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Highly diastereoselective cycloaddition reactions of variously substituted 1-thia- and 1-thia-3-aza-buta-1,3-dienes. Synthesis of enantiomerically pure 5,6-dihydro-4*H*-[1,3]thiazines and 3,4-dihydro-2*H*-thiopyrans

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Abstract—The cycloaddition of 2- or 2,3-substituted 1-thia- and 1-thia-3-aza-4-dimethylamino-buta-1,3-dienes with various dienophiles in the presence of a Lewis acid provides a rapid and diastereoselective access to the 3,4-dihydro-2*H*-thiopyran and 5,6-dihydro-4*H*-[1,3]thiazine backbones. The generally observed *trans* relationship between the two newly created strereogenic centres was demonstrated to be the expression of a thermodynamic control of the reaction. The use of chiral dienophile derived from chiral oxazolidin-2-ones allowed us to prepare enantiopure 5,6-dihydro-4*H*-[1,3]thiazines and 3,4-dihydro-2*H*-thiopyrans. In the asymmetric synthetic process the chiral auxiliary removal step was best accomplished in the presence of samarium triflate in methanol.

1. Introduction

Heterocycles containing nitrogen or sulphur (or both) are common features incorporated in the structures of numerous natural products and pharmaceutical compounds and the development of simple and effective methods for their preparation is a point of major concern in medicinal chemistry. In this regard, the utilisation of the hetero Diels–Alder reaction undoubtedly represents one of the most attractive route for preparing these heterocycles with maximum atom economy and high selectivity.[1]

In our laboratory there has been a long-standing interest for heterodienes incorporating sulphur or sulphur and nitrogen atoms in their structures such as the 1-thia- and 1-thia-3-aza-buta-1,3-dienes **1** and **2**, respectively. In particular, it was demonstrated[2] that these dienes experienced thermal Diels–Alder cycloadditions with electrophilic olefins to give the adducts **3** or their evolution products **4** resulting from the facile loss of dimethylamine as illustrated in general terms in Scheme 1.

Since in the early investigations the major synthetic objective to be pursued was to find routes to the synthesis of cephem analogues from 6*H*-[1,3]thiazines,[3] little attention had been paid to the relative stereochemistry in cycloadducts **3** although it was recognised in two occasions that the two substituents at the newly created chiral centres adopted a *trans* relative disposition.[2c,4]

As part of our continuing program towards the reactivity of heterodienes and the synthesis of potentially pharmacologically active heterocycles we have now investigated the possibility of preparing 5,6-dihydro-4*H*-[1,3]thiazines **3** (X=N) and 3,4-dihydro-2*H*-thiopyran analogues **3** (X=CH) in chiral non-racemic form. Since, based on a large body of literature data, the asymmetric synthesis of labile heterocycles **3** could most certainly not be achieved without the help of a Lewis acid, the question arises of knowing whether such acidic conditions are compatible with the maintenance of their integrity. In this context, we decided to reinvestigate the cycloaddition reaction depicted in Scheme 1 under different activation protocols, paying particular attention in its stereochemical aspects. The results of this study are

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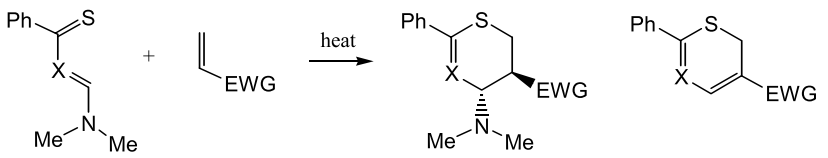


1 X = CH
2 X = N

3 (X = CH, N) **4**

Scheme 1.

presented in this paper along with the successful achievement of the first asymmetric synthesis of heterocycles **3**. Additionally, we will offer arguments proving that the high propensity of this cycloaddition reaction to deliver, in most examples, adducts of relative *trans* stereochemistry is the result of a readily established thermodynamic control.

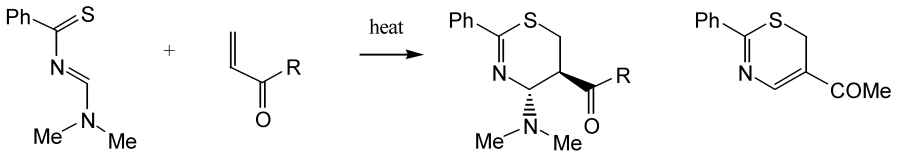
2. Results and discussion

2.1. Cycloaddition reaction of heterodienes 1, 2 and 10

The cycloaddition reactions of diene **2**[5] to methyl vinyl ketone, methyl acrylate and 3-acryloyl-oxazolidin-2-one, **5a**–**c**, under thermal and Lewis acid activations were considered first (Scheme 2).[6]

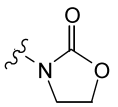
The thermal cycloaddition of diene **2** with a 10-fold excess of methyl vinyl ketone **5a** in toluene (80 °C, 2 h) led mainly to the 6*H*-1,3-thiazine **7** as a result of a dimethylamine elimination process (ratio *trans*-**6a**/**7**=10:90). The initiation of such a facile elimination seems to be attributable to the basicity of the diene. Indeed, when *trans*-**6a** (prepared under Lewis acid activation, vide infra) was heated in toluene (80 °C, 2 h) it was recovered unchanged whereas, in the presence of 1 molar equivalent of diene **2**, in the same conditions as above, the elimination product **7** was quantitatively formed. As expected from the observation, slow addition of diene **2** to an excess of methyl vinyl ketone heated at 80 °C in toluene solution gave adduct *trans*-**6a** though in an always synthetically unfavourable ratio (*trans*-**6a**/**7**=1:1). The reaction of **2** with methyl acrylate **5b** and 3-acryloyl-oxazolidin-2-one **5c** in toluene solution (60 °C, 2 h and reflux, 20 h, respectively) led to *trans*-adducts **6b**,**c** in good chemical yields (80%) when an excess of the dienophile was used. No traces of elimination products were detected in the crude materials by ^{1}H NMR.

Attention was next turned to the approach of forming the adducts **6** under Lewis acid activation. We were initially apprehensive for the success of this activation mode due to the possibility of Lewis acid-induced $NHMe_2$ elimination in the adducts. Fortunately, our concerns proved unfounded since several Lewis acids could be employed to activate the

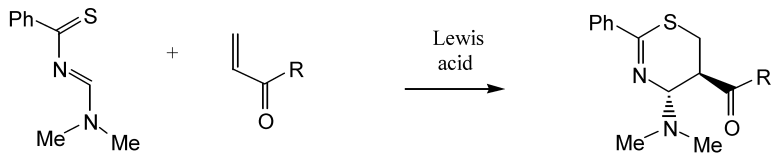


2 **5** *trans*-**6** **7**

a: R=Me; **b**: R=OMe; **c**: R=



Scheme 2.



2 **5** *Trans*-**6 a-c**

a: R = Me
- $TiCl_2(OiPr)_2$, THF, -78°C to -20°C — 78%
- $ZnCl_2$, THF, -10°C to 0°C — 75%

b: R = OMe, **c**: R=

- $MgBr_2$, CH_2Cl_2, 20°C — **b**: 95 % ; **c**: 68%
- Et_2AlCl, CH_2Cl_2, -60°C — **b**: 61 % ; **c**: 0%

Scheme 3.

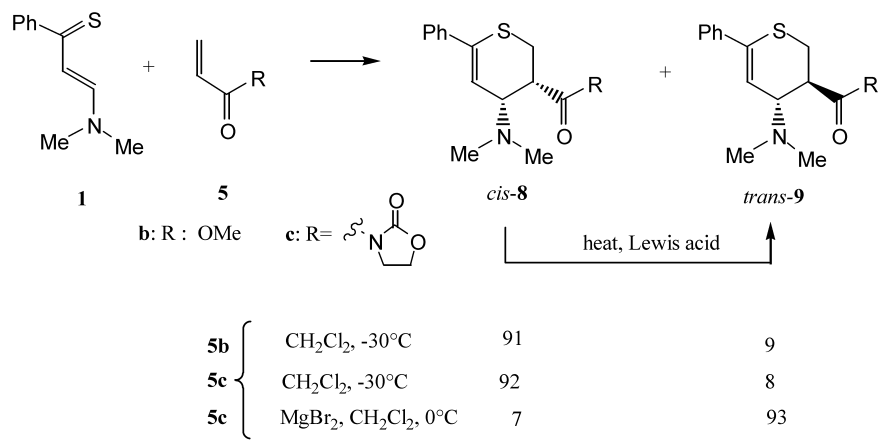
cycloaddition reactions and deliver the adducts in good to excellent chemical yields. Of the various Lewis acids examined, titanium and zinc derivatives (typically 1 molar equivalent with respect to a dienophile) were the best promotors for obtaining adduct *trans*-**6a** when used at low temperature whereas the syntheses of adducts *trans*-**6b**,**c** were best accomplished in the presence of magnesium bromide at room temperature (Scheme 3).

At this point it seems important to notice that the thermal and Lewis acid-promoted reactions are all highly stereoselective and led to the exclusive formation of *trans* adducts irrespective of the activation mode, the solvent and temperature employed. This remarkable feature is somewhat striking because closely related dienes were reported to give predominantly *cis* adducts in the cycloaddition with various electron-poor dienophiles, even at relatively high temperatures.[7] We will return to this problem later.

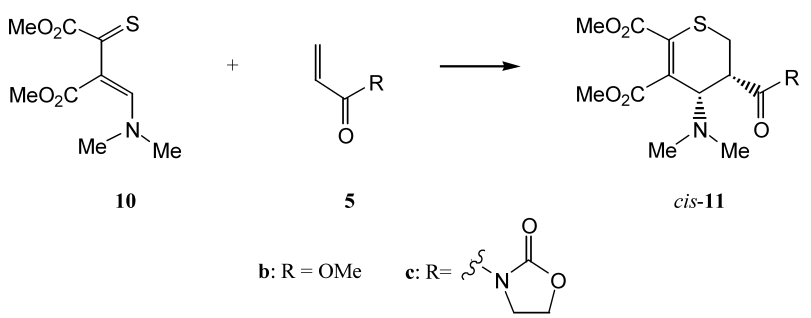
For comparison purposes we next examined the behaviour of diene **1**[8,9] toward the same set of dienophiles as above (Scheme 4). The main differences between the two dienes reside in the greater reactivity of **1** and its marked tendency to give *cis* adducts predominantly at low temperatures. Thus, whereas diene **2** needed long reaction time and elevated temperature to undergo cycloaddition with methyl acrylate, the reaction with diene **1** was complete within 1.5 h at −30 °C producing a mixture of adducts **8b** and **9b** (ratio *cis*-**8b**/*trans*-**9b**: 91:9) in almost quantitative yield. A similar result was also achieved with 3-acryloyl-oxazolidin-2-one as the dienophile. Another noticeable point associated with the reactivity of **1** is the reversal in stereochemistry of the *cis* adducts as the reaction temperature is raised. Thus, when a sample of the initially formed 90:10 mixture of adducts *cis*-**8b**/*trans*-**9b** was heated at 80 °C in toluene for 3 h, the *trans* adduct **9b** only resulted. The reversal in stereochemistry was even more easier for adduct *cis*-**8c** since it occurred on standing the corresponding *cis*-**8c**/*trans*-**9c** mixture at 20 °C for 3 h.

By recourse to competitive crossover experiments, for instance by exposing *cis*-**8b** to a large excess of 3-acryloyl-oxazolidin-2-one **5c** or, conversely, *cis*-**8c** to an excess of methyl acrylate, the evolution of the *cis*-adducts toward the more stable *trans*-adducts was demonstrated to arise via a sequential retro Diels–Alder—Diels–Alder sequence (thermodynamic control). The equilibration process was facilitated under Lewis acid conditions. For instance, the reaction of **1** with 3-acryloyl-oxazolidin-2-one **5c** in the presence of magnesium bromide in methylene chloride at −78 °C gave a ca. 1 to 1 mixture of the corresponding adducts *cis*-**8c** and *trans*-**9c**, whereas adduct *trans*-**9c** was largely predominant at 0 °C (ratio *cis*-**8c**/*trans*-**9c**=7:93). The ease with which the thermodynamic control establishes also depends on the nature of the substituents in the diene. Thus, the cycloaddition reactions of diene **10**[10] with methyl acrylate **5b** and 3-acryloyl-oxazolidin-2-one **5c** afforded the sole *cis*-adducts **11** at 20 °C (Scheme 5). *Trans* adducts were formed, however, in the presence of magnesium bromide (vide infra).

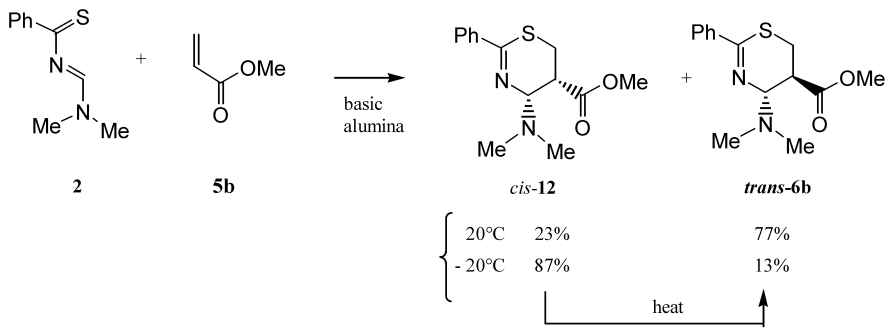
The results displayed by diene **1** now bring us to the



Scheme 4. Ratios of diastereomers were derived by integration of the NMe_2 peaks (or CO_2Me, if present) in the ^1H NMR spectra (400 MHz) of the unpurified cycloaddition products.



Scheme 5.



Scheme 6. Ratios of diastereomers were derived by integration of the NMe_2 peaks (or CO_2Me peaks) in the ^1H NMR spectra (400 MHz) of the unpurified cycloaddition products.

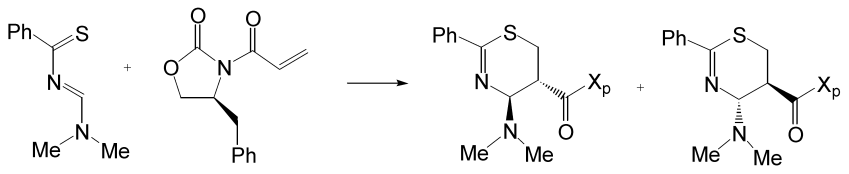
question of whether *trans*-adducts **6**, originating from diene **2**, were also the result of an equilibration process that would establish rapidly, even at very low temperature. The answer to that question emerged fortuity as we studied the condensation of **2** with methyl acrylate on basic alumina (Scheme 6). In these particular conditions the cycloaddition reaction continued to give preference to the *trans*-adduct **6b** although, for the first time, small amount of the *cis*-adduct **12** could be detected in the NMR spectrum of the crude material. Interestingly, decrease of the reaction temperature favoured the formation of the *cis*-adduct (ratio *trans*-**6b**/*cis*-**12**=13:87 at − 20 °C). Without real surprise, brief heating of the *cis*/*trans* adduct mixture in chloroform at 40 °C transformed the *cis*-adduct **12** towards its more stable *trans*-diastereomer **6b**,[11] thereby demonstrating its high thermodynamic instability. Thus, by comparison with the behaviour of *cis*-adducts **8**, it may be concluded that the nitrogen N-3 greatly accelerates the conversion of primary (generally not appeared) *cis*-adducts resulting from the cycloaddition of diene **2** with dienophiles, into their most stable *trans* diastereomers **6**.[12]

Two salient points emerged from the studies reported above: (1) the cycloaddition reactions of diene **2** can be realised in the presence of a Lewis acid without compromising the structural integrity of the adducts formed (no loss of dimethylamine), (2) rapid establishment of the thermodynamic control results in isolation of the sole *trans*-adducts. These observations will be now exploited to develop an efficient route to prepare the 5,6-dihydro-4*H*-1,3-thiazine and 3,4-dihydro-2*H*-thiopyran heterocycles in chiral non-racemic form.

2.2. Asymmetric cycloaddition reactions

When designing an asymmetric diastereoselective synthesis of heterocycle **6b**, two strategies presented itself, i.e. (1) recourse to a chiral heterodiene or (2) utilisation of a chiral dienophile. At first glance, the first strategy seems attractive since it may be envisaged to exchange the dimethylamino group to a chiral amine and excellent selectivities in [4+2] cycloaddition processes had already been displayed with chiral 1-aza-buta-1,3-dienes[13,14] bearing a proline-derived amino-substituent at the N-1 position. However, in the case at hand, any attempts to recover the chiral amino moiety would most certainly be thwarted by a chirality destructive β-elimination process. Attachment of a chiral auxiliary at carbon C-2 represents a second distinct possibility to introducing chirality on the diene. This possibility was already tested in our laboratory[3] but the results were rather disappointing in terms of diastereoselectivity. For all the above reasons it finally appeared to us that a strategy based on an appropriately chosen chiral dienophile would certainly be the most secured method for achieving our goal. Within this context the chiral acrylate derived from ethyl-(*S*)-lactate could be a good candidate as it is easily prepared and reported to give excellent diastereoselectivities in Diels–Alder reactions.[15] While its cycloaddition with diene **2** in the presence of $TiCl_4$ proceeded in a respectable yield of 80% the diastereoselectivity was poor. The weakness of this route prompted us to explore a different approach based on the utilisation of chiral 3-acryloyl-oxazolidin-2-one as a dienophile. If these dienophiles were known, in combination with chelating Lewis acids, to react with carbodienes to give adducts with good to excellent diastereoselectivities,[16] there existed, somewhat surprisingly, no reported examples of their use in hetero Diels–Alder reactions at the outset of our study. However, when our work was in progress, Saito and colleagues[17] reported the Lewis-acid-promoted hetero Diels–Alder reaction of a variety of α,β-unsaturated thiocarbonyl compounds (1-thia-buta-1,3-dienes) with some (4*S*)-benzyl-3-alkenoyl-oxazolidin-2-ones to give [4+2] cycloadducts with fair to excellent diastereomeric excesses.

Cycloaddition reaction of diene **2** with (4*S*)-3-acryloyl-4-benzyl-oxazolidin-2-one **13** was studied under thermal and Lewis acid activations.[18] Thus, when diene **2** and an excess (1.5 equiv.) of chiral **13** was heated in toluene for 20 h, a 20:80 mixture of *trans* diastereomeric adducts **14** and **15** was produced in 75% yield (Scheme 7). This diastereoselectivity was reasonably high for an uncatalysed process and each of the diastereomers was obtained in pure form after simple flash-chromatography on silica gel. In light of our previous investigations (vide supra) we next performed the reaction in the presence of magnesium bromide-etherate in CH_2Cl_2. In these conditions we were gratified to find that the reaction was regulated with much higher diastereoselectivity than that previously observed under thermal conditions, and led to the formation of a single *trans* diastereomer **15**. Thus, depending on the way the reaction is performed, it was possible to direct the process toward the formation of either *trans*-**14** or *trans*-**15**. The absolute configurations at carbons C-4 and C-5 of **15**, and therefore **14**, were firmly established by single crystal X-ray analysis[19,20] of *trans*-**15** (Fig. 1).



2 **13** *trans*-**14** *trans*-**15** (X-ray)

110°C, toluene	85	15
$MgBr_2$-Et_2O in CH_2Cl_2, 0°C	0	100

Scheme 7. Ratios of diastereomers were derived by integration of the NMe_2 peaks in the ^1H NMR spectra (400 MHz) of the unpurified cycloaddition products.

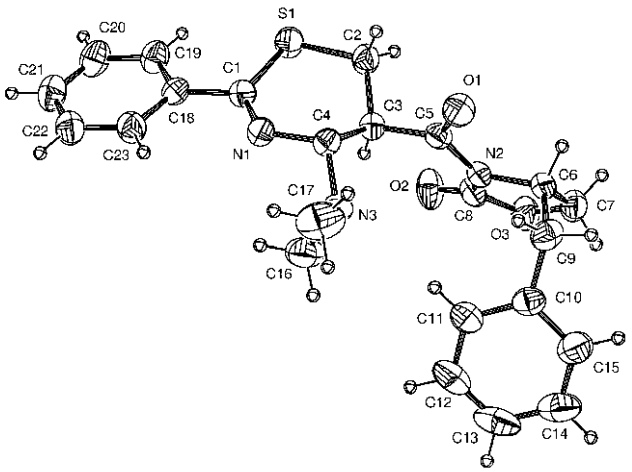


Figure 1. ORTEP drawing of **15**.

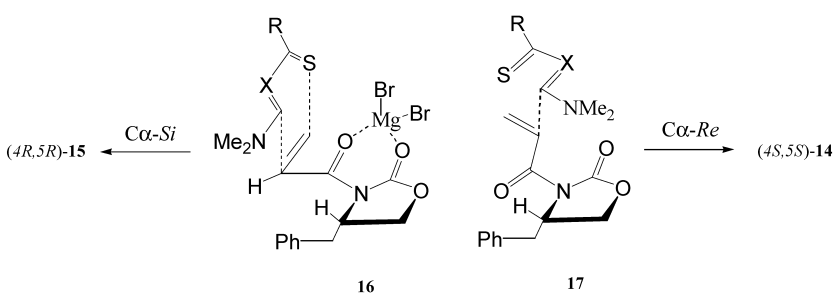
The preferential formation of the (4*R*,5*R*)-adduct **15** under Lewis acid activation may be interpreted by recourse to the Evans model[16] in which magnesium bromide acts as the chelating species. In chelate **16** (R=Ph, X=N), the benzyl group efficiently blocks one diastereotopic face (C_α-*Re*) of the *s-cis* disposed double bond, forcing the heterodiene **2** to approach from the opposite C_α-*Si* face, as depicted in Scheme 8. Under thermal activation, the stereochemical bias provided by the benzyl group in a reactive dienophile conformation close from that shown in **17** (R=Ph, X=N) leads to the preferential formation of the diastereomer (4*S*,5*S*)-**14** (Scheme 8).

The cycloaddition reaction of diene **1** to chiral olefin **13** was less rewarding from a synthetic point of view because each of the four possible *cis* and *trans* stereomers **18**–**21** were formed. If none of these diastereomers could be easily separated from the three others, it was nevertheless possible to determine the diastereomeric ratios for each of the *cis* and *trans* pairs by inspection of the NMR spectra of the crude reaction mixtures (Scheme 9).

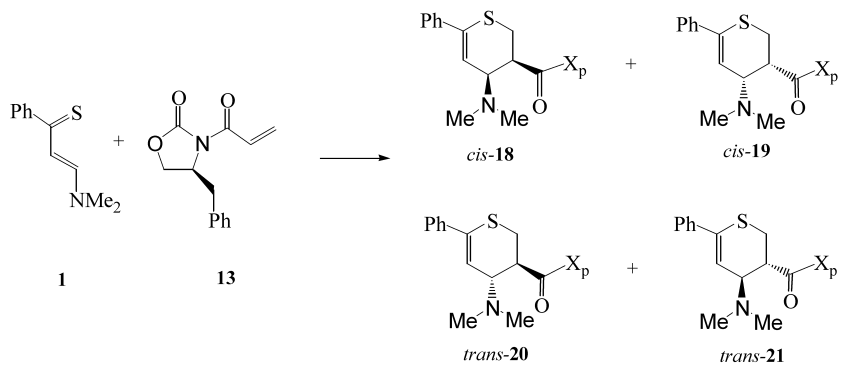
The structures attributed to adducts **18**–**21** were made, as for **14** and **15**, on the basis of the Evans model.[16] As the data indicate, the diastereomeric ratios for *trans* adducts **20** and **21** are quite close to those of the *trans* **14** and **15** adducts obtained under the thermal and Lewis acid-promoted conditions, whereas the corresponding diastereomeric ratios of the *cis* adducts **18** and **19**, respectively, indicate less selective reactions.

More interesting results were obtained in the reaction of **10** with the 3-acryloyl-4-benzyl-oxazolidin-2-one **13**. Scheme 10 and the accompanying data show that the presence (or the absence) of a Lewis acid as well as the reaction temperature are crucial parameters for the establishment of the *cis*/*trans* ratios. Similarly to the precedent reported examples, the cycloaddition reaction can be carried out with high level of diastereoselection when magnesium bromide is the Lewis acid promotor. In these conditions *cis*-**22** and *trans*-**24** are the sole diastereomers formed. Changing the nature of the Lewis acid did not alter the diastereoselectivity for the *trans* adducts (once again **25** was the sole adduct formed when Et_2AlCl was used in place of $MgBr_2$) while the diastereoselectivity for the *cis* adducts **22** and **23** was significantly affected.

Each of the three diastereomers **22**, **23** and **24** that were detected in the above reactions could be easily isolated in pure form by simple flash chromatography on silica. Moreover, the structure of *trans*-**24** was fully ascertained by X-ray analysis.[21] Its formation can be accounted for by

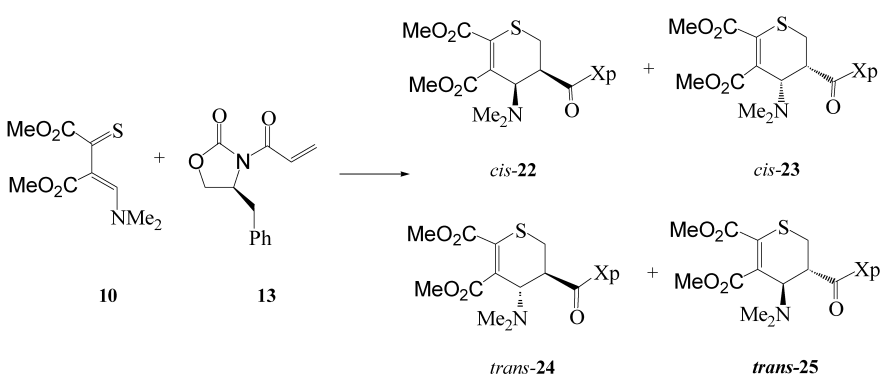


Scheme 8.



Cis:Trans	18:19	20:21
20°C, CH_2Cl_2, 1.5h	75 : 25	25 : 75	15 : 85
$MgBr_2$-Et_2O in CH_2Cl_2, 0°C, 1.5h	55 : 45	80 : 20	**98 : 2**

Scheme 9. Ratios of diastereomers were derived by integration of the NMe_2 peaks in the ^1H NMR spectra (400 MHz) of the unpurified cycloaddition products.



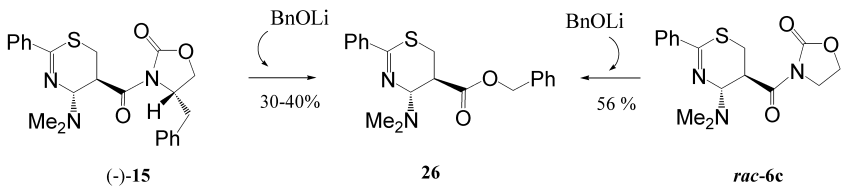
Cis:Trans	22:23	24:25
20°C, CH_2Cl_2, 16h	100:0	15:85	-
$MgBr_2$-Et_2O in CH_2Cl_2 , -10°C, 3h	30:70	100:0	100:0
Et_2AlCl (2 equiv), -60°C, CH_2Cl_2, 3h	78:22	83:17	100:0

Scheme 10. Ratios of diastereomers were derived by integration of the NMe_2 peaks (or CO_2Me peaks) in the ^1H NMR spectra (400 MHz) of the unpurified cycloaddition products.

the Evans transition state model[16] **16** (R=CO_2Me, X=C–CO_2Me) already invoked for the formation of *trans*-**15** adduct (Scheme 8). The structures attributed to the adducts *cis*-**22** and *cis*-**23**, respectively, are based on the reasonable assumption that Evans model is also operative in transition state topographies leading to *cis* adducts.

2.3. Removal of the chiral auxiliary: synthesis of chiral non-racemic heterocycles (+)-6b, (−)-6b, (−)-10b, (−)-27

We have demonstrated that the association (4*S*)-3-acryloyl-4-benzyl-oxazolidin-2-one $MgBr_2$, permitted the highly diastereoselective formation of 5,6-dihydro-4*H*-thiopyrans and 5,6-dihydro-4*H*-[1,3]thiazines when reacted with dienes **1**, **10** and **2**, respectively. It remains now to be demonstrated that the chiral 4-benzyl-oxazolidin-2-one moiety can be easily recovered from the primary Diels–Alder adducts by a simple and high yielding operation. To achieve this ultimate goal, it is necessary that an appropriately chosen nucleophile may be selectively directed to the exocyclic carbonyl of these adducts. While several procedures do succeed in achieving this chemoselective operation,[16] many of them suffer from low efficiency as soon as steric hindrance is involved. Thus, it has been already reported that, in the case where the exocyclic carbonyl is hindered by substituents affixed on the six-membered ring, the nucleophile may well be directed mainly, if not exclusively, to the endocyclic carbonyl, thereby leading to the undesired oxazolidinone ring opening.[16] Due to the presence of the dimethylamino substituent in the vicinity of the exocyclic carbonyl we were thus not surprised to experience some difficulties with adduct **15** upon attempting to recover the chiral auxiliary. To circumvent that problem, the use of lithium peroxide or lithium benzylate, ultimately leading to the replacement of the chiral oxazolin-2-one moiety by an acid or a benzylester,



Scheme 11.

has been equally recommended.[16] In the case at hand, treatment of adduct **15** with lithium peroxide in THF proved unsuccessful, leading to unidentified decomposition products. However, the action of lithium benzylate in THF did afford the expected benzylic ester (−)-**26** in enantiomeric pure form[22] though in unsatisfying low yields (30–40%). At this stage it is not without interest to note that, under the action of the same reagent, the racemic adduct **6c** led to racemic **26** in 56% isolated yield (Scheme 11). This suggests that not only the dimethylamino residue but also the chiral auxiliary benzyl substituent exert an undesirable shielding of the external carbonyl, forcing the benzylate anion to preferentially attack the oxazolidinone ring carbonyl.

After several unsuccessful attempts we were delighted to find that chiral auxiliary removal could be achieved in an acceptable yield of 75% by exposure of adduct **15** to a catalytic amount (0.1 equiv.) of samarium triflate in a 1:1 CH_2Cl_2/MeOH mixture[23] to give (−)-**6b**.[21] Due to the high oxophilicity of samarium, this reaction proceeds most certainly via a chelated intermediate **27** as shown in Scheme 12.

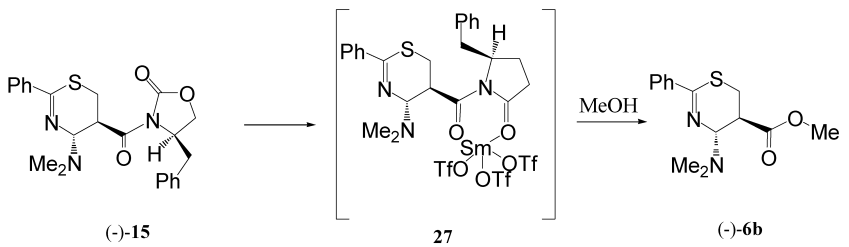
The use of this procedure was also successfully achieved in several other examples, showing its general applicability for substituted 5,6-dihydro-4*H*-[1,3]thiazine and 5,6-dihydro-4*H*-thiopyran compounds (Scheme 13, ee>95% in all examples[21]).

The ability of samarium triflate to form six-membered ring chelates prompts us to determine if this Lewis acid is capable of effecting the [4+2] cycloaddition of diene **2** with chiral dienophile **13** (cf. Scheme 7). Admixture of both components in the presence of a catalytic amount of $Sm(OTf)_3$ in dichloromethane solution led to the expected formation of *trans* adducts **14** and **15** with an encouraging diastereoselection of 89:11 in favour of **15**. By contrast, almost no selectivity was obtained under ytterbium and scandium triflate activations. The preferred formation of adduct **15** in the presence of $Sm(OTf)_3$ can be accounted for by invoking a transition state topography similar to that depicted in Scheme 8 (**15**, R=Ph, X=N, samarium triflate for magnesium bromide). A distinct feature of the $Sm(OTf)_3$ procedure is that the primary adduct need not to be isolated but can be directly transformed in its methyl ester derivative (one pot transformation) by simply adding methanol to the reactional mixture after completion of the cycloaddition. This was demonstrated for the reaction depicted in Scheme 14.

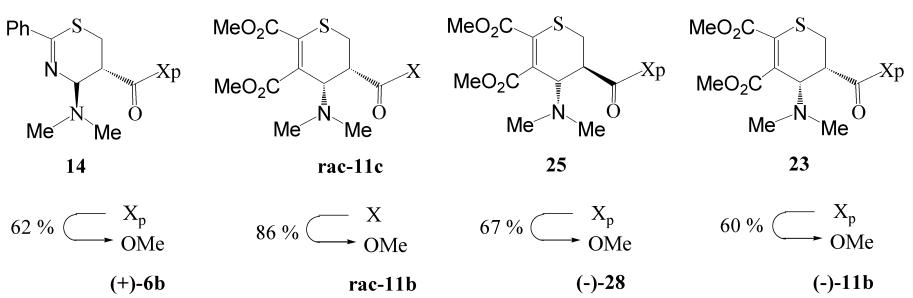
Another potential interest is that the utilisation of samarium triflate in catalytic amount opens the door for achieving a catalytic asymmetric synthesis of the above adducts, using a in situ generated chiral Lewis acid as the reaction promotor.

3. Conclusions

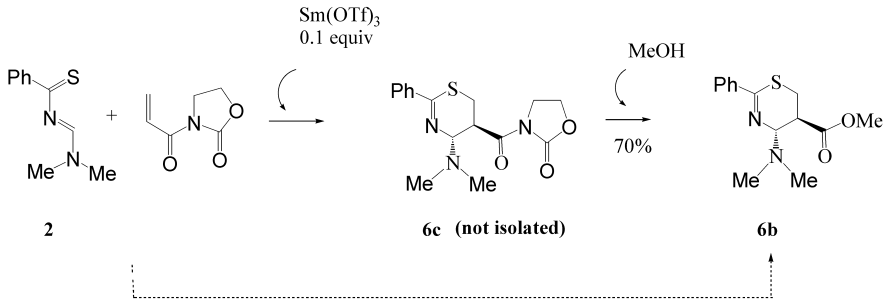
We have described the first approach towards the asymmetric synthesis of the 5,6-dihydro-4*H*-[1,3]thiazine skeleton. The strategy featured the use of the chiral



Scheme 12.



Scheme 13.



Scheme 14.

non-racemic (4*S*)-3-acryloyl-4-benzyl-oxazolidin-2-one **13** which was condensed with the 1-thia-3-aza-buta-1,3-diene **2**. The cycloaddition reaction can be carried out with a very high level of diastereoselection provided magnesium bromide is added to form a chelate with **13**. The only formation of adduct *trans*-**15** in these conditions may be rationalised on the basis of the Evans model. The decisive role of magnesium bromide was also appreciated when chiral dienophile **13** was reacted with 1-thia-buta-1,3-dienes **1** and **10** to give 5,6-dihydro-4*H*-thiopyrans with the same high level of diastereoselection as above. Interestingly, in the absence of a Lewis acid, a still synthetically useful diastereoselectivity of 70% was recorded in all the examples studied. The removal of the chiral auxiliary moiety from the adducts proved to be a non-trivial operation. We discovered that it could be accomplished at best by employing a catalytic amount of samarium triflate in a 1:1 CH_2Cl_2/MeOH mixture. Under these reaction conditions the resulting adducts bearing a methyl ester functionality at C-5 were isolated in yields ranging from 60 to 86%. Finally, it was demonstrated that the general trend of diene **2** to lead to the most stable *trans* adducts, even at low temperatures and in the absence of a Lewis acid, was the result of a thermodynamic control of the cycloaddition reaction.

4. Experimental

4.1. General

Melting points were determined using a Reichert-Jung Thermo Galen Kofler block. Optical rotations were measured at ambient temperature using an Optical Activity Ltd AA-10 polarimeter and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Microanalysis was carried out at the 'Services de Microanalyses du CNRS de Vernaison—France'. IR spectra were recorded on a Bruker IFS 45 WHR spectrometer. ^{1}H NMR spectra were recorded on a Bruker AC200 spectrometer at 200 MHz or on a Bruker ARX400 spectrometer at 400 MHz. ^{13}C NMR spectra were recorded on a Bruker AC200 spectrometer at 50 MHz or on a Bruker ARX400 spectrometer at 100 MHz. All NMR spectra used tetramethylsilane as the internal standard and were run in deuterated solvents. *J* Values are given in Hz. The mass spectra were obtained in GC/MS mode (EI, 70 eV). Thin layer chromatography (TLC) was carried out on Merck 5735 Kieselgel 60 F_{254} fluorescent plates. Flash chromatography was performed with silica gel (Merck Geduran SI 60 Art.11567).

Reactions carried out under an inert atmosphere refer to the use of argon or nitrogen. Diethyl ether, tetrahydrofuran (THF) and benzene were dried by being distilled from sodium and benzophenone. Dichloromethane, toluene, acetone and carbon tetrachloride were dried by distillation from calcium hydride. All other reagents were purified by distillation, the pressure being reduced if the boiling point of the compound was greater than 110 °C at atmospheric pressure.

4.2. Synthesis of racemic heterocycles

4.2.1. 1-(2-Phenyl-6*H*-1,3-thiazin-5-yl)-ethanone: 7. To a solution of 4-dimethylamino-2-phenyl-1-thia-3-aza-buta-1,3-diene (*N*-[(dimethyl-amino)methylene]-benzene-carbothioamide) **2** (0.25 g, 1.3×10^{-3} mol) in dry toluene (10 mL) were added methyl vinyl ketone (1 mL, 12×10^{-3} mol) and hydroquinone (few crystals). The reaction mixture was stirred for 2 h at 110 °C then, after cooling at room temperature, concentrated under reduced pressure. Analysis of the crude product by ^{1}H NMR showed the presence of both **6a** and **7** in a 1:9 ratio. Purification of the residue by chromatography on silica (petroleum ether/ethyl acetate 4:1) gave **7** (90%) as a yellow solid; R_f 0.59 (petroleum ether/ethyl acetate 4:1); mp 108–109 °C (diethyl ether/petroleum ether); ν_{max}/cm^{-1} 1689, 1648, 1504, 693; δ_H (200 MHz; $CDCl_3$): 2.46 (3H, s), 3.70 (2H, s), 7.50 and 8.05 (6H, 2m); δ_C (50 MHz; $CDCl_3$): 21.1, 25.7, 116.4, 129.0, 129.1, 132.9, 137.2, 147.9, 169.4, 196.4; *m/z* (EI) 217 ($M^{+\cdot}$, 31), 202 (27), 175 (100), 174 (54), 121 (19), 105 (83), 77 (58), 51 (20), 43 (14), 39 (7), 15 (3).

4.2.2. *trans*-1-[4-(Dimethylamino)-2-phenyl-5,6-dihydro-4*H*-1,3-thiazin-5-yl]ethanone: 6a. *Zinc chloride activation.* A 1 M zinc chloride solution in diethyl ether (1 mL, 10^{-3} mol) was diluted at room temperature in dry THF (4 mL) placed under inert atmosphere. Methyl vinyl ketone (0.21 mL, 2.5×10^{-3} mol) was added and the mixture was stirred for 10 min. After cooling at −20 °C, a solution of 4-dimethylamino-2-phenyl-1-thia-3-aza-buta-1,3-diene **2** (0.2 g, 1.04×10^{-3} mol) in dry THF (1 mL) was syringed in. The reaction mixture was stirred for 2 h between −20 and −10 °C. After dilution with ethyl acetate (10 mL) at room temperature then successive washings with 10% aqueous potassium hydrogen carbonate (2×10 mL) and brine (2×10 mL), the organic layer was extracted, dried ($MgSO_4$), filtered and concentrated. Purification by crystallisation (diethyl ether/petroleum ether) gave **6a** as yellow crystals (0.2 g, 75%).

Titanium dichlorodiisopropoxide activation. Titanium tetrachloride (0.22 mL, 2×10^{-3} mol) then titanium

tetraisopropoxide (0.6 mL, 2×10^{-3} mol) were sequentially added at room temperature to dry THF (20 mL) placed under inert atmosphere. The mixture was stirred for 10 min then cooled at −78 °C. Methyl vinyl ketone (0.32 mL, 3.8×10^{-3} mol) was added. After 20 min, a solution of 4-dimethylamino-2-phenyl-1-thia-3-aza-buta-1,3-diene **2** (0.5 g, 2.6×10^{-3} mol) in dry THF (4 mL) was syringed in. The reaction mixture was stirred for 3 h allowing to warm to −20 °C. After dilution with ethyl acetate (20 mL) at room temperature then successive washings with 10% aqueous potassium hydrogen carbonate (2×20 mL) and brine (2×20 mL), the organic layer was extracted, dried ($MgSO_4$), filtered and concentrated. Purification by crystallisation (diethyl ether/petroleum ether) gave **6a** as yellow crystals (0.53 g, 78%); mp 73–74 °C; ν_{max}/cm^{-1} 1710, 1700, 690; δ_H (200 MHz; $CDCl_3$): 2.30 (3H, s), 2.42 (6H, s), 2.83 (1H, ddd, J=3.8, 10.0, 11.9 Hz), 2.94 (1H, dd, J=3.8, 12.1 Hz), 3.44 (1H, dd, J=11.9, 12.1 Hz), 4.39 (1H, d, J=10.0 Hz), 7.38 and 7.83 (5H, 2m); δ_C (50 MHz; $CDCl_3$) 27.8, 30.4, 40.3, 45.0, 79.8, 126.6, 128.4, 129.1, 138.5, 157.5, 210.3; m/z (EI) 262 ($M^{+}\cdot$, 1), 192 (100), 159 (80), 121 (79), 89 (85), 77 (35), 44 (66); Anal. calcd for $C_{14}H_{18}N_2OS$: C, 64.09; H, 6.92; N, 10.68; found: C, 63.87; H, 6.85; N, 10.58.

4.2.3. *trans*-Methyl 4-(dimethylamino)-2-phenyl-5,6-dihydro-4*H*-1,3-thiazine-5-carboxylate: 6b. *Thermal activation*. To a solution of 4-dimethylamino-2-phenyl-1-thia-3-aza-buta-1,3-diene **2** (0.5 g, 2.6×10^{-3} mol) in dry dichloromethane (30 mL) were added methyl acrylate (2.1 mL, 23.3×10^{-3} mol) and hydroquinone (few crystals). The reaction mixture was stirred for 24 h at 40 °C then, after cooling at room temperature, concentrated under reduced pressure. Purification by flash chromatography on silica (petroleum ether/ethyl acetate 80:20) gave **6b** as a pale yellow solid (0.59 g, 81%).

Magnesium bromide activation. Magnesium turnings (0.08 g, 3.29×10^{-3} mol) in dry diethyl ether (4 mL) were placed under inert atmosphere. 1,2-Dibromoethane (0.28 mL, 3.25×10^{-3} mol) was added dropwise and the reaction mixture was slightly heated to induce the formation of magnesium bromide. When all the magnesium turnings were consumed, diethyl ether was removed by several pumping and venting cycles (argon) to leave a white powder. Dichloromethane (8 mL), then methyl acrylate (0.175 mL, 1.94×10^{-3} mol) were syringed in at room temperature. After 10 min, a solution of 4-dimethylamino-2-phenyl-1-thia-3-aza-buta-1,3-diene **2** (0.25 g, 1.3×10^{-3} mol) in dry dichloromethane (2 mL) was added and the reaction mixture was stirred at room temperature for 3 h. After dilution with dichloromethane (10 mL) then successive washings with 10% aqueous potassium hydrogen carbonate (2×10 mL) and brine (2×10 mL), the organic layer was extracted, dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica (petroleum ether/ethyl acetate 4:1) gave **6b** as a pale yellow solid (0.34 g, 95%).

Diethylaluminium chloride activation. Diethylaluminium chloride (1 M in hexane) (1.95 mL, 1.95×10^{-3} mol) was added under inert atmosphere to dichloromethane (10 mL) cooled at −78 °C followed by methyl acrylate (0.175 mL, 1.94×10^{-3} mol). The mixture was stirred for 10 min allowing to warm to −20 °C. After cooling at −78 °C, a solution of 4-dimethylamino-2-phenyl-1-thia-3-aza-buta-1,3-diene **2** (0.25 g, 1.3×10^{-3} mol) in dry dichloromethane (2 mL) was added and the reaction mixture was stirred at −60 °C for 3 h. After dilution with dichloromethane (10 mL) at room temperature then successive washings with 10% aqueous potassium hydrogen carbonate (2×10 mL) and brine (2×10 mL), the organic layer was extracted, dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica (petroleum ether/ethyl acetate 4:1) gave **6b** as a pale yellow solid (0.22 g, 61%); R_f 0.32 (petroleum ether/ethyl acetate 4:1); mp 78 °C (ethyl acetate/petroleum ether); ν_{max}/cm^{-1} 1725, 1612, 1356, 690; δ_H (400 MHz; $CDCl_3$) 2.42 (6H, s), 2.73 (1H, ddd, J=3.8, 10.2, 12.1 Hz), 3.10 (1H, dd, J=3.8, 12.2 Hz), 3.52 (1H, dd, J=12.1, 12.2 Hz), 3.78 (3H, s), 4.44 (1H, d, J=10.2 Hz), 7.40 and 7.84 (5H, 2m); δ_C (50 MHz; CD_3COCD_3) 28.7, 40.3, 40.8, 52.4, 80.1, 127.2, 129.3, 131.6, 139.5, 158.2, 174.1; m/z (EI): 278 ($M^{+}\cdot$, 1), 192 (80), 159 (59), 121 (44), 89 (100), 77 (19), 51 (8), 44 (56).

4.2.4. *trans*-3-{[4-(Dimethylamino)-2-phenyl-5,6-dihydro-4*H*-1,3-thiazine-5-yl]carbonyl}-1,3-oxazolidin-2-one: 6c. *Thermal activation*. To a solution of 4-dimethylamino-2-phenyl-1-thia-3-aza-buta-1,3-diene **2** (0.05 g, 2.6×10^{-4} mol) in dry toluene (2 mL) was added a solution of 3-(prop-2-enoyl)-oxazolidin-2-one (0.055 g, 3.9×10^{-4} mol) in dry toluene (8 mL). The reaction mixture was stirred for 20 h at 110 °C then, after cooling at room temperature, concentrated under reduced pressure. Purification by flash chromatography on silica (petroleum ether/acetone 2:3) gave **6c** as white needles (0.07 g, 81%).

Magnesium bromide activation. Compound **6c** was prepared according to the same procedure as compound **6b**. Flash-chromatography on silica (petroleum ether/acetone 2:3) produced the title compound as white needles (0.16 g, 68%); R_f 0.67 (petroleum ether/acetone 2:3); mp 108–109 °C (ethyl acetate/petroleum ether); ν_{max}/cm^{-1} 1768, 1700, 1616, 1393, 1225, 685; δ_H (200 MHz; $CDCl_3$): 2.41 (6H, s), 3.10 (1H, dd, J=3.8, 12.2 Hz), 3.47 (1H, dd, J=12.2, 12.2 Hz), 4.10 (2H, m), 4.33 (1H, ddd, J=3.8, 10.2, 12.2 Hz), 4.45 (2H, m), 4.68 (1H, d, J=10.2 Hz), 7.60 and 7.85 (5H, 2m); δ_C (50 MHz; $CDCl_3$): 28.5, 36.7, 40.7, 43.1, 62.1, 79.5, 126.7, 128.5, 130.9, 138.6, 153.6, 157.5, 174.6; m/z (EI): 333 ($M^{+}\cdot$, 1), 192 (100), 159 (70), 141 (13), 121 (83), 113 (32), 89 (56), 77 (32), 44 (54).

4.2.5. *cis* and *trans* Methyl 4-(dimethylamino)-6-phenyl-3,4-dihydro-2*H*-1,3-thiopyran-3-carboxylate: 8b and 9b. The title compounds and **8c** and **9c** were prepared according to the same procedure as compounds **6b** and **6c**. They were separated and obtained pure (except for **8c**) by chromatography on silica (petroleum ether/ethyl acetate 3:2) and isolated in yields greater than 90% (see text for information about the *cis*/*trans* ratios).

Compound **8b**. Pale yellow solid; R_f 0.40 (petroleum ether/ethyl acetate 3:2); mp 83–84 °C (ethyl acetate); ν_{max}/cm^{-1} 1734, 1342, 691; δ_H (400 MHz; $CDCl_3$): 2.37 (6H, s), 2.90 (1H, ddd, J=3.4, 5.0, 13.1 Hz), 3.00 (1H, dd, J=3.4, 13.1 Hz), 3.36 (1H, dd, J=13.1, 13.1 Hz), 3.76 (3H, s and

1H, m), 6.16 (1H, d, J=6.0 Hz), 7.34 and 7.50 (5H, 2m); δ_H (400 MHz; C_6D_6): 2.21 (6H, s), 2.71 (1H, ddd, J=3.4, 5.0, 13.1 Hz), 2.80 (1H, dd, J=3.4, 13.1 Hz), 3.41 (1H, m and 3H, s), 3.62 (1H, dd, J=5.0, 6.0 Hz), 6.01 (1H, d, J=6.0 Hz), 7.12 and 7.55 (5H, 2m); δ_C (50 MHz; $CDCl_3$): 24.3, 44.7, 46.0, 51.8, 58.3, 116.8, 126.7, 128.5, 137.6, 139.7 (2C), 173.4; *m/z* (EI): 277 ($M^{+}\cdot$, 1), 233 (6), 191 (50), 158 (100), 121 (13), 115 (18), 77 (8); Anal. calcd for $C_{15}H_{19}NO_2S$: C, 64.95; H, 6.90; N, 5.05; found: C, 65.15; H, 6.67; N, 5.05.

Compound **9b**. Pale yellow solid; R_f 0.21 (petroleum ether/ethyl acetate 3:2); mp 60–61 °C (diethyl ether/petroleum ether); ν_{max}/cm^{-1} 1740, 1347; δ_H (400 MHz; $CDCl_3$): 2.36 (6H, s), 2.99 (1H, dd, J=2.8, 12.4 Hz), 3.03 (1H, ddd, J=2.8, 9.3, 10.5 Hz), 3.30 (1H, dd, J=10.5, 12.4 Hz), 3.75 (3H, s), 3.82 (1H, dd, J=2.9, 9.3 Hz), 6.04 (1H, d, J=2.9 Hz), 7.33 and 7.48 (5H, 2m); δ_C (50 MHz; $CDCl_3$): 29.4, 41.0, 42.6, 52.4, 61.9, 118.4, 126.6, 128.6, 137.1, 139.4 (2C), 174.6; *m/z* (EI): 277 ($M^{+}\cdot$, 6), 262 (14), 246 (2), 233 (9), 191 (34), 158 (100); Anal. calcd for $C_{15}H_{19}NO_2S$: C, 64.95; H, 6.90; N, 5.05; found: C, 65.18; H, 6.89; N, 4.83.

4.2.6. *cis* and *trans* 3-{[4-(Dimethylamino)-6-phenyl-3,4-dihydro-2*H*-thiopyran-3-yl]carbonyl}-1,3-oxazolin-2-one: 8c and 9c. *Compound* **8c**. δ_H (400 MHz; C_6D_6): 2.19 (6H, s), 2.76 (1H, dd, J=3.2, 13.2 Hz), 3.18 (4H, m), 3.60 (1H, dd, J=13.2, 13.2 Hz), 4.16 (1H, ddd, J=3.2, 6.9, 13.2 Hz), 4.36 (1H, dd, J=5.0, 6.9 Hz), 6.14 (1H, d, J=5.0 Hz), 7.11 and 7.57 (5H, 2m).

Compound **9c**. R_f 0.36 (ethyl acetate/acetone 1:1); mp 131–132 °C (ethyl acetate/petroleum ether); ν_{max}/cm^{-1} 1770, 1693, 694; δ_H (400 MHz; $CDCl_3$): 2.35 (6H, s), 2.98 (1H, dd, J=2.8, 12.7 Hz), 3.25 (1H, dd, J=11.0, 12.7 Hz), 4.07 (3H, m), 4.44 (2H, ddd, J=2.5, 7.7, 8.6 Hz), 4.47 (1H, ddd, J=2.8, 10.1, 11.0 Hz), 6.07 (1H, d, J=2.7 Hz), 7.33, 7.48 (5H, 2m); δ_H (400 MHz; C_6D_6): 2.25 (6H, s), 2.78 (1H, dd, J=2.8, 12.6 Hz), 3.00 (4H, m), 3.24 (1H, dd, J=11.2, 12.6 Hz), 4.10 (1H, dd, J=2.6, 10.4 Hz), 4.82 (1H, ddd, J=2.8, 10.4, 11.2 Hz), 6.04 (1H, d, J=2.6 Hz), 7.12 and 7.60 (5H, 2m); δ_C (100 MHz; $CDCl_3$): 29.9, 40.3, 41.2, 43.1, 62.1, 62.2, 117.8, 126.7, 128.6, 137.2, 139.5, 131.9, 153.5, 174.5; *m/z* (EI: 332 ($M^{+}\cdot$, 1), 191 (49), 158 (100), 143 (21), 121 (26), 115 (34), 55 (98); Anal. calcd for $C_{17}H_{20}N_2O_3S$: C, 61.43; H, 6.06; N, 8.43; found: C, 61.00; H, 6.09; N, 8.22.

4.2.7. *cis*-Trimethyl-4-(dimethylamino)-3,4-dihydro-2*H*-thiopyran-3,5,6-tricarboxylate: 11b. To a solution of 4-dimethylamino-2,3-dimethoxycarbonyl-1-thia-buta-1,3-diene **10** (0.1 g, 4.33×10^{-4} mol) in dry dichloromethane (5 mL) was added methyl acrylate (0.06 mL, 6.66×10^{-4} mol). The reaction mixture was stirred for 4 h at room temperature then concentrated under reduced pressure. Purification by flash chromatography on silica (petroleum ether/ethyl acetate 1:1) gave **11b** as white crystals (0.124 g, 91%); R_f 0.66 (petroleum ether/ethyl acetate 1:1; mp 76 °C (diethyl ether); ν_{max}/cm^{-1} 1735, 1725, 1440, 1314, 1247, 729; δ_H (400 MHz; $CDCl_3$): 2.34 (6H, s), 2.59 (1H, ddd, J=3.2, 3.6, 13.2 Hz), 3.08 (1H, ddd, J=1.6, 3.2, 13.2 Hz), 3.31 (1H, dd, J=13.2, 13.2 Hz), 3.77 (3H, 3s), 3.79 (3H, 3s), 3.84 (3H, 3s), 4.33 (1H, dd, J=1.6, 3.3 Hz); δ_C (100 MHz; $CDCl_3$): 22.8, 44.7, 44.9, 52.1, 52.5, 53.3, 56.8, 123.0, 142.1, 166.0, 166.3, 172.0; *m/z* (EI): 317 ($M^{+}\cdot$, 11), 286 (7), 270 (7), 258 (17), 231 (50), 213 (20), 199 (100), 184 (19), 172 (61), 141 (40), 129 (13), 113 (13), 72 (24), 42 (32), 15 (22); Anal. calcd for $C_{13}H_{19}NO_6S$: C, 49.20; H, 6.03; N, 4.41; found: C, 49.34; H, 6.26; N, 4.51.

4.2.8. *cis*-Dimethyl 4-(dimethylamino)-3-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]-3,4-dihydro-2*H*-thiopyran-5,6-dicarboxylate: 11c. The title compound was prepared according to the same procedure as compound **11b** starting from 0.2 g of diene **10**. White crystals (0.216 g, 75%); R_f 0.25 (petroleum ether/ethyl acetate 3:7; mp 114 °C (petroleum ether/ethyl acetate); ν_{max}/cm^{-1} 1776, 1739, 1710, 1693, 1447, 1333, 1262, 1242, 719; δ_H (200 MHz; $CDCl_3$): 2.32 (6H, s), 2.89 (1H, dd, J=3.0, 13.0 Hz), 3.47 (1H, dd, J=2.1, 13.0 Hz), 3.72 (1H, ddd, J=3.0, 3.0, 13.0 Hz), 3.77 (3H, s), 3.84 (3H, s), 4.09 (2H, m), 4.40 (1H, d, J=3.0 Hz), 4.46 (1H, m); δ_C (100 MHz; $CDCl_3$): 22.9, 42.8, 44.5, 44.6, 52.4, 53.2, 57.0, 62.4, 123.5, 141.7, 153.1, 165.7, 166.1, 172.1; *m/z* (EI): 372 ($M^{+}\cdot$, 6), 231 (50), 199 (100), 172 (65), 141 (37), 113 (28), 55 (39); calcd for $C_{14}H_{20}N_2O_6S$: C, 48.83; H, 5.85; N, 8.13; found: C, 49.03; H, 6.47; N, 8.25. HRMS (LSIMS): *m/z*=373 $[M+H]^+$, calcd for $C_{15}H_{21}N_2O_7S$: 373.1070; found: 373.1066.

4.3. Cycloaddition of diene 2 with methyl acrylate catalysed by alumina: obtention of the *cis*- and *-trans* methyl 4-(dimethylamino)-2-phenyl-5,6-dihydro-4*H*-1,3-thiazine-5-carboxylates 12 and 6b

A solution of 4-dimethylamino-2-phenyl-1-thia-3-aza-buta-1,3-diene **2** (0.5 g, 2.6×10^{-3} mol) and methyl acrylate (2.3 mL, 26×10^{-3} mol) in dry dichloromethane (5 mL) was added to 1.5 g of basic alumina (Merck, type E). The reaction mixture was vigorously stirred for 1 h at 20 °C (or 0 °C). After addition of dichloromethane (40 mL) the resulting slurry was filtered on a pad of celite and the solvent concentrated (no heating!) under reduced pressure. NMR analysis of the crude mixture revealed, next to unreacted material, the presence of two diastereomeric adducts, **6b** and **12**, in a ratio depending on the reaction temperature (see text). Flash chromatography on silica (petroleum ether/ethyl acetate 80:20) gave **6b** (0.477 g, 66%). Due to its extremely facile conversion into *trans*-**6b**, the *cis* adduct **12** could not be isolated. Main NMR characteristic values for **12** (cf. **6b**): δ_H (200 MHz; $CDCl_3$): 2.52 (3H, s); 3.75 (3H, s); 4.62 (1H, d, J=4.0 Hz).

4.4. Synthesis of chiral non-racemic heterocycles

Thermal activation. To a solution of 4-dimethylamino-2-phenyl-1-thia-3-aza-buta-1,3-diene **2** (0.05 g, 2.6×10^{-4} mol) in dry toluene (2 mL) was added a solution of (4*S*)-4-benzyl-3-(prop-2-enoyl)-oxazolidin-2-one **13** (0.09 g, 3.9×10^{-4} mol) in dry toluene (10 mL). The reaction mixture was stirred for 20 h at 110 °C then, after cooling at room temperature, concentrated under reduced pressure. Purification by flash chromatography on silica (petroleum ether/ethyl acetate 1:1 then 1:4) gave **14** and **15** (ratio: 85:15) as white needles (0.082 g, 75%).

Magnesium bromide activation. Magnesium turnings (0.021 g, 8.6×10^{-4} mol) in dry diethyl ether (4 mL) were

placed under inert atmosphere. 1,2-Dibromoethane (0.073 mL, 8.47×10^{-4} mol) was added dropwise and the reaction mixture was slightly heated to start the formation of the catalyst $MgBr_2$. When all the magnesium turnings were consumed, diethyl ether was removed by several pumping and venting cycles (argon) to leave a white powder. Dichloromethane (8 mL) was syringed in, then the temperature was cooled to 0 °C. A solution of (4*S*)-4-benzyl-3-(prop-2-enoyl)-oxazolidin-2-one **13** (0.09 g, 3.9×10^{-4} mol) in dry dichloromethane (1 mL) was added followed, after 15 min, by a solution of 4-dimethylamino-2-phenyl-1-thia-3-aza-buta-1,3-diene **2** (0.05 g, 2.6×10^{-4} mol) also in dry dichloromethane (1 mL). The reaction mixture was stirred at 0 °C for 3 h. After dilution with dichloromethane (10 mL) at room temperature then successive washings with 10% aqueous potassium hydrogen carbonate (2×15 mL) and brine (2×15 mL), the organic layer was extracted, dried ($MgSO_4$), filtered and concentrated. A washing of the residue with cold diethyl ether gave **15** as white needles (0.075 g, 68%).

4.4.1. (4*S*)-3-{[(4*S*,5*S*)-4-(Dimethylamino)-2-phenyl-5,6-dihydro-4*H*-1,3-thiazine-5-yl] carbonyl}-4-benzyl-1,3-oxazolidin-2-one: 14. *Compound* **14**. R_f 0.40 (petroleum ether/ethyl acetate 1:4); mp 107–108 °C (diethyl ether/petroleum ether); $[\alpha]_D^{21.5}=+196.4$ (*c* 0.28, $CHCl_3$); ν_{max}/cm^{-1} 1762, 1692, 1616, 1396, 1256, 690; δ_H (400 MHz; $CDCl_3$): 2.40 (6H, s), 2.82 (1H, dd, *J*=8.6, 13.7 Hz), 3.14 (1H, dd, *J*=3.7, 12.0 Hz), 3.30 (1H, dd, *J*=3.2, 13.7 Hz), 3.47 (1H, dd, *J*=12.0, 12.0 Hz), 4.24 (2H, m), 4.26 (1H, ddd, *J*=3.7, 10.1, 12.0 Hz), 4.71 (1H, d, *J*=10.1 Hz), 4.79 (1H, m), 7.32 and 7.85 (10H, 2m); δ_C (100 MHz; $CDCl_3$): 28.5, 37.0, 38.1, 40.7, 55.8, 66.5, 79.2, 126.7, 127.5, 128.4, 129.1, 129.5, 130.8, 135.2, 138.5, 153.5, 157.5, 174.2; *m*/*z* (CI): 423 ($M^{+}\cdot$); (EI): 192 (28), 159 (20), 121 (24), 55 (100), 44 (25); Anal. calcd for $C_{23}H_{25}N_3O_3S$: C, 65.23; H, 5.95; N, 9.92; found: C, 64.69; H, 5.93; N, 9.87.

4.4.2. (4*S*)-3-{[(4*R*,5*R*)-4-(Dimethylamino)-2-phenyl-5,6-dihydro-4*H*-1,3-thiazine-5-yl] carbonyl}-4-benzyl-1,3-oxazolidin-2-one: 15. *Compound* **15**. R_f 0.88 (petroleum ether/ethyl acetate 1:4); mp 125–126 °C (diethyl ether/petroleum ether); $[\alpha]_D^{20}=-65.4$ (*c* 0.52, $CHCl_3$); ν_{max}/cm^{-1} 1762, 1692, 1616, 1396, 690; δ_H (400 MHz; $CDCl_3$): 2.47 (6H, s), 2.88 (1H, dd, *J*=8.6, 13.7 Hz), 3.10 (1H, dd, *J*=3.7, 12.0 Hz), 3.26 (1H, dd, *J*=3.2, 13.7 Hz), 3.55 (1H, dd, *J*=12.0, 12.0 Hz), 4.20 (2H, m), 4.38 (1H, ddd, *J*=3.7, 10.1, 12.0 Hz), 4.69 (1H, d, *J*=10.1 Hz), 4.79 (1H, m), 7.35 and 7.85 (10H, 2m); δ_C (100 MHz; $CDCl_3$): 28.3, 36.7, 37.4, 40.7, 55.3, 65.9, 80.5, 126.7, 127.4, 128.4, 129.0, 129.8, 130.8, 135.3, 138.6, 153.5, 157.5, 174.9; *m*/*z* (CI): 423 ($M^{+}\cdot$); (EI): 192 (28), 159 (20), 121 (24), 55 (100), 44 (25); HRMS (LSIMS): *m*/*z*=424 $[M+H]^+$, calcd for $C_{23}H_{25}N_3O_3S$: 424.1695; found: 424.1694.

Thermal activation. A mixture of dimethyl (2*E*)-[(dimethylamino)methylene]-3-thiosuccinate **10** (1.10 mmol) and (4*S*)-3-acryloyl-4-benzyl-1,3-oxazolidin-2-one **13** (1.10 mmol) in anhydrous CH_2Cl_2 (10 mL) was stirred at room temperature during 16 h. The concentrated crude mixture was then flash-chromatographed on silica (eluent: petroleum ether/AcOEt, 7:3) to afford *cis*-**23** (310 mg, 61%) along with its diastereoisomer *cis*-**22** (50 mg, 10%).

Magnesium bromide activation. To a suspension of activated magnesium turnings (3.25 mmol) in dry Et_2O was added 1,2-dibromoethane (3.25 mmol). The resulting mixture was stirred until disappearance of all magnesium turnings and solvent evaporated under N_2 draught. After addition of dry CH_2Cl_2 (10 mL), (4*S*)-3-acryloyl-4-benzyl-1,3-oxazolidin-2-one **13** (1.10 mmol) in anhydrous CH_2Cl_2 (3 mL) was added at −10 °C. After 15 min stirring at −10 °C, dimethyl (2*E*)-[(dimethylamino)methylene]-3-thiosuccinate **10** (1.10 mmol) was slowly added. The reaction mixture was then stirred at −10 °C for 3 h. Saturated $NaHCO_3$ (5 mL) was added and the organic layer was washed with saturated $NaHCO_3$ (2×5 mL), water (5 mL) and brine (5 mL). The CH_2Cl_2 extract was then dried over anhydrous $MgSO_4$, filtered and concentrated. The crude mixture was flash-chromatographed on silica (eluent: petroleum ether/AcOEt, 7:3) to afford *trans*-**25** (285 mg, 57%) as white crystals along with its diastereoisomer *cis*-**22** (142 mg, 28%).

4.4.3. Dimethyl (3*R*,4*R*)-4-(dimethylamino)-3-{[(4*S*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl] carbonyl}-3,4-dihydro-2*H*-thiopyran-5,6-dicarboxylate: 22. *Compound* (3*R*,4*R*)-**22**. $[\alpha]_D^{20}=+371.0$ (*c* 0.52, $CHCl_3$); δ_H (400 MHz; $CDCl_3$): 2.39 (6H, s); 2.70 (1H, dd, *J*=13.0, 11.4 Hz); 2.92 (1H, ddd, *J*=12.4, 2.3, 1.6 Hz); 3.50–3.57 (2H, m); 3.67 (1H, m); 3.79, 3.84 (6H, 2s); 4.20 (2H, m); 4.56 (1H, dd, *J*=3.3, 1.6 Hz); 4.74 (1H, m); 7.25–7.37 (5H, m); δ_C (100 MHz; $CDCl_3$): 23.2, 38.5, 44.9, 45.1, 52.5, 53.3, 55.6, 60.5, 66.9, 123.9, 127.5, 129.2, 129.4, 135.5, 141.4, 153.2, 166.1, 172.0, 184.9; HRMS (LSIMS): *m*/*z*=463 $[M+H]^+$, calcd for $C_{22}H_{27}N_2O_7S$: 463.1539; found: 463.1534.

4.4.4. Dimethyl (3*S*,4*S*)-4-(dimethylamino)-3-{[(4*S*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl] carbonyl}-3,4-dihydro-2*H*-thiopyran-5,6-dicarboxylate: 23. *Compound* (3*S*,4*S*)-**23**. $[\alpha]_D^{20}=-310.4$ (*c* 0.52, $CHCl_3$); δ_H (400 MHz; $CDCl_3$): 2.35 (6H, s), 2.78 and 3.41 (2H, AB part of an ABX system, *J*=13.3, 9.8, 3.2 Hz), 2.97 and 3.52 (2H, AB part of an ABX system, *J*=13.1, 13.0, 3.0 Hz), 3.72–3.82 (1H, m), 3.76, 3.84 (6H, 2s), 4.23 (2H, m), 4.30 (1H, dd, *J*=3.4, 1.2 Hz), 4.63 (1H, m), 7.22–7.36 (5H, m); δ_C (100 MHz; $CDCl_3$): 23.1, 37.8, 44.8, 52.5, 53.3, 56.4, 57.2, 66.6, 123.4, 127.6, 129.1, 129.5, 135.3, 141.9, 153.0, 165.8, 166.2, 172.1; HRMS (LSIMS): *m*/*z*=463 $[M+H]^+$, calcd for $C_{22}H_{27}N_2O_7S$: 463.1539; found: 463.1535.

4.4.5. Dimethyl (3*R*,4*S*)-4-(dimethylamino)-3-{[(4*S*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl] carbonyl}-3,4-dihydro-2*H*-thiopyran-5,6-dicarboxylate 24. *Compound* (3*R*,4*S*)-**24**. Mp 134 °C. $[\alpha]_D^{20}=-102.1$ (*c* 0.52, $CHCl_3$); δ_H (400 MHz; $CDCl_3$): 2.36 (6H, s), 2.70 and 3.31 (2H, AB part of an ABX system, *J*=12.8, 9.8, 3.2 Hz), 3.14 (2H, d, *J*=4.7 Hz), 3.80, 3.81 (6H, 2s), 4.17–4.26 (3H, m), 4.53 (1H, dd, *J*=4.9, 4.7 Hz), 4.69 (1H, m), 7.20–7.35 (5H, m); δ_C (100 MHz; $CDCl_3$): 27.2, 37.6, 38.8, 41.9, 52.5, 53.1, 55.6, 60.1, 66.5, 127.5, 129.1, 129.5, 135.2, 130.7, 136.4, 153.3, 165.2, 167.5, 171.5; HRMS (LSIMS): *m*/*z*=463 $[M+H]^+$, calcd for $C_{22}H_{27}N_2O_7S$: 463.1539. Found:

463.1534; Anal. calcd for $C_{22}H_{26}N_2O_7S$ (462.52): C, 57.13; H, 5.67; N, 6.06; found: C, 57.22; H, 5.79; N, 5.98.

4.5. Chiral auxiliary removal

4.5.1. Preparation of an authentic sample of benzyl-4-(dimethylamino)-2-phenyl-5,6-dihydro-4*H*-1,3-thiazine-5-carboxylate: 26. To a solution of 4-dimethylamino-2-phenyl-1-thia-3-aza-buta-1,3-diene **2** (0.5 g, 2.6×10^{-3} mol) in dry toluene (30 mL) were added benzyl acrylate (1 g, 6.17×10^{-3} mol) and hydroquinone (few crystals). The reaction mixture was stirred for 5 h at 110 °C then, after cooling at room temperature, concentrated under reduced pressure. Purification by flash chromatography on silica (petroleum ether/ethyl acetate 7:3) gave the title compound as a white solid (0.87 g, 95%).

4.5.2. Benzyl (4*R*,5*R*)-4-(dimethylamino)-2-phenyl-5,6-dihydro-4*H*-1,3-thiazine-5-carboxylate: 26. Benzyl alcohol (0.073 mL, 7×10^{-4} mol) was diluted in dry THF (6 mL) and placed under inert atmosphere. The solution was cooled to −78 °C and *n*-butyllithium (1.6 M in hexane, 0.33 mL, 5.28×10^{-4} mol) was added dropwise. After 5 min, a solution of adduct **15** (0.15 g, 3.5×10^{-4} mol) in dry THF (0.45 mL) was syringed in. The temperature was allowed to warm to room temperature and after 5 h, saturated aqueous ammonium chloride (3 mL) was added. The reaction mixture was concentrated under reduced pressure. The residue was diluted with dichloromethane (10 mL) and washed with brine (1×10 mL). The organic layer was extracted, dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica (petroleum ether/ethyl acetate 7:3) gave **26** as white needles (0.04 g, 32%); R_f 0.47 (petroleum ether/ethyl acetate 1:1); mp 88–89 °C (diethyl ether/petroleum ether); $[\alpha]_D^{20}=-123.1$ (*c* 0.26, $CHCl_3$); ν_{max}/cm^{-1} 1733, 1612; δ_H (400 MHz; $CDCl_3$): 2.41 (6H, s), 2.76 (1H, ddd, *J*=3.9, 10.1, 12.2 Hz), 3.11 (1H, dd, *J*=3.9, 12.2 Hz), 3.54 (1H, dd, *J*=12.2, 12.2 Hz), 4.45 (1H, d, *J*=10.1 Hz), 5.20 (1H, d, *J*=12.4 Hz), 5.25 (1H, d, *J*=12.4 Hz), 7.38 and 7.83 (10H, 2m); δ_C (100 MHz; $CDCl_3$): 28.3, 40.1, 40.3, 66.8, 79.2, 126.6, 128.2, 128.3, 128.4, 128.6, 130.8, 136.0, 138.5, 157.8, 173.4; *m/z* (EI): 354 ($M^{+}\cdot$, 3), 192 (100), 159 (68), 121 (55), 89 (89), 77 (34), 55 (33), 44 (52); Anal. calcd for $C_{20}H_{22}N_2O_2S$: C, 67.77; H, 6.26; N, 7.90; found: C, 67.40; H, 6.29; N, 7.89.

4.5.3. General procedure with $Sm(OTf)_3$. To a mixture of cycloadduct (0.2 mmol) in anhydrous CH_2Cl_2 (2 mL) was added samarium triflate (0.25 equiv.). The resulting solution was stirred for 15 min at room temperature before the addition of MeOH (2 mL). After an additional 18 h of stirring the reaction mixture was concentrated to a residue that was purified by silica gel chromatography (petroleum ether/AcOEt 4:1).

Trimethyl (3*S*,4*S*)-4-dimethylamino-3,4-dihydro-2*H*-thiopyran-3,5,6-dicarboxylate: (−)-**11b**

White solid; mp 99 °C. $[\alpha]_D^{20}=-440.0$ (*c* 0.75, $CHCl_3$).

4.5.4. Trimethyl (3*R*,4*S*)-4-dimethylamino-3,4-dihydro-2*H*-thiopyran-3,5,6-dicarboxylate: (−)-28. $[\alpha]_D^{20}=-162.2$ (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 1734, 1716, 1700, 1436, 1258, 730; δ_H (400 MHz; $CDCl_3$): 2.31 (6H, s); 3.09–3.13 (1H, m); 3.21–3.28 (2H, m,); 3.72 (3H, s), 3.77 (3H, s), 3.79 (3H, s), 4.16 (1H, dd, *J*=1.2, 5.2 Hz); δ_C (100 MHz; $CDCl_3$): 26.3, 39.3, 42.0, 52.4, 52.5, 53.1, 59.2, 129.6, 136.6, 165.3, 167.2, 171.9; HRMS (ESI+), $[M+H]^+$ calcd for $C_{13}H_{20}NO_6S$: 318.1011; found: 318.1016.

4.5.5. Methyl (*R*,*R*)- and methyl (*S*,*S*)-4-(dimethylamino)-2-phenyl-5,6-dihydro-4*H*-1,3-thiazine-5-carboxylates. (+)-**6b**. $[\alpha]_D^{20}=+155.5$ (*c*=0.67, $CHCl_3$).

(−)-**6b**. $[\alpha]_D^{20}=-156.2$ (*c*=0.86, $CHCl_3$).

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