Trygve Andreassen

# New Methods for Preparation of Optically Active Unsaturated Amines

Thesis for the degree of Philosophiae Doctor

Trondheim, January 2009

Norwegian University of Science and Technology
Faculty of Natural Sciences and Technology
Department of Chemistry

NTNU
Norwegian University of
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Trygve Andreassen
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# Contents

# Preface

The work presented in this text spans over different attempted strategies for preparing enantiomerically enriched compounds. Initially, the project goal was to explore a potential new general route to optically active allylic amines (and allylic alcohols). As the project evolved, it became apparent that the broader title "New methods for preparation of optically active unsaturated amines" would be a more suitable description of the work presented in this thesis. The first chapter gives a short introduction with emphasis on the importance of chirality in chemistry. Chapter 2 deals with ene-reactions between aza-analogues of sulfur dioxide (**1** and **7**) and alkenes, where reactivity and stereoselectivity were induced by chiral Lewis acids. The resulting ene-products were rearranged to *N*-substituted allylic amines by [2,3]-sigmatropic rearrangement. After obtaining low stereoselectivities, our attention was shifted towards similar reactions with the chiral sulfinyl sulfinamide **1f** as enophile (Chapter 3). Although selectivities were improved for these reactions, the following rearrangements were unsuccessful. Chapter 4 (Papers I and II) describes our work with aza-Diels-Alder reactions between *N*-sulfinyl α-imino esters (**25**) and dienes. This lead to a number of six-membered aza-cycles (**29**) not previously reported, reaching excellent stereoselectivities. Easy removal of the *N*-substituent also contributes to making this a useful route to new non-proteinogenic amino acid derivatives (**38**). Attempts to use different aromatic heterocycles as dienes in the same aza-Diels-Alder reactions, revealed a new route to heteroaromatic glycine derivatives (**39**) (Paper III).

# Appended papers

I) Andreassen, T., Haaland, T., Hansen, L. K. and Gautun, O. R.
Asymmetric aza-Diels-Alder reactions of an *N*-*tert*-butanesulfinyl α-imino ester
*Tetrahedron Lett.*, 2007, **48**, 8413-8415.

II) Andreassen, T., Lorentzen, M., Hansen, L. K. and Gautun, O. R.
The use of two optically active *N*-sulfinyl α-imino esters in the stereoselective aza-Diels-Alder reaction
*Tetrahedron*, accepted.

III) Andreassen, T., Hansen, L. K. and Gautun, O. R.
Diastereoselective synthesis of heteroaromatic glycine derivatives
*Eur. J. Org. Chem.*, 2008, 4871-4876.

# Abbreviations and symbols

| | |
|---|---|
| BINAP | 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl |
| BINOL | 1,1'-binaphtalene-2,2'-diol |
| Bn | benzyl |
| Box | bis(oxazoline) |
| Bu | butyl |
| Cbz | benzyloxycarbonyl |
| DAG | diacetone-α-*D*-glucofuranose |
| de | diastereomeric excess |
| dr | diastereomeric ratio |
| DIBAL-H | diisobutylaluminium hydride |
| ee | enantiomeric excess |
| EI | electron impact |
| ESI | electrospray ionisation |
| Et | ethyl |
| *et al.* | *et alia* (and others) |
| equiv. | equivalent |
| HDA | hetero Diels-Alder |
| HOMO | highest occupied molecular orbital |
| HMDS | hexamethyldisilazane |
| HPLC | high performance liquid chromatography |
| HSAB | hard-soft acid-base |
| IR | infra red |
| LA | Lewis acid |
| LUMO | lowest unoccupied molecular orbital |
| *m*-CPBA | *meta*-chloroperbenzoic acid |
| Me | methyl |
| MS | mass spectrometry |
| NMR | nuclear magnetic resonance |
| o.n. | overnight |
| Ph | phenyl |
| Pr | propyl |
| PyBox | bis(oxazolinyl)pyridine |
| r.t. | room temperature |
| TADDOL | α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanol |
| TBS | *tert*-butyldimethylsiloxy |
| temp. | temperature |
| Tf | trifluoromethanesulfonyl |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TMS | trimethylsilyl or tetramethylsilane |
| Tol | tolyl |
| Ts | tosyl, *p*-toluenesulfonyl |
| UV | ultra violet |

# 1 Introduction

When a molecule and its mirror image are non-superimposable, they are defined as chiral and form an enantiomeric pair. Chirality is found everywhere in nature and is an important factor in most chemical processes in living organisms. Two enantiomeric molecules may have different effects on an organism, due to its chiral nature. This can be well exemplified by considering how enantiomeric compounds may have different odour, explained by different behaviour towards the chiral receptor sites in the nose. For instance, the enantiomers (*R*)- and (*S*)-carvone smell of spearmint and caraway respectively.[1] A more critical area is the therapeutic effect of chiral drugs on the human body. The most famous example is thalidomide, a sedative and anti-nausea drug used in Europe from late 1950's to early 1960's.[2] Whereas the *R*-isomer had the desired effects, the *S*-isomer proved to be responsible for a large number of birth defects in children born to women using this drug while pregnant. The drug was later shown to racemise *in vivo*, also making the *R*-isomer ineligible for the pregnant.

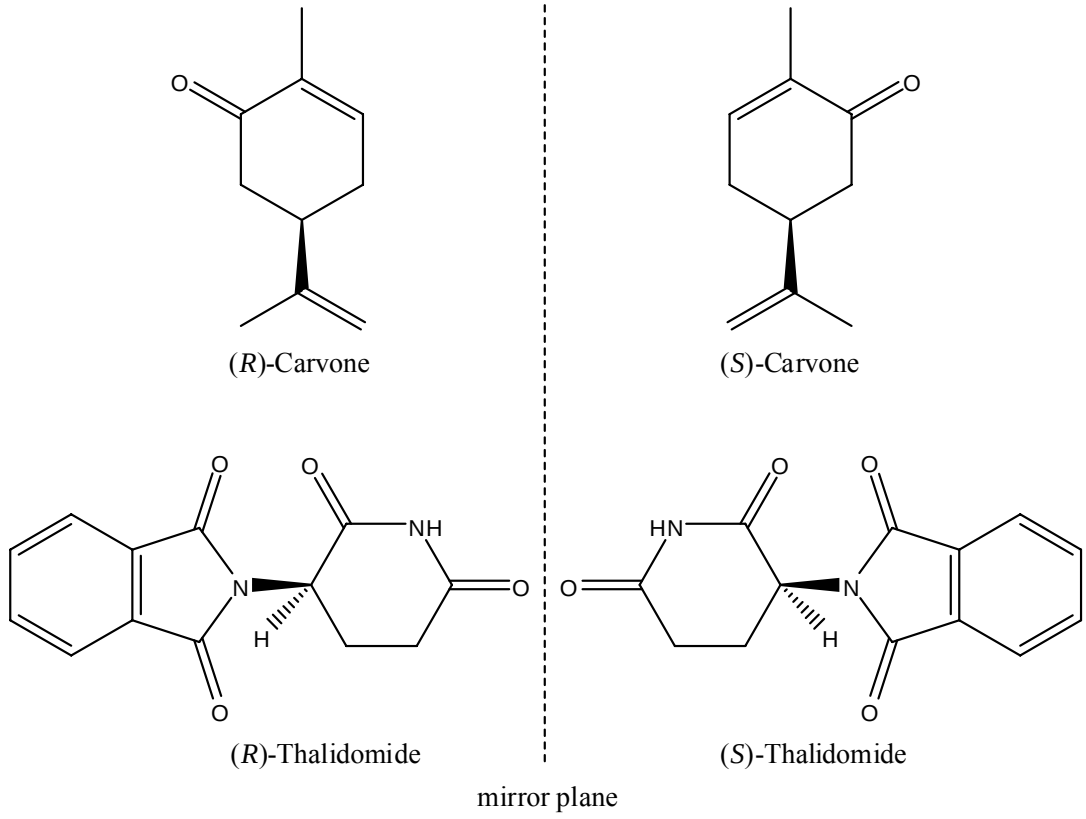
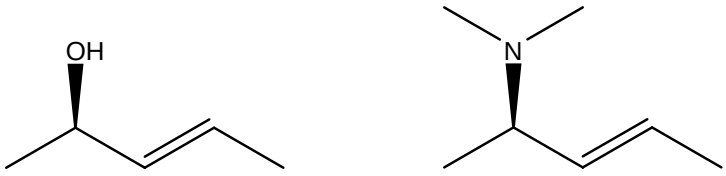



**Figure 1.1** Stereoisomers of carvone and thalidomide.

With the thalidomide tragedy fresh in mind, the need for optically pure drugs is obvious. Finding new methods for preparing enantiomerically enriched compounds has become an important basic research area worldwide. As late as 2001, William S. Knowles, Ryoji Noyori and K. Barry Sharpless were awarded the Nobel Prize in chemistry for their important contributions to the field.

The original goal in this project was to explore a potential new general route to enantiomerically enriched allylic amines and alcohols (Figure 1.2). These structural elements are found in countless of physiologically active compounds, and new strategies for preparing them enantiomerically pure are highly welcome. Besides being important synthetic targets in their own respect, allylic amines and alcohols are readily transformed to other functionalities, making them excellent precursors in organic synthesis. Good reviews on preparation of allylic amines and alcohols have been written by Johannsen/Jørgensen[3] and Banerjee *et al.*[4] respectively.




Allylic alcohol Allylic amine

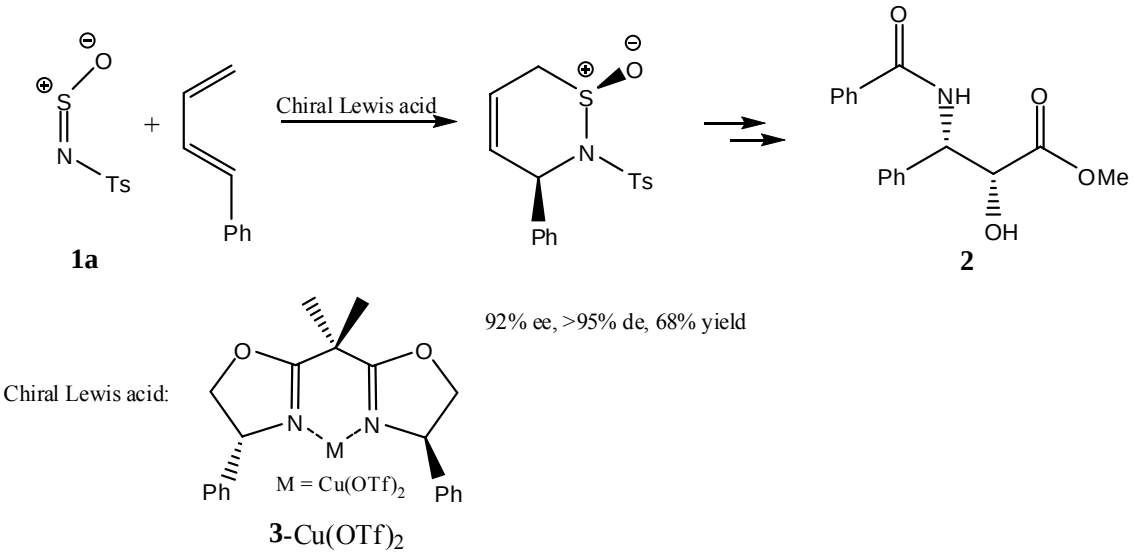
**Figure 1.2** Targeted structural elements.

Already at this stage, it should be pointed out that gradual changes of the project goals were required during the work period, and some of the new methods described in this work have little focus on the allylic functionality. Also, due to time constraints, our efforts were restricted to the formation of amino-compounds. The chapters have been written in chronological order, introducing new background material as it becomes relevant to the work presented.

# 2 Enantioselective ene-reactions with aza analogues of sulfur dioxide

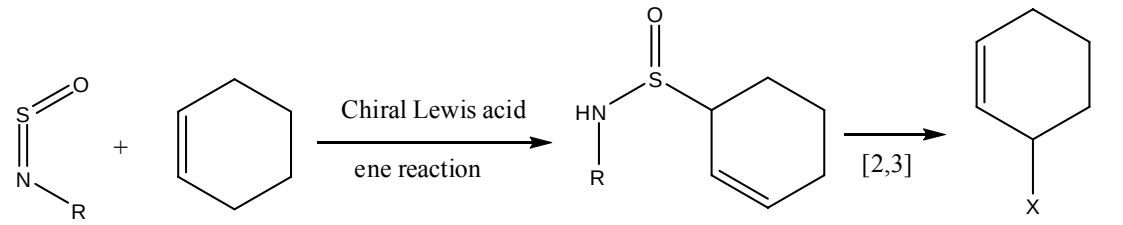
## 2.1 Background

During the last decade, Gautun and co-workers have developed a method for preparing enantiomerically enriched hetero Diels-Alder (HDA) products using *N*-sulfinyl compounds (**1**) as dienophiles.[5-11] The enantiomeric selectivity is induced by catalytic amounts of chiral Lewis acids. These products have been further transformed into synthetically interesting target molecules like (2*R*,3*S*)-*N*-benzoylphenylisoserine methyl ester (**2**), a derived side chain of paclitaxel (taxol) (Scheme 2.1).[5]




**Scheme 2.1**

The success with asymmetric HDA reactions raised the question whether or not this protocol could be extended to other reactions as well. Besides being good dienophiles, *N*-sulfinyl compounds are prone to undergo ene-reactions with alkenes.[12-14] The following ene-products can be transformed to either chiral allylic amines or alcohols through [2,3]-sigmatropic rearrangements by choosing the appropriate reaction conditions. Such a two-step sequence forms a general and highly valuable route to the targeted allylic compounds as described in Scheme 2.2.




**1a**: R = Ts
**1b**: R = Cbz

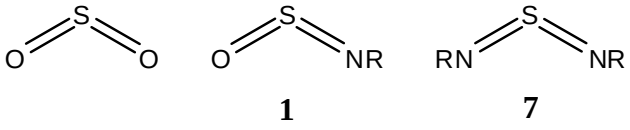
**4a-1**: R = Ts
**4b-1**: R = Cbz

**5a-1**: X = NHTs
**5b-1**: X = NHCbz
**6-1** : X = OH

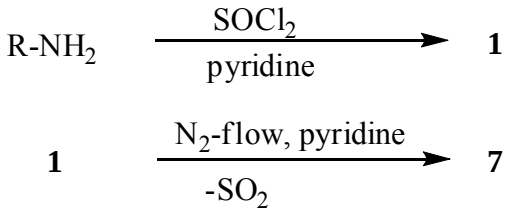
**Scheme 2.2**

### 2.1.1 Aza analogues of sulfur dioxide

*N*-Sulfinyl compounds (**1**) and sulfur diimides (**7**) can be regarded as aza analogues of sulfur dioxide (Scheme 2.3). Reacting amino groups with thionyl chloride and pyridine is the most preferred route to *N*-sulfinyl compounds. The sulfur diimides may be formed quantitatively from **1** in presence of pyridine and a nitrogen purge to remove the $SO_2$ liberated.[15] Due to high reactivity towards water and other nucleophiles, preparation and handling of both **1** and **7** requires inert conditions.



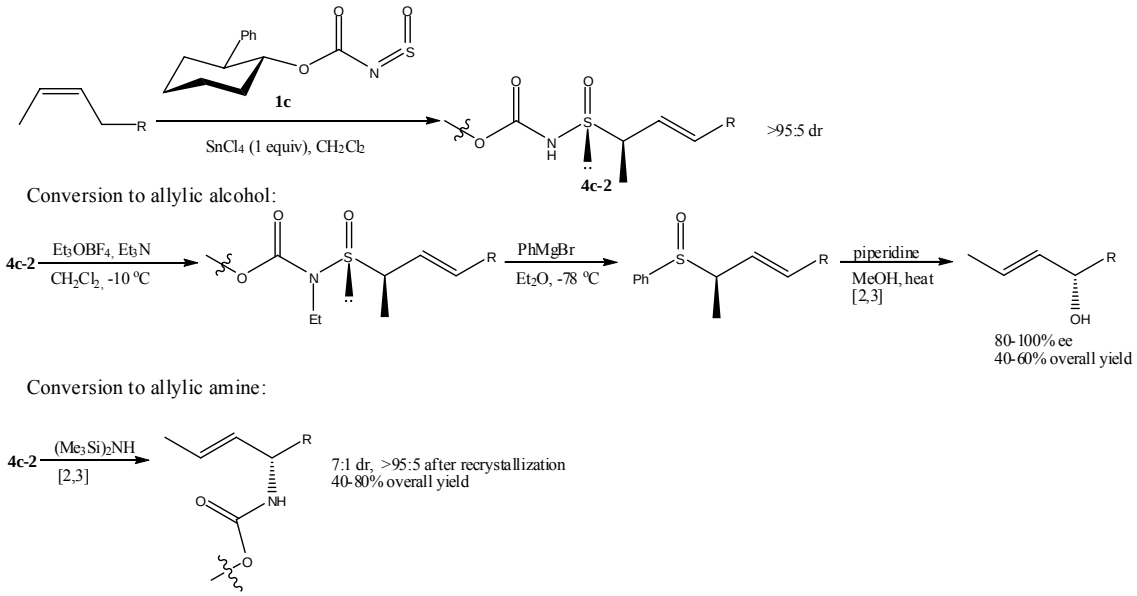
**1** **7**




**Scheme 2.3**

The first *N*-sulfinyl compounds were identified as early as 1890 by Michaelis and Herz.[16] In the 60's Kresze and co-workers initiated their pioneering work with utilizing these compounds, as well as the sulfur diimides, in organic synthesis.[15,17,18] Throughout the 70's and 80's the compounds found use as enophiles, largely thanks to the work of Kresze[12-14,19-21] and Sharpless[22].

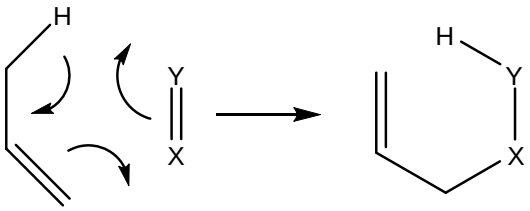
The first reports on enantioselective *N*-sulfinyl ene-reactions came from Whitesell and co-workers between the late 80's and early 90's.[23-25] Their strategy was to use chiral *N*-sulfinyl carbamates as enophiles, forming ene-products of high diastereomeric excess. An application of the *N*-sulfinyl carbamate **1c**, including the two alternative pathways to either allylic amine or allylic alcohol, is shown In Scheme 2.4.[24] The observed loss of chirality in the final products was attributed to stereomutation of the initial ene-products.




**Scheme 2.4**

## 2.1.2 Ene-reactions

The ene-reaction is related to the better known Diels-Alder reaction, since both reactions can proceed through a concerted cyclic transition state involving six electrons (Scheme 2.5). The concerted process has been designed as $[_{\sigma}2_s + _{\pi}2_s + _{\pi}2_s]$ in the Woodward-Hoffmann notation, involving the HOMO of the ene, LUMO of the allylic C-H bond, and LUMO of the enophile.[26,27] This can be interpreted to that allylic compounds ("enes") react most efficiently with electron deficient enophiles. The introduction of Lewis acids as catalysts has made these reactions more synthetically useful, lowering the necessary reaction temperatures to room temperature and below. Additionally, the use of chiral Lewis acids is already well established for ene-reactions, obtaining products of high optical purity.[28]



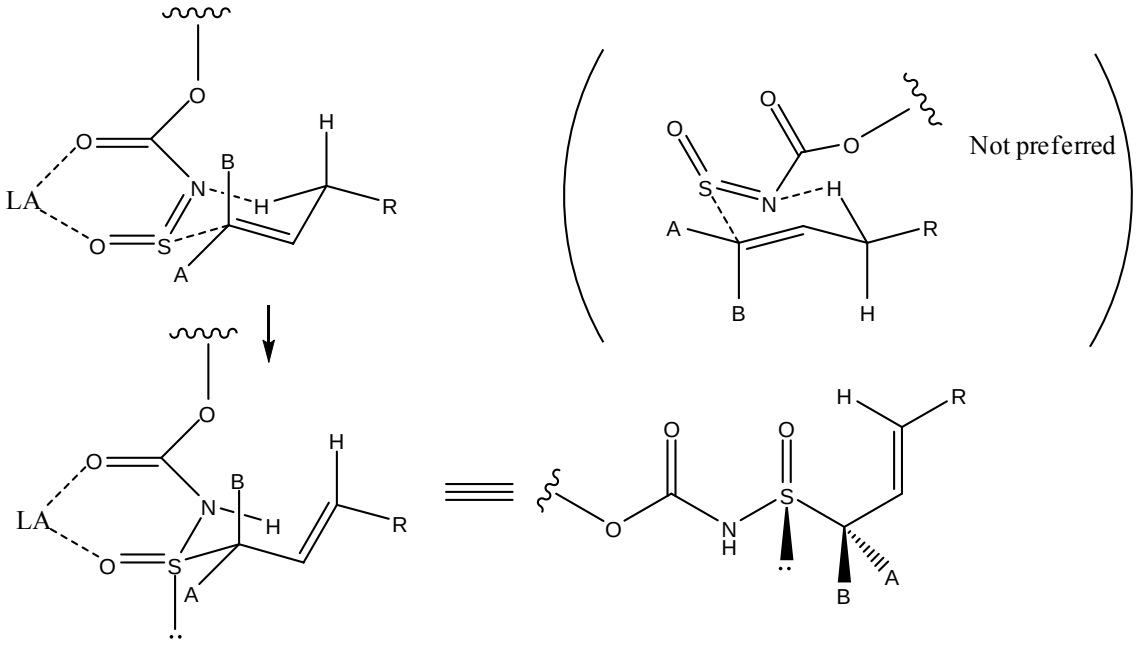

ene enophile

**Scheme 2.5**

Besides concerted mechanisms, the ene-reactions are also reported to follow stepwise mechanisms, proceeding through a zwitterionic or biradical intermediate.[29] Especially for Lewis acid-catalysed reactions, a polarised transition state or stepwise mechanism, is expected.[28] Being highly dependent on the nature of the reacting molecules, as well as the influence of Lewis acids, further discussions about the mechanism will revolve around reactions with the $SO_2$ aza-analogues.

Kresze and co-workers have undertaken an extensive study of the reactivity and selectivity of ene-reactions with both *N*-sulfinyl compounds and sulfur diimides.[12,20,21] Briefly summarised, the ene-products tend to form in such way to give the most substituted double bond. The reactivity of the alkenes is in this order: tetra- > tri- > 1,1-di- > (*E*)-1,2-di- >(*Z*)-1,2-di- > mono-substituted. Cyclic alkenes react slower than the corresponding open chained *Z*-alkenes. The reactions also take place with high regioselectivity, making the method applicable beyond symmetric alkenes.

Whitesell *et al*. proposed a concerted mechanism with a chair-like transition state for their ene-reactions, positioning the sulfoxide oxygen and the carbonyl oxygen in a favourable arrangement for bidentate complexation to a Lewis acid (Scheme 2.6).[24] Alternatively, the opposite side of the alkene could be approachable by a similar transition state (also shown in Scheme 2.6). The authors provide no explanation to why the former is exclusively preferred. Whitesell also found a large kinetic isotope effect for the allylic hydrogen, proving that H-transfer is involved in the rate determining step.[24]



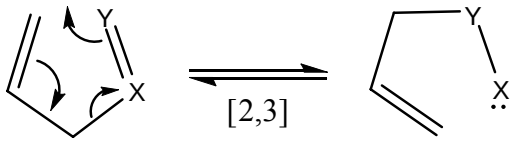

**Scheme 2.6**

The chiral substituent on the *N*-sulfinyl carbamate shields off the *si*-side, leaving the *re* side open for approach (not shown in the scheme). Any substituent in the allylic position will preferably adopt a pseudo-equatorial position to reduce steric interactions, leading to a *trans*-product. This preference is even stronger when the B-position is occupied by a substituent, corresponding to a *cis* starting material. For the same reasons, *trans*-alkenes reacts faster than *cis* alkenes, position A being the sterically preferred position in the transition state. The model also explains how *trans* and *cis* alkenes give products that are epimers at the carbon closest to sulfur, where as the sulfur chirality is the same. Since Whitesell's reactions were carried out by the aid of Lewis acids, it is conceivable that the actual mechanism involves a partial positive charge on the ene-adduct, but without diminishing the proposed model.

Although the model originally was suggested for reactions with *N*-sulfinyl compounds, the similarities of the enophiles should justify its validity for reactions with sulfur diimides as well.

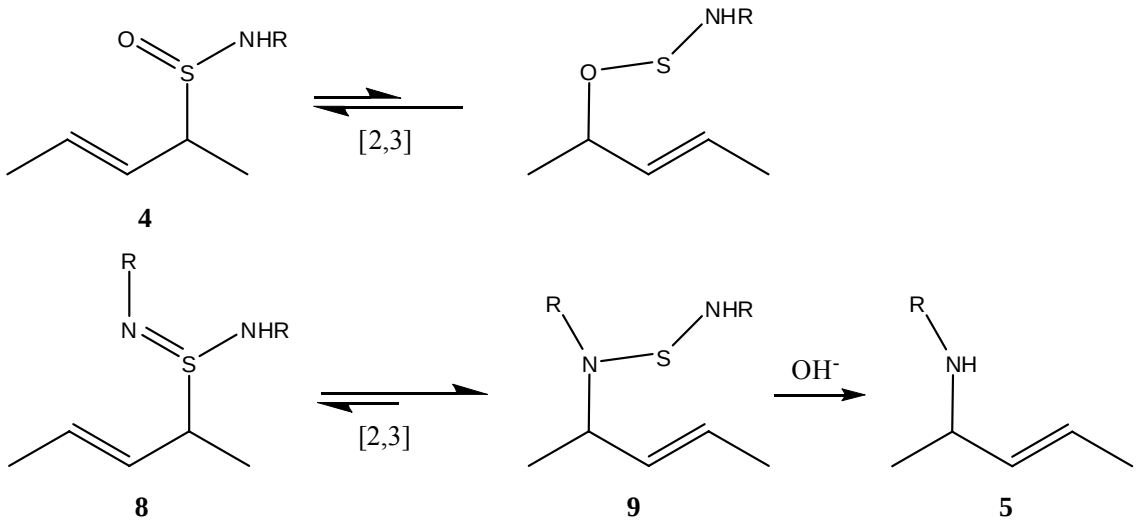
### 2.1.3 [2,3]-Sigmatropic rearrangements

A [2,3]-sigmatropic rearrangement is a pericyclic reaction, described as the two ends of a σ-bond, flanked by two π-systems, migrating over two and three bonds respectively (Scheme 2.7).[30]




**Scheme 2.7**

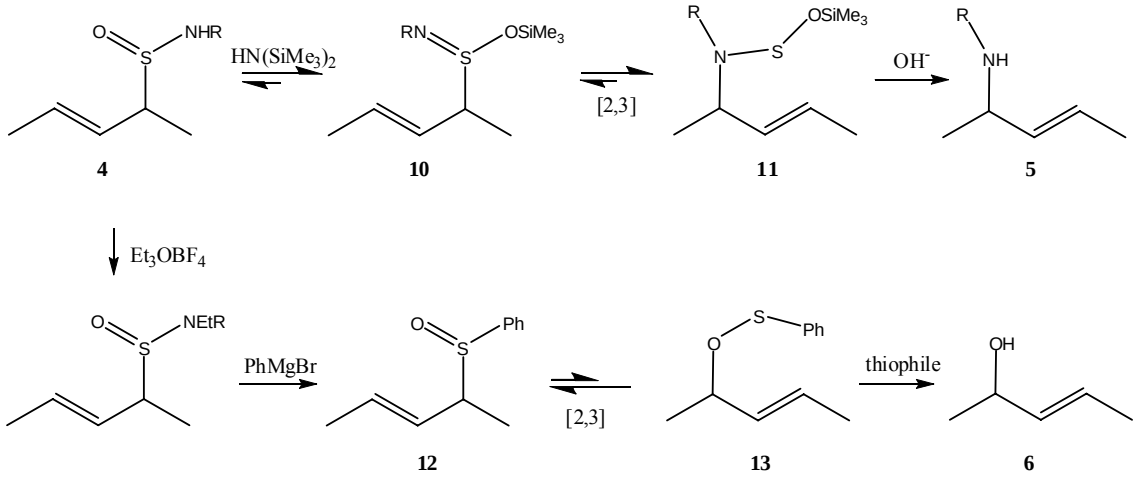
For this rearrangement, the ene-products of *N*-sulfinyl compounds and sulfur diimides, (**4**) and (**8**) respectively, show different characteristics. Both considered being reversible reactions, the equilibrium of the former rearrangement lies to the left, where as the latter lies to the right (Scheme 2.8).[21] As a consequence, (**8**) is easily transformed to the targeted allylic amine (**5**) by mild hydrolysis of the rearranged product (**9**).




**Scheme 2.8**

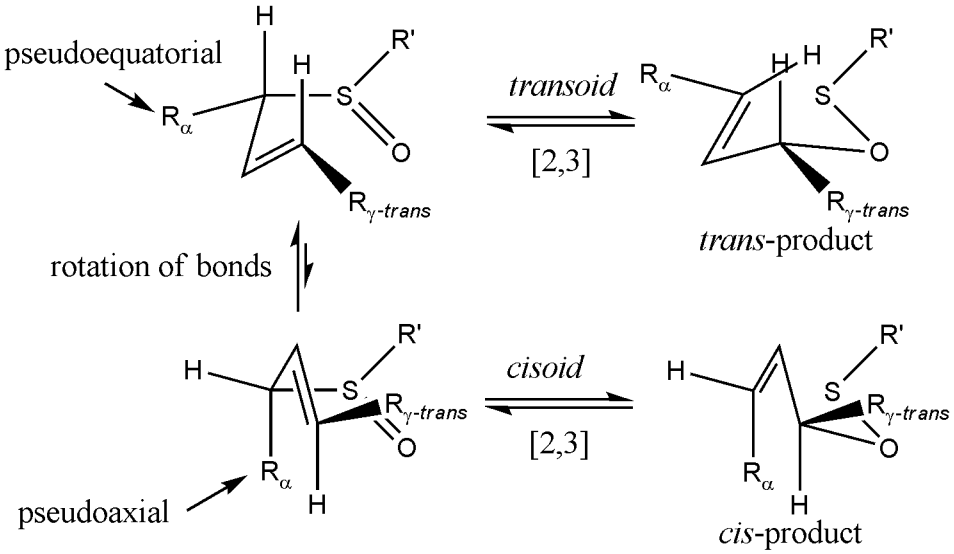
In order to facilitate rearrangement of the ene-products of *N*-sulfinyl compounds (**4**), *O*-silylation has been performed, transforming the sulfinamide into **10** (Scheme 2.9). This compound shows resemblance to **8**, having a S=N double bond, and rearranges accordingly, to **11**.[31] For preparation of allylic alcohols, **4** has to be transformed into the allylic sulfoxide **12** through subsequent *N*-alkylation and nucleophilic displacement by a Grignard reagent.[24] [2,3]-Sigmatropic rearrangement of allylic sulfoxides is well

documented and is commonly known as the Mislow-Evans rearrangement.[32,33] Although the equilibrium lies to the left, added thiophiles like $P(OMe)_3$ may react with **13**, bringing the reaction to completion. A similar addition of thiophiles in order to promote the rearrangement of allylic sulfinamides **4** directly, has been tried without success. The temperature required to facilitate this rearrangement directly appears to exceed the conditions for a non-catalysed retro-ene reaction.[24]



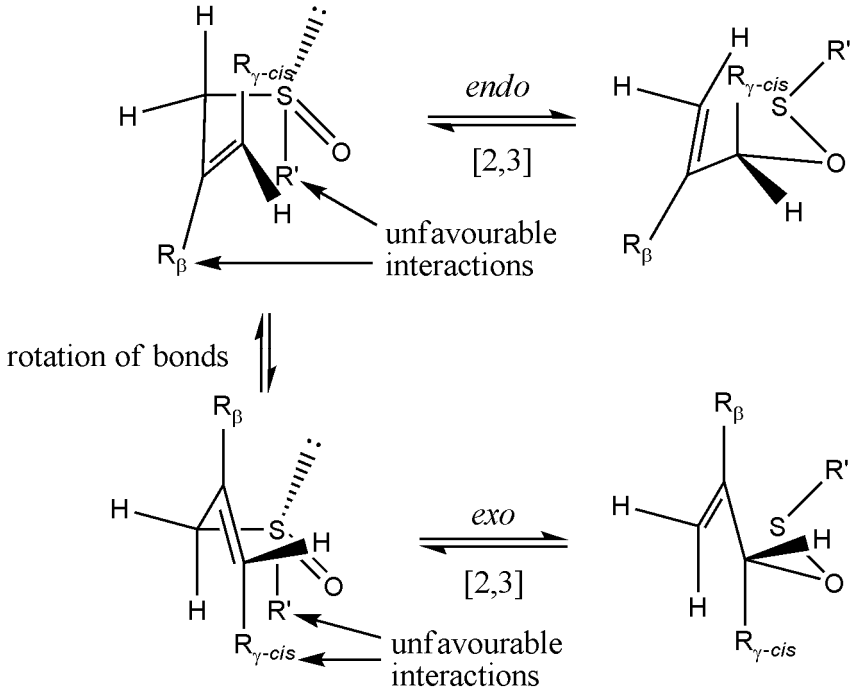

**Scheme 2.9**

Even with a highly enantioselective ene-reaction in the first step, the method still depends on an efficient chirality-transfer in the following [2,3]-sigmatropic rearrangement. A detailed overview of such rearrangements has been given by Hoffmann and Zeiss.[34] The transition state can be described as an envelope as shown in Scheme 2.10. Compounds with a substituent on the α-carbon, rearrange with high stereoselectivity, owing to the different energies of the *cisoid* and *transoid* transition states. The α-substituent will adopt a pseudoequatorial position, avoiding the more strained pseudoaxial orientation, yielding a *trans*-product. The sulfur stereocentre does not affect the stereoselectivity in this case.




**Scheme 2.10**

For compounds with two identical substituents in the α-position (including two hydrogens), chirality transfer from the sulfur atom is effective. For the selectivity to be satisfactory, a bulky substituent in either the β or the γ-*cis* position (and not both) is required. The two possible transition states are noted, *endo* and *exo*, differentiating by the orientation of the sulfur substituent R' and leading to products of opposite stereochemistry (Scheme 2.11). A substituent in the β-position destabilises the *endo* transition state, where as a substituent in the γ-*cis* position destabilises the *exo* transition state. Since chirality is lost on sulfur in the rearranged product, a thiophile must be present in order to hinder racemisation. A fast reaction with the thiophile makes the rearrangement practically irreversible.




**Scheme 2.11**

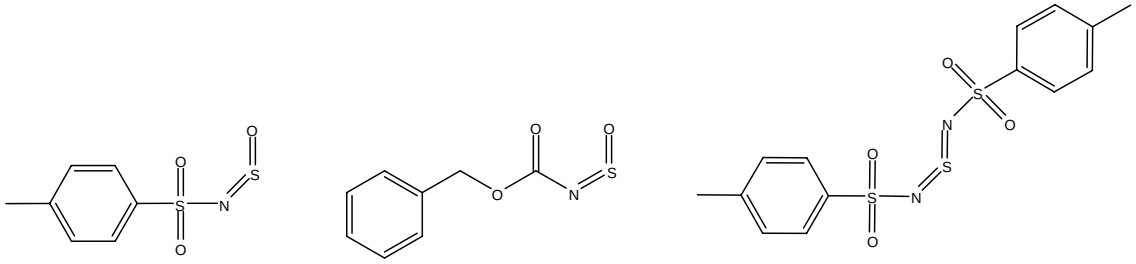
### 2.1.4 Lewis acid-catalysed reactions

The Lewis acids play two key roles in this project, activating the substrates to facilitate reactions, and simultaneously inducing chirality. Finding a suitable LA is not straightforward, the reactivity being highly dependent on the substrates and not easily predicted. One of the tools available is the hard-soft acid-base (HSAB) principle, which rationalises the affinity of the LA towards different nuclei.[35] However, for most synthetic chemists, the preferred strategy is simply to try out a large number of Lewis acids in a test reaction, and optimize the conditions of the most promising cases. For more efficiency, chemometry-derived methods can be used in the selection of Lewis acids. One such method has been presented by Carlson *et al*., where a 2-dimensional diagram has been formed on the basis of several LA-characteristics (descriptors).[36] The diagram puts "similar" Lewis acids in the vicinity of each other and "dissimilar" Lewis acids far away from each other. Although, this method might provide a crude roadmap for finding the best LA, the presence of chiral ligands will undoubtedly change the characteristics of the catalyst and complicate the search.

## 2.2 Results and discussion

### 2.2.1 Preparation of *N*-sulfinyl compounds and sulfur diimide

In an earlier performed screening of *N*-sulfinyl compounds in HDA-reactions, *N*-sulfinyl tosylamide (TsNSO) (**1a**) and benzyl *N*-sulfinylcarbamate (Cbz-NSO) (**1b**) were found to be the most suitable, based on their reactivity and versatile preparation.[11] For the same reasons, these compounds were considered most promising for the ene-reactions as well (Scheme 2.12). Where as **1a** was expected to be more reactive than **1b**, due to the highly electron withdrawing Ts-group, the Cbz-group would be easier to remove from the final product.[37] This provides an advantage which justified more effort in finding a successful system with **1b** as enophile. Based on its readily preparation from **1a** and reported reactivity, *N*,*N'*-ditosyl sulfur diimide (**7a**) was a natural choice amongst potential sulfur diimides. Compounds **1a**[18], **1b**[38], and **7a**[39] were prepared according to literature procedures. Attempts to prepare Cbz-NSN-Cbz (**7b**) from **1b** by the same protocol as for **7a**, were not successful.



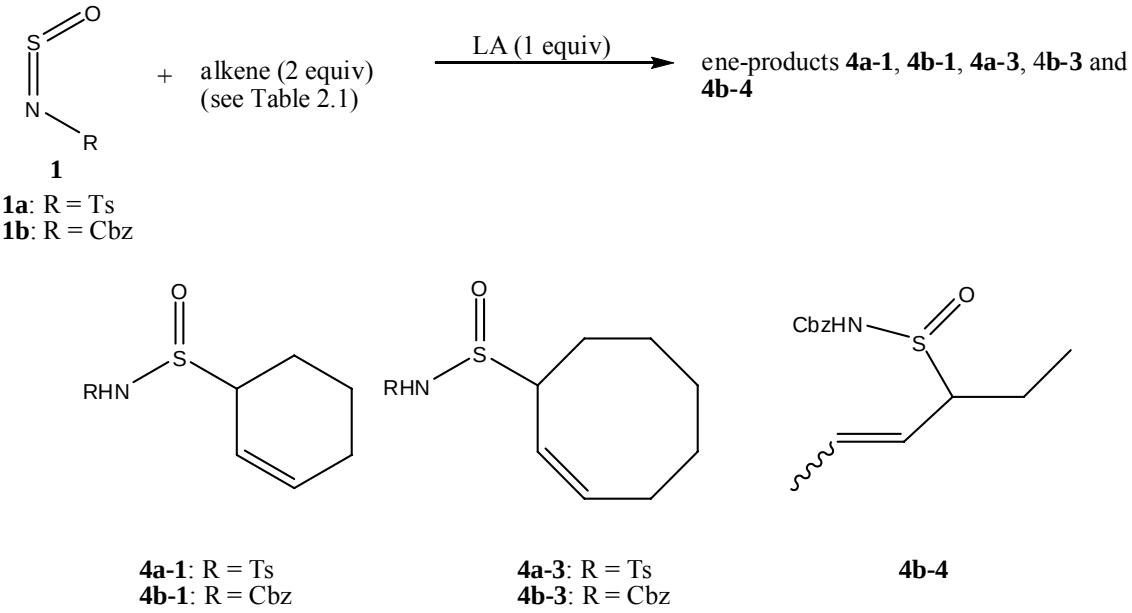
**1a** **1b** **7a**

**Scheme 2.12**

### 2.2.2 Racemic ene-reactions with *N*-sulfinyl compounds

Before searching for a suitable asymmetric catalytic system, a selection of racemic products to be used as analytic references for chiral HPLC measurements, had to be obtained. From the work of Whitesell, it was already known that addition of $SnCl_4$ in similar reactions allowed the reactions to take place at low temperatures and with short reaction times.[23] Cyclohexene, cyclooctene and 3-hexene were chosen as suitable alkenes. Being symmetric around the double bond, these alkenes allowed us to focus on

stereoselectivity, since regioselectivity is of no concern. The reactions and results are shown in Scheme 2.13 and Table 2.1.




**Scheme 2.13**

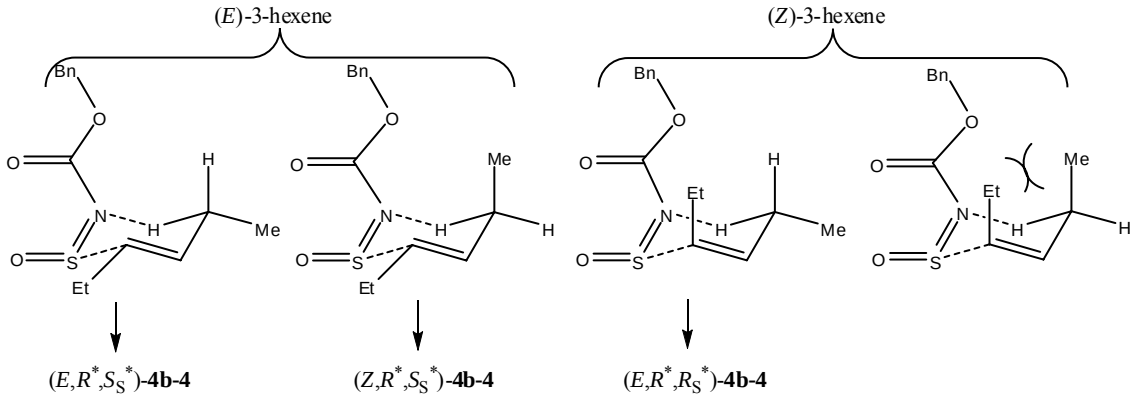
**Table 2.1** Results of racemic ene-reactions with $SnCl_4$ or without LA.

| Entry | Eno-phile | Ene | LA | Temp [°C] | Reaction-time | Product | Diastereo-selectivity | Yield [%] |
|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | Cyclohexene | None | r.t. | o.n, | **4a-1** | Undetermined | 38[a] |
| 2 | **1a** | Cyclohexene | $SnCl_4$ | r.t. | o.n. | **4a-1** | Undetermined | 95 |
| 3 | **1a** | Cyclooctene | $SnCl_4$ | r.t. | o.n. | **4a-3** | Undetermined | 99 |
| 4 | **1b** | Cyclohexene | None | 0 | 3 h | - | - | 0 |
| 5 | **1b** | Cyclohexene | $SnCl_4$ | -78 | 20 min | **4b-1** | 1 isomer | 77 |
| 6 | **1b** | Cyclooctene | $SnCl_4$ | -78 | 20 min | **4b-3** | 1 isomer | 92 |
| 7 | **1b** | (*E*)-3-Hexene | None | r.t. | 27 h | **4b-4** | Mostly $E,R^*,R_S^*$ | 2[a] |
| 8 | **1b** | (*E*)-3-Hexene | $SnCl_4$ | -78 | 35 min | **4b-4** | $E,R^*,S_S^*$ + $Z,R^*,S_S^*$ (78:22) | 82 |
| 9 | **1b** | (*Z*)-3-Hexene | $SnCl_4$ | -78 | 35 min | **4b-4** | $E,R^*,R_S^*$ + $E,R^*,S_S^*$ (91:9) | 76 |

[a] Yield determined from crude $^1$H NMR spectrum.

In absence of $SnCl_4$, the reaction was slow at room temperature. This was an encouraging observation, since a competing racemic background reaction would

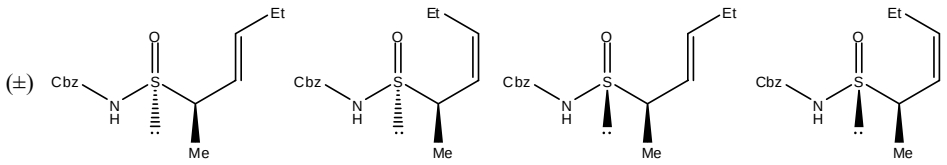
diminish the stereoselectivity in the following asymmetric reactions. The use of $SnCl_4$ at room temperature for the **1b**-reactions resulted in low yields, presumably because of incompatibility with these relatively harsh conditions. Adjustments were made by lowering the temperature and shortening the reaction time as shown in the table. Both diastereomers of **4a-1** and **4a-3** could be seen in the $^1$H NMR spectrum, possibly through reversible [2,3]-sigmatropic rearrangements and racemisation on sulfur. For **4b-1** and **4b-3**, only one diastereomer could be seen, suggesting a well-defined transition state and low degree of [2,3]-sigmatropic rearrangement at low temperature. Taking Whitesell's model into consideration (Scheme 2.6), the compounds should be ($R^*$,$R_S^*$)-**4b-1** and ($R^*$,$R_S^*$)-**4b-3**, but this was not confirmed. The reaction with (*E*)-3-hexene in entry 8 led to a mixture of two diastereomers, presumably (*E*,$R^*$,$S_S^*$)-**4b-4** and (*Z*,$R^*$,$S_S^*$)-**4b-4**. The composition may be explained from Whitesell's model, where the relatively small methyl group may occupy both pseudo-equatorial and –axial positions. The *cis* and *trans* isomers are easily differentiated by the olefinic $^3J_{H\text{-}H}$-couplings found from $^1$H NMR experiments. To test the model, **1b** was also reacted with (*Z*)-3-hexene (entry 9). Here, the pseudo-axial position is more sterically hindered due to diaxial-interaction, leading exclusively to *E*-products. As expected, the main product is epimeric at carbon, compared to the products of the (*E*)-3-hexene-reaction. The selectivities of the reactions with 3-hexenes are visualized in Scheme 2.14. The minor isomer in entry 9 indicates that other transition states might be of importance, but undoubtedly, Whitesell's model gives a rational explanation for the selectivities observed.




**Scheme 2.14**

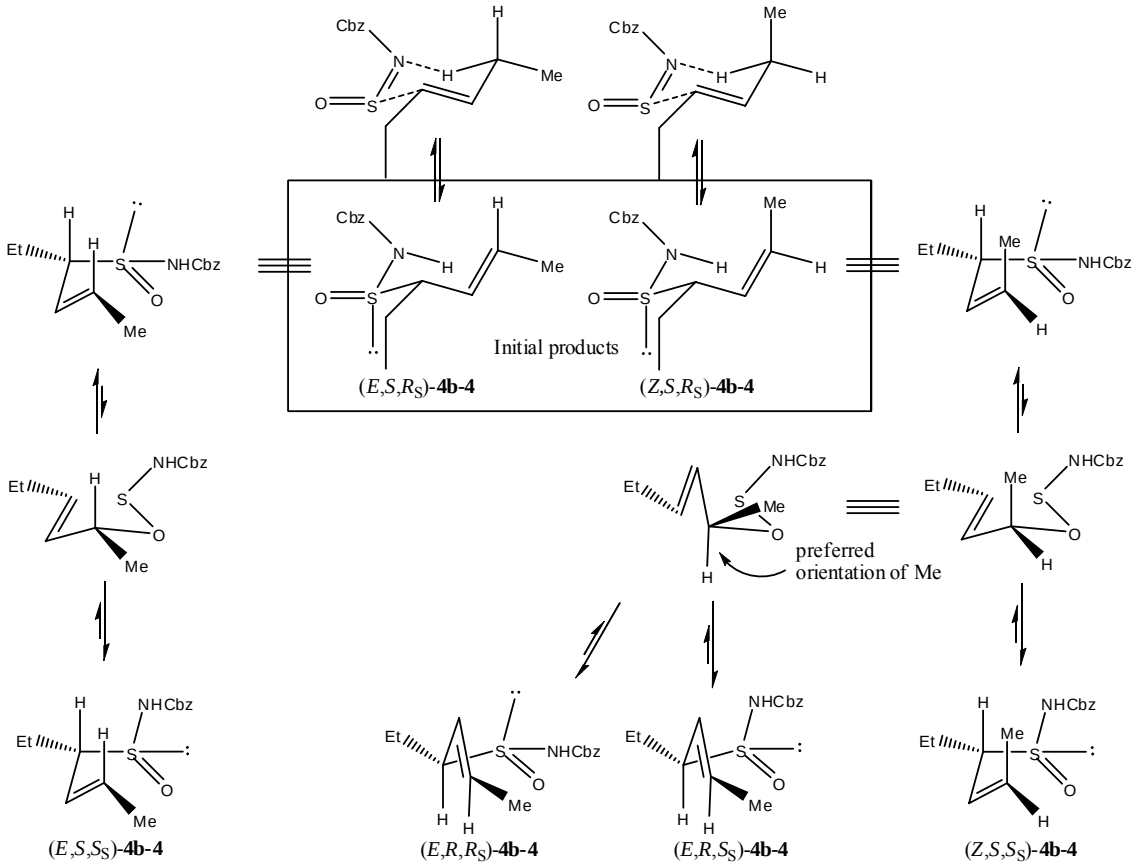
Upon storage in $CDCl_3$ at room temperature, the **4b-4**-mixture from entry 8 slowly changed composition, introducing two new isomers, presumably ($E$,$R^*$,$R_S^*$)-**4b-4** and ($Z$,$R^*$,$R_S^*$)-**4b-4**. The mixture seemed to be at equilibrium after 1 month, where the composition revealed ($E$,$R^*$,$R_S^*$)-**4b-4** as the thermodynamically most stable isomer (also supported by entry 7 in Table 2.1). The results of the $^1$H NMR investigations of the reaction mixture at selected time-intervals are shown in Table 2.2.

**Table 2.2** Equilibration of **4b-4** in $CDCl_3$.




| Elapsed time | ($E$,$R^*$,$S_S^*$)-**4b-4** | ($Z$,$R^*$,$S_S^*$)-**4b-4** | ($E$,$R^*$,$R_S^*$)-**4b-4** | ($Z$,$R^*$,$R_S^*$)-**4b-4** |
|---|---|---|---|---|
| Initial result | 78 | 22 | 0 | 0 |
| 19 h | 68 | 21 | 12 | 0 |
| 6 d | 41 | 14 | 45 | <1 |
| 5 weeks | 33 | 4 | 60 | 3 |

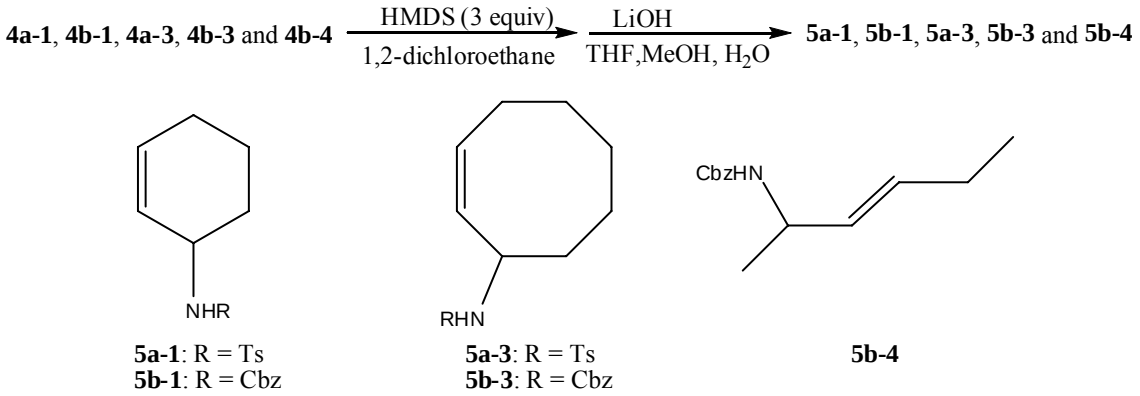
The observed results can be rationalised from series of reversible *transoid* [2,3]-sigmatropic rearrangements (Scheme 2.10). Since chirality on sulfur is lost in the rearranged product, racemisation on sulfur is an expected consequence. Scheme 2.15 illustrates this fact, presenting the potential pathways for the *S*-isomers. As explained earlier (on page 9), the chirality on sulfur has no significant effect on the crucial chirality transfers for these compounds. Of more concern, however, is that the initial *trans* and *cis* isomers are expected to rearrange to allylic compounds of opposite stereochemistry. The initially formed *cis*-product (*Z*,*S*)-**4b-4** is transformed into the *trans* product with opposite stereocentre on carbon [(*E*,*R*)-**4b-4**)]. Similarly, a small portion of the initial *trans*-product (*E*,*S*)-**4b-4** would be expected to rearrange into *cis* product, (*Z*,*R*)-**4b-4**, at equilibrium (not shown). As a result, the moderate *E*/*Z* selectivity of this reaction might seem fatal for the method's versatility with open alkenes like (*E*)-3-hexene. However, a catalytic system able to induce high enantioselectivity in this reaction might increase the *E*/*Z*-selectivity as well.




**Scheme 2.15**

## 2.2.3 Preparation of allylic amines

Because of the instability and reversibility of the initial ene-products, the more stabile allylic amines were prepared prior to chiral HPLC analysis. Amines were preferred over alcohols because of the substituent present at nitrogen, making a convenient chromophore for the UV detected analysis. Not forgetting the crucial *E*/*Z* selectivity revealed by $^{1}$H NMR spectroscopy, the chiral HPLC analysis of the rearranged (and hydrolysed) products gives an unambiguous measurement of the method's overall success. The ene-products were transformed to their respective allylic amines following the literature procedure (Scheme 2.16).[31] The results are shown in Table 2.3.




**Scheme 2.16**

**Table 2.3** Transformation of ene-products to allylic amines.

| Entry | Ene-product | Allylic amine | Yield [%] |
|---|---|---|---|
| 1 | **4a-1** | **5a-1** | 60 |
| 2 | **4b-1** | **5b-1** | 72 |
| 3 | **4a-3** | **5a-3** | 4 |
| 4 | **4b-3** | **5b-3** | 35 |
| 5 | **4b-4** | **5b-4** | 81 |

As expected from the preferred *transoid* transition state, only *trans* products are observed in entry 5. Attempts to improve the poor yields in entry 3 and 4 were not undertaken.

## 2.2.4 Preparation of chiral Lewis acids

As a part of finding a suitable catalytic system for the asymmetric ene-reactions, several optically pure ligands had to be obtained (Figure 2.1). Ph-Box (**3**)[40], Ph-Pybox (**14**)[41], TADDOL (**15**)[42] and bis(sulfoximine)-ligand (**16**)[43] were prepared according to literature procedures. Both enantiomers of BINOL (**17**) are commercially available.

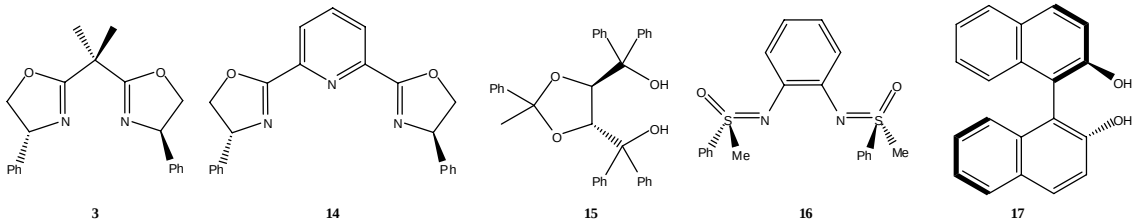
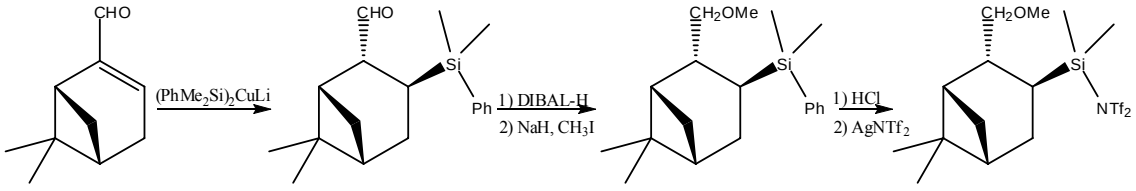



**Figure 2.1** Chiral ligands used in the asymmetric ene-reactions.

The chiral Lewis acid complexes were formed by stirring an equimolar solution of ligands and metal salts / organometals in dichloromethane for two hours. The formations of TADDOL complex **15**-$TiCl_2$[8] and BINOL complex $(\mathbf{17})_2$-Sn[44] were performed according to literature procedures. Inspired by promising results with $TMSNTf_2$ (Table 2.4, entry 2), the chiral silicone-LA **18** was attempted prepared from (-) myrtenal by modified literature procedures (Scheme 2.17).[45,46]

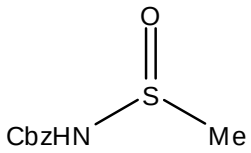



(-)-myrtenal **18**

**Scheme 2.17**

## 2.2.5 Screening of Lewis acids

To avoid potential problems with regio- and *E*/*Z*-selectivity, cyclohexene was chosen as a suitable substrate for screening of Lewis acids. To prevent acid-catalysed hydrolysis during aqueous work-up, all reactions were quenched with a phosphate solution, buffered to pH 7. Several Lewis acids, with and without chiral ligands, were tested in stoichiometric amounts with the *N*-sulfinyl compounds. The same reaction conditions as for Whitesell's reactions were initially used (-78 $^oC$ and 35 min reaction time). The following Lewis acids were tested with both **1a** and **1b** as enophile, unfortunately without success: **3**-$Cu(OTf)_2$, **3**-$Zn(OTf)_2$, **3**-$Sn(OTf)_2$, **3**-$Mg(ClO_4)_2$, **14**-$Sn(OTf)_2$, $TiCl_4$ and **15**-$TiCl_2$. In addition the following Lewis acids were exclusively tested with **1b** (most without ligands): $Cu(OTf)_2$, $Zn(OTf)_2$, $Sn(OTf)_2$, $Mg(ClO_4)_2$, $Mg(OTf)_2$, **16**-$Cu(OTf)_2$, $AlBr_3$, $Mg(OTf)_2$, $Me_2SnCl_2$, $AlMe_3$, $BF_3{\cdot}OEt_2$, $BBr_3$, $Cr(AcAc)_3$, $Sm(OTf)_3$, $Gd(OTf)_3$. Extending the reaction time to overnight, and altering the temperature up to room temperature did not improve the results. All reactions yielded mainly the corresponding amine-adduct (sulphonamide for **1a**, and carbamate for **1b**) expected from aqueous quenching of the *N*-sulfinyl compounds. The reactions with $AlMe_3$ led to methylation of **1b**, resulting in the sulfinamide **19** (75% yield, 26 h, -78 $^oC$).




**19**

The only LA found to promote the reaction, except $SnCl_4$, was TMSOTf, yielding 63% for **1b** after 35 min at -78 °C. With the hopes of improved results, a new round of screening was initiated with (*E*)-3-hexene, since *trans*-alkenes were expected to be more reactive than *cis*-alkenes. These reactions were restricted to **1b** for practical reasons. Again, several Lewis acids, including **3**-$Cu(OTf)_2$, $Zn(OTf)_2$, **3**-$Zn(OTf)_2$, $Sn(OTf)_2$, $Mg(OTf)_2$, **15**-$TiCl_2$, (**17**)$_2$-Sn, $Me_2SnCl_2$ and **18**, failed to yield ene-products. Unlike with cyclohexene, $Mg(OCl_4)_2$ provided some ene-product, but only at temperatures considerably higher than -78 °C. The best conditions using **3**-$Mg(OCl_4)_2$, were found to be at room temperature, providing 27% yield after 17 hours. After rearrangement, the enantiomeric purity was found to be 10-15% ee. Lowering the temperature reduced the yield without any improvement of the enantioselectivity. Difficulties with characterising **18**, leaves room for doubt whether the last step in Scheme 2.17 was unsuccessful or if the LA failed to promote the reaction. The most positive results with **1b** and (*E*)-3-hexene are shown in Table 2.4.

**Table 2.4** Effective Lewis acids found for reactions between **1b** and (*E*)-3-hexene.

| Entry | LA | Temp. [°C] | Reaction-time | Yield (**4**), ene-reaction [%] | Yield (**5**), over two steps [%] | Selectivity [% ee] |
|---|---|---|---|---|---|---|
| 1 | $TiCl_4$ | -78 | 3 h | 51 | - | - |
| 2 | $TMSNTf_2$ | -78 | 1 h | 82* | | |
| 3 | $Mg(OCl_4)_2$ | r.t. | 21 h | 25 | - | - |
| 4 | **3**-$Mg(OCl_4)_2$ | -45 | 19 h | 3 | - | - |
| 5 | **3**-$Mg(OCl_4)_2$ | 0 | 18 h | 25 | 23 | 10-15 |
| 6 | **3**-$Mg(OCl_4)_2$ | r.t. | 17 h | 27 | <27 | 10-15 |
| 7 | **16**-$Mg(OCl_4)_2$ | r.t. | 19 h | 10 | 9 | ~10 |

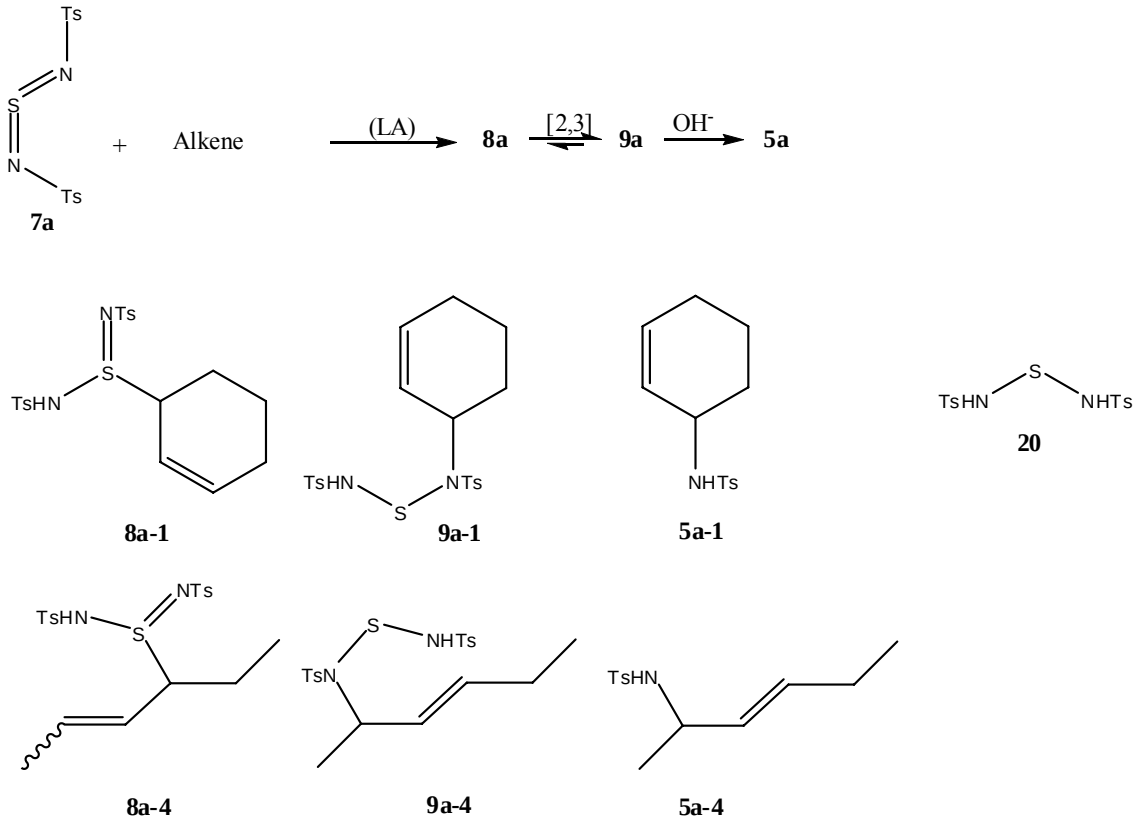
* Yield determined from crude $^1$H NMR spectrum

Because of partial overlap of the peaks in HPLC-analysis, the ee's measured include some uncertainty. The reaction with **16**-ligand (entry 7) provided the same main enantiomer as the other non-racemic reactions. The main diastereomer from all the ene-

reactions in the table, except entry 2, was the thermodynamically most stable ($E$,$R^*$,$R_S^*$)-**4b-4**. It might be formed by a different mechanism than the one proposed for $SnCl_4$, but can also be the result of Lewis acid-catalysed equilibration of the ene-product (through [2,3]-sigmatropic rearrangements). $TMSNTf_2$ in entry 2 provided the same diastereomeric composition as found for the $SnCl_4$ reactions.

### 2.2.6 Reactions with sulfur diimide

The expected higher reactivity of the sulfur diimides compared to *N*-sulfinyl compounds was confirmed by the readily formation of ene-products without the need of Lewis acids. The reaction between **7a** and (*E*)-3-hexene took place at -78 $^oC$, where as the reaction with cyclohexene had to be performed at room temperature. After the initial ene-reaction, hydrolysis was performed according to a procedure reported by Sharpless.[22] In the presence of Lewis acids, the reactions gave large amounts of the by-product *N*,*N*'-thiobis-(*p*-toluenesulfonamide) (**20**). The combination of extensive formation of **20** and a competing racemic background-reaction, left little hope for a successful asymmetric version of this reaction. Scheme 2.18 and Table 2.5 summarises some of the racemic results with **7a** as enophile.




**Scheme 2.18**

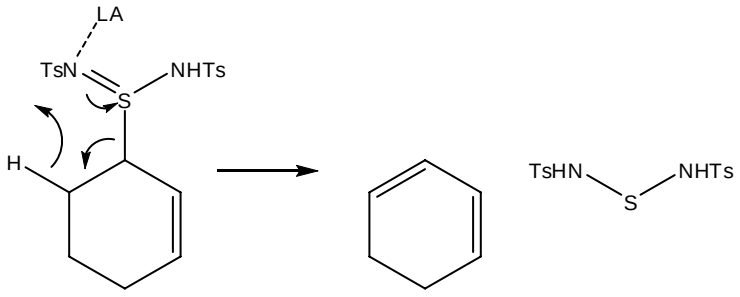
**Table 2.5** Racemic reactions with **7a** as enophile.

| Entry | Alkene | LA | Temp [°C] | Reaction time | Yields, 1 or 2 steps [%] | By-product **20** [%] |
|---|---|---|---|---|---|---|
| 1 | Cyclohexene | None | r.t. | 18 h | 49 (**5a-1**) | - |
| 2 | Cyclohexene | None | -45 | 15 h | No reaction | - |
| 3 | Cyclohexene | $SnCl_4$ | r.t. | 2.5 h | 10 (**5a-1**) | >50 |
| 4 | (*E*)-3-hexene | None | r.t. | 21.5 h | ~100 (**5a-4**) | - |
| 5 | (*E*)-3-hexene | None | -78 | 25 min | 10 (**8a-4**/**9a-4**)* | - |
| 6 | (*E*)-3-hexene | $SnCl_4$ | -78 | 20 min | 0 | 23* |

* Yield determined from crude $^1$H NMR spectrum

The ene-products were hydrolysed without prior isolation (except entry 5). In entry 3, no hydrolysis was needed, since the reaction conditions provided **5a-1** (and **20**) directly. Entry 5 illustrates that the reaction with (*E*)-3-hexene takes place at low temperature without Lewis acid. The diastereoselectivity in entry 4 was *E*/*Z* (10:1), indicating that the *cisoid* transition state is possible for this system. The following chiral Lewis acids

failed to promote the formation of ene-products (compared to the background reaction) and resulted in variable amounts of **20**: $Cu(OTf)_2$, **3**-$Cu(OTf)_2$, **3**-$Zn(OTf)_2$, **15**-$TiCl_2$. Formation of **20** can be rationalised by a hydride-transfer as shown in Scheme 2.19. The Lewis acids are assumed to catalyse the reaction by reducing the electron density around the involved nitrogen atom. Owing to their volatility, the resulting dienes were not found amongst the products. Sulfur diimides have previously been reported to function as dehydrogenation agents.[47]




**8a-1** **20**

**Scheme 2.19**

The $^1$H NMR spectra of the ene-products **8a** showed unusually broad peaks, especially with (*E*)-3-hexene. A closer inspection of the (*E*)-3-hexene reaction, using NMR techniques, could explain the broadening as a consequence of the reversible [2,3]-sigmatropic rearrangement taking place at a certain rate. Lowering the temperature in the NMR-tube, effectively gave sharper peaks and revealed a mixture of **8a-4** and **9a-4**. At room temperature, the rearrangement took place during acquisition of the NMR spectrum, providing peaks that were a mixture of signals from the two compounds. Reducing the temperature, slowed down the rearrangement, and allowed appearance of the individual set of signals. Exchange spectroscopy (EXSY) correlated the two different signals of each proton. The relative integrals of the rearranging compounds correspond to the equilibrium composition. As expected, the rearranged adduct (**9a-4**) was slightly more stable than **8a-4**, with the integral ratios of 3:2 corresponding to a free energy difference of 0.8 kJ/mol (at -26 $^o$C). Figure 2.2 clearly shows the effect of cooling down the sample. The $^1$H NMR spectra also show the presence of two minor compounds (amounting to approximately 6%). Even though they could not be found to exchange with the major isomers, the *Z*-isomer in the final product (**5a-4**) suggests that (*Z*)-**9a-4** is one of the minor compounds.

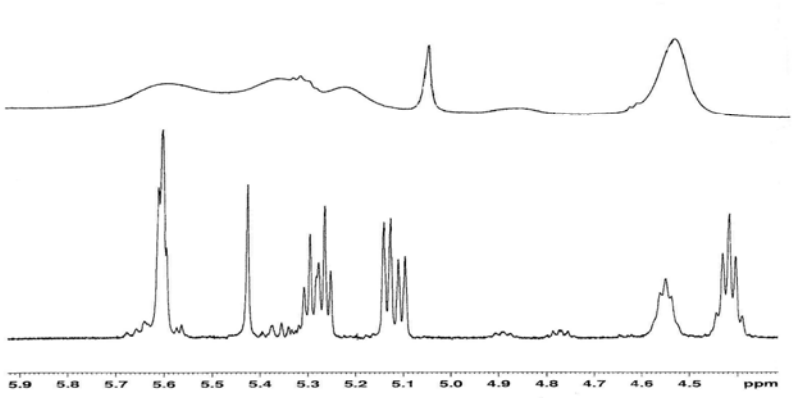



**Figure 2.2** Part of $^{1}$H NMR spectra of **8a-4**/**9a-4**. Top: room temperature, bottom: -26 $^{o}$C.

## 2.3 Summary

Several chiral Lewis acids were tested to facilitate asymmetric ene-reactions with aza-analogues of sulfur dioxide as enophiles. The resulting ene-products were rearranged to allylic amine by reported methods. A small degree of asymmetric induction was found for $Mg(ClO_4)_2$ with two different ligands (**3** and **16**), but the reactions only took place at relatively high temperatures, leading to low selectivities (10-15% ee). The future may reveal new chiral catalysts that could resurrect this route to allylic amines and alcohols. Reactions with the sulfur diimide **7a** took place at -78 $^{o}$C. The racemic background reactions, combined with formation of by-product **20** in the presence of Lewis acids, caused the failure of the asymmetric reactions.

## 2.4 Experimental

### 2.4.1 General

These general remarks apply for all the experimental sections in this thesis.

All chemicals used were of synthetic grade and used without purification unless otherwise noted. Dichloromethane, toluene and pyridine were dried by distillation over calcium hydride. Tetrahydrofuran and diethyl ether were dried by distillation over sodium / benzophenone.

TLC was performed on Merck silica gel 60 $F_{254}$ plates, with detection by UV light at 312 nm, molybdophosphoric acid (5% in EtOH), vanillin (in $EtOH/H_2SO_4$) or anisaldehyde (in $EtOH/H_2SO_4$). Flash chromatography was performed with silica gel from Merck (60, 43-60 μm) or with Supelco VersaFlash High Throughput Flash Purification System, using pre-packed cartridges with spherical silica.

NMR spectra were obtained on a Bruker Avance DPX 300 / 400 or Bruker Avance 600 fitted with a TCI cryoprobe. TMS was used as reference for both $^{1}H$ and $^{13}C$ signals. Different 2D techniques (COSY, NOESY, HSQC and HMBC) were used to aid in the assignment of $^{1}H$ and $^{13}C$ signals.

IR spectra were obtained by a Thermo Nicolet FT-IR NEXUS instrument, and only the strongest and structurally important peaks have been reported.

MS spectra were obtained on a Finnigan MAT 95 XL mass spectrometer using electron impact (EI) (200 $^{o}C$, 70 eV) or electron spray ionisation (ESI).

Melting points are uncorrected and measured by a Büchi melting point apparatus.

Optical rotation was performed on a Perkin-Elmer 243B Polarimeter.

For chiral HPLC analysis, Daicel columns Chiralpak AD (250x4.6 mm), Chiralcel OJ (250x4.6 mm) or Chiralcel OD-H (250x4.6 mm) were used with UV detection.

For chiral GC analysis, a CP-Chirasil-dex CB column was used.

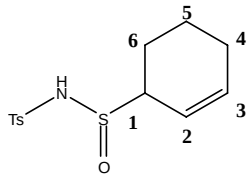
Elemental analyses were obtained from Mikroanalytisches Labor Beller, Göttingen, Germany.

## 2.4.2 Procedures and analytical data

*N*-Sulfinyl-*p*-toluenesulfonamide (**1a**)[18], *N*-sulfinylbenzylcarbamate (**1b**)[38] and sulfur diimide (**7a**)[39] were prepared according to literature procedures.

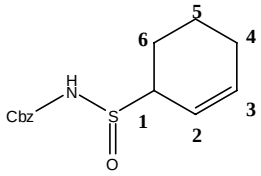
**General procedure for ene-reactions with *N*-sulfinyl compounds (1).** Lewis acid (0.15-0.25 mmol) was diluted with dry $CH_2Cl_2$ (2 ml) and cooled to preferred temperature (see Table 2.1 and Table 2.4). To this mixture was added pre-cooled alkene (2-3 equiv., neat or 1 M solution in $CH_2Cl_2$) and a pre-cooled solution of enophile (**1**) (1 equiv., 0.3-0.5 M in $CH_2Cl_2$). The reaction was carried out under an inert argon atmosphere and eventually quenched* with a phosphate buffered (pH 7) aqueous solution (10 ml). The aqueous layer was extracted with $CH_2Cl_2$ (3 x 5 ml) and the combined organic phases dried over $MgSO_4$ before concentration *in vacuo*. The crude product was purified by flash chromatography (FC).

*)For reactions without Lewis acid, the quenching and following extraction with $CH_2Cl_2$ were not performed.



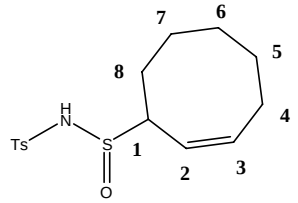

**4a-1**

***N*-(Cyclohex-2-enylsulfinyl)-*p*-toluenesulfonamide (4a-1)**.[12] (Diastereomeric mixture). FC (MeOH/$Et_2O$, 1:9) provided **4a-1** as a white solid, mp: 108-110 $^oC$; $^1H$ NMR (300 MHz, $CDCl_3$, selected signals) δ 7.9-7.8 (2H, app. d, $J$ = 8.4 Hz, Ts), 7.35-7.3 (2H, app. d, $J$ = 8.0 Hz, Ts), 6.3-6.15 (1H, m, H-3), 5.8-5.7 (1H, m, H-2), 3.7-3.5 (1H, m, H-1), 2.44 (3H, s, Ts), 2.2-1.5 (6H, m, H-4,5 and 6); IR (neat) ν 3358 (s), 3261 (s), 1528 (m), 1302 (s), 1159 (s), 1097 (m), 904 (m), 817 (m); EIMS *m*/*z* (% relative intensity) 299 ($M^+$, <1), 171 (11), 156 (12), 155 (43), 92 (20), 91 (100), 81 (75), 80 (25), 79 (41), 77 (17), 65 (27).



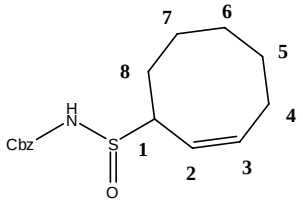

**4b-1**

**Benzyl (1*R**,*R*S*)-*N*-(cyclohex-2-enylsulfinyl)carbamate (4b-1).** FC (EtOAc/hexane 1:1) provided **4b-1** as a white solid; mp 106.5-107.5 °C; TLC (EtOAc/hexane, 1:1) $R_f$ 0.5; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.3-7.4 (5H, m, Ph), 6.91 (1H, br, NH), 6.19 (1H, m, H-3), 5.79 (1H, m, H-2), 5.21 (2H, s, PhC**H$_2$**O), 3.54 (1H, m, H-1), 2.10 (2H, m, H-4,5 or 6), 1.95 (1H, m, H-4,5 or 6), 1.82 (2H, m, H-4,5 or 6), 1.60 (1H, m, H-4,5 or 6); $^{13}$C NMR (75 MHz) δ 154.1, 135.5, 135.0, 128.7, 128.6, 128.4, 119.6, 68.5, 60.6, 24.7, 22.5, 19.9; IR (KBr) ν 3091 (m), 3037 (w), 2949 (w), 2925 (w), 2867 (w), 2828 (w), 1733 (s), 1441 (s), 1243 (s), 1209 (s), 1076 (s), 1057 (s), 843 (s), 747 (s), 697 (s); EIMS *m*/*z* (% relative intensity) 279 ($M^+$, <1), 138 (10), 111 (11), 109 (14), 108 (27), 107 (18), 91 (57), 82 (10), 81 (100), 80 (18), 79 (78), 77 (35); HPLC (Chiralpak AD, *i*-PrOH/hexane, 10/90, 1.0 mL min$^{-1}$, 230 nm) $t_R$ 11.7 and 24.0 min.



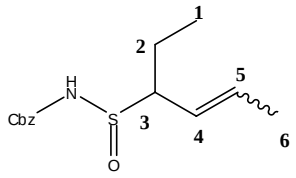

**4a-3**

***N*-(Cyclooct-2-enylsulfinyl)-*p*-toluenesulfonamide (4a-3).**[12] (Diastereomeric mixture). FC ($Et_2O$/MeOH, 9:1); $^1$H NMR (300 MHz, $CDCl_3$, selected signals) δ 7.9-7.8 (2H, app. d, *J* = 8.3 Hz, Ts), 7.35-7.3 (2H, app. d, *J* = 8.2 Hz, Ts), 6.25-5.2 (2H, m, H-2 and 3), 4.0-3.6 (1H, m, H-1), 2.44 (3H, s, Ts), 2.3-1.25 (10H, m, H-4,5,6,7 and 8); IR (neat) ν 3448 (br), 2923 (m), 2851 (w), 1596 (w), 1442 (w), 1356 (m), 1297 (m), 1171 (s), 1070 (s), 812 (s), 656 (m), 549 (s), 454 (m); EIMS *m*/*z* (% relative intensity) 328 ($M^+$+1, 14), 327 ($M^+$, 2), 220 (29), 215 (20), 205 (12), 171 (44), 155 (42), 149 (10), 135 (17), 121 (13), 111 (11), 110 (19), 109 (36), 108 (25), 107 (24), 97 (17), 96 (15), 95 (28), 93 (14), 92 (11), 91 (100), 82 (15), 81 (37), 79 (20), 77 (10), 69 (21), 67 (36), 65 (22), 55 (27), 41 (18), 39 (10).




**4b-3**

**Benzyl (1*R**,*R*S*)-*N*-(cyclooct-2-enylsulfinyl)carbamate (4b-3)**. FC (EtOAc/hexane, 2:3); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.45-7-3 (5H, m, Ph), 6.82 (1H, br, NH), 6.20 (1H, app. q, *J* = 9.0 Hz, H-3), 5.86 (1H, ddd, *J* = 10.4, 9.1, 1.2 Hz, H-2), 5.23 (1H, d, *J* = 12.1 Hz, PhC**H**H'), 5.20 (1H, d, *J* = 12.0 Hz, PhCH**H'**), 3.64 (1H, app. ddd, *J* = 12.5, 9.1, 3,8 Hz, H-1), 2.3-1.3 (10H, m, H-4,5,6,7 and 8); IR (neat) ν 3088 (m), 3023 (w), 2927 (m), 2863 (w), 1726 (s), 1426 (s), 1200 (s), 1067 (s), 844 (s), 752 (m), 697 (m); EIMS *m*/*z* (% relative intensity) 307 ($M^+$, <1), 129 (12), 115 (12), 109 (17), 108 (33), 107 (27), 106 (19), 105 (23), 104 (13), 97 (13), 95 (18), 94 (15), 93 (22), 91 (95), 89 (11), 83 (18), 82 (17), 81 (29), 80 (20), 79 (83), 78 (27), 77 (62), 73 (15), 71 (15), 70 (12), 69 (31), 68 (15), 67 (59), 66 (14), 65 (32), 64 (18), 63 (16), 60 (18), 57 (33), 56 (19), 55 (55), 54 (18), 53 (20), 52 (14), 51 (37), 50 (24), 48 (10), 45 (14), 44 (100), 43 (47), 42 (17), 41 (79), 40 (12), 39 (68), 38 (15), 36 (49), 35 (10), 34 (14), 32 (10), 29 (24), 28 (45), 27 (39), 26 (16).

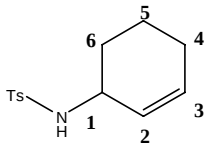



**4b-4**

**Benzyl *N*-(hex-4-en-3-ylsulfinyl)carbamate (4b-4).** FC ($Et_2O$) provided **4b-4** as a colourless viscous oil. Data for mixture: TLC ($Et_2O$) $R_f$ 0.4-0.5; IR (neat) ν 3448 (w), 3168 (m), 3090 (w), 3066 (w), 3033 (w), 2967 (m), 2937 (w), 2876 (w), 1737 (s), 1454 (s), 1291 (s), 1217 (s), 1069 (s), 969 (m), 833 (m), 748 (m), 698 (m). Data for (*E*,3*R**,*S*S*)-**4b-4**: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.4-7.3 (5H, m, Ph), 6.75 (1H, br, NH), 5.83 (1H, dqd, *J* = 15.4, 6.5, 0.8 Hz, H-5), 5.35 (1H, ddq, *J* = 15.4, 8.4, 1.7 Hz, H-4), 5.25-5.15 (2H, m, PhC**H$_2$**O), 3.33 (1H, app. td, *J* = 8.9, 4.7 Hz, H-3), 1.9-1.8 (1H, m, H-

2), 1.76 (3H, dd, *J* = 6.3, 1.3 Hz, H-6), 1.7-1.5 (1H, m, H-2'), 1.00 (3H, t, *J* = 7.5 Hz, H-1). Data for (*Z*,3*R**,*S*S*)-**4b-4**: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.4-7.3 (5H, m, Ph), 6.88 (1H, br, NH), 5.96 (1H, dqd, *J* = 10.9, 7.1, 0.6 Hz, H-5), 5.25-5.15 (3H, overlap, PhC**H$_2$**O and H-4), 3.78 (1H, app. td, *J* = 10.2, 3.6 Hz, H-3), 1.71 (3H, dd, *J* = 7.0, 1.8 Hz, H-6), 0.97 (3H, t, *J* = 7.4 Hz, H-1). Data for (*E*,3*R**,*R*S*)-**4b-4**: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.4-7.3 (5H, m, Ph), 7.01 (1H, br, NH), 5.83 (1H, app. dq, *J* = 15.4, 6.5 Hz, H-5), 5.47 (1H, ddq, *J* = 15.4, 9.8, 1.6 Hz, H-4), 5.25-5.15 (2H, m, PhC**H$_2$**O), 2.95 (1H, app. td, *J* = 9.5, 5.7 Hz, H-3), 2.0-1.9 (1H, m, H-2), 1.83 (3H, dd, *J* = 6.5, 1.7 Hz, H-6), 1.75-1.65 (1H, m, H-2'), 1.03 (3H, t, *J* = 7.4 Hz). Data for (*Z*,3*R**,*R*S*)-**4b-4**: $^1$H NMR (400 MHz, $CDCl_3$, selected signals) δ 7.4-7.3 (5H, m, Ph), 6.14 (1H, dqd, *J* = 10.8, 6.8, 0.8 Hz, H-5), 5.55-5.45 (1H, overlap, H-4), 5.25-5.15 (1H, overlap, PhC**H$_2$**O), 3.41 (1H, m, H-3), 1.71 (3H, dd, *J* = 7.0, 1.8 Hz, H-6), 1.06 (3H, t, *J* = 7.2 Hz, H-1).

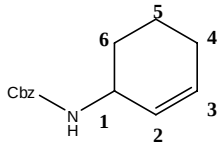
**General procedure for silylation and rearrangement of ene-products.** Ene-product (**4**) (0.2-1.3 mmol) was dissolved in 1,2-dichloroethane (3 ml) and added HMDS (3 equiv.) at room temperature. The mixture was stirred under an inert atmosphere for 1.5 h, before increasing the temperature to 50 °C. After another 1.5 h, the temperature was increased to 90 °C and the reaction was refluxed overnight. After removal of solvent *in vacuo*, the crude product was dissolved in THF/$H_2O$/MeOH (3:1:1, 50 ml) and added LiOH (5 equiv.). The mixture was stirred at room temperature for 3 h before addition of water and extraction with EtOAc. The combined organic phases were washed with brine, and dried over $MgSO_4$. After filtration, the solvent was removed *in vacuo* and the product purified by flash chromatography.




**5a-1**

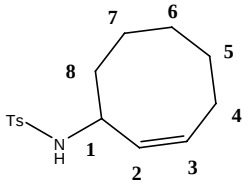
***N*-(Cyclohex-2-enyl)-*p*-toluenesulfonamide (5a-1)**.[48] FC (EtOAc/hexane, 1:4) provided **5a-1** as a white solid; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.77 (2H, app. d, *J* = 8.2 Hz, Ts), 7.31 (2H, app. d, *J* = 8.1 Hz, Ts), 5.76 (1H, m, H-3), 5.33 (1H, m ,H-2), 4.36

(1H, br. d, *J* = 8.5, NH), 3.83 (1H, m, H-1), 2.43 (3H, s, Ts), 2.0-1.45 (6H, m, H-4,5 and 6); IR (neat) ν 3272 (m), 2926 (s), 2856 (m), 1447 (m), 1322 (m), 1159 (s), 1069 (m), 890 (m), 811 (m), 707 (m), 672 (s), 581 (m), 553 (s); EIMS *m*/*z* (% relative intensity) 252 ($M^+$+1, 1), 251 ($M^+$, 4), 223 (45), 187 (38), 186 (23), 159 (12), 155 (51), 105 (11), 96 (67), 92 (22), 91 (100), 81 (19), 80 (12), 79 (14). HPLC (Chiralpak OJ, *i*-PrOH /hexane, 7/93, 1.0 mL $min^{-1}$, 254 nm) $t_R$ 13.5 and 15.2 min.




**5b-1**

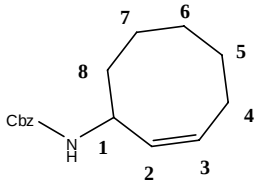
**Benzyl *N*-(cyclohex-2-enyl)carbamate (5b-1)**.[49] FC (EtOAc/hexane, 1:4) provided **5b-1** as a white solid; mp 71-72 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.4-7.3 (5H, m, Ph), 5.83 (1H, m, H-3), 5.61 (1H, m, H-2), 5.11 (1H, d, *J* = 12.4, PhC**H**H'), 5.09 (1H, d, *J* = 12.5 Hz, PhCH**H'**), 4.72 (1H, br, NH), 4.23 (1H, m, H-1), 2.00 (2H, m, H-4 or 6), 1.91 (1H, m, H-4 or 6), 1.64 (2H, m, H-4,5 or 6), 1.6-1.5 (1H, m, H-4,5 or 6); IR (neat) ν 3212 (s), 3062 (w), 3034 (w), 2938 (m), 2863 (w), 1685 (s), 1531 (s), 1305 (m), 1243 (s), 1038 (s), 1026 (s), 736 (m), 695 (m); EIMS *m*/*z* (relative intensity) 232 ($M^+$+1, 3), 231 ($M^+$, 9), 187 (11), 186 (16), 170 (21), 144 (10), 141 (10), 140 (100), 96 (10), 91 (56). HPLC (Chiralpak OJ, *i*PrOH/hexane, 7/93, 1.0 mL $min^{-1}$, 254 nm) $t_R$ 12.2 and 19.6 min.




**5a-3**

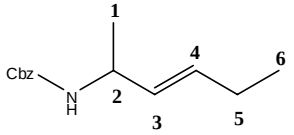
***N*-(Cyclooct-2-enyl)-*p*-toluenesulfonamide (5a-3)**.[50] FC (EtOAc/hexane, 1:4); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.74 (2H, app. d, *J* = 8.3 Hz, Ts), 7.28 (2H, app. d, *J* = 8.1 Hz, Ts), 5.56 (1H, dtd, *J* = 10.5, 8.2, 1.3 Hz, H-3), 5.12 (1H, app. dd, *J* = 10.5, 8.0 Hz, H-2), 4.37 (1H, br. d, *J* = 7.0 Hz, NH), 4.19 (1H, m, H-1), 2.42 (3H, s, Ts), 1.85-1.15

(10H, m, H-4,5,6,7 and 8); IR (neat) ν 3272 (m), 3021 (w), 2926 (s), 2855 (m), 1727 (w), 1599 (w), 1450 (m), 1323 (m), 1161 (s), 1094 (m), 1063 (m), 912 (m), 814 (m), 733 (s), 667 (s), 573 (s), 549 (m); EIMS *m*/*z* (% relative intensity) 280 ($M^+$+1, 6), 279 ($M^+$, 28), 236 (30), 210 (22), 184 (13), 157 (11), 155 (66), 125 (11), 124 (100), 108 (15), 107 (12), 92 (19), 91 (99), 82 (11), 81 (18), 80 (18), 79 (14), 68 (12), 67 (12), 65 (18), 55 (16), 41 (16). HPLC (Chiralpak AD, *i*-PrOH/hexane, 10/90, 1.0 mL $min^{-1}$, 254 nm) $t_R$ 11.2 and 15.3 min.




**5b-3**

**Benzyl *N*-(cyclooct-2-enyl)carbamate (5b-3)**. FC (EtOAc/hexane, 1:4); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.45-7.25 (5H, m, Ph), 5.69 (1H, app. dt, *J* = 10.3, 8.9 Hz, H-3), 5.30 (1H, app. dd, *J* = 10.5, 9,5 Hz, H-2), 5.10 (2H, s, $PhCH_2$), 4.75 (1H, br, NH), 4.58 (1H, m, H-1), 2.4-1.2 (10H, m, H-4,5,6,7 and 8); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 155.6, 136.6, 131.8, 130.0, 128.5, 128.2, 128.1, 66.6, 49.0, 36.6, 29.0, 26.5, 26.2, 24.3; IR (neat) ν 3331 (s), 3031 (w), 2924 (m), 2851 (m), 1687 (s), 1545 (s), 1453 (m), 1311 (s), 1259 (s), 1045 (s), 969 (m), 765 (m); EIMS *m*/*z* (% relative intensity) 259 ($M^+$, 2), 172 (29), 168 (21), 91 (100). HPLC (Chiralpak AD, *i*-PrOH/hexane, 5/95, 1.0 mL $min^{-1}$, 254 nm) $t_R$ 29.1 and 31.6 min.




**5b-4**

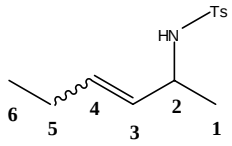
**Benzyl (*E*)-*N*-(hex-3-en-2-yl)carbamate (5b-4).** FC (EtOAc/hexane, 1:9); TLC (EtOAc/hexane, 1:9) $R_f$ 0.1; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.4-7.25 (5H, m, Ph), 5.62 (1H, app. dt, *J* = 15.6, 5.9 Hz, H-4), 5.39 (1H, app, dd, *J* = 15.4, 5.6 Hz, H-3), 5.10 (2H, s, $PhCH_2$), 4.66 (1H, br, NH), 4.25 (1H, m, H-2), 2.02 (2H, app. pd, *J* = 7.5, 1.0 Hz, H-

5), 1.21 (3H, d, $J$ = 6.8, H-1), 0.97 (3H, t, $J$ = 7.5 Hz, H-6); HPLC (Chiralpak AD, *i*-PrOH/hexane, 1/99, 0.7 mL $min^{-1}$, 258 nm) $t_R$ 18.6 and 20.1 min.

**General procedure for preparation of allylic amines (5) with sulfur diimide (7).** Lewis acid (0.2-0.5 mmol) was diluted with dry $CH_2Cl_2$ (2 ml) and cooled to preferred temperature. To this mixture was added pre-cooled alkene (1 equiv.) and a pre-cooled solution of sulfur diimide **7a** (1 equiv., 0.5 M in $CH_2Cl_2$). The reaction was carried out under an inert atmosphere and eventually quenched* with a phosphate buffered (pH 7) aqueous solution (2 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 x 2 ml) and the organic phases were concentrated *in vacuo*. The crude product was diluted in MeOH/$H_2O$ (3:2, 3 ml) and added $K_2CO_3$ (6 equiv.). After 15 h at room temperature, diethyl ether (20 ml) was added. The ether phase was separated and washed with NaOH/brine (2:1, 3 ml), $H_2O$ (3 ml) and brine (3 ml) before drying over $MgSO_4$ and concentration *in vacuo*. The crude product was purified by flash chromatography.

*)For reactions without Lewis acid, the quenching and following extraction with $CH_2Cl_2$ were not performed.

Experimental data for **5a-1** from this reaction was compatible with the data already reported for the **1a** reaction.

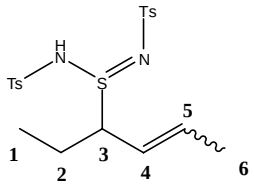



**5a-4**

**(*N*)-(Hex-3-en-2-yl)-*p*-toluenesulfonamide** (**5a-4**)[51]: *E*-isomer: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.74 (2H, app. d, $J$ = 8 Hz, Ts), 7.28 (2H, app. d, $J$ = 8 Hz, Ts), 5.44 (1H, app. dt, $J$ = 15.4, 6.3 Hz, H-4), 5.14 (1H, app. dd, $J$ = 15.4, 6.6 Hz, H-3), 4.69 (1H, d, $J$ = 7.3 Hz, NH), 3.86 (1H, m, H-2), 2.42 (3H, s, Ts), 1.86 (2H, m, H-5), 1.16 (3H, d, $J$ = 6.7 Hz, H-1), 0.83 (3H, t, $J$ = 7.4 Hz, H-6); *Z*-isomer: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.8-7.7 (2H, overlap, Ts), 7.35-7.2 (2H, overlap, Ts), 5.24 (1H, app. dt, $J$ = 10.7, 7.5 Hz, H-4),

5.06 (1H, m, H-3), 4.73 (1H, d, *J* = 6.4 Hz, NH), 4.16 (1H, m, H-2), 1.9-1.8 (2H, overlap, H-5), 1.2-1.1 (3H, overlap, H-1), 0.85-0.8 (3H, overlap, H-6).

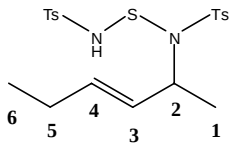
**Preparation of 8a-4/9a-4 for $^1$H NMR analysis**. (*E*)-3-Hexene (0.2 mmol) was dissolved in dry $CH_2Cl_2$ (2 ml) and added sulfur diimide **7a** (0.2 mmol). After stirring at room temperature for 1 h, the solution was concentrated *in vacuo*. $TsNH_2$ from hydrolysed **7a** precipitated out with addition of EtOAc/cyclohexane. After filtering, the remaining solution was concentrated *in vacuo* without further purification.




**8a-4**

The temperature during NMR experiments was calibrated from MeOH signals as reported by Ammann *et al.*.[52]

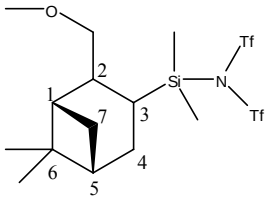
Data for initial ene-product product **(8a-4)**: $^1$H NMR (500 MHz, $CDCl_3$, -26 $^o$C) δ 7.87-7.70 (4H, overlap, Ts), 7.38-7.27 (4H, overlap, Ts), 5.69-5.56 (2H, m, H-3 and 4), 4.55 (1H, m, H-5), 2.5-2.4 (6H, overlap, Ts), 1.98 (2H, m, H-2), 1.30 (3H, d, *J* = 6.7 Hz, H-6), 0.94 (3H, t, *J* = 7.5 Hz, H-1).




**9a-4**

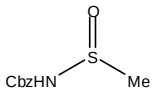
Data for rearranged ene-product (**9a-4**):$^1$H NMR (500 MHz, $CDCl_3$, -26 $^o$C) δ 7.87-7.70 (4H, overlap, Ts), 7.38-7.27 (4H, overlap, Ts), 5.28 (app. dt, 15.3, 6.4 Hz, H-4), 5.12 (1H, app. dd, *J* = 15.4, 7.0 Hz, H-3), 4.42 (1H, app. p, *J* = 7.0, H-2), 2.5-2.4 (6H, overlap, Ts), 1.83 (app. p, *J* = 7.2 Hz, H-5), 1.26 (3H, d, *J* = 6.5 Hz, H-1), 0.78 (3H, t, *J* = 7.4 Hz, H-6).

**Preparation of 18**. Silylcupration of (-)-myrtenal was performed according a literature procedure.[45] The resulting aldehyde (0.804 g, 2.81 mmol) was dissolved in dry THF (16 ml) and cooled to 0 $^{o}$C. DIBAL-H (1.0 M in toluene, 5.6 ml, 5.6 mmol) was added drop-wise over a period of 5-10 min. The solution was stirred for another 10 min before it was allowed to warm to room temperature. After stirring at room temperature for 2 h, methanol (5 ml) was added. The solution was transferred to a stirred mixture of aqueous solution of potassium tartrate (10 w%, 40 ml) and EtOAc (100 ml). The phases were separated and the aqueous phase was back extracted with EtOAc (4x 100 ml). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography ($Et_2O$/hexane, 3:7); 76% yield. The resulting alcohol (0.607 g, 2.10 mmol) was dissolved in dry THF (10 ml) and cooled to 0 $^{o}$C under Ar-atmosphere. NaH (0.168 g, 7.01 mmol) was added and the resulting suspension was stirred for 5 min before addition of $CH_3I$ (0.38 ml, 6.1 mmol). The mixture was allowed to warm to room temperature and stirred for 17.5 h before quenching by addition of water (5 ml). The resulting mixture was transferred to a mixture of $CH_2Cl_2$ (20 ml) and water (15 ml). The layers were separated and the aqueous phase back extracted with $CH_2Cl_2$ (4 x 20 ml). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography ($Et_2O$/hexane, 1:24) provided the compound as a colourless oil (89%). The resulting compound (0.200 g, 0.642 mmol) was dissolved in dry $CHCl_3$ (10 ml) and bubbled with dry HCl gas at room temperature for 24 h. Subsequent purge with nitrogen for 20 min removed excess HCl in the reaction vessel. The solution was transferred by canula to a sealed round flash covered with Al-foil, containing $AgNTf_2$ (0.248 g, 0.642 mmol). The white suspension was stirred for 16 h at room temperature, before filtering under $N_2$-atmosphere. The filtrate was concentrated *in vacuo* to a viscous brown oil. A sample was dissolved in dry $CD_2Cl_2$ for NMR analysis. Due to impurities, the yield in the last step was not determined.



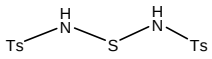

**18**

Lewis acid **18**. $^1$H NMR (400 MHz, $CD_2Cl_2$, selected signals) δ 3.69 (1H, dd, *J* = 11.3, 8.5 Hz, MeOC**H**H'), 3.61 (1H, dd, *J* = 8.5, 3.5 Hz, MeOCH**H'**), 3.57 (3H, s, MeO), 1.21 (3H, s, Me-6), 1.05 (3H, s, Me-6'), 0.40 (6H, s, SiMe).




**19**

**Benzyl *N*-(methylsulfinyl)carbamate** (**19**). FC ($Et_2O$) provided **19** as white crystals; TLC ($Et_2O$) $R_f$ 0.05; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.45-7.3 (5H, m, Ph), 7.12 (1H, br, NH), 5.22 (2H, s, PhC**H$_2$**O), 2.09 (3H, s, Me); IR (KBr) ν 3105 (m), 2870 (w), 1732 (m), 1453 (m), 1229 (s), 1059 (s), 832 (s), 742 (s), 698 (m).



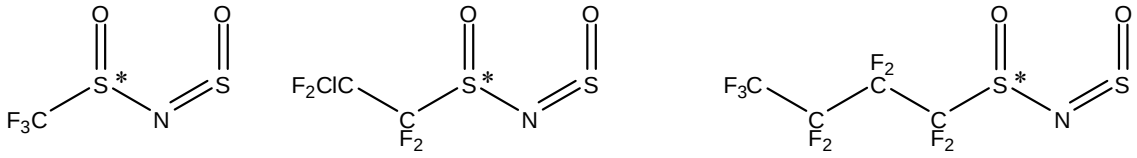

**20**

***N,N'*-Thiobis(*p*-toluenesulfonamide) (20)**.[53] FC ($Et_2O$/pentane, 1:1) provided **19** as a white solid; mp 162-164 °C (litt.[47] 175-176 °C); TLC ($Et_2O$) $R_f$ = 0.55; $^1$H NMR (300MHz, $CDCl_3$) δ 7.77 (4H, app. d, *J* = 8.3 Hz, Ts), 7.36 (4H, app. d, *J* = 8.4 Hz, Ts), 6.54 (2H, s, NH), 2.46 (6H, s, Ts); IR (KBr) ν 3228 (s), 1597 (m), 1364 (s), 1316 (s), 1303 (w), 1155 (s), 1089 (m), 905 (s), 823 (s), 779 (s), 660 (s), 586 (m), 550 (s); EIMS *m*/*z* (% relative intensity) 171 (74), 155 (63), 108 (16), 107 (21), 92 (11), 91 (100).

# 3 Ene-reactions with *N*-sulfinyl sulfinamides

## 3.1 Background

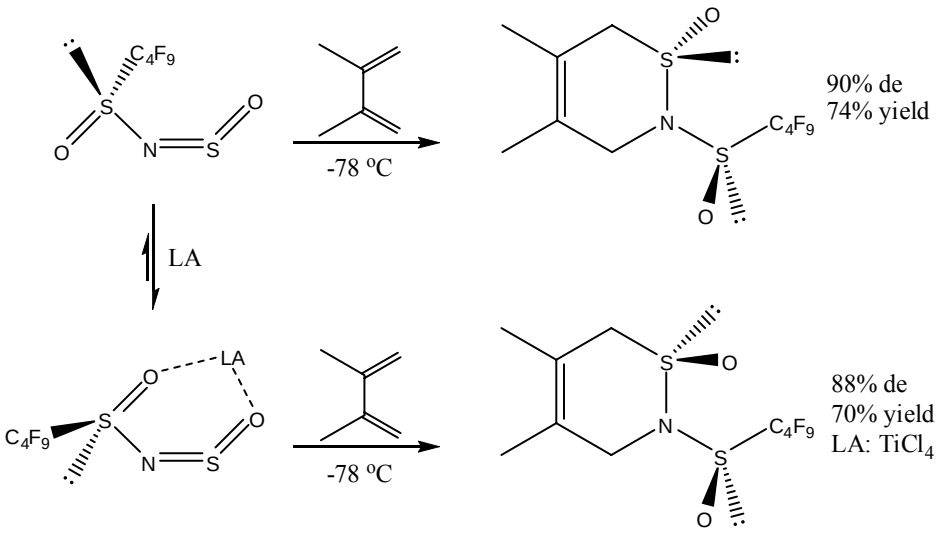
The lack of success in the previous chapter demanded a new strategy in order to reach the pronounced goals of attaining enantiomerically enriched allylic amines and alcohols. Since chiral Lewis acids proved difficult to implement in these reactions, our attention was again drawn to the work of Whitesell and the use of chiral enophiles.[23-25] Even though Whitesell achieved good diastereoselectivities of the initial ene-reaction, it is a captivating thought to exploit the stereocentre of a sulfoxide-substituent in this position. Having a chiral group in the neighbouring position of the reacting double bond, gave expectations of considerable diastereoselectivity. Only three *N*-sulfinyl sulfinamides have been reported to this date; *N*-sulfinyl-trifluoromethanesulfinamide (**1d**)[54], *N*-sulfinyl-2-chloro-tetrafluoroethanesulfinamide (**1e**)[55] and *N*-sulfinyl-nonafluorobutanesulfinamide (**1f**)[55] (Scheme 3.1).



**1d** **1e** **1f**

**Scheme 3.1**

Compound **1d** was reported already in 1976, but their synthetic potential was not fully explored.[54] In 2005, Liu reported the use of **1e** and **1f** in hetero Diels-Alder reactions, providing diastereoselectivities up to 96% de with moderate to good yields.[55] Although the reactions were racemic, the results show that the sulfoxide substituent serves as an efficient shield against a diene-approach. Interestingly, the selectivity was reversed when the reaction took place in the presence of Lewis acids like $TiCl_4$ and $SnCl_4$. This could be explained as a conformational change of the dienophile. Without LA, the two sulfinyl oxygens are oriented as shown in Scheme 3.2 to minimize electrostatic interaction. With a LA present, a bidentate chelate with both oxygens is formed, causing the sulfinyl substituent to point in the opposite direction.




**Scheme 3.2**

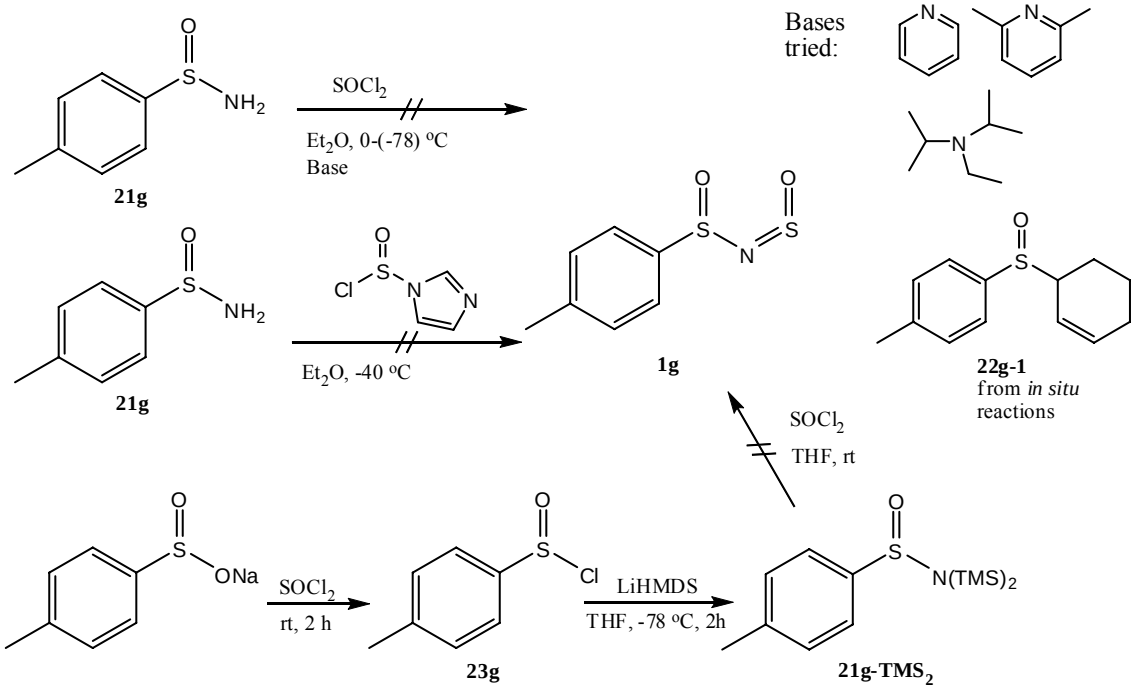
Having documented their diastereoselective potential, the project presented two challenges. The chiral *N*-sulfinyl sulfinamides had to be prepared, and their reactivity and stereoselectivity as enophiles had to be studied. Sulfinyl-groups have previously been used as *N*-protecting groups, being stable under basic conditions but easily hydrolysed in the presence of acid.[56] This could provide an important advantage for compounds for which mild conditions for hydrolysis are required.

## 3.2 Results and discussion

### 3.2.1 Preparation of *N*-sulfinyl sulfinamides

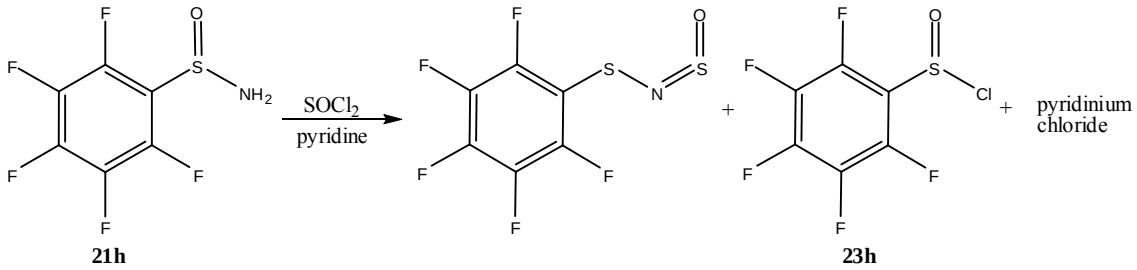
Undismayed by the fact that only perfluorated *N*-sulfinyl sulfinamides had been reported, attempts to form *N*-sulfinyl *p*-toluenesulfinamide (**1g**) were undertaken. With the synthetic precursor *p*-toluene sulfinamide (**21g**) being commercially available in both enantiomeric forms, **1g** made an attractive enophile for these reactions. Unfortunately, despite several attempts, **1g** could not be effectively formed (see Scheme 3.3) and complex product-mixtures were obtained instead. Different reaction conditions based on the experience from the preparation of *N*-sulfinylbenzylcarbamate (**1b**) were applied, mixing the sulfinamide with thionyl chloride in the presence of pyridine. Since nucleophilic attack by the pyridine was suspected to cause problems, different sterically

hindered bases were tried out, but without improvement of the results. A milder sulfinylation agent, *N*-(chlorosulfinyl) imidazole[57], did not solve the problem. Since the precursors in the preparation of the perfluorated analogues were *N*-silylated sulfinamides (both mono and bis silylated), *N*-bis(trimethylsilyl)-*p*-toluene sulfinamide (**21g-TMS$_2$**) was prepared and used in the same manner, yielding the same discouraging results as before.



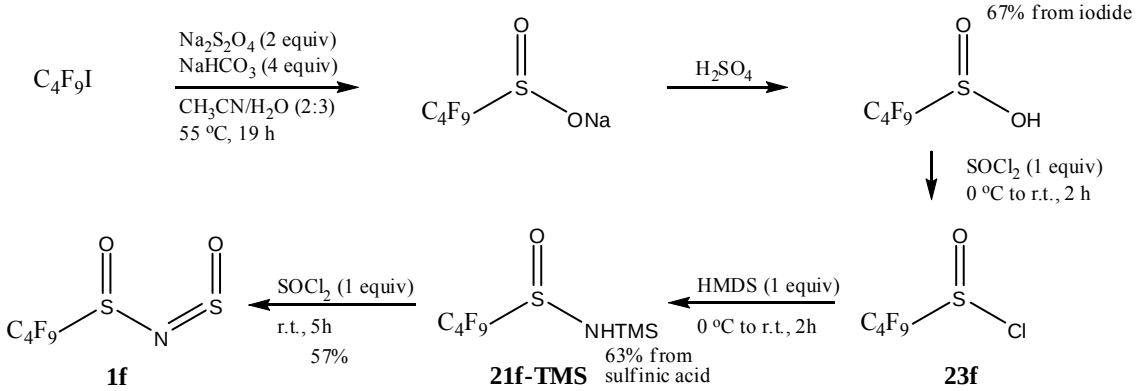

**Scheme 3.3**

Attempts to form **1g** *in situ* in the presence of cyclohexene, led to *p*-tolyl-cyclohex-2-enyl sulfoxide **22g-1**, pointing to *p*-toluenesulfinyl chloride (**23g**) as one of the by-products. In a reported attempt to form *N*-sulfinyl pentafluorobenzenesulfinamide, the sulfinyl chloride (**23h**) was indeed one of the isolated by-products Scheme 3.4.[58]




**Scheme 3.4**

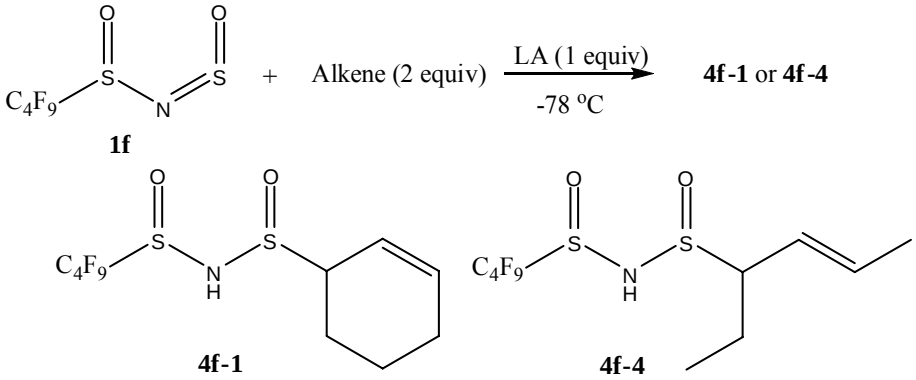
In retrospect, the powerful electron withdrawing groups in **1d**, **1e** and **1f** seem to be of crucial importance for the formation and/or stability of the *N*-sulfinyl compounds. To ensure progress of the project, the remaining work was performed with already known **1f**. Since the diastereomeric composition of the expected ene-products provides the necessary information regarding stereoselectivity, racemic **1f** was initially formed using a modified version of the procedure reported by Wang and Liu (Scheme 3.5).[55]




**Scheme 3.5**

## 3.2.2 Ene-reactions with an *N*-sulfinyl sulfinamide

As with the ene-reactions with **1a** and **1b**, $SnCl_4$ proved to be an efficient Lewis acid for promoting the reaction. The reactions between **1f** and cyclohexene, (*E*)-3-hexene and (*Z*)-3-hexene at -78 °C are shown in Scheme 3.6 and the results in Table 3.1.




**Scheme 3.6**

**Table 3.1** Reactions with **1f** and alkenes at -78 °C.

| Entry | Alkene | LA | Reaction-time | Product | Diastereo-selectivity[a] D1:D2:D3:D4 | Yield [%] |
|---|---|---|---|---|---|---|
| 1 | (*E*)-3-hexene | None | 23 h | - | - | 0 |
| 2 | (*E*)-3-hexene | $SnCl_4$ | 30 min | **4f-4** | 67:15:17:0 | 29 |
| 3 | (*E*)-3-hexene | $SnCl_4$ | 23 h | **4f-4** | 74:11:8:7 | 96 |
| 4 | (*E*)-3-hexene | $TiCl_4$ | 19 h | **4f-4** | 8:92:0:0 | -[b] |
| 5 | (*Z*)-3-hexene | $SnCl_4$ | 19 h | **4f-4** | 50:17:17:16 | 95 |
| 6 | Cyclohexene | $SnCl_4$ | 18 h | **4f-1** | 64:18:18 | 15 |

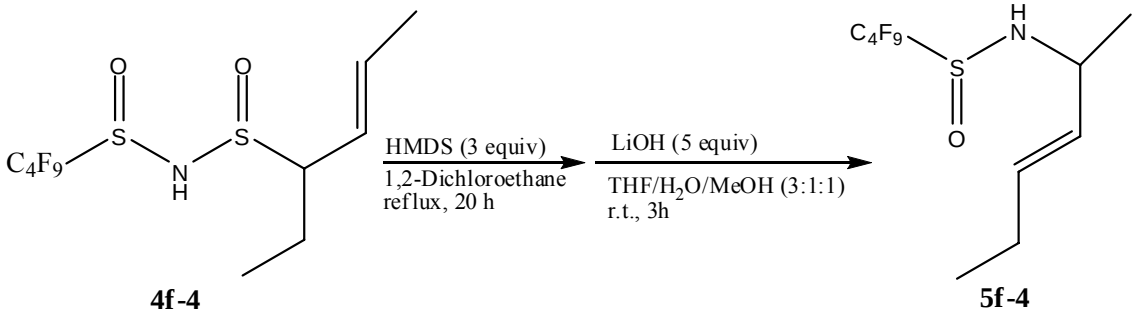
[a]Diastereomers were named D1-D4 since no absolute configurations were determined.
[b]Due to a significant amount of by-products, the yield could not be accurately measured from the crude $^1$H NMR spectrum.

Because of instability, the products could not be purified by flash chromatography, and the yields had to be calculated from comparing the integrals of ene-products with those of nonafluorobutanesulfinamide (**21f**) (from hydrolysis of **1f**). Even after 1 day in an NMR tube, the sample composition changed significantly, probably due to a mixture of reversible [2,3]-sigmatropic rearrangements and degradation. Because of the massive overlap caused by these changes, no meaningful information could be drawn from the NMR spectra over time. To provide information about the initial ene-products, the samples were studied by $^1$H NMR spectroscopy as soon as possible after preparation. Determined from the $^3J_{H\text{-}H}$ coupling constant, the isomers D1-D4 of **4f-4** were found to be *trans*. Only trace amounts of *cis* isomers could be found. The great number of diastereomers indicates that other transition states than the one suggested by Whitesell[24] are effective. Additionally, (*Z*)-3-hexene provided the same main diastereomer as the *E*-alkene, in contrary to Whitesell's model. As a result, no assignment of stereochemistry on the basis of this model could be performed. Interestingly, reaction with $TiCl_4$ as LA (entry 4) provided "D2" as the major isomer. However, due to significant amounts of by-products, no more attempts with this LA were considered. Prolonging the reaction time in entry 3 (compared to entry 2), introduced the fourth isomer "D4". Based on the compositions, this isomer seems to stem from "D3", presumably from reversible rearrangements. Since the composition of all reactions with 3-hexene were different, a thermodynamic equilibration of the isomers under the reaction conditions seems

unlikely. Any satisfying explanation to why "D3" seemingly rearranged to "D4" could not be found.

### 3.2.3 Rearrangement of the ene-products

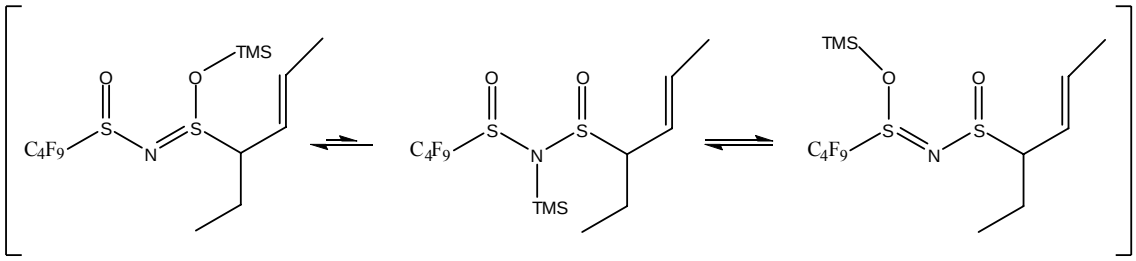
The crude ene-products from the (3)-hexene reactions were swiftly silylated by HDMS and transformed to the allylic amines by the same protocol as for the Cbz-reactions.[31] The allylic amine **5f-4** was obtained in 25% yield, with a diastereomeric ratio of 3:1 (both *trans*) (Scheme 3.7). Removal of the sulfinyl group in **5f-4** was expected to require higher temperatures and longer reaction time, or more preferably, acidic conditions.




**4f-4** **5f-4**

**Scheme 3.7**

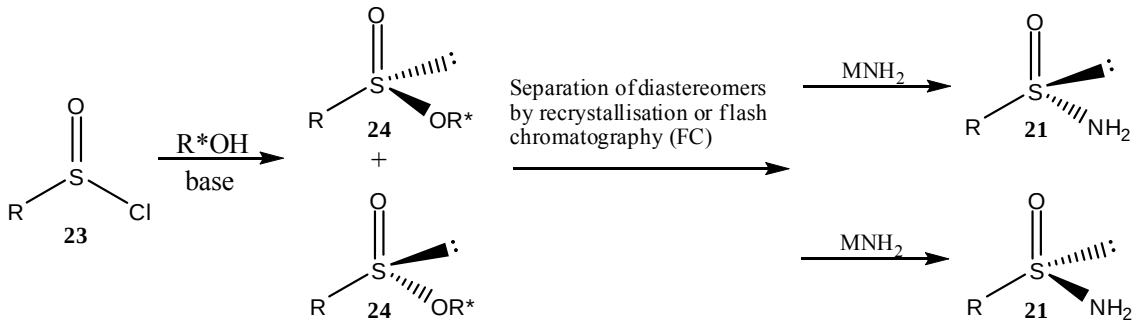
Refluxing in 1,2-dichloroethane (83 $^{o}$C) overnight seems incompatible with the suspected instability of the ene-products mentioned earlier, and could be responsible for the low yield. Other attempts to facilitate the rearrangement were undertaken with the more reactive silylation agent, TMSOTf, at lower temperature. Additionally, the thiophiles $NEt_3$ and $P(OMe)_3$ were added in attempts to "trap" the rearranged compound. Unfortunately, none of the attempts were successful, leading to messy mixtures of unknown compounds. The ene-products of *N*-sulfinyl sulfinamides have two sulfinyl groups connected to the same nitrogen. Upon silylation, the silyl group could possibly migrate to any of the sulfinyl-oxygens, although the oxygen closest to the strongly electron withdrawing nonafluorobutyl group should be less nucleophilic. This effect has not been found for the corresponding rearrangement of Cbz-products, and could be another explanation for the lower yields. Scheme 3.8 displays this possible extra tautomer.



**Scheme 3.8**

### 3.2.4 Work towards non-racemic *N*-sulfinyl sulfinamide

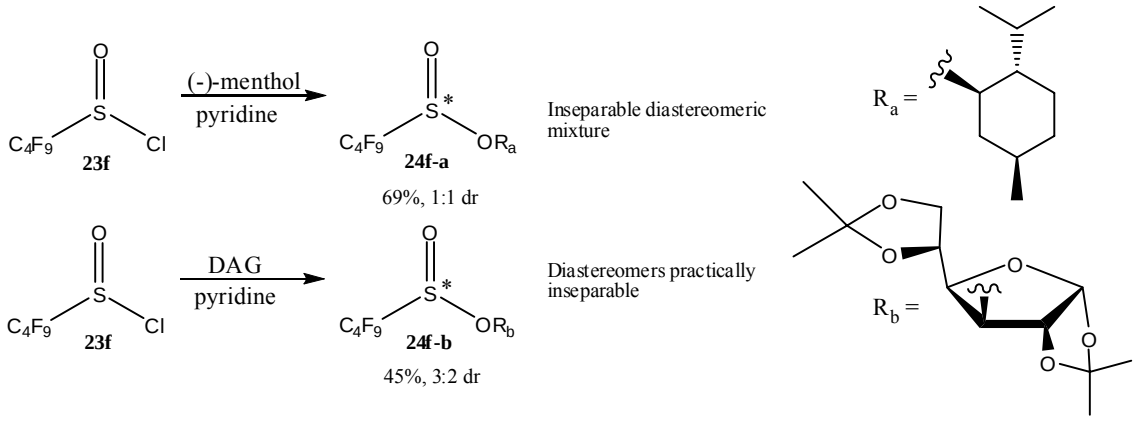
Not previously reported, a route to enantiomerically enriched *N*-sulfinyl sulfinamide **1f** had to be found. Sulfinamides (**21**) may be prepared enantiomerically pure by resolution of sulfinate esters (**24**), followed by aminolysis. Nucleophilic substitutions at chiral sulfinyl derivatives generally proceed with inversion of configuration.[59] Among potential chiral alcohols, (-)-menthol[60] and diacetone-α-*D*-glucofuranose (DAG)[61] have been used with success by others . The principle is described in Scheme 3.9.




**Scheme 3.9**

Nonafluorosulfinyl chloride (**23f**) was prepared as shown in Scheme 3.5. Initially, (-)-menthyl nonafluorobutanesulfinate (**24f-a**) was prepared in 69% yield with 1:1 diastereomeric ratio. However, the diastereomers could not be separated by flash chromatography. With DAG, the sulfinate (**24f-b**) was formed in 45% yield with 2:3 diastereomeric ratio. A slight difference in retention was found on TLC, but the separation with FC required multiple runs, isolating only small amounts of optically pure diastereomers each time. As a result, the obtained yields of each diastereomer were below practical levels (approximately 5% yield of each compound, >98% de). Since

both sulfinates were oils, recrystallisation was not an available separation method. Scheme 3.10 presents the results with preparation of optically pure sulfinate esters.




**Scheme 3.10**

At this stage in the project, the disappointing results from the racemic reactions covered in the last chapter, were known. Not wanting to waste valuable time, no more lab hours were spent to pursue the goal of enantiomerically pure *N*-sulfinyl sulfinamides.

## 3.3 Summary

Attempts to prepare *N*-sulfinyl *p*-toluenesulfinamide (**1g**) failed, leading to *p*-toluenesulfinyl chloride (**23g**) as one of the by-products. Racemic *N*-sulfinyl nonafluorosulfinamide (**1f**) was prepared after a modified literature procedure, providing almost quantitative yields of **4f-4** with moderate to good selectivities, in the reaction with 3-hexene. Problems were encountered with the following rearrangement to allylic amine (**5f-4**), only providing 25% yield and diminished selectivity (3:1 dr). Despite our efforts, a more efficient rearrangement procedure could not be found. Diacetone-*D*-glycosyl nonafluorobutanesulfinate (**24f-b**) was prepared and isolated in both diastereomeric forms. The separation, however, required excessive flash chromatography, ultimately providing low yields of each isolated diastereomer. (*L*)-menthyl nonafluorobutanesulfinate (**24f-a**) was also prepared, but the two diastereomers could not be separated.

## 3.4 Experimental

For general descriptions, see experimental section of Chapter 2.

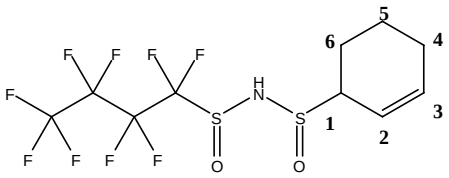
**Preparation of *N*-sulfinyl nonafluorobutanesulfinamide (1f).**[55] $Na_2S_2O_4$ (85%, 59.4 g, 0.29 mol) and $NaHCO_3$ (48.7 g, 0.58 mol) was added water (180 ml) and acetonitrile (120 ml). While stirring, nonafluoro iodide (50 g, 0.14 mol) was added dropwise over 1 h at 55 $^oC$. The reaction mixture was stirred at this temperature for another 19 h. The actonitrile was removed *in vacuo* and water was added to dissolve the remaining salts. The mixture was extracted with EtOAc (3 x 200 ml) and the combined organic phases were washed with brine (2x) and dried over $MgSO_4$. The solution was filtered and evaporated under reduced pressure to provide a white solid, which was dissolved in $H_2SO_4$ (conc., 75 ml). Upon distillation, nonafluorosulfinic acid was collected at 66-68 $^oC$ / 0.4 torr as a transparent oil (27.5 g, 67%).

**Nonafluorobutanesulfinic acid** (19.5 g, 0.069 mol) was added dropwise over a period of 15 min to thionyl chloride (5.0 ml, 0.069 mol) with stirring under nitrogen atmosphere at 0 $^oC$. After further stirring at room temperature for 2 h, the reaction mixture was added dropwise to HMDS (14.8 ml, 0.069 mol) over a period of 10 min at 0 $^oC$. The mixture was stirred for 2 h at room temperature and distilled under reduced pressure to provide *N*-TMS-nonafluorobutanesulfinamide (**21f-TMS**) at 70-72 $^oC$ / 0.05 torr as a yellow oil that solidifies on refrigeration (15.4 g, 63%).

***N*-TMS-nonafluorobutanesulfinamide** (**21f-TMS**) (13.5 g, 0.038 mol) was added dropwise over 10 min to thionyl chloride (2.8 ml, 0.038 mol) with stirring under nitrogen atmosphere at room temperature. The solution was stirred additionally for 5 h at this temperature before distillation at reduced pressure. *N*-sulfinyl nonafluorobutanesulfinamide (**1f**) was collected at 60-63 $^oC$ / 3 torr as a yellow oil (7.18 g, 57%). The products was dissolved in dry $CH_2Cl_2$ and stored in freezer (-20 $^oC$).

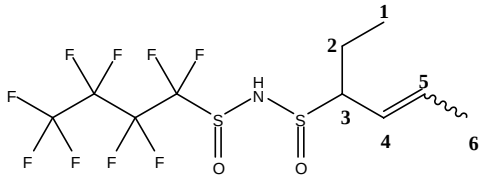
**General procedure for ene-reactions.** A solution of *N*-sulfinyl nonafluorosulfinamide (**1f**) (0.30 M in $CH_2Cl_2$, 1.0 ml, 0.30 mmol) was cooled down to -78 $^oC$ under nitrogen

atmosphere. $SnCl_4$ (1 equiv.) was added followed by a solution of alkene (0.25 M in $CH_2Cl_2$, 2 equiv.). The reaction was quenched with phosphate buffer (pH = 7, 3 ml) after the specified reaction time (see Table 3.1), and allowed to warm to room temperature. More water (20 ml) was added, and the aqueous phase was extracted with $CH_2Cl_2$ (4 x 25 ml). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and evaporated *in vacuo*, providing a slightly coloured oil.



**4f-1**

***N*-(Nonafluorobutylsulfinyl)-cyclohex-2-ene-sulfinamide** (**4f-1**). The diastereomeric composition was determined from integration of three distinct different H-2 signals in $^1$H NMR from crude product. All other signals overlapped. **Main diastereomer (D1)**: $^1$H NMR (300 MHz, $CDCl_3$, selected signals) δ 6.35-6.15 (1H, m, H-3), 5.82 (1H, m, H-2), 3.9-3.7 (1H, m, H-1), 2.2-1.5 (6H, m, H-4,5 and 6). **Diastereomer D2**: $^1$H NMR (300 MHz, $CDCl_3$, selected signals) δ 6.35-6.15 (1H, m, H-3), 5.74 (1H, m, H-2), 3.9-3.7 (1H, m, H-1), 2.2-1.5 (6H, m, H-4,5 and 6). **Diastereomer D3**: $^1$H NMR (300 MHz, $CDCl_3$, selected signals) δ 6.35-6.15 (1H, m, H-3), 5.64 (1H, m, H-2), 3.9-3.7 (1H, m, H-1), 2.2-1.5 (6H, m, H-4,5 and 6).

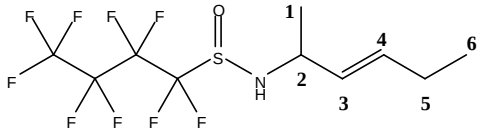


**4f-4**

***N*-(Nonafluorobutylsulfinyl)-hex-4-ene-3-sulfinamide** (**4f-4**). **Main diastereomer (D1)**: $^1$H NMR (300 MHz, $CDCl_3$, selected signals) δ 5.93 (1H, app. dq, $J$ = 15.4, 6.5 Hz, H-5), 5.47 (1H, ddq, $J$ = 15.4, 9.8, 1.7 Hz, H-4), 3.17 (1H, app. td, 9.5, 5.7 Hz, H-3), 2.03 (1H, m, H-2), 1.89 (3H, dd, $J$ = 6.5, 1.7 Hz, H-6), 1.85-1.7 (1H, m, H-2'), 1.08 (3H, t, $J$ = 7.4 Hz, H-1). **Diastereomer D2**: $^1$H NMR (300 MHz, $CDCl_3$, selected signals) δ

6.0-5.8 (1H, overlap, H-5), 5.55-5.4 (1H, overlap, H-4), 3.08 (1H, app. td, 9.5, 5.5 Hz, H-3), 2.1-1.7 (5H, overlap, H-2 and H-6), 1.04 (3H, t, *J* = 7.5 Hz, H-1). **Diastereomer D3**: $^1$H NMR (300 MHz, $CDCl_3$, selected signals) δ 6.0-5.8 (1H, overlap, H-5), 5.37 (1H, app. ddq, *J* = 15.4, 6.6, 1.7 Hz, H-4), 3.53 (1H, app. td, *J* = 9.1, 4.6 Hz, H-3), 2.1-1.7 (5H, overlap, H-2 and H-6), 1.07 (3H, t, *J* = 7.4 Hz, H-1). **Diastereomer D4**: $^1$H NMR (300 MHz, $CDCl_3$, selected signals) δ 6.0-5.8 (1H, overlap, H-5), 5.31 (1H, app. ddq, *J* = 15.4, 8.7, 1.6 Hz, H-4), 3.65-3.5 (1H, overlap, H-3), 2.1-1.7 (5H, overlap, H-2 and H-6), 1.15-1.0 (3H, overlap, H-1).

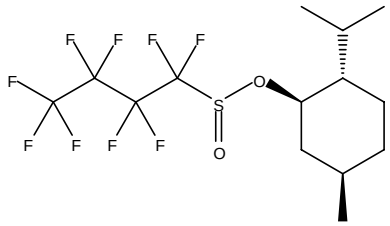
**Preparation of *N*-(hex-3-en-2-yl)-nonafluorobutanesulfinamide (5f-4)**. The crude product from the ene-reaction (**4f-4**) was dissolved in 1,2-dichloroethane (4 ml) and added HMDS (3 equiv.). The solution was stirred at room temperature for 90 min, then at 50 °C for 90 min and finally refluxed overnight (20 h) under nitrogen atmosphere. The solvent and excess reagent was removed under reduced pressure and the oily residue was stirred for 3 h with LiOH (5 equiv.) in a 3:1:1 mixture of THF/water/methanol (50 ml) at room temperature. Water (200 ml) and EtOAc (100 ml) were added, the layers separated, and the aqueous phase extracted with EtOAc (3 x 50 ml). The combined organic phases were washed with brine (2x), dried over $MgSO_4$, filtered and evaporated *in vacuo*, providing a brown oil (25%).




**5f-4**

***N*-(Hex-3-en-2-yl)-nonafluorobutanesulfinamide** (**5f-4**). **Main diastereomer (D1)**: $^1$H NMR (300 MHz, $CDCl_3$) δ 5.65 (1H, dtd, *J* = 15.4, 6.3, 0.7 Hz, H-4), 5.28 (1H, ddt, *J* = 15.4, 7.6, 1.5 Hz, H-3), 3.55 (1H, m, H-2), 2.88 (1H, br, NH), 2.1-2.0 (2H, m, H-5), 1.22 (3H, d, *J* = 6.5 Hz, H-1), 0.99 (3H, t, *J* = 7.4 Hz, H-6). **Minor diastereomer (D2)**: $^1$H NMR (300 MHz, $CDCl_3$, selected signals) δ 5.79 (1H, dtd, *J* = 15.5, 6.3, 1.3 Hz, H-4), 5.44 (1H, ddt, *J* = 15.5, 5.9, 1.6 Hz, H-3), 2.1-2.0 (2H, m, H-5),1.37 (3H, d, *J* = 6.7 Hz, H-1), 1.00 (3H, t, *J* = 7.5 Hz, H-6).

**Preparation of (*L*)-menthyl nonafluorobutanesulfinate (24f-a)**. Nonafluorobutanesulfinic acid was prepared as described above. The sulfinic acid (10.1 g, 0.0355 mol) was added dropwise to thionyl chloride (2.6 ml, 0.036 mol) over a period of 15 min at 0 $^{o}$C under nitrogen atmosphere. The solution was stirred for 2.5 h at room temperature. Dry diethyl ether (30 ml) was added, and the solution was cooled down to 0 $^{o}$C. (*L*)-Menthol (6.1 g, 0.039 mol) was dissolved in pyridine (4.9 ml) and added dropwise over 5 min. The mixture was stirred at room temperature overnight (20 h). Ice (14 g) was added, the layers separated, and the aqueous phase extracted with diethyl ether (100 ml). The organic phases were washed with HCl-solution (20%, 3 x 50 ml), dried over $Na_2SO_4$, filtrated and evaporated *in vacuo*. The crude product was purified by flash chromatography ($CH_2Cl_2$) providing a colourless oil (69% yield from sulfinic acid).

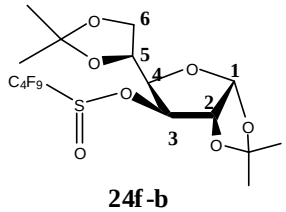


**24f-a**

**(*L*)-Menthyl nonafluorobutanesulfinate (24f-a)**. Two inseparable isomers (1:1). TLC ($CH_2Cl_2$) $R_f$ 0.75. **Diastereomer D1**: $^{1}$H NMR (300 MHz, $CDCl_3$) δ 4.29 (1H, app. td, *J* = 10.8, 4.6 Hz, OCH), 2.25-2.0 (2H, m), 1.8-1.6 (2H, m), 1.6-1.0 (5H, m), 1.0-0.75 (9H, m, Me). **Diastereomer D2**: $^{1}$H NMR (300 MHz, $CDCl_3$) δ 4.25 (1H, app. td, *J* = 10.9, 4.6 Hz, OCH), 2.25-2.0 (2H, m), 1.8-1.6 (2H, m), 1.6-1.0 (5H, m), 1.0-0.75 (9H, m, Me).

**Preparation of diacetone-*D*-glucosyl nonafluorobutanesulfinate (24f-b)**. Nonafluorobutanesulfinic acid was prepared as described above. The sulfinic acid (12.8 g, 0.0451 mol) was added dropwise to thionyl chloride (3.3 ml, 0.045 mol) over a period of 15 min at 0 $^{o}$C under nitrogen atmosphere. The solution was stirred for 3 h at room temperature. Dry THF (35 ml) was added, and the solution was cooled down to 0 $^{o}$C. Diacetone-α-*D*-glucofuranose (DAG) (12.9 g, 0.0496 mol) was added pyridine (10 ml) and transferred to the sulfinyl chloride mixture by canula at 0 $^{o}$C under nitrogen

atmosphere. The mixture was stirred at room temperature overnight (19 h). Ice (16 g) was added, the layers separated, and the aqueous phase extracted with ethyl acetate (250 ml). The organic phases were washed with HCl-solution (20%, 3 x 80 ml), dried over $MgSO_4$, filtrated and evaporated *in vacuo*. The crude product was purified by flash chromatography (*i*-PrOH/hexane, 1:9) providing a colourless oil (45% yield from sulfinic acid). The diastereomers were separated by flash chromatography (EtOAc/hexane, 1:19) (repeated runs).



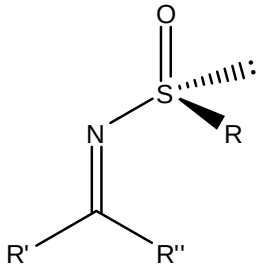

**24f-b**

**Diacetone-*D*-glucosyl nonafluorobutanesulfinate (24f-b)**. **Main isomer (D1)**: TLC (Acetone/hexane, 1:4) $R_f$ 0.43; $[\alpha]^{r.t.}_D$ + 8.9 (*c* 1.48, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.97 (1H, d, *J* = 3.6 Hz, H-1), 4.94 (1H, d, *J* = 2.5 Hz, H-3), 4.74 (1H, d, *J* = 3.6 Hz, H-2), 4.2-4.1 (3H, overlap, H-4 and 6), 3.97 (1H, app. td, *J* = 7, 3.4 Hz, H-5), 1.52 (3H, s, Me), 1.42 (3H, s, Me), 1.33 (3H, s, Me), 1.29 (3H, s, Me); IR (neat) ν 2991 (w), 2941 (w), 2894 (w), 1458 (w), 1376 (w), 1352 (w), 1237 (m), 1216 (s), 1139 (m), 1078 (m), 1026 (m), 1000 (w), 953 (w), 886 (w), 841 (m), 747 (w), 725 (w), 694 (w); EIMS *m*/*z* (% relative intensity) 512 (10), 511 (65), 453 (14), 292 (24), 249 (33), 234 (14), 191 (20), 149 (13), 127 (21), 101 (100), 100 (14), 85 (11), 81 (11), 77 (14), 69 (10), 59 (16), 43 (59). **Minor isomer (D2)**: TLC (Acetone/hexane, 1:4) $R_f$ 0.47; $[\alpha]^{r.t.}_D$ – 9.0 (*c* 1.26, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 5.96 (1H, d, *J* = 3.4 Hz, H-1), 4.94 (1H, d, *J* = 2.3 Hz, H-3), 4.61 (1H, d, *J* = 3.5 Hz, H-2), 4.3-4.1 (3H, overlap, H-4,5 and 6), 3.97 (1H, dd, *J* = 8.3, 4.8 Hz, H-6'), 1.52 (3H, s, Me), 1.44 (3H, s, Me), 1.36 (3H, s, Me), 1.34 (3H, s, Me); IR (neat) ν 2991 (m), 2941 (w), 2894 (w), 1457 (w), 1376 (m), 1352 (m), 1217 (s), 1166 (w), 1138 (m), 1078 (m), 1026 (m), 999 (w), 954 (w), 885 (w), 837 (m), 747 (w), 725 (w), 692 (w); EIMS *m*/*z* (% relative intensity) 511 (47), 453 (14), 325 (12), 292 (67), 249 (13), 234 (17), 228 (27), 213 (25), 191 (12), 185 (15), 127 (36), 111 (10), 101 (50), 100 (18), 99 (12), 85 (18), 83 (10), 81 (16), 73 (26), 71 (10), 69 (14), 59 (23), 55 (10), 43 (100), 41 (16), 27 (11).

# 4 Asymmetric reactions with sulfinimines

## 4.1 Background

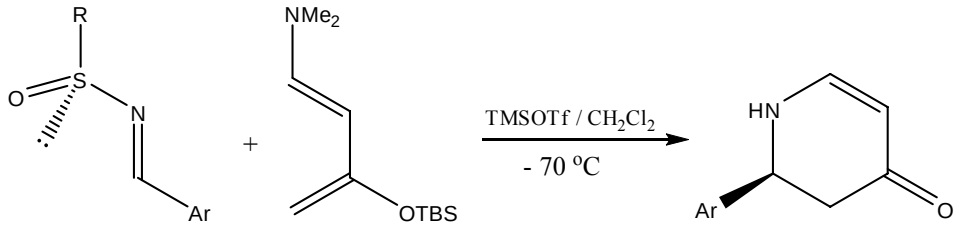
The work with obtaining optically pure sulfinamides (**21**), summarised in Chapter 3, led the project in a new direction. An important application for these sulfinamides is preparation of optically pure sulfinimines (**25**) (Figure 4.1).[62]




**25**

**Figure 4.1** General sulfinimine.

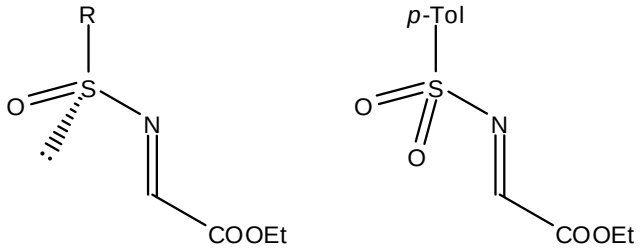
These sulfinimines caught our interest as potential dienophiles for preparation of optically pure cyclic allylic amines through aza-Diels-Alder reactions. A large number of other optically pure imines have found use as dienophiles in these reactions, but they often lead to troublesome removal of the chiral auxiliary on nitrogen from the final product.[63] Removal of sulfinyl groups are effectively carried out under mild acidic conditions.[56] Despite a large number of papers reporting the use of sulfinimines in asymmetric synthesis,[56,62,64] only one paper by Kawęcki could be found reporting their use as dienophiles.[65] The successful results in this report were limited to reactions with the electron rich Rawal diene (**26a**) as shown in Scheme 4.1.[66] The reaction took place through a step-wise mechanism, followed by elimination of dimethylamine before the final product could be isolated.




**25** (R' = Ar, R" = H) **26a**

**Scheme 4.1**

Asymmetric Diels-Alder reactions can also be facilitated by asymmetric catalysis, as exemplified by Jørgensen *et al.* [67]. In this paper, *N*-tosyl α-imino ester (**27**) was reacted with different dienes in the presence of chiral BINAP-copper(I) complexes. Although selectivities were good in many cases, difficult removal of the *p*-toluenesulfonyl group presents a major drawback. The similarities between the α-imino esters (**27**) and **25** (R' = COOEt, R" = H) (Figure 4.2), inspired us to test the latter in aza-Diels-Alder reactions with the same dienes as in Jørgensens work.




**25** (R' = COOEt, R" = H) **27**

**Figure 4.2** α-Imino esters **25** (R' = COOEt, R" = H) and **27**.

Before elaborating further on the sulfinimines, some general aspects about imines in asymmetric Diels-Alder reactions are presented in the next section.

### 4.1.1 Asymmetric Diels-Alder reactions with imines

The aza-Diels-Alder reaction between dienes and imines is a powerful tool for the formation of highly functionalized six-membered nitrogen heterocycles.[68] As with other Diels-Alder reactions, the reactivity can be rationalised considering the energies of the

frontier molecular orbitals (FMOs) involved. The reactivity increases as the energy gap between the FMOs is reduced.[63] For the normal electron demand, which is most often encountered, the reaction occurs between electron deficient dienophiles ($LUMO_{dienophile}$) and electron rich dienes ($HOMO_{diene}$). In addition to having electron withdrawing substituents on the imine, the reactivity may be further increased by the aid of Lewis acids as outlined in Figure 4.3.

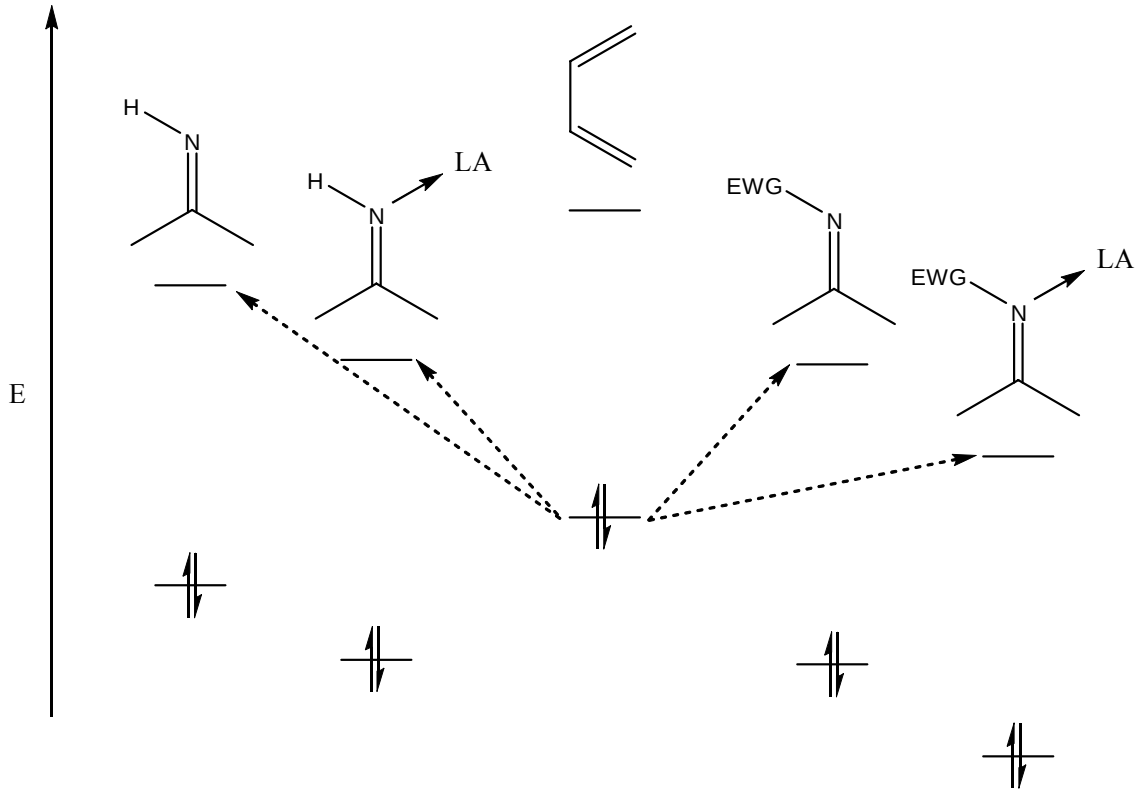



**Figure 4.3** FMO diagram of the normal electron demand aza-Diels-Alder reaction.

Although most aza-Diels-Alder reactions are concerted, there are many examples of stepwise Mannich-Michael type mechanisms.[68] Most of these examples involve electron-rich oxygenated dienes or the use of Brønsted acids as catalysts, which leads to relatively stable intermediates. The concerted reactions are often asynchronous in nature, meaning that the forming bonds are unequally developed in the transition state. This causes slightly polarised transition states, where the nature and position of substituents are important stabilising factors. In turn, this can explain the high regioselectivity often reported. One example is shown in Figure 4.4 where the new C-C bond is more developed than the C-N bond in the transition state. The preferred isomer is formed due to better stabilisation of the partial positive charge.

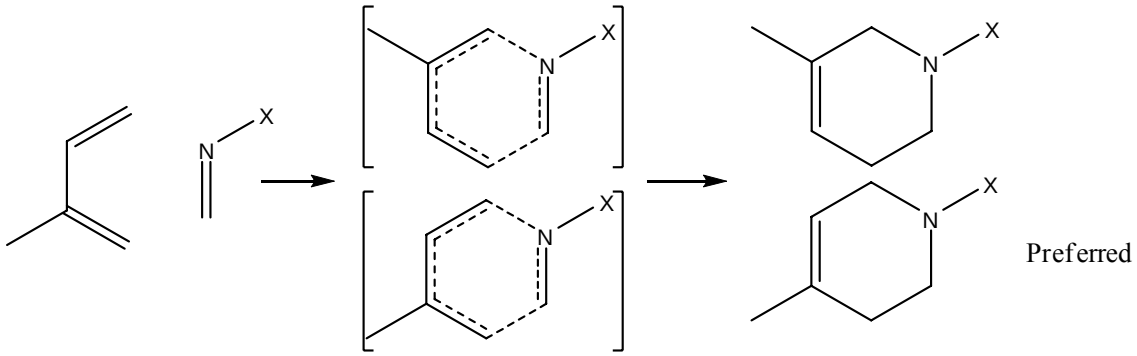



**Figure 4.4** Explanation for regioselectivity in asynchronous aza-Diels-Alder reaction.

Disregarding any chiral substituent on nitrogen, there are two possible relative orientations of the reacting compounds. The transition state with the lone pair on nitrogen in an *exo* orientation, is generally more stable than the corresponding *endo* transition state. This has been attributed to electronic repulsion between the lone pair on nitrogen and the π-electrons on the diene.[69] Taking into account a chiral auxiliary on nitrogen, the two faces of the imine carbon become diastereotopic, making the transition states for the *re* and *si* approach different in energy. Figure 4.5 summarises the stereoisomeric considerations of the asymmetric aza-Diels-Alder reaction.

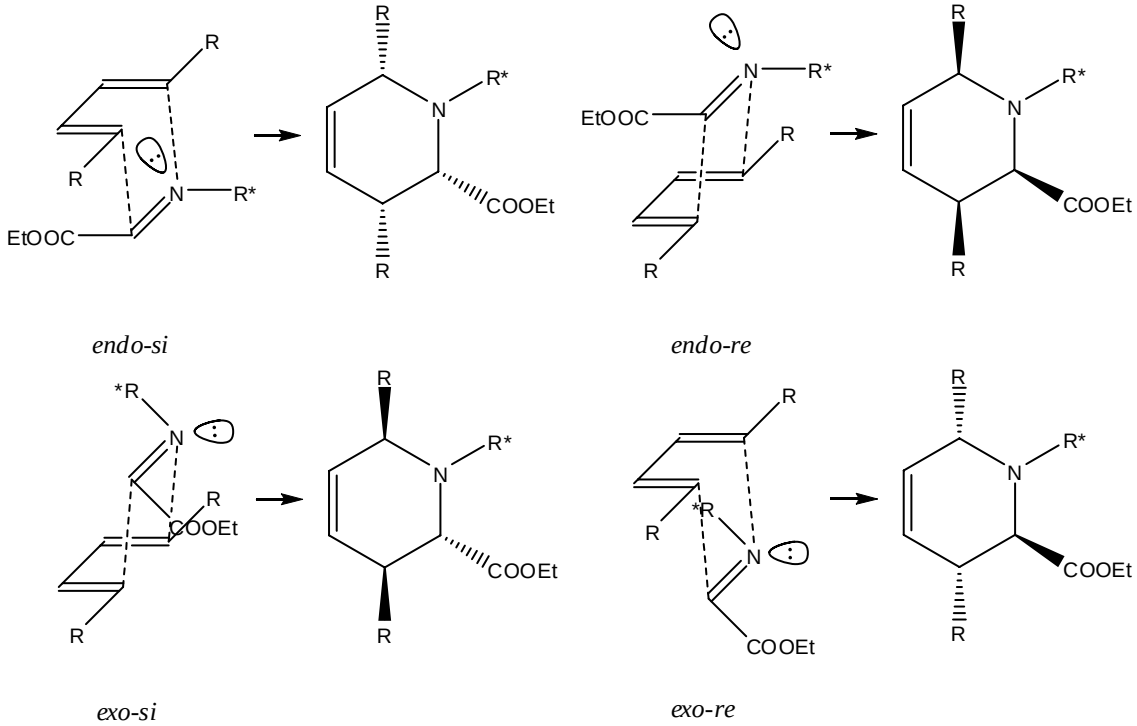
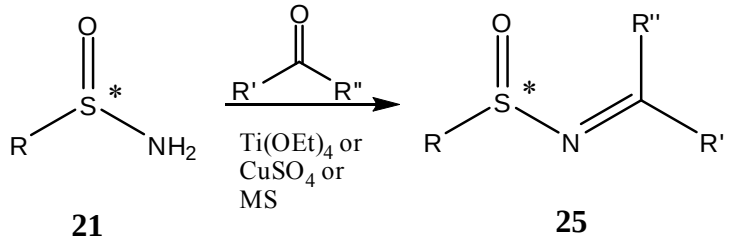



**Figure 4.5** Possible transition states and resulting diastereomeric aza-Diels-Alder products.

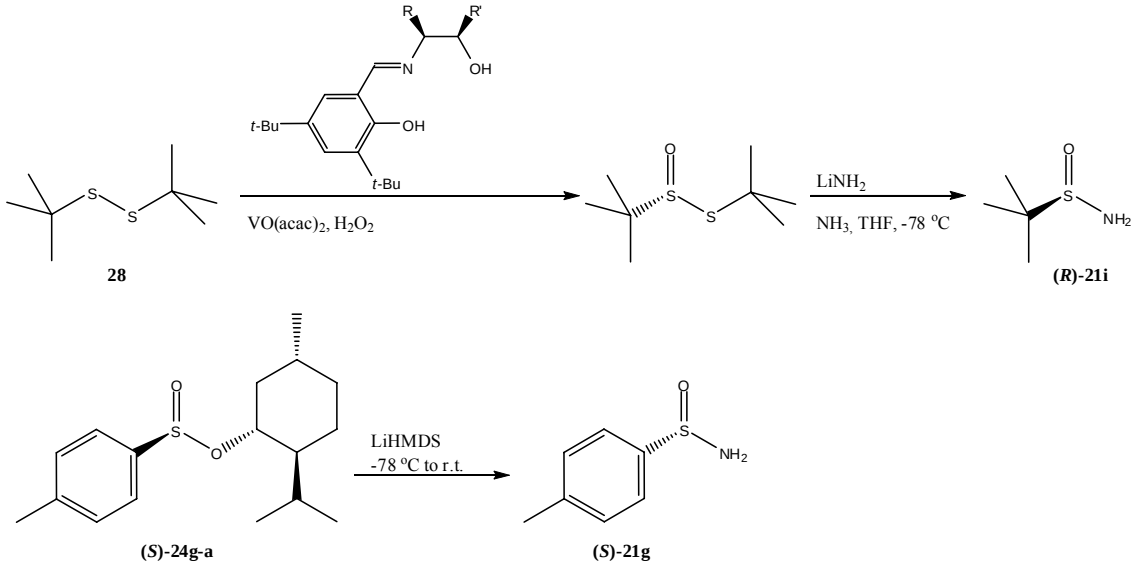
### 4.1.2 Sulfinimines

Sulfinimines (**25**) have received increasing attention since their first preparation in the mid 70's, resulting in a number of review articles.[56,62,64] They have found use in several asymmetric synthesis, in most cases initiated by nucleophilic attack at the iminium carbon. Although a series of synthetic routes to sulfinimines have been developed throughout the years, condensation of sulfinamides (**21**) with aldehydes and ketones stands out as the most important method. A general example is shown in Scheme 4.2, where $Ti(OEt)_4$, $CuSO_4$ or molecular sieves (MS) are used as activating Lewis acids and water scavengers. The *E*/*Z* selectivities are generally high, and become increasingly higher for larger R-substituents. Only the *E*-isomer is formed when there is a considerable steric difference between the R' and R" substituents.[56]




**Scheme 4.2**

Especially two different groups of sulfinimines have received great attention; the *p*-toluenesulfinyl imines by the work of Davis,[64] and the *tert*-butanesulfinyl imines by the work of Ellman.[56] Both imines derive from sulfinamides that have become commercially available in both enantiomeric forms, and can be prepared by aminolysis of optically resolved sulfinate esters (as already described in Scheme 3.9). An improved route to *tert*-butanesulfinamide (**21i**) was developed by Ellman, starting from the inexpensive oil waste by-product *tert*-butyl disulfide (**28**).[70,71] Since the chiral auxiliary is consumed in the various reactions with these sulfinimines, it is of tremendous importance that the optically pure compounds can be formed at a low cost. Preparations of *p*-toluenesulfinamide (**21g**) and *tert*-butanesulfinylamide (**21i**) are shown in Scheme 4.3.




**Scheme 4.3**

Sulfinimines adopt a semi-rigid synperiplanar orientation of the sulfoxide oxygen with the imine double bond as shown in Figure 4.6.[72] Calculations on *N*-methylenemethanesulfinamide have shown a considerable stronger preference for this orientation compared to the corresponding vinyl sulfoxide. This has been attributed to a stabilising interaction between the nitrogen lone pair and the anti-bonding orbital of the S-O bond ($n_N$-$\sigma^*_{S\text{-}O}$).[72] Due to repulsion between the oxygen and the imine group, the C-N-S-O torsional angle deviates slightly from 0 °, eliminating chances for C-N-S π delocalization.[73] This orientation shields one side of the sulfinimine efficiently, serving as an explanation for the high stereoselectivities reported in various syntheses.

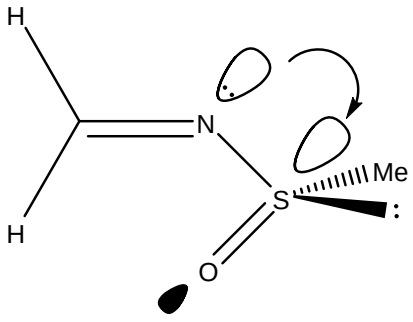



**Figure 4.6** Most stable conformer of *N*-methylenemethanesulfinamide with the stabilising $n_N$-$\sigma^*_{S\text{-}O}$ interaction shown.

Addition of Lewis acids changes little concerning the orientation of the bonds. Calculations and NMR investigations of $BF_3$-sulfinimine complexes by Kawęcki *et al.*,

have shown two equally possible centra for Lewis acid binding, the sulfoxide oxygen and the nitrogen.[74] Davis *et al.*, on the other hand, has proposed a double activated complex with $BF_3$ attached to both centres in order to explain their success with using two equivalents of Lewis acid.[75] For more sterically demanding Lewis acids, like TMSOTf, it is reasonable to believe that *N*-complexation leads to considerable steric strain, making the sulfoxide oxygen a more suitable target for complexation.

Although the most stable conformer of free sulfinimine shields one of the sides efficiently, there are many examples of nucleophilic attack at the "crowded" side. This occurs when the nucleophile is able to form a stabilised 6-membered chelate with the sulfinimine.[76,77] Figure 4.7 shows such a transition state with an organolithium compound acting as a nucleophile. It has been speculated that ester groups on the sulfinimine oppose such chelate formation.[75]

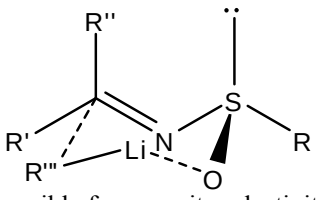
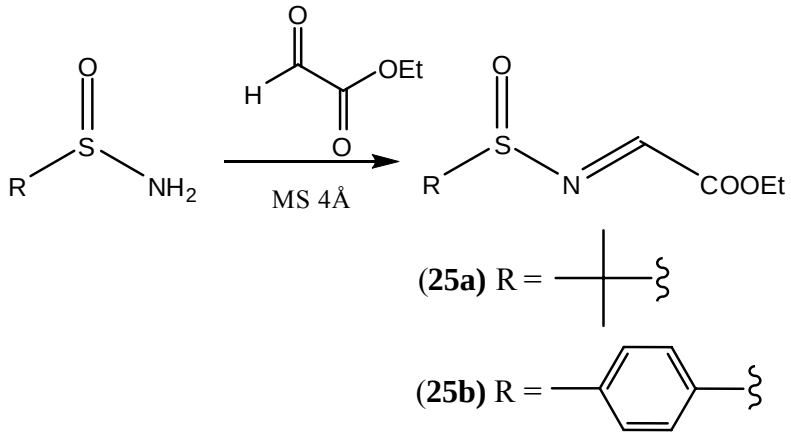



**Figure 4.7** Six-membered chelate responsible for opposite selectivity compared to the free sulfinimine.

### 4.1.3 *N*-sulfinylimino esters

Condensing the sulfinamides with glyoxylate, provides *N*-sulifinylimino esters (Scheme 4.4).[75] Remembering the results of Kawęcki (Scheme 4.1)[65], an ester group in these compounds should reduce the energy of the $LUMO_{dienophile}$, hopefully allowing reactions with a wider selection of dienes. The ester moiety may add further interest in the expected HDA-products, making them non-proteinogenic amino acid derivatives. With the sulfinamide precursors being commercially available in enantiomerically pure forms, ethyl (*N*-*tert*-butanesulfinyl)imino acetate (**25a**) and ethyl (*N*-*p*-toluenesulfinylimino) acetate (**25b**) were found promising for HDA-reactions.



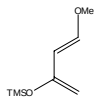
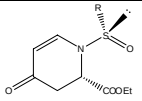
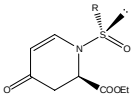
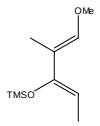
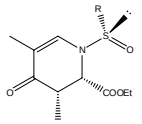
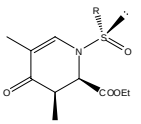
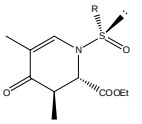
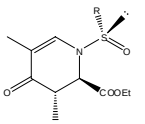
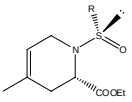
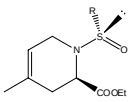
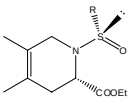
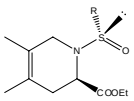
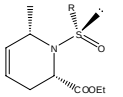
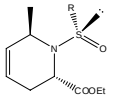
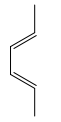
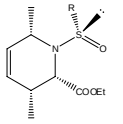
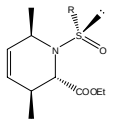
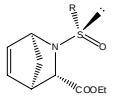
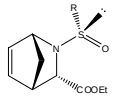
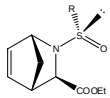
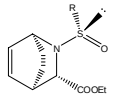
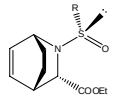

**Scheme 4.4**

## 4.2 Results and discussion

### 4.2.1 Hetero Diels-Alder reactions

The *N*-sulfinylimino esters (*S*)-**25a** and (*S*)-**25b** were prepared according to a literature procedure.[75] The racemic sulfinimines were also prepared to provide reference compounds for chiral GC and HPLC analysis. After initial screening of several Lewis acids in the reactions with the activated Danishevky's diene (**26b**) and non-activated 1,3-cyclohexadiene (**26i**), $BF_3{\cdot}OEt_2$ and TMSOTf were found to be most promising. Using less than 1 equivalent of the LA provided inferior results, indicating that the LA was consumed during the reaction. Table 4.1 summarises the formation of various HDA-products (**29**), using TMSOTf and $BF_3{\cdot}OEt_2$ as Lewis acids.

**Table 4.1** HDA reactions of **25a** and **25b** with dienes (**26b-i**) (1.4-2.0 equiv.) promoted by LA (1.0-1.4 equiv.).

| Entry | Dienophile | Diene | LA | Conditions | Products (with ratios)[a] | | | | | | | Yield [%][b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | |  | | |  | |  | | | | | |
| | | **26b** | | | (2*S*,$S_S$)-**29b** | | (2*R*,$S_S$)-**29b** | | | | | |
| 1 | **25a** (R = *t*-Bu) | | None | 40 °C, 40 h | 2.3 | : | 1 | | | | | 62 |
| 2 | **25a** | | $BF_3{\cdot}OEt_2$ | -78 °C, 20 h | 5.4 | : | 1 | | | | | 76 |
| | |  | | |  | |  | |  | |  | |
| | | **26c** | | | (2*S*,3*S*,$S_S$)-**29c** | | (2*R*,3*R*,$S_S$)-**29c** | | (2*S*,3*R*,$S_S$)-**29c** | | (2*R*,3*S*,$S_S$)-**29c** | |
| 3 | **25a** (R = *t*-Bu) | | None | r.t., ~1 week | - | | - | | - | : | - | 0 |
| 4 | **25a** | | $BF_3{\cdot}OEt_2$ | -78 °C, 17.5 h | 54 | : | 26 | : | 16 | : | 4 | 81 |
| | |  | | |  | |  | | | | | |
| | | **26d** | | | (2*S*,$S_S$)-**29d** | | (2*R*,$S_S$)-**29d** | | | | | |
| 5 | **25a** (R = *t*-Bu) | | $BF_3{\cdot}OEt_2$ | 0 °C, 1 h | >99 | : | <1 | | | | | 19 |
| 6 | **25a** | | TMSOTf | -78 °C, 22 h | >99 | : | <1 | | | | | 25 |
| 7 | **25a** | | TMSOTf | -78 °C, 21.5 h | >99 | : | <1 | | | | | 48[c] |
| 8 | **25b** (R = *p*-Tol) | | TMSOTf | -78 °C, 18 h | 3 | : | 2 | | | | | 18 |
| | |  | | |  | |  | | | | | |
| | | **26e** | | | (2*S*,$S_S$)-**29e** | | (2*R*,$S_S$)-**29e** | | | | | |
| 9 | **25a** (R = *t*-Bu) | | $BF_3{\cdot}OEt_2$ | 0 °C, 2 h | >99 | : | <1 | | | | | 42 |
| 10 | **25a** | | TMSOTf | -78 °C, 18.5 h | >99 | : | <1 | | | | | 64 |
| 11 | **25b** (R = *p*-Tol) | | $BF_3{\cdot}OEt_2$ | 0 °C, 3.5 h | 4 | : | 1 | | | | | 35 |
| 12 | **25b** | | TMSOTf | -78 °C, 5.5 h | 7 | : | 3 | | | | | 48 |
| | |  | | |  | |  | | | | | |
| | | **26f** | | | (2*S*,6*S*,$S_S$)-**29f** | | (2*S*,6*R*,$S_S$)-**29f** | | | | | |
| 13 | **25a** (R = *t*-Bu) | | TMSOTf | -78 °C, 20 h | 2 | : | 1 | | | | | 7 |
| | |  | | |  | |  | | | | | |
| | | **26g** | | | (2*S*,3*R*,6*S*,$S_S$)-**29g** | | (2*S*,3*S*,6*R*,$S_S$)-**29g** | | | | | |
| 14 | **25a** (R = *t*-Bu) | | TMSOTf | -78 °C, 23 h | 97 | : | 3 | | | | | 14 |
| | |  | | |  | |  | |  | | | |
| | | **26h** | | | (1*S*,3*S*,4*R*,$S_S$)-**29h** | | (1*R*,3*S*,4*S*,$S_S$)-**29h** | | (1*R*,3*R*,4*S*,$S_S$)-**29h** | | | |
| 15 | **25a** (R = *t*-Bu) | | $BF_3{\cdot}OEt_2$ | -50 °C, 25 h | 88 | : | 12 | : | 0 | | | 52 |
| 16 | **25a** | | TMSOTf | -78 °C, 18 h | >99 | : | <1 | : | 0 | | | 49 |
| 17 | **25b** (R = *p*-Tol) | | $BF_3{\cdot}OEt_2$ | - 50 °C, 30 min | 89 | : | 7 | : | 4 | | | 48 |
| 18 | **25b** | | TMSOTf | -78 °C, 17 h | 89 | : | 7 | : | 4 | | | 63 |
| | |  | | |  | |  | | | | | |
| | | **26i** | | | (1*S*,3*S*,4*R*,$S_S$)-**29i** | | (1*R*,3*S*,4*S*,$S_S$)-**29i** | | | | | |
| 19 | **25a** (R = *t*-Bu) | | TMSOTf | -78 °C, 16 h | 87 | : | 13 | | | | | 8 |

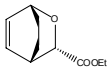
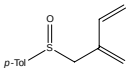
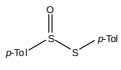
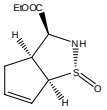
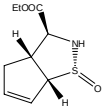
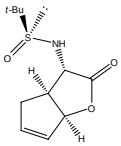
[a]The product ratio was determined by $^1$H NMR spectroscopy of the crude product.
[b]Total yields of isolated isomers.
[c]Twenty equivalents of **3d** and ten equivalents of TMSOTf were added to one equivalent of **25a**.

In the presence of Lewis acids, some of the dienes underwent polymerisation at rates competitive to the preferred HDA-reactions. For this reason, some excess (1.3-2 equiv.) diene was generally used. Especially for isoprene (**26d**), a significant improvement of the yield was observed when using an even larger excess of diene (entry 7). Without exception, all reactions with (**25a**) were more selective that the reactions with (**25b**), owing to the bulkiness of the *tert*-butyl group. A strong preference for *re*-approach was observed, especially for the *tert*-butyl products. In fact, for all non-activated dienes, *tert*-butyl products were apparently formed exclusively with *S*-configuration at the α-carbon (α to the ester group), with the diastereomeric diversity originating from *endo* / *exo* approach. Although the absolute configurations of the minor diastereomers were not determined, observations of only two products (*endo* + *exo*), indicate that the proposed configurations are correct. More evidently, the *tert*-butyl reactions of isoprene (**26d**) and 2,3-dimethyl butadiene (**26e**) provided only one observable diastereomer, since *endo* / *exo* approach leads to identical products in these cases. The expected *exo* – preference was found for reaction with the cyclic dienes (**26h** and **26i**), but the products deriving from acyclic dienes (**26c**, **26f** and **26g**) showed the opposite *endo* preference. A possible explanation could be more steric repulsion between the diene and the sulfinyl group in the *exo* transition state for these reactions. Products from the activated dienes (entries 1-4), are conspicuously less selective, forming diastereomers with both configurations at the α-carbon. This could result from a less selective, possibly stepwise, mechanism, as suggested by Kawęcki.[65] Also complementing Kawęckis results, the initial HDA-products could not be observed, yielding the products after elimination of methanol instead. The excellent selectivities for products **29d**, **29e**, and **29h** are far better than what has been obtained by reported asymmetric catalytic methods. As mentioned, Jørgensen *et al.* used a chiral BINAP-copper(I)-complex to catalyse the HDA-reactions between tosyl-imine (**27**) and dienes. For the reactions with 2,3-dimethylbutadiene (**26e**) and cyclopentadiene (**26h**), selectivities were 65% ee and 83% ee respectively.[67]

### 4.2.2 By-products from the HDA-reactions.

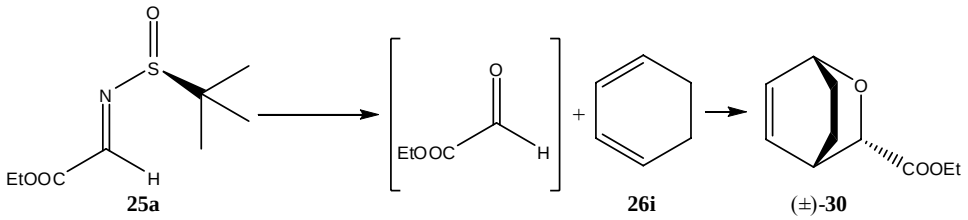
Several by-products were formed and identified during the course of this work. Although not always structurally interesting, attention to these products can provide new insight into the reaction. Table 4.2 shows the most interesting by-products encountered and the reaction conditions under which they were formed. It should be pointed out that attempts to improve the yields of these products were not undertaken.

**Table 4.2** By-products from HDA reactions.

| Entry | Dienophile | Diene | LA | Conditions | By-products (yields, %)[a] | | | HDA-products (combined yields, %)[b] |
|---|---|---|---|---|---|---|---|---|
| | |  | | |  (racemic) | | | |
| | | **26i** | | | **30** | | | |
| 1 | **25a** | | $Zn(OTf)_2$ | r.t., 4.5 d | 25 | | | 0 |
| | |  | | |  |  |  | |
| | | **26d** | | | **31** | **32** | **33** | |
| 2 | **25b** | | TMSOTf | -78 °C, 20 h | 12 (40% ee) | 6 | 8 | 18 |
| 3 | **25b** | | TMSOTf | 0 °C, 1 h | 27 | 28 | 0 | 10 |
| | |  | | |  |  |  | |
| | | **26h** | | | (3*S*,3a*S*,6a*S*,$R_S$)-**34** | (3*S*,3a*R*,6a*R*,$R_S$)-**34** | **35** | |
| 4 | **25a** | | TMSOTf | -78 °C, 15.5 h | 17 | 0 | 11 | 44 |
| 5 | **25a** | | $BF_3OEt_2$ | -50 °C, 25 h | 13 | 0 | 3 | 52 |
| 6 | **25a** | | $BF_3OEt_2$ | r.t., 17.5 h | 38[c] | 4[c] | 0 | 0 |

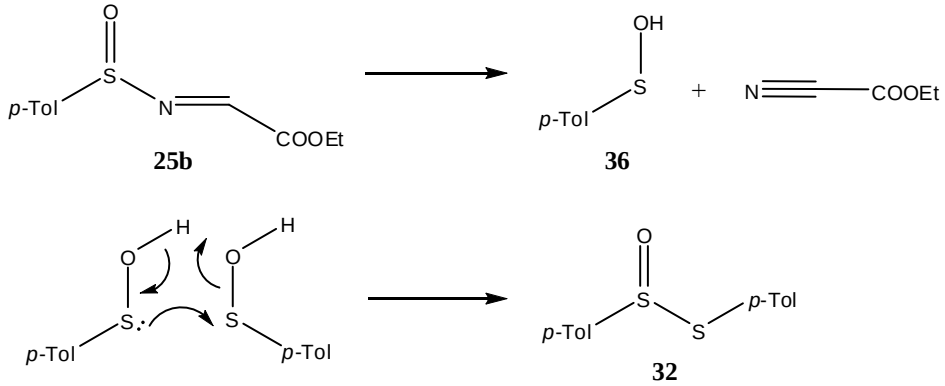
[a] Isolated yields.
[b] Combined yields of HDA-products.
[c] Isolated as mixture of isomers.

Compound **30**[78] (entry 1) was frequently encountered during the screening of Lewis acids, early in this project. The sulfinimine is presumably transformed back to glyoxylate under these conditions, the oxygen somehow deriving from the sulfinyl group (Scheme 4.5). Consequently, racemic **30** was formed, even when using enantiomerically pure **25a**. In agreement with the *endo*-rule[79] (and in contrary to the formation of **29i**), only the *endo*-isomer was formed.



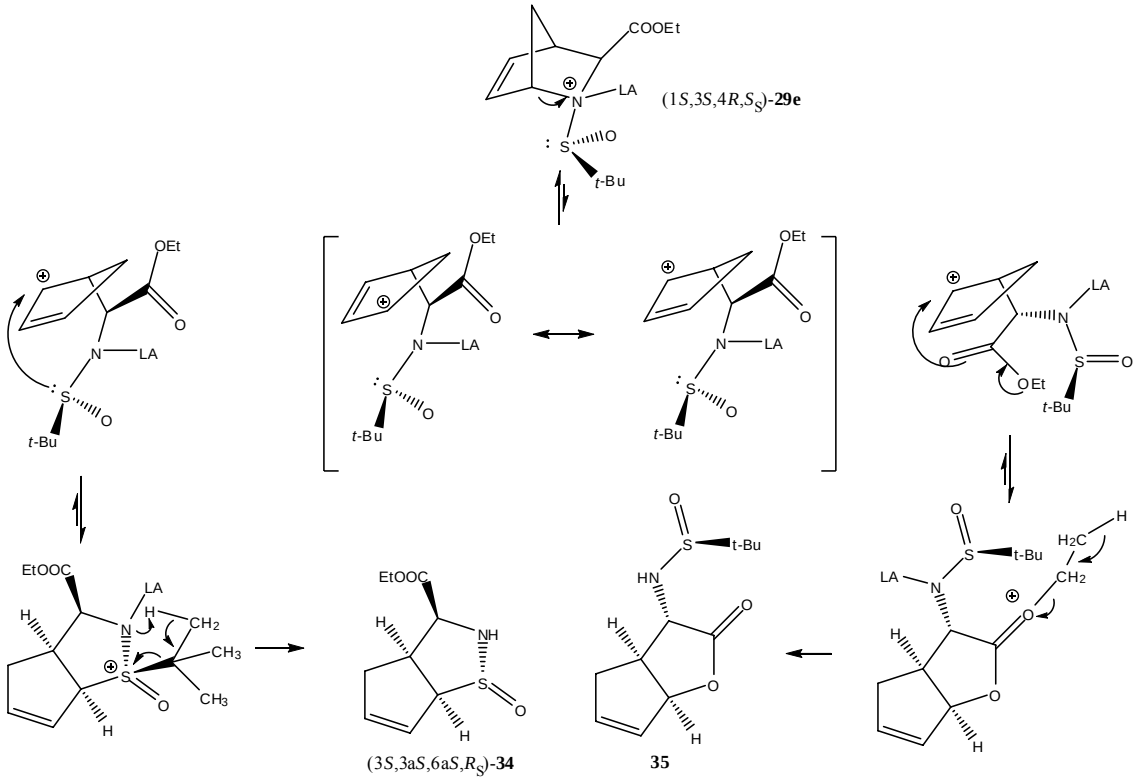

**Scheme 4.5**

Inspection of the obtained by-products also revealed differences between the reactivity of the sulfinimines. Formation of products **31**, **32** and **33** (entries 2 and 3) must involve breakage of the sulfur-nitrogen bond of **25b** at some stage. It is obvious that a potential *p*-tolyl sulfoxide cation – or radical, would be more stabilised by resonance than the corresponding *tert*-butyl analogue. This would make it a more probable intermediate, and would explain why similar reactions with **25a** could not be observed. Ene-reactions with *p*-tolyl sulfoxide cation, formed *in situ* from the sulfinamide (**21g**), have been reported[80], which can explain the formation of the ene-product **31**. It was observed in small yields (2-12%) when the reaction took place at -78 $^{o}$C, but at higher temperature (0 $^{o}$C) the yield improved significantly (27%) (entry 3). Chiral HPLC analysis showed that some degree of chiral induction took place in these reactions (40% ee), indicating that the sulfur-nitrogen bond could not have been completely broken during addition to the diene. Nucleophilic attack by an ethoxide rather than diene would provide **33**. This ethoxide would most likely come from the ethyl ester group of the sulfinimine, but the details around the reaction remain unclear. The thiosulfinate (**32**) was observed in various amounts in all HDA reactions with **25b**. In most reactions, the yields were lower than 10%, but at higher temperatures (0 $^{o}$C), 28% was isolated (entry 3). The yields were calculated as the portion of **25b** consumed to form **32**, since two equivalents of **25b** are used in the formation of **32**. The thiosulfinates may be formed by dehydration of the sulfenic acid (**36**) as shown in Scheme 4.6.[81] The sulfenic acid may derive from decomposition of **25b**, which has been reported for other sulfinimines (Scheme 4.6).[82,83]




**Scheme 4.6**

The HDA-products from cyclopentadiene-reactions with **25a** were not particularly stable, and several by-products were identified. Shortening the reaction time did not provide higher yields of HDA-products. A rationale for the formation of (3*S*,3a*S*,6a*S*,$R_S$)-**34** and **35** from the *exo* HDA-product [(1*S*,3*S*,4*R*,$S_S$)-**29h**] is shown in Scheme 4.7.




**Scheme 4.7**

Initiated by a Lewis acid, the C-N bond breaks to form an allylic cation, which is attacked by either the ester or sulfinyl group. Rearrangement of a similar compound has

been reported by Kobayashi *et al.*, although the ester was first hydrolysed in their paper.[84] Since our reactions were carried out in anhydrous environment, an alternative removal of the ethyl group is proposed. The shown mechanism for the formation of (3*S*,3a*S*,6a*S*,$R_S$)-**34** includes an attack by the sulfinyl-sulfur lone pair, which provides a satisfactory explanation to the inversion of the sulfinyl stereocentre. Similar nucleophilic attack by the sulfur in *tert*-butanesulfinyl compounds has been suggested by Davis, with the expulsion of isobutylene as an important driving force.[85] A similar rearrangement of the *endo* product (1*R*,3*S*,4*S*,$S_S$)-**29e** would give (3*S*,3a*R*,6a*R*,$R_S$)-**34**.

### 4.2.3 Determining relative and absolute configuration

None of the prepared HDA-products were previously reported, and most of them had to be transformed into reported compounds in order to determine absolute configurations. Compounds **29b**, **29c** and **34** were crystalline, allowing us to obtain X-ray crystallographic data of the main isomers after recrystallisation (Figures 4.8-4.10).

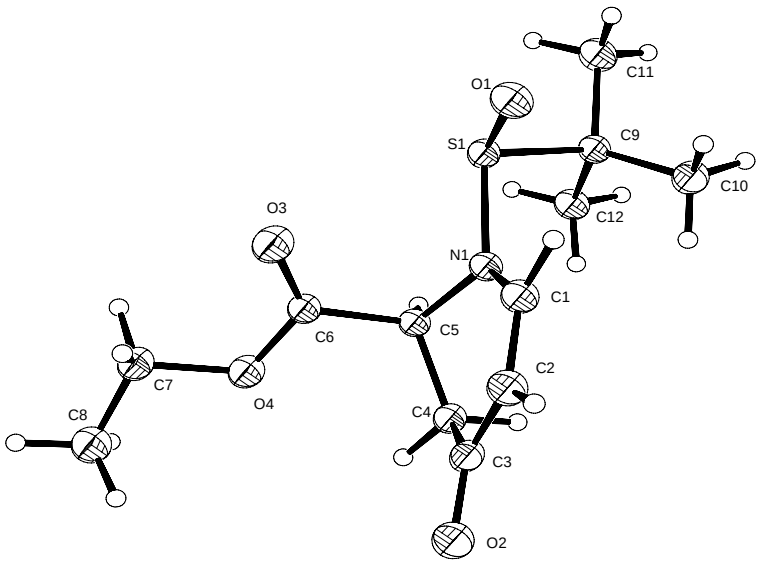



**Figure 4.8** X-ray crystal structure of (2*S*,$S_S$)-**29b**.

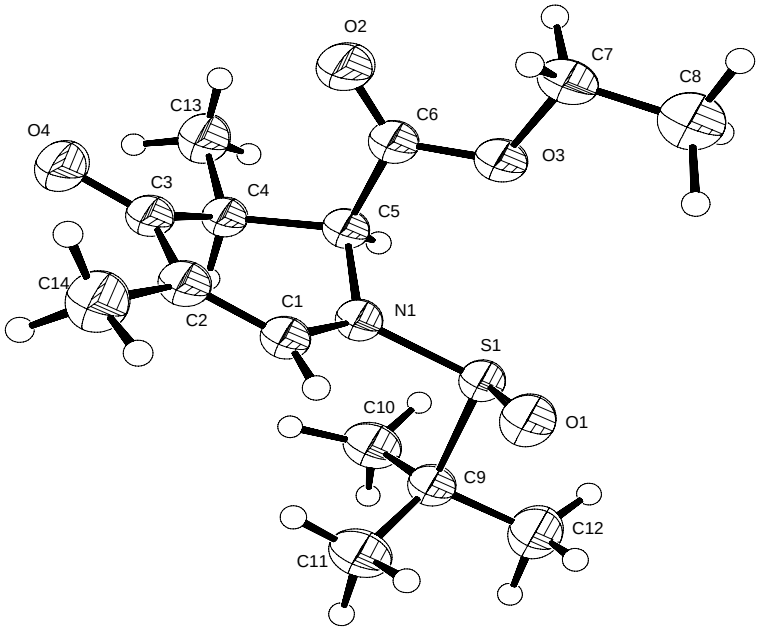



**Figure 4.9** X-ray crystal structure of (2S,3*S*,$S_S$)-**29c**.

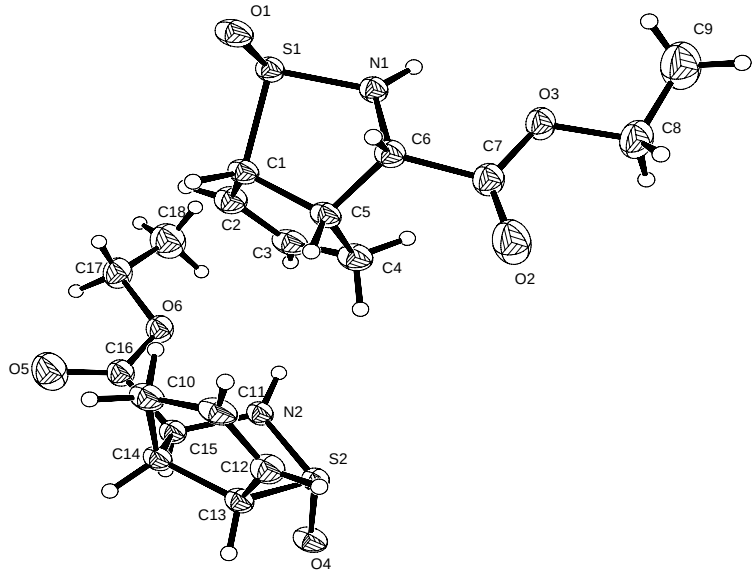



**Figure 4.10** X-ray crystal structures of (3*S*,3a*S*,6a*S*,$R_S$)-**34**.

The relative configuration of (2*R*,3*R*,$S_S$)-**29c** was determined by $^1$H NMR, showing similar vicinal $^1$H-$^1$H coupling (6.5 Hz) between H-2 and H-3 as for (2*S*,3*S*,$S_S$)-**29c** (6.0 Hz) (Figure 4.11). The corresponding coupling constants for (2*S*,3*R*,$S_S$)-**29c** and

(2*R*,3*S*,$S_S$)-**29c** were found to be 1.7 Hz and 2.3 Hz, respectively. The absolute configurations of the latter **29c**-isomers could not be determined, and the proposed structures in Table 4.1 are based on the general preference for *S*-configuration at the α-carbon (α to the ester group) in these reactions. The relative configurations of **29f**, **29g**, **29h**, **29i** and **35**, disregarding the sulfinyl group, were found from NOE experiments. Structure-determining NOEs are summarised in Figure 4.11.

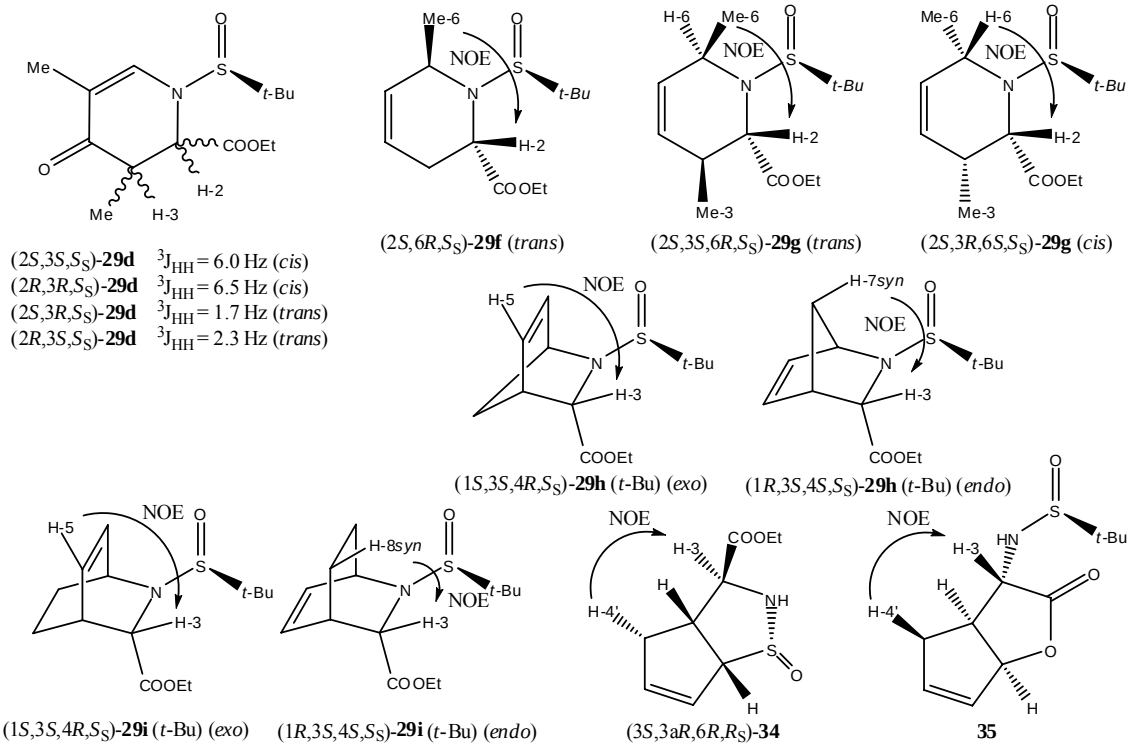
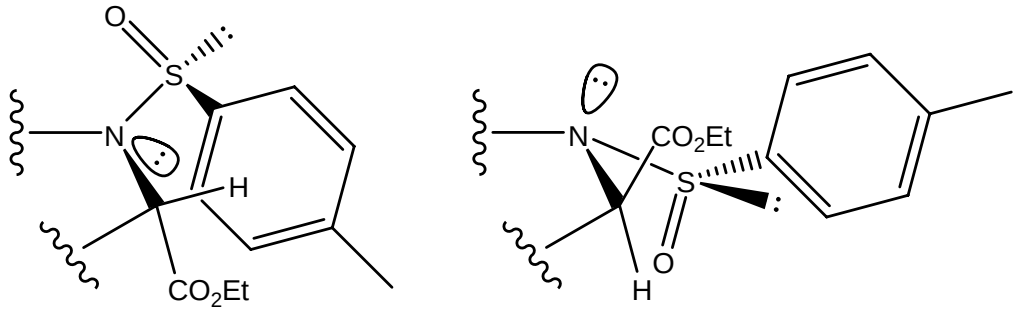



**Figure 4.11** Determination of relative configuration by NMR experiments.

The configuration of the *p*-toluene isomers of **29h** were deduced by a closer investigation of the $^1$H NMR spectra. These HDA-products are formally sulfinamides, with the nitrogen atom taking part in a cyclic structure. Focusing on the substituents from the parent sulfinimine, the sulfinyl group on nitrogen and the ester group, some unexpected $^1$H NMR chemical shifts can be rationalised. To reduce van-der-Waals strain, the bulky sulfinyl group would preferably adopt an orientation *trans* to the ethyl ester group (Figure 4.12). Considering the orientation of the N-S bond, there is a general preference for a staggered orientation of sulfinamides, with the nitrogen lone pair *anti* to the sulfinyl oxygen.[86] This can be attributed to a stabilising interaction between the

nitrogen lone pair and the anti bonding σ-orbital of the S-O bond. In our work, compounds with (*S*)-configuration were prepared without any sign of racemisation. This leads to two diastereomeric arrangements (ignoring the remaining part of the molecule) due to (*R*) or (*S*)-configuration of the carbon α to the ester group (Figure 4.12).




($S,S_S$) ($R,S_S$)

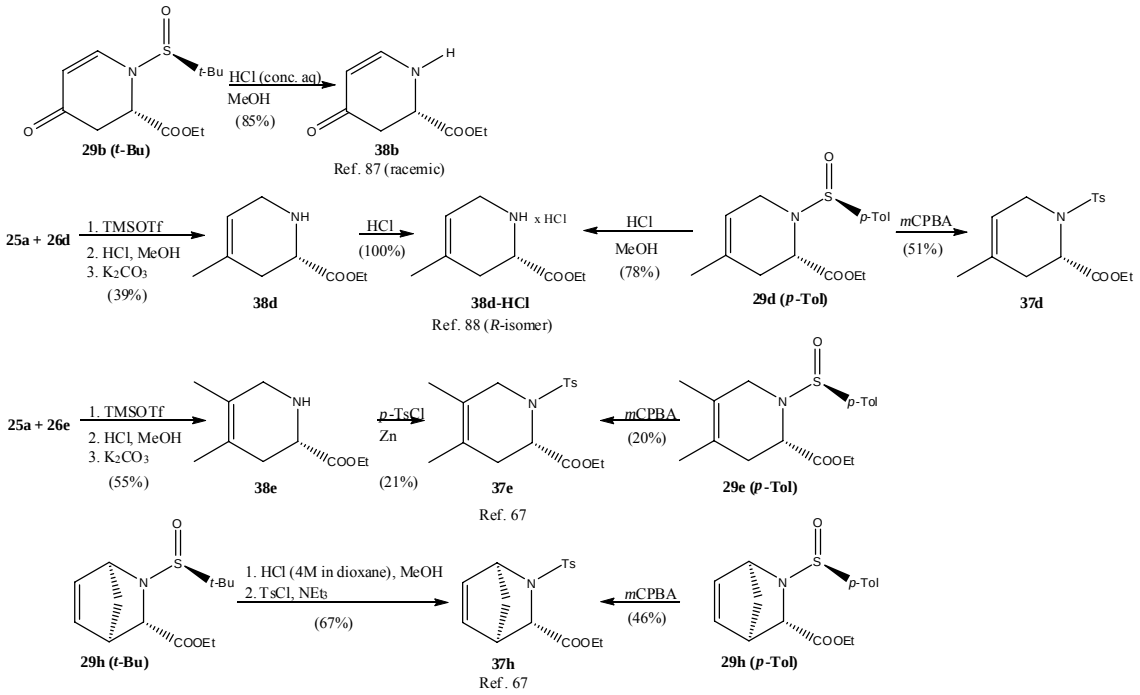
**Figure 4.12** Preferred conformations of α-C epimers of **29** (*p*-toluene).

The preferred conformation of ($S,S_S$) puts the *p*-tolyl group in the vicinity of the ester group, leading to significant shielding of the ethyl ($OCH_2H_3$) $^1$H NMR signals. The ($R,S_S$)-diastereomer, however, does not show this effect. Table 4.3 shows the ethyl proton shifts of the *p*-tolyl HDA-products prepared by us. Chemical shifts around 3.6-3.7 ppm for (1*S*,3*S*,4*R*,$S_S$)-**29h** (*p*-Tol) and (1*R*,3*S*,4*S*,$S_S$)-**29h** (*p*-Tol) suggests *S*-configuration at C-3 (α-C) and 4.29 ppm for (1*R*,3*R*,4*S*,$S_S$)-**29h** (*p*-Tol) suggests *R*-configuration at C-3.

**Table 4.3** Configuration at α-C versus $OCH_2H_3$ shift.

| *p*-Tol HDA-products | (*S*) / ppm | (*R*) / ppm |
|---|---|---|
| (2*S*,$S_S$)-**29d** + (2*R*,$S_S$)-**29d** | 4.15 | 4.22 |
| (2*S*,$S_S$)-**29e** + (2*R*,$S_S$)-**29e** | 4.13 | 4.22 |
| (1*S*,3*S*,4*R*,$S_S$)-**29h** | 3.67, 3.62 | |
| (1*R*,3*S*,4*S*,$S_S$)-**29h** | 3.7-3.6 | |
| (1*R*,3*R*,4*S*,$S_S$)-**29h** | | 4.29 |

Chemical derivatisation was also implemented in order to determine both structure and configuration of the compounds. Removal of the sulfinyl group allowed comparison of NMR data for structures **38b**[87] and **38d-HCl**[88]. Optical rotation of the latter compound has been reported (*R*-isomer), allowing determination of the absolute configuration of **38d-HCl**.[89] Transformation of **29e** and **29h** into the reported tosyl analogues **37e** and **37h** confirmed both structures and configurations.[67] This was performed by either oxidation using *m*-CPBA (*p*-Tol analogues) or by sequential hydrolysis and tosylation (*t*-Bu analogues). Due to poor yields, no derivatisation of compounds **29f**, **29g** and **29i** were undertaken in order to determine the configurations. However, the observation of only two diastereomers of **29g** with the relative configurations found from NOE, strongly indicates that the proposed *S*-configuration at the α-carbon is correct. Hydrolysis of **29d** and **29e** could also be achieved directly from the crude product mixture. By controlling the pH of the aqueous phase, **38d** and **38e** were purified with extraction alone, avoiding the need for flash chromatography. Scheme 4.8 summarises all chemical derivatisations used for the HDA-products in order to determine absolute configurations. Only the major diastereomers are shown.



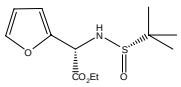
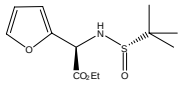
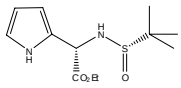
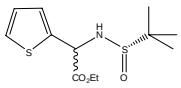
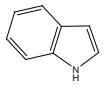
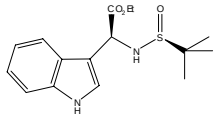
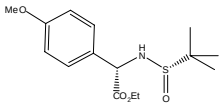
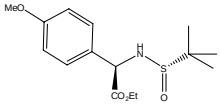
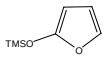
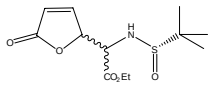
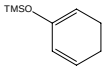
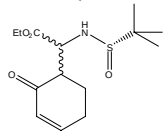
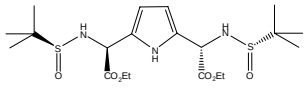

**Scheme 4.8**

Fearing that the compounds could racemise in the presence of base, a base-free tosylation procedure was used in the preparation of **37e**.[90] However, the procedure provided low yields, and for the preparation of **37h**, a standard method was used, showing no indication of racemisation.

### 4.2.4 Additions to *N*-sulfinylimino ester

Some potential dienes showed a different reaction pattern, providing addition-products instead of the expected HDA-products. One of these was furan (**26j**), which encouraged us to try other heterocycles in these reactions. *N*-Sulfinylimino esters have been described as chiral glycine cation equivalents for the asymmetric synthesis of α-amino acids.[75] Although a number of papers describe addition to these imines, ranging from addition of Grignard and dialkylzinc reagents[75,91] to more elaborate use of transition metal catalysts,[92-95] most of the addition products we encountered had not previously been reported. The results are shown in Table 4.4. All ratios in the table were estimated from crude $^1$H NMR spectra, and for entries 4, 10 and 11, the absolute configurations were not determined. The diastereomeric mixtures formed in entries 1, 4, 9, 10 and 11, were only partly separable by flash chromatography.

**Table 4.4** Additions of compounds (**26j-q**) (1-2 equiv.) to **25a** promoted by TMSOTf (1 equiv.).

| Entry | Substrate | Conditions | Products | Yield [%] |
|---|---|---|---|---|
| |  | |   | |
| | **26j** | | ($S$,$S_S$)-**39j** ($R$,$S_S$)-**39j** | |
| 1 | | -78 °C, 21 h | 5 : 1 | 56[a] |
| |  | |  | |
| | **26k** | | ($S$,$S_S$)-**39k** | |
| 2 | | -78 °C, 17.5 h | | 92 |
| |  | |  | |
| | **26l** | | **39l** | |
| 3 | | -78 °C, 17.5 h | no reaction | 0 |
| 4 | | -20 °C, 20 h | ratio: 1 : 1.5 | 40[a] |
| |  | |  | |
| | **26m** | | ($S$,$S_S$)-**39m** | |
| 5 | | -78 °C, 17 h | | 82 |
| |  | | | |
| | **26n** | | | |
| 6 | | -78 °C, 20 h | no reaction | 0 |
| 7 | | r.t., 20 h | no reaction | 0 |
| |  | |   | |
| | **26o** | | ($S$,$S_S$)-**39o** ($R$,$S_S$)-**39o** | |
| 8 | | -78 °C, 17 h | no reaction | 0 |
| 9 | | -20 °C, 20 h | ratio: 1 : 2.6 | 65[a] |
| |  | |  | |
| | **26p** | | **39p** | |
| 10 | | -78 °C, 18 h | 2 isomers; ratio: 1 : 1.3 | 70[a] |
| |  | |  | |
| | **26q** | | **39q** | |
| 11[b] | | -78 °C, 2 d | 3 isomers; ratio: 1 : 1.1 : 4 | 32[a] |
| |  | | | |
| | **26k** | | **41** | |
| 12[c] | | -78 °C, 20 h | | 77 |

[a]Total yield of isolated isomers.
[b]$BF_3{\cdot}OEt_2$ (1 equiv.) was used as LA instead of TMSOTf.
[c]Two equivalents of **25a** and TMSOTf were added to one equivalent of **26k**.

The furan-products (**39j**) (entry 1) were transformed to the reported *N*-acetyl derivatives (**40**), and optical rotations compared to reveal the absolute configurations (Scheme 4.9).[96] The excellent yield and selectivity of the pyrrole reaction (entry 2), providing only one isomer (**39k**) in 92% yield, encouraged us to try a double addition as shown entry 10. Not only did the reaction proceed with high yield and selectivity (one isomer of **41**, 77%), but the compound formed crystals eligible for X-ray analysis, determining the absolute configuration of both **41** and (indirectly) **39k** (Figure 4.13).

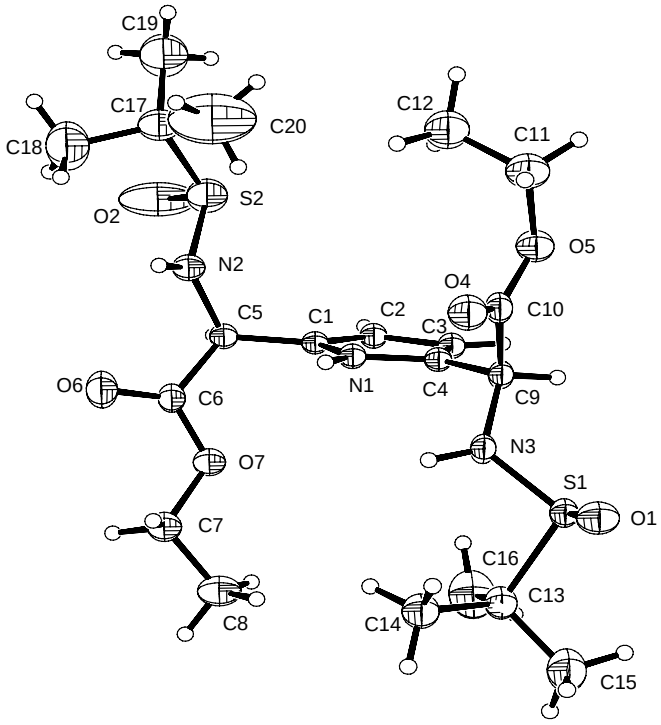
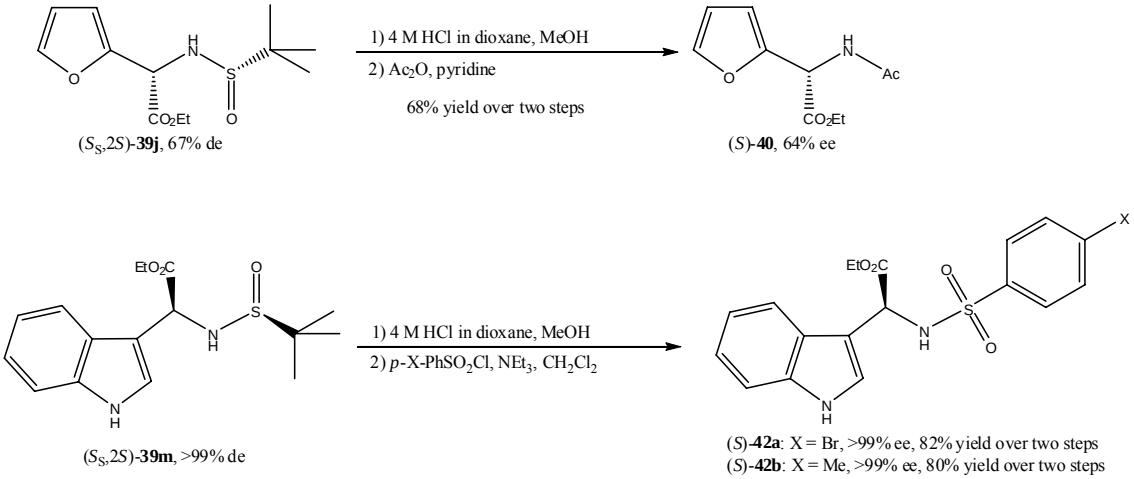



**Figure 4.13** X-ray crystal structure of **41**.

Thiophene (**26l**) is less reactive than furan (**26j**) and pyrrole (**26k**), and demanded higher temperature to react (entries 3 and 4), providing moderate yields of **39l** with poor selectivity (40%, dr 1 : 1.5). The indole product (**39m**, entry 5) was isolated diastereomerically pure after flash chromatography in high yield (82%). Transformation to **42a** (see Scheme 4.9) provided a crystalline compound which allowed determination of the absolute configuration by X-ray analysis (Figure 4.14). The Me-analogue (**42b**) has been previously reported with optical rotation, but without the known absolute

configuration.[97] Therefore, **42b** was formed from **39m**, giving similar optical rotation as reported, and thus identifying them both as the *S*-isomer (Scheme 4.9). Pyridine (**26n**) did not prove reactive in these reactions, even at room temperature (entries 6 and 7), but anisole (**26o**) provided a mixture of *para*-products (**39o**) at elevated temperature, but with low selectivity (dr 1 : 2.6) (entry 9). Since the ($R_S$,2*R*)-isomer of **39o** has been previously reported[92], comparison of NMR data identified the minor isomer as ($S_S$, 2*S*)-**39o**. Surprisingly, this makes ($S_S$, 2*R*)-**39o** the major isomer, in contrary to the expected *S*-selectivity at the α-carbon.




**Scheme 4.9**

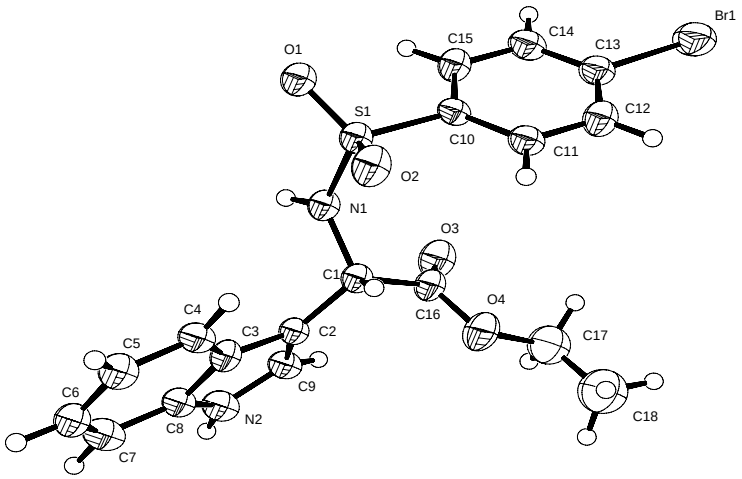



**Figure 4.14** X-ray crystal structure of (*S*)-**42a**.

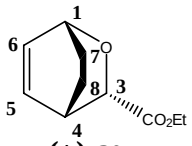
## 4.3 Summary

*N*-sulfinyl imino esters **25a** and **25b** have shown reactivity towards a number of dienes in the hetero Diels-Alder reaction, forming several new interesting compounds. Yields ranged from poor to good, with selectivities higher than 99% de in some cases. Especially the reactions between **25a** and the terminal dienes **26f** and **26g** proved successful, forming practically only one diastereomer of **39f** and **39g**. Some reactions resulted in addition products instead of the intended HDA-products. Consequently, a series of new heteroaromatic glycine derivatives were formed with moderate to excellent yields and up to 99% de. The formation of the pyrrole and indole products **39k**, **39m** and **41** was especially successful, where only one diastereomer of each compound could be found. Through X-ray analysis and chemical derivatisations of both HDA- and addition products, the stereochemical preference was found to be as expected from the proposed model.

## 4.4 Experimental

The full experimental description for Chapter 4 is reported in Papers II and III. This section only includes experimental procedures and data for compounds **30**, **39p** and **39q**, since these were not reported in the mentioned papers.

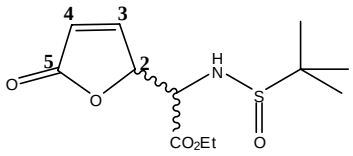
**Preparation of ethyl 2-oxabicyclo[2.2.2]oct-5-ene-3-*endo*-carboxylate (30).** $Zn(OTf)_2$ (90 mg, 0.25 mmol) was added dry $CH_2Cl_2$ (2 ml) and a solution of sulfinimine **25a** in $CH_2Cl_2$ (0.20 ml, 1.26 M, 0.25 mmol). Cyclohexadiene (2 equiv.) was added and the mixture was stirred for 4.5 days. The reaction was quenched by addition of phosphate buffer (pH 7, 3 ml) and the mixture was extracted with $CH_2Cl_2$ (3 x 3 ml). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (FC) (EtOAc/hexane, 1:5), providing a colourless oil (11.6 mg, 25%).




**(±)-30**

Data for **30**: GC [CP Chirasil Dex CB, 110 °C (0 min) - 2 °C $min^{-1}$ - 180 °C (2 min), $t_R$ 4.9 and 5.2 min; $^1$H NMR (400 MHz) δ 6.53 (1H, ddd, *J* = 8.2, 5.4, 1.5 Hz, H-6), 6.27 (1H, ddd, *J* = 8.0, 6.6, 1.3 Hz, H-5), 4.58 (1H, app. ddt, *J* = 5.4, 3.8, 1.5 Hz, H-1), 4.30 (1H, d, *J* = 1.8 Hz, H-3), 4.15 (2H, app. q, *J* = 7.1 Hz, $OCH_2$), 3.10 (1H, m, H-4), 2.07 (1H, m, H-7*syn*), 1.74 (1H, m, H-8*syn*), 1.40 (1H, m, H-8*anti*), 1.33 (1H, m, H-7*anti*), 1.24 (3H, t, *J* = 7.1 Hz, $OCH_2C\mathbf{H}_3$); $^{13}$C NMR (100 MHz) δ 172.3 (**C**OOEt), 134.7 (C-6), 130.5 (C-5), 74.2 (C-3), 66.5 (C-1), 60.8 ($OCH_2$), 33.2 (C-4), 25.7 (C-7), 20.8 (C-8), 14.2 ($OCH_2\mathbf{C}H_3$); IR (neat) ν 3055 (w), 2979 (m), 2901 (w), 2869 (w), 1756 (s), 1723 (s), 1373 (m), 1266 (m), 1191 (s), 1163 (m), 1088 (m), 1052 (m), 1016 (m), 882 (w), 702 (m); EIMS *m*/*z* (% relative intensity) 183 ($M^+$+1, 4), 182 ($M^+$, 34), 110 (31), 109 (96), 91 (49), 82 (24), 81 (97), 80 (91), 79 (100), 77 (46), 53 (43), 41 (29), 39 (23). NMR data for **30** was compatible with reported data.[78]

**Preparation of ethyl 2-(*tert*-butylsulfinamido)-2-(5-oxo-2,5-dihydrofuran-2-yl)acetate (39p).** A solution of sulfinimine **25a** in $CH_2Cl_2$ (0.22 ml, 1.15 M, 0.25 mmol) was added more dry $CH_2Cl_2$ (2 ml), and cooled to -78 $^oC$. Compound **26p** (2 equiv.) and TMSOTf (1.6 equiv.) was added and the solution stirred at -78 $^oC$ for 18 h. The reaction was quenched by addition of phosphate buffer (pH 7, 3 ml) and the mixture was extracted with $CH_2Cl_2$ (3 ml). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (FC) (EtOAc/hexane, 1:1), providing an inseparable diastereomeric mixture of **39p** (**D1** and **D2**, ratio: 1 : 1.3) as a colourless oil (50.8 mg, 70%).

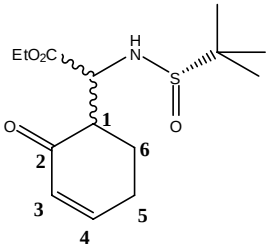



**39p**

Data for mixture: TLC $R_f$ = 0.2 (EtOAc); ESIMS *m*/*z* (% relative intensity) 313 (14), 312 ($M^+$+Na, 100), 291 (11), 290 ($M^+$+1), 216 (29); HRMS (ESI) calcd for: $C_{12}H_{19}NNaO_5S$ 312.0876 ($M^+$+Na), found 312.0871; Data for **39p-D1**: $^1$H NMR (400 MHz) δ 7.32 (1H, dd, *J* = 5.8, 1.5 Hz, H-3), 6.25 (1H, dd, *J* = 5.8, 2.0 Hz, H-4), 5.34 (1H, app. dt, *J* = 4.3, 1.6 Hz, H-2), 4.45 (1H, dd, *J* = 7.5, 4.3 Hz, NCH), 4.31 (2H, app. q, *J* = 7.1 Hz, $OCH_2$), 4.04 (1H, d, *J* = 7.5 Hz, NH), 1.33 (3H, t, *J* = 7.2 Hz), 1.21 (9H, s, *t*-Bu); $^{13}$C NMR (100 MHz) δ 171.6 (C-5), 169.0 (**C**OOEt), 151.1 (C-3), 124.5 (C-4), 82.3 (C-2), 63.0 ($OCH_2$), 58.7 (NCH), 56.7 (**C**$(CH_3)_3$), 22.5 (C(**C**$H_3)_3$), 14.1 ($OCH_2$**C**$H_3$). Data for **39p-D2**: $^1$H NMR (400 MHz, selected signals) δ 7.45 (1H, dd, *J* = 5.7, 1.6 Hz, H-3), 6.21 (1H, dd, *J* = 5.7, 2.0 Hz, H-4), 5.51 (1H, m, H-2), 4.36 (1H, m, NCH), 4.31 (2H, app. q, *J* = 7.1 Hz, $OCH_2$), 1.34 (3H, t, *J* = 7.1 Hz), 1.21 (9H, s, *t*-Bu); $^{13}$C NMR (100 MHz) δ 172.0 (C-5), 168.7 (**C**OOEt), 152.5 (C-3), 124.0 (C-4), 82.6 (C-2), 63.2 ($OCH_2$), 57.2 (**C**$(CH_3)_3$), 56.7 (NCH), 22.7 (C(**C**$H_3)_3$), 14.1 ($OCH_2$**C**$H_3$).

**Preparation of ethyl 2-(*tert*-butylsulfinamido)-2-(2-oxocyclohex-3-enyl)acetate (39q).** A solution of sulfinimine (**25a**) in $CH_2Cl_2$ (0.20 ml, 1.26 M, 0.25 mmol) was added more dry $CH_2Cl_2$ (2 ml) and cooled down to – 78 $^oC$. Compound (**26q**) (1.2 equiv.) and $BF_3{\cdot}OEt_2$ (1 equiv.) was added and the solution stirred at -78 $^oC$ for 2 days.

The reaction was quenched by addition of phosphate buffer (pH 7, 3 ml) and the mixture was extracted with $CH_2Cl_2$ (3 x 3 ml). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (FC) (EtOAc/hexane, 1:1), providing a partly separable diastereomeric mixture of **39q** (**D1**, **D2**, **D3**, ratio: 4 : 1 : 1.1) as a colourless viscous oil (24 mg, 32%).




**39q**

Data for mixture of **39q-D1** and **39q-D2**: IR (neat) ν 3449 (w), 3284 (w), 2978 (w), 2958 (w), 2927 (w), 2870 (w), 1736 (s), 1676 (s), 1459 (w), 1389 (w), 1366 (w), 1258 (m), 1210 (m), 1076 (s); ESIMS *m*/*z* (% relative intensity) 324 ($M^+$+Na, 29), 302 ($M^+$+1, 29); HRMS (ESI) calcd for: $C_{14}H_{24}NO_3S$ 302.1421 ($M^+$+1), found 302.1421; $C_{14}H_{23}NNaO_3S$ 324.1240 ($M^+$+Na), found 324.1243 .Data for D1: TLC $R_f$ = 0.3 (EtOAc); $^1$H NMR (400 MHz) δ 6.98 (1H, app. dt, *J* = 10.1, 4.1 Hz, H-4), 6.00 (1H, app. dt, *J* = 10.1, 1.9 Hz, H-3), 4.49 (1H, d, *J* = 6.6 Hz, NH), 4.25 (2H, app. q, *J* = 7.1 Hz, $OCH_2$), 4.03 (1H, dd, *J* = 6.6, 3.0 Hz, NCH), 3.15 (1H, ddd, *J* = 11.3, 7.0, 3.0 Hz, H-1), 2.49 (2H, m, H-5), 2.06 (2H, m, H-6), 1.28 (3H, t, *J* = 7.1 Hz, $OCH_2C\mathbf{H}_3$), 1.24 (9H, s, *t*-Bu); $^{13}$C NMR (100 MHz) δ 197.8 (C-2), 171.5 (**C**OOEt), 150.5 (C-4), 129.7 (C-3), 62.1 ($OCH_2$), 58.1 (NCH), 56.5 ($\mathbf{C}(CH_3)_3$), 50.9 (C-1), 26.2 (C-6), 25.8 (C-5), 22.8 ($C(\mathbf{C}H_3)_3$), 14.0 ($OCH_2\mathbf{C}H_3$). Data for D2: TLC $R_f$ = 0.25 (EtOAc); $^1$H NMR (400 MHz) δ 6.98 (1H, H-4), 6.05 (1H, ddd, *J* = 10.0, 2.5, 1.3 Hz, H-3), 4.71 (1H, dd, *J* = 8.0, 3.3 Hz, NCH), 4.25 (2H, app. q, *J* = 7.1 Hz, $OCH_2$), 4.11 (1H, d, *J* = 8.3 Hz, NH), 2.81 (1H, ddd, *J* = 13.3, 4.9, 3.0 Hz, H-1), 2.44 (2H, m, H-5), 1.92 (2H, m, H-6), 1.28 (3H, t, *J* = 7.1 Hz, $OCH_2C\mathbf{H}_3$), 1.19 (9H, s, *t*-Bu). $^{13}$C NMR (100 MHz) δ 196.5 (C-2), 172.6 (**C**OOEt), 150.2 (C-4), 129.8 (C-3), 62.1 ($OCH_2$), 57.0 (NCH), 56.3 ($\mathbf{C}(CH_3)_3$), 50.3 (C-1), 25.4 (C-5), 23.3 (C-6), 22.6 ($C(\mathbf{C}H_3)_3$), 14.1 ($OCH_2\mathbf{C}H_3$). Data for **39q-D3**: TLC $R_f$ = 0.2 (EtOAc); $^1$H NMR (400 MHz) δ 6.99 (1H, m, H-4), 6.00 (1H, app. dt, *J* = 10.0, 1.9 Hz, H-3), 4.22 (1H, NH), 4.22 (1H, dq, *J* = 10.8, 7.1 Hz, OC**H**H'), 4.21 (1H, dq, *J* =

10.8, 7.1 Hz, OCH**H'**), 3.98 (1H, dd, *J* = 9.6, 3.1 Hz, NCH), 3.29 (1H, ddd, *J* = 14.0, 4.7, 3.1 Hz, H-1), 2.52 (2H, m, H-5), 2.37 (1H, m, H-6), 2.09 (1H, m, H-6'), 1.28 (3H, t, *J* = 7.2 Hz, $OCH_2C\mathbf{H}_3$), 1.26 (9H, s, *t*-Bu). $^{13}$C NMR (100 MHz) δ 199.0 (C-2), 171.6 (**C**OOEt), 151.1 (C-4), 129.6 (C-3), 61.7 ($OCH_2$), 60.1 (NCH), 57.0 ($\mathbf{C}(CH_3)_3$), 50.5 (C-1), 26.1 (C-6), 26.0 (C-5), 22.5 ($C(\mathbf{C}H_3)_3$), 14.1 ($OCH_2\mathbf{C}H_3$).

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# Paper I

Andreassen, T., Haaland, T., Hansen, L. K. and Gautun, O. R.

**Asymmetric aza-Diels-Alder reactions of an *N*-*tert*-butanesulfinyl α-imino ester**

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# Asymmetric aza-Diels–Alder reactions of an *N-tert*-butanesulfinyl α-imino ester

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**Abstract**—Diastereoselective aza-Diels–Alder (aza-DA) reactions of an *N-tert*-butanesulfinyl α-imino ester with different dienes including activated and non-activated dienes in the presence of $BF_3{\cdot}OEt_2$ are described. Diastereoselectivities up to 99% were observed for acyclic unactivated dienes. The absolute configurations of two aza-DA products have been solved by X-ray analysis.
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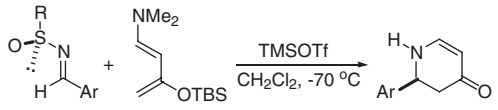
The aza-Diels–Alder (aza-DA) reaction of imino dienophiles is a powerful tool for the rapid construction of highly functionalized six-membered nitrogen heterocycles such as piperidines and tetrahydroquinolines.[1] Usually, this reaction can only be performed with activated dienes like Danishefsky's diene or using imines substituted with an electron withdrawing group. The use of Lewis acids to counteract the low reactivity of imino dienophiles has further increased their potential in organic synthesis. Several asymmetric protocols have appeared, either through the diastereoselective aza-DA reaction applying chiral imines[2] or more recently, a catalytic enantioselective reaction.[3]

Considerable efforts have been devoted to nucleophilic addition reactions of chiral *N*-sulfinyl imines (sulfinimines) in the asymmetric synthesis of amines, β-amino carbonyl compounds (aldehydes, ketones, acids), and aziridines.[4] On the contrary, only one recent report of an aza-DA reaction of *N*-sulfinyl imines reacting as dienophile is known,[5] where optically active *N*-sulfinyl imines, promoted by TMSOTf, reacted with the Rawal diene to give enantiomerically enriched dihydropyridinones in high yields with ees up to 90% (see Scheme 1). The sulfinyl auxiliary was removed during workup of the reaction mixture. The method was however, limited to 2-aryl substituted *N*-sulfinyl imines and to the Rawal diene.




**Scheme 1.**

Attempts with the activated Danishefsky diene failed. These results inspired us to investigate the aza-DA chemistry of the doubly activated *N-tert*-butanesulfinyl α-imino ester **1**[6] (see Table 1) in order to see if we could expand the scope and limitations of the reaction.

Herein, we present our preliminary findings applying **1** with activated and non-activated dienes in the presence of Lewis acid catalysts.

Initially, a series of Lewis acids including $Cu(OTf)_2$, $Zn(OTf)_2$, $ZnBr_2$, $Mg(ClO_4)_2$, $Yb(OTf)_3$, $SnCl_4$, $AlCl_3$, TMSOTf, and $BF_3{\cdot}Et_2O$ were screened as promoters (1 equiv) for the stereoselective aza-DA reaction of **1** (1 equiv) with Danishefsky's diene **2a** (2 equiv). The most promising results are presented in Table 1. The survey revealed that $BF_3{\cdot}Et_2O$ (Table 1, entry 4) was the most selective and activating Lewis acid, but the best diastereomeric ratio of products **3a** and **4a** was only 4 to 1. Reactions promoted by $Cu(OTf)_2$ turned out to be slower with **3a**:**4a** ratios ranging from 7:3 (entry 3, reaction at −35 °C) to 3:2 (entry 2, reaction at 20 °C)

*Keywords*: Asymmetric induction; Aza-Diels–Alder reactions; Sulfinimine; Non-activated dienes.
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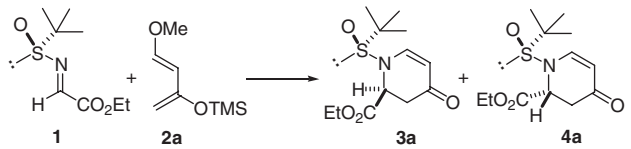
**Table 1.** Aza-DA reactions of **1** (1 equiv) with **2a** (2 equiv) in dry $CH_2Cl_2$ under an argon atmosphere



**1** **2a** **3a** (major) **4a** (minor)

| Entry | Conditions | Ratio[a] **3a**:**4a** | Yield[b] (%) |
|---|---|---|---|
| 1 | 50 °C, 40 h | 7:3 | 62 |
| 2 | 20 °C, 35 min, $Cu(OTf)_2$ (100 mol %) | 3:2 | (50)[c] |
| 3 | −35 °C, 22 h, $Cu(OTf)_2$ (100 mol %) | 7:3 | (38)[c] |
| 4 | −78 °C, 1.5 h, $BF_3{\cdot}OEt_2$ (100 mol %) | 4:1 | 63 (84)[c] |
| 5 | −78 °C, 16 h, $BF_3{\cdot}OEt_2$ (10 mol %) | — | [d] |

[a] The product ratio was determined by $^1H$ NMR (400 MHz) on the crude product.
[b] Isolated yield of **3a** and **4a**.
[c] Yield of **3a** and **4 b** based on $^1H$ NMR on the crude product.
[d] No **3a** or **4a** was observed.

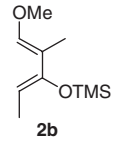
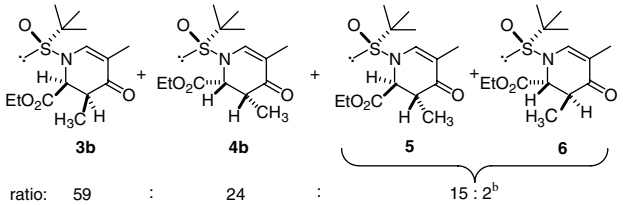
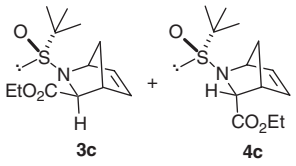
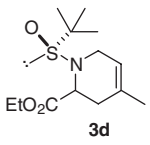
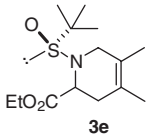
depending on the reaction temperature. The uncatalyzed reaction afforded, after refluxing in dichloromethane for 40 h, a product mixture of **3a** and **4a** in the ratio 7:3 and in 62% yield (entry 1).

Attempts to run the reaction with catalytic amounts of $BF_3{\cdot}Et_2O$ (10 mol %) failed (entry 5). This might result from a strong coordination of the Lewis acid to the imine nitrogen atom leading to inhibition or decomposition of the Lewis acid.[3e]

Separation of **3a** and **4a** by flash chromatography did not succeed. However, recrystallization of the mixture from 10% isopropanol in *n*-hexane afforded the major isomer in pure form, and an X-ray analysis established the relative configuration to be that shown in **3a**.[7]

Encouraged by the results obtained with **2a** other dienes were tested in the presence of stoichiometric amounts of $BF_3{\cdot}Et_2O$. The results are summarized in Table 2. The reaction with the activated dimethyl-substituted Danishefsky's diene, **2b**, yielded a product mixture of **3b**:**4b**:**5**:**6** in the ratio 59:24:15:2 and 73% combined yield (Table 2, entry 1). We were able to separate **3b**/**4b** from **5**/**6** by flash chromatography (EtOAc/*n*-hexane, 1:2), and crystallization ($Et_2O$/*n*-pentane) of the former fraction yielded pure **3b**. The absolute configuration was established by X-ray analysis.[7] The structure of compounds **4b**, **5**, and **6** were determined by NMR ($^1H$, $^{13}C$, COSY, HSQC, and HMBC). The cis and trans orientations of the methyl and $CO_2Et$ groups in the six-membered ring were determined from their geminal

**Table 2.** Aza-DA reactions of **1** (1 equiv) with dienes **2b**–**2e** (2 equiv) promoted by $BF_3{\cdot}Et_2O$ (1 equiv) in dry $CH_2Cl_2$ under an argon atmosphere

| Entry | Diene | Conditions | Aza-Diels–Alder adduct[a] | Yield % |
|---|---|---|---|---|
| 1 |  **2b** | −78 °C, 15 h |  **3b** **4b** **5** **6** ratio: 59 : 24 : 15 : 2[b] | 73[c] |
| 2 |  **2c** | −50 °C, 19 h |  **3c** **4c** ratio: 9 : 1 | 47[c,d] |
| 3 |  **2d** | 0 °C, 1 h |  **3d** | 19[d] |
| 4 |  **2e** | 0 °C, 2 h |  **3e** | 42[d] |

[a] The product ratio was determined by $^1H$ NMR (400 MHz) on the crude product.
[b] The major isomers of 5 or 6 were not determined.
[c] Total yield of isolated isomers.
[d] Absolute configuration was not determined.

H vicinal coupling constants (cis ~6 Hz and trans 1.7 Hz). The major diastereoisomers of **5** and **6** were not determined.

We were pleased to observe that the sulfinyl α-imino ester **1** also reacted with the non-activated dienes **2c**–**2e** to form aza-DA adducts. The reaction with cyclopentadiene **2c** gave a 9:1 mixture of the *exo* adduct **3c** and the *endo* adduct **4c** in 47% combined yield (Table 2, entry 2). The *endo*/*exo*-orientation was concluded from NOESY experiments. Reactions with the acyclic unactivated dienes **2d** (entry 3) and **2e** (entry 4) showed only one diastereomeric aza-DA adduct **3d** and **3e** in 19 and 42% yields, respectively. The stereoselectivities were determined by NMR and GC. $^1$H NMR of the crude products also showed some unidentified impurities (not aza-DA adducts) that were difficult to remove by flash chromatography. The configurations of **3c**, **4c**, **3d**, and **3e** were not determined.

The sulfinyl auxiliary in **3d** was cleaved by acidic hydrolysis (HCl, MeOH, rt, 5 h). The resulting amino ester was obtained in 70% yield. Chiral GC analysis (Chiralsil Dex CB column) of the product showed that no racemization occurred during the hydrolysis.

A typical experiment for the asymmetric aza-DA reaction was as follows: to a stirred and precooled solution of the Lewis acid (0.25 mmol) in dry dichloromethane (2 ml) under an argon atmosphere was added a solution of sulfinyl α-imino ester **1** (0.25 mmol, 1.2–1.4 M in dichloromethane) and diene (0.50 mmol) via syringe. After the specified reaction time (see Tables 1 and 2), the reaction was quenched by addition of phosphate buffer (3 ml, pH = 7), allowed to warm to room temperature and extracted with dichloromethane (3 × 3 ml). The combined organics were dried ($MgSO_4$) and concentrated. The crude product was analyzed by $^1$H NMR to determine the diastereomeric ratio and, thereafter, purified by flash chromatography.

In summary, we have demonstrated that optically active *N*-*tert*-butanesulfinyl α-imino ester **1** reacts as a dienophile in reactions with both activated and non-activated dienes in the presence of $BF_3{\cdot}OEt_2$. The aza-DA adducts were obtained in modest yields and in diastereoselectivities ranging from poor for the activated Danishefsky type dienes to excellent for the unactivated acyclic dienes. Further work investigating the stereoselectivity of other *N*-sulfinyl α-imino esters in the aza-DA reaction in the presence of Lewis acid catalysts is in progress and will be reported elsewhere.

## Acknowledgments

We thank the Norwegian Research Council (Grant 160099 to T.A.) for generous financial support. We also thank Mrs. Julie Jackson (NTNU) for performing the mass spectrometric measurements.

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7. Inquiries concerning X-ray analysis should be addressed to L.K.H. (e-mail: lars-kristian.hansen@chem.uit.no). CCDC 651781 (for **3a**) and CCDC 651782 (for **3b**) contain the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

# Paper II

Andreassen, T., Lorentzen, M., Hansen, L. K. and Gautun, O. R.

**The use of two optically active *N*-sulfinyl α-imino esters in the stereoselective aza-Diels Alder reaction**

*Tetrahedron*, accepted.

Pergamon

TETRAHEDRON

# The use of two optically active *N*-sulfinyl α-imino esters in the stereoselective aza-Diels-Alder reaction

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**Abstract**—Diastereoselective aza-Diels-Alder (aza-DA) reactions of ethyl (*S*)-*N*-(*tert*-butanesulfinyl)iminoacetate (**2a**) and ethyl (*S*)-*N*-(*p*-toluenesulfinyl)iminoacetate (**2b**) with different dienes including activated, non-activated, cyclic and acyclic dienes in the presence of Lewis acids are described. Reactions with **2a** were found to be more selective. Reactions of unactivated dienes (acyclic and cyclic) with stoichiometric amounts of TMSOTf as Lewis acid afforded the aza-DA adducts in modest yields and in diastereoselectivities up to 99%. A strong preference for *Re*-approach was observed for **2a**. Cyclic dienes gave the exo adducts as major products. For the aza-DA reaction with activated Danishefsky type dienes poor diastereoselectivities were observed. In these cases, the best results were obtained using stoichiometric amounts of $BF_3{\cdot}Et_2O$ as Lewis acid (up to 69% de, 76% yield). The absolute configurations of six of the addition products were established by chemical correlation with known compounds. Acidic cleavage of the sulfinyl group occurred without racemization to optically active nonproteinogenic α-amino acid ethyl esters. *Keywords*: Asymmetric induction / Aza-Diels-Alder reactions / Sulfinimines / Non-activated dienes © 2009 Elsevier Science. All rights reserved.

## 1. Introduction

The aza-Diels-Alder (aza-DA) reaction between dienes and imines is a powerful synthetic method for preparation of highly functionalized six-membered aza-cycles such as piperidines and tetrahydroquinolines.[1] In general, this reaction requires a highly activated (electron-rich) diene like the Danishefsky's diene and an electron-poor imine. The aza-DA reaction is usually slow due to the low reactivity of the imine functionality. The reactivity can often be increased by incorporation of an electron withdrawing substituent on the imine and by addition of a Lewis acid to the reaction system. Several asymmetric protocols have appeared, involving either a diastereoselective aza-DA reaction applying chiral imines[2] or more recently, a catalytic enantioselective reaction.[3]

In 2000, K. A. Jørgensen and coworkers reported excellent results for the catalytic enantioselective aza-DA reaction by reacting the double activated *N*-tosyl α-imino ester **1** (see Figure 1) with different dienes including activated, non-activated, cyclic and acyclic dienes in presence of chiral BINAP-copper(I) complexes.[3e] The described reaction provided an effective route to optically active nonproteinogenic α-amino acids of the piperidine type. A major drawback with this method is the removal of the *p*-toluenesulfonyl group (*p*Ts), which requires harsh conditions.[4]

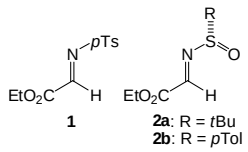



**Figure 1.** Activated dienophiles for the aza-Diels-Alder reaction.

The chiral nonracemic *N*-sulfinylimino esters **2**, which are the sulfinyl analogs of **1** (see Figure 1), have been described in the literature as "chiral glycine cation equivalents" for the asymmetric synthesis of α-amino acids with excellent diastereoselectivities.[5] The chiral and electron-withdrawing sulfinyl group has been shown to activate the C=N bond for nucleophilic addition with high and predictable asymmetric induction, and is easily removed from the product.[6]

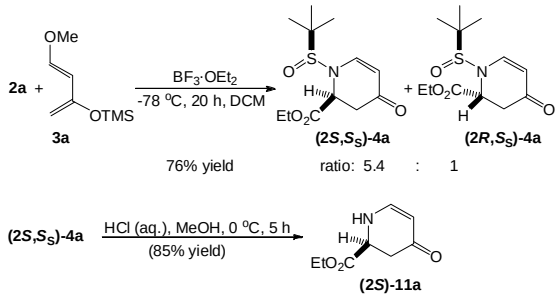
Since the known aza-DA chemistry of chiral *N*-sulfinyl imines (sulfinimines) as dienophiles was limited to only one report describing the reaction of 2-aryl substituted *N*-sulfinyl imines to the highly activated (electron-rich) Rawal diene,[7] an investigation of the aza-DA reaction of **2a** was initiated. We recently communicated that **2a** reacts with both activated and non-activated dienes in the presence of $BF_3{\cdot}OEt_2$.[8] The aza-DA adducts were obtained in modest yields and in diastereoselectivities ranging from poor for the activated Danishefsky type dienes to excellent for the unactivated acyclic dienes (up to 99% de). Here, we present

a more detailed report on this reaction with the α-imino ester dienophiles **2a** and **2b**. Assignment of the absolute configuration of the aza-DA adducts, a model explaining the stereochemical outcome of the reaction, and a study of the by-products in the reaction are addressed. Finally, hydrolysis of the aza-DA adducts for removal of the chiral sulfinyl auxiliary to afford optically active nonproteinogenic α-amino acid ethyl esters is presented.

## 2. Results and Discussion

### 2.1. The aza-Diels-Alder reaction

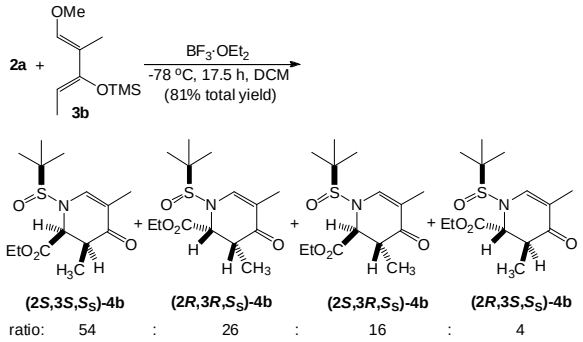
A series of Lewis acids (1 equiv) has previously been screened as promoters for the diastereoselective aza-DA test reaction of **2a** (1 equiv) with the activated Danishefsky's diene **3a** (2 equiv), shown in Scheme 1.[8] The best result was obtained with a stoichiometric amount of $BF_3{\cdot}OEt_2$ at -78 °C for 1.5 h in dry dichloromethane, yielding an epimeric mixture of **(2*S*,$S_S$)-4a** and **(2*R*,$S_S$)-4a** in ratio 5.4:1, and 76% combined yield. Using less than 1 equivalent of the Lewis acid provided inferior results, indicating that it was consumed during the reaction. Recrystallization of the mixture from 10% isopropanol in *n*-hexane provided the major isomer in pure form, and an X-ray analysis established the relative configuration shown in **(2*S*,$S_S$)-4a**.[8]




**Scheme 1.**

Attempts to cleave off the sulfinyl group in **(2*S*,$S_S$)-4a** with concentrated HCl solution (aqueous) in methanol at room temperature failed, resulting in several decomposition products. However, repeating the experiment at 0 °C afforded the desired product **(2*S*)-11a** in 85% yield (see Scheme 1), and high purity (>99% ee) according to chiral GC analysis. Interestingly, when mixtures of **(2*S*,$S_S$)-4a** and **(2*R*,$S_S$)-4a** were treated with 1 M HCl solution (aqueous) in THF at 0 °C, a rate difference in cleavage of the sulfinyl group was observed for the two compounds. In general, the minor epimer **(2*R*,$S_S$)-4a** was cleaved at a faster rate, as exemplified in the experiment starting from a 81:19 mixture of **(2*S*,$S_S$)-4a** and **(2*R*,$S_S$)-4a** and 10 minutes reaction time, giving **11a**, **(2*S*,$S_S$)-4a** and **(2*R*,$S_S$)-4a** in ratio 11 : 77 : 12, respectively.

The aza-DA reaction of **2a** with *trans*-1-methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-pentadiene (**3b**), in the presence of stoichiometric amounts of $BF_3{\cdot}OEt_2$ (-78 °C, 17.5 h), afforded a mixture of four diastereomeric compounds as shown in Scheme 2. We were able to separate **(2*S*,3*S*,$S_S$)-4b**/**(2*R*,3*R*,$S_S$)-4b** from **(2*S*,3*R*,$S_S$)-4b**/**(2*R*,3*S*,$S_S$)-4b** by flash chromatography, and crystallization of the former fraction yielded pure **(2*S*,3*S*,$S_S$)-4b**. The absolute configuration was established by X-ray.[8] The relative configuration of **(2*R*,3*R*,$S_S$)-4b** was determined by $^1$H NMR spectroscopy, showing a similar vicinal $^1$H-$^1$H coupling constant (6.5 Hz) between H-2 and H-3 as for **(2*S*,3*S*,$S_S$)-4b** (6.0 Hz). The corresponding coupling constants for **(2*S*,3*R*,$S_S$)-4b** and **(2*R*,3*S*,$S_S$)-4b** were found to be 1.7 Hz and 2.3 Hz, respectively.

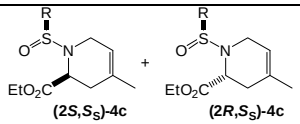
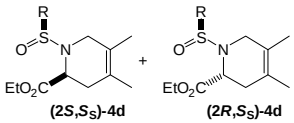
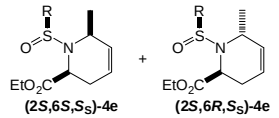
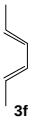
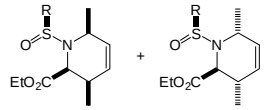
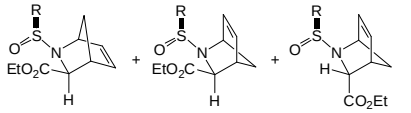
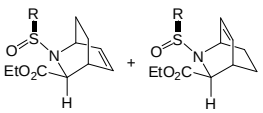



**Scheme 2.**

The absolute configurations of the latter two isomers could not be determined, and the proposed structures in Scheme 2 are based on the general preference for (*S*) configuration at the α-carbon (α to the ester group) in these reactions (see stereochemical model discussed below). The stereochemical result shown in Scheme 2 deviates from the results obtained by Jørgensen *et al*., where a chiral BINAP-copper(I)-complex catalyzed the aza-DA reaction of tosyl imine **1** with **3b**, giving the trans adduct (corresponding to our minor **(2*S*,3*R*,$S_S$)-4b** and **(2*R*,3*S*,$S_S$)-4b**) as the major product.[3e] Their best result was a 10:1 ratio of the trans and cis adducts, and the former diastereomer was isolated in 83% yield and 94% ee. The cis adduct (corresponding to our **(2*S*,3*S*,$S_S$)-4b** and **(2*R*,3*R*,$S_S$)-4b**) was isolated in 8% yield (racemic).

A series of Lewis acids including $SnCl_4$, $Zn(OTf)_2$, $Cu(OTf)_2$, $Yb(OTf)_3$, trimethylsilyl trifluoromethanesulfonate (TMSOTf), $Mg(ClO_4)_2$, $AlBr_3$ and $BF_3{\cdot}Et_2O$ was screened as promoters (1 equiv) for the stereoselective aza-DA reaction of **2a** with non-activated dienes (acyclic and cyclic). The survey pointed out TMSOTf and $BF_3{\cdot}Et_2O$ to be the most selective and activating Lewis acids for the reaction. The more promising results are presented in Table 1. For comparison, results from reactions applying the *p*-toluenesulfinylimino ester **2b** as dienophile are included in Table 1. In the presence of Lewis acids, some of the dienes underwent polymerization at rates competitive to the preferred aza-DA reactions. For this reason, some excess diene (2 equiv) was generally used. Especially for isoprene (**3c**), a significant improvement of the yield was observed when using an even larger excess of **3c**. The yield of **(2*S*,$S_S$)-4c** was raised from 25% (Table 1, entry 2) to 48% (Table 1, entry 3) by increasing the amount of **3c** from 2 to 20 equivalents.

**Table 1.** Aza-DA reactions of **2a**-**2b** (1 equiv) with non-activated dienes **3c**-**3h** (2 equiv) promoted by Lewis acid (1 equiv) in $CH_2Cl_2$ under argon atm.

| Entry | Imine | Diene | Lewis acid | Conditions | Aza-Diels-Alder adduct[a] | Yield %[b] |
|---|---|---|---|---|---|---|
| | | | | |  **(2*S*,$S_S$)-4c** **(2*R*,$S_S$)-4c** | |
| 1 | **2a** (R = *t*Bu) |  **3c** | $BF_3{\cdot}Et_2O$ | 0 °C, 1 h | ratio: >99 : < 1 | 19 |
| 2 | **2a** | | TMSOTf | -78 °C, 22 h | ratio: >99 : < 1 | 25 |
| 3 | **2a** | | TMSOTf | -78 ºC, 22 h | ratio: >99 : < 1 | 48[c] |
| 4 | **2b** (R = *p*Tol) | | TMSOTf | -78 ºC, 20 h | ratio: 3 : 2 | 18 |
| | | | | |  **(2*S*,$S_S$)-4d** **(2*R*,$S_S$)-4d** | |
| 5 | **2a** (R = *t*Bu) |  **3d** | $BF_3{\cdot}Et_2O$ | 0 °C, 2 h | ratio: >99 : < 1 | 42 |
| 6 | **2a** | | TMSOTf | -78 ºC, 5 h | ratio: >99 : < 1 | 64 |
| 7 | **2b** (R =*p*Tol) | | $BF_3{\cdot}Et_2O$ | 0 °C, 3.5 h | ratio: 4 : 1 | 35 |
| 8 | **2b** | | TMSOTf | -78 ºC, 5.5 h | ratio: 7 : 3 | 48 |
| 9 | **2a** (R = *t*Bu) |  **3e** | TMSOTf | -78 ºC, 20 h |  **(2*S*,6*S*,$S_S$)-4e** **(2*S*,6*R*,$S_S$)-4e** ratio: 2 : 1 | 7[d] |
| 10 | **2a** (R = *t*Bu) |  **3f** | TMSOTf | -78 °C, 23 h |  **(2*S*,3*R*,6*S*,$S_S$)-4f** **(2*S*,3*S*,6*R*,$S_S$)-4f** ratio: 97 : 3 | 14[d] |
| | | | | |  **(1*S*,3*S*,4*R*,$S_S$)-4g** **(1*R*,3*S*,4*S*,$S_S$)-4g** **(1*R*,3*R*,4*S*,$S_S$)-4g** | |
| 11 | **2a** (R = *t*Bu) | | $BF_3{\cdot}Et_2O$ | -50 ºC, 25 h | ratio: 88 : 12 : 0 | 52 |
| 12 | **2a** |  **3g** | TMSOTf | -78 ºC, 18 h | ratio: >99 : <1 : 0 | 49 |
| 13 | **2b** (R = *p*Tol) | | $BF_3{\cdot}Et_2O$ | -50 °C, 0.5 h | ratio: 89 : 7 : 4 | 48 |
| 14 | **2b** | | TMSOTf | -78 ºC, 17 h | ratio: 89 : 7 : 4 | 63 |
| 15 | **2a** (R = *t*Bu) |  **3h** | TMSOTf | -78 °C, 16 h |  **(1*S*,3*S*,4*R*,$S_S$)-4h** **(1*R*,3*S*,4*S*,$S_S$)-4h** ratio: 87 : 13 | 8[d] |

[a]The product ratio was determined by $^1$H NMR (400 Hz) spectroscopy of the crude product.
[b]Total yield of isolated isomers.
[c]Twenty equivalents of **3c** and ten equivalents of TMSOTf were added to one equivalent **2a**.
[d] The proposed configurations were not determined, but rationalized by NOE experiments and from the stereochemical model discussed below.

Without exception, all reactions with **2a** were more selective than the reactions with **2b**, owing to the bulkiness of the *t*-butyl group. In general, the best diastereoselectivities were obtained in reactions applying **2a** in combination with TMSOTf. The *t*-butyl reactions of isoprene (**3c**, Table 1, entries 1, 2 and 3) and 2,3-dimethyl butadiene (**3d**, Table 1, entries 5 and 6) provided only one observable diastereomere according to $^1$H NMR (400 MHz) spectroscopy of respective crude products. Our results showed better selectivities (>99% de) versus the reported enantioselective aza-DA reaction of **1** with diene **3d** catalyzed by chiral BINAP-copper (I) complexes (up to 65% ee).[3e]

The aza-DA reaction of **2a** with (*E*)-1,3-pentadiene (**3e**, Table 1, entry 9) and (*E*,*E*)-2,4-hexadiene (**3f**, Table 1, entry 10) afforded mixtures of cis/trans adducts in 7 and 14% combined yields, respectively. The diastereomeric products in both reactions could be separated by flash chromatography. The proposed absolute configurations shown in Table 1 were not determined, but were based on NMR spectroscopy assigning the relative configuration between the Me/$CO_2$Et groups (see Figure 2), and from the stereochemical model discussed below showing a preference for (*S*) configuration at the α-carbon (α to the ester group).

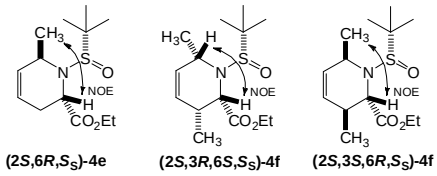
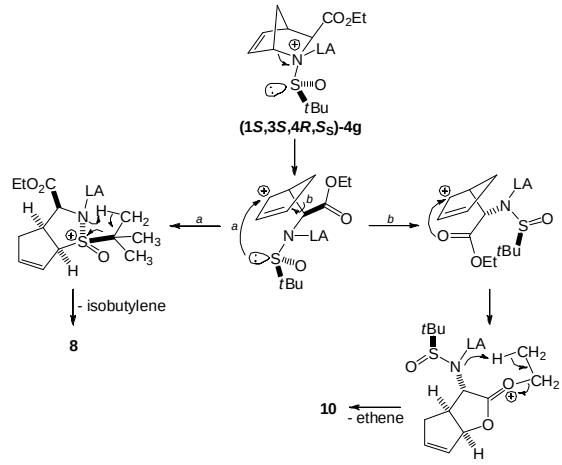



**Figure 2.** Relative configurations shown from NOE experiments.

An exo preference was found for **2a** in reactions with cyclopentadiene (**3g**, Table 1, entries 11 and 12) and cyclohexadiene (**3h**, Table 1, entry 15). The TMSOTf promoted reaction of **3g** at -78 ºC afforded only one observable diastereomer **(1*S*,3*S*,4*R*,*S*$_S$)-4g** (*t*Bu) in 49% yield (entry 12), while $BF_3{\cdot}Et_2O$ provided a 88:12 mixture of the exo **(1*S*,3*S*,4*R*,*S*$_S$)-4g** (*t*Bu) and the endo **(1*R*,3*S*,4*S*,*S*$_S$)-4g** (*t*Bu) in 52% combined yield (entry 11). The aza-DA reaction of **2b** with **3g** afforded a 89:7:4 mixture of **(1*S*,3*S*,4*R*,*S*$_S$)-4g** (*p*Tol), **(1*R*,3*S*,4*S*,*S*$_S$)-4g** (*p*Tol) and **(1*R*,3*R*,4*S*,*S*$_S$)-4g** (*p*Tol), respectively (Table 1, entries 13 and 14). Recrystallization of the mixture from 10% isopropanol in *n*-hexane afforded the major isomer almost pure (97% de). The exo preference observed in reactions with unactivated cyclic dienes is in accordance with results reported for the enantioselective aza-DA reactions of **1** with **3g** and **3h**, catalyzed by chiral BINAP-copper (I) complexes.[3e] Yields and enantioselectivities of the major exo aza-DA adducts from **3g** and **3h** were reported up to 85% (83% ee) and 52% (95% ee), respectively.[3e]

### 2.2. By-products in the aza-Diels-Alder reaction

Several by-products were formed and identified during the course of this work. Although not always structurally

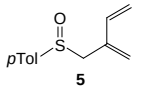
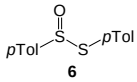
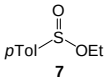
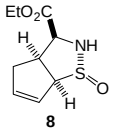
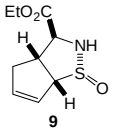
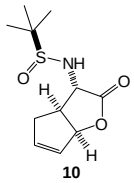



**Scheme 3.**

interesting, attention to these products can provide new insight into the reaction. We did not observe any imine ene by-products in our reaction systems as reported for the chiral BINAP-copper(I)-complex catalyzed aza-DA of tosyl imine **1**.[3e] Table 2 shows the most interesting by-products encountered and the reaction conditions under which they were formed. It should be pointed out that attempts to improve the yields of these products were not undertaken. Formation of products **5**, **6**[9] and **7**[10] (Table 2, entries 1 and 2) must involve breaking of the sulfur-nitrogen bond of **2b** at some stage. It is obvious that a potential *p*-tolyl sulfoxide cation – or radical, would be more stabilized by resonance than the corresponding *t*-butyl analogue. Similar reactions with **2a** were not observed. Ene reactions with *p*-tolyl sulfoxide cation (formed *in situ* from *p*-toluenesulfinamide) have been reported,[11] which can explain the formation of the ene product **5**. Ene product **5** was observed in low yields (2-12%) when the reaction took place at -78 ºC, but at higher temperature (0 ºC) the yield improved (27%, Table 2, entry 2). Chiral HPLC analysis of **5** (Table 2, entry 1) showed that some degree of chiral induction took place in these reactions (40% ee), indicating that the sulfur-nitrogen bond could not have been completely broken during addition to the diene. Nucleophilic attack by an ethoxide rather than diene would provide **7**. This ethoxide would most likely come from the ethyl ester group of the sulfinimine, but details around the reaction remain unclear. The thiosulfinate **6** was observed in all aza-DA reactions with **2b** in various amounts. In most reactions, the yields were lower than 10%, but at higher temperatures (0 ºC) more **6** was formed (28%, Table 2, entry 2). A decomposition of sulfinimine to sulfenic acid,[12] and a bimolecular dehydration of the sulfenic acid[13] can explain the formation of **6**.

The aza-DA adducts from cyclopentadiene reactions with **2a** were not particularly stable, and several by-products were identified (see Table 2, entries 3, 4 and 5). Shortening the reaction time did not provide higher yields. A rationale for the formation of **8** and **10** from the exo aza-DA product **(1*S*,3*S*,4*R*,*S*$_S$)-4g** (*t*Bu) is shown in Scheme 3. Initiated by a Lewis acid (LA), the C-N bond breaks to form an allylic cation, which is attacked by either the ester or sulfinyl

**Table 2.** By-products from the aza-Diels-Alder reaction of sulfinimines **2a** and **2b**.

| Entry | Imine | Diene | Lewis acid | Conditions | By-products/yields (%)[a] | | | Aza-DA/yields (%)[b] |
|---|---|---|---|---|---|---|---|---|
| | | | | |  **5** |  **6** |  **7** | |
| 1 | **2b** | **3c** | TMSOTf | -78 ºC, 20 h | 12 (40% ee) | 6 | 8 | 18 |
| 2 | **2b** | **3c** | TMSOTf | 0 ºC, 1 h | 27 | 28 | 0 | 10 |
| | | | | |  **8** |  **9** |  **10** | |
| 3 | **2a** | **3g** | TMSOTf | -78 ºC, 15.5 h | 17 | 0 | 11 | 44 |
| 4 | **2a** | **3g** | $BF_3{\cdot}Et_2O$ | -50 ºC, 25 h | 13 | 0 | 3 | 52 |
| 5 | **2a** | **3g** | $BF_3{\cdot}Et_2O$ | r.t., 17.5 h | 38[c] | 4[c] | 0 | 0 |

[a]Isolated yields.
[b]Combined yield of aza-DA adducts.
[c]Mixture of **8** and **9**.

group. Rearrangement of a similar compound has been reported by Kobayashi *et al*., although the ester was first reported hydrolyzed in this paper.[14] Since our reactions were carried out in anhydrous environment, we propose an alternative removal of the ethyl group. The proposed mechanism for the formation of **8** includes an attack by the sulfinyl-sulfur lone pair, explaining the inversion of the sulfinyl stereocentre. Similar nucleophilic attack by the sulfur in *t*-butanesulfinyl compounds has been suggested by Davis and co-workers, with the expulsion of isobutylene as an important driving force.[15] A similar rearrangement of the endo product **(1*R*,3*S*,4*S*,*S*$_S$)-4g** (*t*Bu) would give **9**. The absolute configuration of **8** was determined by X-ray.[16] The relative configurations of **9** and **10** were found from NOE experiments. Structure determining NOE's are shown in Figure 3.

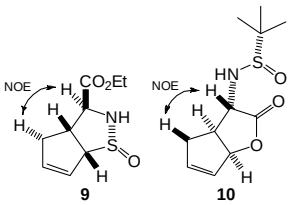



**Figure 3.** Structure determing NOE's for **9** and **10**.

### 2.3. Stereochemical model

Although most aza-Diels-Alder reactions are concerted, there are many examples of stepwise Mannich-Michael type mechanisms.[1] Most of these examples involve electron-rich oxygenated dienes or use of Brønsted acids as catalysts, leading to relative stable intermediates. The absolute configurations of the major cycloadducts **(2*S*,*S*$_S$)-4a**, **(2*S*,3*S*,*S*$_S$)-4b**, **(2*S*,*S*$_S$)-4c** (*t*Bu and *p*Tol), **(2*S*,*S*$_S$)-4d** (*t*Bu and *p*Tol) and **(1*S*,3*S*,4*R*,*S*$_S$)-4g** (*t*Bu and *p*Tol) were determined (as described below). All major products had

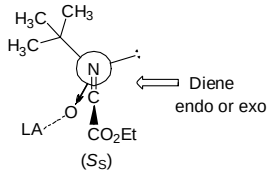
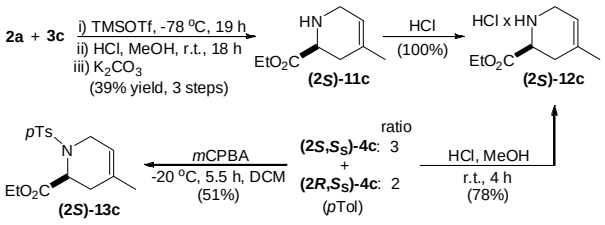



**Figure 4.** Stereochemical model.

the (*S*)-configuration at the α-carbon atom (α to the ester group). A strong preference for *Re*-approach was observed for **2a** (*t*Bu). In fact, for all unactivated dienes, *tert*-butyl products were apparently formed exclusively with (*S*)-configuration at the α-carbon, with the diastereomeric diversity originating from endo / exo approach. More evidently, *tert*-butyl reactions of isoprene (**3c**) and 2,3-dimethylbutadiene (**3d**) provided only one observable diastereomer, since endo / exo approaches lead to identical products in these cases. The expected exo preference was found for reactions with the cyclic dienes **3g** and **3h**,[3e] but the products deriving from acyclic dienes **3b**, **3e** and **3f** showed the opposite endo preference. Products from the activated Danishefsky's dienes **3a** and **3b** are conspicuously less selective, forming diastereomers with both configurations at the α-carbon atom. This could result from a less selective, possibly step-wise, mechanism as suggested by Kawęcki.[7] However, we were not able to identify intermediate products in these reactions. The stereochemical outcome of the aza-DA reactions of **2a** and **2b** can be rationalized according to the model shown in Figure 4. The shown conformation has been confirmed by calculations on different sulfinimines, both with and without Lewis acids (LA) present.[17] The model has earlier been used to explain the stereochemical outcome of Lewis acid promoted additions of both Grignard reagents[5a] and silyl nucleophiles[18] to sulfinimines.

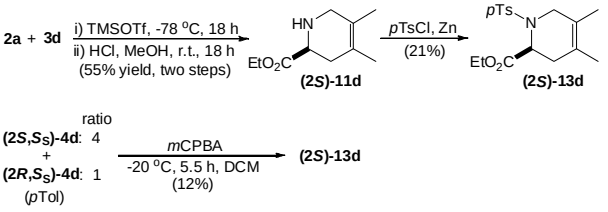
### 2.4. Configuration of the aza-Diels-Alder products

The determination of the absolute configuration of the aza-DA adducts **(2*S*,$S_S$)-4a** and **(2*S*,3*S*,$S_S$)-4b** have been described elsewhere.[8] Absolute configurations of the major aza-DA adducts **(2*S*,$S_S$)-4c** (*t*Bu and *p*Tol), **(2*S*,$S_S$)-4d** (*t*Bu and *p*Tol) and **(1*S*,3*S*,4*R*,$S_S$)-4g** (*t*Bu and *p*Tol) were established by chemical correlation with the known HCl salt **(2*R*)-12c** (see Scheme 4),[19] **(2*S*)-13d** (Scheme 5)[3e] and **(1*S*,3*S*,4*R*)-13g** (Scheme 6),[3e] respectively.




**Scheme 4.**

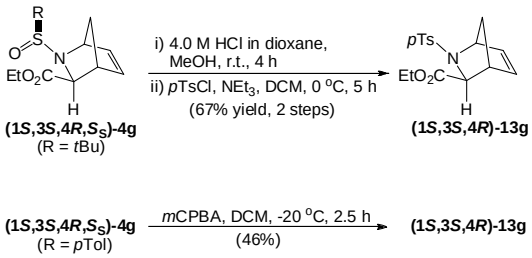
The crude aza-DA adduct **(2*S*,$S_S$)-4c** (*t*Bu), obtained by reacting **2a** with 20 equivalents of **3c** in the presence of 10 equivalents TMSOTf, was treated with concentrated aqueous HCl in methanol to afford the HCl salt **(2*S*)-12c** (see Scheme 4). By controlling the pH of the water phase, **(2*S*)-12c** was purified with extraction alone. Basic adjustment afforded enantiopure **(2*S*)-11c** (according to chiral GC analysis), and was then transformed back to **(2*S*)-12c** in concentrated aqueous HCl. Similarly, acidic removal of the tolyl sulfinyl group in a 3:2 mixture of **(2*S*,$S_S$)-4c** (*p*Tol) and **(2*R*,$S_S$)-4c** (*p*Tol) afforded the enriched **(2*S*)-12c** in 78% yield. The toly sulfinyl group in the aza-DA mixture was also oxidised with *m*CPBA at -20 °C to the enantiomerically enriched tosyl analogue **(2*S*)-13c** in 51% yield.




**Scheme 5.**

Crude **(2*S*,$S_S$)-4d** (*t*Bu), obtained from the aza-DA reaction of **2a** with **3d** (see Scheme 5), was hydrolyzed in accordance with the method mentioned above for **(2*S*,$S_S$)-4c** (*t*Bu) to **(2*S*)-11d**, and then tosylated under neutral conditions[20] to the known **(2*S*)-13d** (>99% ee, HPLC).[3e] The configuration of a 4:1 mixture of **(2*S*,$S_S$)-4d** (*p*Tol) and **(2*R*,$S_S$)-4d** (*p*Tol) was established by a *m*CPBA oxidation to the enantiomerically enriched **(2*S*)-13d**.

The absolute configuration of **(1*S*,3*S*,4*R*,$S_S$)-4g** (*t*Bu) was determined by cleavage of the sulfinyl group[5e] and subsequent tosylation to the known *N*-tosyl compound **(1*S*,3*S*,4*R*)-13g**[3e] in 67% total yield (see Scheme 6). The configuration of **(1*S*,3*S*,4*R*,$S_S$)-4g** (*p*Tol) was assigned by oxidation to **(1*S*,3*S*,4*R*)-13g**.




**Scheme 6.**

The relative configurations of the other isomers of **4g** and **4h**, disregarding the configuration at the α-carbon atom (α to the ester group), were found from NOE experiments. The structure determining NOE's are summarized in Figure 5. From the stereochemical model discussed above we assume (*S*)-configuration at the α-carbon, and with (*S*)-configuration fixed at sulfur, the following structures shown in Figure 5 are proposed.

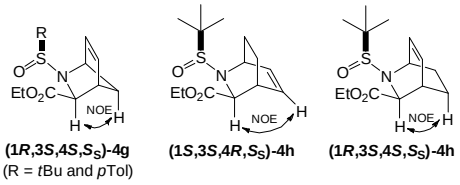



**Figure 5.** Proposed configurations for bicyclic aza-DA adducts.

The configurations of the *p*-toluene isomers **(1*R*,3*S*,4*S*,$S_S$)-4g** and **(1*R*,3*R*,4*S*,$S_S$)-4g** were deduced by the following reasoning: The aza-DA adducts are formally sulfinamides with the nitrogen taking part in a cyclic structure. Focusing only on the substituents from the parent sulfinimine, the sulfoxygroup on nitrogen and the ester group on the neighbouring carbon (α-C), some general observations can be rationalized for the aza-DA adducts of *p*-toluensulfinimine. To reduce van-der-Waals strain, the bulky sulfoxy-group would preferably adopt an orientation trans to the ester group (see Figure 6). Considering the rotation of the N-S bond, there is general preference for a staggered orientation of the sulfinamides, with the nitrogen lone pair anti to the sulfoxide oxygen.[21] This can be attributed to a stabilizing interaction between the nitrogen lone pair and the anti bonding σ-orbital of the S-O bond. In our work, compounds with (*S*)-configuration on sulfur were prepared, without any sign of racemization. This leads to two diastereomeric arrangements (ignoring the remaining part of the molecule), due to (*R*) or (*S*)-configuration of the carbon α to the ester group (see Figure 6).

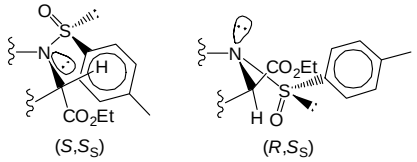



**Figure 6.** Model explaining observed shielding for ($S$,$S_S$)-isomers in $^1$H NMR.

**Table 3.** Configuration at α-C versus $OCH_2CH_3$ proton shift.

| *p*Tol aza-DA adducts | (*S*) / ppm | (*R*) / ppm |
|---|---|---|
| **(2*S*,$S_S$)-4c + (2*R*,$S_S$)-4c** | 4.15 | 4.22 |
| **(2*S*,$S_S$)-4d + (2*R*,$S_S$)-4d** | 4.13 | 4.22 |
| **(1*S*,3*S*,4*R*,$S_S$)-4g** | 3.67, 3.62 | |
| **(1*R*,3*S*,4*S*,$S_S$)-4g** | 3.7-3.6 | |
| **(1*R*,3*R*,4*S*,$S_S$)-4g** | | 4.29 |

As shown in Figure 6, the preferred conformer of the (*S*,$S_S$)-diastereomer puts the tolyl group in the vicinity of the ester group, leading to significant shielding of the ethyl ($OCH_2CH_3$) proton NMR signals. The (*R*,$S_S$)-diastereomer, however, does not show this effect. Table 3 shows the ethyl proton shifts for all tolyl aza-DA adducts described in this paper. A chemical shift at 3.6-3.7 for **(1*R*,3*S*,4*S*,$S_S$)-4g** supports (*S*)-configuration at C-3 (α-C), and a chemical shift at 4.29 for **(1*R*,3*R*,4*S*,$S_S$)-4** supports (*R*)-configuration at C-3.

## 3. Conclusion

In conclusion, diastereoselective aza-Diels-Alder (aza-DA) reactions of ethyl (*S*)-*N*-(*tert*-butanesulfinyl)iminoacetate (**2a**) and ethyl (*S*)-*N*-(*p*-toluenesulfinyl)iminoacetate (**2b**) in the presence of stoichiometric amounts of Lewis acids have been presented. A range of dienes have been applied. The reactions with **2a** were found to be the most selective. Reactions of unactivated dienes with TMSOTf as Lewis acid afforded aza-DA adducts in modest yield and diastereoselectivities up to 99%. A strong preference for the *Re*-approach was observed for **2a**. Cyclic dienes gave exo adducts as major products. For the aza-DA reactions with activated Danishefsky type dienes, poor diastereoselectivities were observed. In these cases the best results (up to 69% de, 76% yield) were obtained with $BF_3{\cdot}Et_2O$ as Lewis acid. Treatment of selected aza-DA adducts with HCl resulted in cleavage of the sulfinyl group without racemization, yielding optically active nonproteinogenic α-amino ethyl esters.

## 4. Experimental

### *4.1. General remarks*

All reactions were performed under an argon or nitrogen atmosphere. Tetrahydrofuran (THF) was distilled under nitrogen from Na/benzophenone. Dichloromethane was distilled under nitrogen from calcium hydride. Sulfinimines **2a** and **2b** were prepared according to the literature.[5a] The racemic sulfinimines were also prepared to provide reference compounds for chiral GC and HPLC analysis. Melting points were determined on a Buchi 535 apparatus and are uncorrected. TLC was performed on Merck silica gel 60 $F_{254}$ plates, using UV light at 312 nm and a 5% alcoholic molybdophosphoric acid for detection. Silca gel for flash chromatography was purchased from Merck. Optical rotations were measured with a Perkin-Elmer 241 Polarimeter. Enantiomeric excesses were determined by HPLC analysis, using Daicels columns Chiralcel OD-H and OJ and Chiralpak AD (250x4.6 mm), or by GC using CP Chirasil Dex CB column. $^1$H and $^{13}$C NMR spectra (Bruker Avance DPX instruments 300/75 MHz and 400/100 MHz) were obtained from solutions of $CDCl_3$, and chemical shifts are in ppm and referenced to TMS *via* the lock signal of the solvent. $^1$H and $^{13}$C NMR signals were assigned by 2D correlation techniques (COSY, HSQC, HMBC, NOESY). IR spectra were run on a Thermo Nicolet FT-IR NEXUS instrument, and only the strongest/structurally most important peaks are listed. The mass spectra were recorded on a Finnigan MAT 95XL mass spectrometer. The electron-impact mass spectra, MS (EI), were recorded at 50 eV with a direct inlet, and the electron spray ionization mass spectra, MS (ESI), at 4.7 kV for low resolution spectra and 10 kV for high resolution spectra. The high resolution mass spectra, HRMS (EI) and (ESI), were obtained by using perfluorokerosene (PFK) and polyethyleneimine (PEI) as standards, respectively to provide the reference masses. The elemental analyses were performed at the Mikroanalytisches labor Beller, Göttingen, Germany.

### *4.2. General procedure for aza-Diels-Alder reactions.*

Sulfinimine **2** (1.2 - 1.5 M in $CH_2Cl_2$, 0.25 mmol) was dissolved in dried $CH_2Cl_2$ (2 ml) and cooled down to the specified temperature (see Table 1) under an argon atmosphere. The diene **3** (1.4 – 2.0 equiv) and the Lewis acid (1.0 – 1.2 equiv) were added via syringe and the resultant mixture was stirred. After the appropriate reaction time (see Table 1), the reaction mixture was quenched by the addition of a phosphate buffer (pH = 7, 3 ml), and allowed to warm to room temperature. The mixture was extracted with $CH_2Cl_2$ (4 x 4 ml) and the combined organics were dried ($MgSO_4$) and concentrated. The crude product was analyzed by $^1$H NMR spectroscopy to determine the diastereomeric ratio and, thereafter, purified by flash chromatography.

#### *4.2.1. Ethyl (2S,$S_S$)-1-(tert-butylsulfinyl)-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate, **(2S,$S_S$)-4a**, and ethyl (2R,$S_S$)-1-(tert-butylsulfinyl)-4-oxo-1,2,3,4-tetrahydro-pyridine-2-carboxylate, **(2R,$S_S$)-4a**.*

The asymmetric aza-DA reaction between sulfinimine **2a** (0.52 mmol) and the Danishefsky's diene **3a** (1.0 mmol) according to to the general procedure (2 x scale) at -78 ºC for 20 h afforded a 5.4:1 mixture of **(2*S*,$S_S$)-4a** and **(2*R*,$S_S$)-4a**, which were not separable by flash chromatography (EtOAc/*n*-hexane, 1:1). The mixture was isolated as a pale yellow viscous oil (total yield: 108.3 mg, 76%). Crystallization of the mixture from 10% *i*-PrOH in *n*-hexane afforded the major isomer in pure form (white solid), and an X-ray analysis established the relative configuration to be that shown in **(2*S*,$S_S$)-4a**.[8] Anal. Calcd of the mixture $C_{12}H_{19}NO_4S$: C, 52.73; H, 7.01; N, 5.12; S, 11.73. Found: C, 52.69; H, 7.02; N, 5.05; S, 11.79. Data for **(2*S*,$S_S$)-4a**: $R_F$ (EtOAc/*n*-hexane, 1:1) = 0.1. Mp = 127 –

128 °C (from 10% *i*-PrOH/*n*-hexane). $[\alpha]_D^{rt}$ -166 (*c* 0.30, $CHCl_3$). HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 10/90, 1.0 ml $min^{-1}$, 230 nm): $t_R$ 23.3 min. $^1$H NMR (400 MHz): δ 7.52 (dd, 1H, *J*=8.2, 1.4 Hz, H-6), 5.42 (dd, 1H, *J*=8.2, 1.3 Hz, H-5), 4.37 (ddd, 1H, *J*=7.0, 2.1, 1.4 Hz, H-2), 4.25 (q, 2H, *J*=7.1 Hz, OC*H*$_2$), 3.05 (ddd, 1H, *J*=16.8, 2.1, 1.3 Hz, *trans*-H-3), 2.86 (dd, 1H, *J*=16.8, 7.0 Hz, *cis*-H-3), 1.28 (t, 3H, *J*=7.1 Hz, OCH$_2$C*H*$_3$), 1.26 (s, 9H, *t*-Bu). $^{13}$C NMR (100 MHz): δ 190.10 (C-4), 169.0 (*C*O$_2$Et), 142.8 (C-6), 106.2 (C-5), 62.8 (O*C*H$_2$), 59.78 (*C*Me$_3$), 59.4 (C-2), 38.3 (C-3), 21.7 (C*Me*$_3$), 14.04 (OCH$_2$*C*H$_3$). IR (KBr tablet): 3050 (w), 3001 (m), 2979 (m), 2912 (m), 1740 (s), 1649 (s), 1577 (s), 1479 (m), 1421 (m), 1337 (m), 1295 (s), 1234 (s), 1194 (s), 1096 (s), 1042 (s), 1021 (m), 992 (s), 930 (m) $cm^{-1}$. MS (EI) *m/z* (% rel. int.): 274 (M+1, 1), 217 (13), 169 (18), 144 (86), 96 (100), 95 (19), 78 (13), 68 (33), 67 (22), 57 (21), 41 (89), 39 (15). HRMS (EI) calcd for $C_{12}H_{19}NO_4S$ 273.1035 ($M^+$), found 273.1039. HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 10/90, 1.0 ml $min^{-1}$, 230 nm) of a racemic sample **(2*R**,*R*$_S$*)-4a**: $t_R$ 24.6 and 30.5 min. Data for **(2*R*,*S*$_S$)-4a**: $R_F$ (EtOAc/*n*-hexane, 1:1) = 0.1. HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 10/90, 1.0 ml $min^{-1}$, 230 nm): $t_R$ 17.9 min. $^1$H NMR (400 MHz): δ 7.29 (dd, 1H, *J*=8.0, 1.5 Hz, H-6), 5.31 (dd, 1H, *J*=8.0, 1.3 Hz, H-5), 4.70 (ddd, 1H, *J*=7.2, 2.1, 1.5 Hz, H-2), 4.20 (q, 2H, *J*=7.1 Hz, OC*H*$_2$), 3.04 (ddd, 1H, *J*=17.1, 2.1, 1.3 Hz, H-3A), 2.90 (dd, 1H, *J*=17.1, 7.2 Hz, H-3B), 1.26 (t, 3H, *J*=7.1 Hz, OCH$_2$C*H*$_3$), 1.26 (s, 9H, *t*-Bu). $^{13}$C NMR (100 MHz): δ 190.12 (C-4), 168.9 (*C*O$_2$Et), 147.9 (C-6), 105.0, (C-5), 62.4 (O*C*H$_2$), 59.77 (*C*Me$_3$), 52.6 (C-2), 39.0 (C-3), 21.8 (C*Me*$_3$), 14.02 (OCH$_2$*C*H$_3$). HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 10/90, 1.0 ml $min^{-1}$, 230 nm) of a racemic **(2*R**,*S*$_S$*)-4a**: $t_R$ 18.2 and 41.0 min.

*4.2.2. Ethyl (2S,3S,S$_S$)-1-(tert-butylsulfinyl)-3,5-dimethyl-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate,* ***(2S,3S,S$_S$)-4b****, ethyl (2R,3R,S$_S$)-1-(tert-butylsulfinyl)-3,5-dimethyl-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate,* ***(2R,3R,S$_S$)-4b****, ethyl (2S,3R,S$_S$)-1-(tert-butylsulfinyl)-3,5-dimethyl-4-oxo-1,2,3,4-tetrahydrapyridine-2-carboxylate,* ***(2S,3R,S$_S$)-4b****, and ethyl (2R,3S,S$_S$)-1-(tert-butylsulfinyl)-3,5-dimethyl-4-oxo-1,2,3,4-tetra-hydropyridine-2-carboxylate,* ***(2R,3S,S$_S$)-4b****.*

The asymmetric aza-DA reaction between sulfinimine **2a** (0.52 mmol) and the dimethyl substituted Danishefsky's diene **3b** (0.99 mmol) according to the general procedure (2 x scale) at -78 °C for 17.5 h afforded a 54:26:16:4 mixture of **(2*S*,3*S*,*S*$_S$)-4b**, **(2*R*,3*R*,*S*$_S$)-4b**, **(2*S*,3*R*,*S*$_S$)-4b** and **(2*R*,3*S*,*S*$_S$)-4b**, respectively. Flash chromatography (EtOAc/*n*-hexane, 1:2) separated **(2*S*,3*S*,*S*$_S$)-4b**/**(2*R*,3*R*,*S*$_S$)-4b** from **(2*S*,3*R*,*S*$_S$)-4b**/**(2*R*,3*S*,*S*$_S$)-4b** (total yield: 126.2 mg, 81%). Recrystallization of the main fraction from Et$_2$O/*n*-pentane yielded **(2*S*,3*S*,*S*$_S$)-4b** pure as white crystals (55.4 mg, 35%), and the absolute configuration was established by X-ray analysis.[8] Data for **(2*S*,3*S*,*S*$_S$)-4b**: $R_F$ (EtOAc/*n*-hexane, 1:1) = 0.3. Mp 87 - 88 °C (from Et$_2$O/*n*-pentane). $[\alpha]_D^{rt}$ -123 (*c* 1.0, $CHCl_3$). HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 5/95, 1.0 ml $min^{-1}$, 230 nm): $t_R$ 11.3 min. $^1$H NMR (400 MHz): δ 7.24 (m, 1H, H-6), 4.24 (dd, 1H, *J*=6.0, 1.3 Hz, H-2), 4.20 (q, 2H, *J*=7.1 Hz, OC*H*$_2$), 2.94 (qd, 1H, *J*=7.1, 6.0 Hz, H-3), 1.74 (d, 3H, *J*=1.0 Hz, Me-5), 1.30 (d, 3H, *J*=7.1 Hz, Me-3), 1.26 (s, 9H, *t*-Bu), 1.25 (t, 3H, *J*=7.1 Hz, OCH$_2$C*H*$_3$). $^{13}$C NMR (100 MHz): δ 193.3 (C-4), 168.0 (*C*O$_2$Et), 137.4 (C-6), 113.1 (C-5), 64.4 (C-2), 61.9 (OCH$_2$), 59.6 (*C*Me$_3$), 41.9 (C-3), 21.9 (C*Me*$_3$), 13.97 (OCH$_2$*C*H$_3$), 12.9 (Me-5), 11.3 (Me-3). IR (KBr tablet): 3037 (w), 2988 (m), 1737 (s), 1688 (s), 1606 (s), 1381 (m), 1366 (m), 1293 (m), 1194 (s), 1093 (s), 1027 (m), 941 (m), 914 (m), 879 (m) $cm^{-1}$. MS (EI) *m/z* (% rel. int.): 301 ($M^+$, 1), 245 (63), 197 (87), 125 (22), 124 (100), 123 (32). HRMS (EI) calcd for $C_{14}H_{23}NO_4S$ 301.1348, found 301.1336. Anal. Calcd for $C_{14}H_{23}NO_4S$: C, 55.79; H, 7.69; N, 4.65; S, 10.64. Found: C, 55.68; H, 7.63, N, 4.64; S, 10.65. HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 5/95, 1.0 ml $min^{-1}$, 230 nm) of a racemic sample **(2*R**,3*R**,*R*$_S$*)-4b**: $t_R$ 11.3 and 13.3 min. Data for **(2*R*,3*R*,*S*$_S$)-4b**: $R_F$ (EtOAc/*n*-hexane, 1:1) = 0.3. HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 5/95, 1.0 ml $min^{-1}$, 230 nm): $t_R$ 13.9 min. $^1$H NMR (400 MHz): δ 7.10 (m, 1H, H-6), 4.51 (dd, 1H, *J*=6.5, 1.3 Hz, H-2), 4.16 (m, 2H, OCH$_2$), 2.99 (qd, 1H, *J*=7.1, 6.5 Hz, H-3), 1.73 (d, 3H, *J*=1.0 Hz, Me-5), 1.27 (d, 3H, *J*=7.1 Hz, Me-3), 1.27 (s, 9H, *t*-Bu), 1.24 (t, 3H, *J*=7.2 Hz, OCH$_2$C*H*$_3$). $^{13}$C NMR (100 MHz): δ 193.1 (C-4), 168.5 (*C*O$_2$Et), 143.1 (C-6), 118.8 (C-5), 61.5 (OCH$_2$), 60.1 (*C*Me$_3$), 59.3 (C-2), 42.1 (C-3), 22.1 (C*Me*$_3$), 14.01 (OCH$_2$*C*H$_3$), 12.7 (Me-5), 11.1 (Me-3). HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 5/95, 1.0 ml $min^{-1}$, 230 nm) of a racemic sample **(2*R**,3*R**,*S*$_S$*)-4b**: $t_R$ 12.7 and 13.9 min. Data for **(2*S*,3*R*,*S*$_S$)-4b**: $R_F$ (EtOAc/*n*-hexane, 1:1) = 0.25. HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 5/95, 1.0 ml $min^{-1}$, 230 nm): $t_R$ 17.8 min. $^1$H NMR (400 MHz): δ 7.33 (m, 1H, H-6), 4.22 (q, 2H, *J*=7.1 Hz, OCH$_2$), 4.12 (app. t, 1H, *J*=1.6 Hz, H-2), 3.08 (qd, 1H, *J*=7.5, 1.7 Hz, H-3), 1.74 (d, 3H, *J*=1.0 Hz, Me-5), 1.31 (d, 3H, *J*=7.5 Hz, Me-3), 1.27 (s, 9H, *t*-Bu), 1.26 (t, 3H, *J*=7.1 Hz, OCH$_2$C*H*$_3$). $^{13}$C NMR (100 MHz): δ 194.4 (C-4), 169.4 (*C*O$_2$Et), 139.1 (C-6), 111.8 (C-5), 65.2 (C-2), 62.5 (OCH$_2$), 60.1 (*C*Me$_3$), 43.1 (C-3), 22.1 (C*Me*$_3$), 17.5 (Me-3), 14.0 (OCH$_2$*C*H$_3$), 13.1 (Me-5). HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 5/95, 1.0 ml $min^{-1}$, 230 nm) of a racemic sample **(2*R**,3*S**,*R*$_S$*)-4b**: $t_R$ 15.1 and 17.7 min. Data for **(2*R*,3*S*,*S*$_S$)-4b**: $R_F$ (EtOAc/*n*-hexane, 1:1) = 0.25. HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 5/95, 1.0 ml $min^{-1}$, 230 nm): $t_R$ 15.2 min. $^1$H NMR (400 MHz): δ 7.12 (m, 1H, H-6), 4.32 (dd, 1H, *J*=2.3, 1.5 Hz, H-2), 4.18 (m, 1H, OC*H*H), 4.16 (m, 1H, OCH*H*), 2.98 (qd, 1H, *J*=7.4, 2.3 Hz, H-3), 1.72 (d, 3H, *J*=1.0 Hz, Me-5), 1.33 (d, 3H, *J*=7.4 Hz, Me-3), 1.27 (s, 9H, *t*-Bu), 1.25 (overlap, 3H, OCH$_2$C*H*$_3$). $^{13}$C NMR (100 MHz, selected signals): δ 169.4 (*C*O$_2$Et), 144.3 (C-6), 62.1 (OCH$_2$), 60.2 (C-2), 60.2 (*C*Me$_3$), 43.7 (C-3), 21.9 (C*Me*$_3$), 17.5 (Me-3), 13.5 (Me-5).

*4.2.3. Ethyl (2S,S$_S$)-1-(tert-butylsulfinyl)-4-methyl-1,2,3,6-tetrahydropyridine-2-carboxylate,* ***(2S,S$_S$)-4c*** *(tBu).*

The asymmetric aza-DA reaction between sulfinimine **2a** and isoprene (**3c**) according to the general procedure (described above) afforded only **(2*S*,*S*$_S$)-4c** (*t*Bu) as aza-DA adduct. The crude product was purified by flash chromatography (EtOAc/*n*-hexane, 1:5). Data for **(2*S*,*S*$_S$)-4c** (*t*Bu): viscous colorless oil. $R_F$ (EtOAc/*n*-hexane, 1:1) =

0.35. $[\alpha]_D^{rt}$ -36 (*c* 1.59, $CH_2Cl_2$). GC [CP Chirasil Dex CB, 80 °C (0 min) – 4 °C $min^{-1}$ – 190 °C (2 min)]: $t_R$ 18.0 min. $^1$H NMR (400 MHz): δ 5.34 (m, 1H, H-5), 4.39 (dd, 1H, *J*=6.5, 1.6 Hz, H-2), 4.20 (q, 2H, *J*=7.1, $OCH_2$), 3.82 (app. dp, 1H, *J*=18, 2.4 Hz, H-6), 3.60 (br. d, 1H, *J*=18 Hz, H-6), 2.45 (br. d, 1H, *J*= 17 Hz, H-3), 2.36 (br. d, 1H, *J*=17 Hz, H-3), 1.69 (s, 3H, Me-4), 1.27 (t, 3H, *J*=7.1 Hz, $OCH_2CH_3$), 1.17 (s, 9H, *t*-Bu). $^{13}$C NMR (100 MHz): δ 172.0 ($CO_2$Et), 131.3 (C-4), 117.6 (C-5), 61.2 ($OCH_2$), 59.0 ($CMe_3$), 51.8 (C-2), 45.1 (C-6), 32.0 (C-3), 23.5 (Me-4), 22.3 ($CMe_3$), 14.0 ($OCH_2CH_3$). IR (thin film, NaCl): 2958 (m), 2928 (m), 1736 (s), 1448 (m), 1362 (m), 1194 (s), 1077 (s), 917 (m) $cm^{-1}$. Anal. Calcd for $C_{13}H_{23}NO_3S$: C, 57.11; H, 8.48; N, 5.12. Found: C, 57.21; H, 8.62, N, 5.10. GC [CP Chirasil Dex CB, 80 °C (0 min) – 4 °C $min^{-1}$ – 190 °C (2 min)] of a racemic sample **(2*R**,*R*$_S$*)-4c** (*t*Bu): $t_R$ 17.8 and 17.9 min.

*4.2.4. Ethyl (2S,S$_S$)-4-methyl-1-(p-tolylsulfinyl)-1,2,3,6-tetrahydropyridine-2-carboxylate,* ***(2S,S$_S$)-4c*** *(pTol), ethyl (2R,S$_S$)-4-methyl-1-(p-tolylsulfinyl)-1,2,3,6-tetrahydro-pyridine-2-carboxylate,* ***(2R,S$_S$)-4c*** *(pTol), and 2-(p-tolyl-sulfinylmethyl)-1,3-butadiene,* ***5.***

The asymmetric aza-DA reaction between sulfinimine **2b** and isoprene (**3c**) according to the general procedure (described above) afforded an inseparable mixture of **(2*S*,*S*$_S$)-4c** (*p*Tol) and **(2*R*,*S*$_S$)-4c** (*p*Tol). In addition, various amounts of **5**, **6**[9] and **7**[10] were formed dependent on the reaction conditions applied (see Table 2, Entries 1 and 2). The mixture of **(2*S*,*S*$_S$)-4c** (*p*Tol) and **(2*R*,*S*$_S$)-4c** (*p*Tol) was purified by flash chromatography (EtOAc/*n*-hexane, 3:7) and obtained as a colorless oil. Anal. Calcd of the mixture $C_{16}H_{21}NO_3S$: C, 62.51; H, 6.89; N, 4.56; S, 10.43. Found: C, 62.31; H, 6.75; N, 4.46; S, 10.28. IR of the mixture (thin film, NaCl): 2923 (m), 2852 (m), 1738 (s), 1446 (m), 1380 (m), 1338 (m), 1279 (m), 1197 (s), 1093 (s), 1072 (s) $cm^{-1}$. Data for **(2*S*,*S*$_S$)-4c** (*p*Tol): $R_F$ (EtOAc/*n*-hexane, 3:7) = 0.2. HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 2/98, 1.0 ml $min^{-1}$, 230 nm): $t_R$ 35.8 min. $^1$H NMR (300 MHz): δ 7.57 (app. d, 2H, *J*=8.2 Hz, tolyl), 7.29 (app. d, 2H, *J*=8.2 Hz, tolyl), 5.35 (app. s, 1H, H-5), 4.27 (dd, 1H, *J*=6.5, 2.2 Hz, H-2), 4.15 (q, 2H, *J*=7.1 Hz, $OCH_2$), 3.99 (d, 1H, *J*=17.1 Hz, H-6), 3.56 (d, 1H, *J*=17.1 Hz, H-6), 2.65 – 2.38 (m, 2H, H-3), 2.41 (s, 3H, Ar$CH_3$), 1.70 (s, 3H, Me-4), 1.25 (t, 3H, *J*=7.1 Hz, $OCH_2CH_3$). $^{13}$C NMR (100 MHz): δ 171.0 ($CO_2$Et), 141.2 (Ar), 140.4 (Ar), 131.1 (C-4), 129.7 (Ar), 126.5 (Ar), 118.0 (C-5), 61.2 ($OCH_2$), 55.5 (C-2), 42.8 (C-6), 32.7 (C-3), 23.4 (Me-4), 21.3 (Ar$CH_3$, 14.1 ($OCH_2CH_3$). HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 2/98, 1.0 ml $min^{-1}$, 230 nm) of a racemic sample **(2*R**,*R*$_S$*)-4c** (*p*Tol): $t_R$ 35.8 and 44.9 min. Data for **(2*R*,*S*$_S$)-4c** (*p*Tol): $R_F$ (EtOAc/*n*-hexane, 3:7) = 0.2. HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 2/98, 1.0 ml $min^{-1}$, 230 nm): $t_R$ 47.5 min. $^1$H NMR (300 MHz): δ 7.64 (app. d, 2H, *J*=8.2 Hz, tolyl), 7.32 (app. d, 2H, *J*=8.2 Hz, tolyl), 5.31 (app. s, 1H, H-5), 4.47 (dd, 1H, *J*=6.1, 2.4 Hz, H-2), 4.22 (q, 2H, *J*=7.1 Hz, $OCH_2$), 3.56 (d, 1H, *J*=17.1 Hz, H-6), 3.38 (d, 1H, *J*=17.1, H-6), 2.65-2.38 (m, 2H, H-3), 2.42 (s, 3H, $ArCH_3$), 1.70 (s, 3H, Me-4), 1.30 (t, 3H, *J*=7.1 Hz, $OCH_2CH_3$). $^{13}$C NMR (100 MHz): δ 171.4 ($CO_2$Et), 141.22 (Ar), 140.7 (Ar), 130.6 (C-4), 129.7 (Ar), 126.5 (Ar), 118.1 (C-5), 61.3 ($OCH_2$), 57.9 (C-2), 39.4 (C-6), 32.8 (C-3), 23.4 (Me-4), 21.3 (Ar$CH_3$), 14.2 ($OCH_2CH_3$). HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 2/98, 1.0 ml $min^{-1}$, 230 nm) of a racemic sample **(2*R**,*S*$_S$*)-4c** (*p*Tol): $t_R$ 43.9 and 47.6 min. Data for **5**: $R_F$ (EtOAc/*n*-hexane, 3:7) = 0.12. $[\alpha]_D^{rt}$ -56.5 (*c* 0.4, $CHCl_3$). HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 10/90, 1.0 ml $min^{-1}$, 230 nm): 40% ee, $t_R$ 8.9 (minor) and 10.5 (major) min.$^1$H NMR (300 MHz): δ 7.51 (app d, 2H, *J*=8.1 Hz, tolyl), 7.31 (app d, 2H, *J*=8.1 Hz, tolyl), 6.37 (dd, 1H, *J*=17.6, 10.8 Hz, H-3), 5.33 (d, 1H, *J*=17.6 Hz, H-4), 5.23 (m, 1H, H-1), 5.19 (m, 1H, H-4), 5.00 (app s, 1H, H-1), 3.79 (dd, 1H, *J*=12.5, 0.8 Hz, $CH_2$), 3.56 (dd, 1H, *J*=12.5, 0.6 Hz, $CH_2$), 2.41 (s, 3H, Ar$CH_3$). $^{13}$C NMR (100 MHz): δ 141.7 (Ar), 140.7 (Ar), 137.0 (C-3), 135.7 (C-2), 129.7 (Ar), 124.4 (Ar), 122.7 (C-1), 115.4 (C-4), 61.5 ($CH_2$), 21.4 (Ar$CH_3$). IR (KBr tablet): 2932 (w), 1727 (m), 1445 (m), 1152 (m), 1085 (s), 1050 (s) $cm^{-1}$. HRMS (EI) calcd for $C_{12}H_{14}OS$ 206.0760 ($M^+$), found 206.0763.

*4.2.5. Ethyl (2S,S$_S$)-1-(tert-butylsulfinyl)-4,5-dimethyl-1,2,3,6-tetrahydropyridine-2-carboxylate,* ***(2S,S$_S$)-4d*** *(tBu).*

The asymmetric aza-DA reaction between sulfinimine **2a** and 2,3-dimethylbutadiene (**3d**) according to the general procedure (described above) afforded only **(2*S*,*S*$_S$)-4d** (*t*Bu) as aza-DA adduct. The crude product was purified by flash chromatography (EtOAc/*n*-hexane, 1:5). Data for **(2*S*,*S*$_S$)-4d** (*t*Bu): viscous colorless oil. $R_F$ (EtOAc/*n*-hexane, 1:1) = 0.45. $[\alpha]_D^{rt}$ -23.7 (*c* 1.0, $CHCl_3$). GC [CP Chirasil Dex CB, 110 °C (0 min) – 1 °C $min^{-1}$ – 150 °C (0 min) – 15 °C $min^{-1}$ – 180 (5 min)]: $t_R$ 32.0 min. $^1$H NMR (400 MHz): δ 4.32 (dd, 1H, *J*=6.5, 0.9 Hz, H-2), 4.18 (q, 2H, *J*=7.1 Hz, $OCH_2$), 3.71 (br. d, 1H, *J*=17 Hz, H-6), 3.40 (br. d, 1H, *J*=17 Hz, H-6), 2.47 (br. d, 1H, *J*=17 Hz, H-3), 2.32 (br. d, 1H, *J*=17 Hz, H-3), 1.63 (s, 3H, Me-4), 1.57 (s, 3H, Me-5), 1.26 (t, 3H, *J*=7.1 Hz, $OCH_2CH_3$), 1.17 (s, 9H, *t*-Bu). $^{13}$C NMR (100 MHz): δ 172.0 ($CO_2$Et), 123.1 (C-4), 122.5 (C-5), 61.1 ($OCH_2$), 58.9 ($CMe_3$), 52.4 (C-2), 49.4 (C-6), 33.0 (C-3), 22.4 ($CMe_3$), 18.9 (Me-4), 15.9 (Me-5), 14.2 ($OCH_2CH_3$). IR (thin film, NaCl): 2925 (m), 1736 (s), 1448 (m), 1362 (m), 1193 (s), 1135 (m), 1081 (s), 915 (m) $cm^{-1}$. MS (EI) *m/z* (% rel. int.): 287 (M, 1), 231 (49), 183 (34), 182 (87), 158 (20), 157 (22), 110 (100), 108 (45), 57 (34). Anal. Calcd for $C_{14}H_{25}NO_3S$: C, 58.50; H, 8.77; N, 4.87; S, 11.16. Found: C, 58.42; H, 8.77; N, 4.94; S, 11.10. GC [CP Chirasil Dex CB, 110 °C (0 min) – 1 °C $min^{-1}$ – 150 °C (0 min) – 15 °C $min^{-1}$ – 180 (5 min)] of a racemic sample **(2*R**,*R*$_S$*)-4d** (*t*Bu): $t_R$ 31.7 and 32.0 min.

*4.2.6. Ethyl (2S,S$_S$)-4,5-dimethyl-1-(p-tolylsulfinyl)-1,2,3,6-tetrahydropyridine-2-carboxylate,* ***(2S,S$_S$)-4d*** *(pTol), and ethyl (2R,S$_S$)-4,5-dimethyl-1-(p-tolylsulfinyl)-1,2,3,6-tetrahydro-pyridine-2-carboxylate,* ***(2R,S$_S$)-4d*** *(pTol).*

The asymmetric aza-DA reaction between sulfinimine **2b** and 2,3-dimethylbutadiene (**3d**) according to the general procedure (described above) afforded an inseparable mixture of **(2*S*,*S*$_S$)-4d** (*p*Tol) and **(2*R*,*S*$_S$)-4d** (*p*Tol). The mixture was purified by flash chromatography (EtOAc/*n*-

hexane, 15:85): colorless oil. Anal. Calcd of the mixture $C_{17}H_{23}NO_3S$: C, 63.52; H, 7.21; N, 4.36. Found: C, 63.51; H, 7.24; N, 4.16. IR of the mixture (thin film, NaCl): 2981 (m), 2917 (m), 2859 (m), 1738 (s), 1491 (m), 1446 (m), 1384 (m), 1285 (m), 1197 (s), 1135 (m), 1092 (s), 1071 (s), 1023 (s) $cm^{-1}$. Data for **(2*S*,*S*$_S$)-4d** (*p*Tol): $R_F$ (EtOAc/*n*-hexane, 1:1) = 0.40. HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 2/98, 1.0 ml $min^{-1}$): $t_R$ 33.2 min. $^1$H NMR (300 MHz): δ 7.57 (app. d, 2H, *J*=8.2 Hz, tolyl), 7.29 (app. d, 2H, *J*=8.2 Hz, tolyl), 4.21 (d, 1H, *J*=7.2 Hz, H-2), 4.13 (q, 2H, *J*=7.2 Hz, $OCH_2$), 3.90 (app. d, 1H, *J*=16.9 Hz, H-6), 3.38 (app. d, 1H, *J*=16.9 Hz, H-6), 2.63-2.36 (m, 2H, H-3), 2.41 (s, 3H, Ar$CH_3$), 1.64 (s, 3H, Me-4), 1.54 (s, 3H, Me-5), 1.23 (t, 3H, *J*=7.2 Hz, $OCH_2CH_3$). $^{13}$C NMR (100 MHz): δ 171.1 ($CO_2$Et), 141.1 (Ar), 140.6 (Ar), 129.6 (Ar), 126.5 (Ar), 122.9 (C-4), 122.8 (C-5), 61.0 ($OCH_2$), 55.5 (C-2), 47.0 (C-6), 33.9 (C-3), 21.3 (Ar$CH_3$), 18.8 (Me-5), 15.8 (Me-4), 14.1 ($OCH_2CH_3$). HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 2/98, 1.0 ml $min^{-1}$) of a racemic sample **(2*R**,*R*$_S$*)-4d** (*p*Tol): $t_R$ 33.3 and 37.2 min. Data for **(2*R*,*S*$_S$)-4d** (*p*Tol): $R_F$ (EtOAc/*n*-hexane, 1:1) = 0.40. HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 2/98, 1.0 ml $min^{-1}$, 230 nm): $t_R$ 31.5 min. $^1$H NMR (300 MHz): δ 7.65 (app. d, 2H, *J*=8.4 Hz, tolyl), 7.32 (app. d, 2H, *J*=8.4 Hz, tolyl), 4.41 (dd, 1H, *J*=6.3, 2.5 Hz, H-2), 4.22 (q, 2H, *J*=7.2 Hz, $OCH_2$), 3.38 (app. d, 1H, *J*=17 Hz, H-6), 3.25 (app. d, 1H, *J*=17 Hz, H-6), 2.63-2.36 (m, 2H, H-3), 2.42 (s, 3H, Ar$CH_3$), 1.64 (s, 3H, Me-4), 1.49 (s, 3H, Me-5), 1.29 (t, 3H, *J*=7.2 Hz, $OCH_2CH_3$). $^{13}$C NMR: δ 171.6 ($CO_2$Et), 141.1 (Ar), 140.3 (Ar), 129.5 (Ar), 126.5 (Ar), 123.0 (C-4), 122.6 (C-5), 61.2 ($OCH_2$), 58.2 (C-2), 43.2 (C-6), 33.8 (C-3), 21.3 (Ar$CH_3$), 18.8 (Me-4), 15.9 (Me-5), 14.1 ($OCH_2CH_3$). HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 2/98, 1.0 ml $min^{-1}$, 230 nm) of a racemic sample **(2*R**,*S*$_S$*)-4d** (*p*Tol): $t_R$ 31.5 and 42.5 min. **5d** and **6**.

*4.2.7. Ethyl (2S,6S,S$_S$)-1-(tert-butylsulfinyl)-6-methyl-1,2,3,6-tetrahydropyridine-2-carboxylate, **(2S,6S,S$_S$)-4e**, and ethyl (2S,6R,S$_S$)-1-(tert-butylsulfinyl)-6-methyl-1,2,3,6-tetra-hydropyridine-2-carboxylate, **(2S,6R,S$_S$)-4e**.*

The asymmetric aza-DA reaction between sulfinimine **2a** and (*E*)-1,3-pentadiene (**3e**) according to the general procedure afforded a mixture of **(2*S*,6*S*,*S*$_S$)-4e** and **(2*S*,6*R*,*S*$_S$)-4e** which were separated by flash chromatography (2 columns: first EtOAc/*n*-hexane, 1:1, and then $Et_2O$/*n*-pentane. 1:1). Data for **(2*S*,6*S*,*S*$_S$)-4e**: viscous colorless oil. $R_F$ (EtOAc/*n*-hexane, 1:1) = 0.4. $[\alpha]_D^n$ -50 (*c* 0.77, $CHCl_3$). HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 2/98, 1.0 ml $min^{-1}$, 230 nm): $t_R$ 12.0 min. $^1$H NMR (400 MHz): δ 5.84 (app. ddt, 1H, *J*=10.4, 6.4, 3.4 Hz, H-4), 5.59 (app. dtd, 1H, *J*=10.4, 3.0, 0.8 Hz, H-5), 4.51 (dd, 1H, *J*=6.8, 1.3 Hz, H-2), 4.19 (dq, 1H, *J*=10.6, 7.2 Hz, O$CH_2$), 4.17 (dq, 1H, *J*=10.6, 7.2 Hz, O$CH_2$), 3.98 (m, 1H, H-6), 2.54 (app. dd, 1H, *J*=17.2, 6.4 Hz, H-3), 2.35 (app. ddtd, 1H, *J*=17.2, 6.8, 3.1, 2.4 Hz, H-3), 1.28 (t, 3H, *J*=7.2 Hz, $OCH_2CH_3$), 1.25 (s, 9H, *t*-Bu), 1.24 (d, 3H, *J*=7.2 Hz, Me-6). $^{13}$C NMR (100 MHz): δ 173.0 ($CO_2$Et), 128.8 (C-5), 123.4 (C-4), 61.2 ($OCH_2$), 58.3 ($CMe_3$), 55.0 (C-6), 48.7 (C-2), 26.3 (C-3), 22.9 ($CMe_3$), 22.7 (Me-6), 14.1 ($OCH_2CH_3$). IR (thin film, NaCl): 3034 (w), 2979 (m), 2954 (m), 2931 (m), 1735 (s), 1456 (m), 1368 (m), 1283 (m), 1210 (m), 1189 (s), 1135 (m), 1103 (m), 1075 (s), 1040 (m), 970 (m) $cm^{-1}$. Anal. Calcd for $C_{13}H_{23}NO_3S$: C, 57.11; H, 8.48; N, 5.12; S, 11.73. Found: C, 57.05; H, 8.34; N, 5.06; S, 11.57. HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 2/98, 1.0 ml $min^{-1}$, 230 nm) of a racemic sample **(2*R**,6*R**,*R*$_S$*)-4e**: $t_R$ 10.2 and 12.1 min. Data for **(2*S*,6*R*,*S*$_S$)-4e**: viscous colorless oil. $R_F$ (EtOAc/*n*-hexane, 1:1) = 0.3. HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 2/98, 1.0 ml $min^{-1}$, 230 nm): $t_R$ 14.2 min. $^1$H NMR (400 MHz): δ 5.78 (dddd, 1H, *J*=10.2, 4.3, 3.5, 2.0 Hz, H-4), 5.64 (app. ddt, 1H, *J*=10.2, 3.0, 2.0 Hz, H-5), 4.28 (m, 1H, H-2), 4.24 (dq, 1H, *J*=10.8, 7.1 Hz, O$CH_2$), 4.18 (m, 1H, H-6), 4.16 (dq, 1H, *J*=10.8, 7.1 Hz, O$CH_2$), 2.62 (m, 1H, H-3), 2.39 (m, 1H, H-3), 1.35 (d, 3H, *J*=7.1 Hz, Me-6), 1.28 (t, 3H, *J*=7.1 Hz, $OCH_2CH_3$), 1.23 (s, 9H, *t*-Bu). $^{13}$C NMR (100 MHz, selected signals): δ 131.3 (C-5), 123.7 (C-4), 61.2 ($OCH_2$), 59.1 ($CMe_3$), 53.6 (C-2), 48.4 (C-6), 27.2 (C-3), 23.5 ($CMe_3$), 20.1 (Me-6), 14.2 ($OCH_2CH_3$). HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 2/98, 1.0 ml $min^{-1}$, 230 nm) of a racemic sample **(2*R**,6*S**,*R*$_S$*)-4e**: $t_R$ 14.4 and 17.2 min.

*4.2.8. Ethyl (2S,3R,6S,S$_S$)-1-(tert-butylsulfinyl)-3,6-dimethyl-1,2,3,6-tetrahydropyridine-2-carboxylate, **(2S,3R,6S,S$_S$)-4f**, and ethyl (2S,3S,6R,S$_S$)-1-(tert-butylsulfinyl)-3,6-dimethyl-1,2,3,6-tetrahydropyridine-2-carboxylate, **(2S,3S,6R,S$_S$)-4f**.*

The asymmetric aza-DA reaction between sulfinimine **2a** and (*E*,*E*)-2,4-hexadiene (**3f**) according to the general procedure afforded a mixture of **(2*S*,3*R*,6*S*,*S*$_S$)-4f** and **(2*S*,3*S*,6*R*,*S*$_S$)-4f** which were separated by flash chromatography (EtOAc/*n*-hexane, 1:5). Data for **(2*S*,3*R*,6*S*,*S*$_S$)-4f**: viscous colorless oil. $R_F$ (EtOAc/*n*-hexane, 1:1) = 0.4. $[\alpha]_D^n$ -87 (*c* 1.35, $CHCl_3$). HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 2/98, 1.0 ml $min^{-1}$, 230 nm): $t_R$ 10.6 min. $^1$H NMR (400 MHz): δ 5.59 (m, 2H, H-4 and H-5), 4.38 (d, 1H, *J*=6.3 Hz, H-2), 4.17 (dq, 1H, *J*=10.8, 7.1 Hz, $OCH_2$), 4.14 (dq, 1H, *J*=10.8, 7.1 Hz, $OCH_2$), 4.03 (app. qd, 1H, *J*=7.1, 3.1 Hz, H-6), 2.58 (m, 1H, H-3), 1.30 (d, 3H, *J*=7.1 Hz, Me-6), 1.27 (t, 3H, *J*=7.1 Hz, $OCH_2CH_3$), 1.24 (s, 9H, *t*-Bu), 1.07 (d, 3H, *J*=7.5 Hz, Me-3). $^{13}$C NMR (100 MHz): δ 170.9 ($CO_2$Et), 128.3 (C-4), 128.1 (C-5), 60.5 ($OCH_2$), 58.1 ($CMe_3$), 54.7 (C-6), 53.0 (C-2), 31.8 (C-3), 23.4 ($CMe_3$), 23.0 (Me-6), 17.3 (Me-3), 14.2 ($OCH_2CH_3$). IR (thin film, NaCl): 3029 (w), 2972 (m), 2933 (m), 1744 (s), 1458 (m), 1367 (m), 1156 (s), 1073 (s), 1029 (m), 979 (m) $cm^{-1}$. MS (ESI) *m*/*z* (% rel. int): 310 ($M^+$+Na, 16), 288 ($M^+$+1, 2), 185 (10), 184 (100). HRMS (ESI) calcd for $C_{14}H_{25}NNaO_3S$ 310.1447 ($M^+$+Na), found 310.1447. HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 2/98, 1.0 ml $min^{-1}$, 230 nm) of a racemic sample **(2*R**,3*S**,6*R**,*R*$_S$*)-4f**: $t_R$ 8.7 and 10.6 min. Data for **(2*S*,3*S*,6*R*,*S*$_S$)-4f**: viscous colorless oil. $R_F$ (EtOAc/*n*-hexane, 1:1) = 0.3. HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 2/98, 1.0 ml $min^{-1}$, 230 nm): $t_R$ 11.2 min. $^1$H NMR (400 MHz): δ 5.62 (m, 1H, H-4), 5.60 (m, 1H, H-5), 4.24 (m, 1H, H-6), 4.12 (app. q, 2H, *J*=7.1 Hz, $OCH_2$), 3.93 (br. d, 1H, *J*=5.4 Hz, H-2), 2.79 (m, 1H, H-3), 1.37 (d, 3H, *J*=6.9 Hz, Me-6), 1.26 (t, 3H, *J*=7.1 Hz, $OCH_2CH_3$), 1.18

(s, 9H, *t*-Bu), 1.08 (t, 3H, *J*=6.9 Hz, Me-3). $^{13}$C NMR (100 MHz): δ 171.2 (*C*$O_2$Et), 60.4 ($OCH_2$), 58.9 (C-2), 48.4 (C-6), 20.2 (Me-6), 19.2 (Me-3), 14.1 ($OCH_2CH_3$). HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 2/98, 1.0 ml min$^{-1}$, 230 nm) of a racemic sample **(2*R**,3*R**,6*S**,*R*$_S$*)-4f**: $t_R$ 11.2 and 15.9 min.

*4.2.9. Ethyl (1S,3S,4R,S$_S$)-2-(tert-butylsulfinyl)-2-aza-bicyclo[2.2.1]hept-5-ene-3-carboxylate, **(1S,3S,4R,S$_S$)-4g** (tBu), and ethyl (1R,3S,4S,S$_S$)-2-(tert-butylsulfinyl)-2-azabicyclo[2.2.1]-hept-5-ene-3-carboxylate, **(1R,3S,4S,S$_S$)-4g** (tBu).*

The asymmetric aza-DA reaction between sulfinimine **2a** and cyclopentadiene (**3g**) according to the general procedure afforded either **(1*S*,3*S*,4*R*,*S*$_S$)-4g** (*t*Bu) pure or as a mixture of **(1*S*,3*S*,4*R*,*S*$_S$)-4g** (*t*Bu) and **(1*R*,3*S*,4*S*,*S*$_S$)-4g** (*t*Bu). In addition various amounts of **8**, **9** and **10** were formed dependent on the reaction conditions applied (see Table 2, entries 3, 4 and 5). The crude product was purified by flash chromatography (EtOAc/*n*-hexane, 1:5). The mixture of **(1*S*,3*S*,4*R*,*S*$_S$)-4g** (*t*Bu) and **1*R*,3*S*,4*S*,*S*$_S$)-4g** (*t*Bu) was inseparable. Anal. Calcd of the mixture $C_{13}H_{21}NO_3S$: C, 57.54; H, 7.80; N, 5.16; S, 11.82. Found: C, 57.25; H, 7.64; N, 5.20; S, 12.10. Data for **(1*S*,3*S*,4*R*,*S*$_S$)-4g** (*t*Bu): viscous colorless oil. $R_F$ (EtOAc/*n*-hexane, 1:1) = 0.35. $[\alpha]_D^{rt}$-134 (*c* 1.17, $CHCl_3$). HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 2/98, 1.0 ml min$^{-1}$, 230 nm): $t_R$ 18.2 min. $^1$H NMR (400 MHz): δ 6.50 (dd, 1H, *J*=5.6, 2.1 Hz, H-6), 6.35 (m, 1H, H-5), 4.28 (m, 1H, H-1), 4.21 (dq, 1H, *J*=10.9, 7.1 Hz, $OCH_2$), 4.18 (dq, 1H, *J*=10.9, 7.1 Hz, $OCH_2$), 3.62 (s, 1H, H-3), 3.32 (m, 1H, H-4), 2.10 (ddd, 1H, *J*=8.7, 1.9, 1.5 Hz, H-7*syn*), 1.35 (app. d, 1H, *J*=8.7 Hz, H-7*anti*), 1.28 (t, 3H, *J*=7.1 Hz, $OCH_2CH_3$), 1.14 (s, 9H, *t*-Bu). $^{13}$C NMR (100 MHz): δ 173.0 (*C*$O_2$Et), 136.5 (C-5), 135.2 (C-6), 68.5 (C-1), 61.0 ($OCH_2$), 57.4 (*C*Me$_3$), 53.5 (C-3), 50.5 (C-4), 45.1 (C-7), 22.7 (C*Me$_3$*), 14.2 ($OCH_2CH_3$). IR (thin film, NaCl): 3067 (w), 2957 (m), 1743 (s), 1448 (m), 1362 (m), 1243 (m), 1188 (s), 1081 (m), 1061 (m), 963 (m), 875 (s) cm$^{-1}$. HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 2/98, 1.0 ml min$^{-1}$, 230 nm) of a racemic sample **(1*R**,3*R**,4*S**,*R*$_S$*)-4g** (*t*Bu): $t_R$ 18.3 and 25.7 min. Data for **(1*R*,3*S*,4*S*,*S*$_S$)-4g** (*t*Bu): viscous colorless oil. $R_F$ (EtOAc/*n*-hexane, 1:1) = 0.35. HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 2/98, 1.0 ml min$^{-1}$, 230 nm): $t_R$ 20.9 min. $^1$H NMR (400 MHz): δ 6.45 (app. dd, 1H, *J*=5.6, 3.0 Hz, H-6), 6.20 (app. dd, 1H, *J*=5.6, 2.8 Hz, H-5), 4.47 (d, 1H, *J*=3.5 Hz, H-3), 4.43 (m, 1H, H-1), 4.13 (q, 2H, *J*=7.1 Hz, $OCH_2$), 3.49 (m, 1H, H-4), 1.90 (app. dt, 1H, *J*=8.5, 1.5 Hz, H-7*syn*), 1.55 (app. d, 1H, *J*=8.5 Hz, H-7*anti*), 1.25 (t, 3H, *J*=7.1 Hz, $OCH_2CH_3$), 1.17 (s, 9H, *t*-Bu). $^{13}$C NMR (100 MHz): δ 172.1 (*C*$O_2$Et), 137.5 (C-5), 136.6 (C-6), 73.7 (C-1), 60.8 ($OCH_2$), 57.7 (*C*Me$_3$), 52.7 (C-3), 48.7 (C-7), 22.9 (C*Me$_3$*), 14.3 ($OCH_2CH_3$). HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 2/98, 1.0 ml min$^{-1}$, 230 nm) of a racemic sample **(1*R**,3*S**,4*S**,*S*$_S$*)-4g** (*t*Bu): $t_R$ 16.7 and 21.0 min.

*4.2.10. Ethyl (3S,3aS,6aS,R$_S$)-1-oxo-3,3a,4,6a-tetrahydro-2H-cyclopenta[d]isothiazole-3-carboxylate **(8)** and ethyl (3S,3aR,6aR,R$_S$)-1-oxo-3,3a,4,6a-tetrahydro-2H-cyclopenta[d]isothiazole-3-carboxylate **(9)**.*

The general procedure for the asymmetric aza-DA reaction was followed reacting **2a** with **3g** using $BF_3{\cdot}OEt_2$ as the Lewis acid and 17.5 h reaction time at room temperature (Table 2, entry 5). Flash chromatography (EtOAc/*n*-hexane, 1:1) purification of the crude product, after work up, provided an inseparable mixture (viscous oil) of **8** and **9** (ratio 9.5:1, 22.4 mg, 42% total yield). Compound **8** was further purified by recrystallization from EtOAc/*n*-hexane, providing colorless crystals (9.3 mg, 17%). Data for **8**: $R_F$ (acetone) = 0.5. GC [CP Chirasil Dex CB, 80 °C (0 min) – 4 °C min$^{-1}$ – 190 °C (2 min)]: $t_R$ 24.2 min. $^1$H NMR (400 MHz): δ 5.92 (app. dq, 1H, *J*=5.8, 2.0 Hz, H-5), 5.85 (app. dq, 1H, *J*=5.8, 2.3 Hz, H-6), 5.12 (dd, 1H, *J*=5.8, 1.0 Hz, H-3), 4.68 (br. s, 1H, NH), 4.32 (dq, 1H, *J*=10.8, 7.1 Hz, $OCH_2$), 4.25 (dq, 1H, *J*=10.8, 7.1 Hz, $OCH_2$), 4.17 (m, 1H, H-6a), 3.57 (app. ddtd, 1H, *J*=9.1, 7.5, 5.7, 1.2 Hz, H-3a), 2.61 (app. ddtd, 1H, *J* = 17.6, 9.1, 2.2, 0.9 Hz, H-4), 2.18 (app. dddt, 1H, *J*=17.6, 5.6, 3.3, 2.4 Hz, H-4'), 1.32 (t, 3H, *J*=7.1 Hz, $OCH_2CH_3$). $^{13}$C NMR (100 MHz): δ 170.0 (*C*$O_2$Et), 137.9 (C-5), 123.9 (C-6), 85.6 (C-6a), 64.5 (C-3), 61.7 ($OCH_2$), 41.8 (C-3a), 35.9 (C-4), 14.24 ($OCH_2CH_3$). IR (thin film, NaCl): 3447 (br), 3135 (br), 1733 (s), 1379 (m), 1265 (m), 1255 (m), 1243 (m), 1218 (m), 1107 (m), 1037 (s) cm$^{-1}$. MS (ESI) *m/z* (% rel. int.): 238 ($M^+$+Na, 100), 216 ($M^+$+1, 26). HRMS (ESI) calcd for $C_9H_{14}NO_3S$ 216.0689 ($M^+$+1), found 216.0684. HRMS (ESI) calcd for $C_9H_{13}NNaO_3S$ 238.0508 ($M^+$+Na), found 238.0509. The absolute configuration of **8** was corroborated by X-ray crystallographic analysis.[16] GC [CP Chirasil Dex CB, 80 °C (0 min) – 4 °C min$^{-1}$ – 190 °C (2 min)] of racemic **8**: $t_R$ 23.6 and 24.4 min. Data for **9**: GC [CP Chirasil Dex CB, 80 °C (0 min) – 4 °C min$^{-1}$ – 190 °C (2 min)]: $t_R$ 23.4 min. $^1$H NMR (400 MHz): δ 6.14 (app. dq, 1H, *J*=5.8, 1.9 Hz, H-5), 5.65 (app. dq, 1H, *J*=5.8, 2.3 Hz, H-6), 4.63 (m, 1H, H-6a), 4.60 (m, 1H, NH), 4.47 (dd, 1H, *J*=8.0, 1.8 Hz, H-3), 4.26 (overlap, 2H, $OCH_2$), 3.27 (dddd, 1H, *J*=9.6, 8.9, 8.0, 4.0 Hz, H-3a), 2.76 (app. ddtd, 1H, *J*=17.6, 8.9, 2.4, 1.6 Hz, H-4), 2.56 (overlap, 1H, H-4'), 1.32 (overlap, 3H, $OCH_2CH_3$). $^{13}$C NMR (100 MHz): δ 171.1 (*C*$O_2$Et), 137.6 (C-5), 123.4 (C-6), 78.7 (C-6a), 67.1 (C-3), 61.9 ($OCH_2$), 44.8 (C-3a), 37.3 (C-4), 14.17 ($OCH_2CH_3$).

*4.2.11. Ethyl (3S,3aS,6aS,R$_S$)-1-oxo-3,3a,4,6a-tetrahydro-2H-cyclopenta[d]isothiazole-3-carboxylate **(8)** and 2-methyl-N-(2-oxo-3,3a,4,6a-tetrahydro-2H-cyclopenta[b]-furan-3-yl)propane-2-sulfinamide **(10)**.*

The asymmetric aza-DA reaction between sulfinimine **2a** and **3g** using TMSOTf as the Lewis acid at -78 ºC for 15.5 h (Table 2, entry 3) afforded a mixture of **8** and **10** after flash chromatography (EtOAc/*n*-hexane, 1:1). Further purification by flash chromatography (acetone/pentane, 1:4) allowed separation of **8** (9.0 mg, 17%) and **10** (6.6 mg, 11%). For analytical data of **8** see Chapter 4.2.10. Data for **10**: Colorless viscous oil, $R_F$ (acetone) = 0.6. GC [CP Chirasil Dex CB, 80 °C (0 min) – 3 °C min$^{-1}$ – 190 °C (2 min)]: $t_R$ 29.67 min. $^1$H NMR (400 MHz): δ 6.10 (m, 1H,

H-5), 5.91 (app. ddt, 1H, *J*=5.8, 2.6, 1.8 Hz, H-6), 5.59 (app. dp, 1H, *J*=7.8, 1.6, H-6a), 3.95 (dd, 1H, *J*=7.7, 2.0 Hz, H-3), 3.92 (br s, 1H, NH), 3.10 (app. qd, 1H, *J*=7.7, 1.5 Hz, H-3a), 2.81 (app. dddt, 1H, *J*=17.4, 7.1, 2.5, 2.1 Hz, H-4), 2.72 (m, 1H, H-4'), 1.27 (s, 9H, *t*-Bu). $^{13}$C NMR (100 MHz): δ 175.2 (C-2), 136.5 (C-5), 129.2 (C-6), 88.0 (C-6a), 58.4 (C-3), 56.2 (*C*Me$_3$), 44.1 (C-3a), 37.3 (C-4), 22.4 (C*Me$_3$*). IR (thin film, NaCl): 3442 (br), 3279 (br), 1774 (s), 1641 (m), 1365 (m), 1134 (m), 1042 (s), 991 (m) cm$^{-1}$. MS (ESI) *m/z* (% rel. int.): 266 ($M^+$+Na, 18), 244 ($M^+$+1, 100), HRMS (ESI) calcd for $C_{11}H_{18}NO_3S$ 244.1002 ($M^+$+1), found 244.1001. HRMS (ESI) calcd for $C_{11}H_{17}NNaO_3S$ 266.0821 ($M^+$+Na), found 266.0819. GC [CP Chirasil Dex CB, 80 °C (0 min) – 3 °C min$^{-1}$ – 190 °C (2 min)] of racemic **10**: $t_R$ 29.66 and 29.81 min.

*4.2.12. Ethyl (1S,3S,4R,S$_S$)-2-(p-tolylsulfinyl)-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate,* ***(1S,3S,4R,S$_S$)-4g*** *(pTol), ethyl (1R,3S,4S,S$_S$)-2-(p-tolylsulfinyl)-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate,* ***(1R,3S,4S,S$_S$)-4g*** *(pTol) and ethyl (1R,3R,4S,S$_S$)-2-(p-tolylsulfinyl)-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate,* ***(1R,3R,4S,S$_S$)-4g*** *(pTol).*

The asymmetric aza-DA reaction between sulfinimine **2b** and cyclopentadiene (**3g**) according to the general procedure yielded mixtures of **(1*S*,3*S*,4*R*,*S*$_S$)-4g** (*p*Tol), **(1*R*,3*S*,4*S*,*S*$_S$)-4g** (*p*Tol) and **(1*R*,3*R*,4*S*,*S*$_S$)-4g** (*p*Tol) dependent on the reaction conditions applied (see Table 1, entries 13 and 14). Separation of the diastereomers by flash chromatography (EtOAc/*n*-hexane, 15:85 to 25:75) did not succeed, but recrystallization of the mixture from 10% *i*-PrOH in *n*-hexane afforded the major isomer **(1*S*,3*S*,4*R*,*S*$_S$)-4g** (*p*Tol) as a white solid (97% de). Data for **(1*S*,3*S*,4*R*,*S*$_S$)-4g** (*p*Tol): $R_F$ (EtOAc/*n*-hexane, 25:75) = 0.1. Mp = 78 – 79 °C (from 10% *i*-PrOH in *n*-hexane). $[\alpha]_D^{rt}$ +20.7 (*c* 1.07, $CH_2Cl_2$). $^1$H NMR (400 MHz): δ 7.53 (app. d, 2H, *J*=8 Hz, tolyl), 7.23 (app. d, 2H, *J*=8 Hz, tolyl), 6.53 (dd, 1H, *J*=5.2, 2.2 Hz, H-6), 6.35 (m, 1H, H-5), 4.62 (m, 1H, H-1), 3.69 (dq, 1H, *J*=10.8, 7.1 Hz, OCH$_2$), 3.62 (dq, 1H, *J*=10.8, 7.1 Hz, OCH$_2$), 3.42 (s, 1H, H-3), 3.13 (br s, 1H, H-4), 2.36 (s, 3H, ArC*H$_3$*), 2.22 (br d, 1H, *J*=8.6 Hz, H-7), 1.45 (br d, 1H, *J*=8.6 Hz, H-7), 0.94 (t, 3H, *J*=7.1 Hz, OCH$_2$C*H$_3$*). $^{13}$C NMR (100 MHz): δ 171.7 (*C*O$_2$Et), 141.1 (Ar), 140.7 (Ar), 135.5 (C-6), 135.3 (C-5), 129.03 (Ar), 125.77 (Ar), 67.2 (C-1), 60.6 (OCH$_2$), 53.0 (C-3), 49.7 (C-4), 46.2 (C-7), 21.2 (Ar*C*H$_3$), 13.7 (OCH$_2$*C*H$_3$). IR (KBr tablet): 2990 (m), 2959 (m), 2929 (m), 1724 (s), 1474 (m), 1449 (m), 1370 (m), 1252 (m), 1234 (m), 1191 (s), 1167 (s), 1094 (s), 1069 (s), 1053 (s), 1024 (m), 964 (s) cm$^{-1}$. MS (EI) *m/z* (% rel. int): 305 ($M^+$, 3), 257 (7), 240 (12), 232 (11), 166 (11), 141 (5), 140 (15), 139 (100), 138 (3), 123 86), 120 (5), 94 (5), 93 84), 92 (17), 91 (16), 77 (5), 67 (7), 66 (22), 65 (15). Anal. Calcd for $C_{16}H_{19}NO_3S$: C, 62.93; H, 6.27; N, 4.59; S, 10.50. Found: C, 62.97; H, 6.32, N, 4.35; S, 10.22. Data for **(1*R*,3*S*,4*S*,*S*$_S$)-4g** (*p*Tol): $^1$H NMR (400 MHz): δ 7.55 (app. d, 2H, *J*=8.3 Hz, tolyl), 7.21 (overlap, 2H, tolyl), 6.63 (dd, 1H, *J*=5.5, 3.0 Hz, H-6), 6.16 (dd, 1H, *J*=5.5, 2.6 Hz, H-5), 4.62 (overlap, 1H, H-1), 4.32 (d, 1H, *J*=3.2 H, H-3), 3.7-3.6 (overlap, 2H, OCH$_2$), 3.42 (overlap, 1H, H-4), 2.35 (s, 3H, ArC*H$_3$*), 2.06 (br d, 1H, *J*=8.4 Hz, H-7), 1.63 (br d, 1H, *J*=8.4 Hz, H-7), 0.92 (overlap, 3H, OCH$_2$C*H$_3$*). $^{13}$C NMR (100 MHz, selected signals): δ 137.8 (C-6), 137.1 (C-5), 129.01 (Ar), 125.82 (Ar), 69.8 (C-1), 60.3 (O*C*H$_2$), 52.3 (C-3), 49.0 (C-7), 47.3 (C-4), 14.2 (OCH$_2$*C*H$_3$). Data for **(1*R*,3*R*,4*S*,*S*$_S$)-4g** (*p*Tol): $^1$H NMR (400 MHz): δ 7.72 (app. d, 2H, *J*=8 Hz, tolyl), 7.33 (app. d, 2H, *J*=8 Hz, tolyl), 6.44 (dd, 1H, *J*=5.6, 2.4 Hz, H-6), 6.32 (m, 1H, H-5), 4.29 (q, 2H, *J*=7.1 Hz, OCH$_2$), 3.92 (m, 1H, H-1), 3.74 (s, 1H, H-3), 3.42 (overlap, 1H, H-4), 2.43 (s, 3H, ArC*H$_3$*), 1.75 (br d, 1H, *J*=8.9 Hz, H-7), 1.35 (t, 3H, *J*=7.1 Hz, OCH$_2$C*H$_3$*), 1.32 (overlap, 1H, H-7). $^{13}$C NMR (100 MHz): δ 171.9 (*C*O$_2$Et), 141.2 (Ar), 141.0 (Ar), 138.0 (C-6), 133.8 (C-5), 129.5 (Ar), 126.2 (Ar), 62.0 (C-1), 61.5 (C-3), 61.3 (O*C*H$_2$), 49.2 (C-4), 45.8 (C-7), 21.3 (Ar*C*H$_3$), 14.2 (OCH$_2$*C*H$_3$).

*4.2.13. Ethyl (1S,3S,4R,S$_S$)-2-(tert-butylsulfinyl)-2-azabicyclo[2.2.2]oct-5-ene-3-carboxylate,* ***(1S,3S,4R,S$_S$)-4h****, and ethyl (1R,3S,4S,S$_S$)-2-(tert-butylsulfinyl)-2-azabicyclo[2.2.2]oct-5-ene-3-carboxylate,* ***(1R,3S,4S,S$_S$)-4h****.*

The asymmetric aza-DA reaction between sulfinimine **2a** and 1,3-cyclohexadiene (**3h**) provided a inseparable mixture of **(1*S*,3*S*,4*R*,*S*$_S$)-4h** and **(1*R*,3*S*,4*S*,*S*$_S$)-4h**. The crude mixture was purified by flash chromatography (EtOAc/*n*-hexane, 1:5) yielding a viscous colorless oil. Analytical data of the mixture: IR (thin film, NaCl): 3053 (w), 2955 (m), 2929 (m), 1745 (s), 1461 (m), 1363 (m), 1258 (m), 1176 (s), 1085 (s), 1061 (m), 892 (m) cm$^{-1}$. MS (EI) *m/z* (% rel. int.): 229 (32), 164 (22), 149 (58), 108 (22), 80 (100), 79 (40), 57 (32). MS (ESI) *m/z* (% rel. int.): 308 ($M^+$+Na, 50), 183 (10), 182 (100). HRMS (ESI) calcd for $C_{14}H_{23}NNaO_3S$ 308.1291 ($M^+$+Na), found 308.1288. Anal. Calcd for $C_{14}H_{23}NO_3S$: C, 58.92; H, 8.12; N, 4.91; S, 11.24. Found: C, 59.02; H, 8.12; N, 4.79; S, 11.06. Data for **(1*S*,3*S*,4*R*,*S*$_S$)-4h**: $R_F$ (EtOAc/*n*-hexane, 1:1) = 0.35. HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 2/98, 1.0 ml min$^{-1}$, 230 nm): $t_R$ 18.3 min. $^1$H NMR (400 MHz): δ 6.52 (ddd, 1H, *J*=8.2, 5.1, 1.5 Hz, H-6), 6.47 (ddd, 1H, *J*=8.2, 6.7, 1.6 Hz, H-5), 4.20 (dq, 1H, *J*=10.8, 7.1, OCH$_2$), 4.18 (dq, 1H, *J*=10.8, 7.1 Hz, OCH$_2$), 4.03 (dd, 1H, *J*=3.3, 1.6 Hz, H-3), 3.92 (m, 1H, H-1), 3.02 (m, 1H, H-4), 2.20 (dddd, 1H, *J*=12.9, 9.6, 5.6, 2.7 Hz, H-7*syn*), 1.63 (app. ddt, 1H, *J*=12.6, 9.6, 2.9 Hz, H-8*syn*), 1.38 (m, 1H, H-7*anti*), 1.28 (t, 3H, *J*=7.1 Hz, OCH$_2$C*H$_3$*), 1.12 (s, 9H, *t*-Bu), 1.09 (m, 1H, H-8*anti*). $^{13}$C NMR (100 MHz): δ 127.2 (*C*O$_2$Et), 134.6 (C-5), 133.0 (C-6), 60.8 (OCH$_2$), 57.5 (*C*Me$_3$), 54.8 (C-1), 52.7 (C-3), 33.8 (C-4), 24.3 (C-7), 22.4 (C*Me$_3$*), 20.5 (C-8), 14.3 (OCH$_2$*C*H$_3$). HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 2/98, 1.0 ml min$^{-1}$, 230 nm) of a racemic sample **(1*R**,3*R**,4*S**,*R*$_S$*)-4h**: $t_R$ 18.3 and 20.2 min. Data for **(1*R*,3*S*,4*S*,*S*$_S$)-4h**: $R_F$ (EtOAc/*n*-hexane, 1:1) = 0.35. HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 2/98, 1.0 ml min$^{-1}$, 230 nm): $t_R$ 15.5 min. $^1$H NMR (400 MHz): δ 6.56 (ddd, 1H, *J*= 8.1, 6.7, 1.9 Hz, H-6), 6.19 (app. t, 1H, *J*=7 Hz, H-5), 4.26 (d, 1H, *J*=2.9 Hz, H-3), 4.11 (q, 2H, *J*=7.1 Hz, OCH$_2$), 4.06 (m, 1H, H-1), 3.10 (m, 1H, H-4), 2.28 (dddd, 1H, *J*=13, 9, 4, 3 Hz, H-7*syn*), 1.74 (dddd, 1H, *J*=13, 9, 5, 2 Hz, H-8*syn*), 1.39 (m, 1H, H-8*anti*), 1.26 (m, 1H, H-7*anti*), 1.23 (t, 3H, *J*=7.1 Hz, OCH$_2$C*H$_3$*), 1.14 (s, 9H, *t*-Bu). $^{13}$C NMR (100 MHz): δ 172.3 (*C*O$_2$Et), 134.3 (C-6), 131.6 (C-5),

60.7 ($OCH_2$), 57.3 ($CMe_3$), 54.3 (C-1), 53.1 (C-3), 34.4 (C-4), 26.0 (C-7), 22.8 ($CMe_3$), 20.4 (C-8), 14.2 ($OCH_2CH_3$). HPLC (Chiralpak AD, *i*-PrOH/*n*-hexane, 2/98, 1.0 ml $min^{-1}$, 230 nm) of a racemic sample **(1*R**,3*S**,4*S**,$S_S$*)-4h**: $t_R$ 14.0 and 15.5 min.

*4.3. Chemical derivatization of the aza-DA products.*

*4.3.1. Ethyl (2S)-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate, **(2S)-11a**.*

Diastereomerically pure **(2*S*,$S_S$)-4a** (7.4 mg, 0.027 mmol) was dissolved in MeOH (2mL) and cooled to 0 °C. Aqueous HCl (conc., ~20 equiv) was added and the resultant solution stirred at 0 °C for 5 h before neutralization with phosphate buffer (pH 7, 1.5 mL). The mixture was extracted with $CH_2Cl_2$ (4 x 4 mL) and the combined organic layer was dried ($MgSO_4$). The solution was filtered, concentrated and the residue purified by flash chromatography (EtOAc), providing **(2*S*)-11a** (3.9 mg, 85%) as a white solid. Data for **(2*S*)-11a**: $[\alpha]_D^{rt}$ + 276 (*c* 0.39, $CHCl_3$). GC [CP Chirasil Dex CB, 110 °C (0 min) – 2 °C $min^{-1}$ – 180 °C (2 min)]: >99% ee, $t_R$ 18.1. $^1$H NMR (400 MHz): δ 7.22 (ddd, 1H, *J*=7.5, 6.3, 0.5 Hz, H-6), 5.41 (br. s, 1H, NH), 5.09 (app. d, 1H, *J*=7.5 Hz, H-5), 4.34 (ddd, 1H, *J*=12.8, 6.0, 1.4 Hz, H-2), 4.28 (dq, 1H, *J*=10.7, 7.1 Hz, $OCH_2$), 4.26 (dq, 1H, *J*=10.7, 7.1 Hz, $OCH_2$), 2.78 (app. ddt, 1H, *J*=16.4, 6.0, 0.9 Hz, H-3), 2.71 (dd, 1H, *J*=16.4, 12.8 Hz, H-3), 1.31 (t, 3H, *J*=7.1 Hz, $OCH_2CH_3$). The $^1$H NMR data is compatible with data reported for the racemic **(2*R**)-11a**.[22] GC [CP Chirasil Dex CB, 110 °C (0 min) – 2 °C $min^{-1}$ – 180 °C (2 min)] of racemic **(2*R**)-11a**: $t_R$ 18.1 and 18.7 min.

*4.3.2. Ethyl (S)-4-methyl-1,2,3,6-tetrahydropyridine-2-carboxylate **(2S)-11c**.*

The aza-DA product **(2*S*,$S_S$)-4c** (*t*Bu) was prepared according to the general procedure (Section 4.2) using TMSOTf (10 equiv) as the Lewis acid and a large excess of isoprene (**3c**, 20 equiv.) at -78 °C for 19 h. The crude product was dissolved in MeOH (3 mL), added aqueous HCl (conc., ~5 mmol) and stirred at room temperature for 18 h. The solution was concentrated, added water (5 mL), aqueous HCl (conc., 1 drop) and washed with diethyl ether (9 x 5 mL) to remove impurities. The aqueous phase was basified with $K_2CO_3$ and extracted with diethyl ether (6 x 5 mL). The combined organic phases from the latter extractions were dried ($MgSO_4$), filtered and concentrated to provide **(2*S*)-11c** (16.7 mg, 39% yield from sulfinimine **1a**) as a colorless viscous oil. Data for **(2*S*)-11c**: $[\alpha]_D^{rt}$ -83 (*c* 0.2, $CHCl_3$). GC [CP Chirasil Dex CB, 80 °C (0 min) – 1 °C $min^{-1}$ – 110 °C (0 min) – 20 °C $min^{-1}$ – 180 (3 min)]: >99% ee, $t_R$ 13.1 min. $^1$H NMR (400 MHz): δ 5.43 (m, 1H, H-5), 4.20 (q, 2H, *J*=7.2 Hz, $OCH_2$), 3.56 (dd, 1H, *J*=8.2, 6.1 Hz, H-2), 3.42 (m, 1H, H-6), 3.38 (m, 1H, H-6), 2.22 (m, 1H, H-3), 2.20 (m, 1H, H-3), 1.70 (m, 3H, Me-4), 1.29 (t, 3H, *J*=7.2 Hz, $OCH_2CH_3$). $^{13}$C NMR (100 MHz): δ 173.4 ($CO_2Et$), 131.5 (C-4), 120.1 (C-5), 60.9 ($OCH_2$), 55.3 (C-2), 44.2 (C-6), 32.7 (C-3), 23.3 (Me-4), 14.2 ($OCH_2CH_3$). IR (thin film, NaCl): 3346 (br), 2925 (m), 1736 (s), 1448 (m), 1376 (m), 1181 (s), 1035 (m) $cm^{-1}$. MS (EI) *m/z* (rel. int.): 169 ($M^+$, 8), 148 (20), 96 (100), 94 (24). MS (ESI) *m/z* (% rel. int.): 170 ($M^+$+1, 100). HRMS (ESI) calcd for $C_9H_{16}NO_2$ 170.1176 ($M^+$+1), found 170.1178. GC [CP Chirasil Dex CB, 80 °C (0 min) – 1 °C $min^{-1}$ – 110 °C (0 min) – 20 °C $min^{-1}$ – 180 (3 min)] of racemic **(2*R**)-11c**: $t_R$ 12.7 and 13.1 min.

*4.3.3. The HCl salt of Ethyl (S)-4-methyl-1,2,3,6-tetrahydropyridine-2-carboxylate, **(2S)-12c**.*

(a) Enantiopure **(2*S*)-11c** (12.5 mg, 0.0739 mmol) was added aqueous HCl (conc., ~0.5 mmol) and dried under high vacuum overnight to give **(2*S*)-12c** (15.2 mg, 100%) as a white solid. Data for **(2*S*)-12c**: $[\alpha]_D^{rt}$ -79 (*c* 0.76, EtOH) {lit. data for the (*R*)-enantiomer: $[\alpha]_D^{25}$ +113.7 (*c* 1.0, EtOH)}.[19] $^1$H NMR (300 MHz): δ 10.2 (br s, 1H, NH), 9.98 (br s, 1H, NH), 5.42 (app. s, 1H, H-5), 4.31 (app. q, 2H, *J*=7.0 Hz, $OCH_2$), 4.16 (br s, 1H, H-2), 3.96 (app. d, 1H, *J*=15.9 Hz, H-6), 3.38 (m, 1H, H-6), 2.65 (m, 2H, H-3), 1.78 (s, 3H, H-5), 1.32 (t, 3H, *J*=7.0 Hz, $OCH_2CH_3$). The $^1$H NMR data is compatible with data reported for the racemic **(2*R**)-12c**.[24]

(b) A mixture of **(2*S*,$S_S$)-4c** (*p*Tol) and **(2*R*,$S_S$)-4c** (*p*Tol, in ratio 3:2, 14.2 mg, 0.046 mmol) was dissolved in MeOH (3 mL), added aqueous HCl (conc., 12 drops) and stirred at room temperature for 4 h. The reaction mixture was concentrated in vacou to afford a colorless oil, which precipitated by addition of diethyl ether to provide **(2*S*)-12c** (7.4 mg, 78%) as a white salt. $[\alpha]_D^{rt}$ -68.3 (*c* 0.74, EtOH) {lit. data for the (*R*)-enantiomer: $[\alpha]_D^{25}$ +113.7 (*c* 1.0, EtOH)}.[19]

*4.3.4. Ethyl (2S)-4-methyl-1-(p-tosyl)-1,2,3,6-tetrahydropyridine-2-carboxylate, **(2S)-13c**.*

A mixture of **(2*S*,$S_S$)-4c** (*p*Tol) and **(2*R*,$S_S$)-4c** (*p*Tol, in ratio 3:2, 19.7 mg, 0.064 mmol) was dissolved in $CH_2Cl_2$ (2 mL) and cooled to -20 °C under argon atmosphere. A solution of *m*CPBA (32.1 mg, 0.186 mmol) in $CH_2Cl_2$ (3 mL) was cannulated into the mixture. The resultant mixture was stirred for 5.5 h, then water (2 mL) and an aqueous saturated solution of $K_2CO_3$ (3 mL) was added. The mixture was extracted with $CH_2Cl_2$ (3 x 5 mL). The combined organic layer was washed with brine (3 mL), dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography (EtOAc/*n*-hexane, 18:85) yielding **(2*S*)-13c** (10.6 mg, 51%) as a colorless oil. Data for **(2*S*)-13c**: $[\alpha]_D^{rt}$ +18.7 (*c* 0.33, $CHCl_3$), HPLC (Chiralcel OJ, *i*-PrOH/*n*-hexane, 10/90, 1.0 ml $min^{-1}$, 230 nm): 42% ee, $t_R$ 23.2 (*R*) and 33.4 (*S*) min. $^1$H NMR (300 MHz): δ 7.69 (app. d, 2H, *J*=8.3 Hz, tolyl), 7.28 (app. d, 2H, *J*=8.3 Hz, tolyl), 5.33 (s, 1H, H-5), 4.87 (dd, 1H, *J*=6.6, 1.7 Hz, H-2), 4.04-3.88 (m, 3H, H-6/$OCH_2$), 3.78 (d, 1H, *J*=17.5 Hz, H-6), 2.51-2.35 (m, 2H, H-3), 2.42 (s, 3H, $ArCH_3$), 1.66 (s, 3H, Me-4), 1.08 (t, 3H, *J*=7.1 Hz, $OCH_2CH_3$). $^{13}$C NMR (100 MHz): δ 170.4 ($CO_2Et$), 143.2 (Ar), 136.6 (Ar), 130.3 (C-4), 129.4 (Ar), 127.3 (Ar), 116.9 (C-5), 61.2 ($OCH_2$), 53.1 (C-2), 42.1 (C-6), 32.3 (C-3), 23.2 (Me-4), 21.5 ($ArCH_3$), 13.9 ($OCH_2CH_3$). IR (thin film, NaCl): 2976

(w), 1742 (s), 1343 (s), 1197 (s), 1155 (s), 1099 (s) $cm^{-1}$. Anal. Calcd for $C_{16}H_{21}NO_4S$: C, 59.42; H, 6.54; N, 4.33; S, 9.91. Found: C, 59.20; H, 6.57, N, 4.29; S, 9.93.

*4.3.5. Ethyl (S)-4,5-dimethyl-1,2,3,6-tetrahydropyridine-2-carboxylate,* ***(2S)-11d.***

The aza-DA adduct **(2*S*,$S_S$)-4d** (*t*Bu) was prepared according to the general procedure (Section 4.2) using TMSOTf as the Lewis acid at -78 °C for 18 h. The crude product was hydrolyzed according to the procedure described in Section 4.3.2., afforded **(2*S*)-11d** (25.4 mg, 55% yield from sulfinimine **1a**) as a colorless viscous oil. Data for **(2*S*)-11d**: $^1$H NMR (400 MHz): δ 4.19 (app. q, 2H, *J*=7.1 Hz, $OCH_2$), 3.53 (app. t, 1H, *J*=7.1 Hz, H-2), 3.35-3.20 (m, 2H, H-6), 2.25-2.15 (m, 2H, H-3), 1.97 (br s, 1H, NH), 1.64 (m, 3H, Me-4), 1.57 (m, 3H, Me-5), 1.28 (t, 3H, *J*= 7.1 Hz, $OCH_2CH_3$). $^{13}$C NMR (100 MHz): δ 173.6 ($CO_2$Et), 125.2 (C-5), 123.3 (C-4), 60.8 ($OCH_2$), 55.8 (C-2), 49.4 (C-6), 33.8 (C-3), 18.7 (Me-4), 16.0 (Me-5), 14.2 ($OCH_2CH_3$). IR (thin film, NaCl): 3438 (br), 2985 (m), 2917 (m), 1736 (s), 1638 (s), 1447 (m), 1373 (m), 1303 (m), 1182 (s), 1131 (m), 1031 (m) $cm^{-1}$. MS (EI) *m/z* (% rel. int.): 183 ($M^+$, 15), 124 (29), 110 (100), 108 (45), 107 (68), 94 (20). HRMS (EI) calcd for $C_{10}H_{17}NO_2$ 183.1259 ($M^+$), found 183.1253.

*4.3.6. Ethyl (2S)-4,5-dimethyl-1-(p-tosyl)-1,2,3,6-tetrahydropyridine-2-carboxylate,* ***(2S)-13d.***

(a) The amine **(2*S*)-11d** (22.4 mg, 0.12 mmol) was tosylated by following the general procedure described by Murty *et al.*[20] The crude product was purified by flash chromatography (EtOAc/*n*-hexane, 1:10) providing **(2*S*)-13d** (8.4 mg, 21%) as a light yellow, viscous oil. Data for **(2*S*)-13d**: $R_F$ (EtOAc/*n*-hexane, 1:10) = 0.1. $[\alpha]_D^{rt}$ +16.6 (*c* 0.15, $CHCl_3$) {lit. 65% ee, $[\alpha]_D^{rt}$ +17.4 (*c* 0.4, $CHCl_3$)}.[3e] HPLC (Chiralcel OJ, *i*-PrOH/*n*-hexane, 2/98, 1.0 ml $min^{-1}$, 230 nm): >99% ee, $t_R$ 36.6 min. HPLC (Chiralcel OJ, *i*-PrOH/*n*-hexane, 2/98, 1.0 ml $min^{-1}$, 230 nm) of racemic **(2*R**)-13d**: $t_R$ 27.8 and 37.0 min.

(b) A mixture of **(2*S*,$S_S$)-4d** (*p*Tol) and **(2*R*,$S_S$)-4d** (*p*Tol, in ratio 4:1, 27.5 mg, 0.086 mmol) was oxidized according to the procedure shown in Chapter 4.3.4. Flash chromatography (EtOAc/*n*-hexane, 1:10) of the crude product afforded **(2*S*)-13d** (3.6 mg, 12%) as a colorless oil. Data for **(2*S*)-13d**: $[\alpha]_D^{rt}$ +13.4 (*c* 0.36, $CHCl_3$), {lit. 65% ee, $[\alpha]_D^{rt}$ +17.4 (*c* 0.40, $CHCl_3$)}.[3e] HPLC (Chiralcel OJ, *i*-PrOH/*n*-hexane, 2/98, 1.0 ml $min^{-1}$, 230 nm): 72% ee, $t_R$ 30.8 (*R*) and 40.6 (*S*) min.

*4.3.7. Ethyl (1S,3S,4R)-2-(p-tosyl)-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate,* ***(1S,3S,4R,$S_S$)-13g.***

(a) Pure **(1*S*,3*S*,4*R*,$S_S$)-4g** (*t*Bu, 0.130 g, 0.48 mmol) was dissolved with stirring in MeOH (4 mL) and treated with 4.0 M HCl in dioxane (0.610 mL, 2.44 mmol) at room temperature for 4 h.[5e] The reaction mixture was concentrated under reduced pressure. The residue was dissolved with stirring by addition of dry $CH_2Cl_2$ (2 mL) and triethylamine (0.214 mL, 1.54 mmol), and then cooled to 0 °C. A solution of *p*-TsCl (92.7 mg, 0.486 mmol) in dry $CH_2Cl_2$ (3 mL) was cannulated into the mixture. The resultant mixture was stirred for 5 h at 0 °C and then warmed to room temperature. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography (EtOAc/*n*-hexane, 15:85 to 20:80) affording **(1*S*,3*S*,4*R*,$S_S$)-13g** (0.103 g, 67%) as a white solid. Data for **(1*S*,3*S*,4*R*,$S_S$)-13g**: $R_F$ (EtOAc/*n*-hexane, 1:5) = 0.1. $[\alpha]_D^{rt}$ -241.1 (*c* 1.0, $CHCl_3$), {lit. 83% ee, $[\alpha]_D^{rt}$ -195.7 (*c* 1.0, $CHCl_3$)}.[3e] $^1$H NMR (400 MHz): δ 7.77 (app. d, 2H, *J*=8.3 Hz, Ts), 7.28 (m, 2H, Ts), 6.26 (m, 1H, H-5 or H-6), 6.21 (app dd, 1H, *J*=5.6, 2.1 Hz, H-5 or H-6), 4.59 (m, 1H, H-1), 4.18 (app q, 2H, *J*=7.1 Hz, $OCH_2$), 3.50 (m, 1H, H-3), 3.32 (m, 1H, H-4), 2.43 (s, 3H, Ts), 2.06 (app dt, 1H, *J*=8.7, 1.7 Hz, H-7*syn*), 1.47 (app d, 1H, *J*=8.7 Hz, H-7*anti*), 1.26 (t, 3H, *J*=7.1 Hz, $OCH_2CH_3$).

(b) The *p*-tolylsulfinyl aza-DA adduct **(1*S*,3*S*,4*R*,$S_S$)-4g** (*p*Tol, 0.068 mmol, 97% de) was oxidized according to the procedure shown in Chapter 4.3.4. Flash chromatography (EtOAc/*n*-hexane, 15:85) of the crude product afforded **(1*S*,3*S*,4*R*,$S_S$)-13g** in 46% yield as a white solid. Data for **(1*S*,3*S*,4*R*,$S_S$)-13g**: $[\alpha]_D^{rt}$ -244 (*c* 0.5, $CHCl_3$), {lit. 83% ee, $[\alpha]_D^{rt}$ -195.7 (*c* 1.0, $CHCl_3$)}.[3e] HPLC (Chiralcel OD-H, *i*-PrOH/*n*-hexane, 5/95, 0.5 ml $min^{-1}$, 230 nm): 97% ee, $t_R$ 27.2 (major) and 35.4 min (minor).

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# Paper III

Andreassen, T., Hansen, L. K. and Gautun, O. R.

**Diastereoselective synthesis of heteroaromatic glycine derivatives**

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