Geminal Bis(sulfoximine)s: Synthesis and Applications in Asymmetric Catalysis

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Dedicated to Prof. J. Mulzer on the occasion of his 60th anniversary.

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Abstract: A number of C_2-symmetrical geminal bis(sulfoximine)s have been prepared for the first time and used as ligands in boron-mediated reductions of acetophenone and copper complex-catalyzed 1,4-additions of diethylzinc to 2-cyclohexenone. The copper complex of bis(sulfoximine) **46** was found to be highly active in this type of reaction, furnishing the addition product in nearly quantitative yield even at $-90\,^{\circ}C$. From the reaction of bis(sulfoximine) **42** with $Cu(OTf)_2$ a copper complex was isolated and characterized by X-ray structural analysis. A mixture of SES-Cl and NaN_3 in acetonitrile was found to behave like SES-N_3 in $FeCl_2$-mediated iminations of sulfoxides, affording the corresponding sulfoximines with complete retention of the sulfur configuration.

Keywords: 1,4-addition; asymmetric catalysis; copper; sulfoximines

Introduction

Since their discovery in the early 1950 s[1–5] sulfoximines have developed to a powerful tool in organic synthesis.[6] This is especially true for the chiral non-racemic members of this uncommonly versatile class of compounds. Early work focused on the development of asymmetric alkylidene transfer reagents[7,8] and ketone resolutions based on the reversible formation of β-hydroxysulfoximines.[9–11] More recently, titanated 2-alkenylsulfoximines have been developed to highly diastereoselective allyl transfer reagents[12–17] and as tools for the synthesis of a broad range of isomerically pure oxa-[18–21] and aza-heterocycles.[22–27]

Nowadays sulfoximine chemistry is characterized by a transition from stoichiometric to catalytic applications. This metamorphosis is reflected by an increasing number of publications describing the synthesis of sulfoximine-based ligands as depicted in Figure 1.

Most of the work emanated and still emanates from the laboratories of Bolm. In 1996 he introduced the monosulfoximine **1** as a ligand in a Pd complex-catalyzed asymmetric allylation reaction affording the product with up to 73% ee.[28] Later on he developed a number of C_2-symmetrical bis(sulfoximine)s of types **3** and **4** with impressive results in the already-mentioned reaction as well as in Diels–Alder and hetero-Diels–Alder reactions.[29–32] The very interesting bis(benzothiazine) ligand **2** was synthesized by Harmata[33] and performed well again in the Pd-catalyzed asymmetric allylation (up to 86% ee). Common structural features of the bis(sulfoximine) ligands **2**–**4** are their C_2-symmetry and the two-carbon bridge linking the two sulfoximine nitrogen atoms. This structural motive resembles the bonding situation in the successful salen-type ligands which obviously was the initial motivation for the synthesis of ligands **3** and **4**. On the other hand, facing the immense importance of the chiral, C_2-symmetrical bis(oxazo-

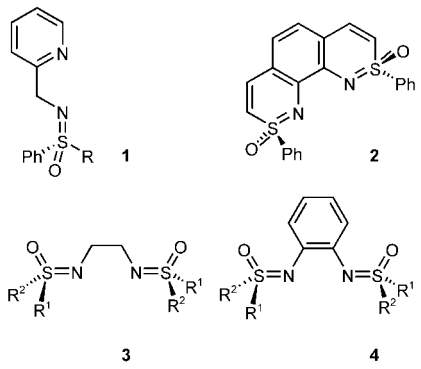

Figure 1. Sulfoximine-based ligands.

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line)s **5** and **6** as ligands in asymmetric catalysis[34–48] we became curious to explore the corresponding potential of the structurally related bis(sulfoximine)s **7** and **8** in this area (Figure 2).

Results and Discussion

At the time we began our studies only two racemic *S,S*-linked bis(sulfoximine)s were known. The ethylene-bridged derivative **9** had been synthesized by Johnson 1980 as a vinylsulfoximine precursor[49] and **10** was prepared as early as 1954 in 9% yield to explore the suspected intrinsic toxicity of the sulfoximine group.[50] The target C_1-bridged bis(sulfoximine)s comprise a class of hitherto unknown compounds.

Synthesis of Geminal Bis(sulfoximine)s

To tackle the problem of their synthesis in enantiomerically pure state we envisaged two major strategies (Scheme 1).

Strategy **A** is based on the possibility to oxidatively iminate chiral sulfoxides with retention of their configuration using reagents acting like nitrenes. The most prominent representatives here are mesitylenesulfonylhydroxylamine (MSH),[51] BOC azide,[52] *N*-aminophthalimide,[53,54] or *N*-tosyliminophenyliodinane.[55] Hydrazoic acid itself is less appropriate due to its incomplete stereoselectivity.

Route **A** seemed to be a rather promising entry to the geminal bis(sulfoximine)s last but not least because the starting bis(sulfoxide) **11** was a known compound[56–59]

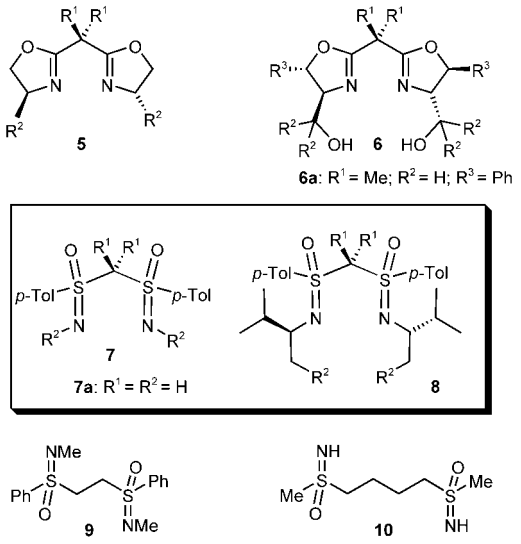
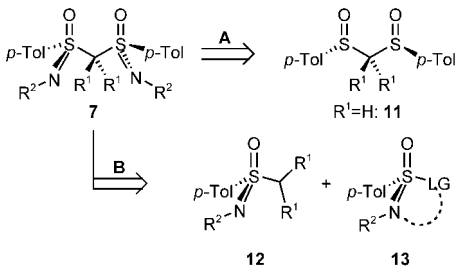


Figure 2. Structural comparison of bis(oxazoline)s **5**, **6** and geminal *S,S*-linked bis(sulfoximine)s **7**, **8** as well as the only two racemic *S,S*-linked bis(sulfoximine)s **9**, **10** known prior to this work.



Scheme 1. Retrosynthetic analysis of target structure **7**; LG = leaving group.

and quite a number of successful stereoselective iminations of other sulfoxides, especially with MSH, have been described.[51,60,61]

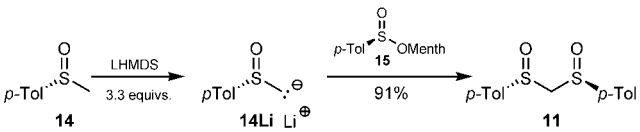
Strategy **B** relies on a C–S bond formation between a sulfur(VI) nucleophile generated from **12** and a sulfur(VI) electrophile **13**. The major problem with this approach was the non-availability of the latter in enantiomerically pure state at the time we started our investigations. For that reason we strongly favoured path **A** and therefore our efforts in that area will be discussed first.

Route A

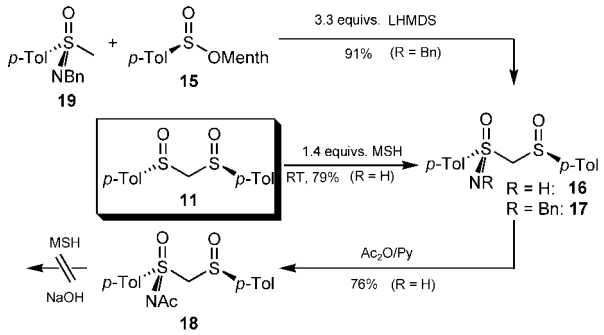
The synthesis of the *S,S*-enantiomer **11** has been described several times in the literature.[58,59] Kunieda was the first who used the Andersen reagent **15** for that purpose furnishing **11** with 35% yield (Scheme 2).[59] To improve this yield it was necessary to account for the increased acidity of the methylene protons in the product **11** compared to those in the starting sulfoxide **14**.

Indeed with an excess of lithium hexamethyldisilazide (LHMDS, 3.3 equivs.) it was possible to obtain **11** as a pure isomer with 91% yield. Next we tried the twofold imination reaction to prepare bis(sulfoximine)s **7a** (Figure 2), which appeared to be especially useful due to its free NH groups allowing further derivatization. For that purpose we employed MSH as a reagent (Scheme 3).

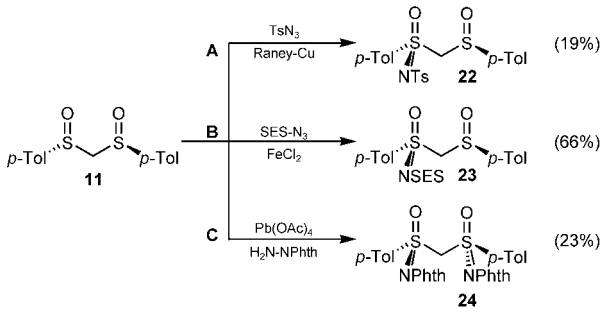
To our surprise only the monosulfoximine **16** was isolated with 79% yield. As a possible explanation for this finding, we suspected the intermediate *S*-aminosulfoxonium salt[61] (not shown) to reduce the nucleophilicity of the second sulfur, thus preventing it from being attacked by MSH [a similar explanation has been put forward by Appel for the failure of the bis-imination of a C_1-bridged



Scheme 2. Improved synthesis of bis(sulfoxide) **11**.



Scheme 3. Attempts to synthesize the geminal bis(sulfoximine) **7a** *via* imination of sulfoxides.



Scheme 5. Action of different nitrene precursors to bis(sulfoxide) **11**. Path B: A new route to SES-protected sulfoximines.

bis(phosphane)].[62] We therefore *N*-protected **16** by acetylation yielding **18** and synthesized the benzyl-protected derivative **17** by application of our LHMDS-based method from **19** and sulfinate **15** with 91% yield.

To our disappointment both protected derivatives failed to react with MSH in the desired manner. The acetylated derivative was completely unreactive whereas the benzylated one underwent a rather surprising transformation to the starting bis(sulfoxide) **11** (34% yield) with complete retention of the *S*-configuration. In addition to that 16% of debenzylated **16** and 31% of the starting material were isolated (Scheme 4).

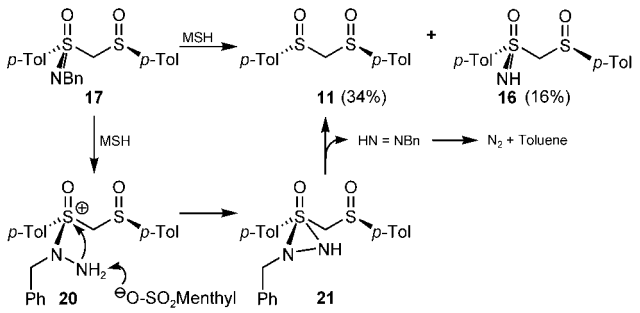
As a plausible mechanistic interpretation of this unusual process we propose an electrophilic attack of MSH onto the electron-rich sulfoximine nitrogen yielding the *S*-aminosulfoxonium salt **20** which may cyclize to the thiadiaziridine *S*-oxide **21**. This latter compound finally undergoes a [1,2]-cycloreversion affording bis (sulfoxide) **11** with retention of the configuration.

As a consequence of these disappointing results, we decided to explore the reactivity of **11** towards various "nitrene" sources (Scheme 5).

The first experiment in this series was a Raney copper-mediated tosyl-imination following the classical procedure developed by Kwart and Kahn in 1967.[63] Again no bis-imination was observed and only 19% of the monosulfoximine **22** was isolated instead. Despite this rather disappointing result, we tried a modification of Bach's imination reaction[52] replacing BOC-azide by trimethylsilylethanesulfonyl azide (SES azide) to avoid acidic deprotection conditions in the final step to the "free" sulfoximine **7a**. SES azide has never been described before and for safety reasons we tried to generate it *in situ* from SES-Cl and sodium azide in CH_3CN. In the event SES-Cl was stirred with NaN_3 in CH_3CN for 16 h at which point the bis(sulfoxide) **11** and anhydrous $FeCl_2$ were added. Alkaline work-up followed by flash column chromatography furnished the SES-protected monosulfoximine **23** in 66% yield as a pure isomer. Although again only monoimination was observed, we were pleased to see that this new stereoselective reaction, leading to sulfoximines with a fluoride ion-cleavable protecting group, worked.

Nevertheless our problem to doubly iminate **11** was still unresolved, and therefore we focused our attention on the $Pb(OAc)_4$-mediated oxidative imination procedure with *N*-aminophthalimide as the nitrogen source (Scheme 5, Path **C**).

This time we isolated an easy to separate mixture of the desired bis(sulfoximine) **24** (23%) and the corresponding monosulfoximine (not shown). Unfortunately it turned out that **24** could not be deprotected. Neither H_2/PtO_2 nor Zn/HOAc worked in the anticipated manner and therefore we had to give up this first promising entry to geminal bis(sulfoximine)s.

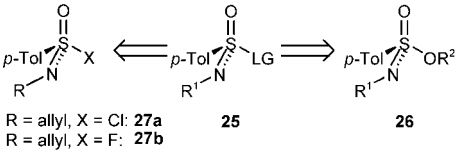


Scheme 4. Mechanistic proposal for the formation of **11** from monosulfoximine **17**.

Route B

As discussed earlier this strategy relies on the availability of a suitable sulfur(VI) electrophile **25** (Scheme 6).

Obvious candidates are sulfonimidoyl halides such as **27** or sulfonimidates **26**. Both types of compounds are problematic from a stereochemical point of view. First of all their synthesis in enantiomerically pure state is rather tedious and the removal of the chiral *N*-bound auxiliary is difficult, if not impossible.[64] Furthermore sulfonimidoyl halides are rather prone to epimerization and finally the nucleophilic displacement reaction with



Scheme 6. Solutions for sulfur(VI) electrophiles.

carbon nucleophiles is vulnerable to reduction and not completely stereoselective.[64]

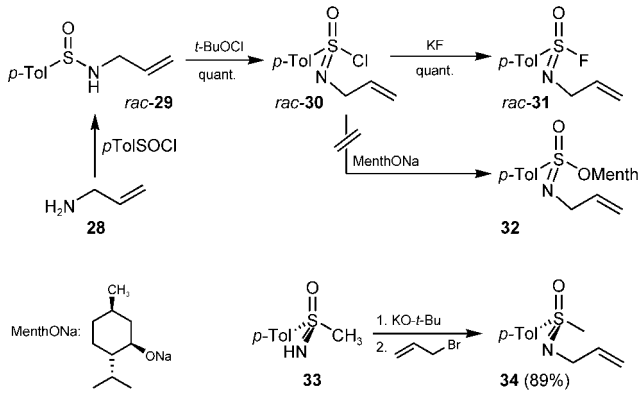
Facing this situation we found it best to employ a racemic sulfonimidoyl fluoride (the chlorides tend to get reduced or to give chlorinated products in their reactions with carbanions)[65–67] with a sterically non-demanding protecting group at nitrogen (Scheme 7). The attempted preparation of the attractive menthyl ester **32** as a sulfur(VI) analogon of the Andersen reagent[68] *via* a nucleophilic displacement reaction with *rac*-**30** as electrophile failed.

As second building block we used *N*-allylsulfoximine **34** which was obtained in 89% yield from the known sulfoximine **33**[51] (synthesized *via* the MSH route from the corresponding sulfoxide in 90% yield).

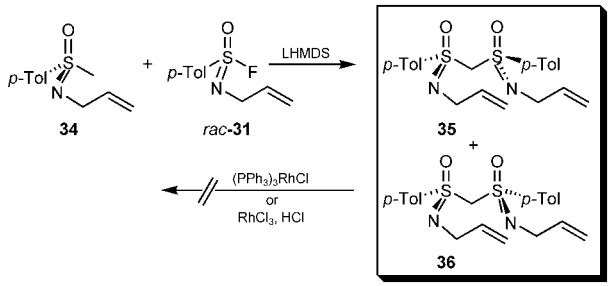
To facilitate the NMR spectroscopic analysis of the coupling products we chose identical *N*-protecting groups on both components. This way the desired compound **35** with identical absolute configuration of both sulfur atoms is C_2-symmetrical with homotopic hydrogens at the methylene carbon, whereas in the C_s-symmetrical *meso* compound **36** these hydrogens are diastereotopic (Scheme 8).

Under the optimized coupling conditions developed for **11** and **17** we were able to isolate 19% of an inseparable 1:1 mixture of the target bis(sulfoximine)s **35** and **36**. Unfortunately again the intended deprotection, this time *via* Rh-catalyzed isomerization of the double bond,[69] failed under a variety of conditions.

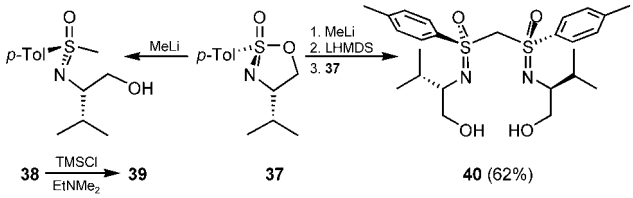
The unexpected breakthrough in this chemistry came by serendipity (Scheme 9)!



Scheme 7. Synthesis of the sulfur(VI) electrophile *rac*-**31** and the sulfur(VI) nucleophile (*R*)-**34**.



Scheme 8. Successful coupling and failed deprotection.



Scheme 9. A stereoselective one-pot-procedure to enantiomerically pure geminal bis(sulfoximine)s *via* sulfonimidate **37**.

In the course of an attempted fluorination of a sulfonimidoyl chloride (not shown) the hitherto unknown heterocycle **37** was obtained as a major product.[70–73] Later on this compound was elaborated to a central starting material for the synthesis of enantiomerically pure 2-alkenylsulfoximines as powerful asymmetric allyl transfer reagents.[12,16,18,19,23]

The cyclic sulfonimidate **37** turned out to be the missing chiral non-racemic sulfur(VI) electrophile. Moreover, contrasting the behaviour of sulfonimidates **26**,[64] **37** reacts readily with carbon nucleophiles, including sulfonimidoyl-substituted derivatives, without reduction and with complete inversion of the sulfur configuration. Reacting **37** with MeLi affords the methylsulfoximine **38** which can be deprotonated by an excess of LHMDS and reacted with a second equivalent of the sulfonimidate yielding the desired bis(sulfoximine) **40** in a one-pot sequence with 62% yield. Alternatively, the *O*-silylated methylsulfoximine **39** can be reacted in a separate step with **37** furnishing **40** with 74% yield after deprotection. It is worth mentioning here that *ent*-**40** can easily be obtained starting from *ent*-**37**.

Structural Modifications of 40

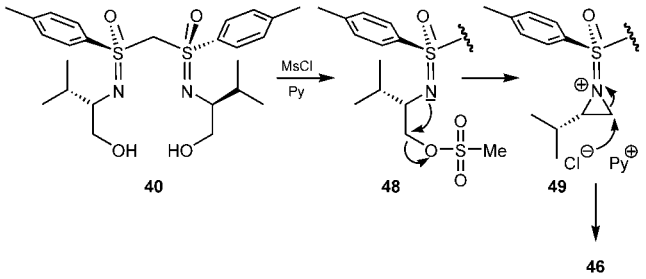
Having found a simple, high yielding entry to bis(sulfoximine) **40** starting from commercially available **37**, we explored possibilities to structurally modify the parent compound. This was regarded as necessary for at least two reasons. Firstly, it is known from the chemistry of the related bis(oxazoline)s **5** and **6** that a replacement of the acidic methylene protons by alkyl groups has a

major influence in catalyst performance.[36,74] This can be traced back to variations of the "bite angle"[74] and to the avoidance of deprotonated species. Indeed the most useful applications of bis(oxazoline) ligands rely on the geminal dimethylated derivatives.[37,40] Secondly, the two hydroxy groups from the valine side-chains offer additional possibilities for ligand design. On the one hand their mere existence in a free or blocked state has proved to have a major impact on the sense of asymmetric induction.[45] Furthermore, these two additional functional groups can possibly be exploited to construct ligands for two-centre catalysis.[75–80] For these reasons we synthesized a number of derivatives as depicted in Scheme 10.

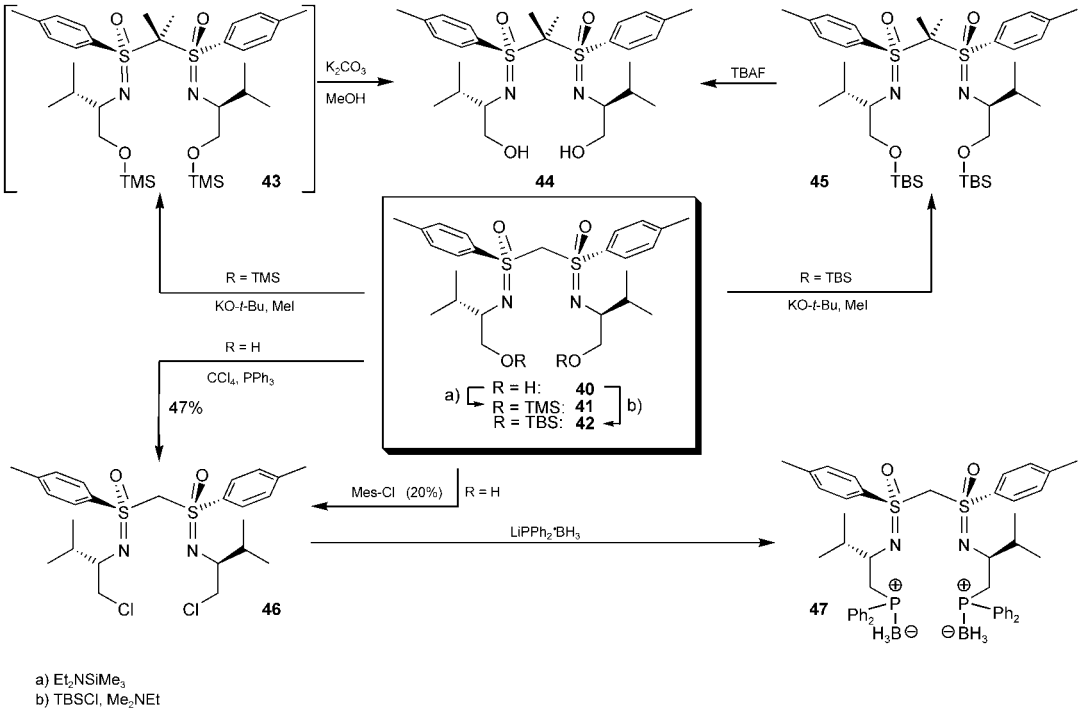
The bis(sulfoximine) **40** can be silylated either using dimethylaminotrimethylsilane or TBSCl to yield **41** or **42**, respectively. The potassium salts of both protected derivatives prepared by deprotonation with potassium *t*-butoxide react readily to the corresponding geminal dimethylated bis(sulfoximine)s **43** and **45**. The diol **44** was generated either by fluoride ion-mediated desilylation or by a solvolysis reaction employing K_2CO_3 in MeOH. The best way to prepare **44** is the route *via* the bis-TMS derivative **43**, which was not isolated, affording the target compound in almost 99% overall yield. The application of potassium *t*-butoxide as a base was found to be crucial to get high yields of the methylated products.

In order to convert the OH groups into leaving groups we tried to mesylate **40** under standard conditions. Interestingly only minor amounts of the mesylated product **48** was isolated besides 20% of the dichlorobis(sulfoximine) **46** (Scheme 11).

A plausible explanation for this finding is the formation of an aziridinium cation **49**, which undergoes ring opening by chloride ion to yield the observed chlorinated product **46**. A much better access to that compound (47% yield) was found by application of the Appel reaction using PPh_3 and CCl_4 (Scheme 10). In the context of our objective to design ligands suitable for heterobimetal catalysis we tried to replace chlorine by phosphorus. This should give access to a new class of *N,P* ligands with the relatively hard nitrogen centres being combined with the soft phosphorus atoms. This kind of ligand should be able to complex early and late transition metals simultaneously. With this in mind, chlorinated bis (sulfoximine) **46** was reacted with the borane complex of lithium diphenylphosphane in THF at $-78\,^{\circ}C$. Although the yield of isolated **47** was only 16% we were



Scheme 11. Unexpected formation of the dichlorobis(sulfoximine) **46**.



Scheme 10. Derivatization of the parent bis(sulfoximine) **40**.

pleased to realize that the reaction worked, at least in principle. As an explanation for the low yield we suspect the presence of the rather acidic protons in the starting material.

Application of the New Ligands: Stoichiometric and Catalytic Reactions

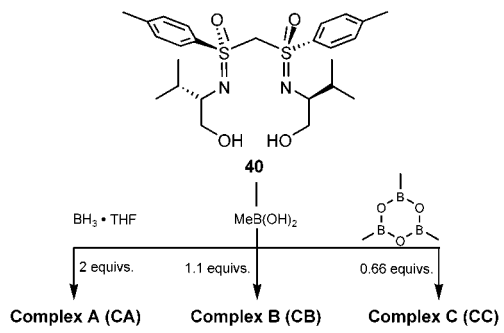
Despite the long history of β-hydroxysulfoximines as ligands in boron-mediated reduction reactions[81–83] nothing is known to date about the applicability of *N*-hydroxyethyl-functionalized sulfoximines for that purpose. Therefore we were curious to see whether different boron complexes of **40** can be used to asymmetrically reduce ketones. To answer that question we reacted **40** with three different boron sources as depicted in Scheme 12.

For the preparation of complex **CA** bis(sulfoximine) **40** was reacted with 2 equivs. of BH_3•THF complex in toluene at ambient temperature. After 40 min reaction time the solvent was removed under vacuum to leave a white solid which was used in stoichiometric amounts to reduce ketone **50** (Table 1).

As reducing agent 0.5 equivs. of BH_3•THF were added whereupon an almost quantitative reduction was observed within 10 min, affording the alcohol (*R*)-**51** with 39% ee. This rather low ee could not be improved by variation of the amount of BH_3•THF used for complexation and/or the amount of BH_3•THF used for the reduction.

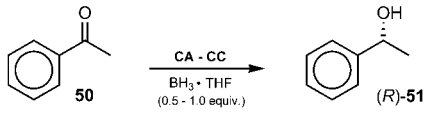
For that reason we changed the boron source to methylboronic acid[85] (Table 1) which was reacted with **40** in toluene to produce complex **CB**. This time the reduction using 0.6 equivs. of BH_3•THF was performed in THF with only 10 mol % of **CB**. Again alcohol (*R*)-**51** was produced in quantitative yield after 10 min at 0 °C but the ee was even lower (28%). Surprisingly the reaction was very much slower in toluene yielding only around 10% **51** within 10 min (not shown).

Finally, we tried complex **CC** which was prepared from trimethylboroxine[85,86] and **40** (Table 1). The most active and selective catalyst was obtained by using



Scheme 12. Boron complexes from **40**.

Table 1. Stoichiometric and catalytic reduction of acetophenone with boron complexes CA to CC.[a]



Complex	BH_3•THF	Solvent	Yield [%]	ee [%][d]
CA[b]	0.5	toluene	99	39
CB[c]	0.6	THF	quant	28
CC	1.0	toluene	58	48

[a] All reactions were run for 10 min at 0 °C.
[b] Compound **50** was added as a toluene solution over a time period of 60 min.
[c] 10 mol % of complex **CB**.
[d] The ee was determined by chiral GC (RT-BDex cst-TM, Restek, see Experimental Section). The configuration was deduced by comparison of the value of the optical rotation with literature data.[84]

0.66 equivs. of the boron heterocycle with respect to the ligand. With stoichiometric amounts of **CC** and 1 equiv. of BH_3•THF **51** was isolated with 58% yield and 48% ee [(*R*)-**51**], again after 10 min at 0 °C.

Although we tried to get some structural information about complexes **CA** – **CC** by NMR (^{1}H, ^{13}C, ^{11}B) and MS no consistent picture emerged from these analyses. For the time being any attempt to assign structures to the complexes would be highly speculative and is therefore avoided. On the other hand, the encouraging results especially from the experiments with complex **CC** stimulated further efforts to learn more about the species formed. These studies are currently in progress.

We next turned our attention to the question of a possible complexation of copper by our new bis(sulfoximine)s. For that purpose the three ligands **40**, **42** and **45** were reacted with $CuCl_2$ and $Cu(OTf)_2$ in different solvents (Table 2).

Although in all cases complete dissolution of the added copper(II) salt could be observed, only the reaction of the bis-protected ligand **42** with copper(II) triflate led to crystalline material (Table 2, entry 7). This copper complex was isolated in 80% yield after the addition of hexanes to induce crystallization. Interestingly the slightly turbid dichloromethane solution generated after combining the ligand with copper triflate at room temperature became clear upon cooling to −78 °C. A similar effect has been observed by Evans during copper complexation by a bis(oxazoline).[39,87] To our delight the crystals obtained were suited for an X-ray structural analysis (Figure 3).[88]

Surprisingly, this copper complex derived from C_2-symmetrical bis(silylated) **42** was found to be desymmetrized due to loss of one silyl substituent! Much like the situation in copper-BOX complexes,[40] the copper atom

Table 2. Complexation experiments with the ligands **40**, **42** and **45**.

Entry	Ligand	Copper salt	Solvent	Conditions	Crystallization
1	**40**	$CuCl_2$	CH_2Cl_2	[a]	no
2	**40**	$CuCl_2$ / $AgSbF_6$	CH_2Cl_2	[a,b,d]	no
3	**40**	$Cu(OTf)_2$	CH_2Cl_2	[a,d]	no
4	**42**	$CuCl_2$ / $AgSbF_6$	CH_2Cl_2	[a,b]	no
5	**42**	$CuCl_2$	EtOH / CH_3CN	[a]	no
6	**42**	$CuCl_2$	EtOH	[a]	no
7	**42**	$Cu(OTf)_2$	CH_2Cl_2	[a,c]	yes
8	**45**	$Cu(OTf)_2$	CH_2Cl_2	[a,c]	no

[a] CuX_2:Ligand = 1 : 1, room temperature, after complete dissolution of the copper(II) salt the solution was filtered and overlayed with hexanes to induce crystallization.
[b] 2 equivs. $AgSbF_6$ then filtration.
[c] Dry stirring of $Cu(OTf)_2$ and ligand under vacuum for 30 min prior to solvent addition.
[d] Slow evaporation of the solvent by a stream of argon bubbled through the solution.

is coordinated in a distorted square pyramidal fashion in which one of the triflate ligands is weakly bound in the apical position (Cu–OTf^1 = 2.33 Å) whereas the other one is fully dissociated (Cu–OTf^2 = 3.30 Å). The distance of the copper atom from the N_2O_2 plane is 0.233 Å. A comparison with the X-ay structure of the metal-free ligand **42** displays only minor structural changes. Most notable is a slight decrease of the C–S bond lengths (from 1.83 to 1.73, 1.79 Å) and a minor enlargement of the S–C–S angle (from 118.7° to 122° in the complex).

Much more interesting is a structural comparison of **52** with a number of Cu-BOX-complexes (Figure 4).

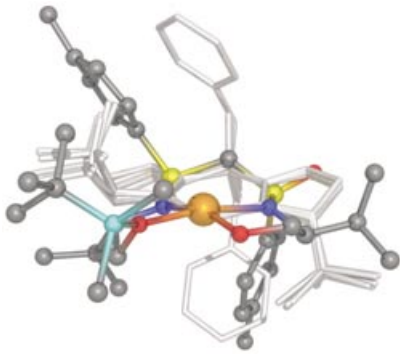


Figure 4. Least squares fit of six bis(oxazoline)-copper complexes (grey sticks) and sulfoximine complex **52**. (coloured ball and stick representation; yellow: S; red: O; cyan: Si; blue: N; dark grey: C; orange: Cu). The counterions and hydrogen atoms have been omitted for clarity.

For that purpose a least squares fit of six Cu-BOX-complexes (CSD-Ref.-Codes: CUHCEN,[42] GIQLUN,[87] GIWHID,[89] GIWHID01,[90] LOXWOK,[91] MISHOL[90]) and **52** with respect to the central Cu–N_2–C_3 six-membered ring has been calculated.[92] From this fit it is obvious that due to the inverted direction of the N–C–C–O chain of the amino acid derived portion of the molecule the space blocked by the *i*-Pr-groups of **52** is inverted too. This entails the expectation that any asymmetrical reaction occurring in the coordination sphere of the copper atom should lead to products with opposite absolute configuration as compared to the induction from BOX ligands, although the absolute configuration of the underlying amino acid is unchanged.[93] Moreover, the structure of **52** reveals that the sulphur-bound *p*-Tol groups should have only a minor influence on the asymmetric induction of this complex. To verify these expectations and, of course, to answer the question whether copper complexes of the bis(sulfoximine)s **40**, **44** and **46** (Scheme 10) are able at all to asymmetrically catalyze C–C bond forming reactions, we chose the Et_2Zn-mediated 1,4-addition to 2-cy-

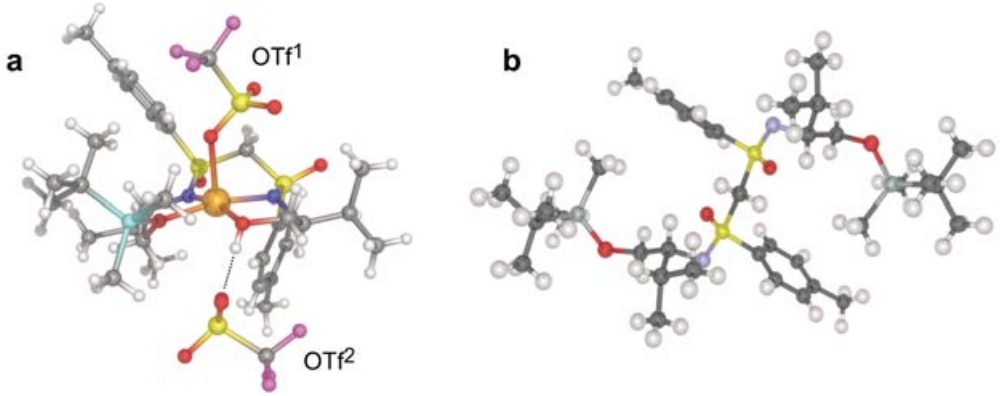


Figure 3. (**a**) X-ray structure of copper complex **52**. (**b**) X-ray structure of the uncomplexed ligand **42**. Colour code: yellow: S; red: O; cyan: Si; blue: N; dark grey: C; magenta: fluorine; orange: Cu.

clohexenone as a model reaction (Table 3). This choice was made because copper complexes of bis(oxazoline)s with unfunctionalized side chains failed to give useful stereoselectivities in these reactions.[36] On the other hand bis(oxazoline)s bearing hydroxy groups in the β-position of the nitrogens perform much better, an observation that has been traced back to a precoordination of the Zn-atom to these oxygens.[36]

To our delight all ligand-copper complexes were found to be highly active catalysts delivering the ethyl group of Et_2Zn in a 1,4-fashion onto the substrate. This was especially true for the dichloro-substituted ligand **46**. A nearly quantitative yield was achieved even at $-90\,^{\circ}C$ using only 2.4 mol % of the catalyst and $CuCl_2$ as the copper source.

On the other hand the enantioselectivities were rather disappointing, with 36% ee as the best value. As expected from the analysis discussed above the major enantiomer was (*R*)-(+)-**54** in all cases. Interestingly, the dimethylated ligand **44** performed even worse contrasting the experiences made with the corresponding dimethylated bis(oxazoline) complexes.[36]

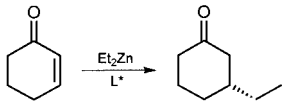
Based on the results achieved so far, it is difficult to analyze the potential role of the ligands' oxygen atoms as a possible coordination site for zinc. This interesting possibility has been discussed by Reiser et al. to explain the effect of *O*-substituents and various additives upon the stereoselection observed with copper complexes of **6a** in the 1,4-addition reaction discussed above (Figure 2).[36]

In summary, we have synthesized for the first time enantiomerically pure C_2-symmetrical geminal bis(sulfoximine)s. Due to the commercially availability of the starting materials **37** and *ent*-**37**, their synthesis is extremely easy and short. Moreover, structural modifications, not only on the valine-derived side chain leading to derivatives such as **41**, **46** and **47** but also on the bridging carbon have been achieved. Future work will be directed towards the synthesis of other phosphinylated ligands as indicated in structure **55**, not only to have access to systems suited for the synthesis of bimetallic complexes but also to improve the asymmetric environment of the complexed metal(s) (Figure 5).

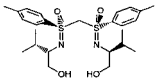
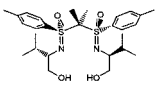
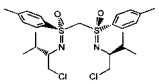
Following these lines we are currently working on the problem to completely remove the *N*-side chain and to exploit the *ortho*-directing group properties of the sulfonimidoyl moiety[70,94–96] to phosphinylate the *ortho*-positions of the tolyl rings.

Beside these constitutional modifications it is important to mention that the described syntheses of the bis(sulfoximine)s are flexible enough to allow configurational adjustments on both the *C*- and *S*-centred configurations. This opens the opportunity to develop ligands with a "matched" relative configuration on these stereogenic units, a situation which might not have been established at the moment.

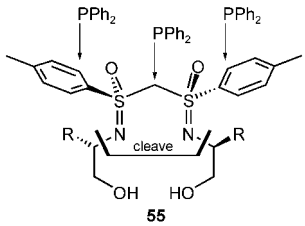
Table 3. Copper complex-catalyzed 1,4-additions to 2-cyclohexenone.



53 (*R*)-**54**

Entry	Ligand	Cu salt	T [°C]	Time [h]	Yield [%]	ee [%][a]
1		$Cu(OTf)_2$	–20	4	82	19
2		$CuCl_2$	–20	3	89	22
	40					
3		$Cu(OTf)_2$	–20	3.5	48	7
4		$CuCl_2$	–20	3.5	68	16
	44					
5		$Cu(OTf)_2$	–20	0.25	99	36
6		$CuCl_2$	–90	18	95	35
	46					

[a] Determined by chiral GC (Beta-Dex120, Supelco, see Experimental Section).



55

Figure 5. Possible sites of phosphinylation and bond cleavage in bis(sulfoximine)s **55**.

Conclusion

The cyclic sulfonimidates **37** and *ent*-**37** offer the opportunity to synthesize new C_2-symmetrical bis(sulfoximine)s for the first time. Due to the acidic protons in the C_1-bridge of these compounds and their functionalized *N*-side chains numerous structural modifications are easy to perform. Furthermore dialkylated derivatives such as **43** or **45** are expected to take part in directed *ortho*-metallation reactions which in turn renders further modifications possible. The boron complex from **40** and trimethylboroxine reduces acetophenone to the corresponding (*R*)-alcohol with 48% ee, whereas the copper complex from the dichloro-substituted ligand **46** was found to be a highly active catalyst for the 1,4-addition reaction of diethylzinc to 2-cyclohexenone. Even at $-90\,^{\circ}C$ a nearly quantitative yield of the addition product was observed with only 2.4 mol % of the catalyst. Given the manifold ways for constitutional and configurational changes of the ligand structure, it seems just a

matter of time to improve the selectivity of the system which is, at the time being, not yet sufficient for preparative purposes (36% ee for the above-mentioned reaction).

Current work focuses on the synthesis of various phosphinylated derivatives (with or without the *N*-side chain) to improve the selectivity and to design ligands suited for hetero-bimetal catalysis.[76,80]

Experimental Section

General Remarks

All manipulations except work-up and chromatographic purification were performed under an atmosphere of dry, oxygen-free argon with Schlenk and syringe techniques. Na_2SO_4 or $MgSO_4$ were applied to dry organic layers. Solvents were purified and dried prior to use by distillation from an appropriate drying agent. Diethyl ether (ether) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. Starting materials were obtained from commercial sources and used without further purification unless otherwise stated. The assay from *n*-BuLi was obtained by titration with menthol in THF in the presence of 1,10-phenanthroline.[97] Analytical thin layer chromatography (TLC): Macherey & Nagel precoated TLC plates (SilG/UV 254). Flash chromatography: E. Merck silica gel 60 (15–40 μm). Enantiomeric excesses were determined by GC analysis of the crude reaction mixture using a Thermo-Finnigan GC 8360 equipped with an appropriate optically active column, as described in the footnotes of the corresponding tables and in the corresponding section of the experimental part. Melting points (mp): Gallenkamp apparatus, uncorrected. Optical rotations: Perkin Elmer 241 polarimeter. IR spectra: Perkin Elmer, FT-IR-Spectrometer 1720X. Elemental analysis; Elementar, Vario EL. ^{1}H and ^{13}C NMR spectra: Bruker DRX 500, AM 300, AC 300, AMX 300, AC 200. ^{1}H NMR and ^{13}C NMR spectra are reported in ppm relative to tetramethylsilane or for DMSO-d_6 as solvent $\delta_H = 2.50$ ppm and $\delta_C = 39.5$ ppm.

Sulfinylsulfoximine 23

In a 25-mL Schlenk flask 0.803 g (4.0 mmol) trimethylsilylethanesulfonyl chloride (SES-Cl) were dissolved in 4 mL acetonitrile at room temperature. Under vigorous stirring 0.364 g (5.6 mmol) NaN_3 were added within 30 min after which the solution was stirred for another 14 h. Then a solution of 0.292 g (1.0 mmol) **11** in 2 mL acetonitrile was added followed by 0.507 g (4.0 mmol) dry $FeCl_2$. After 3 h the reaction mixture was poured onto ice and ether (20 g and 30 mL, respectively). The aqueous layer was extracted with ether (3×30 mL), the combined organic layers were washed first with aqueous 10% NaOH (30 mL) then with brine (30 mL) and finally dried over $MgSO_4$. Removal of the solvent under reduced pressure furnished 0.7 g crude product, which was purified by flash chromatography (EtOAc/hexanes 1:2) affording **23** as a white solid; yield: 311 mg (66%); $R_f = 0.62$ (EtOAc/hexanes, 1:2); mp 62 °C; $[\alpha]_D^{20}$: +264.64 (c 0.9, CH_2Cl_2); ^{1}H NMR (200.13 MHz, $CDCl_3$): $\delta = 0.005$ [9H, s, $Si(CH_3)_3$], 1.163 (2H, m, Si-CH_2), 2.382 (3H, s, SO-C_6H_4-CH_3), 2.477 (3H, s, SON-C_6H_4-CH_3), 3.201 (2H, m, SO_2-CH_2), 4.495 (1H, d, $^2J = 13.3$ Hz, SCHHS), 5.112 (1H, d, $^2J = 13.3$ Hz, SCHHS), 7.300 (2H, d, $^3J = 8.2$ Hz, SO-*m*-CH), 7.449 (2H, d, $^3J = 8$ Hz, SON-*m*-CH), 7.549 (d, $^3J = 8.2$ Hz, SO-*o*-CH), 8.015 (d, $^3J = 8$ Hz, SON-*o*-CH); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = -1.384$ [$Si(CH_3)_3$], 10.35 (Si-CH_2), 21.44 (SO-C_6H_4-CH_3), 21.84 (SON-C_6H_4-CH_3), 54.14 (SO_2-CH_2), 81.36 (S-CH_2-S), 124.09 (SO-*o*-CH), 128.91 (SON-*o*-CH), 130.40 (SO-m-CH), 130.41 (SON-*m*-CH), 132.37 (SO-*ipso*-C), 138.54 (SON-*ipso*-C), 142.73 (SO-*p*-C), 146.91 (SON-*p*-C); anal. calcd. for $C_{20}H_{29}NO_4S_3Si$: C 50.92, H 6.20, N 2.97; found: C 50.92, H 6.21, N 2.93.

Bis(sulfoximine) 40

Method A: One-pot-procedure: The donor flask of an inverse apparatus (see Supporting Information) was charged with 239 mg (1.0 mmol) **37** dissolved in 3 mL THF, the acceptor flask with 383 mg (1.6 mmol) **37** dissolved in 4.8 mL THF. The solutions were cooled to −78 °C. Then 750 μL (1.2 mmol) of an ether solution of MeLi (1.6 molar) were added *via* syringe to the donor flask and 30 min later a freshly prepared solution of 200.5 mg (1.2 mmol) LHMDS in 2.5 mL THF was added dropwise into the same flask. After 35 min of stirring at −78 °C the colourless reaction mixture was transferred to the acceptor flask using an Ar-filled balloon. After 5 min the reaction mixture was allowed to reach 0 °C and was stopped 20 min later by adding 2 mL saturated NH_4Cl solution. After extraction with diethyl ether (3×10 mL) and drying of the organic layers with $MgSO_4$ the solvent was removed under vacuum and the crude product was purified by flash chromatography (EtOAc/hexanes, 3:1) affording **40** as a colourless solid; yield: 309 mg (62%); $R_f = 0.27$ (EtOAc/hexanes, 3:1); mp 109 °C; $[\alpha]_D^{20}$: −54.80 (c 0.98, CH_2Cl_2); IR (KBr): $\nu = 3500$ (OH), 1260, 1130 cm^{-1} (N=S=O); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 0.945$ (6H, d, *i*-Pr CH_3, $^3J = 7.2$ Hz), 0.971 (6H, d, *i*-Pr CH_3, $^3J = 7.2$ Hz), 1.802 (2H, dqq, *i*-Pr CH, ^{3}J = 7.2 Hz, $^3J = 5.2$ Hz), 2.423 (6H, s, C_6H_4-CH_3), 2.902 (2H, dd, OH, $^3J = 9.5$ Hz), 3.227 (2H, ddd, N-CH, $^3J = 8.2$ Hz, $^3J = 3.1$ Hz, $^3J = 5.2$ Hz), 3.457 (2H, ddd, CHH-OH, $^3J = 11.0$ Hz, $^3J = 4.0$ Hz), 3.584 (2H, ddd, CHH-OH, $^3J = 9.5$ Hz, $^3J = 11.0$ Hz), 4.847 (2H, s, S-CH_2-S), 7.245 (4H, d, *m*-CH), 7.752 (4H, d, *o*-CH); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 18.68$ (*i*-Pr CH_3), 19.78 (*i*-Pr CH_3), 21.53 (C_6H_4-CH_3), 31.72 (*i*-Pr CH), 64.23 (N-CH), 65.07 (CH_2-OH), 70.24 (S-C-S), 129.29 (*m*-CH), 129.49 (*o*-CH), 135.06 (S-C), 144.27 (C_6H_4-C); MS (Cl, isobutane): *m/e* = 496 (27.9% $[M+1]^+$), 495 (100% $[M]^+$); anal. calcd. for $C_{25}H_{38}N_2O_4S_2$: C 60.70, H 7.74, N 5.66; found: C 60.85, H 7.57, N 5.70.

Method B: In a 25-mL inverse apparatus (see Supporting Information) the donor flask was charged with 655 mg **39** (2.0 mmol, for the preparation of **39** from **37**, see Supporting Information) and the acceptor flask with 239 mg **37** (1.0 mmol) dissolved in dry THF (3 mL) each. After cooling to −78 °C 747 mg (2.0 mmol) of a hexane solution containing 2.67 mmol/g *n*-BuLi were added to the donor flask *via* syringe. After 40 min of stirring at this temperature the mixture in that flask was transferred dropwise to the solution in the acceptor flask using an Ar-filled balloon. 5 min later the mixture was allowed to reach room temperature, stirred for another 80 min

and then the reaction was stopped by adding 1.5 mL of a saturated NH_4Cl solution. After extraction of the reaction mixture with diethyl ether (3×10 mL) and drying of the combined organic layers with $MgSO_4$ the solvent was removed under vacuum affording 965 mg of a colourless crude product which was dissolved in 6 mL MeOH containing 180 mg (3.0 mmol) K_2CO_3. After 35 min of stirring the solvent was removed, the residue was triturated with 10 mL diethyl ether and evaporated again. This procedure was repeated twice and finally the ether suspension was filtered, the filtrate evaporated and the residue was purified by flash chromatography (EtOAc/hexanes, 2:1) affording **40** as a colourless solid; yield: 367 mg (74%).

Dimethylbis(sulfoximine) 44

In a 25-mL round-bottom flask with a magnetic stirring bar 145 mg (0.293 mmol, 1.0 equiv.) **40** were dissolved in 3 mL *N,N*-dimethylaminotrimethylsilane (DMA-TMS) and the resulting solution was heated to 80 °C. After 3.5 h no more starting material could be detected by TLC in the clear, colourless reaction mixture. The excess DMA-TMS was condensed in a cryo-trap (cooled by N_2) furnishing the bis-silylated sulfoximine **41** in quantitative yield.

78 mg (0.122 mmol, 1 equiv.) of this crude product were dissolved in 1 mL dry THF in a 10-mL round-bottom flask and cooled to 0 °C. At this temperature 28.76 mg (0.256 mmol, 2.1 equivs.) potassium t-butoxide dissolved in 1 mL dry THF were added. After stirring for 15 min 0.03 mL (0.488 mmol, 4.0 equivs.) methyl iodide were added dropwise *via* syringe. The reaction was allowed to reach room temperature within 4 h and stirred for another 24 h. Aqueous work-up (10 mL diethyl ether and 10 mL water) followed by diethyl ether extraction (2×10 mL) and washing of the combined organic layers with 20 mL of a saturated NaCl solution afforded after drying with Na_2SO_4 and concentration under vacuum **43** as a yellow oil which was not further purified for deprotection; yield: 81 mg (99.4%).

In a round-bottom flask 64 mg (0.096 mmol, 1.0 equiv.) of the crude product **43** were dissolved in 2 mL methanol containing 27.8 mg (0.201 mmol, 2.1 equivs.) potassium carbonate. The resulting suspension was stirred for 2 h at room temperature. Then the solvent was removed under vacuum and the resulting residue was triturated with 5 mL water and 5 mL diethyl ether. After separation of the phases the aqueous phase was extracted with diethyl ether (2×10 mL) and the combined organic phases were washed with 15 mL of a saturated NaCl solution. After drying over Na_2SO_4 and removal of the solvent under reduced pressure **44** was obtained as a colourless solid; yield: 46 mg (92%); $R_f = 0.41$ (ether/hexanes, 5:1); mp 87 °C; $[\alpha]_D^{20}$: +7.0 (*c* 1.1, CH_2Cl_2); ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 0.960$ (6H, d, *i*-Pr CH_3, $^3J = 6.9$ Hz), 0.995 (6H, d, *i*-Pr CH_3, $^3J = 6.9$ Hz), 1.569 [6H, s, $S(CH_3)_2$], 1.921 (2H, m, *i*-Pr CH), 2.426 (6H, s, C_6H_4-CH_3), 3.604 (2H, m, N-CH), 3.677 (4H, m, CH_2-OH), 4.352 (2H, br, s, OH), 7.296 (4H, d, *m*-CH, $^3J = 8.2$ Hz), 7.877 (4H, d, *o*-CH, $^3J = 6.9$ Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 19.05$ (*i*-Pr CH_3), 19.27 (*i*-Pr CH_3), 21.63 (C_6H_4-CH_3), 21.96 (S-CH_3), 32.45 (*i*-Pr CH), 63.86 (N-CH), 64.48 (CH_2-OH), 90.01 (S-C-S), 129.31 (*m*-CH), 131.72 (*o*-CH), 134.57 (S-C), 144.11 (C_6H_4-C); MS (ESI, methanol) $m/z = 545.3$ (100%, $[M+Na]^+$); anal. calcd. for $C_{27}H_{42}N_2O_4S_2$: C 62.03, H 8.10, N 5.36; found: C 62.12, H 8.06, N 5.14.

Dichlorobis(sulfoximine) 46

In a Schlenk tube 6 mL dry CCl_4 were cooled to 0 °C and then 100.0 mg (0.202 mmol, 1.0 equiv.) **40** and 106.0 mg (0.404 mmol, 2.0 equiv.) triphenylphosphane were added. After stirring for 2 h at 0 °C the reaction mixture was heated to reflux for 40 h. Then 10 mL of diethyl ether were added inducing precipitation of triphenylphosphane oxide which was filtered off. After removal of all volatiles the remaining yellow oil was purified by flash chromatography (EtOAc/hexanes, 10:1) affording **46** as a colourless solid; yield: 50 mg (47%); $R_f = 0.75$ (EtOAc/hexanes, 1:1); mp 83 °C; $[\alpha]_D^{20}$: −40.65 (*c* 0.31, CH_2C1_2); ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 0.873$ (6H, d, *i*-Pr CH_3, $^3J = 6.8$ Hz), 0.947 (6H, d, *i*-Pr CH_3, $^3J = 6.8$ Hz), 2.074 (2H, dqq, *i*-Pr CH, $^3J = 3.8$ Hz, $^3J = 6.8$ Hz), 2.440 (6H, s, C_6H_4-CH_3), 3.206 (2H, ddd, N-CH, $^3J = 3.8$ Hz, $^3J = 6.5$ Hz), 3.424 (4H, d, CH_2-Cl, $^3J = 6.5$ Hz), 4.803 (2H, s, S-CH_2-S), 7.291 (4H, d, *m*-CH, $^3J = 8.2$ Hz), 7.763 (4H, d, *o*-CH, $^3J = 8.2$ Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 16.34$ (*i*-Pr CH_3), 20.10 (*i*-Pr CH_3), 21.72 (C_6H_4-CH_3), 30.45 (i-Pr CH), 47.39 (CH_2-Cl), 61.31 (N-CH), 71.83 (S-C-S), 129.32 (*o*-CH), 129.72 (*m*-CH), 135.40 (S-C), 144.50 (C_6H_4-C); MS (ESI, methanol): $m/z = 553.2$ (100%, $[M+Na]^+$), 531.3 (23%, $[M+1]^+$); anal. calcd. for $C_{25}H_{36}Cl_2N_2O_2S_2$: C 56.49, H 6.83, N 5.27; found: C 56.49, H 6.82, N 5.24.

Cu Complex 52

In a Schlenk tube 200 mg (0.276 mmol, 1.0 equiv.) **42** and 100 mg (0.276 mmol, 1.0 equiv.) $Cu(OTf)_2$ were stirred for 30 min under vacuum. Then under an atmosphere of dry argon 0.7 mL dry dichloromethane were added *via* syringe. The resulting suspension was stirred for 1 h at room temperature and then filtered using an argon flushed hydrophobic 0.45 μm PTFE syringe filter. The obtained green solution was transferred into a dry 25-mL flask and overlayed with dry hexanes. 24 h later turquoise crystals of **52** had formed; yield: (240 mg, 80%). A single crystal of this material was characterized by X-ray structural analysis.

Reduction of Acetophenone (Table 1, Entry 3)

In a 25-mL Schlenk flask 100 mg (0.202 mmol, 1.0 equiv.) **40** were dissolved in 2 mL toluene, followed by 16.9 mg (0.134 mmol, 0.66 equivs.) trimethylboroxine. After 30 min stirring at room temperature another 10 mL of toluene were added and distilled off under an Ar atmosphere to leave a volume of 2 mL. This procedure was repeated two more times. The third distillation was stopped after reduction of the solution to 3 mL volume at which point the flask was cooled to 0 °C and 0.202 mL (0.202 mmol, 1 equiv.) $BH_3 \cdot THF$ (1 M in THF) were added. 10 min later 24.28 mg (0.202 mmol, 1.0 equiv.) acetophenone were added and again after 10 min the reaction was stopped by adding 1.5 mL of methanol. After removal of all volatiles under vacuum the yield and the enantiomeric excess [48% ee in favour of (+)-(*R*)-phenylethan-1-ol] were determined by chiral GC [RT-BDex cst-TM, Restek; oven: 60 °C to 230 °C, 4°/min; flow N_2: 2 mL/min; Injec. and FID: 230 °C; split 1:100; t_R: acetophenone: 15.82 min, (+)-(*R*)-1-phenylethan-1-ol: 19.63 min, (−)-(*S*)-1-phenylethan-1-

ol: 20.10 min]. The spectroscopic data of the reduction product corresponded to those described in the literature.[84]

1,4-Addition of Diethylzinc to 2-Cyclohexenone (Table 3, Entry 6)

In a Schlenk tube were dissolved 13.0 mg (0.024 mmol, 1.0 equiv.) **46** in 0.4 mL dichloromethane at room temperature. Then 3.28 mg (0.024 mmol, 1.0 equiv.) dry $CuCl_2$ were added and the resulting green solution was cooled to $-90\,^{\circ}C$. At this temperature 96.13 mg (1.0 mmol) 2-cyclohexen-1-one and 2 mL (2 mmol) of a 1 M solution of $ZnEt_2$ in hexane were added *via* syringe. After 18 h the reaction mixture was poured onto 20 mL of a vigorously stirred solution of NH_4Cl at $0\,^{\circ}C$. The phases were separated and the organic layer was extracted with 10 mL of a NH_3/NH_4Cl (pH 9) solution. The aqueous layer was extracted with diethyl ether (3×15 mL) and the combined organic layers were washed with 20 mL of saturated NaCl solution. After drying with Na_2SO_4 the yield and the enantiomeric excess were determined by chiral GC [Beta-Dex120, Supelco; oven: $80\,^{\circ}C$; flow N_2 1 mL/min; Injec. and FID $230\,^{\circ}C$; split 1:100; t_R: 2-cyclohexen-1-on 24.26 min, (+)-(*R*)-3-ethylcylohexanone: 52.56 min; (−)-(*S*)-3-ethylcylohexanone: 53.44 min]. The spectroscopic data of the product corresponded to those described in the literature for the enantiomer.[98] Its absolute configuration was determined by measuring the optical rotation ($[\alpha]_D^{20}$: +2.0 (c 0.15, toluene)).[98,99]

Acknowledgements

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