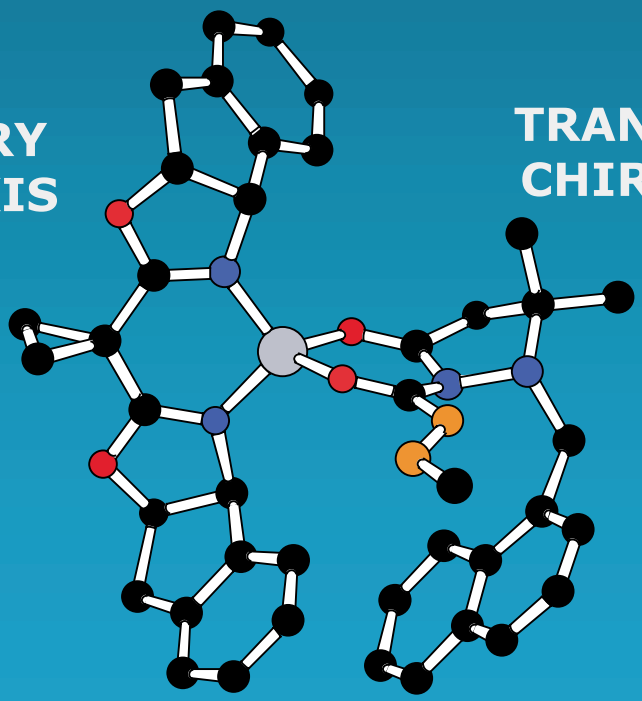
CHIRAL RELAY IN ENANTIOSELECTIVE REACTIONS

TEMPORARY CHIRAL AXIS

TRANSIENT CHIRALITY



CONFORMATIONAL STEREOISOMERISM

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Chiral Relay: A Novel Strategy for the Control and Amplification of Enantioselectivity in Chiral Lewis Acid Promoted Reactions

Olivier Corminboeuf,[a] Laura Quaranta,[a] Philippe Renaud,*[a] Mei Liu,[b] Craig P. Jasperse,[b] and Mukund P. Sibi*[b]

Abstract: Chiral Lewis acid catalysis has emerged as one of the premiere method to control stereochemistry. Much effort has gone into the design of superior ligands with increasing steric extension to shield distant reactive sites. We report here an alternative and complementary approach based on a "chiral relay". This strategy focuses on the improved design of achiral templates which may relay and amplify the stereochemistry from ligands. The essence of this strategy is that the chiral Lewis acid would effectively convert an achiral template into a chiral non-racemic template. This approach combines the advantages of enantioselective catalysis (substoichiometric amount of the chiral inducer) with the ones of chiral auxiliary control (efficient and predictable stereocontrol).

Keywords: asymmetric catalysis · asymmetric synthesis · conformation analysis · enantioselectivity · Lewis acids

Introduction

The design of enantioselective Lewis acid catalyzed reactions is currently under intense scrutiny.[1] Several parameters factor into the design of an enantioselective Lewis acid catalyzed reaction: the nature of the Lewis acid, the nature of the chiral ligand, and the nature of additives and solvent all play important roles, and offer opportunities for the optimization of a reaction. The majority of recent research has focused on developing new and improved chiral ligands. Alternative methods for stereocontrol and enantioselectivity enhancement have also been devised by careful manipulation of the Lewis acid-chiral ligand complex. The most notable of these approaches are 1) autocatalysis,[2] 2) metal-geometry-induced ligand-asymmetry,[3] 3) asymmetric activation of racemic as well as conformationally flexible ligands,[4] and 4) chiral poisoning.[5]

Another component of an asymmetric transformation is the substrate itself and its nature can also play a key role. For instance, the Diels–Alder reactions of *N*-alkenoyl-1,3-oxazolidin-2-ones with dienes has been thoroughly examined and very high levels of enantioselectivity have been achieved with different types of Lewis acids.[6] The 1,3-oxazolidinone auxiliary enables chelation of the metal catalyst by the two carbonyl groups, resulting in a rigid, well-defined conformation of the reactive intermediate complex.[7] The selective face shielding required for enantioselectivity is exclusively provided by the chiral Lewis acid, so naturally optimizing the chiral ligand is the normal way to enhance selectivity. Excellent results have been obtained with relatively sophisticated chiral ligand systems that provide increased levels of steric extension in order to efficiently shield one face of the reaction center. However, the design and optimization of ligands is often time consuming.

Recently, we have launched a program to design alternative achiral templates[8] that differ from oxazolidinones in that they can participate actively in stereoinduction by indirectly relaying and amplifying the stereoinduction originally provided by the chiral Lewis acid. Three desirable outcomes could result: 1) for a given ligand, the modified template will amplify enantioselectivity; 2) for a given ligand, the modified template will reverse the sense of stereoselectivity, and 3) that useful levels of enantioselectivity will be possible even when relatively small and/or cheap chiral ligands are used.

Davies has recently introduced the term "chiral relay" in chiral auxiliary controlled reactions.[9] Davies' strategy is based on the use of conformationally flexible protecting groups that are inserted between the stereogenic center and the prochiral reactive center. Due to steric interactions with the stereogenic center, the conformationally mobile group

[a] Prof. P. Renaud, Dr. O. Corminboeuf, Dr. L. Quaranta
University of Bern
Department of Chemistry and Biochemistry
Freiestrasse 3, 3000 Berne 9 (Switzerland)
Fax: (+41) 31-631-3426
E-mail: philippe.renaud@ioc.unibe.ch

[b] Prof. M. P. Sibi, Dr. M. Liu, Dr. C. Jasperse
Department of Chemistry, North Dakota State University
Fargo, ND 58105-5516 (USA)
Fax: (+1) 701-231-1057
E-mail: mukund.sibi@ndsu.nodak.edu

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adopts a defined conformation that shields efficiently one face of the reaction center. By this process, the stereochemical information is relayed and even amplified, thus enabling efficient control of diastereoselectivity. In Davies' "chiral relay", the chiral source is embedded in the auxiliary, and thus must be built into the substrate itself and cannot be used catalytically.

The approach we have chosen differs from Davies' in that in our relay network, asymmetry originates with a chiral Lewis acid, but is then relayed/amplified via an achiral template. While the auxiliary must be built into the substrate, the fact that asymmetry originates external to the substrate makes possible the use of only catalytic quantities of the chiral source in order to achieve enantioselectivity. This approach has already been reported in the literature but not clearly recognized as a general concept. In this review, we would like to put together reports from the literature using this approach in a conscious or unconscious way and to define general strategies that can be used to efficiently enhance the stereochemical control of chiral Lewis acid-catalyzed reactions.

The essence of this strategy is that the chiral Lewis acid would effectively convert an achiral template into a chiral nonracemic template (or chiral auxiliary).[10] A general scheme summarizing the whole process is depicted in Figure 1. In an ideal case, the role of the Lewis acid would be to induce and control the asymmetry of the template and participate minimally in the control of the reaction selectivity. In real cases, both the chiral auxiliary and the chiral Lewis acid will influence the face selectivity at the reactive unit; thus the stereochemical impact of the chiral Lewis acid and the chiral template may be either matched or mismatched. If the template is structured so that it "matches" the Lewis acid, the result will be amplification of enantioselectivity. In a "mismatched" case in which the chiral template dominates over the chiral Lewis acid, the sense of selectivity will be reversed relative to that caused by the chiral Lewis acid alone.

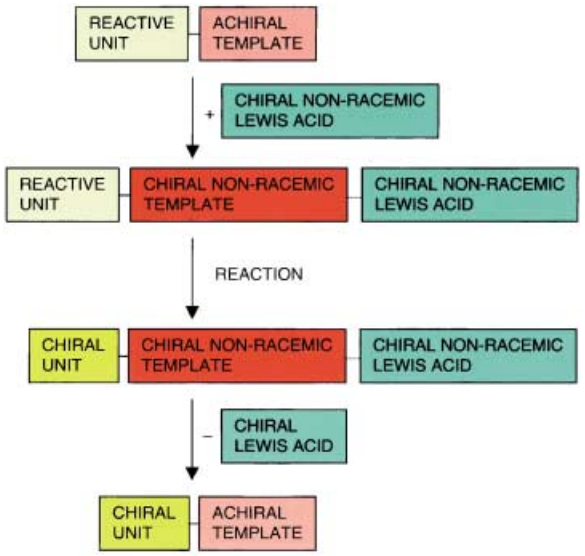

Figure 1. General scheme for chiral relay in Lewis acid promoted reactions. The term achiral template is used in a broad sense that includes rapidly interconverting enantiomeric groups (conformational enantiomers).

The transfer of chirality from the ligand to the template can follow one of two strategies: 1) the complexation locks a conformationally labile template into a chiral conformation; or 2) selective complexation of an enantiotopic group generates a new stereogenic unit (axis or center). Examples following these two strategies are described below.

Conformationally Labile Templates

Pyrazolidinones **1** were investigated by Sibi and co-workers as alternatives to oxazolidinones for enantioselective Diels–Alder reactions of crotonate derivatives (Figure 2).[11] The tetrahedral *N*(1) atom inverts rapidly; however, in the presence of a chiral Lewis acid, it should preferentially exist in one of the two possible asymmetric conformations **2** or **3**. Since the *N*(1) stereogenic center is relatively close to the reaction center, it was expected that it would strongly influence the stereoselectivity of the cycloaddition. The data presented in Figure 2 for reactions with cyclopentadiene in the presence of copper(II) triflate-bisoxazoline [Equation (1)] confirm this: The enantioselectivity for the major *endo* adduct correlates directly with the size of the relay group, going from a low 8% *ee* with R = H to 92% *ee* with R = 1-naphthyl-CH_2. Interestingly, under similar reaction conditions, the 3-crotonyl-oxazolidin-2-one derivative gave the cycloadduct in only 23% *ee*. The low selectivities with R = H and with oxazoli-

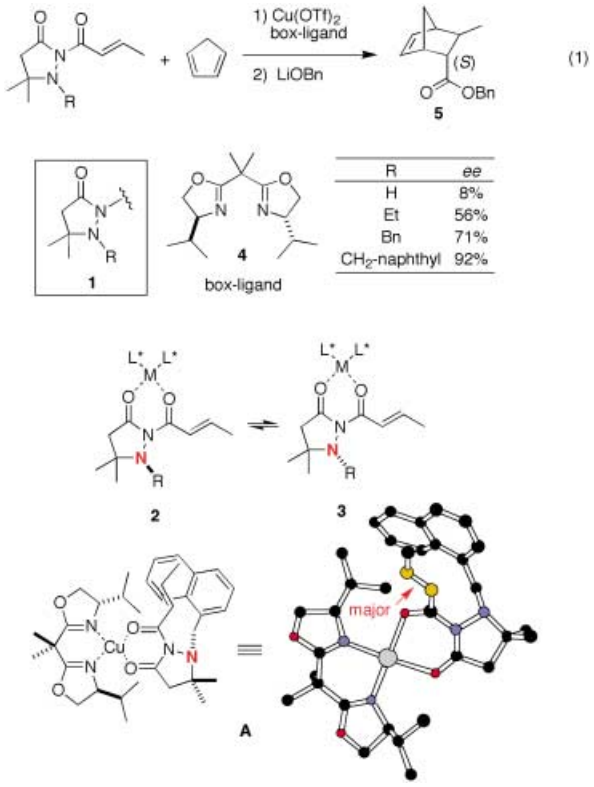

Figure 2. 1-Alkylpyrazolidin-3-one as active template form copper(II) catalyzed enantioselective Diels–Alder reactions.

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dinone as template show that the chiral Lewis acid alone is not sufficient to give efficient face shielding, but that the relay group R in the template is necessary. These results are best explained by a square planar model relative to copper(II) (model **A**).

Enantioselectivity amplification using chiral relay templates has been demonstrated by Sibi and Liu in conjugate amine additions to enoates [Equation (2), Figure 3].[12] The conjugate addition of *N*-methoxybenzylhydroxylamine to enoates **11** in the presence of chiral Lewis acids proceeds with good chemical efficiency and enantioselectivity depending on the template (Figure 3). For example, reaction of the

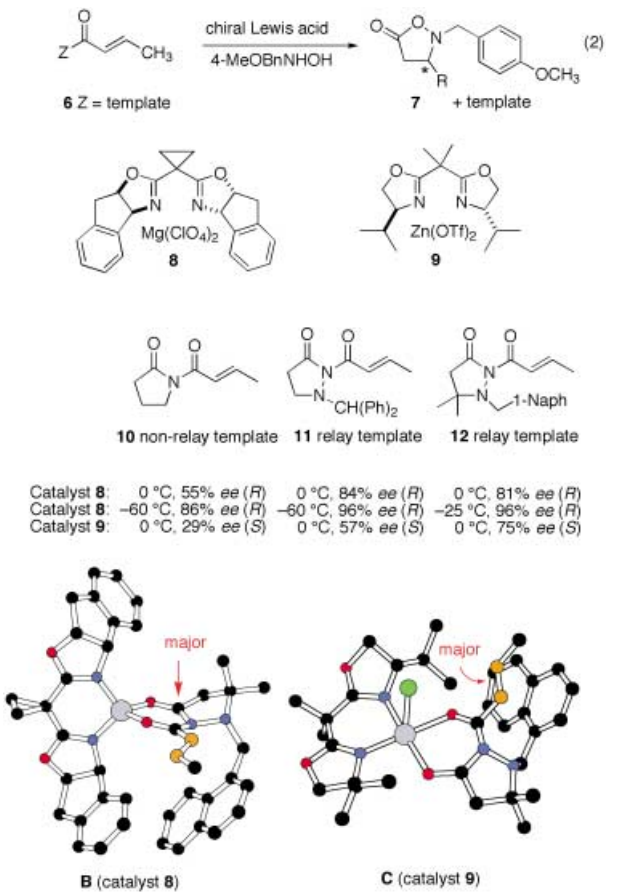

Figure 3. Conjugate amine additions using relay templates. For clarity, the OTf (= OSO_2CF_3) group in model **B** is represented as single green atom.

non-relay pyrrolidinone template **10** gave the product isoxazolidinone **7** in modest *ee* using either catalyst **8** or **9** at 0 °C. It is interesting to note that the configuration of the product is reversed when catalyst **8** and **9** are used although the ligands have the same C-4 stereochemistry. In contrast to reaction with the non-relay template, the two chiral relay templates (**11** and **12**) gave much higher levels of selectivity at 0 °C using either catalyst **8** or **9**. This clearly demonstrates that one can make improvements in selectivity by a mere change in the template. The enantioselectivity amplification using the relay templates is more evident at lower temperatures where high selectivity can be obtained at −25 °C. Tentative models accounting for the reversal in face selectivity using catalysts **8** and **9** are presented in models **B** (tetrahedral magnesium atom) and **C** (square pyramidal zinc atom).

A different strategy has been examined by Renaud using 4-substituted 1,3-benzoxazol-2-(3*H*)-ones **13** as templates for Diels–Alder reaction of acrylate derivatives (Figure 4).[13] Under chelation control with a chiral Lewis acid, the acryloyl

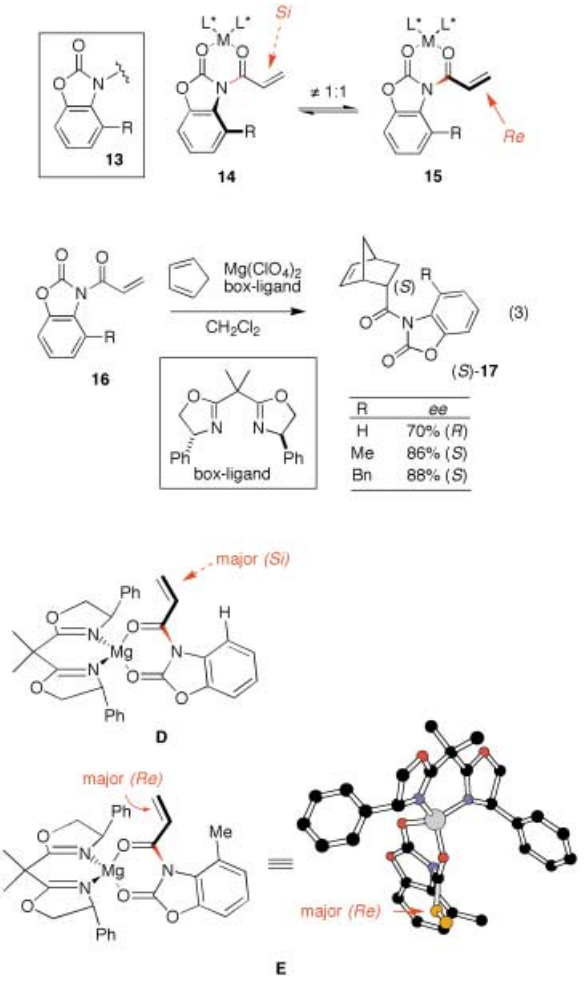

Figure 4. 4-Substituted-1,3-benzoxazol-2-(3*H*)-ones as active achiral template for enantioselective Diels–Alder reactions.

group cannot be coplanar with the aromatic ring and is strongly twisted, so two diastereomeric conformers **14** and **15** are generated. They differ by the absolute configuration of the axis of chirality in the template, with the result that the R group is either on the *Si* or *Re* side of the acrylate. By varying the substituent at C(4) of the 1,3-benzoxazol-2-(3*H*)-ones, the shielding of the acryloyl moiety is changed with a strong influence on the stereochemical outcome of the reaction [Equation (3)]. A dramatic inversion of the absolute configuration of the major *endo* product was observed on going from the nonsubstituted system (R = H) to the alkylated systems (R = Me, Bn). The stereochemical results are rationalized by the models **D** and **E** based on tetrahedral magnesium(II) complexes. When R = H, the chiral axis is in such a configuration that the *Si* face is less shielded (model **D**). But a methyl substituent strongly shields the *Si* face so that the major product instead arises from attack on the *Re* face of the

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acryloyl moiety. This example represents at the moment the only case where a chiral relay effect has led to a reversal of the stereochemical outcome of an enantioselective reaction.

These recent examples of conformationally labile templates participating in chiral relay demonstrate the validity of this approach. However, they represent just three examples out of many possibilities; we anticipate that many other such systems will be developed.

Selective Complexation of Enantiotopic Groups

In the above examples, a chiral Lewis acid could selectively lock one of two conformations for an otherwise conformationally labile template. An alternative situation is when the Lewis acid chooses between two otherwise enantiotopic coordination sites: In the presence of a chiral Lewis acid, two carbonyls which are otherwise enantiotopic become diastereotopic. Likewise sulfone or sulfonamide oxygens become diastereotopic in the presence of a chiral Lewis acid, and even sulfide or ether lone pairs become diastereotopic and can be coordinated selectively. Several examples are known in which selective complexation of enantiotopic groups serves to relay stereochemistry from the chiral Lewis acid to a reaction center. With the exception of the work of Corey,[14] Toru[15] and Hiroi,[16] the importance of the stereogenic relay unit has not been clearly identified and examined.

***N*-Arylmaleimides**: In pioneering work, Corey has reported a highly enantioselective Diels–Alder reaction of *ortho*-substituted *N*-arylmaleimides **21** (Figure 5).[14] When the *ortho* substituent is not a hydrogen atom, the two carbonyl groups of the maleimide are enantiotopic. Upon complexation with a chiral Lewis acid, the two diastereomeric complexes **19** and **20** are generated due to the presence of a novel axis of chirality. Increasing the size of the *ortho* substituent has a very positive effect on the enantioselectivity that can be interpreted as the cumulative effect of ligand control and chiral relay [Equation (4)]. Indeed, as shown in model **F**, the *tert*-butyl group (R in model **F**) strongly shields one face of the maleimide.

Sulfonamides: The sulfur center of sulfonamides **26** is prochiral (Figure 6). By selective complexation of one of the two enantiotopic oxygen atoms, the sulfur becomes a new asymmetric center. For instance, following chelation with a chiral Lewis acid, *N*-sulfonyl carboxamides are converted to the diastereomeric complexes **33** and **34**. Hiroi has taken advantage of this property of sulfonamide to devise enantioselective radical allylation and cyclization reactions [Figure 6, Equations (5) and (6)].[16] In the allylation process, the size of the carbon residue R on the sulfonamide strongly influences the stereochemical outcome, with *ee*'s rising from 5% (R = Me) to 50% (R = Tol) when the Lewis acid generated from titanium tetraisopropoxide and the TADDOL **27** is used. The level of enantioselectivity was dependent on the chiral Lewis acid employed. By changing the Lewis acid to magnesium triflate and using a different ligand, β-hydroxysulfoxide **28**, an *ee* of 83% was obtained in the allylation reaction.

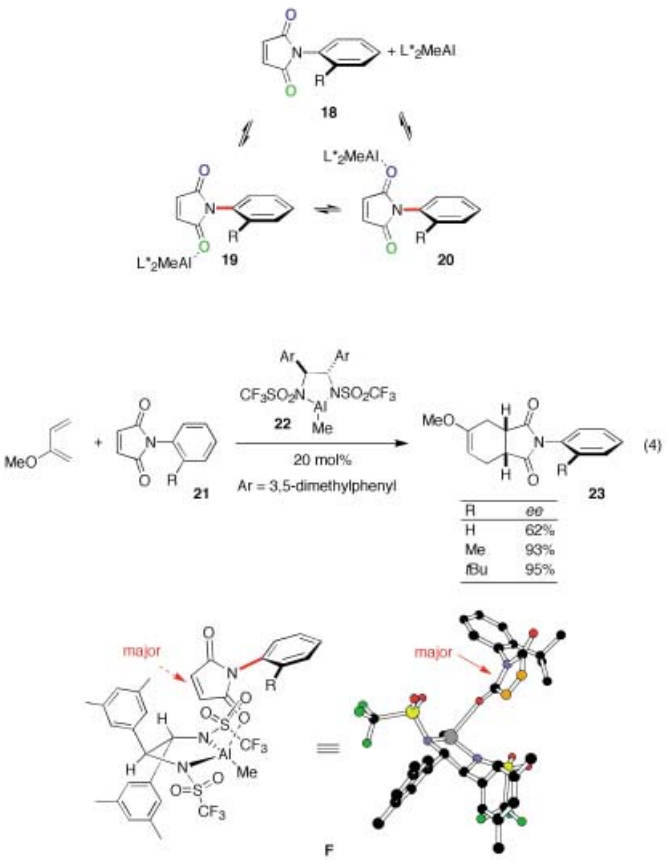

Figure 5. Generation of a chiral axis during enantioselective Diels–Alder reactions of *N*-arylmaleimides.

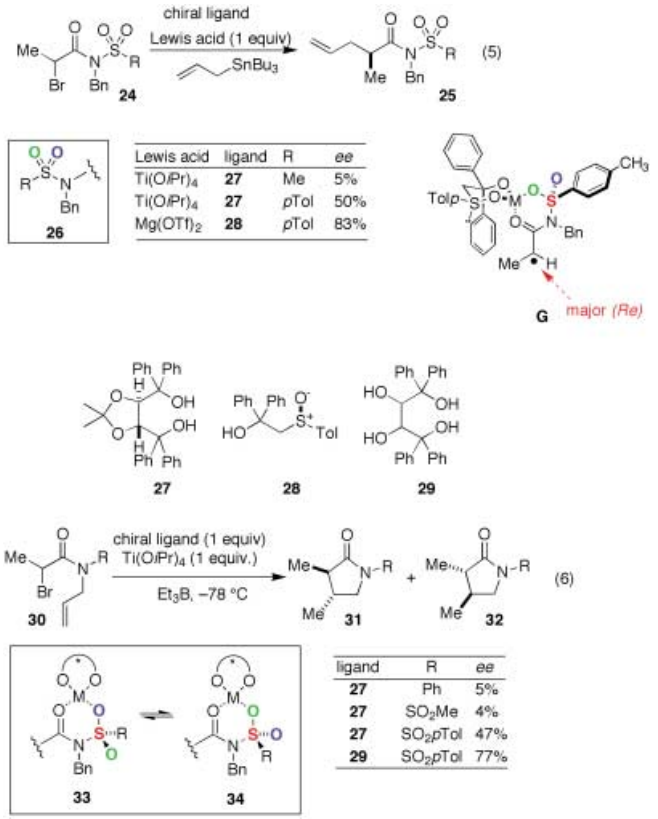

Figure 6. Enantioselective radical allylation and cyclization of *N*-sulfonylcarboxamides.

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Similar results were obtained for the cyclization reaction [Equation (6)]. Quasi racemic products are obtained with both the *N*-phenyl and the *N*-methanesulfonyl moiety. However, the *N*-(*p*-toluenesulfonyl) group gave moderate enantioselectivities up to 77% *ee* under optimized conditions. The model **G** has been proposed to rationalize this result. Preferential attack is occurring *anti* to the *p*-toluenesulfonyl group and is mainly controlled by the chiral sulfur atom (model **G**). When there is no asymmetric sulfur, or when the R group on the asymmetric sulfur is too small to afford face shielding, the selectivity is low.

Jørgensen has recently reported enantioselective aza-Diels–Alder reactions of sulfonyl imines catalyzed by a copper(I)-(*p*-Tol)-BINAP complex (Figure 7).[17] Interestingly, the use of a *p*-toluenesulfonyl group on nitrogen led to a reversal of the stereochemical outcome relative to the simple *N*-phenyl derivative [Equation (7)]. The importance of the chiral sulfur atom is shown in the putative model **H**, with major attack occuring *anti* to the *p*-tolyl group.[18] No attempt to vary the nature of the aryl substituent at the sulfur atom has been made and it is therefore difficult to quantify the role of the chiral relay in this process.

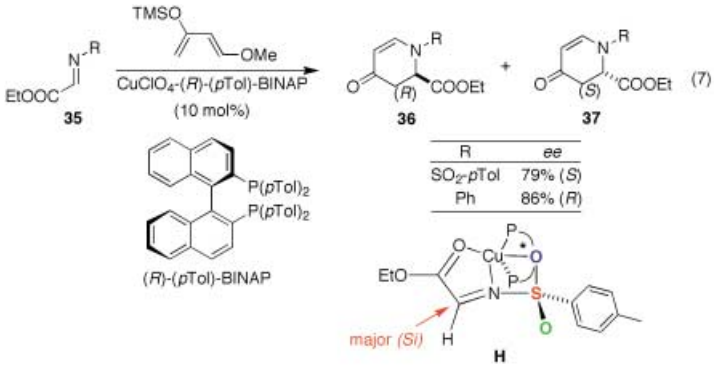

Figure 7. Aza-Diels–Alder reactions of *N*-sulfonylimines.

In a recent report on enantioselective H-atom transfer reactions, Sibi and Sausker have demonstrated the effective use of achiral sultam templates (Figure 8).[19] The addition of nucleophilic radicals to sultam derived enoate **38** using the catalyst **39** followed by enantioselective H-atom transfer gave **40** in high enantioselectivity [Equation (8)]. In contrast, nucleophilic radical addition to the corresponding lactam **41** using catalyst **39** were less successful and the enantioselectivity for the product was very low [Equation (9)]. These results demonstrate the importance of the tetrahedral sulfone moiety for achieving high selectivity. In reactions with the two different templates, the working hypothesis is that the rotamer geometry of the chiral Lewis acid complexed substrate is the key stereo determinant in the H-atom transfer step. Model **I**, in which the sultam is used, accounts for the observed face selectivity. The tetrahedral nature of the sulfone allows for complexation of one of the enantiotopic oxygens allowing for better rotamer control of the α-substituted acrylate. The poor reactivity and selectivity observed with the lactam template has been rationalized using Model **J** in which the trigonal nature of the carbonyl makes rotamer control difficult.

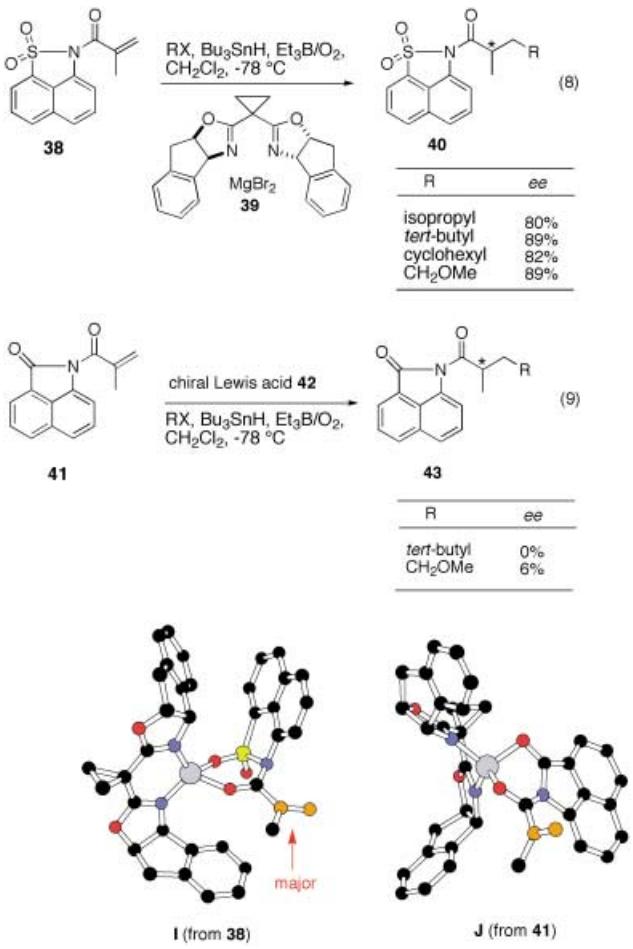

Figure 8. Enantioselective H-atom transfer using sultam templates.

Sulfones: A chiral relay based on the same principle as the one presented for the sulfonamides has been reported with sulfones. Complexation of one oxygen of the sulfone **44** generates a new chiral center, so when the Lewis acid is chiral it gives the diastereomeric complexes **45** and **46** (Figure 9). Toru has applied this principle to devise enantioselective radical addition-allylation reactions of vinyl sulfones.[15] The best results were obtained with 2-(1-benzylbenzimidazolyl) sulfones [Equation (10)] and the results are explained by the model **K** where chelation by a zinc atom efficiently shields the *Re* face and allows the *Si* face free for the radical allylation to occur.

Wada and Kanemasa have reported hetero Diels–Alder[20] and Diels–Alder[21] reactions of alkenyl phenylsulfonylmethyl ketones catalyzed by titanium TADDOLlates [Figure 10, Equations (11) and (12)]. Very high levels of enantioselectivity have been achieved. The complex intermediate **L**, containing a chiral mono-complexed sulfonyl group in which the phenyl group on sulfur provides face shielding, has been postulated. In this case also, only the phenylsulfonyl derivative has been examined and the importance of the chiral relay is not clearly quantified.

Sulfides: Unsymmetrical sulfides can also be used in a chiral relay strategy. Selective complexation with one of the two enantiotopic lone pairs on sulfur makes the sulfur center

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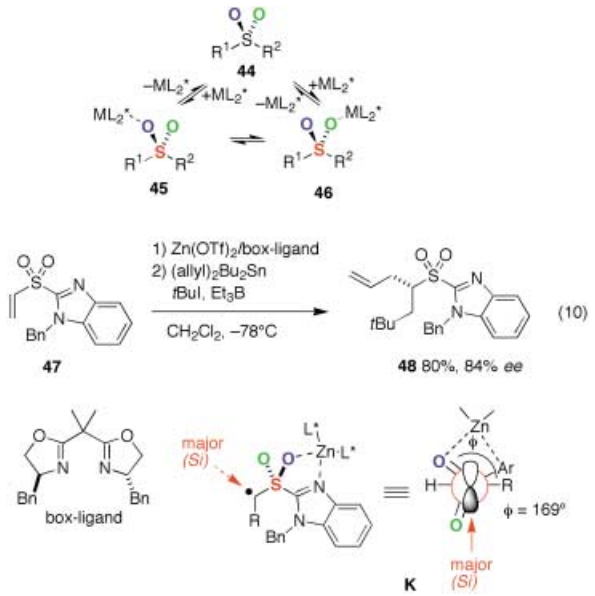

Figure 9. Enantioselective allylation and cyclization of 1-sulfonyl radicals.

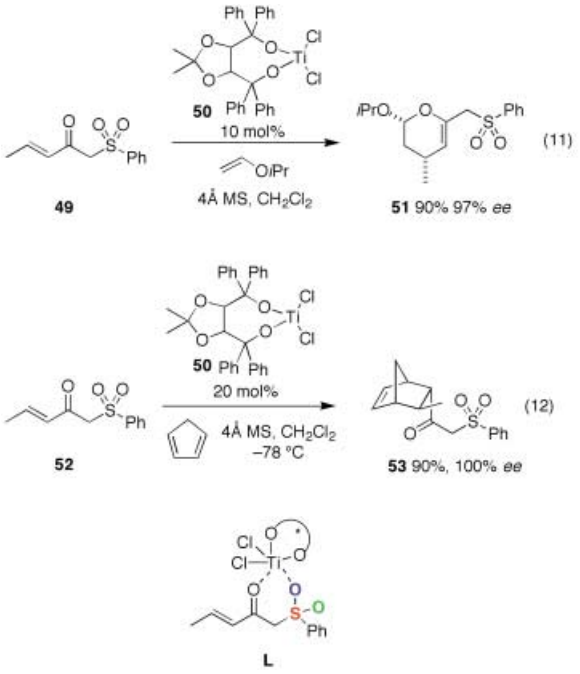

Figure 10. Hetero-Diels–Alder and Diels–Alder reactions of alkenyl phenylsulfonyl ketones.

asymmetric. This is shown in Figure 11 for the 2-alkylthioacrylates **56**, which give diastereomeric complexes **54** and **55** upon complexation with a chiral Lewis acid. In this particular case, the newly created chiral center is very near the reaction center so stereoinduction from the sulfur should be important. For the cycloaddition depicted in Equation (13), Aggarwal has reported that going from a methanethio to a benzenethio brings a significant enhancement of the enantioselectivity.[22] The results are consistent with model **M**, in which the sulfur is complexed such that the phenyl group points away from the phenyl groups on the chiral ligand, and in which preferential attack occurs *anti* to the phenyl group at sulfur. This

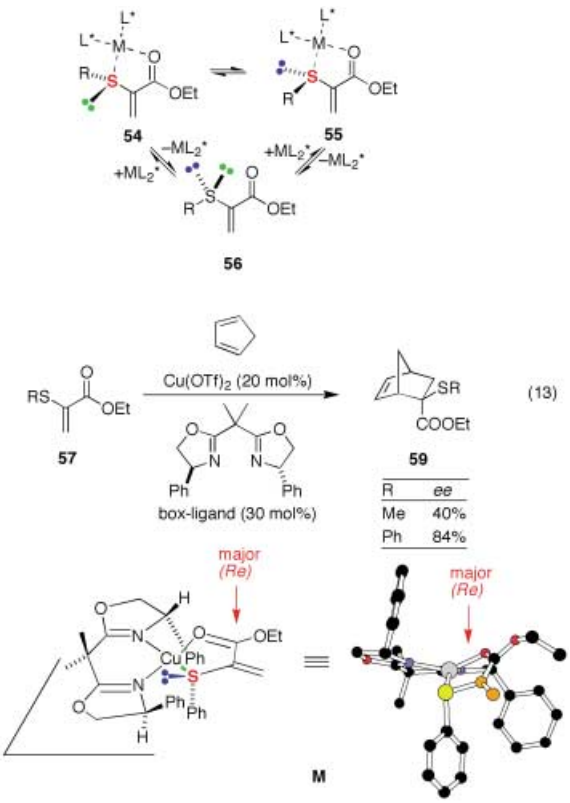

Figure 11. Diels–Alder reaction of 2-phenylthioacrylate.

represents an example where the stereocenter in the ligand and in the relay group appear to be "mismatched", but in which the relay group dominates the outcome at the reaction center.

Conclusion

We have attempted in this account to show different examples of enantioselective reactions demonstrating that by proper choice of the substrate, it is possible to convey stereochemical information from the Lewis acid to the reaction center via a chiral relay. This opens a possible route by which high levels of enantioselectivity may be reached, perhaps without requiring complex chiral ligands. If the relay center provides ample face shielding, the only requirement for the chiral ligand would be that it should be able to discriminate between diastereotopic Lewis acid-substrate complexes. Practical applications of this strategy is certainly going to be important since in Lewis acid catalyzed reactions, catalyst loading is usually important (5–30 mol% in most cases) and recovery of the catalysts is often difficult due to their sensitivity to hydrolysis. One of the major advantages of the relay approach will be in enantioselectivity amplification. The approach should be of great utility when one needs improvement in selectivity from 70% *ee* range to >90% *ee* or situations where one needs to conduct the reactions at a more practical temperature. Chiral relay will clearly not be limited to the cases presented in this account and novel systems allowing efficient relay will be investigated by us and by others.

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