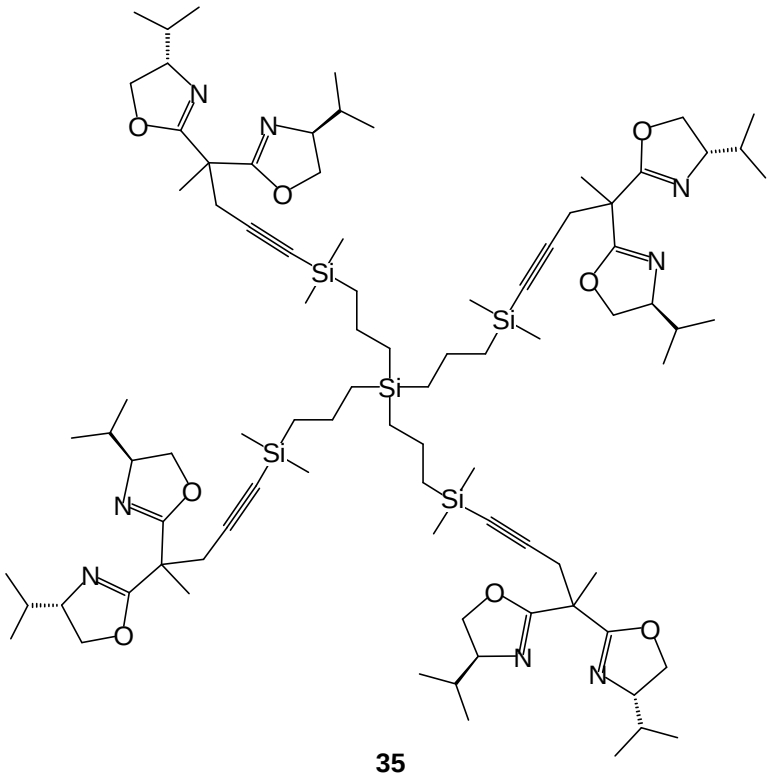

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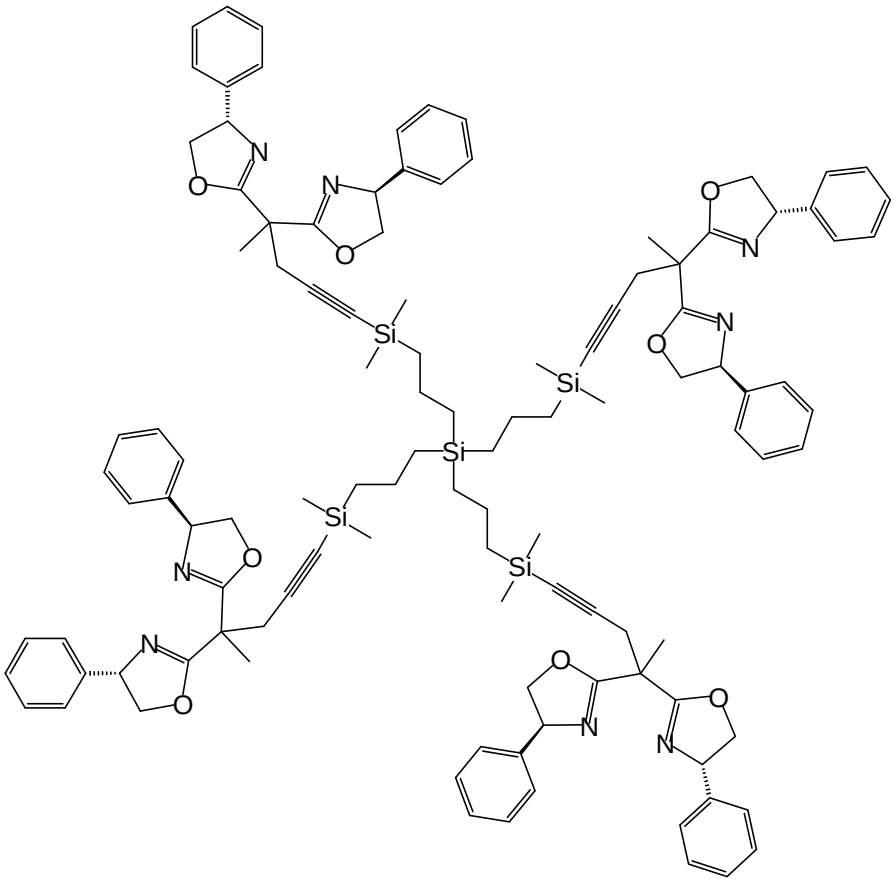

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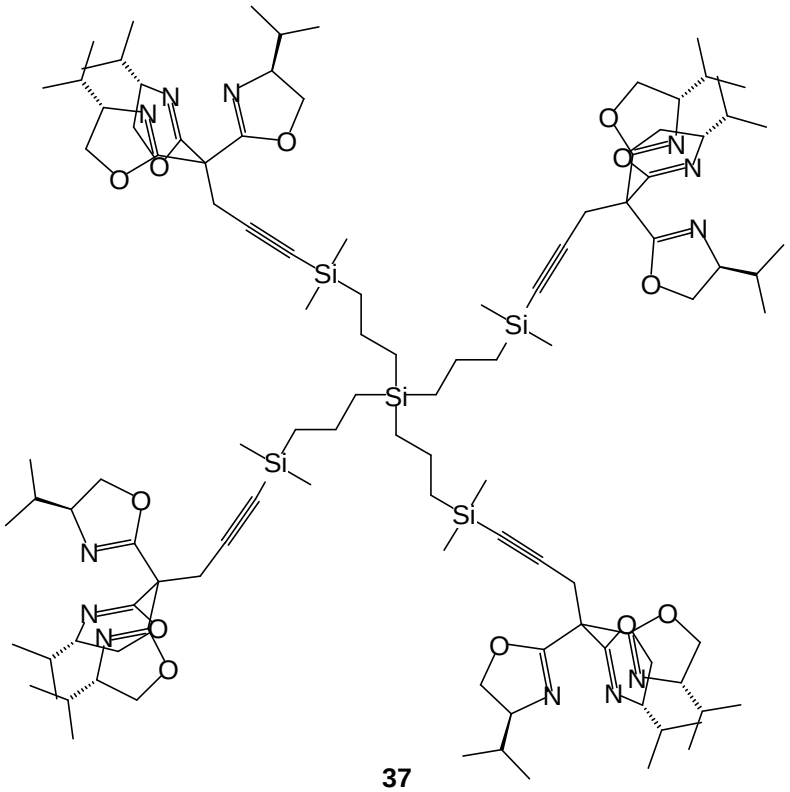

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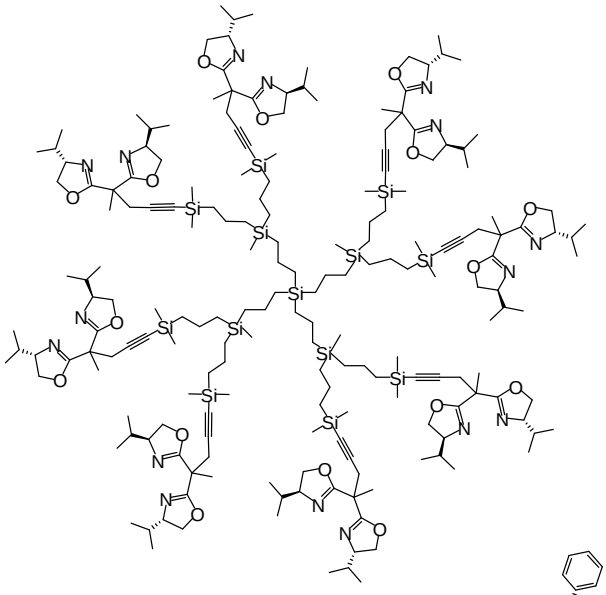

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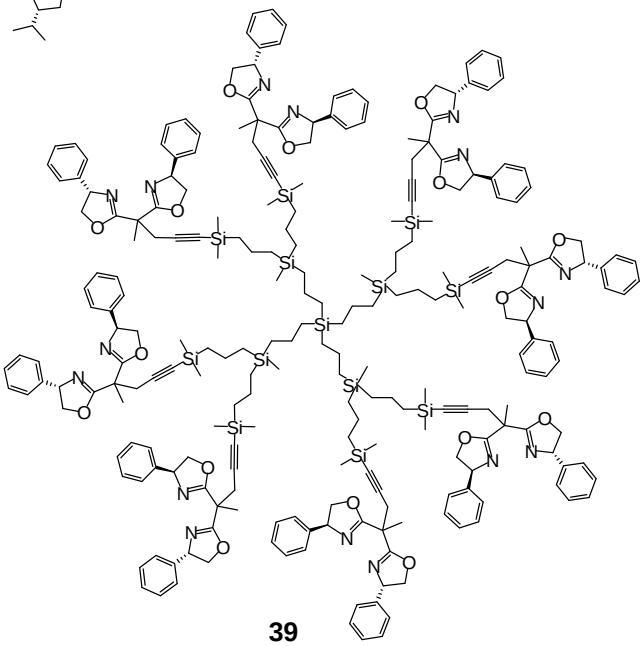

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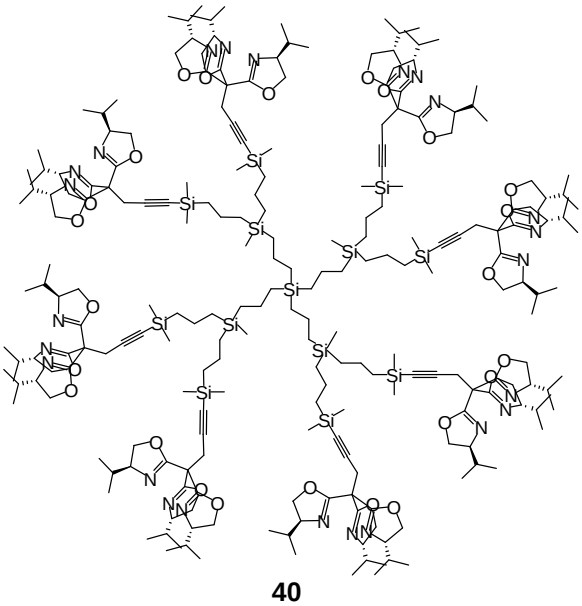

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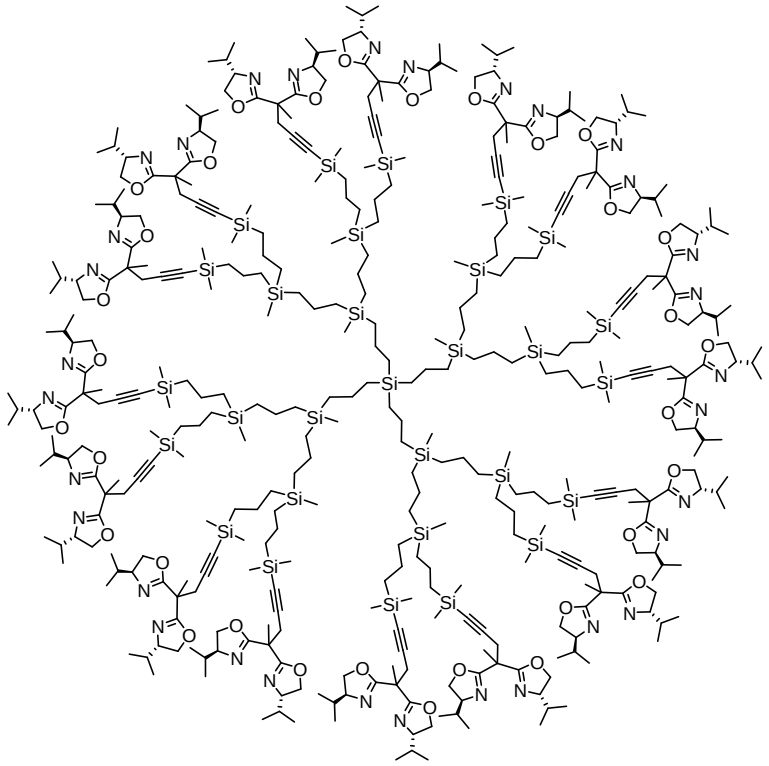

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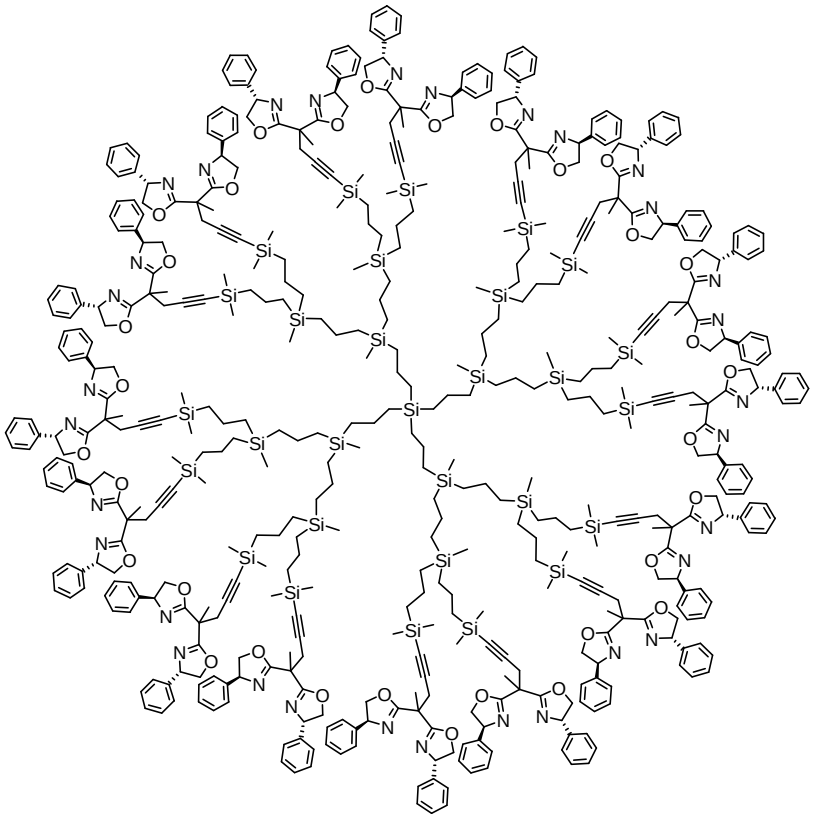

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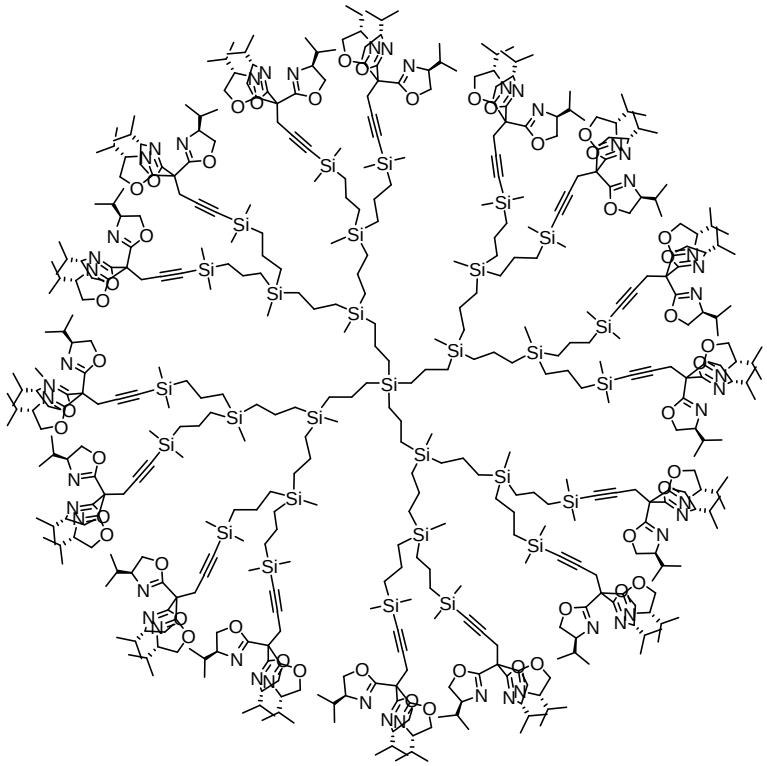

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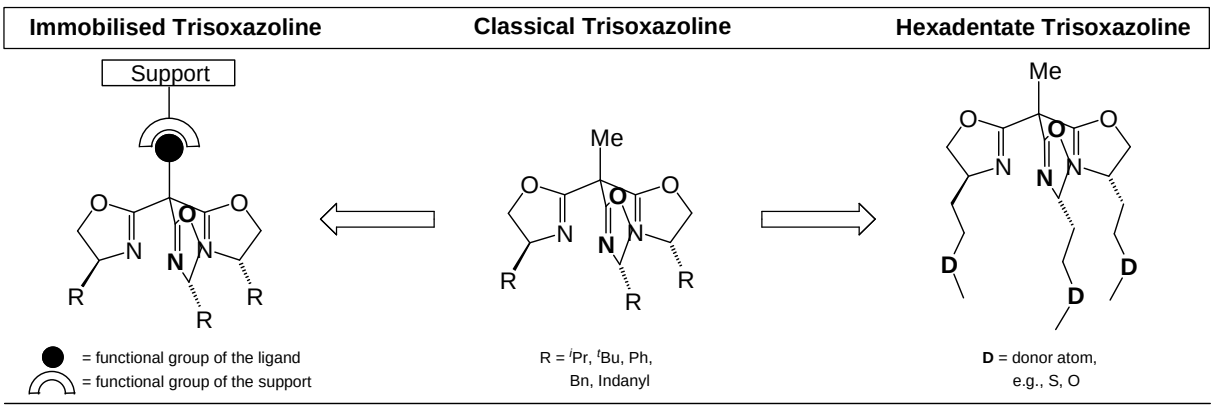
Trisoxazolines de seconde Génération :

Nouveaux ligands multidentates et dendritiques recyclables pour la catalyse asymétrique.

Au cours des 3 dernières décennies, le développement d'un grand nombre de catalyseurs moléculaires a aidé à résoudre un des problèmes clés de la synthèse organique : la formation stéréosélective de liaisons chimiques. Parmi toutes ces avancées, l'oxazoline est devenue une structure privilégiée pour la découverte de nouveaux ligands pour la catalyse asymétrique. Dans cette famille, les dérivés de type 1,1,1-tris(oxazolinyl)éthane (« trisoxazoline ») sont apparus très récemment et se sont avérés très prometteurs. En catalyse énantiosélective, ils donnent de meilleurs résultats que leurs équivalents de type bidentates tels que les bisoxazolines. En effet, ces nouveaux ligands possèdent la géometrie la plus adaptée pour coordiner un métal de façon tridentate et ceci peut être bénéfique dans certains cas.

SCHEMA 1 Structure générale des ligands.



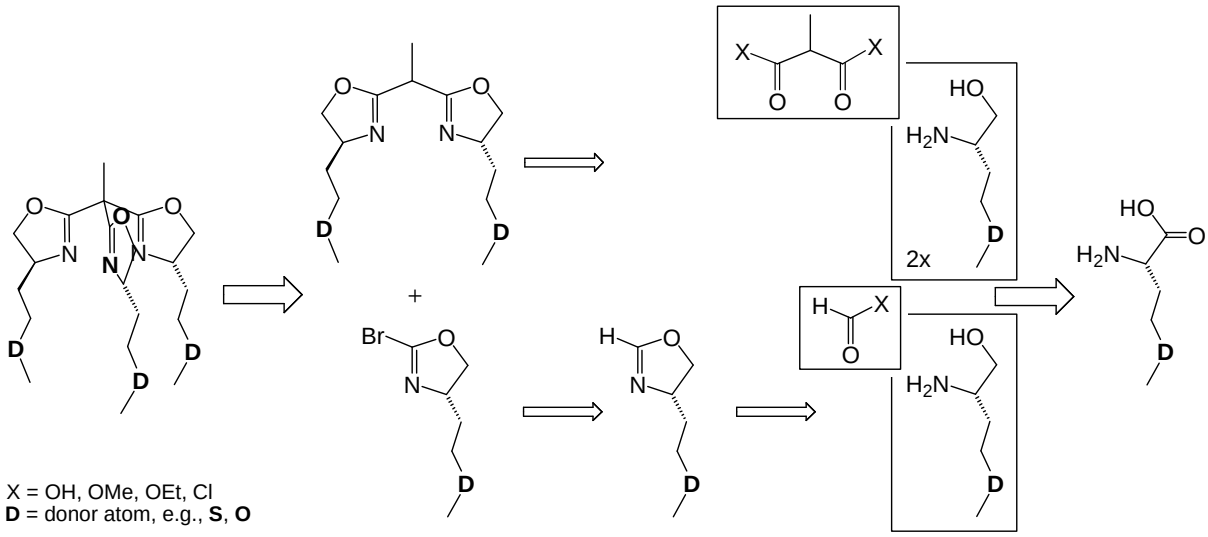
Le but de ce travail a été de concevoir une nouvelle génération de ligands trisoxazoline en greffant notamment des fonctions à la périphérie du squelette (Schéma 1), et ce pour

une application plus étendue et plus économique. Plus précisément, nous avions comme objectif d'introduire des hétéroatomes donneurs supplémentaires qui permettraient la coordination de métaux labiles et de métaux préférant un nombre de coordination élevé. De plus, la création de dérivés trisoxazolines greffés sur un support a été envisagée, cela pour permettre un recyclage des catalyseurs par le biais de l'utilisation de membranes. La question centrale était de déterminer le potentiel de cette dernière approche et l'influence du support sur le comportement des catalyseurs de la famille des oxazolines en catalyse asymétrique.

1 Trisoxazolines penta- et hexadentates

La synthèse des nouveaux ligands de type trisoxazolines est basée sur la méthode mise au point au sein de notre groupe. Cette approche est basée sur le couplage entre une bisoxazoline lithiée et une 2-bromooxazoline. Ces deux unités elles-mêmes sont accessibles par la réaction des alcools aminés chiraux correspondants avec des dérivés d'acide carboxylique (Schéma 2).

SCHEMA 2 Rétrosynthèse générale des trisoxazolines.



Un des problèmes principaux de la synthèse de ces ligands multidentates était la création des précurseurs hautement fonctionnalisés. En conséquence, une synthèse à partir de l'acide aspartique a été mise au point et, en principe, permet l'introduction de divers

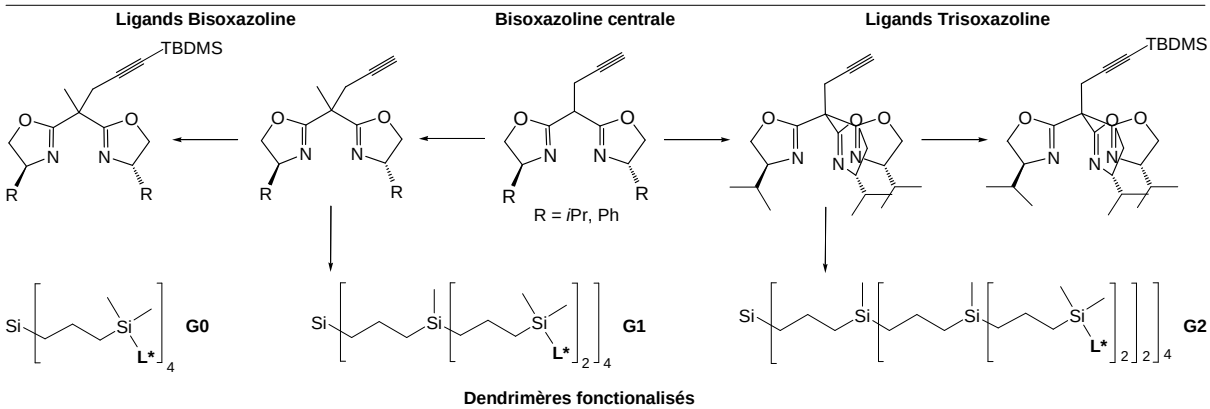
substituants à la périphérie de l'alcool aminé. Dans ce cas, la synthèse de (*S*)-2-amino-4-méthoxybutan-1-ol a été effectuée. Le deuxième problème était l'adaptation de la synthèse générale des trisoxazolines aux exigences des substituants polaires et hydrophiles. Ainsi, deux ligands trisoxazolines hexadentates de symétrie C_3 (contenant trois atomes donneurs supplementaires de soufre ou d'oxygène) et trois ligands pentadentates de symétrie C_1 ont été synthétisés.

2 Oxazolines dendritiques

2.1 Synthèse

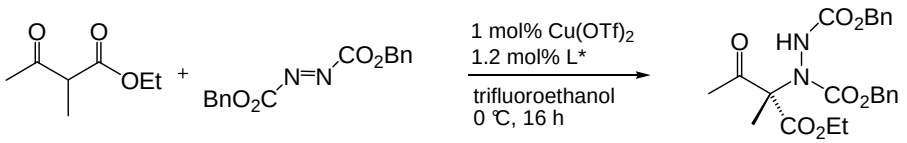
En utilisant la stratégie synthétique décrite ci-dessus, quatre ligands bisoxazoline et trisoxazoline fonctionalisés par un groupement propargylique ont pu être synthétisés. Trois d'entre eux ont été utilisés pour la synthèse de systèmes modèles fonctionalisés par TBDMS, *via* déprotonation et substitution nucléophile. Par une approche similaire, ils ont été immobilisés avec succès sur des dendrimères {G0}-$(SiMe_2Cl)_4$, {G1}-$(SiMe_2Cl)_8$ et {G2}-$(SiMe_2Cl)_{16}$ possédant des groupements chlore terminaux (Schéma 3). Comme l'addition sur la triple liaison des alkynes terminaux est possible, d'autres voies d'immobilisation sont également accessibles.

SCHEMA 3 Les dérivés oxazoline fonctionalisés par un groupement propargylique.



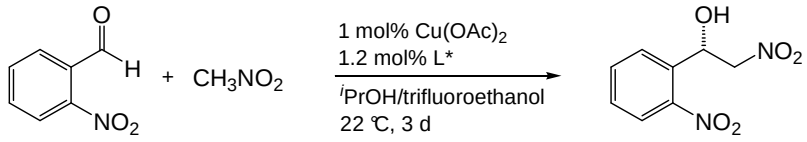
2.2 Etudes catalytiques comparatives

Les nouveaux dendrimères obtenus ont été utilisés dans l'α-amination des β-cétoesters (Equation 1) et dans la réaction de Henry (Equation 2) catalysées par du cuivre(II) afin de déterminer leurs potentiels catalytiques. Pour ces deux réactions, leur comportement a été comparé aux ligands simples analogues. Au total, dix-neuf systèmes catalytiques bisoxazoline et trisoxazoline simples et dendritiques ont été utilisés. Ils portent des substituants de taille croissante à leur position apicale ou leur pont.



EQUATION 1 **α-Amination du éthyl 2-méthylacétoacétate.**

D'excellents rendements (99%) et sélectivités (entre 90 et 99% *ee*) ont été obtenus pour tous les tests catalytiques d'α-amination. En utilisant une charge catalytique de 1 mol% seulement (alors que d'autres systèmes oxazoline supportés nécessitent 5 à 10 mol%), des résultats exceptionnels ont été observés. Une comparaison entre les dérivés mononucléaires et les systèmes dendritiques ainsi que des résultats avec les bisoxazolines et trisoxazolines montrent de légères différences négligeables.



EQUATION 2 **Réaction de Henry du nitrométhane avec le 2-nitrobenzaldéhyde.**

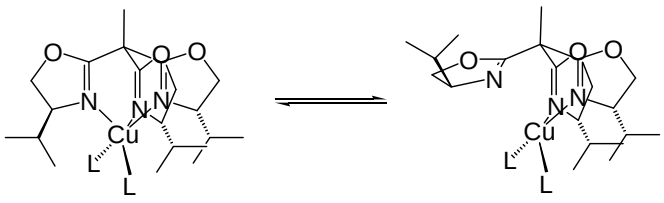
Les résultats obtenus pour la réaction de Henry se sont avérés moins remarquables que pour l'α-amination. Tous les dérivés bisoxazolines ont conduit à de bons et relativement constants rendements et à des excès énantiomériques d'une moyenne de 80%. Les espèces trisoxazolines, par contre, ont montré des résultats modérés (~50% de rendement et d'énantiosélectivité). Dans l'optique d'une comparaison des types de catalyseur, une différence non négligeable entre bisoxazolines/trisoxazolines et catalyseurs mononucléaires/ dendritiques a été observée. Tous les systèmes supportés faisaient l'objet d'un effet dendritique positif : ils ont montré une activité plus stable comparées à celles des espèces

mononucléaires. De plus, une augmentation signifiante de l'énantiosélectivité de l'ordre de 10% a dérivé des systèmes bisoxazolines dendritiques.

2.3 Comparaison de ligands bisoxazoline et trisoxazoline

Une étude de la vitesse de conversion de l'α-amination a été conduite pour comprendre le comportement différent des bisoxazolines et trisoxazolines immobilisées. Il a été démontré qu'un équilibre coordination/décoordination préliminaire du cuivre existe en catalyse avec des catalyseurs trisoxazoline. Cela influence la coordination du substrat et représente la principale différence de ces derniers par rapport aux bisoxazolines (Schéma 4). Les résultats obtenus ont été expliqués sur la base du mécanisme de ces réactions.

SCHEMA 4 Equilibre coordination/décoordination dans le cas des catalyseurs trisoxazoline.



2.4 Recyclage par dialyse

En général, le moyen le plus simple pour recycler un catalyseur reste la filtration. Dans ce sens, des réacteurs équipés de systèmes d'ultra- et de nanofiltration sont employés dans le cadre de catalyse par dendrimères. Ici, retournant à des moyens plus simples, nous utilisons un système de recyclage des catalyseur basé sur la dialyse, les membranes chargées de dendrimères servant de « sachets de thé catalytiquement actif » (Figure 1).

G2-Box(Ph) et **G2-Trisox** ont été utilisés pour comparer les comportements des bisoxazolines et trisoxazolines dans l'étude du recyclage dans le cas de l'α-amination. Sept tours catalytiques successifs ont été effectués avec succès. Chacun des types de catalyseur a permis le recyclage jusqu'à une certaine limite.

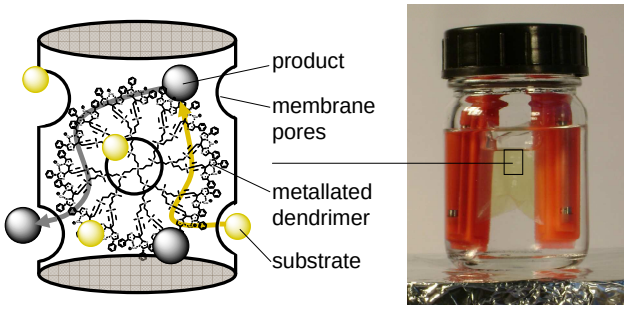


FIGURE 1 **Mise en œuvre du recyclage :** La membrane de dialyse (commerciale) contient le dendrimère et un vial à bouchon à vis sert de contenant (à droite) ; Principe de migration des molécules du substrat/produit par diffusion (à gauche).

Néanmoins, seul le catalyseur dérivé de **G2-Box(Ph)** a pu donné de bons résultats stables (~80% rendement et *ee*) durant l'étude. **G2-Trisox** a donné quant à lui des résultats modérés lors du premier tour catalytique de la série, résultats qui diminueront de façon monotone lors des catalyses suivantes (de 70% *ee* vers 13%). La clé de compréhension de cette différence, basée sur des études précédentes, repose sur l'activité très basse de **G2-Trisox**, en raison de l'encombrement stérique très dense. Ainsi, des temps de réaction beaucoup plus longs ont été nécessaires, favorisant la perte en catalyseur et les réactions parasites.

Manuela Gaab a été membre de la promotion Virginia Woolf du Collège Doctoral Européen des universités de Strasbourg pendant la préparation de sa thèse de 2006 à 2009. Elle a bénéficié des aides spécifiques du CDE et a suivi un enseignement hebdomadaire sur les affaires européennes dispensé par des spécialistes internationaux.

Ses travaux de recherche ont été effectués dans le cadre d'une convention de cotutelle avec la Ruprecht-Karls-Universität de Heidelberg, Allemagne et l'Université Louis Pasteur de Strasbourg, France.

Manuela Gaab was a member of the European Doctoral College of the Universities of Strasbourg from 2006 to 2009, during the preparation of her PhD (class name Virginia Woolf). She benefited from specific financial supports offered by the College and, along with her mainstream research, has followed a special course on topics of general European interests presented by international experts.

This research project has been encoded as a binational thesis (a "cotutelle") between the Ruprecht-Karls-Universität Heidelberg, Germany and the Université Louis Pasteur de Strasbourg, France.

Manuela Gaab war von 2006 bis 2009, begleitend zu ihrer Doktorarbeit, Mitglied des Europäischen Doktorandenkollegs der Straßburger Universitäten (Jahrgang Virginia Woolf). Sie hat von der spezifischen finanziellen Unterstützung durch das Kolleg profitiert und an einem Vorlesungsprogramm internationaler Fachkräfte zu europäischen Themen teilgenommen.

Ihre Forschungsarbeit wurde im Rahmen einer gemeinsamen Vereinbarung (sog. „Cotutelle") zwischen der Ruprecht-Karls-Universität Heidelberg, Deutschland und der Université Louis Pasteur de Strasbourg, Frankreich, angefertigt.