Stereoselective reactions of *N*-acyl thiazolidinethiones with trimethyl orthoformate, acetals and diarylmethyl ethers catalyzed by nickel(II) complexes

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Programa de Doctorat de Química Orgànica

STEREOSELECTIVE REACTIONS OF *N*-ACYL THIAZOLIDINETHIONES WITH TRIMETHYL ORTHOFORMATE, ACETALS AND DIARYLMETHYL ETHERS CATALYZED BY NICKEL(II) COMPLEXES

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El treball experimental d'aquesta Tesi s'ha realitzat íntegrament en el Departament de Química Orgànica de la Universitat de Barcelona des d'octubre de 2010 fins a octubre de 2014 sota la direcció dels Drs. Pedro Romea i Fèlix Urpí. Des d'octubre de 2010 fins a desembre de 2011 he gaudit d'una beca predoctoral d'Ajut de Personal Investigador predoctoral en Formació (APIF) de la Universitat de Barcelona i des de gener de 2011 a setembre de 2014, d'una beca de Formación de Profesorado Universitario (FPU) del Ministerio de Educación, Cultura y Deporte.

En primer lloc, m'agradaria agrair als meus directors de tesi, en Pere i en Fèlix, l'atenció dedicada, les hores de discussió de resultats, la paciència que han mostrat i l'ajut que sempre m'han ofert en qualsevol situació. Junt amb el rigor científic, l'esforç i la dedicació que els caracteritzen fan que siguin, sens dubte, els meus principals referents professionals.

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CONTENTS

GENERAL INTRODUCTION

Stereochemistry is one of the most important concepts in chemistry, since the spatial arrangement of the atoms of a molecule has a tremendous influence on the physical, chemical and biological properties of a compound.[1] This is particularly true for chiral molecules, which are distinguishable from their mirror images. The stereospecific molecular recognition of a compound by biological systems, defined as the accurate three-dimensional interaction between an active site of an enzyme and the substrate, is a clear example (Figure 1). The convenient identification of an active site and the subsequent search for the adequate matching molecule, which can be a natural product or a synthetic drug, can end up in the eradication of a disease.[2] Therefore, the stereocontrolled preparation of chiral compounds holds a prominent position among the current objectives of organic synthesis.

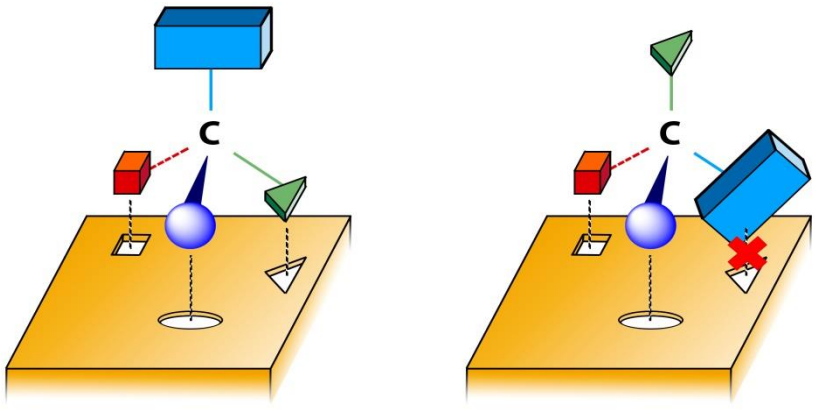
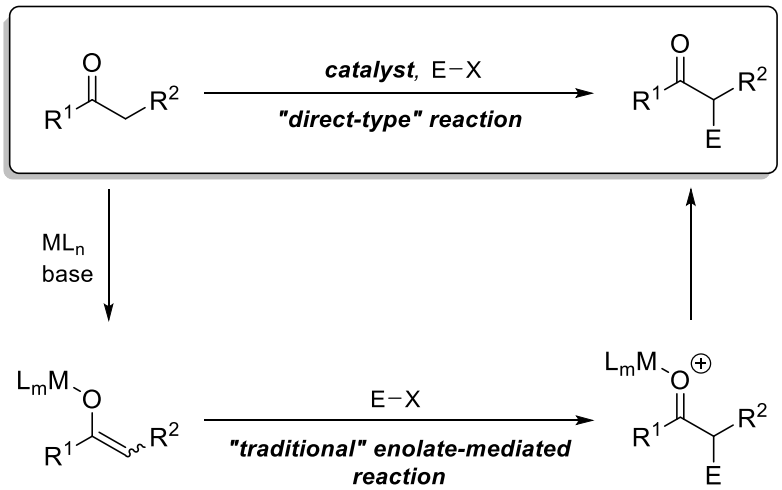


Figure 1

In this context, the development of increasingly more efficient methods for carrying out asymmetric syntheses plays a key role in organic chemistry and in pharmacology.[3] In such a pursuit, the need for new and useful reactivity has become a crucial challenge. Especially, new methods for the stereoselective construction of C–C bonds are highly desirable, since they would allow chemists to build effectively the carbonated backbone skeleton of chiral molecules.[4]

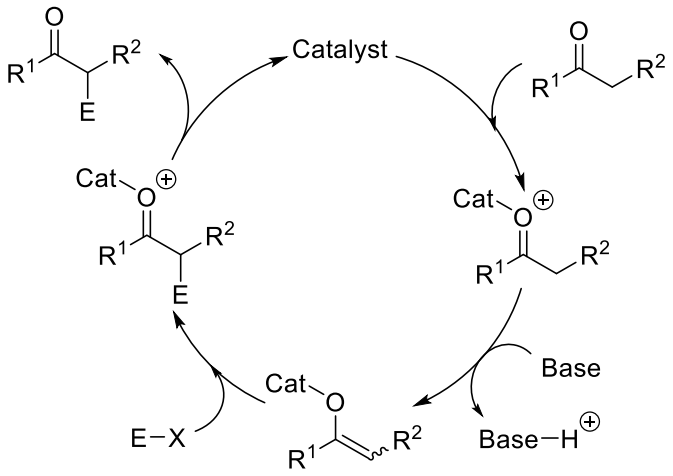
Running parallel, new concerns associated to the manner how the chemical transformations are carried out have aroused during the last two decades. Closely related to the concepts of "Atom Economy" and "Green Chemistry",[5] the development of catalytic processes is a current challenge in organic synthesis due to the small amount of catalyst required, which permits the use of valuable metals and ligands and minimizes the final waste. [3b,3c,6]

Not surprisingly, the catalytic generation of enolates as nucleophiles in C–C bond forming reactions has appeared as one of most trending approaches for such endeavors. Indeed, enolates play a crucial role in seminal transformations as alkylation, aldol or Michael reactions. In contrast to traditional strategies based on the stoichiometric preformation of enolates and subsequent nucleophilic attack to the corresponding electrophile, new trends in catalytic asymmetric reactions involving enolates refer to ***"direct-type reaction"*** (Scheme 1), in which the final adduct is obtained in a one-pot reaction from a mixture of the carbonyl derivative and the electrophile.



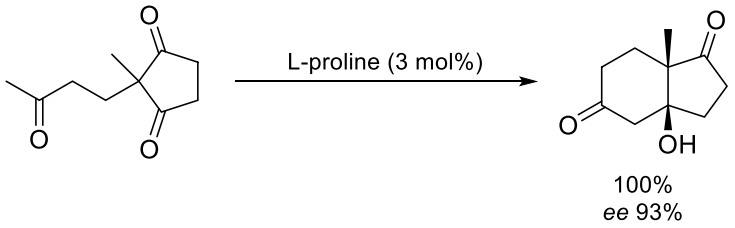
Scheme 1

Such a strategy involves some challenging requirements. As represented in Scheme 2, the formation of the enolate must occur in the presence of the electrophile, the construction of the C–C bond must proceed with high levels of stereocontrol and the resulting adduct must release the catalyst, which could then react with fresh materials.



Scheme 2

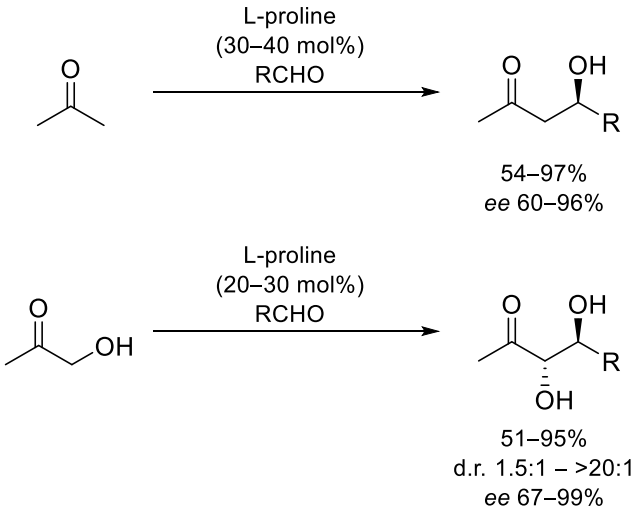
The asymmetric Robinson-annulation reported by Hajos and Parrish in 1974 heralded this sort of transformations.[7] As shown in Scheme 3, the treatment of a prochiral ketone containing three carbonyl groups with L-proline affords the bicyclic ketone quantitatively in an enantiomerically pure and straightforward manner.



Scheme 3

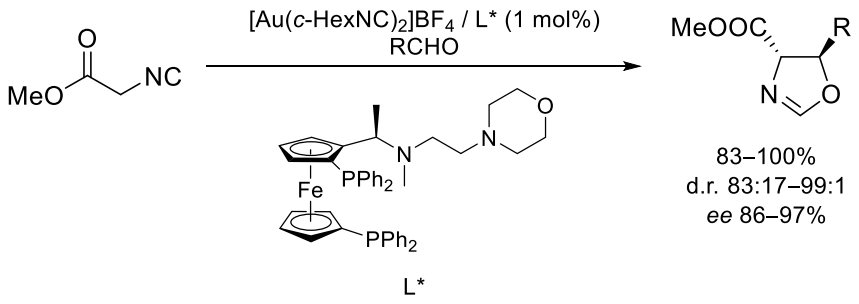
Unfortunately, the Hajos-Parrish-Eder-Sauer-Wiechert cyclization is based on a particular intramolecular aldol reaction with a very narrow scope.[7,8] The low acidity of most of carbonyl compounds restricts the wide application of such a method and requires the use of easily enolizable substrates such as 1,3-dicarbonyl compounds, α-oxygenated or just methyl ketones.

In spite of these restrictions, asymmetric organocatalysis has blossomed in recent years. Inspired by the previous reaction, Barbas and List successfully developed in 2000 intermolecular cross-aldol reactions between acetone and hydroxyacetone with aldehydes catalyzed by L-proline (Scheme 4).[9,10] Although the aldol products are obtained with up to two new controlled stereogenic centers, a large excess of the starting ketone and high loadings of the catalyst were necessary.[11]



Scheme 4

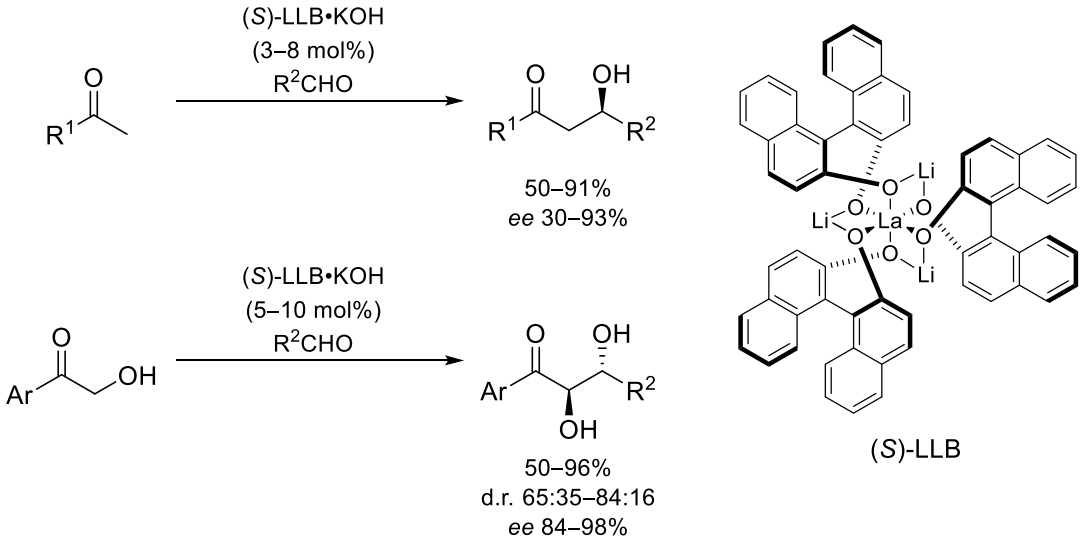
While organocatalysis has been widely exploited since these early methodologies,[11,12] few examples of metal catalysis have been described.[11a] Pioneering studies on metal-catalyzed asymmetric aldol reaction were reported by Ito in 1986, in which the addition of methyl α–isocyanoacetate with aldehydes catalyzed by a Au(I) chiral complex furnished *trans*–oxazolines with good yields and high diastereo and enantioselectivities.[13]



Scheme 5

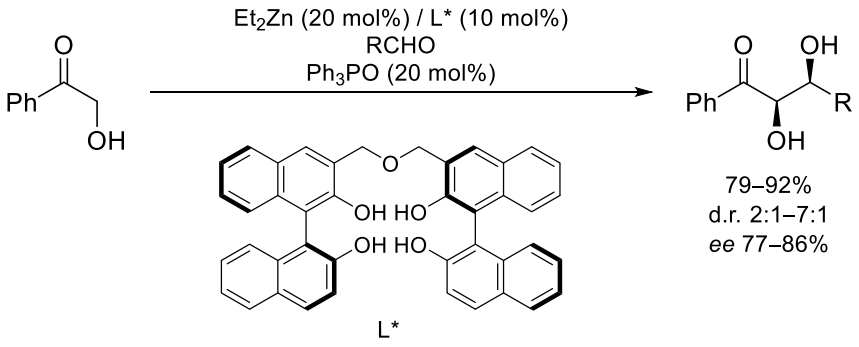
Other procedures using α–isocyanoacetates and related chiral metal complexes were also developed,[11a,14] but they lacked a wide breath of substrates. In this context, bimetallic catalysts were designed to obtain more general methodologies. Such catalysts are defined as multifunctional catalysts, since they exhibit both Brønsted basicity and Lewis acidity.[15] Thus, one of the metal atoms acts as a Brønsted base to facilitate the enolization of the carbonyl substrate, while the other one serves as a Lewis acid and coordinates to the aldehyde to increase its electrophilicity.

Such an approach is represented by Shibasaki's rare earth-alkali metal heterobimetallic chiral catalysts with the general form of (*S*)-M_3[Ln(BINOL)$_3$], in which the lanthanide metal and the alkali metal play the role of Lewis acid and Brønsted base, respectively (Scheme 6).[16] The direct aldol reactions of methyl and α-hydroxy ketones catalyzed by the heterobimetallic (*S*)-Li_3[La(BINOL)$_3$] ((*S*)-LLB) afford enantioselectively the corresponding β-hydroxy and *anti*-α,β-dihydroxy aldol adducts in good yields.[11a,17]



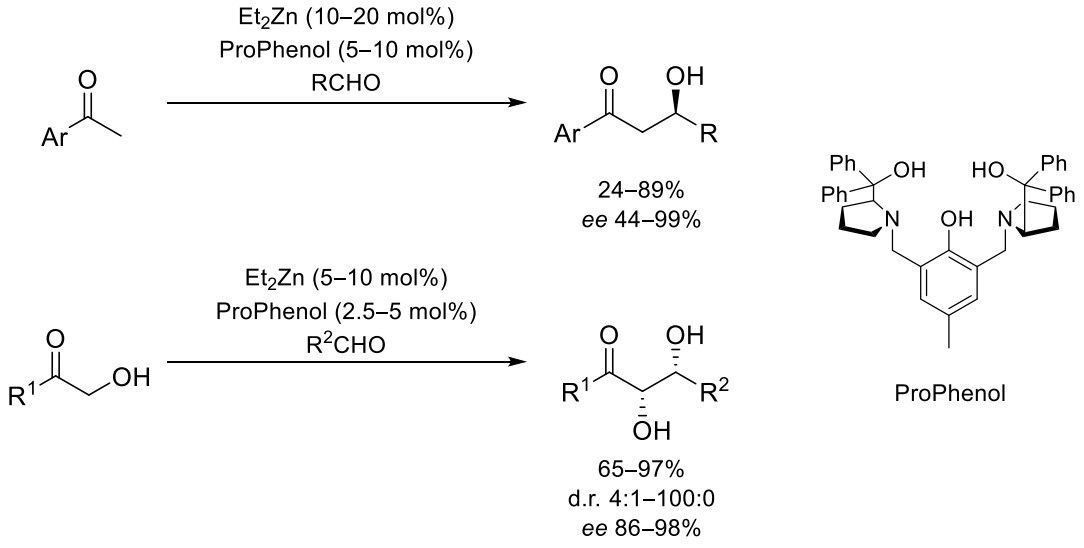
Scheme 6

Further contributions by Shibasaki *et. al.* have established that *syn*-α,β-dihydroxy adducts can also be prepared with a moderate stereocontrol by using a more elaborate (*S,S*)-linked BINOL Zn(II) catalyst (Scheme 7).[18]



Scheme 7

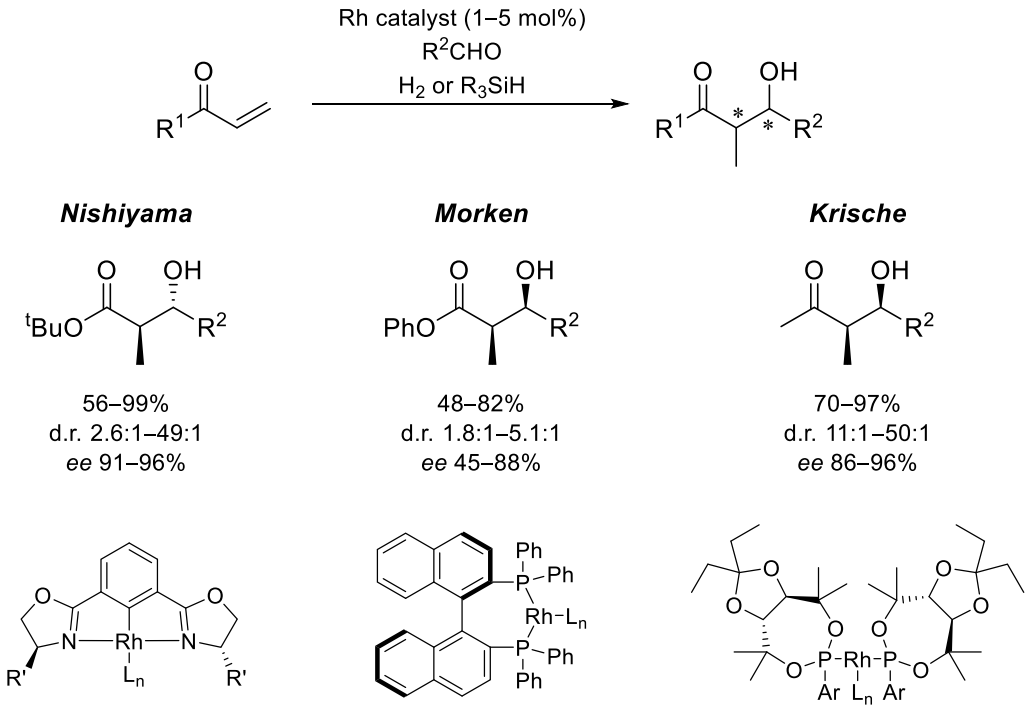
In turn, inspired by the reaction mechanism of class II aldolases and taking advantage of the multifunctional catalyst concept, Trost developed a Zn(II) bimetallic catalyst for the direct aldol reaction (Scheme 8).[11a,19] This catalyst, prepared *in situ* by treatment of ProPhenol ligand with two equivalents of Et_2Zn, provides the corresponding β-hydroxy and *syn*-α,β-dihydroxy aldol adducts with a good stereocontrol and yield.



Scheme 8

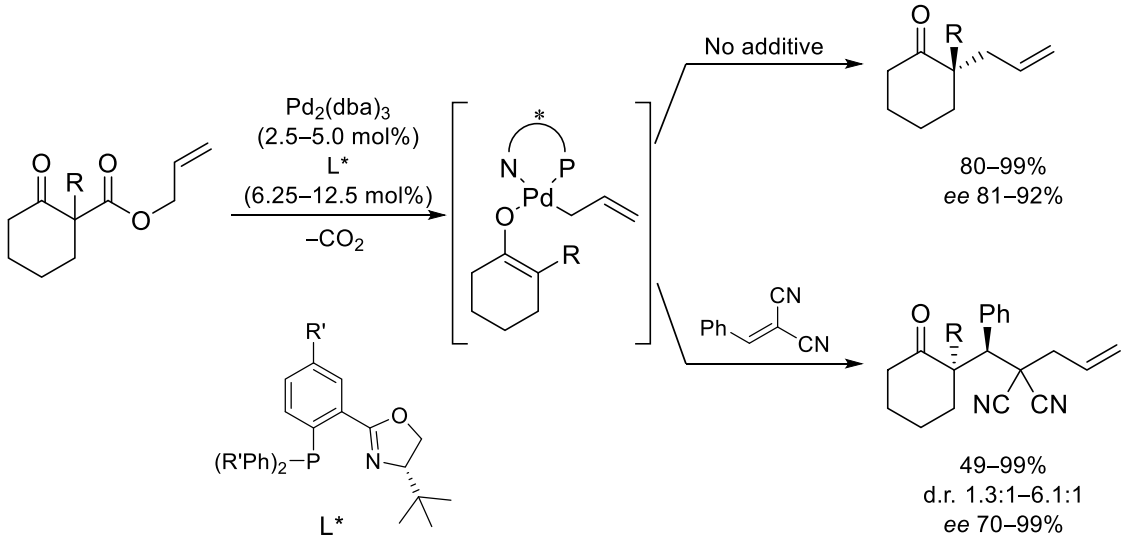
Nevertheless, these methods are restricted to certain carbonyl substrates. In order to attain a broader scope in direct-type reactions, strategies different from multifunctional catalysis have also been used. The catalytic production of a metal enolate induced by a previous chemical reaction instead of the general deprotonation from a Brønsted base has been one of the most recurrent concepts.

In this context, the reductive aldol reaction by means of a catalytic enolate generation from enones developed by Nishiyama, Morken and Krische represents an ingenious alternative to carry out catalytic propionate aldol reactions that were not possible with Shibasaki and Trost procedures (Scheme 9).[20] The partial hydrogenation of the double bond of the enone gives rise to a metal enolate, which subsequently attacks an aldehyde to create the final adduct.



Scheme 9

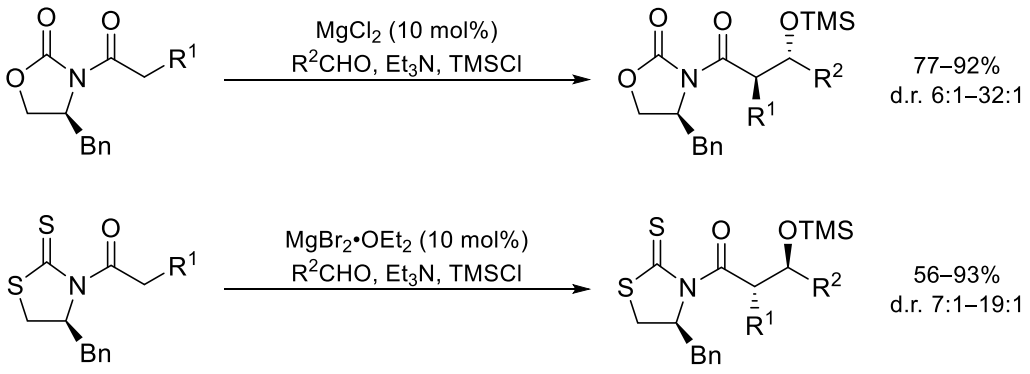
Stoltz *et. al.* adopted a similar strategy for the asymmetric alkylation of cyclohexanone leading to the enantioselective construction of quaternary stereocenters.[21] As shown in Scheme 10, the Pd-mediated enolate alkylation of a β-keto allyl ester proceeds through decarboxylation of the starting material induced by the formation of a π-allyl-Pd(0) complex.



Scheme 10

Alternatively, the catalytic enolization of non particulary acidic substrates has been achieved by attaching oxazolidinone or thiazolidinethione-based auxiliaries to the carbonyl group. Such auxiliaries facilitate the deprotonation of the carbonyl and provide chelated enolates that permit the differentiation of the two faces of the π-bond.[3d,22]

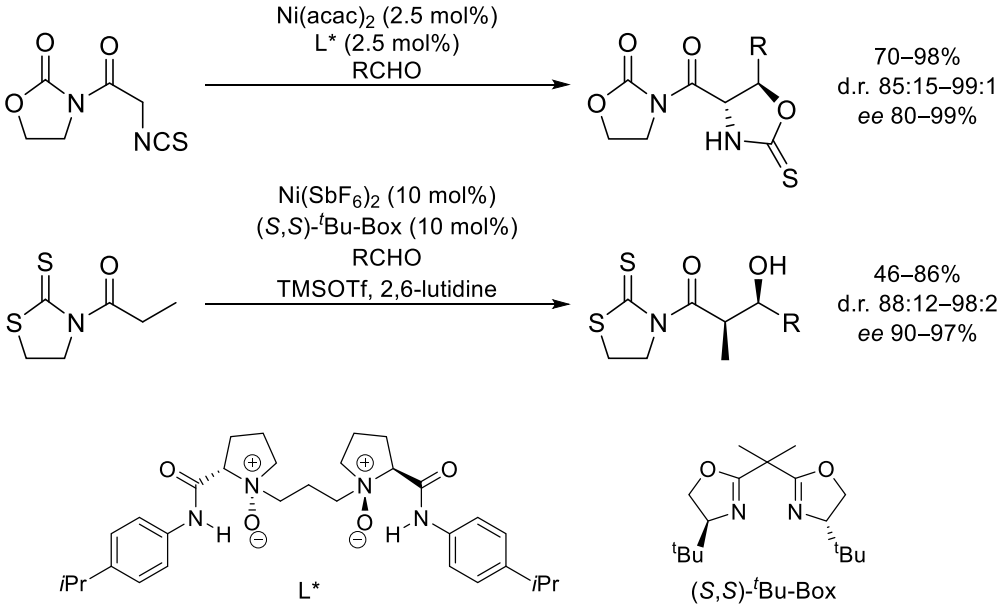
In pioneering studies, Evans disclosed highly diastereoselective aldol reactions from chiral *N*-acyl oxazolidinones and thiazolidinethiones catalyzed by achiral magnesium salts.[23,24] As shown in Scheme 11, the appropriate choice of the chiral auxiliary permits to obtain both *anti*-aldol adducts.



Scheme 11

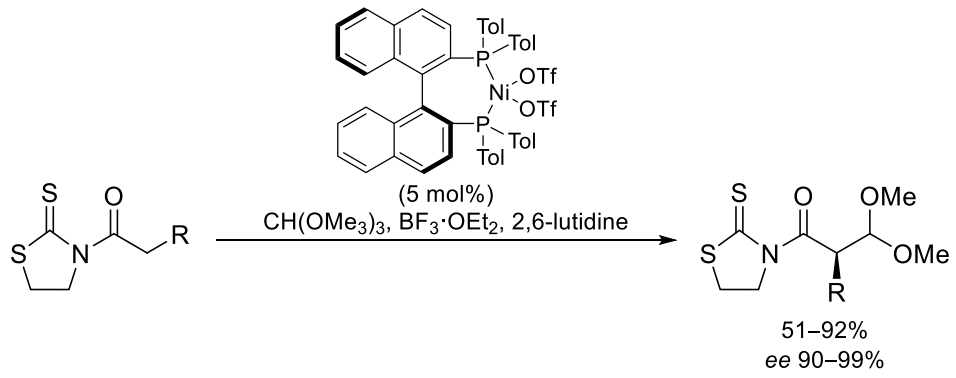
Further advances in this area rely on the use of achiral oxazolidinones or thiazolidinones and chiral catalysts. For instance, Feng reported the synthesis of α-

amino-β-hydroxy acid derivatives from an oxazolidinone with a relatively easy to deprotonate α-nitrogenated acetyl chain catalyzed by a chiral Ni(II) complex.[25] A nucleophilic attack of the aldolate over the isothiocyanato group produces a newly formed oxazolidinethione. In turn, Evans described the *syn*-aldol reaction from achiral *N*-propanoyl-1,3-thiazolidine-2-thione in the presence of a chiral Ni(II)-^{t}Bu-Box catalyst (Scheme 12).[26]



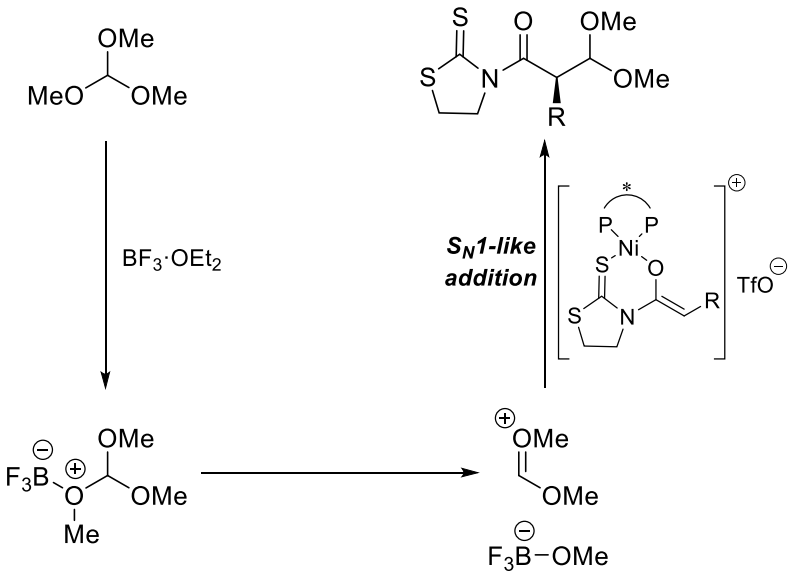
Scheme 12

More recently, Evans reported the enantioselective reaction of *N*-acyl-1,3-thiazolidine-2-thiones with trimethyl orthoformate catalyzed by (*S*)-(Tol-BINAP)Ni(OTf)$_2$ (Scheme 13).[27]



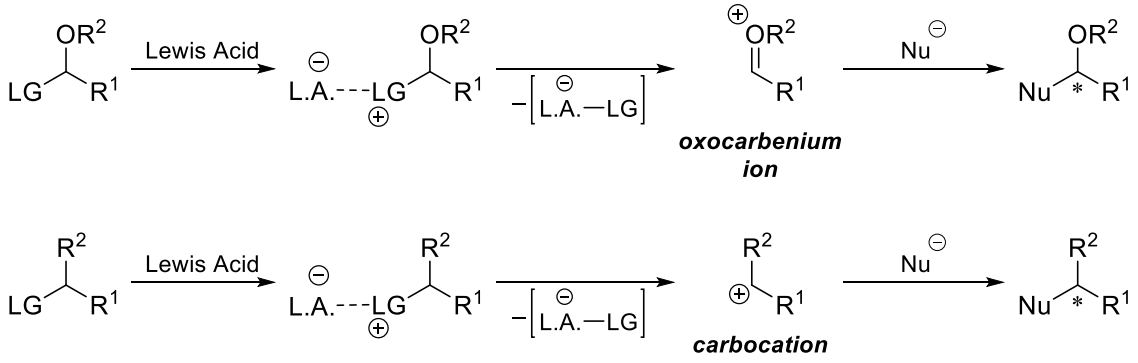
Scheme 13

The mechanism of this transformation relies on the addition of a putative Ni(II) enolate to an oxocarbenium intermediate produced by the *in situ* reaction of trimethyl orthoformate with a Lewis acid ($BF_3 \cdot OEt_2$).[27] Therefore, the stereoselective construction of the C–C bond proceeds through a S_N1-like mechanism.



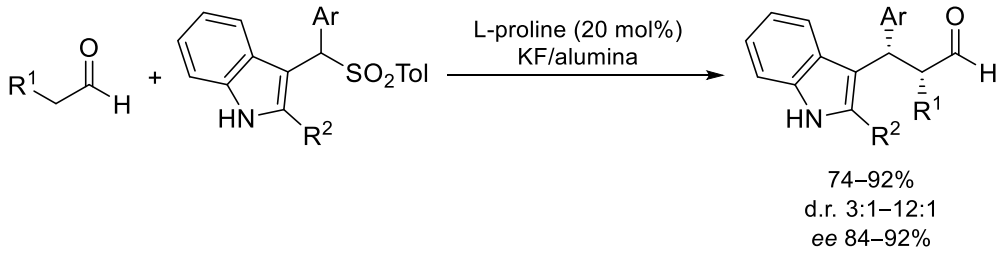
Scheme 14

Catalytic processes based on the addition of a metal enolate to a cationic intermediate through a similar pathway are scarce, but represent an appealing approach since they can give an easy access to complex structures under mild conditions.



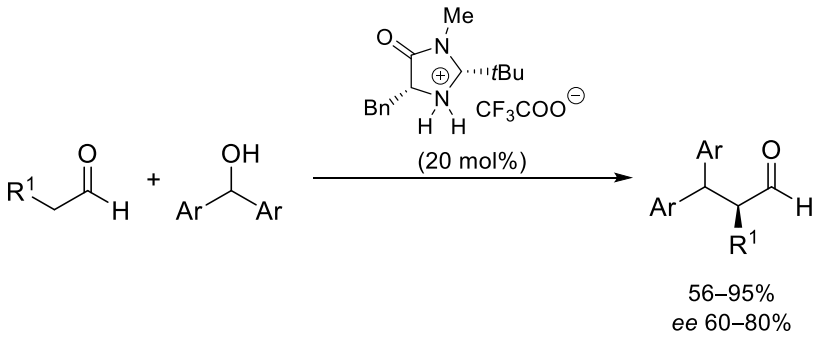
Scheme 15

In this context, Melchiorre reported the first catalytic S_N1-like alkylation of aldehydes with arylsulfonyl indoles catalyzed by proline (Scheme 16).[28] Although the activation of the electrophile does not take place under acidic conditions, the nucleophilic attack step proceeds through a S_N1-like mechanism in which stabilized carbocations are involved.



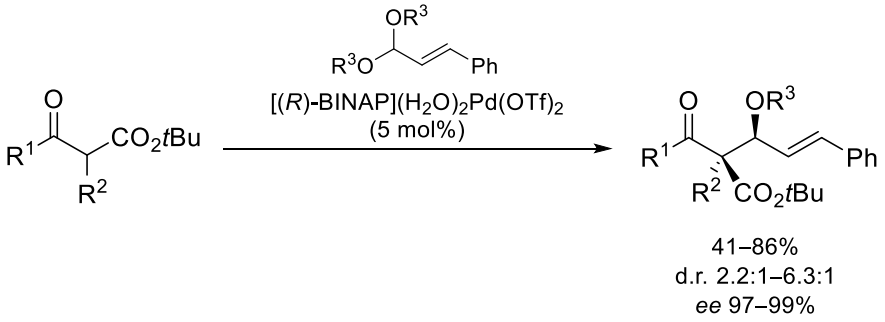
Scheme 16

Later on, Cozzi disclosed highly enantioselective alkylation of aldehydes with activated benzhydryl alcohols catalyzed by a second-generation MacMillan imidazolidinones.[29]



Scheme 17

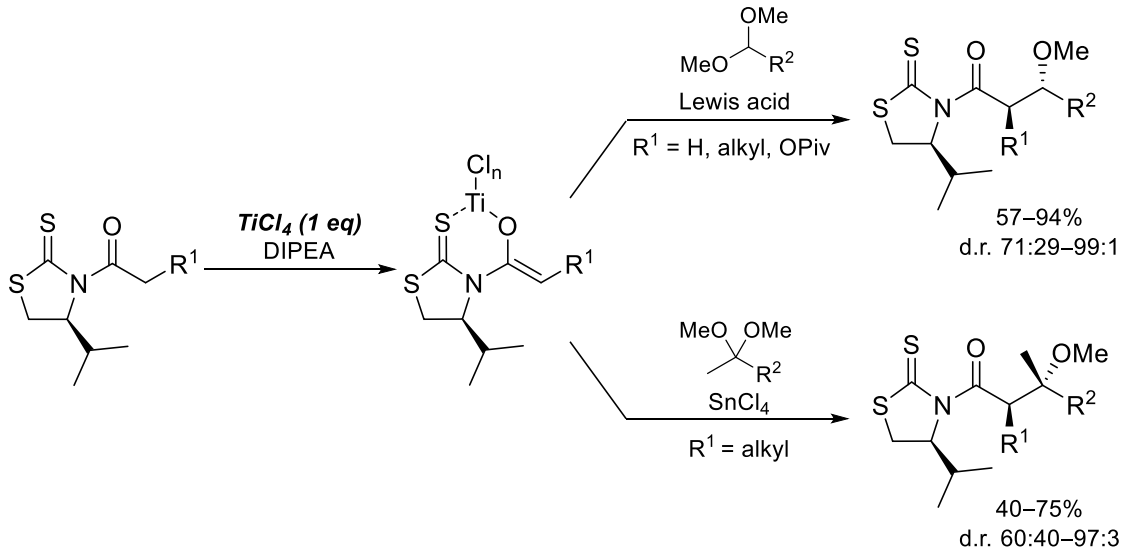
In turn, Sodeoka took advantage of the acidity of β-ketoesters to trigger their addition to α,β-unsaturated acetals in the presence of a Pd(II) catalyst (Scheme 18).[30] This catalyst forms the β-ketoester Pd(II) enolate and activates the acetals to give the corresponding *syn*-α-(*tert*-butoxycarbonyl)-β-alkoxy carbonyl compounds with moderate diastereoselectivites but excellent enantiocontrol.



Scheme 18

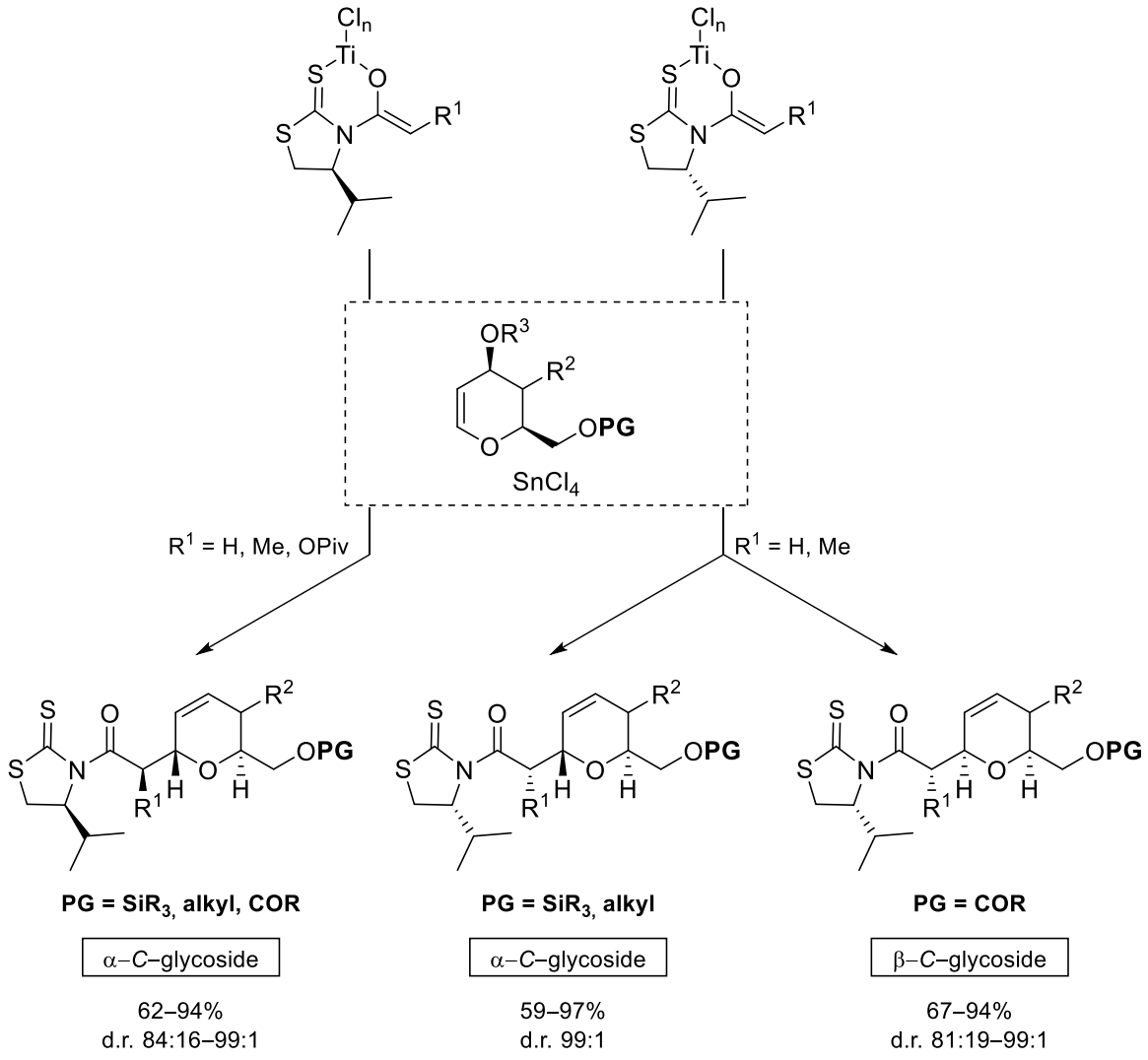
Therefore, the addition of enolates to a wide scope of cationic intermediates is an appealing way for the stereoselective construction of carbon–carbon bonds. In this context, our group has recently launched a research project focused on S_N1-like additions of enolates from chiral *N*-acyl-1,3-thiazolidine-2-thiones produced by catalytic amounts of metal complexes to substrates capable of generating cationic intermediates. Such complexes must be simple, robust, easy to handle, commercially available and potentially suitable to participate in a broad range of transformations.

This project took advantage of a large experience on the diastereoselective Lewis acid-mediated addition of chiral *N*-acyl-1,3-thiazolidine-2-thione titanium(IV) enolates to acetals from aldehydes and ketones. Such studies have firmly established the value of the thiazolidinethione scaffold to isolate the *anti* adducts in high yields (Scheme 19).[31]



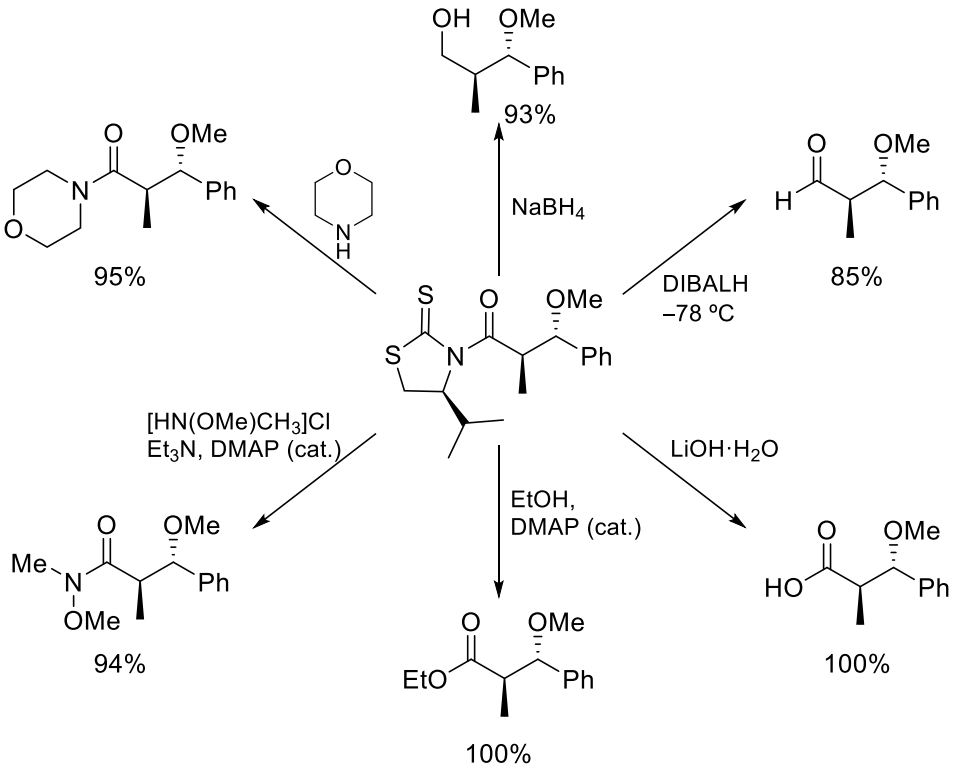
Scheme 19

Furthermore, these titanium enolates have also been used in *C*–glycosidation reactions with great success (Scheme 20). In these reactions, an oxonium ion is generated by treatment of a glycal with $SnCl_4$. Remarkably, the titanium(IV) enolates derived from (*S*)-*N*-propanoylthioimide only afforded α–*C*–glycosides, while the stereochemical outcome of the (*R*)-acyl counterpart rested on the *C*6 *O*-protecting group to afford either α–*C*–glycosides or β–*C*–glycosides.[32]



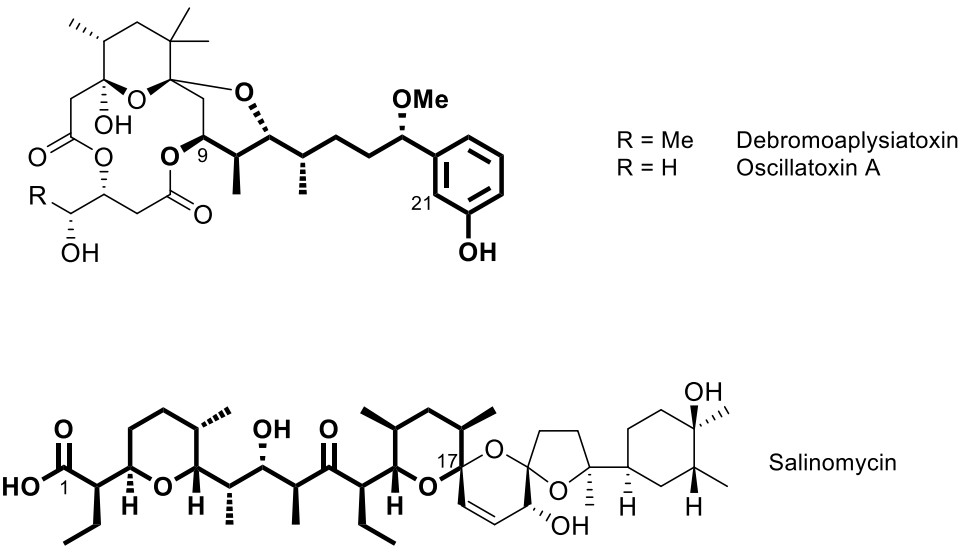
Scheme 20

A crucial issue for chiral auxiliaries in synthetic chemistry is their easy removal and recovery. In that aspect, the *anti* adducts from thiazolidinethiones can be transformed into a wide range of enantiomerically pure compounds under mild conditions and with complete recovery of the chiral auxiliary (Scheme 21).[31,32]



Scheme 21

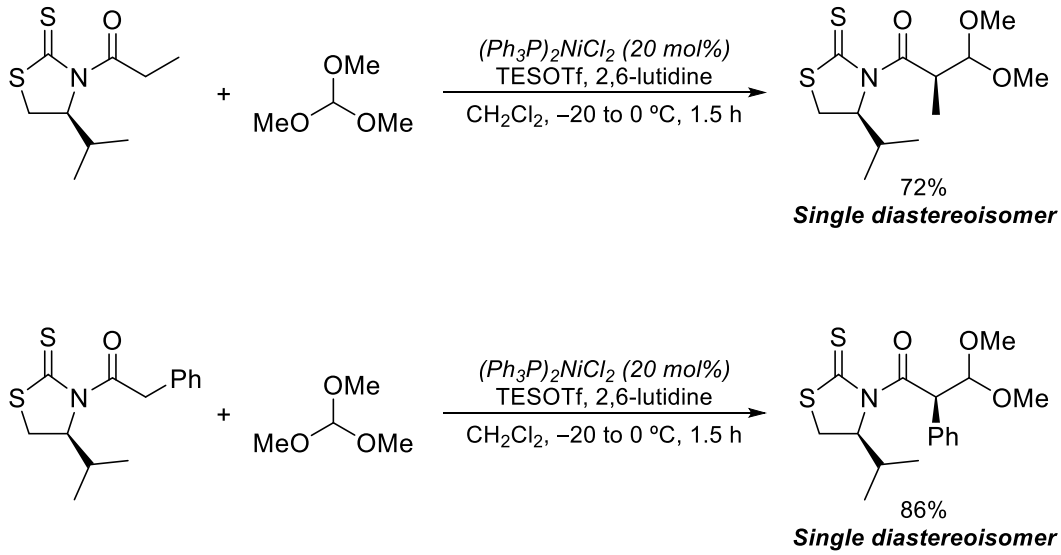
Finally, these methods have been successfully applied to the preparation of the C9–C21 fragment of debromoaplysiatoxin and oscillatoxin A[31d] and the western hemisphere of salinomycin.[32b]



Scheme 22

Nonetheless, there were no precedents of using chiral auxiliaries in "*direct-type*" reactions proceeding through a S_N1-type mechanism in which the enolate was generated catalytically by metal complexes. An important challenge that such a process must overcome is the generation of the enolate from a wide array of carbonyl groups not particularly prone to provide the required enolates in the presence of the catalyst and the electrophilic species. Furthermore, the chiral auxiliary should provide the appropriate environment necessary for the stereocontrolled construction of the carbon–carbon bond.

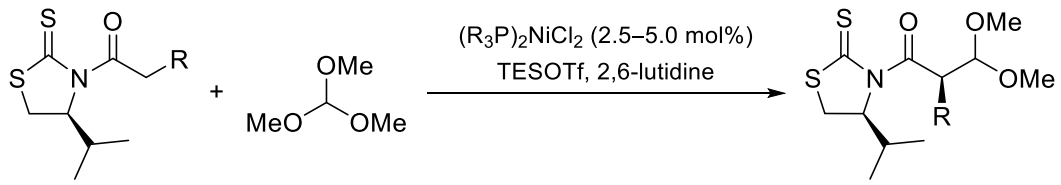
Inspired by Evans' studies depicted in Scheme 13 and taking advantage of our own experience, Erik Gálvez, during his PhD, showed the feasibility of producing β–formylated products ***as single diastereoisomers*** from Ni(II) enolates of (*S*)-*N*-propanoyl and (*S*)-*N*-phenylacetyl-1,3-thiazolidine-2-thiones.[33] The yields were highly satisfactory, but the catalyst loading was too high.



Scheme 23

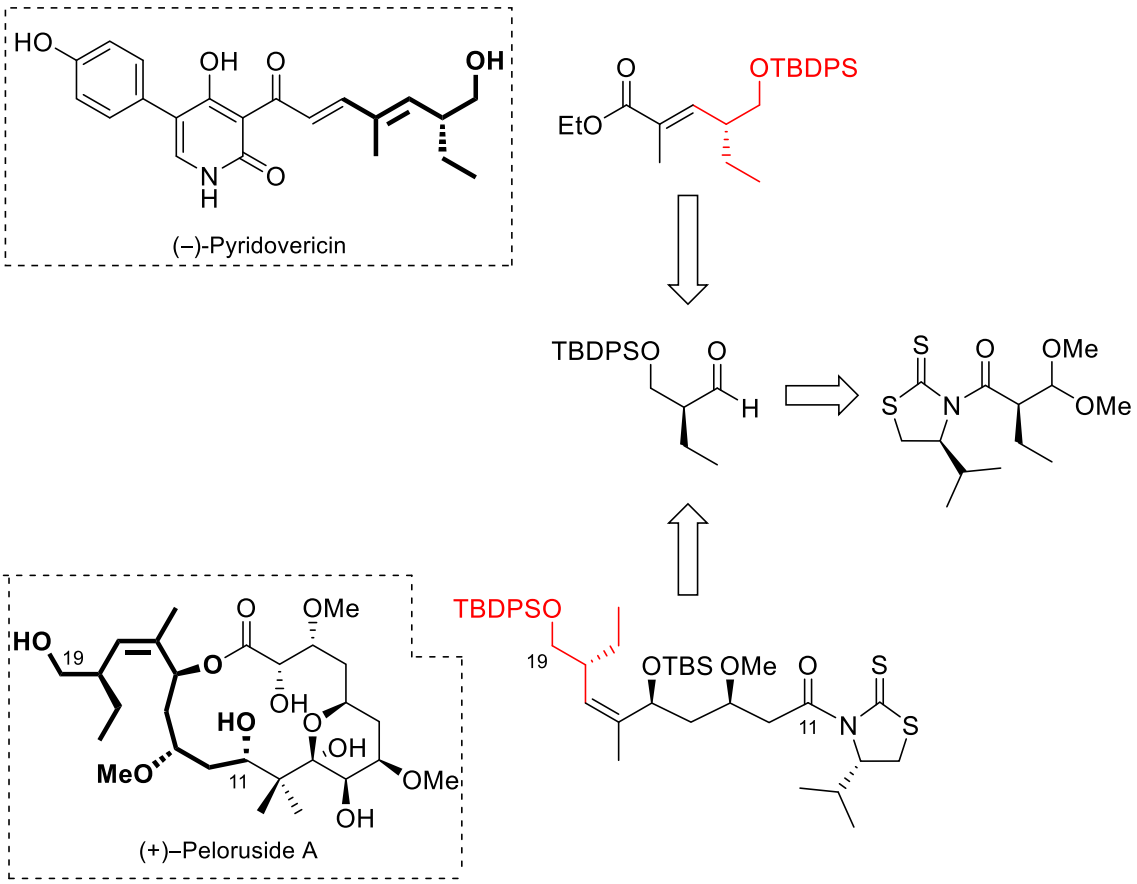
Keeping all these challenges in mind, *the main objective of this thesis was the development and application of new stereoselective carbon–carbon bond forming methods based on the reaction of metal enolates of (S)-N-acyl-4-isopropyl-1,3-thiazolidine-2-thiones with oxonium ions and other stabilized carbocations catalyzed by achiral, commercially available, cheap and structurally simple Ni(II) catalysts.*

In ***Chapter 1***, the previous method for catalytic β–formylation uncovered by Erik Gálvez has been fully developed, optimized and applied to other chiral *N*-acyl thioimides.



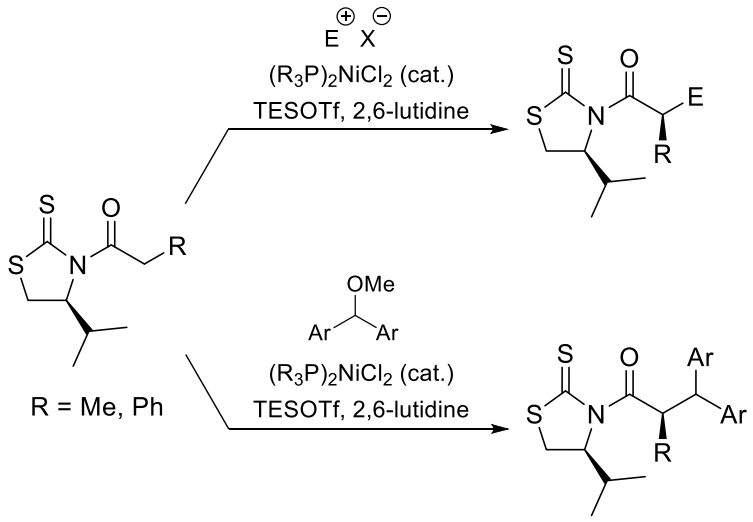
Scheme 24

This method has been used for the synthesis of the side chain of (–)-pyridovericin and the C11–C19 fragment of (+)-peloruside A.



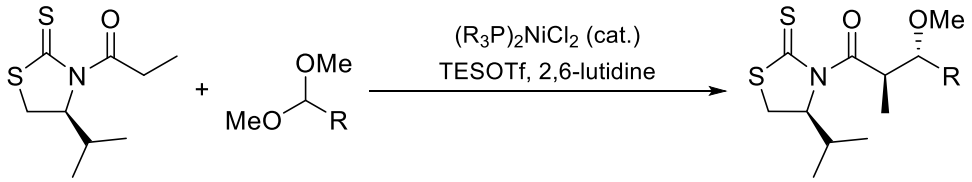
Scheme 25

In ***Chapter 2***, an unprecedented catalytic alkylation reaction of metal enolates with benzhydryl methyl ether derivatives prone to deliver their respective carbocations is described. Parallel, alkylations with commercialy available carbocationic salts have also been considered. These reactions turned out to be completely successful provided that the cationic intermediate is stable enough.



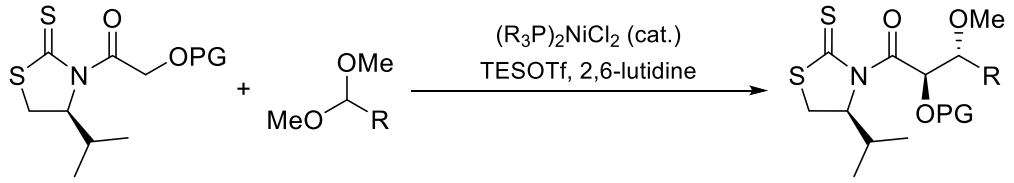
Scheme 26

In ***Chapter 3***, the challenge of assembling two new stereogenic centers in one reaction has been assessed. Particularly, the addition to acetals that cannot undergo α-proton elimination turned out to be moderately diastereoselective.



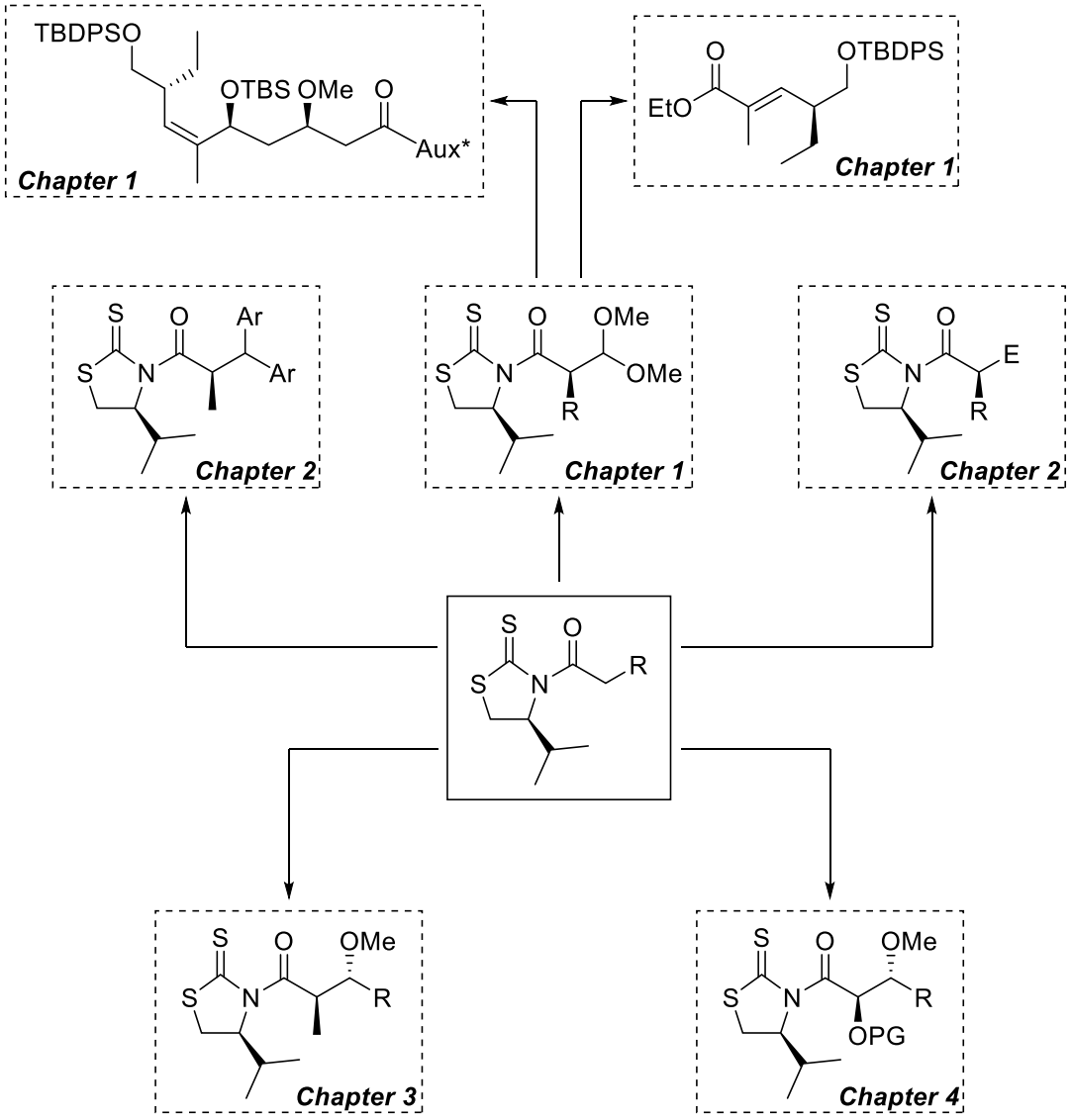
Scheme 27

Finally, in ***Chapter 4*** this method has been applied to *O*-protected (*S*)-*N*-glicolyl-4-isopropyl-1,3-thiazolidine-2-thiones with high success. Interestingly, such a method furnishes 1,2,3-trioxygenated substructures under mild catalytic conditions with good to excellent diastereoselectivities.



Scheme 28

In conclusion, new diastereoselective Ni(II)-catalyzed reactions of chiral *N*-acylthioimides with methyl orthoformate, acetals and other electrophiles prone to deliver a carbocation are described in this Thesis. Furthermore, the synthesis of the side chain of (–)-pyridovericin and the C11–C19 fragment of peloruside A are reported.



Scheme 29

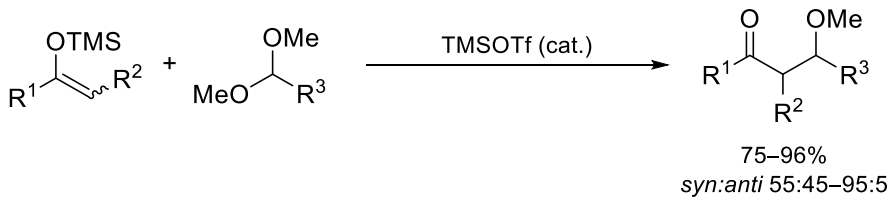
CHAPTER 1

STEREOSELECTIVE Ni(II) CATALYZED REACTIONS OF *N*-ACYL THIAZOLIDINETHIONES WITH METHYL ORTHOFORMATE

1. INTRODUCTION

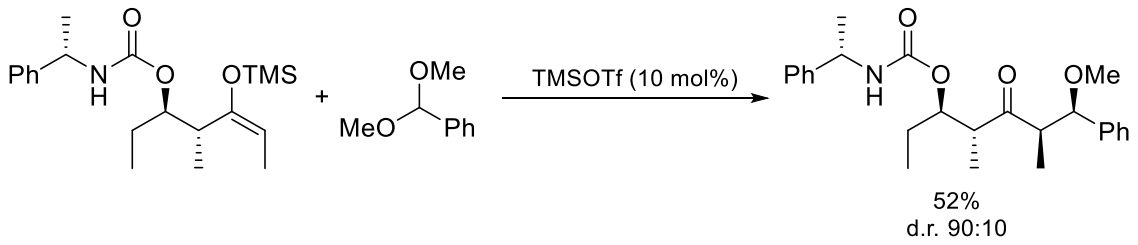
1.1. Precedents on enolate S_N1-like reactions with oxonium ions

Pioneering studies on the S_N1-like additions involving enolates as nucleophiles were reported in the 80s. Particularly, silyl enol ethers held a prominent position since they can be preformed easily and undergo Mukaiyama-like reactions with a broad range of oxocarbenium intermediates prepared by treatment of orthoesters, acetals or ethers with Lewis acids. Indeed, Noyori described diastereoselective additions of silyl enol ethers to dimethyl acetals catalyzed by TMSOTf to afford β-methoxycarbonylic adducts with a *syn* relative stereochemistry, independently from the geometry of the enolate.[34,35]



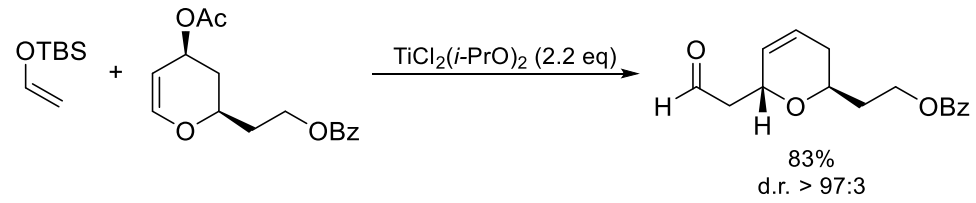
Scheme 30

Later on, Moïse devised a method to control the absolute configuration of the new stereocenters by means of the introduction of chirality over the silicon enolate.[36]



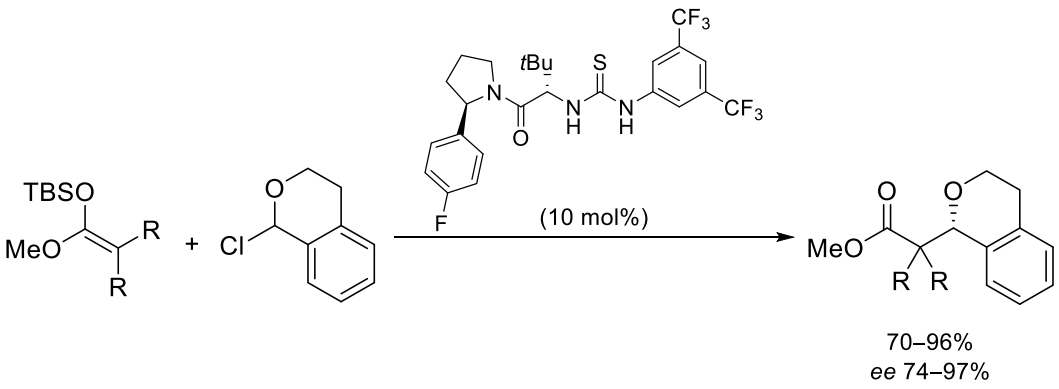
Scheme 31

Alternatively, the source of stereocontrol can also be placed at the electrophile, as occurs on the Lewis acid-mediated reaction of achiral silyl enol ethers with chiral glycals as shown in Scheme 32.[37]



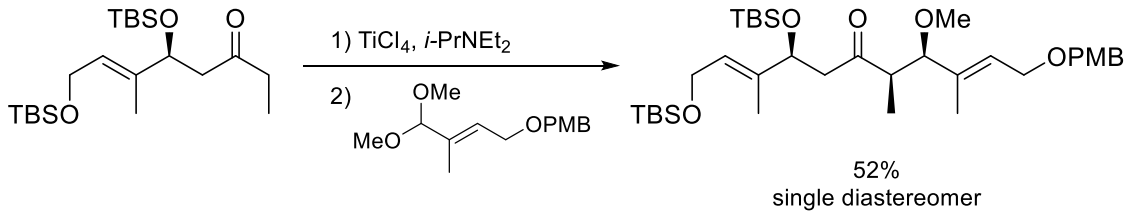
Scheme 32

More recently, Jacobsen reported the asymmetric addition of silyl ketene acetals to cyclic benzylic oxonium ions generated by catalytic amounts of a chiral thiourea (Scheme 33). The corresponding adducts incorporated just one new stereocenter with high enantioselectivities.[38]



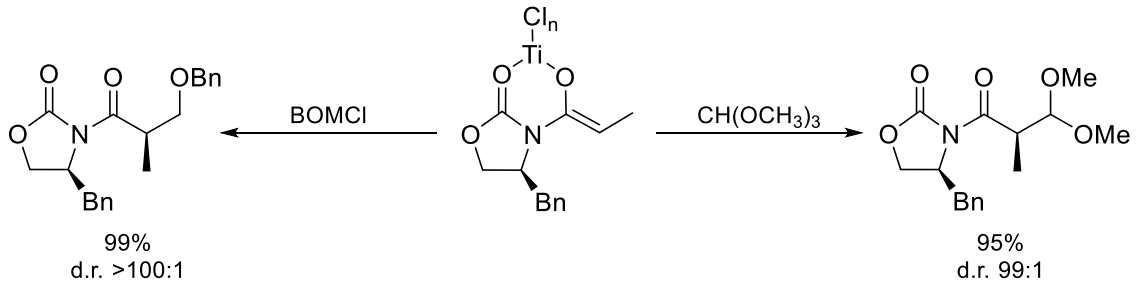
Scheme 33

Running parallel to these accomplishments, different approaches involving other metal enolates have been also under investigation for many years. For instance, Keck described a substrate-controlled addition of a titanium enolate from a chiral ethyl ketone to an α,β-unsaturated dimethyl acetal with moderate yield but excellent diastereoselectivity in the context of the total synthesis of rhizoxin D.[39]



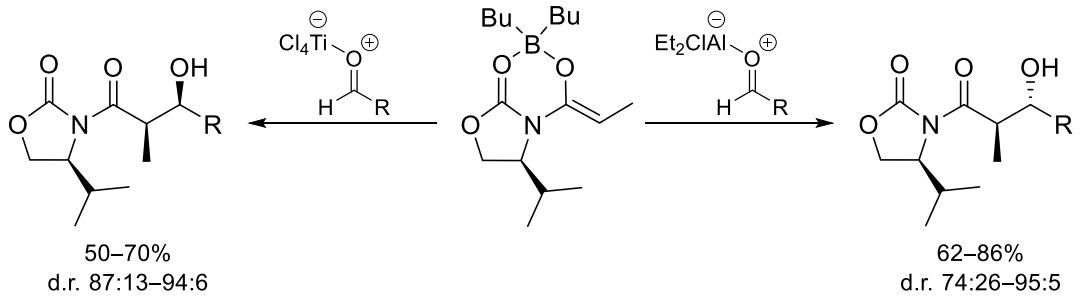
Scheme 34

While this substrate-controlled reaction is restricted to an only substrate, the use of chiral auxiliaries would broaden the scope to a variety of structures. In this context, Evans described that the additions of titanium enolates of chiral 4-benzyl-*N*-propanoyl-1,3-oxazolidin-2-one to trimethyl orthoformate and BOMCl produce the corresponding adducts as single diastereoisomers in high yields (Scheme 35).[40] Although these reactions only create one new stereocenter, they represented the first metal enolate participating in a S_N1 reaction different from the Mukaiyama's approach.



Scheme 35

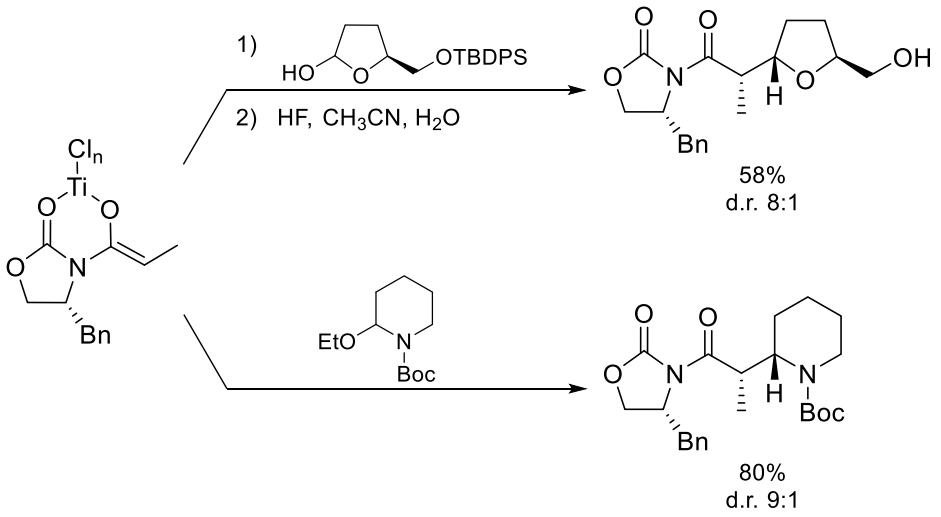
Meanwhile, Heathcock uncovered highly successful aldol additions of boron enolates of *N*-acyl oxazolidinones to aldehydes previously coordinated to a Lewis acid, thus generating oxocarbenium-like species as electrophiles.[41]



Scheme 36

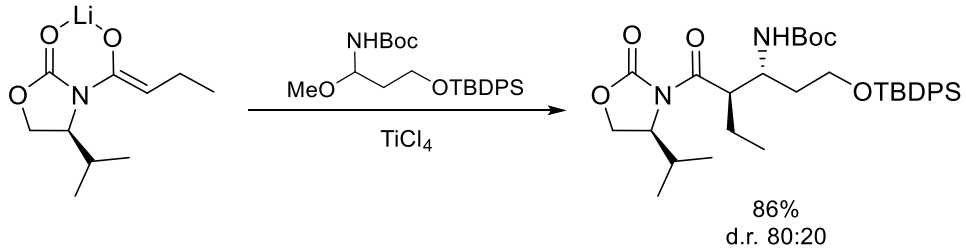
These reports established the feasibility of S_N1-like additions proceeding through open transition states in which the appropriate choice of the reagents permits the stereoselective construction of up to two new stereocenters. Such chemistry has been expanded to other auxiliaries and to other substrates prone to deliver carboxonium ions. For example, Pilli took advantage of the reactivity of titanium enolates of chiral *N*-

propanoyl oxazolidinone to make it react with a γ-lactol derived from (*S*)-glutamic acid and *N*-protected 2-ethoxypiperidines.[42,43]



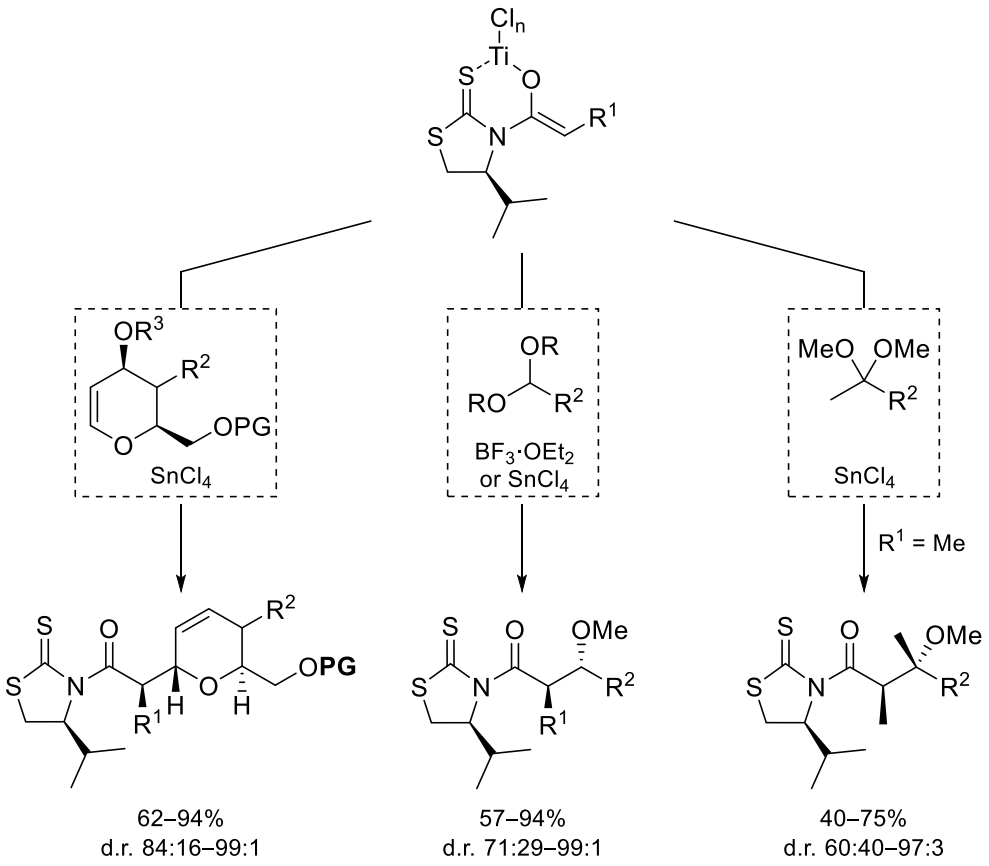
Scheme 37

Furthermore, Kise incorporated an *anti* β-aminocarboxylic moiety by means of a lithium enolate of an *N*-acyl oxazolidinone with an *N*-alkoxycarbonyl-1-methoxyamine.[44]



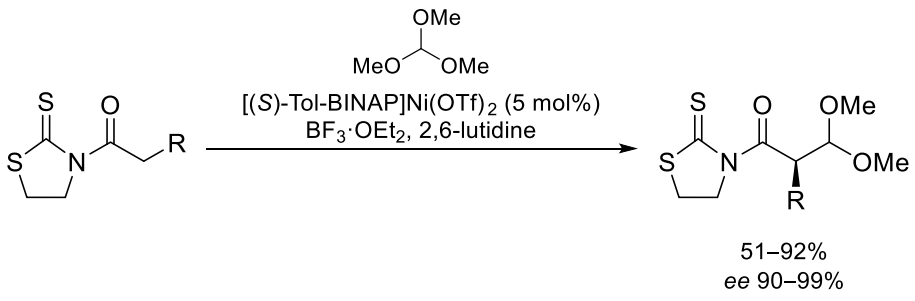
Scheme 38

As explained in the General Introduction, our group has also been interested in the stereoselective Lewis acid-mediated addition of titanium enolates from chiral *N*-acyl-1,3-thiazolidine-2-thiones to dialkyl acetals and glycals and their application to the synthesis of natural products (Scheme 39).[32,33]



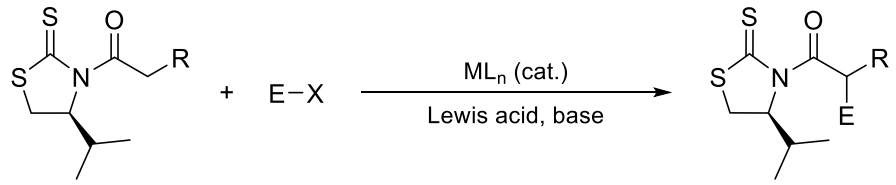
Scheme 39

A seminal contribution to such S_N1-like processes was due to Evans, who described the asymmetric direct-type reaction of *N*-acyl-1,3-thiazolidine-2-thiones with trimethyl orthoformate promoted by a chiral nickel(II) catalyst shown in Scheme 40.[27] Despite the high yields and enantiocontrol achieved by such an addition, the process was seriously hampered by the need of dry-box techniques to synthesize and handle the chiral catalyst and therefore it has been hardly used.



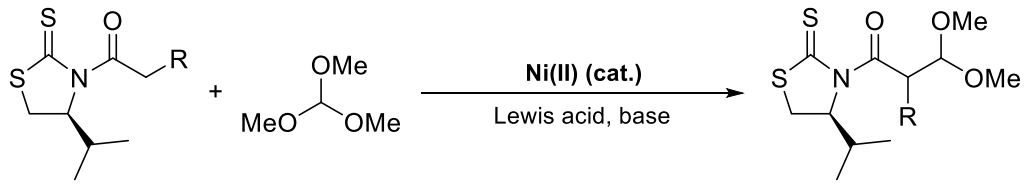
Scheme 40

Inspired by this example and taking advantage of our previous experience, we envisioned a new catalytic process as an alternative to the addition of preformed titanium enolates to oxocarbenium intermediates. We were aware that such a method had to face a variety of puzzling concerns. Using thiazolidinethione chiral auxiliaries as an easily removable platform to control the configuration of the new chiral centers, the new method should be simple, efficient and highly stereoselective with a broad range of electrophiles. In turn, the catalyst should be easy to handle and able to form the corresponding metal enolate at the same time that the oxocarbenium intermediates are generated by the appropriate Lewis acid.



Scheme 41

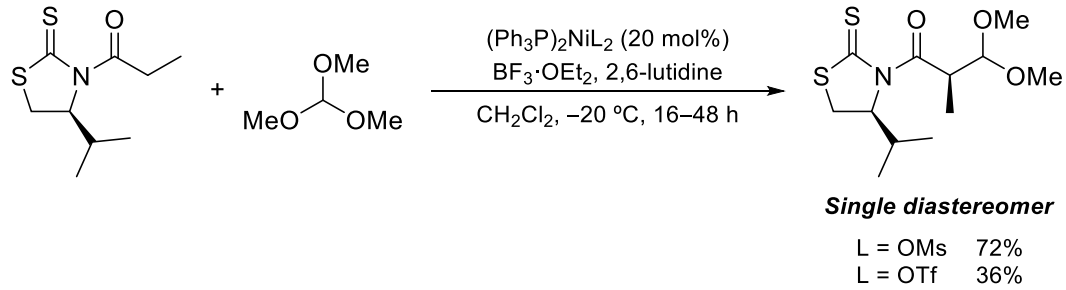
Following Evans' report, we initially chose trimethyl orthoformate as the electrophile and commercially available Ni(II) complexes as the metal catalysts. Therefore, the scenario was set up to assess the use of *chiral N*-acyl-1,3-thiazolidine-2-thiones for the stereoselective construction of carbon–carbon bonds catalyzed by nickel(II) complexes through S_N1-like mechanism.



Scheme 42

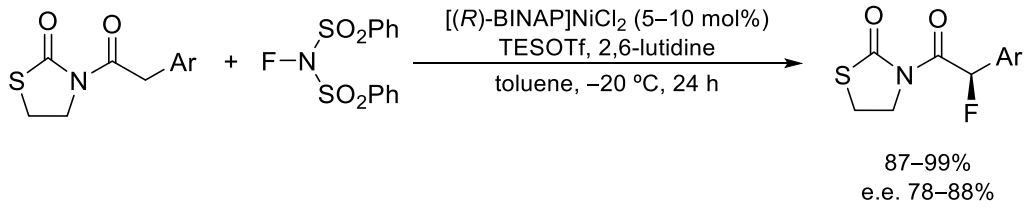
1.2. Previous work

Erik Gálvez, during his PhD,[33] carried out exploratory studies with (*S*)-4-isopropyl-*N*-propanoyl-1,3-thiazolidine-2-thione, $BF_3 \cdot OEt_2$ as the Lewis acid, 2,6-lutidine as the base and several bis(triphenylphosphine)nickel(II) complexes as catalysts. Importantly, the chlorine complex (L=Cl in Scheme 43) did not work, but the sulfonate ones (L=OSO_2R^1 in Scheme 43) did. Although the corresponding triflate complex produced the desired product as ***a single diastereoisomer***, it afforded a moderate yield, probably due to its sensitivity as in the case of Evans' catalyst. Instead, $(Ph_3P)_2Ni(OMs)_2$ gave the formylated adduct in a high yield. Irrespective of these results, long reaction times and the need to prepare the catalyst hampered further advances.



Scheme 43

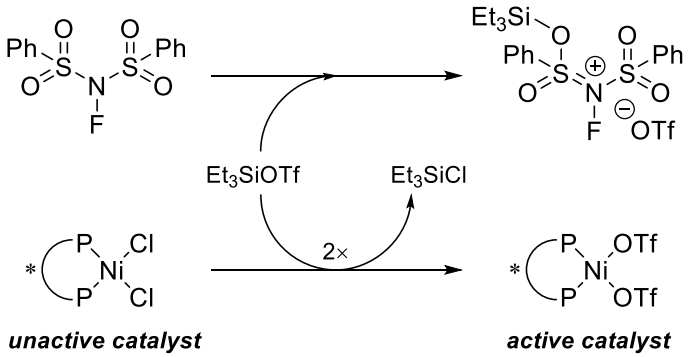
At this point, a new fluorination procedure disclosed by Sodeoka turned out to be very useful to avoid the disadvantages of preparing the catalyst. As shown in Scheme 44, chiral Ni(II) enolates from achiral *N*-(arylacetyl)oxazolidinethiones were fluorinated with NFSI in the presence of TESOTf in excellent yields and high enantiocontrol.[45]



Scheme 44

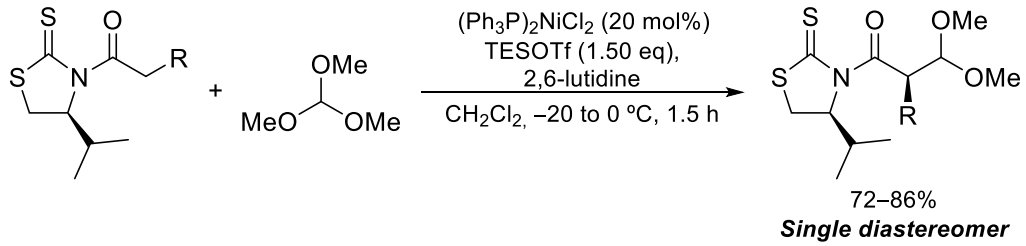
The role of TESOTf was manifold. Indeed, it activated the electrophile but also removed the chlorine ligands from the nickel complex. Such an interchange of chlorines

by triflates increased the acidity of the Ni(II) catalyst and triggered the fluorination reaction.



Scheme 45

Taking advantage of this strategy, we designed a new reaction in which $(Ph_3P)_2NiCl_2$ would act as the unactive catalyst and TESOTf would be the Lewis acid with the aforementioned double functionality. Erik Gálvez demonstrated that the reaction proceeded smoothly either with *N*-propanoyl and *N*-phenylacetyl thioimides to afford ***a single diastereomer*** in high yields by using a relatively large loading of the catalyst.[33]



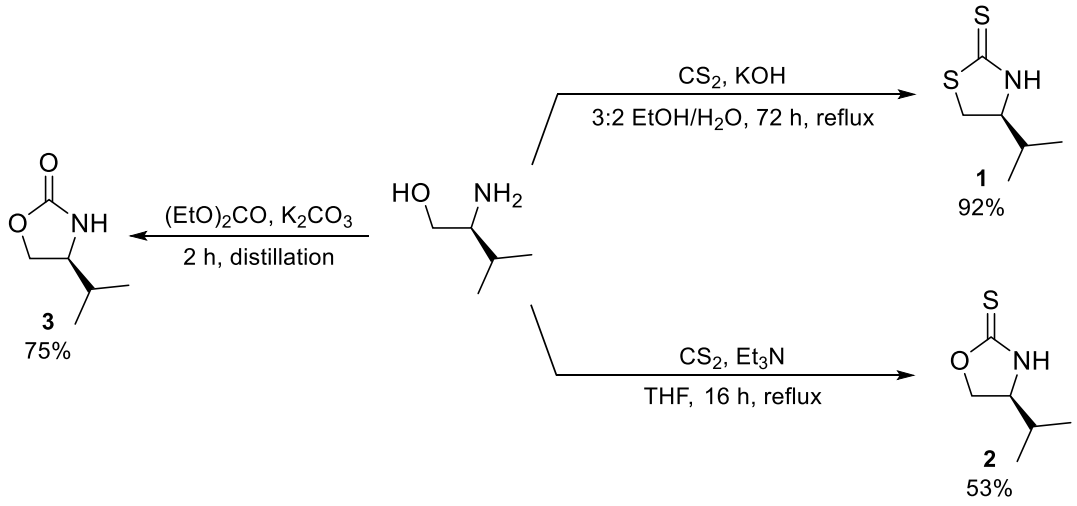
Scheme 46

Keeping the previous comments in mind, the present chapter aims to:

- Reduce the amount of the catalyst.
- Assess the influence of the chiral auxiliary.
- Optimize the reaction conditions with selected Ni(II) catalysts.
- Expand the method to a variety of *N*-acylthioimides.
- Use the method for the synthesis of fragments of natural products, as the lateral chain of (–)-pyridovericin and the C11–C19 fragment of (+)-peloruside A.

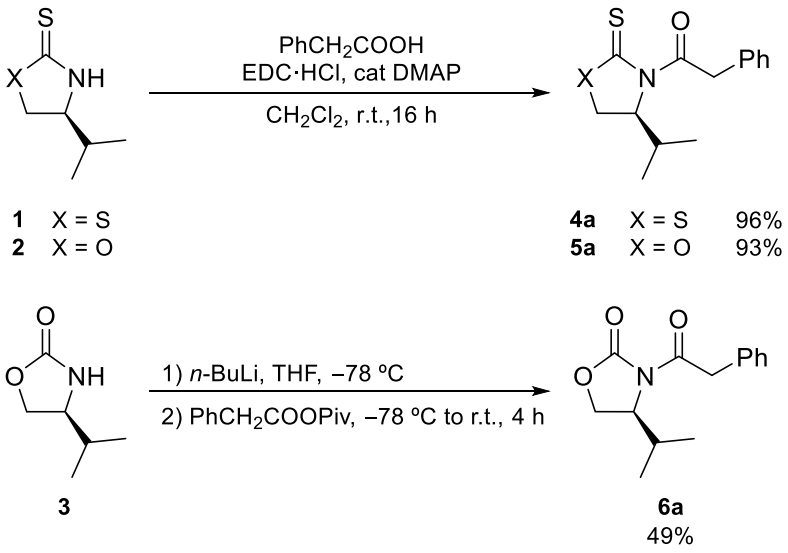
2. SYNTHESIS AND ACYLATION OF CHIRAL AUXILIARIES

The chiral auxiliaries settled to further studies were prepared at multigram scale according to standard procedures found in the literature.[46–49] Remarkably, the experimental conditions reported for the preparation of 1,3-thiazolidine-2-thione **1** and 1,3-oxazolidine-2-thione **2** are crucial.[50] While 1,3-oxazolidine-2-thione was prepared with weak bases and short reaction times, 1,3-thiazolidine-2-thione **1** required a stronger base and at least 72 h of reaction time. In turn, oxazolidinone **3** was obtained by treatment of the valine-derived aminoalcohol with ethyl carbonate.



Scheme 47

These three chiral auxiliaries were acylated to obtain the corresponding *N*-phenylacetylated substrates. The thiazolidinethione **1** and the oxazolidinethione **2** were acylated with phenylacetic acid and a coupling agent, while the *N*-phenylacetyloxazolidinone **6a** was prepared through a mixed anhydride (Scheme 48).



Scheme 48

3. OPTIMIZATION USING (*S*)-4-ISOPROPYL-*N*-PHENYLACETYL-1,3-THIAZOLIDINE-2-THIONE (4a)

3.1. Optimization of the amount of catalyst and reaction time

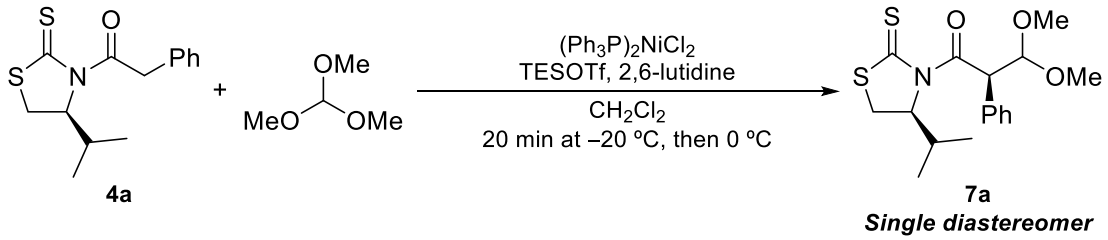
We first tried to establish the most suitable amount of $(Ph_3P)_2NiCl_2$ to carry out the reaction in a reasonable time. It is important to emphasize that the amount of TESOTf that will be used in most of the reactions during this thesis will rest on the type of electrophile and the nickel(II) complex engaged in the process. Briefly, the quantity of TESOTf will be usually calculated using the following equations:

For usual electrophiles: **mol of TESOTf = 1.10 + [2×(amount of catalyst)]**

For cationic salts as electrophiles: **mol of TESOTf = 0.10 + [2×(amount of catalyst)]**

Taking the *N*-acyl thioimide **4a** as the model substrate, we firstly evaluated the possibility of decreasing the amount of catalyst. As Table 1 shows, 1.5 mol% of $(Ph_3P)_2NiCl_2$ was enough to obtain yields up to 91% of the desired adduct as ***a single diastereomer*** in just 1 h (entries 1–3 in Table 1). Smaller loadings of catalyst ended in lower yields even after much longer reaction times (entries 4–6 in Table 1). Finally, a blank reaction without catalyst proved that the Ni(II) complex was completely necessary (entry 7 in Table 1). Since most of the reactions would be carried out at 0.5–

1.0 mmol scale, we decided to set the quantity of 2.5 mol% for future assays to avoid problems related to reproducibility and accuracy in catalyst weighting.



4a **7a**

Single diastereomer

Entry	$(Ph_3P)_2NiCl_2$ (mol%)	t (h)	Yield (%)[a]
1[b]	20.0	3	86
2	2.5	1	94
3	1.5	1	91
4	1.0	1	78
5	1.0	2	80
6	1.0	5	77
7	0	5	n.r.

[a] Isolated yield after column chromatography.

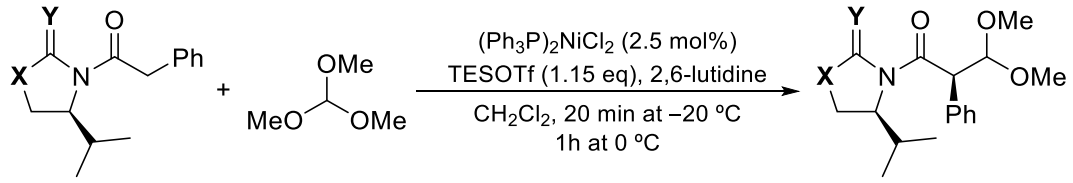
[b] Carried out by Erik Gálvez. 1.50 eq of TESOTf was used.

Table 1

3.2. Influence of the chiral auxiliary

Having established the amount of $(Ph_3P)_2NiCl_2$ to be used, we next evaluated, with the help of Max Kindred,[51] the impact of other chiral auxiliaries. The results are summarized in Table 2.

Compared to thiazolidinethione **4a**, the use of the oxazolidinethione **5a** produced a significant decrease of the yield, and the Evans auxiliary (**6a**) meant an important loss in diastereoselectivity. These results proved that the endocyclic heteroatom played a key role in the yield and that exocyclic C=S group was crucial to achieve high diastereoselectivities. Therefore, the thiazolidinethione **1** was chosen as the most suitable chiral auxiliary.



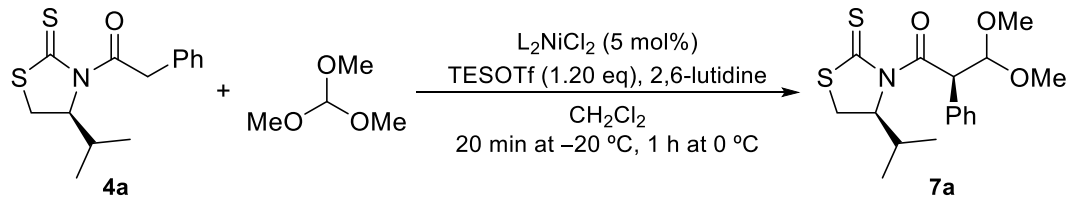
Entry	Substrate	X	Y	Adduct	d.r.[a]	Yield (%)[b]
1	**4a**	S	S	**7a**	>97:3[c]	94
2	**5a**	O	S	**8a**	>97:3[c]	47
3	**6a**	O	O	**9a**	87:13	60

[a] Established by ^{1}H NMR analysis of the crude product.
[b] Isolated yield after column chromatography.
[c] A single diastereomer was observed by ^{1}H NMR of the crude product.

Table 2

3.3. Assessment of different catalysts

Although $(Ph_3P)_2NiCl_2$ already satisfied our expectations, we considered that the method would be of higher value if other complexes could be used. Thus, Ignasi Nubiola undertook a comprehensive analysis of the influence of a variety of commercially available Ni(II) complexes on the reaction with *N*-arylacetylthiazolidinethione **4a**.[52] The results summarized in Table 3 show that most of the catalysts furnish the desired adduct in a highly efficient manner. Indeed, complexes containing small trialkyl phosphines as PMe_3 or PBu_3 afforded **7a** in the same yield as the PPh_3-based complex (see entries 1–3 in Table 3). Interestingly, the yields dropped dramatically with a complex containing a bulkier phosphine as PCy_3 (entry 4 in Table 3). Furthermore, chelating phosphines as dppe or dppp afforded **7a** in moderate yields (entries 5–6 in Table 3). Therefore, the steric hindrance of the phosphine ligands seems to play a crucial role on the kinetics of the process.



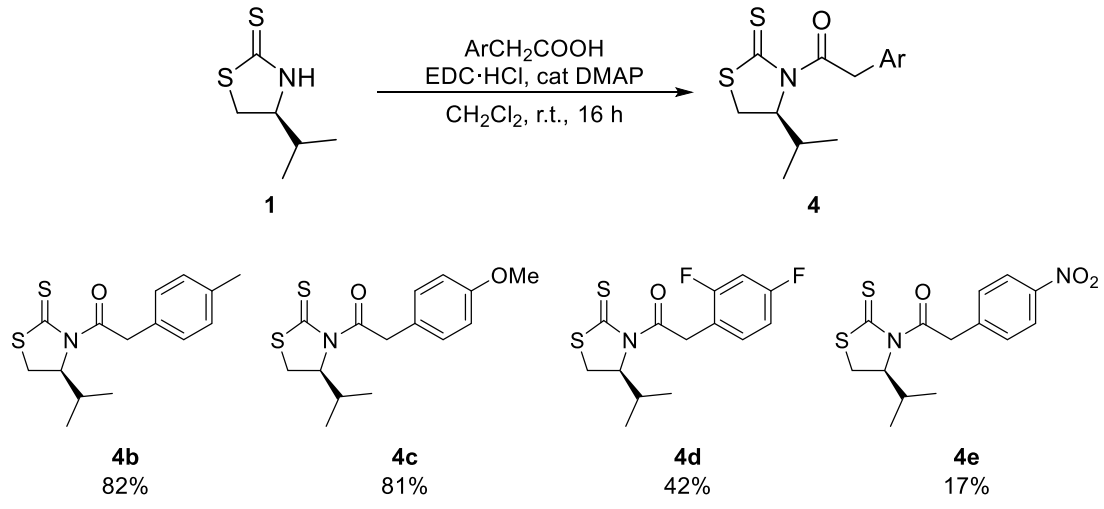
Entry	L_2NiCl_2	Yield (%)[a]
1	$(Ph_3P)NiCl_2$	83
2	$(Me_3P)NiCl_2$	82
3	$(Bu_3P)NiCl_2$	82
4	$(Cy_3P)NiCl_2$	28
5	(dppe)$NiCl_2$	65
6	(dppp)$NiCl_2$	62

[a] Isolated yield after column chromatography.

Table 3

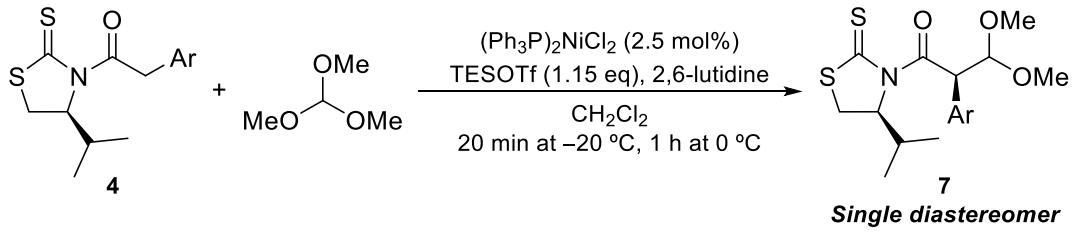
4. INFLUENCE OF THE *N*-ACYL GROUP

Once established the most appropriate reaction conditions, the influence of the *N*-acyl group of several *N*-arylacetyl-4-isopropyl-1,3-thiazolidine-2-thiones was examined. These substrates were prepared by acylation of **1** with the corresponding arylacetic acids as previously described. It must be pointed out that thioimides with electrowithdrawing groups over the aromatic ring turned out to be very sensitive and, therefore, low yields were obtained in their preparation.



Scheme 49

We were pleased to observe that the $(Ph_3P)_2NiCl_2$–promoted reactions of all these substrates worked perfectly well irrespective of the electronic character of the aryl group (see Table 4). Slightly lower yields were obtained with electronically poor aryl groups, likely due to the sensitivity of the corresponding adducts.



Entry	Substrate	Ar	Adduct	Yield (%)[a]
1	**4a**	Ph	**7a**	94
2	**4b**	(4-Me)Ph	**7b**	88
3	**4c**	(4-MeO)Ph	**7c**	91
4	**4d**	(2,4-F_2)Ph	**7d**	74
5	**4e**	(4-NO_2)Ph	**7e**	71

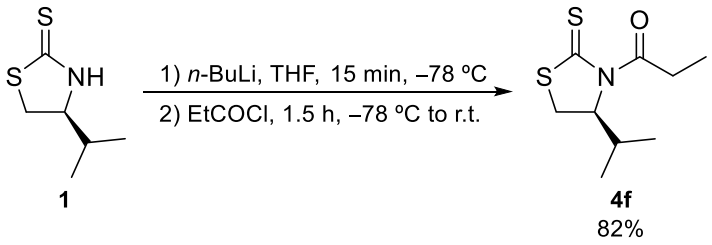
[a] Isolated yield after column chromatography.

Table 4

5. OPTIMIZATION USING (*S*)-4-ISOPROPYL-*N*-PROPANOYL-1,3-THIAZOLIDINE-2-THIONE (4f)

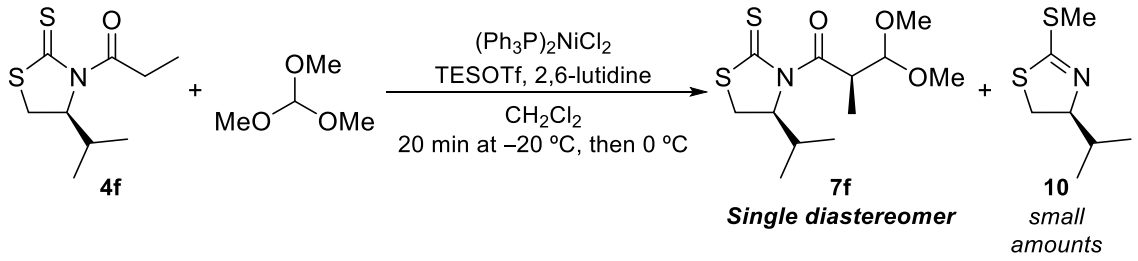
5.1. Influence of the amount of catalyst and the reaction time

At this point, we considered the application of the method to less acidic acyl chains. We chose (*S*)-4-isopropyl-*N*-propanoyl-1,3-thiazolidine-2-thione (**4f**) as the model substrate, which was prepared by deprotonation of the chiral auxiliary **1** and subsequent acylation with propanoyl chloride.



Scheme 50

Exploratory studies showed that the previously optimized experimental conditions afforded low yields of the corresponding adduct (**7f**) even at long reaction times (entry 1 in Table 5). Therefore, a careful analysis of the catalytic loadings established that a 20 mol% of $(Ph_3P)_2NiCl_2$ was required to obtain *a single diastereomer* of **7f** in high yields (compare entries 1–5 in Table 5). Interestingly, long reaction times did not increase the yield (compare entries 5 and 6 in Table 5). Furthermore, small amounts of an *S*-methylated byproduct were observed, which could be the reason why the yield did not reach a higher value.

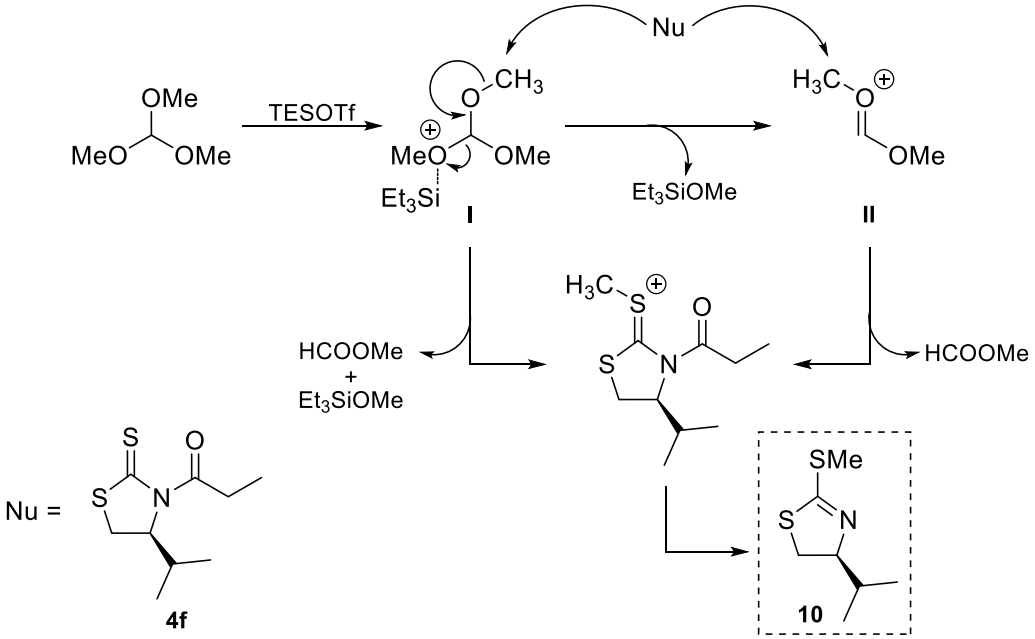


Entry	$(Ph_3P)_2NiCl_2$ (mol%)	TESOTf (eq)	Time (h)	Yield (%)[a]
1	2.5	1.15	15	12
2	10	1.30	15	46
3	20	1.50	0.25	46
4	20	1.50	0.5	68
5	20	1.50	1	72
6	20	1.50	15	75

[a] Isolated yield after column chromatography.

Table 5

The formation of **10** rests on the nucleophilicity of the C=S bond. Indeed, the sulfur atom could attack either the coordinated complex **I** or the oxonium cation **II** (see Scheme 51). After deacylation and/or hydrolysis, **10** may be obtained.



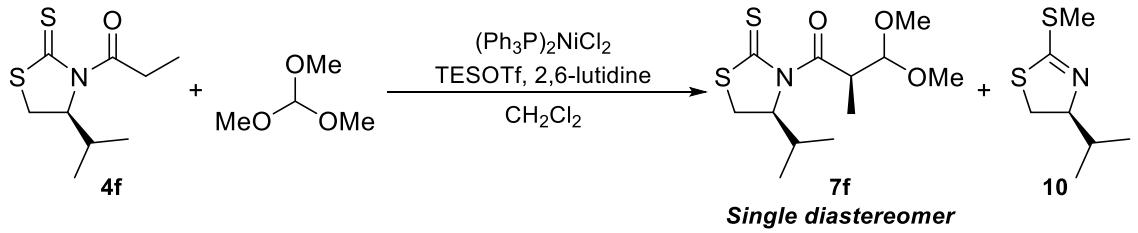
Scheme 51

The different behavior in terms of catalyst loading between **4a** and **4f** could be explained by their different acidity. Indeed, *N*-acyl thioimide **4a** contains an aryl group next to the α position which makes it more likely to be deprotonated. Consequently, the reaction kinetics might be enhanced and the reaction can end up before a possible deactivation. Unfortunately, the less acidic thioimide **4f** reacted slower and allowed side reactions to compete with the β-formylation process.

5.2. Influence of the temperature

With the intention of lowering the loading of catalyst still in mind, we next examined the influence of the temperature on the reaction. As Table 6 shows, similar yields were attained at 0 ºC. However, while stirring previously the reaction mixture at –20 ºC allowed to recover starting material, it was not the case when a temperature of 0 ºC was always used. Instead, important quantities of **10** were obtained (entries 1 and 2 in Table 6). A decrease of the temperature to –20 ºC practically eradicated the side reaction, and the adduct **7f** was obtained in 88% yield after 5 h (entries 3–6 in Table 6). However, less than 20 mol% of catalyst led to a significant decrease of the yield (entries 7–9 in Table 6). Surprisingly, a temperature below –20 ºC did not allow the reaction to

proceed at all. In conclusion, the temperature plays a key role in this reaction. High temperatures (0 ºC) promoted side reactions, while very low ones (–40 ºC) inhibited the process. Instead, keeping the temperature at –20 ºC let the reaction proceed without the formation of any byproduct, thus obtaining the desired product in 84–88% yield as long as the reaction mixtures were stirred during 3–5 h.



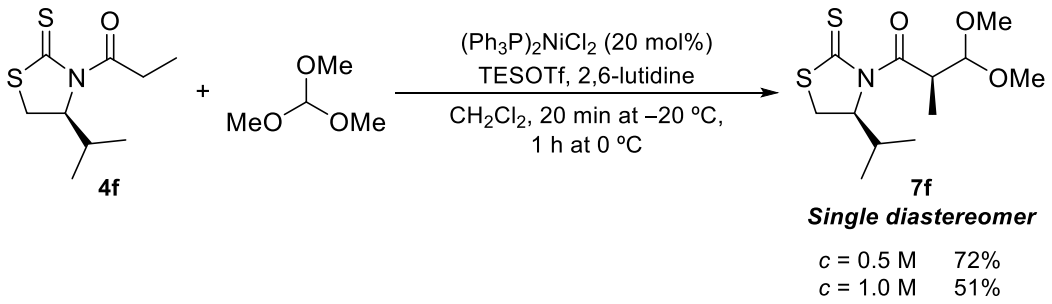
Entry	$(Ph_3P)_2NiCl_2$ (mol%)	TESOTf (eq)	T (ºC)	Time (h)	Yield of **7f** (%)[a]	r.s.m.[b] (%)	**10** (%)[a]
1[c]	20	1.5	0	1	72	21	6
2	20	1.5	0	1.5	66	–	14
3	20	1.5	–20	1.5	73	23	–
4	20	1.5	–20	3	84	16	–
5	20	1.5	–20	5	88	5	–
6	20	1.5	–20	15	82	4	3
7	10	1.3	–20	5	60	32	–
8	10	1.3	–20	15	58	35	6
9	5	1.2	–20	15	47	56	–
10	20	1.5	–40	5	n.r.	–	–

[a] Isolated yield after column chromatography.
[b] r.s.m.: Recovered Starting Material
[c] The reaction mixture was previously stirred for 20 min at –20 ºC.

Table 6

5.3. Influence of the concentration

We also considered the possibility of more concentrated conditions, which could speed up the desired reaction and avoid undesired side processes or early deactivation of the catalyst. However, when the reaction was carried out at 1 M instead of the usual 0.5 M concentration using 20 mol% of the Ni(II) complex the yield decreased dramatically, which closed the doors to a reduction of the amount of catalyst by means of this alternative.

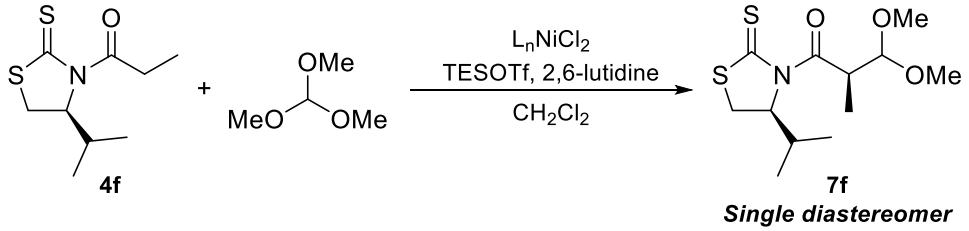


Scheme 52

5.4. Assessment of different catalysts

The important loadings of the catalyst required to obtain high yields led us to search for more active catalysts. In this context, and in collaboration with Ignasi Nubiola,[52] commercially available Ni(II) chloride complexes were examined. The results are summarized in Table 7.

Importantly, a nickel(II) complex containing DME as ligand proved to be completely unactive (entry 1 in Table 7), whereas all the complexes with phosphines as ligands afforded the expected adduct, with the exception of bulky $(Cy_3P)_2NiCl_2$ (entries 2–7 in Table 7). Further studies established that complexes with alkyl phosphines were particularly suitable since a tiny amount catalyzed the reaction at –20 ºC (compare entires 8–11 in Table 7). Especially, $(Me_3P)_2NiCl_2$ turned out to be the most appropriate complex since it afforded the desired adduct in 81–87% yield using 2.5–5 mol% (entries 10–11 in Table 7).



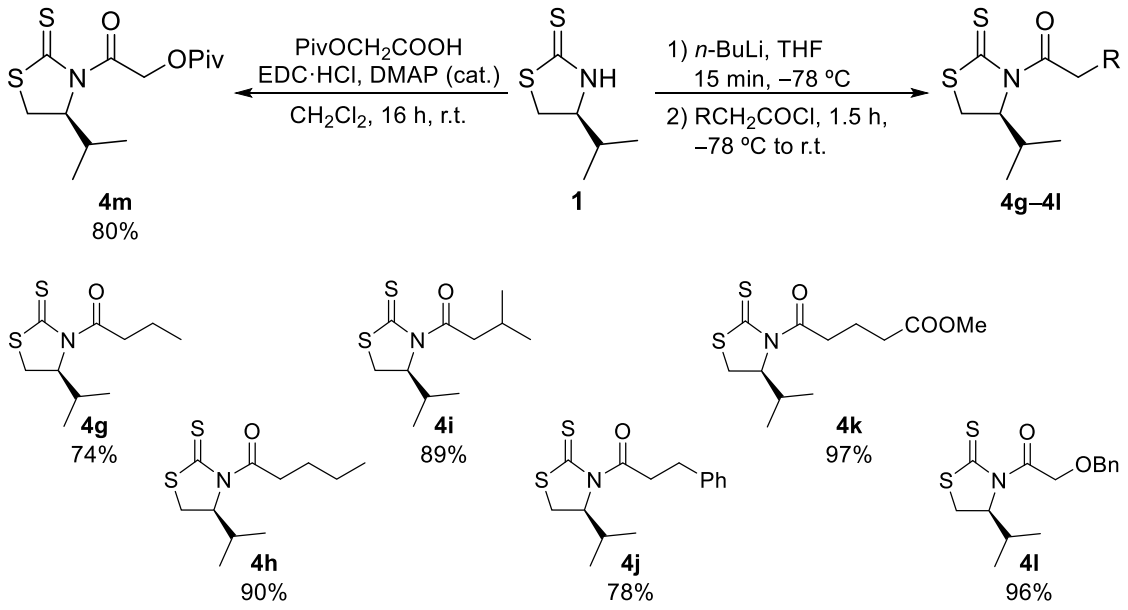
Entry	L_2NiCl_2	mol%	TESOTf (eq)	T (ºC)	Time (h)	Yield (%)[a]
1[b]	$(DME)NiCl_2$	20	1.5	0	4	n.r.
2[b]	$(Ph_3P)_2NiCl_2$	20	1.5	0	1	72
3[b]	$(dppe)NiCl_2$	20	1.5	0	3	80
4[b]	$(dppp)NiCl_2$	20	1.5	0	3	79
5[b]	$(Cy_3P)_2NiCl_2$	20	1.5	0	1	n.r.
6[b]	$(Bu_3P)_2NiCl_2$	20	1.5	0	3	79
7[b]	$(Me_3P)_2NiCl_2$	20	1.5	0	1	70
8	$(Ph_3P)_2NiCl_2$	5	1.2	–20	15	47
9	$(Bu_3P)_2NiCl_2$	5	1.2	–20	1.5	78
10	$(Me_3P)_2NiCl_2$	5	1.2	–20	1.5	87
11	$(Me_3P)_2NiCl_2$	2.5	1.15	–20	1.5	81

[a] Isolated yield after column chromatography.
[b] The reaction mixture was previously stirred for 20 min at –20 ºC.

Table 7

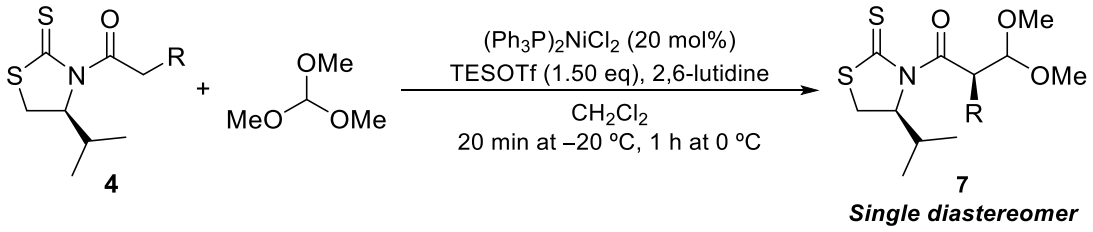
6. APPLICATION TO OTHER *N*-ACYL THIOIMIDES

Having found the most suitable nickel(II) complex for *N*-phenylacetyl thiazolidinethione **4a** and, especially, for *N*-propanoyl thiazolidinethione **4f**, we decided to test the optimized conditions on *N*-acyl thioimides **4g–m** shown in Scheme 53, which were synthesized according to standard procedures.



Scheme 53

Application of the reaction conditions using 20 mol% of $(Ph_3P)_2NiCl_2$ and a temperature of 0 ºC to substrates containing alkyl groups over the acyl chain produced the corresponding adducts in 60–88% yield (see Table 8). However, the reaction failed for the α-benzyloxyacetyl thioimide **4l** (entry 6 in Table 8).

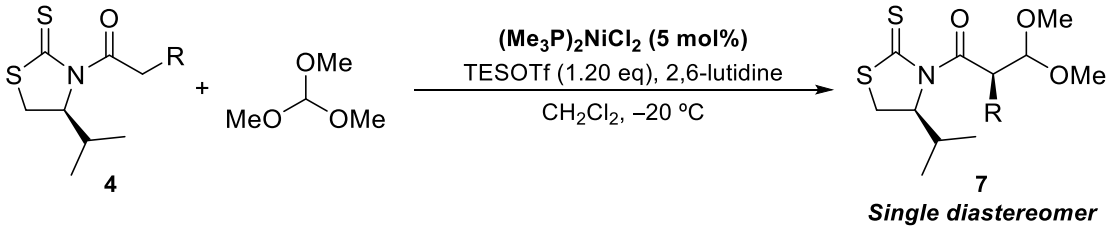


Entry	Substrate	R	Adduct	Yield (%)[a]
1	**4f**	Me	**7f**	72
2	**4h**	*n*-Pr	**7h**	88
3	**4i**	*i*-Pr	**7i**	69
4	**4j**	Bn	**7j**	68
5	**4k**	$(CH_2)_2CO_2Me$	**7k**	60
6	**4l**	OBn	**7l**	n.r.

[a] Isolated yield after column chromatography.

Table 8

Then, in collaboration with Ignasi Nubiola,[52] we carried out parallel studies using 5 mol% of $(Me_3P)_2NiCl_2$ at –20 ºC. The results summarized in Table 9 were excellent and proved the wide scope of the method. A certain loss of yield was identified as the steric hindrance of the alkyl group increased (compare entries 1–6 in Table 9). In addition to the good yields attained with *N*-acyl thioimides **4f–k** containing alkyl R groups, α-oxygenated and nitrogenated groups also delivered excellent results. Remarkably, the *O*-pivaloyl glycolic derivative **4m** turned out to be a suitable substrate, producing adduct **7m** in 82% yield after 3 h (entry 10 in Table 9). In turn, α-nitrogenated substrates worked well either with a phtalimido protecting group or an azido one (**4n** and **4o** respectively). However, they need higher catalyst loadings to reach a moderate yield (entries 11 and 12 in Table 9).



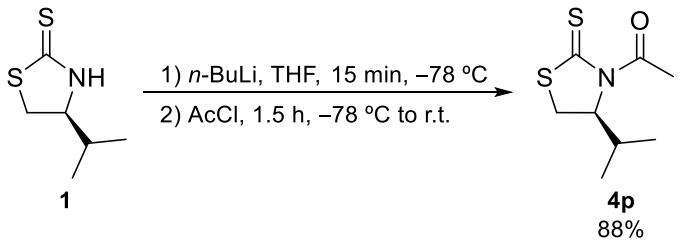
Entry	Substrate	R	Time (h)	Adduct	Yield (%)[a]
1	**4f**	Me	1.5	**7f**	87
2	**4g**	Et	1.5	**7g**	82
3	**4h**	*n*-Pr	1.5	**7h**	81
4	**4i**	*i*-Pr	1.5	**7i**	66
5	**4j**	Bn	1.5	**7j**	73
6	**4k**	$(CH_2)_2CO_2Me$	1.5	**7k**	67
7	**4l**	OBn	1.5	**7l**	<5
8	**4l**	OBn	24	**7l**	64
9	**4m**	OPiv	1.5	**7m**	72
10	**4m**	OPiv	3	**7m**	82
11[b,c]	**4n**	NPhth	15	**7n**	65
12[b,d]	**4o**	N_3	15	**7o**	61

[a] Isolated yield after column chromatography.
[b] Carried out by Javier Fernández-Valparís.[53]
[c] A 10 mol% of $(Me_3P)_2NiCl_2$ and 1.30 equivalents of TESOTf were used.
[d] A 20 mol% of $(Me_3P)_2NiCl_2$ and 1.50 equivalents of TESOTf were used.

Table 9

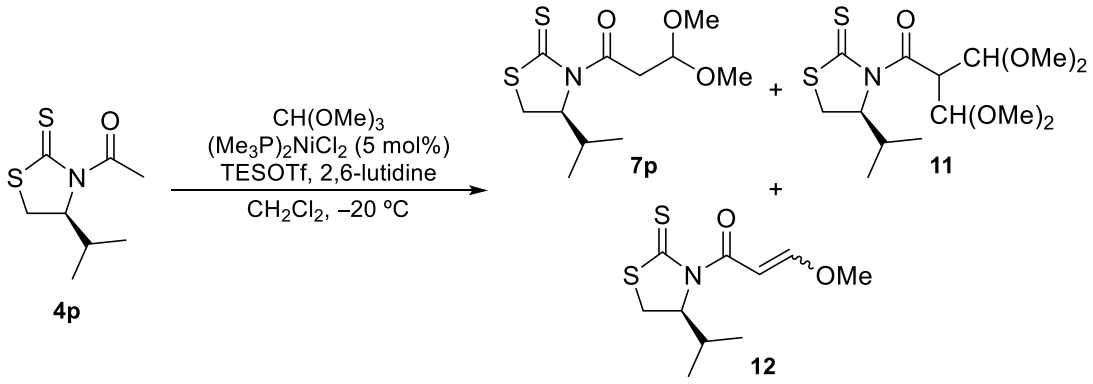
At this point, we wondered if the catalytic system might work in an acetate aldol-like reaction. Obviously, such an addition would not allow the construction of any chiral

center, but it could provide interesting information for further processes involving other electrophiles. The *N*-acetyl thioimide **4p** was then prepared according to the general procedure (Scheme 54).



Scheme 54

When the standard reaction conditions using a 5 mol% of $(Me_3P)_2NiCl_2$ at –20 ºC were tested with the *N*-acetylthioimide **4p**, a mixture of three compounds was obtained: the expected adduct **7p** derived from the addition of only one molecule of trimethyl orthoformate, the diformylated product **11**, and the α,β-unsaturated product **12** coming from an elimination of **7p**. The results summarized in Table 10 suggested that the reaction of **7p** must be very fast, so the diformylation seemed to be unavoidable. Consequently, we tried to obtain **11** as the major product. Unfortunately, long reaction times did not afford **11** in high yields, so it was necessary to add an excess of trimethyl orthoformate to obtain **11** in up to 68% yield.



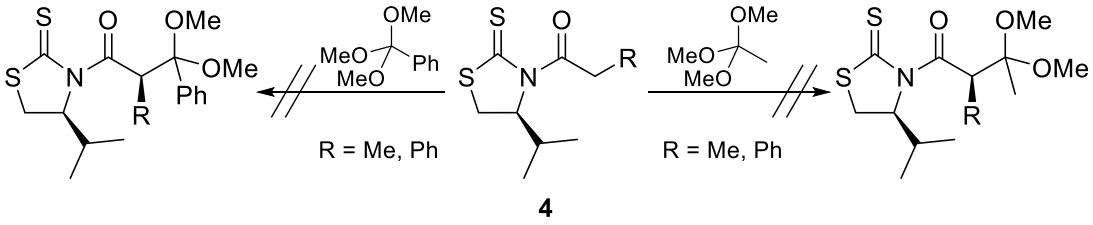
Entry	$CH(OMe)_3$ (eq)	t (h)	**7p** (%)[a]	**11** (%)[a]	**12** (%)[a]	r.s.m.[a,b] (%)
1	1.5	1.5	23	21	11	38
2	1.5	20	24	27	9	29
3	3.0	1.5	9	68	16	4

[a] Isolated yield after column chromatography.
[b] r.s.m.: Recovered Starting Material.

Table 10

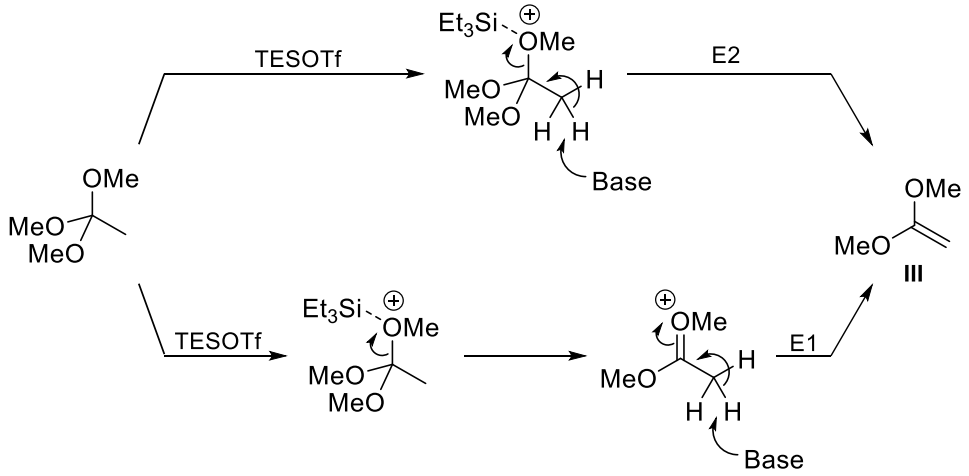
7. REACTIONS WITH OTHER ORTHOESTERS

Having established the method using trimethyl orthoformate, other commercially available orthoesters as trimethyl orthoacetate and trimethyl orthobenzoate were also considered. Unfortunately, these electrophiles did not produce the desired adducts.



Scheme 55

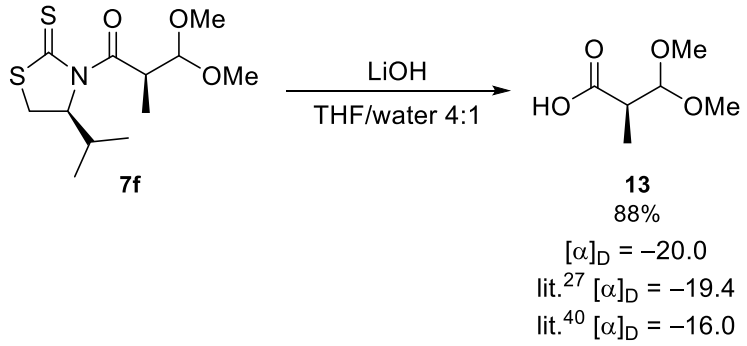
Likely, the most probable drawback in the case of trimethyl orthoacetate was an elimination process, *via* an E1 or E2 mechanism, to produce ketene dimethyl acetal **III**, which would rule out any possibility of nucleophilic attack from the Ni(II) enolate. Regarding trimethyl orthobenzoate, the reasons for such a failure still remain unclear.



Scheme 56

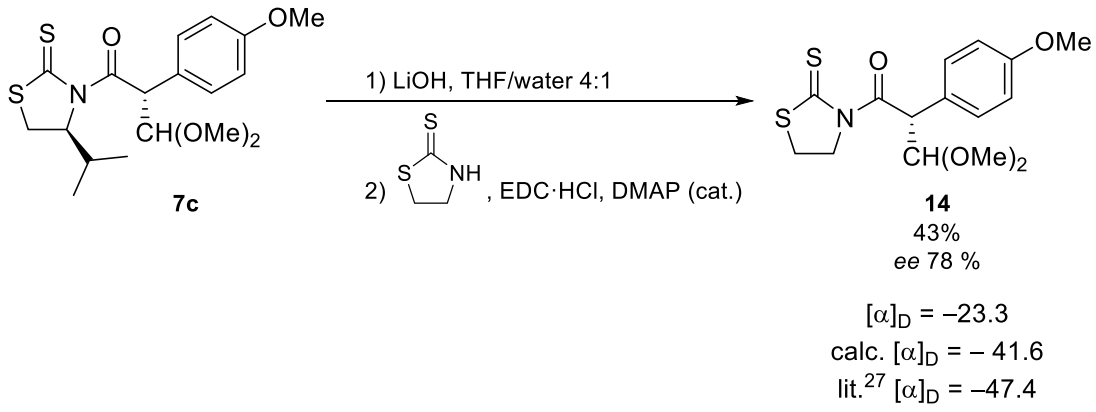
8. ELUCIDATION OF THE ABSOLUTE CONFIGURATION

The absolute configuration of adducts **7** was established through chemical correlation of derivatives from **7c** and **7f**. Initially, hydrolysis of **7f** afforded carboxylic acid **13**, whose physical and spectroscopic data as well as the specific rotation matched with those reported in the literature.[27,40]



Scheme 57

In turn, hydrolysis of adduct **7c** followed by coupling of the resulting acid with achiral 1,3-thiazolidine-2-thione yielded thioimide **14**. Chiral HPLC analysis revealed that the α-stereocenter had partially epimerized. Measurement of the specific rotation and subsequent calculation of the theoretical enantiomerically-pure optical rotation matched with the reported one, which confirmed the stereochemical outcome of the addition to methyl orthoformate.[27]



Scheme 58

Finally, the *R* configuration of the α-stereocenter was firmly confirmed by means of X-ray diffraction of a crystal of **7a**, as shown in Figure 2.

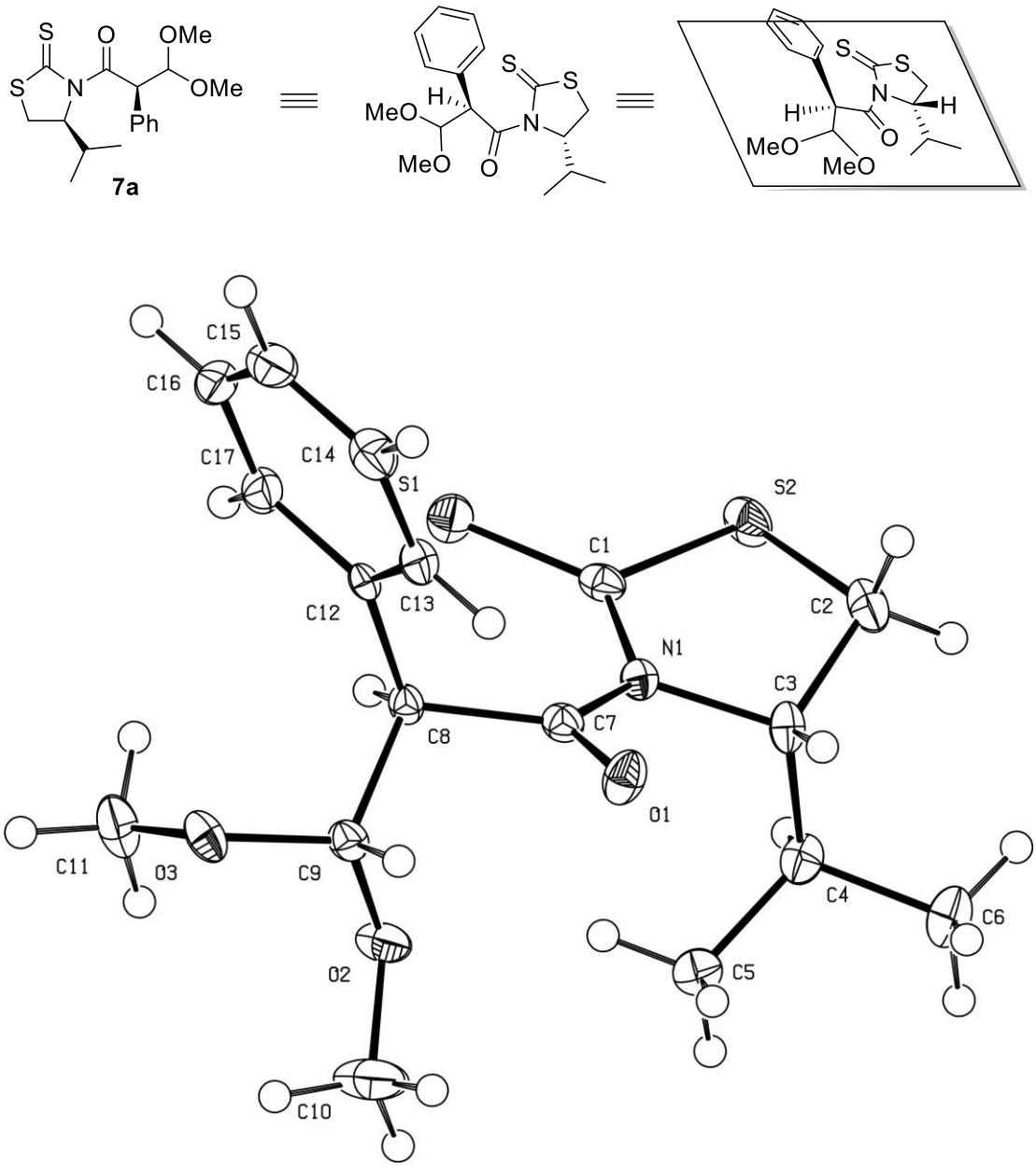
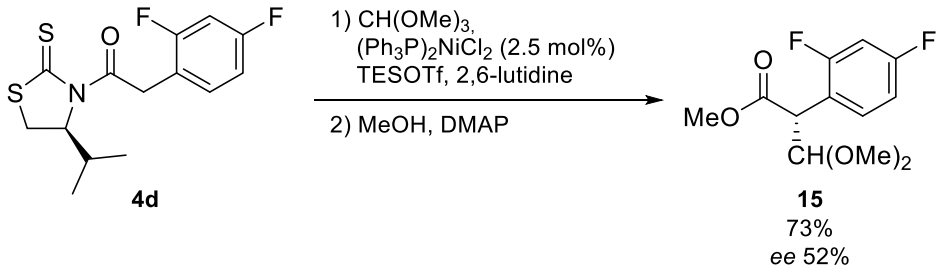


Figure 2

9. CHIRAL AUXILIARY REMOVAL

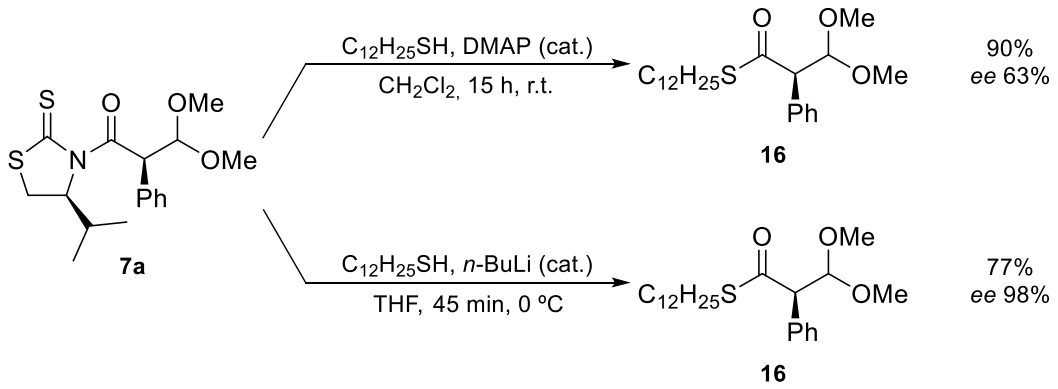
By now, a smooth addition of *N*-acylthiazolidinethiones to methyl orthoformate catalyzed by Ni(II) complexes under mild conditions in a "direct-type" reaction has been achieved. Nevertheless, the use of a chiral auxiliary requires its later removal.

In this context, removal of the chiral auxiliary by addition of methanol and DMAP to the reaction mixture from thioimide **4d** was successfully carried out (Scheme 59), showing that isolation of the formylated thioimide **7d** was not strictly necessary. However, as for the preparation of thioimide **14**, a partial epimerization occurred.



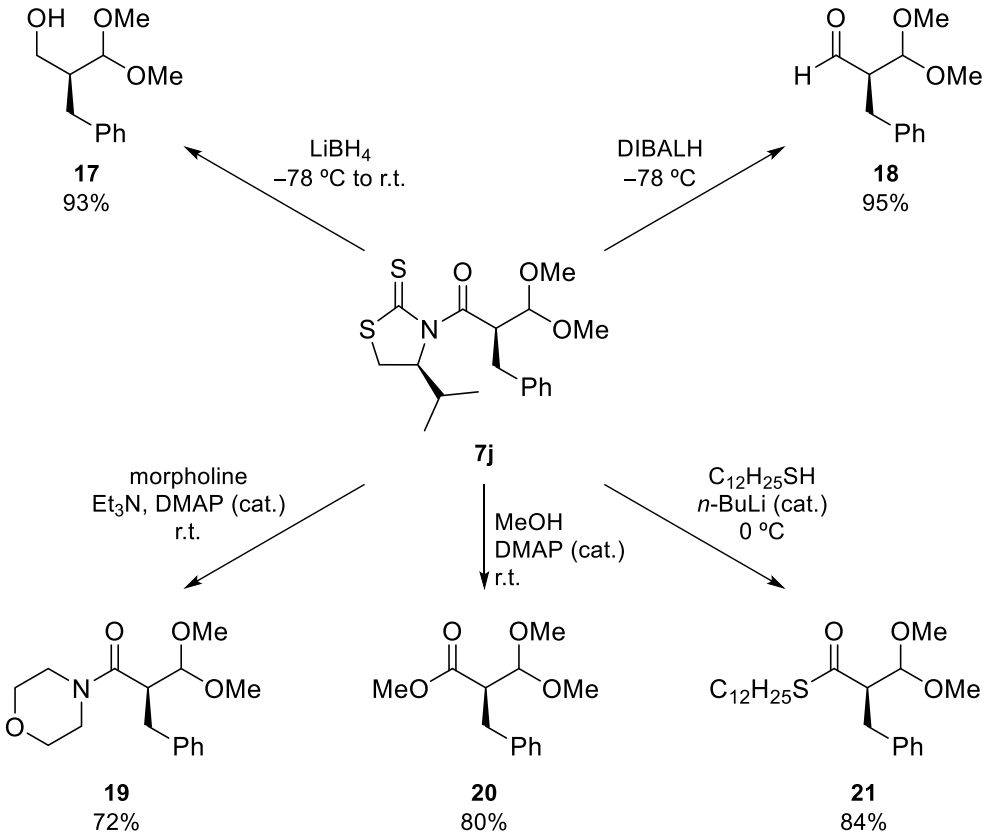
Scheme 59

Alternatively, thioester **16** was obtained from adduct **7a** by reaction with 1-dodecanethiol and DMAP. Again, a partial epimerization took place. These three cases indicated that the use of unhindered amines as bases was troublesome. In order to avoid this problem, the chiral auxiliary of adduct **7a** was displaced with the corresponding thiolate under almost neutral conditions. Fortunately, the thioester derivative **16** was obtained in a high yield and as a single enantiomer (Scheme 60).



Scheme 60

Having observed that mandelic-like substrates were so delicate that they could not be converted safely into a variety of derivatives, our attention was focused on more robust substrates. In this context, Hubert Kowalski has recently been working with the hydrocinnamic derivative **7j** to obtain a wide range of derivatives, which has been achieved with remarkable success.[54]

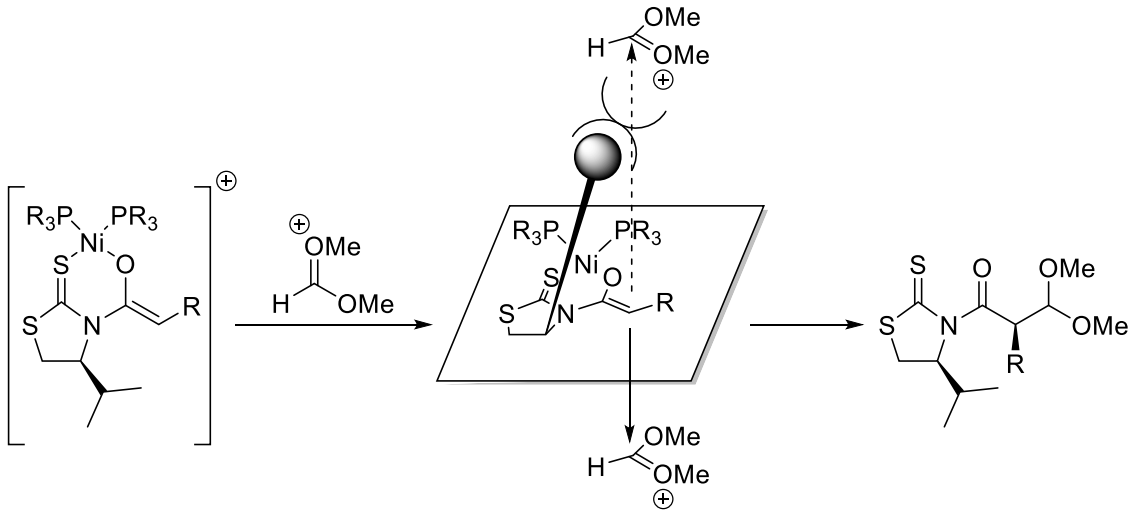


Scheme 61

All together, these results prove that the chiral auxiliary can be safely removed to afford a wide range of enantiomerically pure compounds provided that the experimental conditions are mild enough to avoid the undesired epimerization of the α-stereocenter. However, this drawback is particularly important for mandelic-like substrates shown in Schemes 58–60.

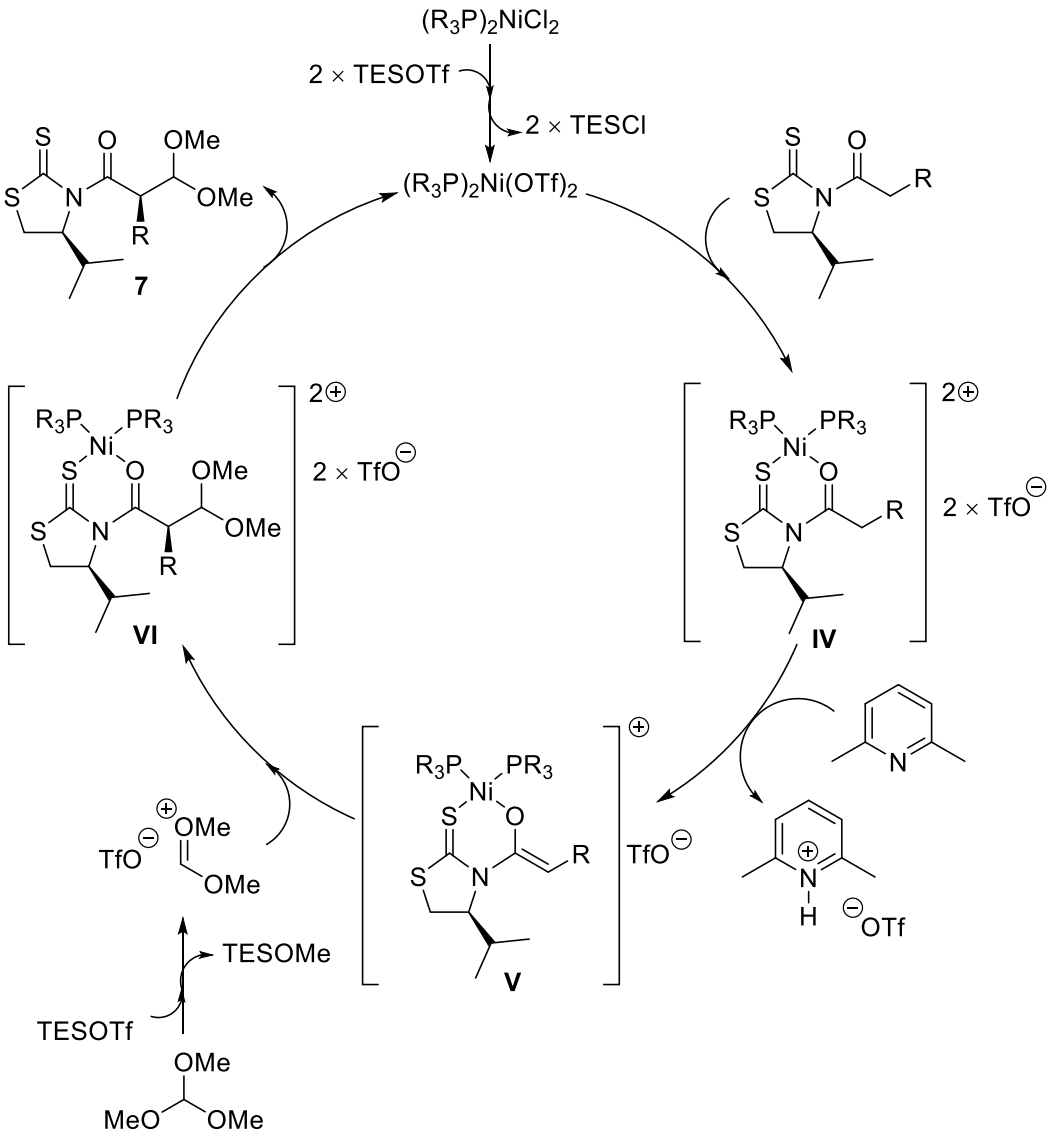
10. MECHANISTIC HYPOTHESIS

The fact that our method as well as the Evans'[27] or the Sodeoka's[45] ones always give an excellent stereocontrol suggests the formation of a chelated *Z*-enolate bound to a distorsioned square-planar Ni(II) complex. This might be the nucleophilic species. In our case, such a chelated enolate would direct the approach of the electrophilic oxocarbenium cation toward the less sterically hindered face, as shown in Scheme 62.



Scheme 62

In turn, Sodeoka stated that TESOTf acts as Lewis acid to activate an electrophilic substrate, but also participates in a chlorine-triflate ligand exchange.[45] Some studies on the interchange of halide ligands by trifluoromethyl groups in Ni(II) complexes by means of TMS–CF_3 indicate that silyl compounds could act as ligand interchange promoter.[55,56] These precedents suggest that the same process might be active in our reaction. So, we hypothesize that a catalytic cycle similar to that proposed by Evans could account for the TESOTf–mediated addition of thioimides **4** to methyl orthoformate catalyzed by nickel(II) complexes (Scheme 63). First, the ligand interchange produces the real catalytic species. Then, it would coordinate to the *N*-acylthiazolidinethione. The coordinated complex **IV** would be a deprotonated to furnish the corresponding chelated *Z*-enolate **V**. This enolate would attack the oxonium cation coming from trimethyl orthoformate to create adduct **VI** which, in turn, would give the final adduct **7** and the Ni(II) catalyst ready to start a new catalytic cycle again.

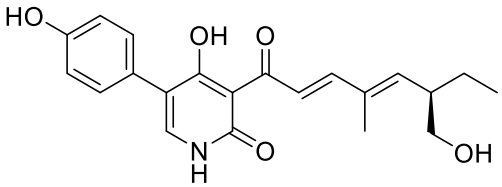

(R3P)2NiCl2
2 × TESOTf
2 × TESCl
(R3P)2Ni(OTf)2
7
VI
IV
V
2 × TfO
TESOMe
TESOTf
TfO
OTf

Scheme 63

11. SYNTHETIC STUDIES

11.1. Side chain of (–)-pyridovericin

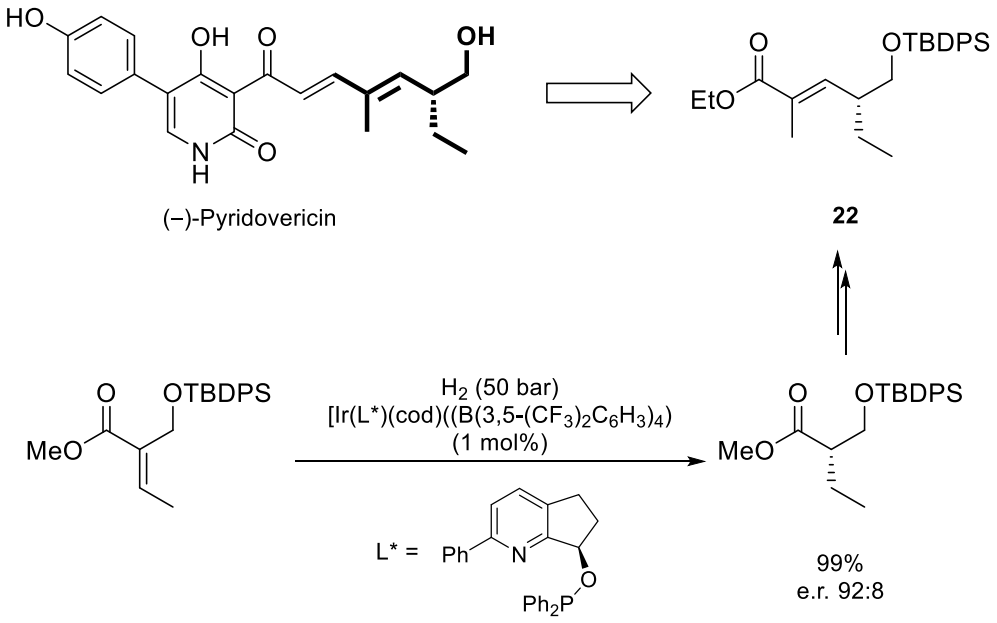
(–)-Pyridovericin is a secondary metabolite from the entomopathogenic fungus *Beauveria bassiana* isolated and characterized in 1998 by Takahashi.[57] Pyridovericin features a central 4-hydroxy-2-pyridone ring with a chiral 3-acylpolyene side chain (Figure 3). Interestingly, it has been reported that it is a promising lead compound for the development of novel anti-allergic drugs.[58] Despite the interest that its biological activity arouses, the scarcity of this natural product restricts further clinical applications.



(+)–Pyridovericin

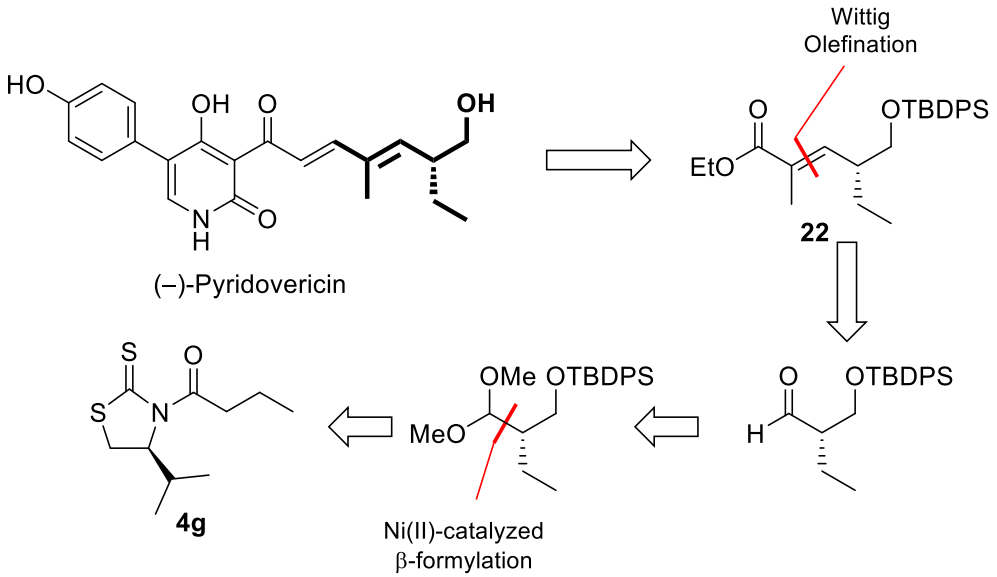
Figure 3

A total enantioselective synthesis[59] and two other synthetic studies have been reported so far.[60,61] Remarkably, the abovementioned total synthesis rest on an iridium–catalyzed asymmetric hydrogenation, as represented in Scheme 64.



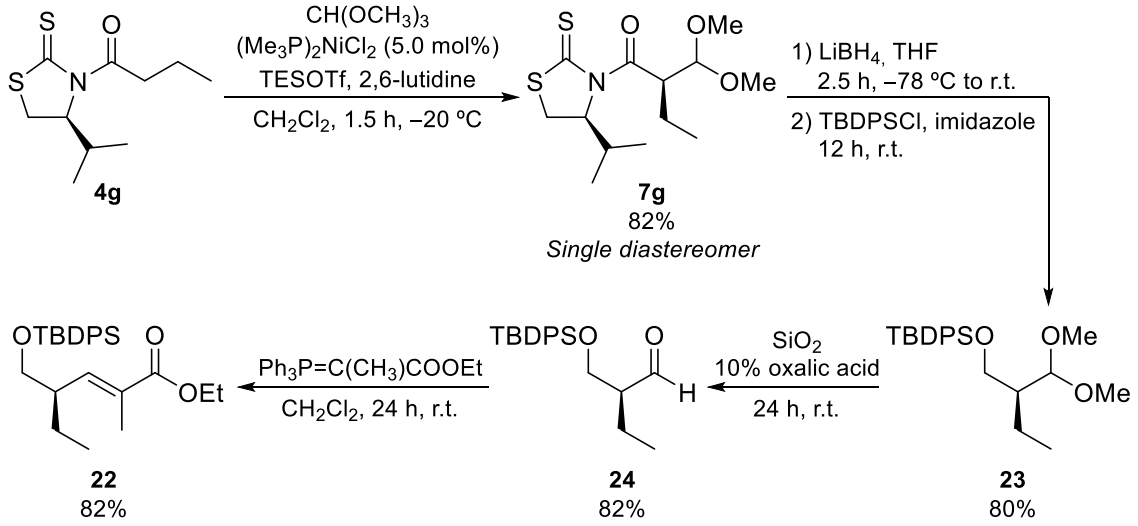
Scheme 64

In this context, we envisaged that ester **22** might be prepared by means of our diastereoselective reaction, thus installing the chiral center in a high yield and with a complete stereocontrol. Our retrosynthetic analysis was based on a linear sequence depicted in Scheme 65, which involves our formylation reaction and a Wittig olefination of a chiral aldehyde.



Scheme 65

Our synthesis started with the reaction between the thioimide **4g** and trimethyl orthoformate catalyzed by 5 mol% of $(Me_3P)_2NiCl_2$ (Scheme 66). It was possible to carry out this reaction at a multigram scale obtaining a high yield of adduct **7g** as a single diastereomer. Then, removal of the chiral auxiliary with a reducing agent and protection of the resulting alcohol afforded acetal **23**, which, in turn, gave aldehyde **24** under mild acidic conditions.[62] Finally, a Wittig reaction afforded the desired α,β-unsaturated ester **22** with complete stereocontrol of the double bond.[59]



Scheme 66

In conclusion, the side chain of (–)-pyridovericin has been synthesized in five steps from (*S*)-*N*-butanoyl-4-isopropyl-1,3-thiazolidine-2-thione (**4g**) with an overall yield of 44%. The stereogenic center has been successfully built thanks to our stereoselective Ni(II) catalyzed reaction.

11.2. Synthesis of the C11–C19 fragment of (+)-peloruside A

(+)-Peloruside A is a polyketide isolated from the marine sponge *Mycale hentscheli* in Pelorus Sound, New Zealand, by West and Northcote.[63] This initial disclosure demonstrated that (+)-peloruside A displays a potent antitumor activity against P388 murine leukemia cells with an IC_{50} value of 10 ng mL^{-1}.[64] In addition, it shows a microtubule-stabilizing activity synergistic with paclitaxel arresting cells in the G2–M phase of the cell cycle.[65–69]

(+)-Peloruside A is a 16-membered ketolactone decorated with a variety of oxygenated stereocenters. Noteworthy, it contains a pyran ring arising from an intramolecular hemiketal formation and an unsaturated lateral chain.

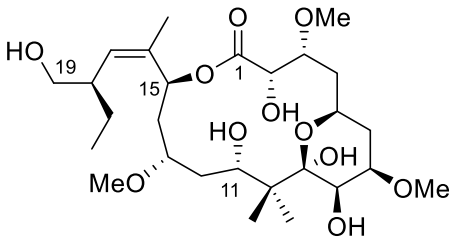
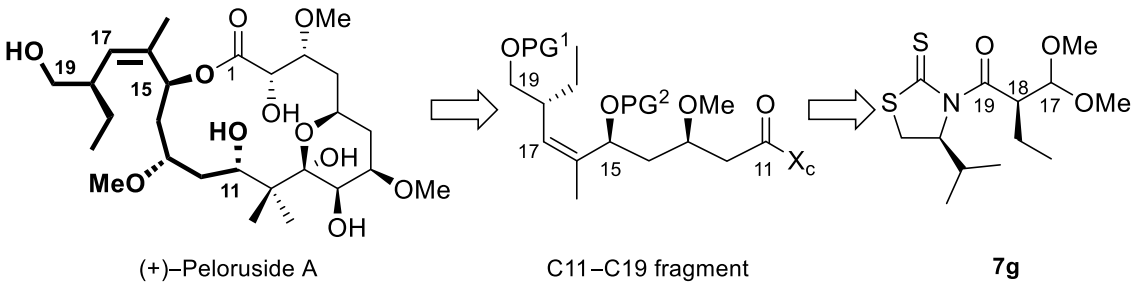


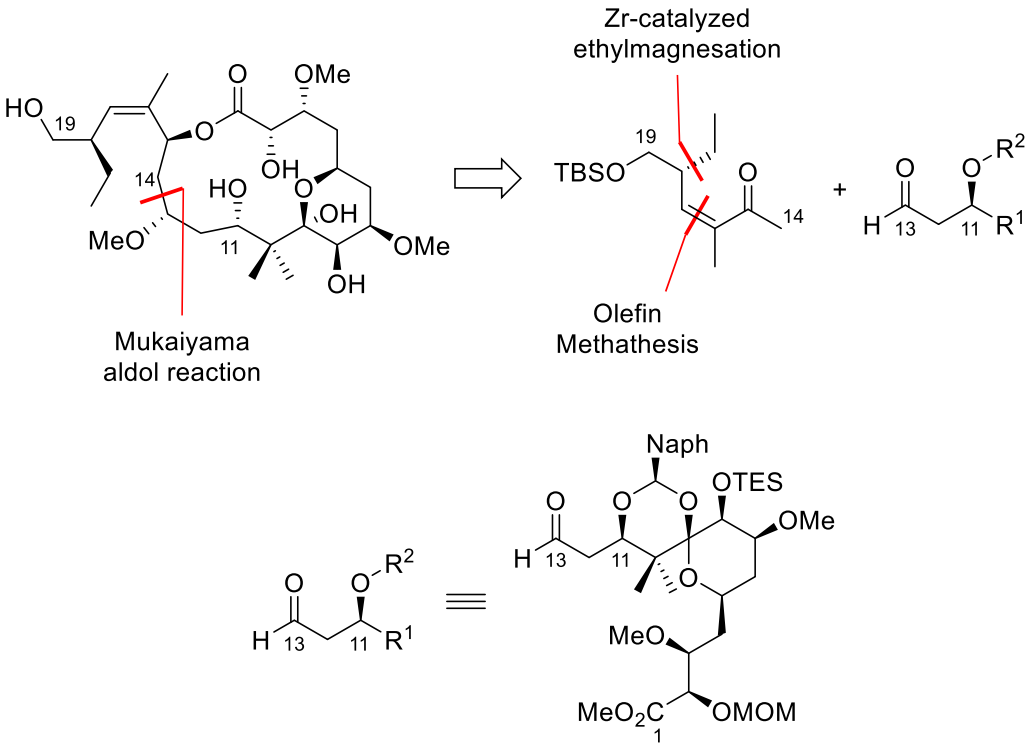
Figure 4

This lateral chain attracted our attention because of its resemblance to that of (–)-pyridovericin. Furthermore, we envisaged that the C11–C19 fragment of (+)-peloruside A might be synthesized by using the nickel-mediated reaction described in this chapter and other methods developed in our group based on the reactivity of thiazolidinethione chiral auxiliary.



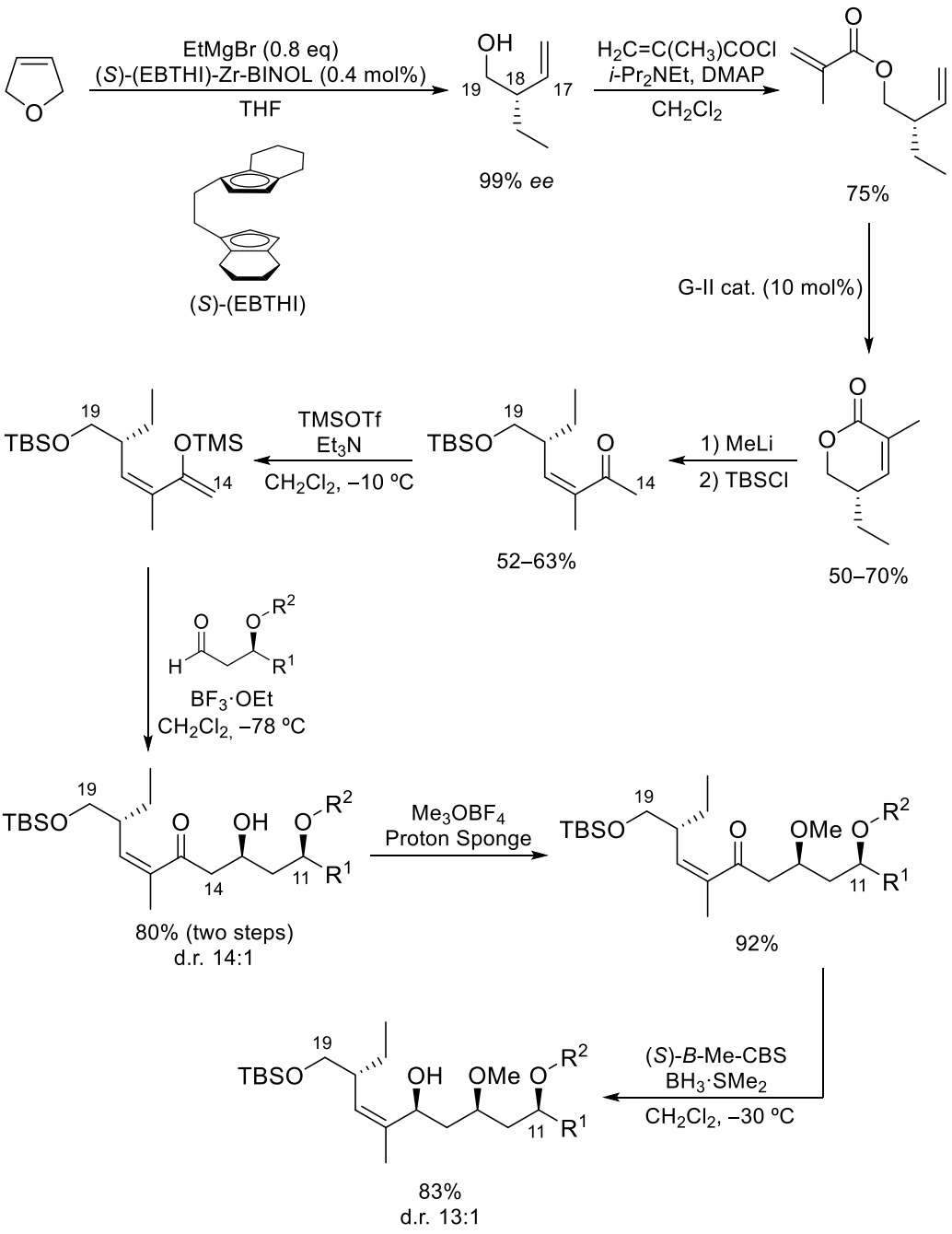
Scheme 67

The first total synthesis of (+)-peloruside A reported by De Brabander confirmed the absolute configuration of this natural product.[70] His strategy for the construction of the C11–C19 fragment was based on the coupling of the C14–C19 fragment and the C1–C13 one by a diastereoselective Mukaiyama aldol reaction. Furthermore, the asymmetric construction of the C14–C19 fragment required the enantioselective Zr-catalyzed ethylmagnesation and a ring-closing metathesis for assembling the trisubstituted C17–C18 olefin.



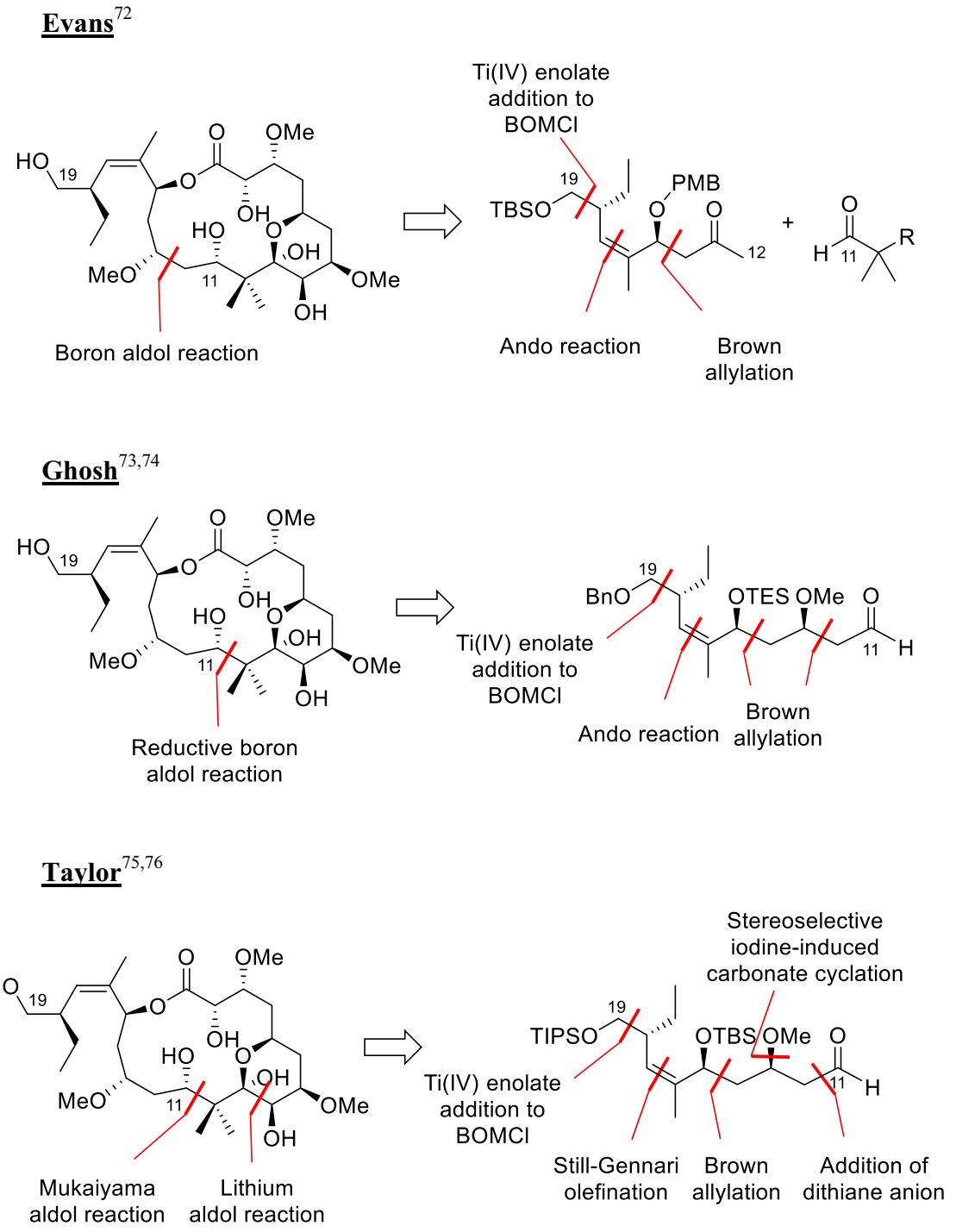
Scheme 68

The synthesis commenced with the Zr-catalyzed enantioselective ethylmagnesation of 2,5-dihydrofuran[71] to obtain an homoallylic alcohol with an excellent stereocontrol (Scheme 69). The acylation with methacryloyl chloride and a subsequent ring-closing metathesis reaction afforded a lactone with the desired trisubstituted *Z*-olefin, which was then treated with methyllithium and the resulting alcohol protected with TBSCl to obtain the C14–C19 fragment. Finally, a Mukaiyama aldol reaction followed by the stereoselective reduction of the resultant ketone furnished the desired C11–C19 fragment.



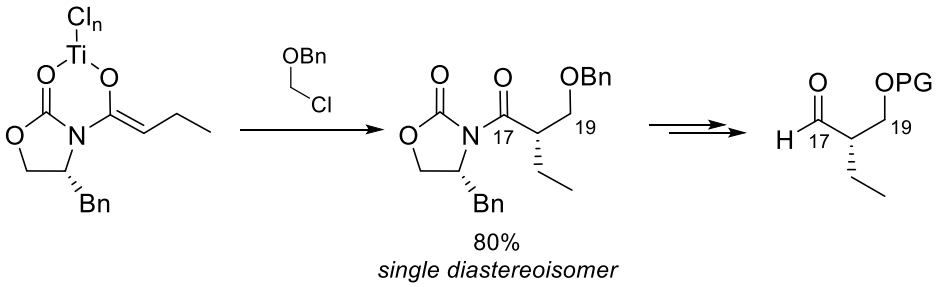
Scheme 69

The total syntheses after De Brabander's one have followed strategies with certain similarities concerning the C11–C19 fragment. Clearly, the construction of the C18–C19 and C14–C15 bonds as well as the *Z*-olefin share common approaches. A brief summary of the most interesting approaches towards the C11–C19 fragment is depicted in Scheme 70.



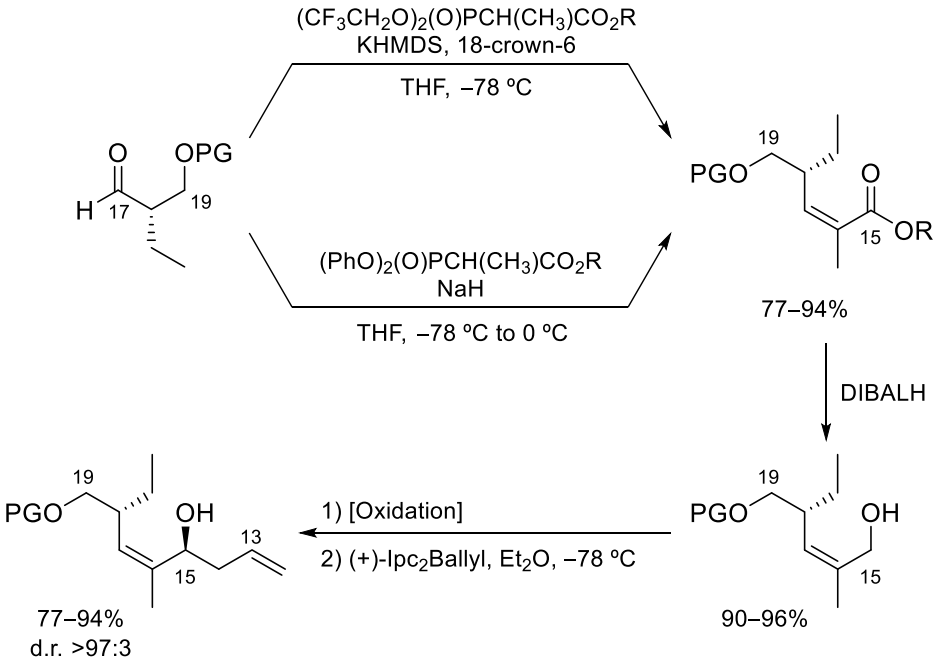
Scheme 70

The totally diastereoselective addition of the titanium enolate of (*S*)-4-benzyl-*N*-butanoyl-1,3-oxazolidin-2-one to chloromethyl benzyl ether (BOMCl) previously reported by Evans illustrates one of the most appealing approaches.[40] Such a reaction gives a single diastereomer in high yields, which can be converted into a variety of protected aldehydes (Scheme 71).



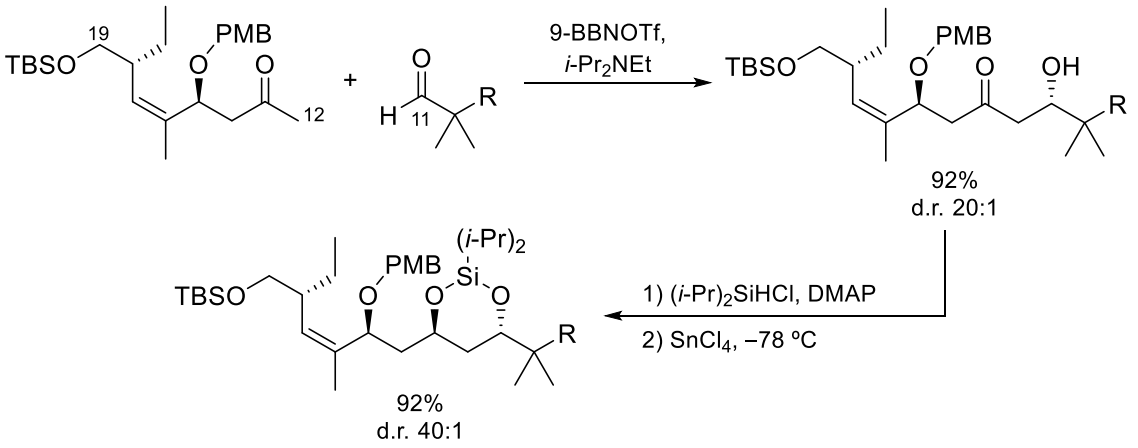
Scheme 71

These aldehydes served as precursors of the trisubstituted *Z*-olefin through either a Still-Gennari olefination[77] or an Ando reaction[78]. Then, the resultant conjugated ester was converted into a formyl group, which was submitted to a highly stereoselective Brown's allylation.



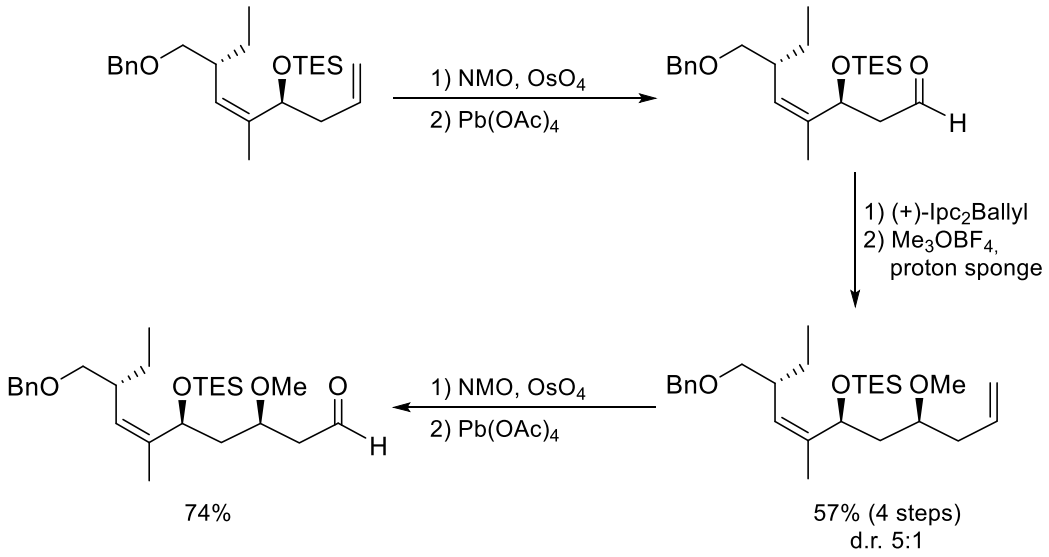
Scheme 72

From this intermediate the approaches for the construction of the whole C11–C19 fragment are diverse. For example, Evans carried out a boron aldol reaction in late stages of his synthesis and reduced the carbonyl group with an stereoselective intramolecular hydride reduction promoted by a Lewis acid.[72]



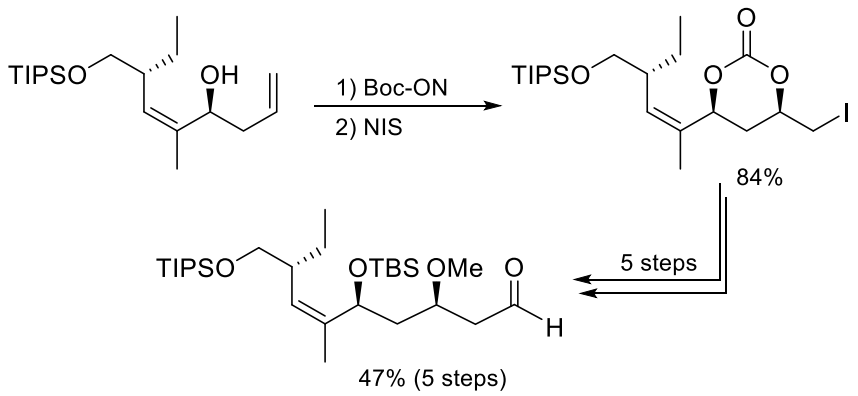
Scheme 73

As for Ghosh's synthesis, an oxidation–Brown's allylation–oxidation sequence was carried out from the previously described C13–C19 precursor.[74]



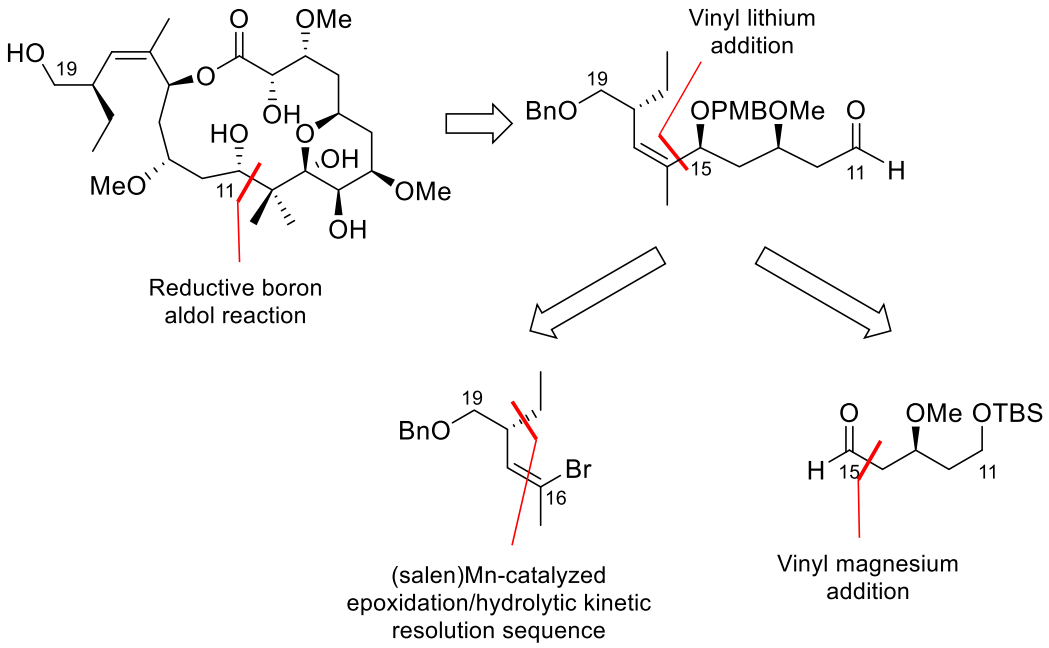
Scheme 74

In turn, Taylor applied a slightly modified stereoselective iodine-induced carbonate cyclization to control the installation of the C13 stereocenter. Finally, a five-step sequence ended up in the desired C11–C19 fragment.[75]



Scheme 75

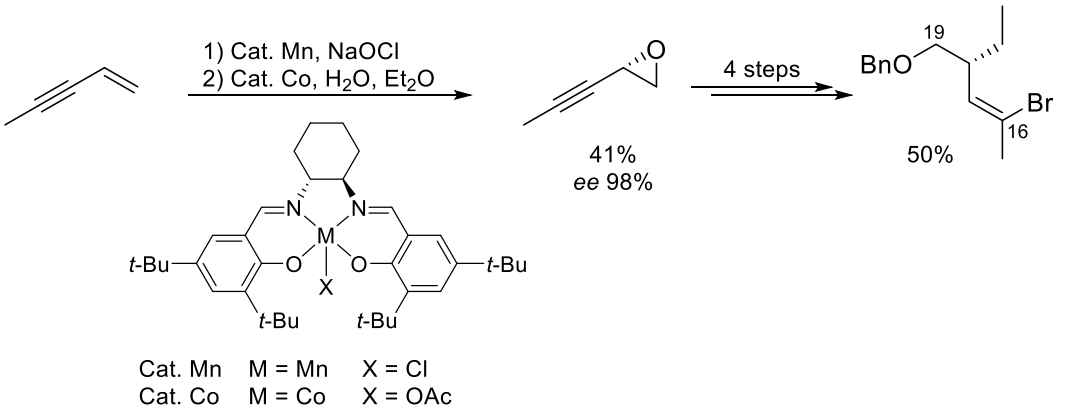
Finally, Jacobsen devised a different approach in which the C11–C19 fragment is synthesized by a reductive boron aldol reaction (Scheme 76).[79] Besides, this fragment was prepared by lithiation of the C16–C19 fragment and subsequent addition to the formyl group of the C11–C15 one.



Scheme 76

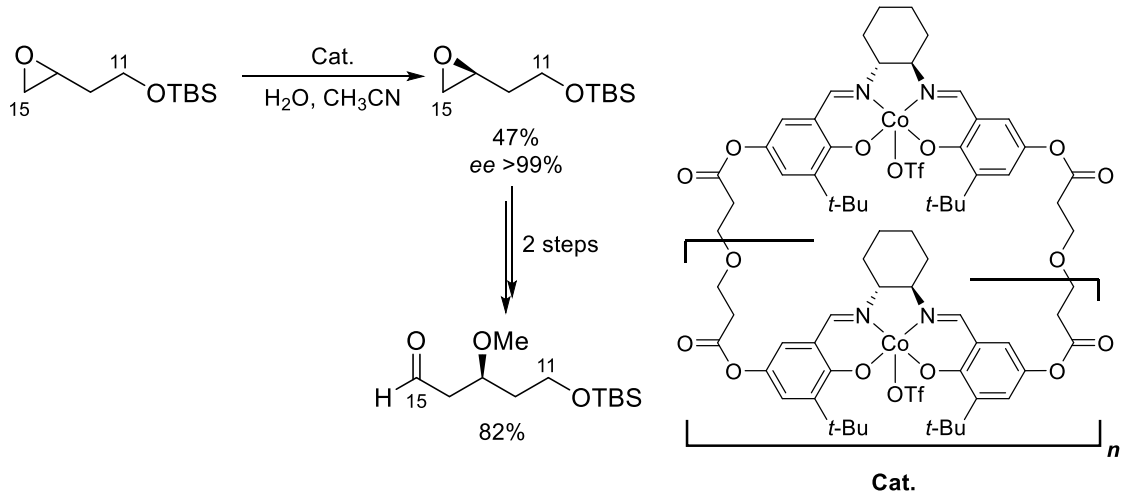
Remarkably, the stereogenic centers of both fragments were prepared by epoxidation and hydrolytic kinetic resolution (HKR) methods developed by Jacobsen.[80–82] As shown in Scheme 77, 1-penten-3-yne was the starting material for the preparation of the C16–C19 fragment. Using a (salen)manganese-catalyzed epoxidation/HKR

sequence, an enantiopure epoxide was obtained, where appropriate manipulation afforded the C16–C19 fragment.



Scheme 77

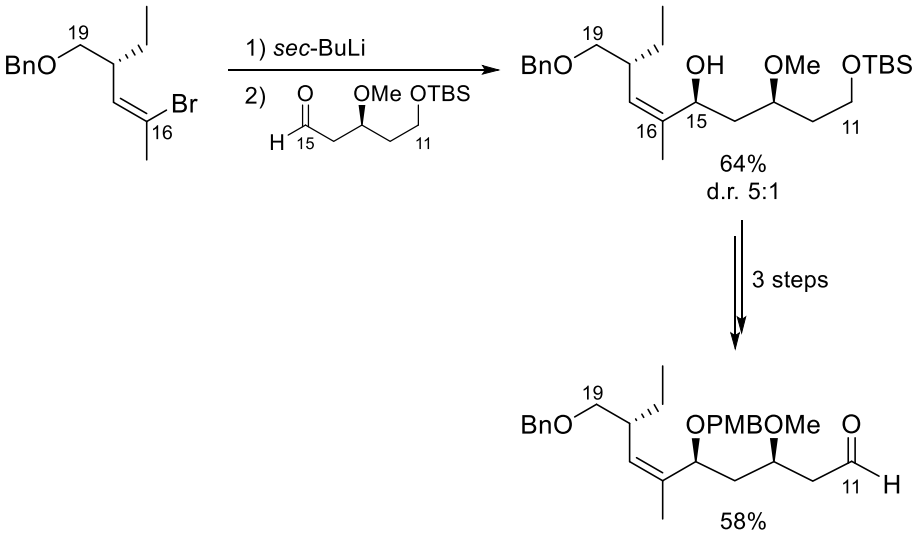
The synthesis of the C11–C15 fragment started with a racemic epoxide, which was treated with an oligomeric cobalt salen catalyst in a HKR reaction (Scheme 78).[83,84] With the resultant enantiopure epoxide at hand, a two-step sequence allowed the preparation of the desired fragment.



Scheme 78

Both fragments were coupled by lithiation of the C16–C19 fragment and stereoselective addition to the C11–C15 one. The C11–C19 fragment was thus obtained

after hydroxyl protecting/deprotecting and oxidation reactions of different primary alcohol groups, summarized in Scheme 79.

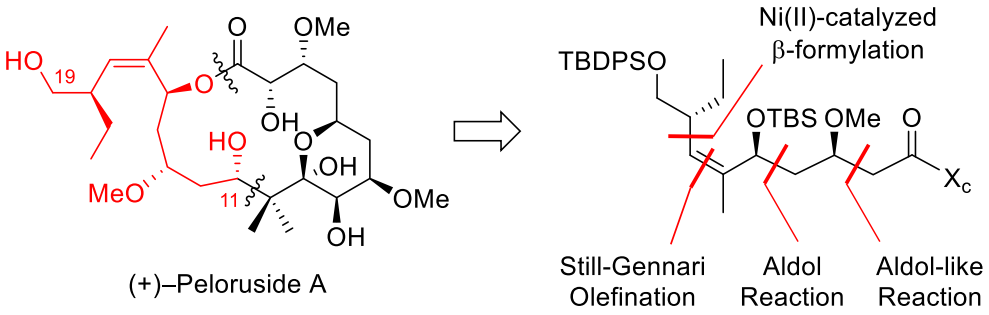


Scheme 79

In addition to these contributions, other total synthesis[85] and a variety of synthetic approaches have been published during the last years.[86,87] Thus, (+)-peloruside A represents an appropriate benchmark to test the efficiency of new synthetic procedures.

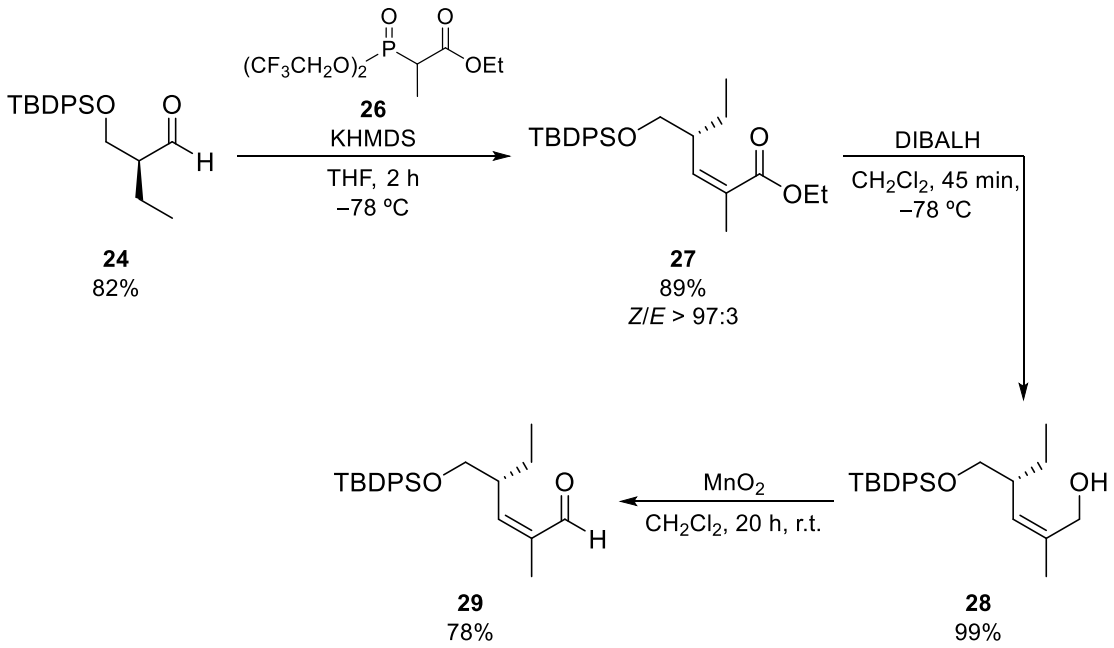
In this context, we were interested in challenging the nickel-mediated asymmetric transformation developed in this Chapter for the construction of the C11–C19 fragment containing three stereocenters and a trisubstituted *Z*-olefin.

Our retrosynthetic analysis depicted in Scheme 80 was based on a linear sequence that involves our formylation reaction for installing the C18 stereocenter, a Still-Gennari *Z*-olefination, a stereoselective acetate aldol reaction for the formation of the chiral center at C15, and a stereoselective addition to a late dimethyl acetal to generate the C13 stereocenter. Especially, we planned to apply the titanium enolates of *N*-acyl thiazolidinethiones to carry out these last two key steps.



Scheme 80

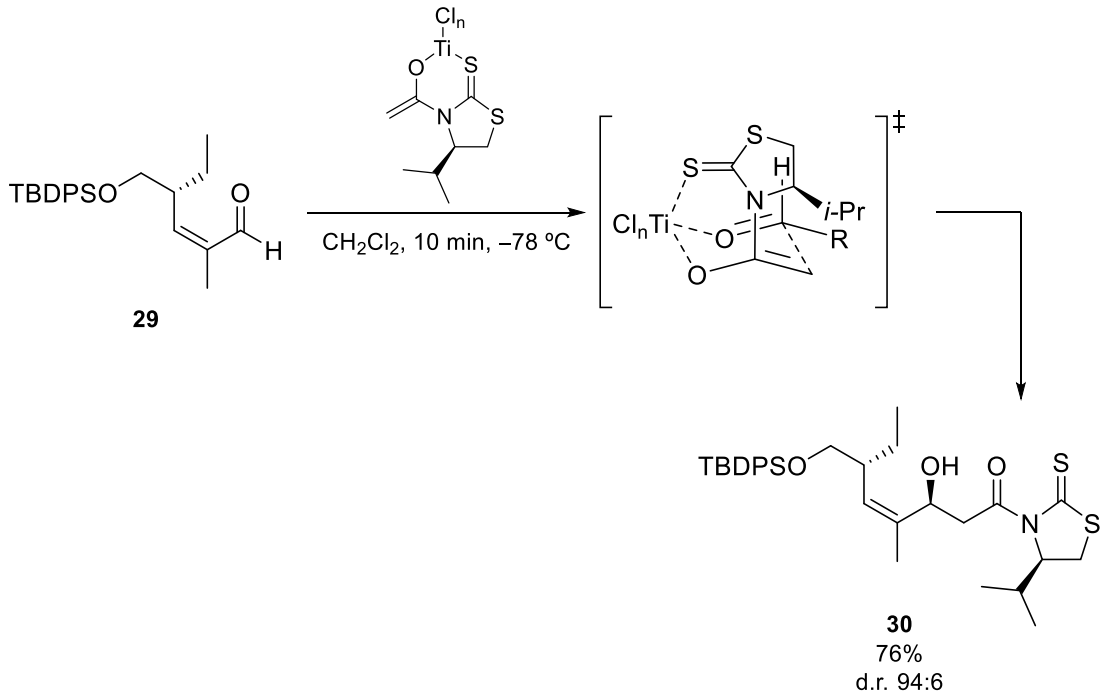
Our synthesis took advantage of the preparation of the side chain of (–)-pyridovericin. Thus, we started with the olefination of the previously synthesized aldehyde **24** *via* a Still-Gennari reaction using phosphonate **26**[*] to afford the desired *Z*-trisubstituted double bond of the α,β–unsaturated ester **27** as a single isomer with a 89% yield (Scheme 81).[77] Reduction to alcohol **28** followed by an allylic oxidation with MnO_2 afforded the required aldehyde **29** to undergo the next aldol reaction.



Scheme 81

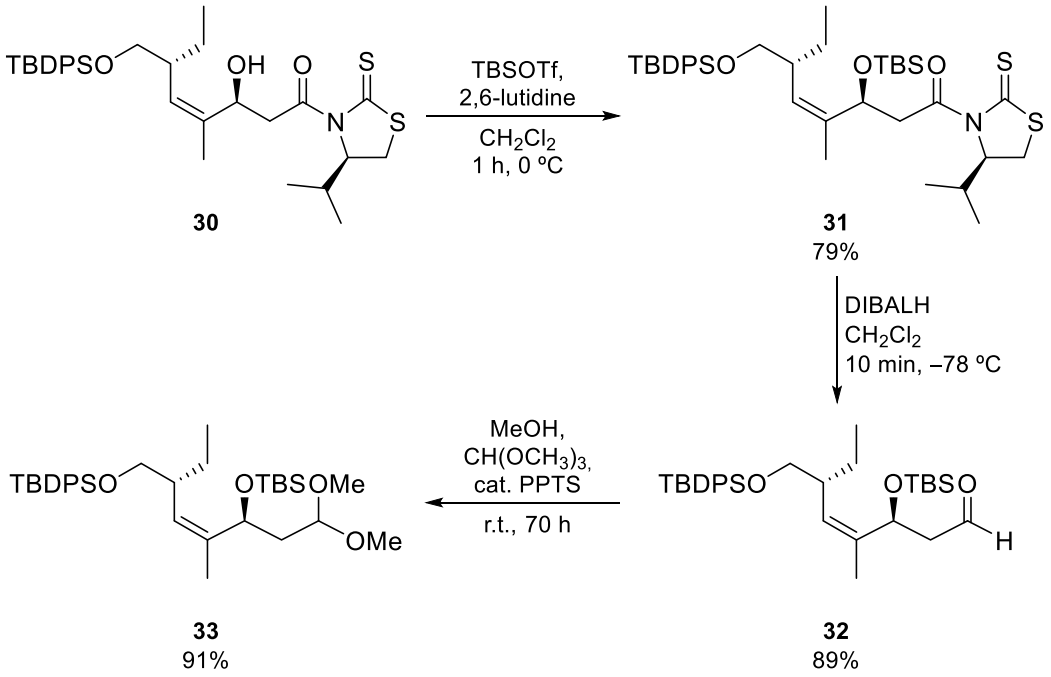
[*] Ethyl 2-[bis(2,2,2-trifluoroethoxy)phosphoryl]propanoate (**26**) was prepared from ethylbis(2,2,2-trifluoroethyl)phosphine oxide (**25**) according to a reported procedure.[88] For more information see "Experimental Section" of this Thesis.

The subsequent acetate aldol reaction involved the titanium enolate of (*R*)-*N*-acetylthioimide *ent*-**4p** and aldehyde **29**. The stereochemical outcome of this reaction can be explained through a chair-like transition state, most commonly known as Zimmerman-Traxler transition state, in which the steric repulsions are minimized (Scheme 82). Importantly, the sulfur atom of the C=S bond is bound to the metal and the stereocenter at the chiral auxiliary determines the approach to the *Si*-face of the carbonyl bond of the aldehyde.[89] For our pleasure, the aldol adduct **30** was obtained in an excellent 94:6 diastereomeric ratio and was easily isolated with a 76% yield.



Scheme 82

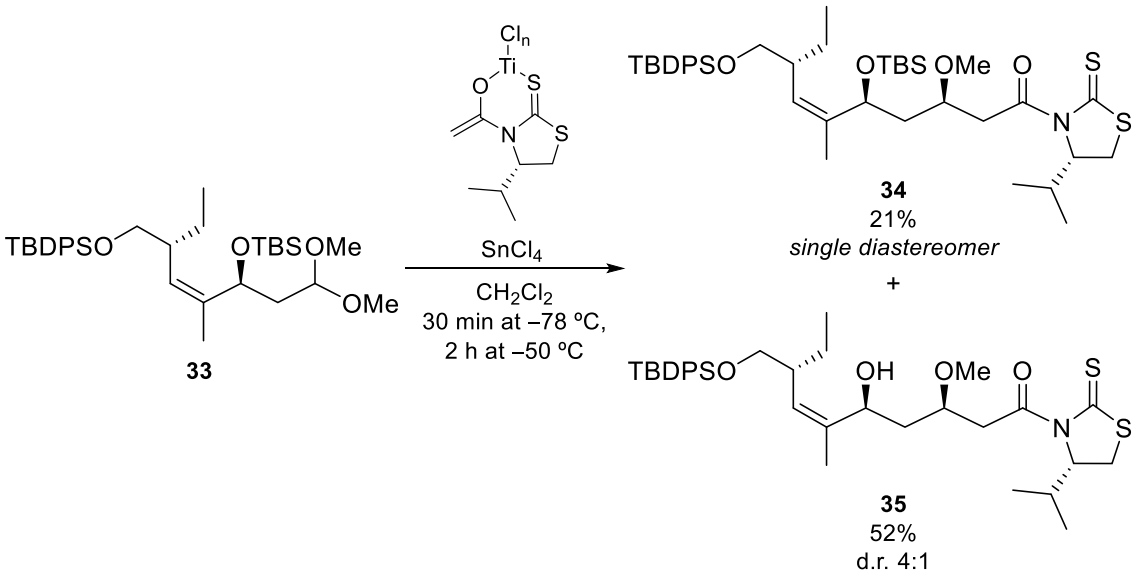
Aldol adduct **30** was protected as a silyl derivative and the chiral auxiliary was removed by treatment with DIBALH to afford aldehyde **32** in 70% two-steps yield (Scheme 83). The corresponding dimethyl acetal **33** was then prepared from **32** in anhydrous MeOH and trimethyl orthoformate under acidic conditions in 91% yield. In summary, enantiomerically pure acetal **33** had been prepared from aldehyde **24** in seven steps and 33% yield.



Scheme 83

Then, we evaluated several options to complete the synthesis. Looking back again at the precedents in our group, we paid attention to the method presented in the Introduction that involves the Lewis acid-mediated addition of titanium enolates of *N*-acyl thiazolidinethiones to dimethyl acetals. Indeed, Annabel Cosp had established that the $SnCl_4$–mediated addition of the titanium enolates from *N*-acetyl thiazolidinethiones to dialkyl acetals of aliphatic aldehydes provided the corresponding β–methoxy adducts in good to high yields.[90,91] In our hands, such an addition to acetal **33** afforded the desired adduct **34** as a single diastereomer in a 21% yield (Scheme 84). Furthermore, a 4:1 diastereomeric mixture of the adduct **35** coming from a deprotection of the hydroxyl of C15 was isolated in a 51% yield. This deprotection might likely occur due to the excess of metal enolate. This result indicated that the *minor* adduct had been desilylated completely, while the *major* diastereomer was much more robust.

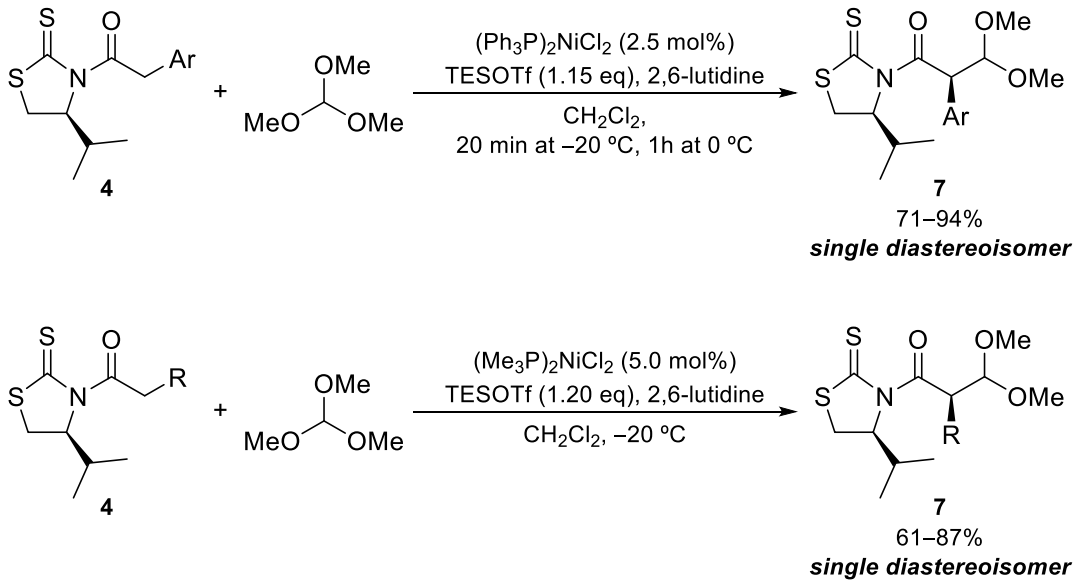
In an overall view, the reaction afforded a 63% yield of two different *anti* adducts and a 10% yield of a *syn* one, which indicate that the reaction works with high yields and a diastereomeric ratio of approximately 86:14. Encouraged by this result, current studies of this reaction are trying to reduce the acidity of the reaction mixture and thus reduce the amount of desilylated products.



Scheme 84

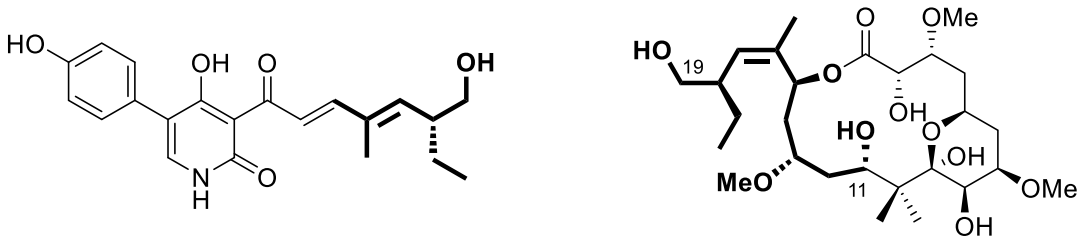
12. SUMMARY AND CONCLUSIONS

To summarize, in this chapter a new stereoselective and catalytic reaction based on the nickel(II)-mediated addition of enolates from *N*-acyl-4-isopropyl-1,3-thiazolidine-2-thiones to trimethyl orthoformate has been developed (Scheme 85). The experimental conditions turned out to be slightly different depending on the acyl chain, but tiny amounts (2.5–5 mol%) of commercially available and structurally simple nickel(II) complexes are always necessary. The configuration of the resultant adducts has been established through chemical correlation and X–ray studies and it has been demonstrated that the chiral auxiliary can be removed smoothly to yield a wide range of functional groups.



Scheme 85

Finally, such a reaction has been used for the asymmetric synthesis of the side chain of (–)-pyridovericin and the C11–C19 fragment of (+)-peloruside A.



(–)-pyridovericin

(+)-peloruside A

Scheme 86

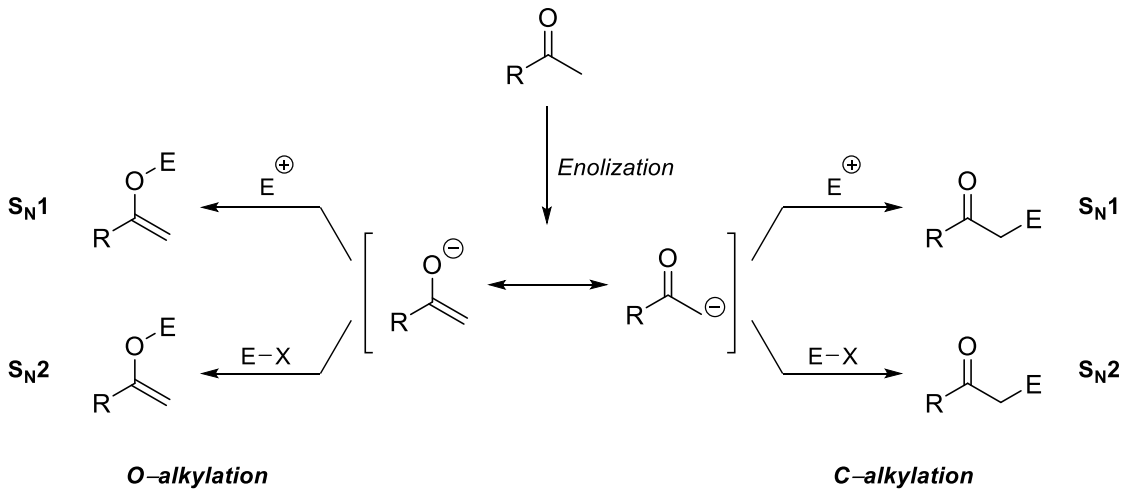
CHAPTER 2

STEREOSELECTIVE Ni(II) CATALYZED ALKYLATION REACTIONS OF *N*-ACYL THIAZOLIDINETHIONES

1. INTRODUCTION

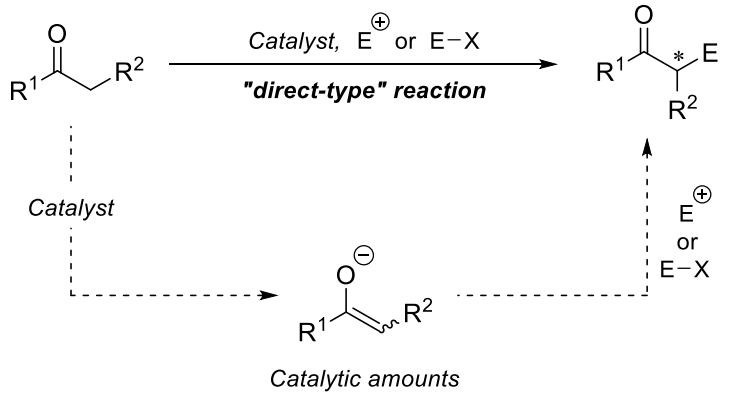
1.1. Alkylation of enolates

C–Alkylation of enolates is one of the most important tools for the stereoselective construction of carbon–carbon bonds.[4,92] As represented in Scheme 87, alkylation of the nucleophilic enolate can occur at the oxygen (*O*–alkylation) or at the α–carbon atom (*C*–alkylation) through a S_N1– or S_N2–like mechanism depending on the electrophile. The electrophilic center in a S_N2–like mechanism is a non-sterically hindered sp^3–carbon bound to a good leaving group, whereas a S_N1–like process involves a cationic sp^2–carbon that is usually generated in the reaction medium. That is the reason why the feasibility of a S_N1–like process mostly depends on both the thermodynamics and the kinetics of the formation of the carbocationic species. Therefore, the electrophile holds a prominent position in such sort of transformations and must be carefully examinated.



Scheme 87

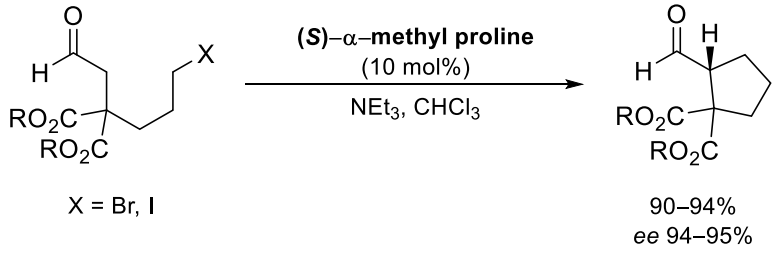
As mentioned before, there is a clear trend to develop new stereoselective catalytic *C*–alkylation procedures. More precisely, "*direct-type*" reactions, in which the corresponding enolates are produced catalytically in the presence of the electrophilic species, have attracted much attention and some methods based on this idea, which are described below, are already available for a variety of alkylation reactions.



Scheme 88

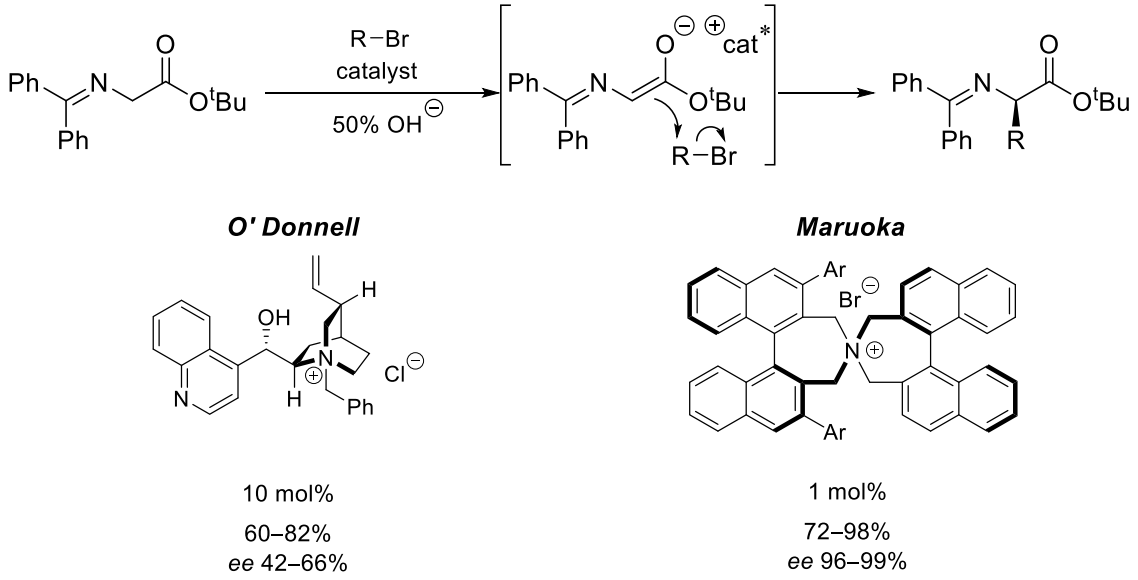
1.2. Precedents on catalytic direct alkylation

One of the earliest examples described by List involves the intramolecular cyclization of ω-bromo and ω-iodoaldehydes by means of (*S*)-α-methyl proline catalysis.[93]



Scheme 89

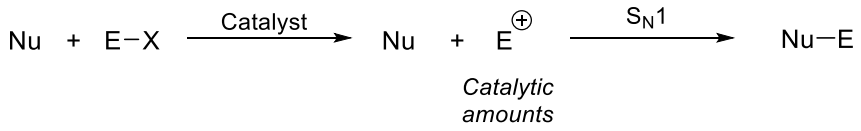
Other processes based on phase transfer catalysis (PTC) have a much broader scope.[94–96] In these reactions, the asymmetric induction comes from the counterion part of the enolate, which is added in substoichiometric amounts. Such a strategy has been adopted for the synthesis of asymmetric α-amino acids. O' Donnell's and Maruoka's groups contributed to the S_N2–like alkylation of *N*-protected glycine esters with catalysts derived from chinchona alkaloids or *N*–spiro C_2–symmetric chiral quaternary ammonium bromides, respectively.[97–100] More efficient variants from O' Donnell's approach have also been developed by Corey [101] and Lygo.[102–104]



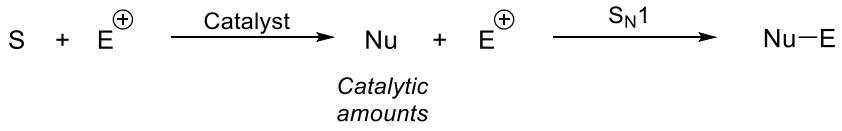
Scheme 90

All these examples can be classified as S_N2–type reactions. By contrast, S_N1 alkylation processes are much more challenging and just a few methods have been reported so far. Depending on the role of the catalyst, these alkylations can be divided into two different groups: catalytic activation of the electrophile or catalytic generation of the nucleophile. Insightful approaches based on the activation of the electrophile have been developed, which implies the catalytic generation of a carbocation, usually by catalytic amounts of a Lewis acid. In turn, the use of a catalyst to generate the nucleophile is less common. In enolate chemistry, it involves a "*direct-type*" S_N1-like reaction between a catalytically generated enolate and a carbocationic precursor. Finally, a few methods combine organocatalysis with a metal Lewis acid catalyst and adhere to both concepts.[105–107]

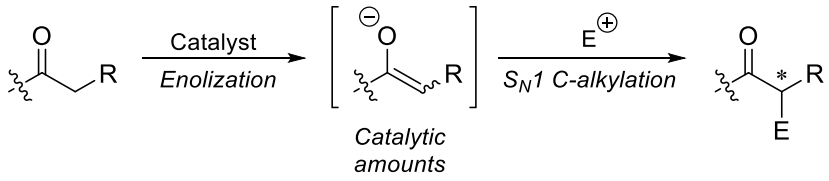
Catalytic activation of the electrophile



Catalytic generation of the nucleophile

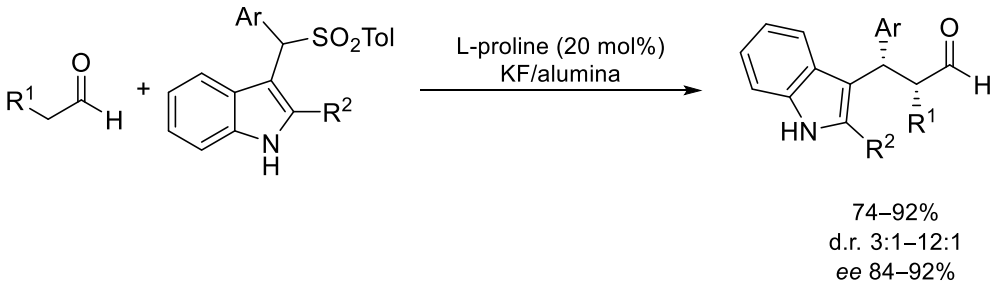


"Direct-type" α-alkylation reaction



Scheme 91

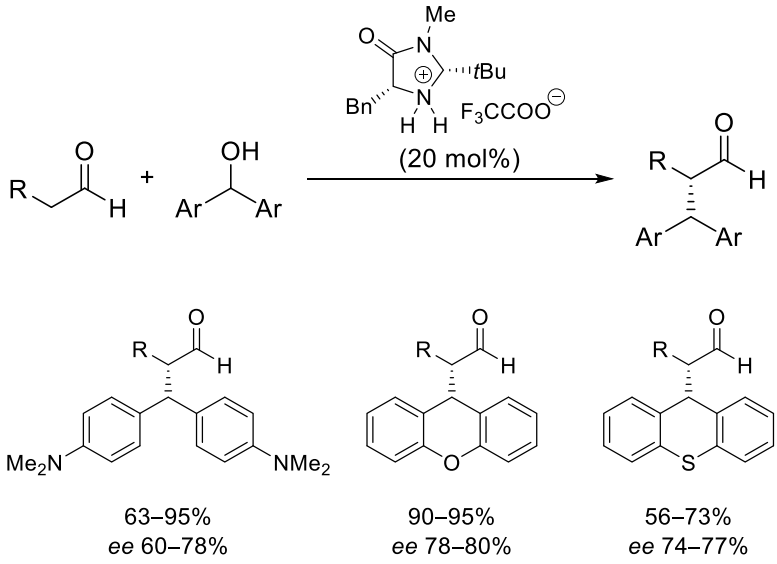
Melchiorre reported the first catalytic S_N1-like alkylation of aldehydes with arylsulfonyl indoles catalyzed by proline (Scheme 92).[28] Although the activation of the electrophile does not take place under acidic conditions, the nucleophilic attack step proceeds through a S_N1-like mechanism in which stabilized carbocations are involved. The alkylation products containing two new stereocenters are obtained in high yields with moderate to high stereocontrol.



Scheme 92

In turn, Cozzi disclosed a similar process involving diarylcarbenium cations (Scheme 93). π-Electrodonating groups on the aryl moieties are necessary to induce a

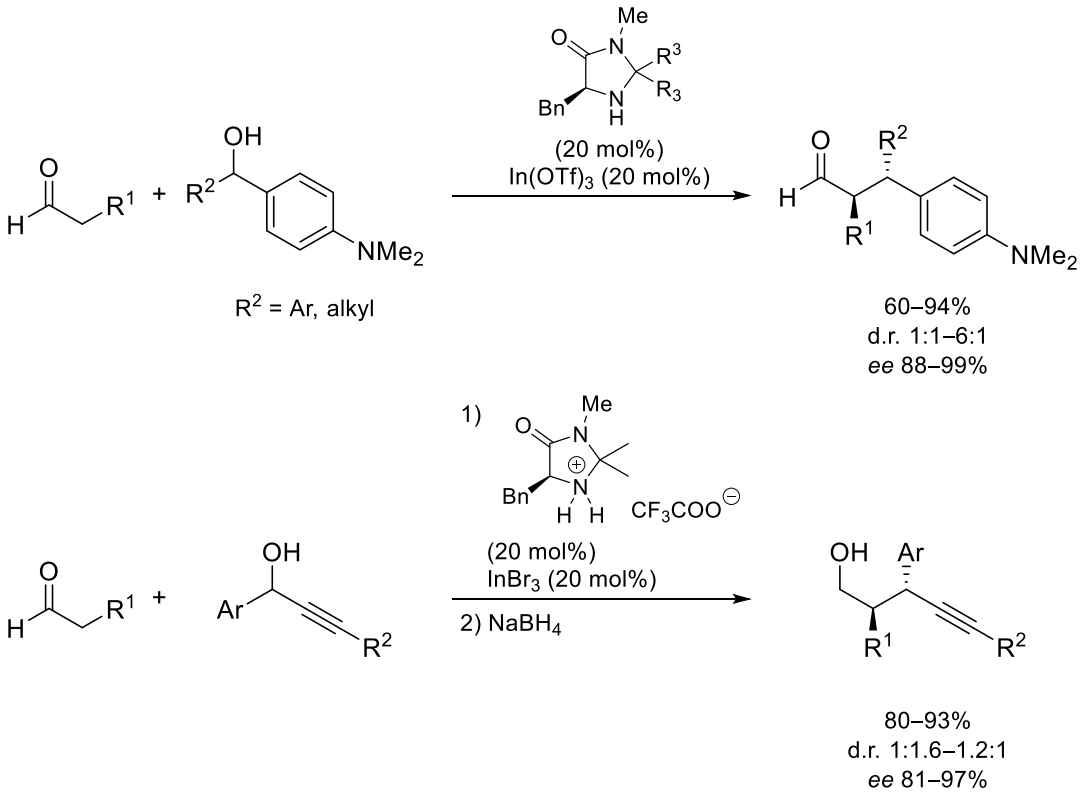
proper activation of the alcohols and produce stabilized enough carbocations.[108] The alkylation products are isolated in good to high yields and good enantioselectivities.



Scheme 93

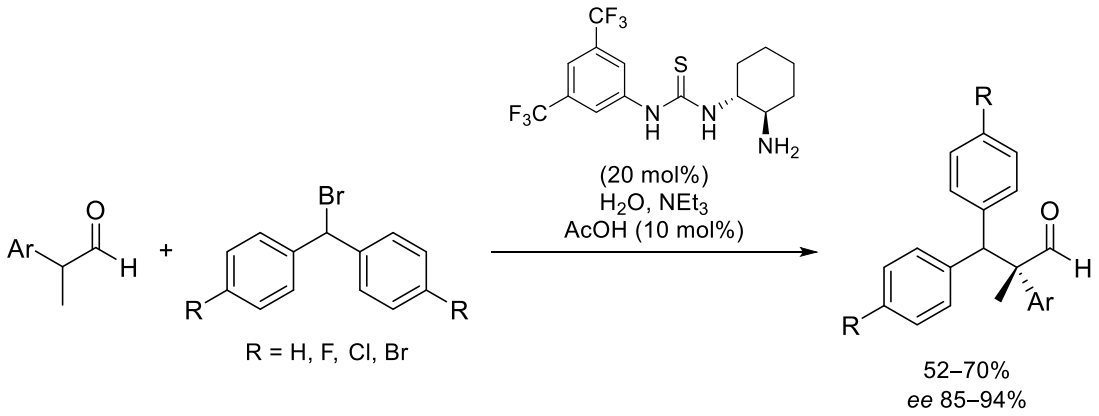
Other benzylic alcohols less prone to generate the corresponding carbocations require a more strong activation by indium salts (Scheme 94). Interestingly, the reaction of these prochiral alcohols produces *anti*-aldehydes or alcohols with a modest to good diastereoselectivity and excellent enantiocontrol.[109,110]

In addition to these examples, some other alkylations with diarylcarbenium alcohols have also been reported, like α-alkylation and γ-alkylation of α,β-unsaturated aldehydes,[111,112] or alkylation of β-ketoesters.[113]



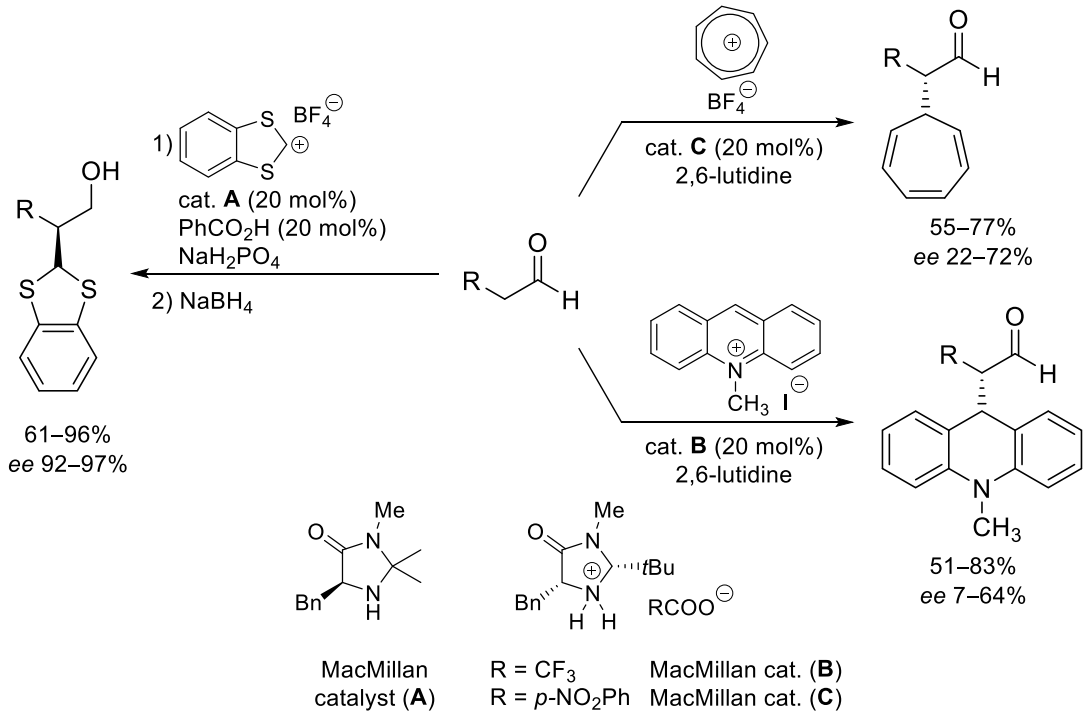
Scheme 94

Alternatively, Jacobsen designed a new organocatalytic approach in which diarylcarbenium bromides were activated with a dual-active catalyst. Such a catalyst forms the enamine from the aldehyde (the nucleophile), while its thiourea scaffold simultaneously acts as anion binding of the bromine atom by hydrogen-bond donor, which prompted the bromine atom to become a better leaving group (Scheme 95).[114] This approach worked properly for diarylcarbenium substrates with electrowithdrawing groups, which was not possible with Cozzi's approach. Remarkably, the alkylated products bear a new quaternary stereocenter whose configuration is controlled by the thiourea in a straightforward and excellent manner.



Scheme 95

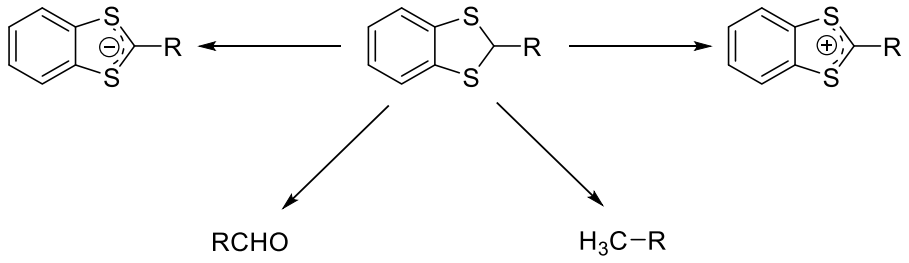
More recently, Cozzi has demonstrated that aldehydes can be alkylated with commercially available carbocation salts using MacMillan catalysts.[115,116] As shown in Scheme 96, these reactions involve benzodithiolylium tetrafluoroborate, tropylium cation and 10-methylacridine iodide.



Scheme 96

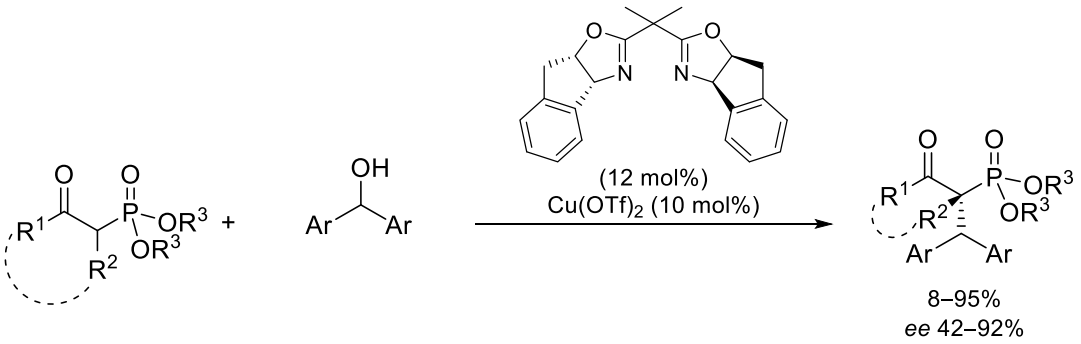
It is worth highlighting the importance of 1,3-benzodithiolylium tetrafluoroborate. The reaction is similar to our previous β-formylated process, providing a masked formyl group, but the benzodithiol group is also a highly versatile synthon[117] (Scheme 97). It

can be a precursor of either anionic[118] or cationic[119] species, and, alternatively, can be removed to give an aldehyde or treated with Raney Ni to produce a methyl group.



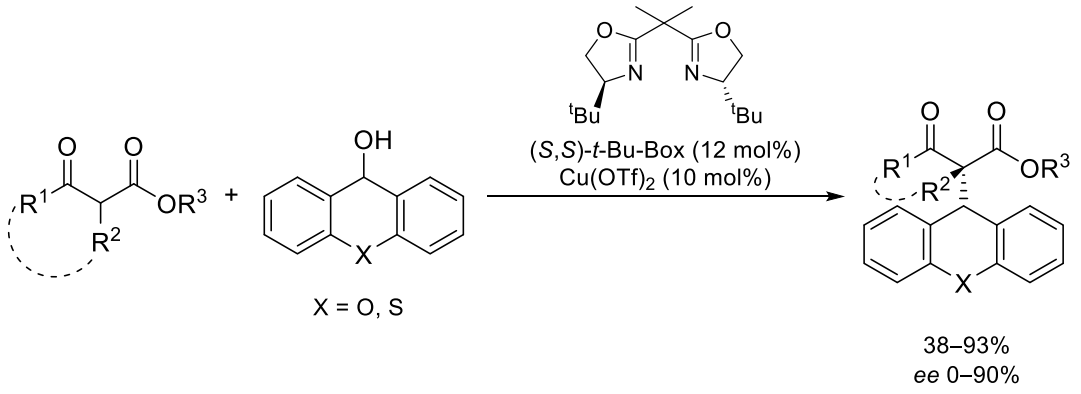
Scheme 97

While S_N1-type catalytic alkylations have been the focus of certain organocatalytic approaches, just a handful of examples concerning metal enolates have been reported. Furthermore, these are restricted to easily enolizable substrates as those represented in Schemes 98 and 99. For example, Nishibayashi alkylated cyclic β-ketophosphonates with diarylcarbenium ions with relative success (Scheme 98). As in Cozzi's method, only stabilized carbocations with π-electrodonating groups over the aryl scaffolds were possible.[120]



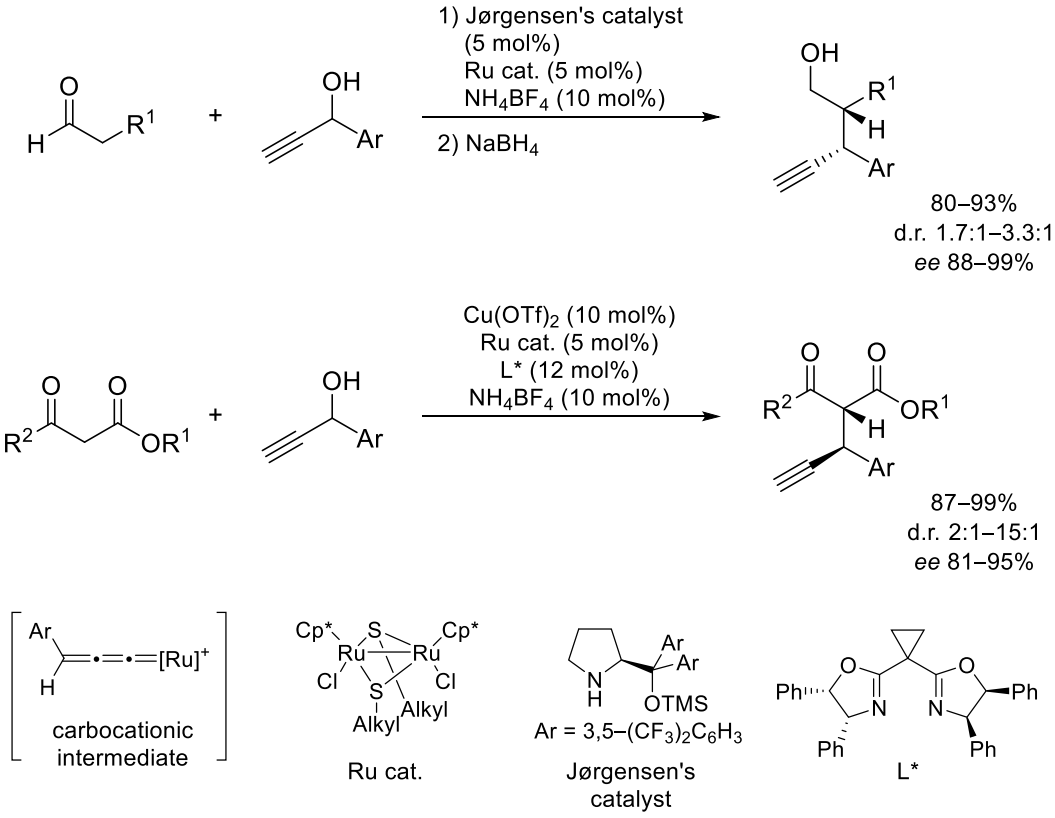
Scheme 98

Nájera developed a similar transformation in which enolates from cyclic β-ketoesters are alkylated with xanthydrol or thioxanthydrol (Scheme 99).[121]



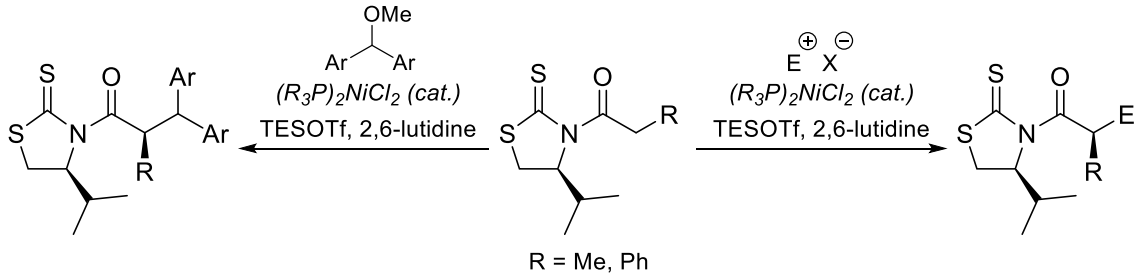
Scheme 99

Propargyl alcohols can be precursors of organometallic ruthenium-based intermediate carbocations, which can also act as good alkylating agents of aldehydes and β-ketoesters by means of organocatalysis or Cu(I) catalysis, respectively (Scheme 100). The desired products were obtained in excellent yields and high stereocontrol on the two new stereocenters.[122,123]



Scheme 100

However, no metal-catalyzed enolate-based method has been developed yet for the S_N1 alkylation of low acidic carboxylic substrates. Therefore, we envisaged that our Ni(II)-catalyzed system could also render α-alkylated products in a straightforward manner. At first, we assessed the addition of commercially available carbocation salts. Later, the scope was expanded to diaryl carbenium cations (Scheme 101).

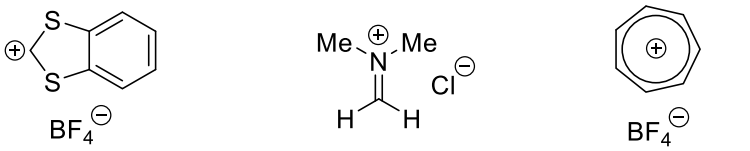


Scheme 101

2. REACTIONS WITH CATIONIC SALTS

2.1. Cationic salts

Considering the novelty of the S_N1-like addition of nickel(II) enolates from *N*-acyl thiazolidinethiones to cationic species, we initially assessed the feasibility of such a transformation on commercially available cationic salts as 1,3-benzodithiolilium tetrafluoroborate, the Eschenmoser's salt or tropylium tetrafluoroborate shown in Figure 5.



1,3-Benzodithiolylium tetrafluoroborate | Eschenmoser's salt | Tropylium tetrafluoroborate

Figure 5

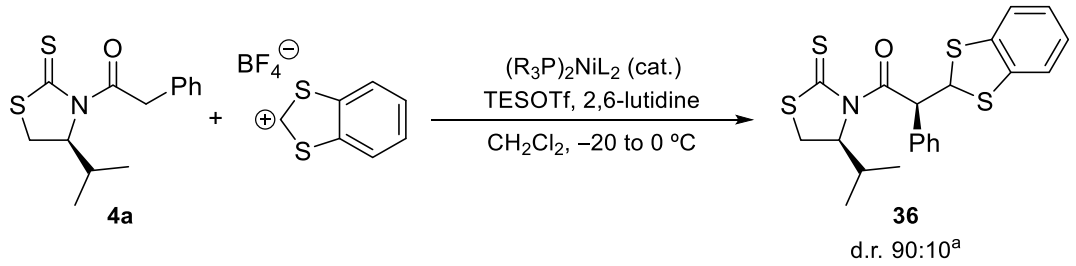
Certainly, the 1,3-dibenzodithiolylium cation and the Eschenmoser's salt are no true carbocations, but they could shed light on the clues of the reaction and expand the scope of the whole approach.

2.2. Reactions with 1,3-benzodithiolylium tetrafluoroborate

The 1,3-dibenzodithiolylium tetrafluoroborate was our first choice to study such a new approach since it looked like the reaction with orthoformate presented in Chapter 1.

Exploratory experiments were carried out with thioimide **4a** under standard conditions (2.5 mol% of $(Ph_3P)_2NiCl_2$, 20 min at –20 ºC and 1 h at 0 ºC), just using the required amount of TESOTf to activate the nickel(II) complex. The results are summarized in Table 11. Unexpectedly, only traces of the desired adduct were detected (entry 1 in Table 11). It was necessary to increase the quantity of catalyst up to 20 mol% to obtain a 9:1 mixture of the corresponding diastereomers in 22–24% yield (entries 2 and 3 in Table 11), irrespective of the temperature. Even with 40 mol% of

catalyst, the yields was still moderate (entry 4 in Table 11). Furthermore, $(Me_3P)_2NiCl_2$ catalyst afforded tiny amounts of alkylation product **36**.

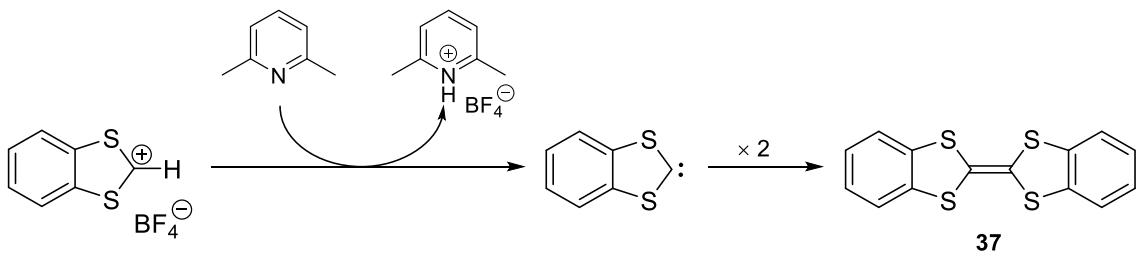


Entry	$(R_3P)NiCl_2$	mol%	TESOTf (eq)	Time at –20 ºC	Time at 0 ºC (h)	Yield (%)[b]
1	$(Ph_3P)NiCl_2$	2.5	0.15	20 min	1	< 5
2	$(Ph_3P)NiCl_2$	20	0.5	3 h	1	24
3	$(Ph_3P)NiCl_2$	20	0.5	20 min	86	22
4	$(Ph_3P)NiCl_2$	40	0.9	20 min	5	29
5	$(Me_3P)NiCl_2$	20	0.5	20 min	5	< 5

[a] Established by ^1H NMR analysis of the crude product.
[b] Isolated yield after column chromatography.

Table 11

The main product through all this optimization was a yellow and apolar solid that was isolated by column chromatography. A simple mass spectrum revealed that this solid corresponded to tetrathiofulvalene **37** (Scheme 102). Likely, the deprotonation of the electrophile by 2,6-lutidine would lead to the corresponding carbene, which would form the dimeric tetrathiofulvalene. Similar evidences had also been detected in early optimizations by Cozzi instead of the desired product.[115] This may be the reason why the yields were so poor.



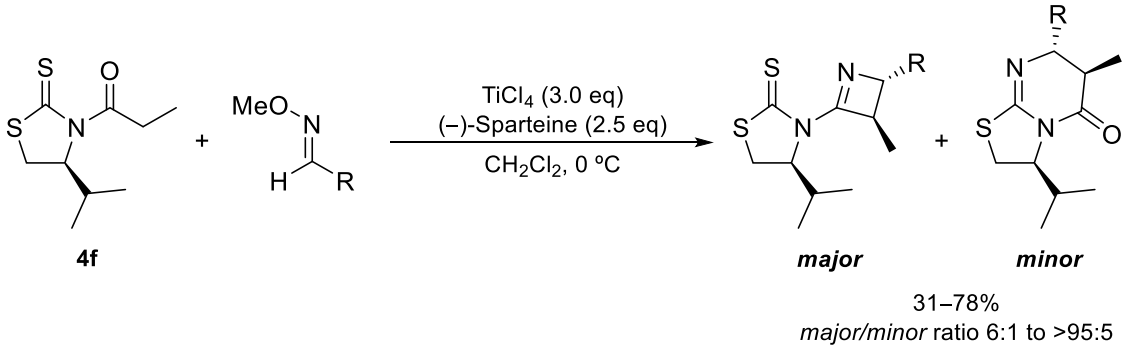
Scheme 102

2.3. Reactions with the Eschenmoser's salt

Another commercially available cationic salt that attracted our attention was the Eschenmoser's salt, which corresponds to the *N,N*-dimethylmethyleneiminium cation. Actually, this is a preformed ion. The addition of an enolate to this substrate is a Mannich reaction in which no stereogenic center is generated at β position. In this context, this substrate can be viewed as the first step towards Ni(II)-catalyzed Mannich-like reactions in which only one stereocenter would be created.

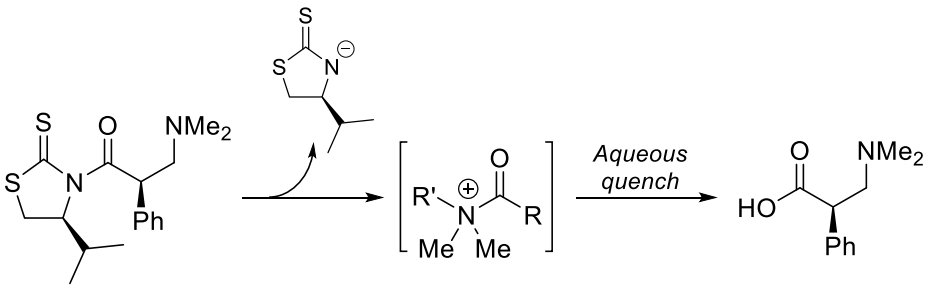
In a preliminary attempt, a reaction of thioimide **4a** with the Eschenmoser's salt was carried out with 20 mol% $(Ph_3P)_2NiCl_2$. Unfortunately, the expected adduct was not formed at all and the deacylated chiral auxiliary **1** was the only product obtained instead.

Then, we came across a method based on the addition of the Ti(IV) enolate of the *N*-propanoyl thioimide **4f** to aldoxime ethers in which the final products contain a new heterocycle as the result of an intramolecular condensation between the nucleophilic nitrogen atom and the carbonyl or thiocarbonyl groups.[124]



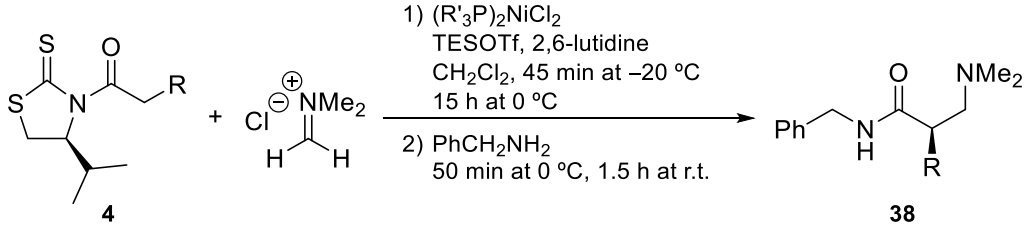
Scheme 103

This example brought us to speculate that the deacylation of the putative adduct might be caused by the nucleophilic attack of the resultant terminal tertiary amine over the carboxyl group, which would produce a carboxylic acid after the acidic aqueous quench (see Scheme 104). This carboxylic acid might well be lost during the work-up or the column chromatography.



Scheme 104

In order to check our hypothesis and take advantage of this unexpected process, we envisioned that the putative electrophilic intermediate could be trapped with a nucleophile to produce a stable derivative. Therefore, we carried out the same reaction using 2.5 mol% of $(Ph_3P)_2NiCl_2$ and the mixture was quenched with benzylamine, a well-known nucleophile, instead of an acid aqueous solution as usual. To our pleasure, amide **38a** was obtained with a yield of 54% (entry 1 in Table 12). A further optimization let us discover that a 20 mol% of the catalyst was necessary to obtain excellent yields (compare entries 1–3 in Table 12). On the other hand, the *N*-propanoyl counterpart **4f** did not afford the expected product either with $(Ph_3P)_2NiCl_2$ or $(Me_3P)_2NiCl_2$ (entries 4 and 5 in Table 12). This result confirmed our hypothesis and opened a way to a new catalytic method of β-amination of *N*-acylthioimides with direct derivatization.

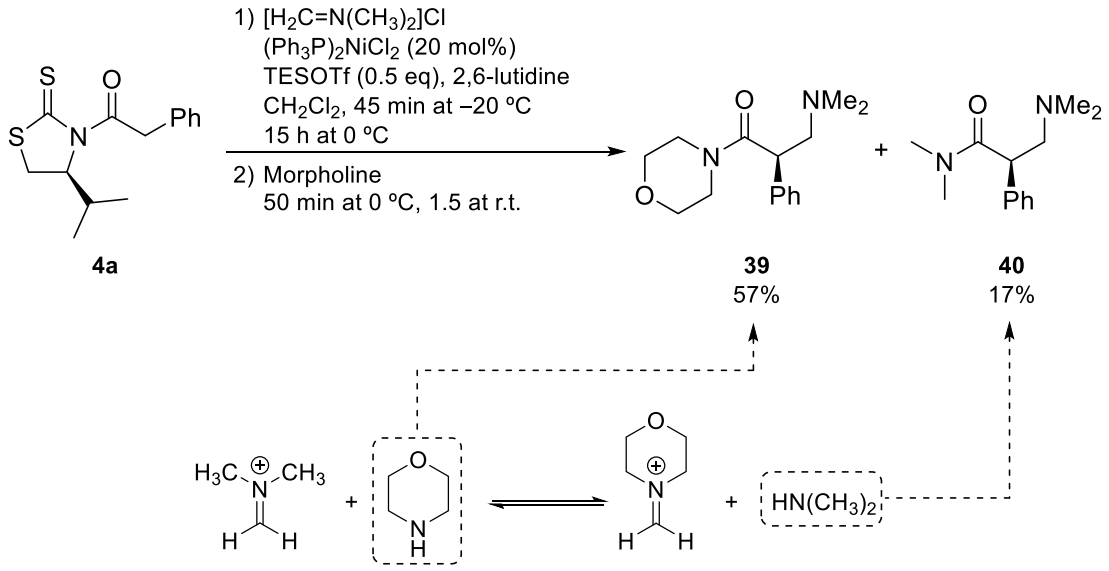


Entry	Substrate	R	$(R'_3P)_2NiCl_2$	mol%	TESOTf (eq)	Adduct	Yield (%)[a]
1	**4a**	Ph	$(Ph_3P)_2NiCl_2$	2.5	0.07	**38a**	54
2	**4a**	Ph	$(Ph_3P)_2NiCl_2$	5.0	0.20	**38a**	84
3	**4a**	Ph	$(Ph_3P)_2NiCl_2$	20.0	0.50	**38a**	92
4	**4f**	Me	$(Ph_3P)_2NiCl_2$	20.0	0.50	–	n.r.
5	**4f**	Me	$(Me_3P)_2NiCl_2$	20.0	0.50	–	n.r.

[a] Isolated yield after column chromatography.

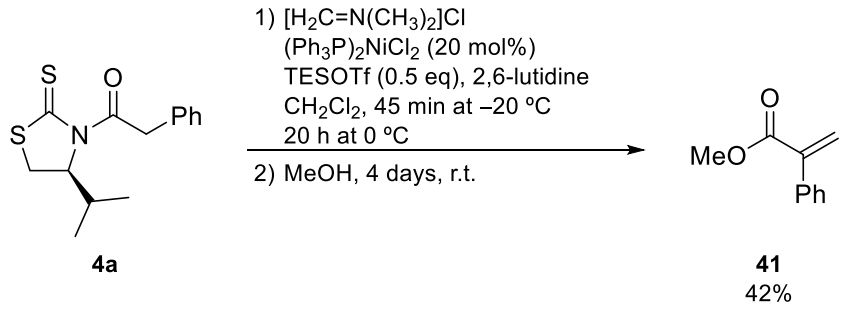
Table 12

Next, such a trapping was assayed with other nucleophiles as morpholine, alcohols or chiral benzylamines. Morpholine amides are synthetically equivalent to Weinreb amides[125] and the use of chiral benzylic amines could provide interesting information about the stereoselectivity of these reactions. Unfortunately, the addition of morpholine resulted in a mixture of two amides (Scheme 105). The *major* amide **39** corresponded to the expected product in 57% yield, while the *minor* amide **40**, obtained with a 17% yield, arose from the nucleophilic attack of dimethylamine, which might be formed from the reaction between the Eschemoser's salt and morpholine.



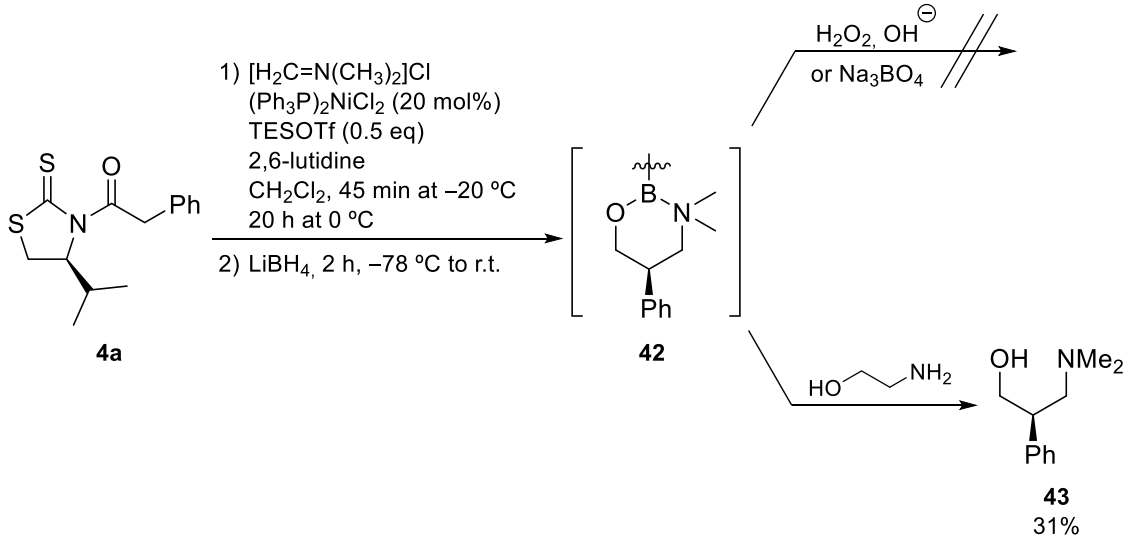
Scheme 105

The use of methanol was also tested. As represented in Scheme 106, α,β–unsaturated ester **41** was obtained instead of the expected β–aminoester. Ester **41** may come from the elimination of dimethylamine over the desired ester. This is not surprising, since the Eschenmoser's salt is often used for the α-methylenation of enolates from esters and lactones.[126,127]



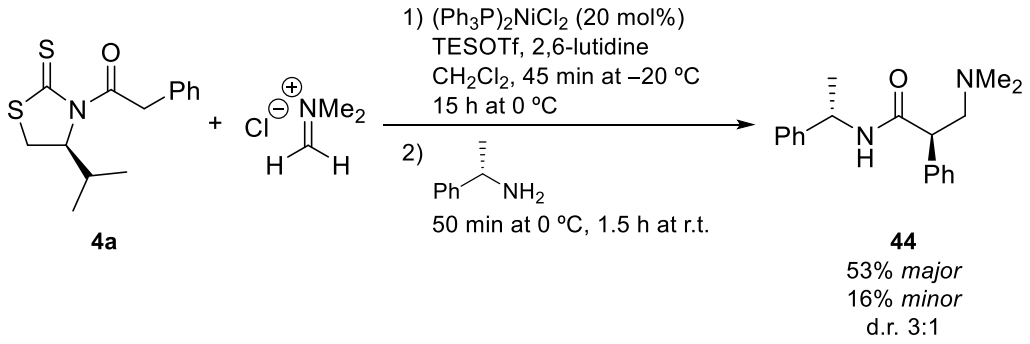
Scheme 106

The reduction of the intermediate using $LiBH_4$ was also assayed. Apparently, it produced boron chelated product **42**, whose structure was not totally confirmed. Attempts to get rid of the boron chelation of **42** under oxidative and basic conditions were unsuccessful. Inspired by an example on the literature,[128] a huge excess of ethanolamine was added in order to transfer the boron to this new aminoalcohol. Thus, the desired product **43** was isolated in 31% yield.



Scheme 107

Importantly, it was impossible to determine the diastereoselectivity of these reactions by ^1H NMR because the chiral auxiliary had been removed. For this reason, a commercially enantiopure benzylic chiral amine was used as nucleophile to uncover a 3:1 mixture of two diastereoisomers. Such a moderate stereoselectivity might be due to a partial epimerization of the intermediate.

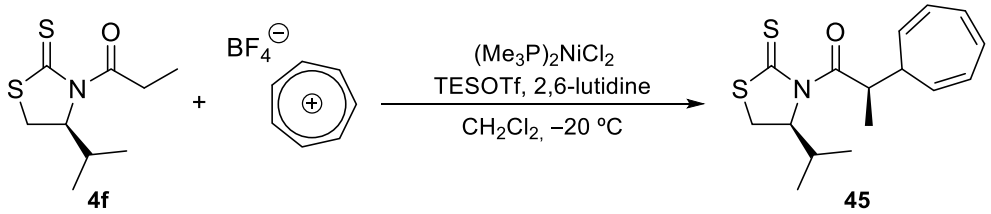


Scheme 108

2.4. Reactions with tropylium tetrafluoroborate

The introduction of a tropylium group appeared as a simple process from the commercially available tropylium tetrafluoroborate salt, which might undergo our desired S_N1-like process as a true carbocation.

In this case, the *N*-propanoylthioimide **4f** was chosen as the model substrate. The reaction using the standard conditions (5 mol% of $(Me_3P)_2NiCl_2$ at –20 ºC) gave only one diastereoisomer by ^1H NMR, but in low yields even at long reaction time (entry 1 in Table 13). As the problem might rest on a side reaction similar to that observed with benzodithiolylium cation, we tried to fight against the putative disappearance of the electrophile by adding an excess of electrophile. Surprisingly, the desired product was not observed (entry 2 in Table 13). On the contrary, adduct **45** was isolated in 40% yield by using 0.5 equivalents of the tropylium salt (entry 4 in Table 13). Also, when higher catalyst loadings were used the results were improved until a 74% yield (entries 5 and 6 in Table 13). The reasons of such a limited success still remain unclear.



Entry	$(Me_3P)_2NiCl_2$ (mol%)	$[C_7H_7]BF_4$ (eq)	TESOTf (eq)	t (h)	Yield (%)[a]
1	5	1.5	0.20	20	29
2	5	3.0	0.20	2	n.r.
3	5	1.1	0.20	2	19
4	5	0.5	0.20	2.5	40[b]
5	10	1.5	0.30	2	47
6	20	1.5	0.50	2	74

[a] Isolated yield after column chromatography.

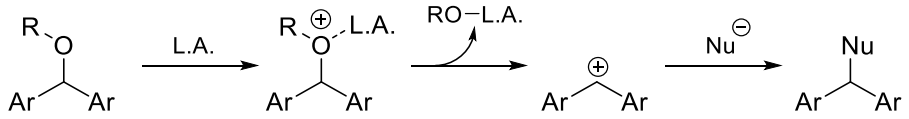
[b] Obtained yield with respect to the amount of tropylium tetrafluoroborate used.

Table 13

3. REACTIONS WITH DIARYLCARBENIUM SUBSTRATES

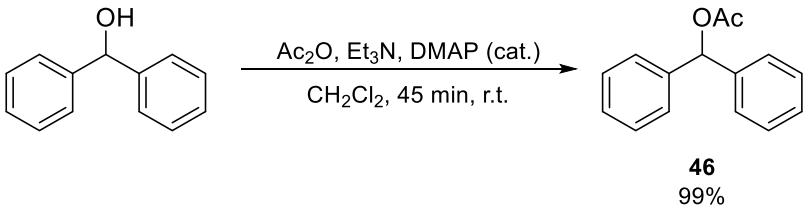
3.1. Preliminary experiments

Once established the feasibility of the S_N1-like addition of *N*-acylthioimides to cationic salts, we channeled our efforts into diarylcarbinol substrates. In this case, the carbocation must be generated *in situ*. Therefore, a Lewis acid-based activation was required again.



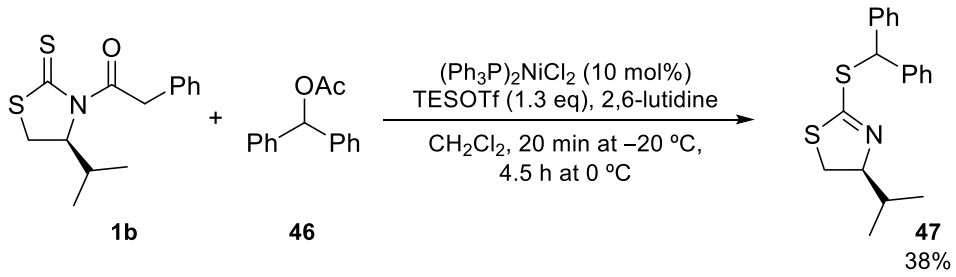
Scheme 109

At first, the chosen model substrate corresponded to benzhydryl acetate (**46**) (Scheme 110), the most simple arylcarbenium derivative, which was prepared by acylation of the parent alcohol with acetic anhydride in basic media in the presence of catalytic amounts of DMAP.



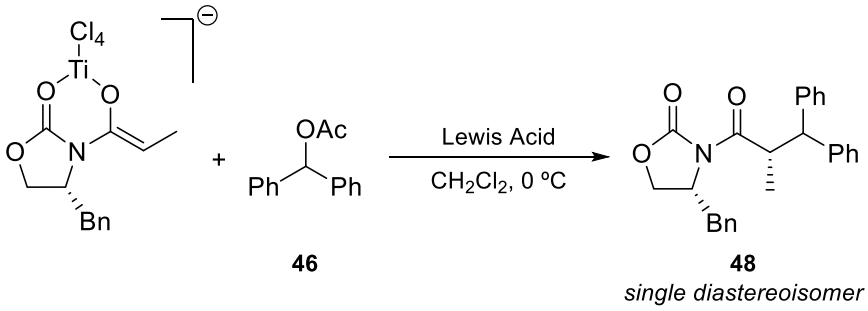
Scheme 110

Unfortunately, early attempts with thioimide **4a** only afforded the *S*–alkylated product **47** produced as a result of the nucleophilicity of the C=S bond and unaltered starting material. *C*–Alkylated adduct was never observed.



Scheme 111

Considering that **46** might be difficult to activate with such a relatively weak Lewis acid as TESOTf, we then examined the capability of several Lewis acids to activate it and subsequently be attacked by a Ti(IV) enolate of an *N*-propanoyloxazolidinone, which are known to undergo S_N1-like alkylation reactions. The results, summarized in Table 14, proved that the yields depended on the strength of the Lewis acid: the stronger was the Lewis acid, the more activated was the electrophile, so higher yields were obtained. TESOTf, the mildest Lewis acid of the Table, resulted in very low yield (entry 3 in Table 14). This was probably one of the reasons why the Ni(II) did not catalyze the reaction properly. Therefore, the benzhydryl aetate **46** was ruled out as an alkylating agent.

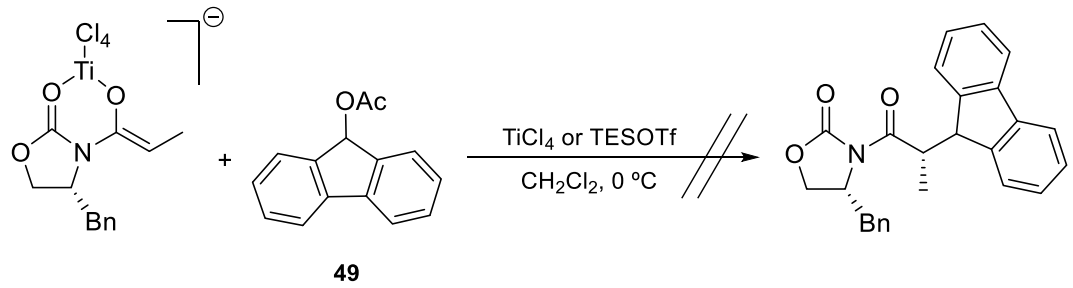


Entry	Lewis acid	t (h)	Yield (%)[a]
1	$TiCl_4$	2	71
2	$BF_3{\cdot}OEt_2$	4.5	25
3	TESOTf	4.5	13

[a] Isolated yield after column chromatography.

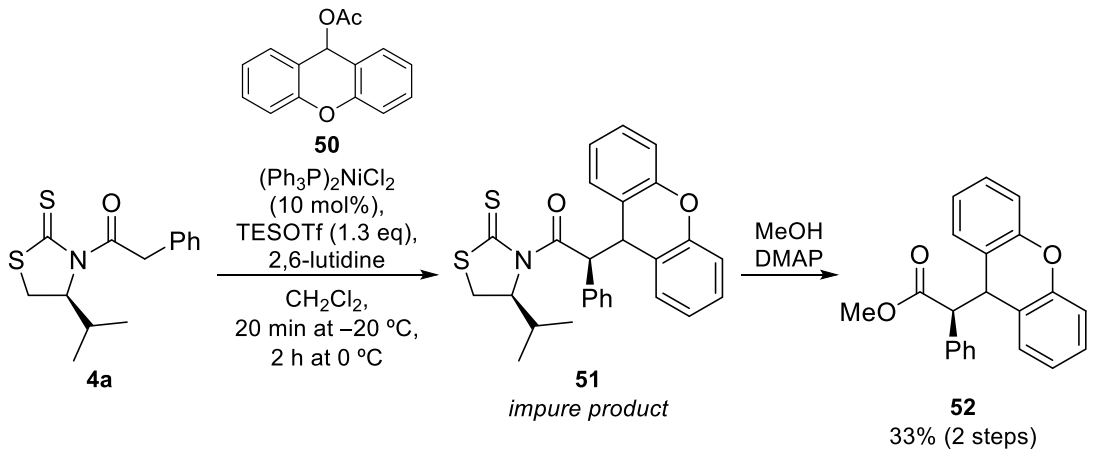
Table 14

Our next choice was 9*H*-fluoren-9-yl acetate (**49**). Likely, it could provide a more stabilized carbocation. However, no alkylated product was observed with the previous Ti(IV) enolate. Again, a difficult activation seemed the most probable reason for such a failure.



Scheme 112

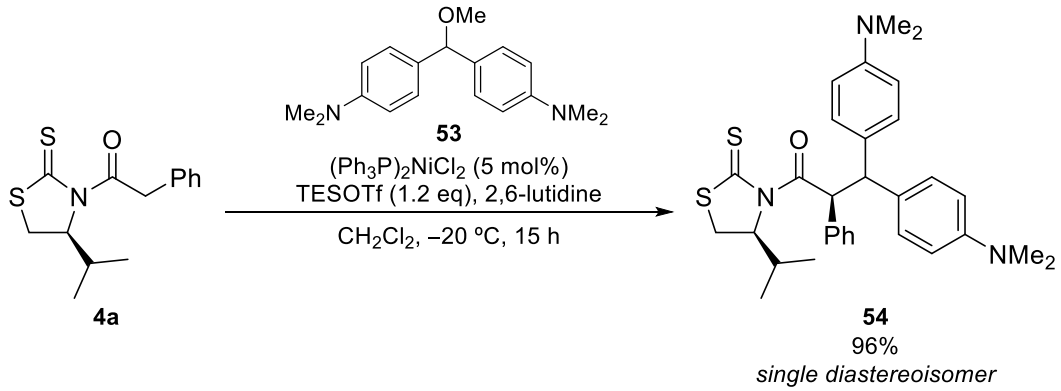
It was clear that we needed a more stable diarylcarbenium ion. 9*H*-Xanthen-9-yl acetate (**50**) attracted our attention, since its endocyclic oxygen might well give electron density to the π system and, therefore, stabilize the carbocation. For our pleasure, the reaction with this substrate afforded a single diastereomer of alkylated product **51**, but it was impurified because of the continuous degradation of the electrophile. This alkylated product **51** was necessarily derivatized to ester **52** to isolate it as a pure product. The whole process gave a 33% yield (Scheme 113). Irrespective of the low yields, this result proved that the Ni(II) complexes can catalyze the alkylation reaction provided that appropriate diarylcarbenium derivatives were found.



Scheme 113

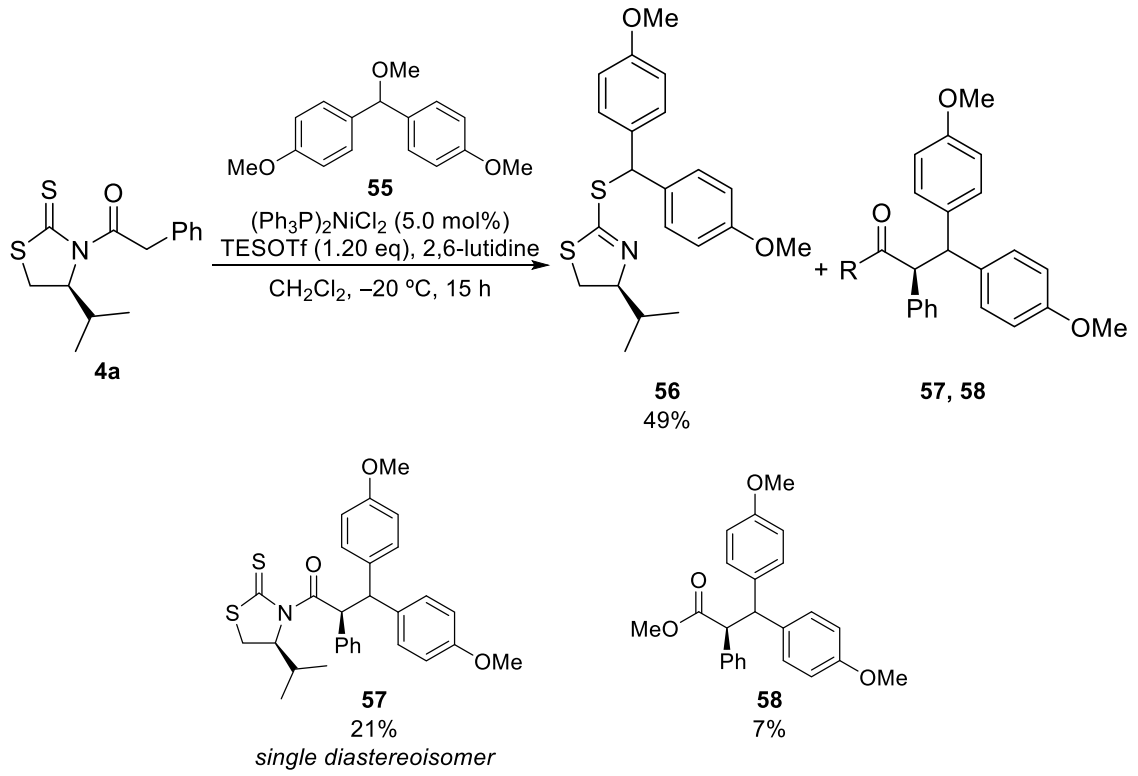
At this point, we were aware that the low yield of ester **52** might also be due to a possible undesired reaction of the acetate group with TESOTf and 2,6-lutidine. Such a side reaction would reduce the amount of electrophile and would jeopardize the whole approach. Furthermore, ester **50** could not be purified by column chromatography and unknown impurities could hamper the reactivity of the nickel enolates.

Therefore, we looked for another electrophile to avoid the aforementioned drawbacks, choosing diarylcarbenium ether **53** as a good electrophilic substrate (Scheme 114). This new substrate contained a methoxy moiety as a leaving group and two amino groups over the aromatic rings that would enhance its activation thanks to the resulting highly stabilized carbocation. In contrast to ester **50**, this new electrophile **53** was obtained pure enough without further purifications. To our pleasure, the Ni(II) catalyzed alkylation reaction with this substrate afforded the pure desired product **54** with almost quantitative yield as a single diastereomer with only 5 mol% of catalyst (Scheme 114).



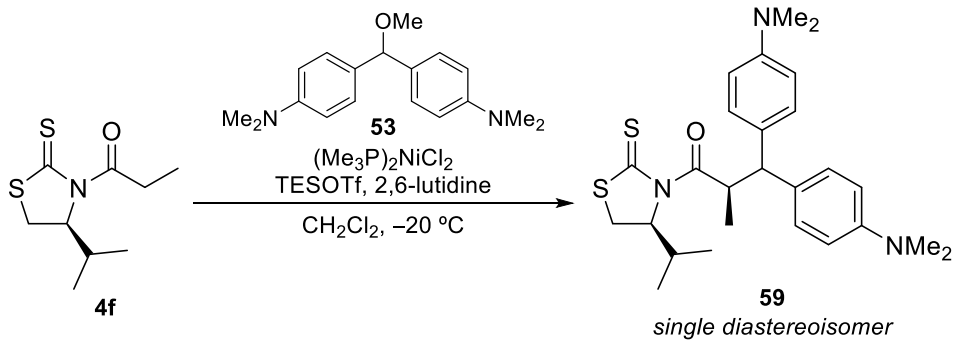
Scheme 114

Encouraged by this result, we next tried the reaction with diarylmethyl ether **55**, which was also prepared with high purity and it is a less activated substrate. However, the reaction gave the *S*–alkylated derivative (**56**) as the major product. Again, the nucleophilicity of the C=S bond and the easy deacylation of this mandelic-like acyl group were the reasons of these poor results.



Scheme 115

As thioimide **4a** turned out to be a non–representative starting material because of its narrow scope with different diarylcarbenium derivatives, we chose the *N*-propanoyl thiazolidinethione **4f** counterpart to overcome these difficulties. Now, the Ni(II) catalyzed alkylation of **4f** with methyl ether **53** worked smoothly with 2.5 mol% of catalyst to afford the desired adduct **59** as a single diastereomer in 62% yield after 1.5 h (entry 1 in Table 15). Higher loadings of nickel(II) complex produced a moderate increase of the yield (compare entries 1–3 in Table 15). Alternatively, longer reaction times allowed us to use only a 5 mol% of Ni(II) salt with almost quantitative yield (entries 4 and 5 in Table 15). Particularly, the addition proved to be highly reliable by keeping the reaction mixture at –20 ºC overnight with 5 mol% of $(Me_3P)_2NiCl_2$.



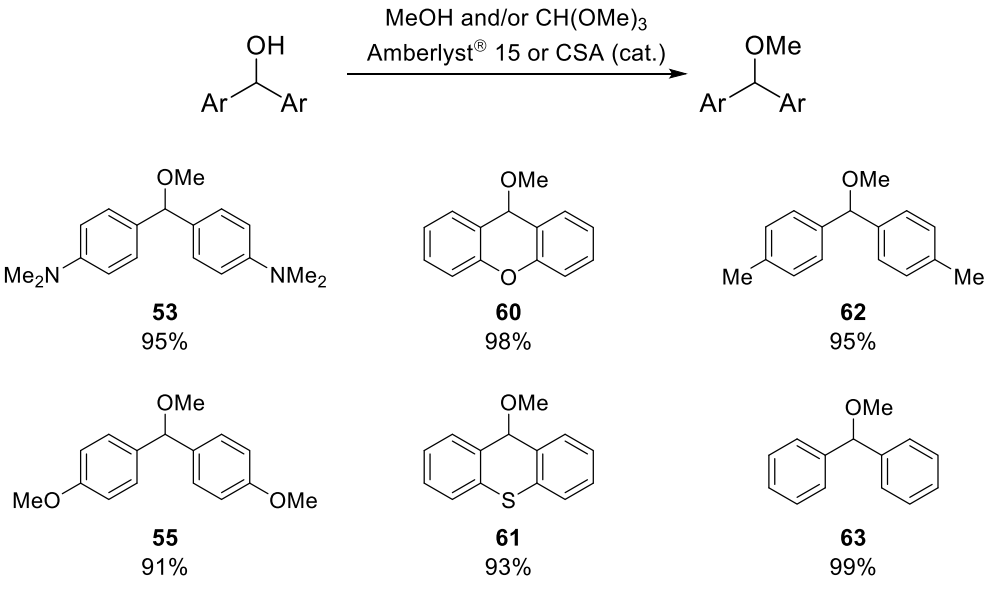
Entry	$(Me_3P)_2NiCl_2$ (mol%)	TESOTf (eq)	t (h)	Yield (%)[a]
1	2.5	1.15	1.5	62
2	5	1.2	1.5	65
3	20	1.5	1.5	77
4	2.5	1.15	15	67
5	5	1.2	15	96

[a] Isolated yield after column chromatography.

Table 15

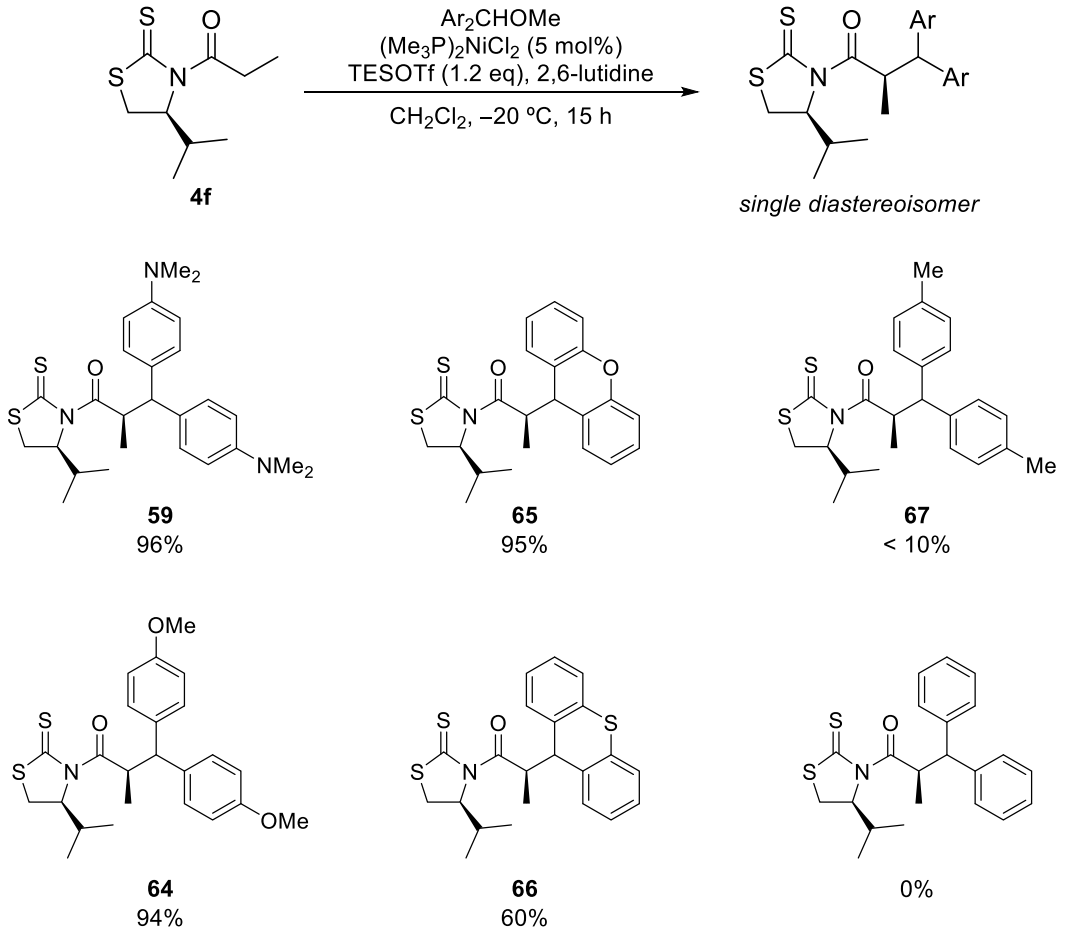
3.2. Alkylation reactions with diarylcarbenium ethers

Once the reaction conditions had been established, the method was next applied to several diarylcarbinol methyl ethers (Scheme 116), which were prepared from the corresponding alcohols in the presence of methanol and trimethyl orthoformate in acidic medium and obtained with high purity.



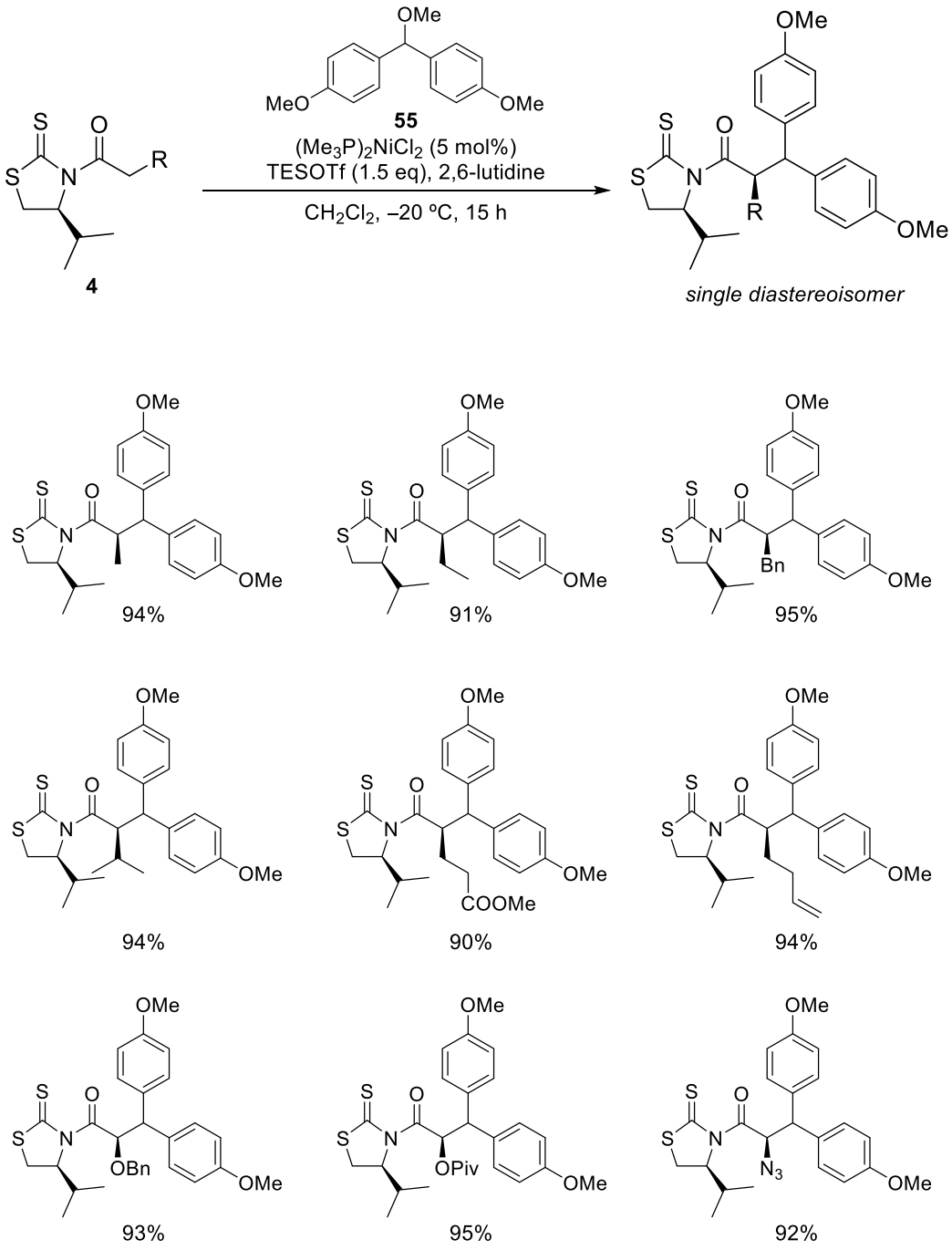
Scheme 116

The alkylated adducts from activated substrates were isolated in excellent yields, except for that derived from thioxanthydryl methyl ether (**61**), which was obtained with a moderate yield due to its sensitivity (Scheme 117). In all cases, a single diastereomer was observed in the ^{1}H NMR of the reaction mixtures. In turn, 4,4'-dimethylbenzhydryl methyl ether **62** afforded alkylation product **67** in low yield because of the poor activation. Finally, only byproducts related with C=S nucleophilicity were detected in the crude product of benzhydryl methyl ether **63**, as expected.



Scheme 117

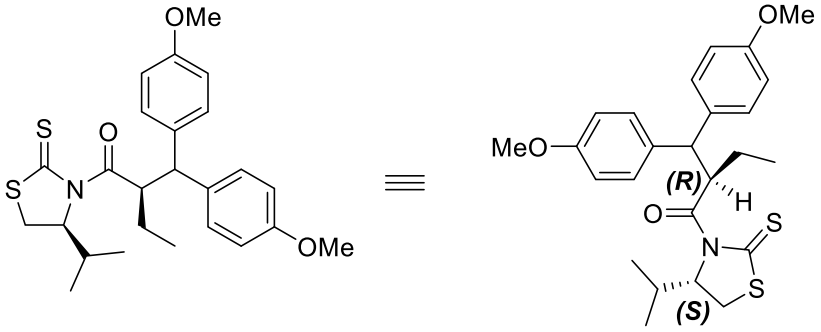
Javier Fernández-Valparís, during his PhD thesis,[53] has studied the effect of different acyl chains of the thioimide with methyl ether **55**. A wide range of acyl derivatives worked perfectly well, including those coming from glycolic acid and glycine derivative, provided that 1.5 equivalents of TESOTf used (Scheme 118). These last examples are remarkable, since they represent a catalytic entry to enantiopure α–hydroxy acids and α–amino acids.


OMe
MeO
OMe
55
(Me3P)2NiCl2 (5 mol%)
TESOTf (1.5 eq), 2,6-lutidine
CH2Cl2, –20 °C, 15 h
4
single diastereoisomer
94%
91%
95%
94%
90%
94%
93%
95%
92%
Bn
OBn
OPiv
N3
COOMe

Scheme 118

4. ELUCIDATION OF THE ABSOLUTE CONFIGURATION

Finally, the absolute configuration was confirmed through X-ray analysis of one of the compounds prepared by Javier Fernández-Valparís.[53] As expected, the new stereocenter had the *R* configuration.



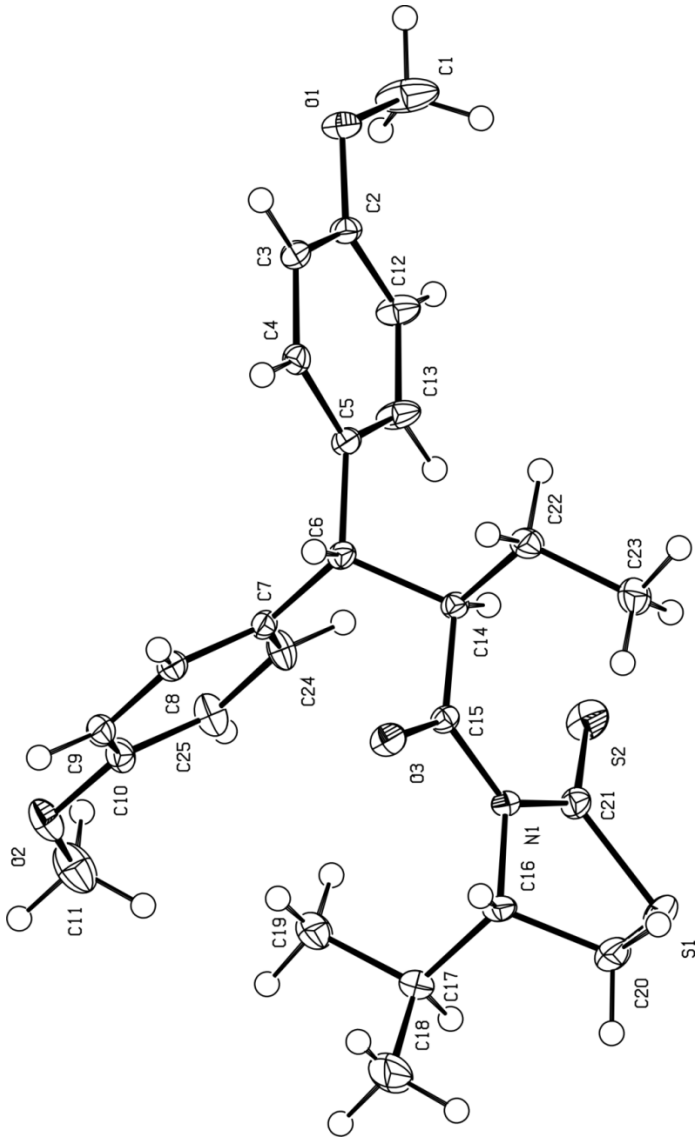
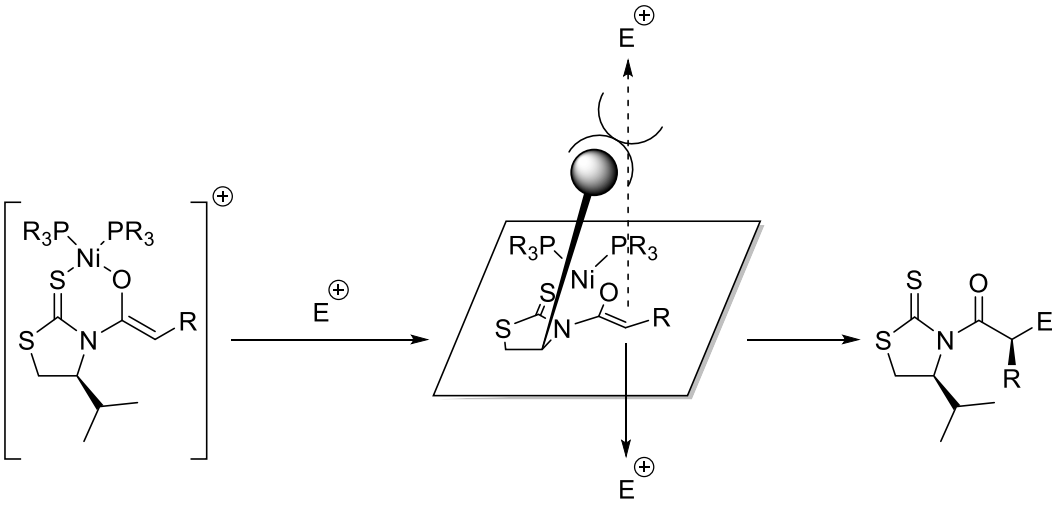


Figure 6

5. MECHANISTIC AND KINETICAL HYPOTHESIS

5.1. Mechanism of the alkylation reaction

It seems reasonable that the catalytic cycle and the transition state for the attack of the Ni(II) enolate to the carbocation is pretty much the same as in the case of the β-formylation reaction. Thus, the approach of the carbocation by the less hindered face of the chelated enolate also accounts for the stereochemical outcome of this S_N1-like process. This Ni(II) enolate is basically planar except for the isopropyl group, which sterically hinders the *Re* face of the enolate.



Scheme 119

Apart from such a mechanistic model, certain issues related to the kinetics of these reactions can be analysed to shed light on the success or failure of our reactions. The scales of "nucleophilicity" and, especially, "electrophilicity" established by Mayr can be incredibly useful for a better understanding of such alkylation reactions.

5.2. Mayr's scales of nucleophilicity and electrophilicity

Alkylation methods that proceed through an S_N1 mechanism mostly work with relatively stabilized carbocations. Therefore, π-donor functional groups are introduced into the aromatic rings of diarylcarbenium ions to attain such stabilization. This has been observed in our Ni(II)-catalyzed alkylation reaction. The reason for this behavior seems to be related to the activation of such electrophiles. Thus, the more stable are the carbocations, the easier is to produce them from a precursor. By contrast, the less electrophilic will be. Therefore, a balance between activation and reactivity must be taken into account, so any relationship between the concepts of activation and reactivity with the electrophilicity of a cation would be welcome. As a compass in the dark, such a relationship would help to find the right course by choosing the most appropriate partners in the S_N1-like processes.

In that sense, Mayr has been working during the last decades on the study of a scale of electrophilicity and nucleophilicity in polar organic reactions, like S_N1 processes. Assuming that the kinetics of such reactions depends on the nucleophile and the electrophile independently, two solvent-dependent factors are defined for the nucleophile, named the nucleophilicity parameter *N* and the slope parameter *s*, while for the carbocation, just a single electrophilicity parameter *E* is required.[129]

$$\log k_{20\,^{\circ}C} = s\,(N + E)$$

Defining two reference parameters, $E[(p\text{-}MeOC_6H_4)CH^+] = 0$ and s(2-methyl-pent-1-ene) = 1, extensive kinetic studies were carried out to determine the rate constants of a wide combination of nucleophiles and electrophiles. Indeed, experimental log *k* were plotted against *E* for additions of π–nucleophiles to diarylcarbenium cations. The least-squares treatment to the date provided the *E*, *N*, and *s* parameters and the resulting relationships fit straight-lines represented in Figure 7.[129–133]

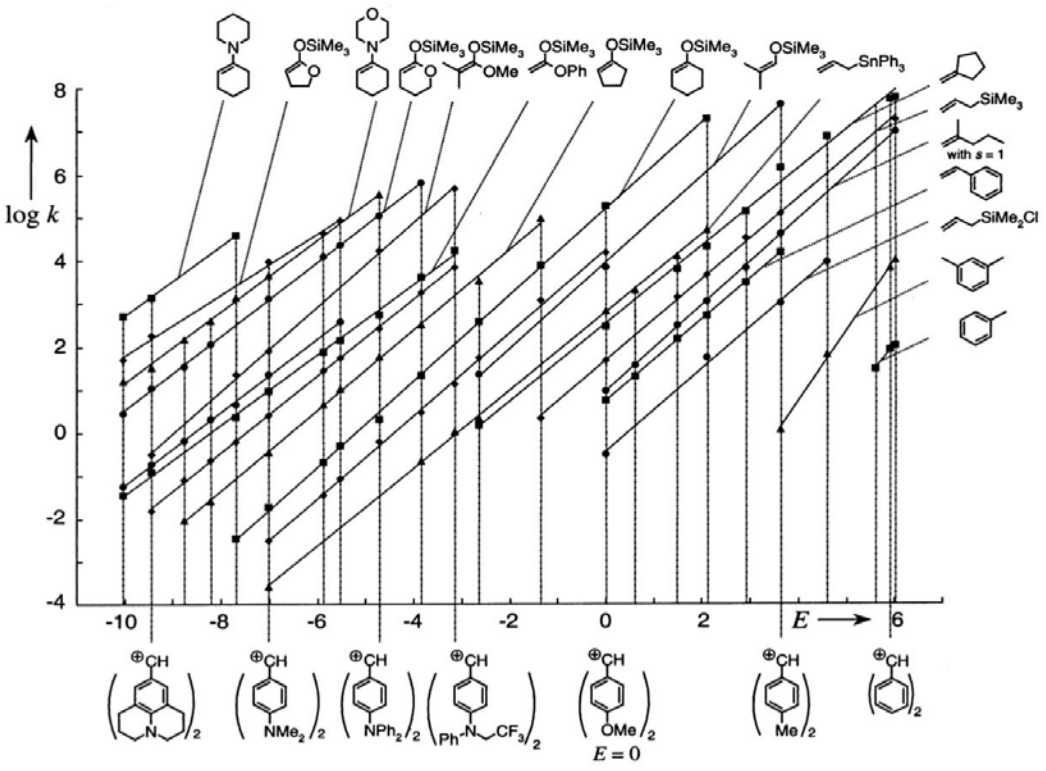


Figure 7. Source: *Acc. Chem. Res*. **2003**, *36*, 66.

Deviations of these correlations are found at "*diffusion control conditions*" in which the rate determining step of a reaction is not the bond formation between the two counterparts, but the diffusion (or movement) of the species through the medium. This usually implies very high reaction rates and a loss of selectivity on the desired reaction.

As far as Mayr's studies are concerned, the diffusion control appears when strong nucleophiles (high *N*) react with strong electrophiles (high *E*) in a constant rate of about $k > 10^9$–10^{10} $M^{-1}s^{-1}$. Therefore, a reaction will only follow Mayr's correlations if $N + E < 9$, approximately. By contrast, if weak nucleophiles are in presence of weak electrophiles (low *N* and *E*) the desired reaction will be slow. The *rule of thumb*, postulated by Mayr, states that electrophiles cannot be expected to react with nucleophiles at room temperature when $N + E < -5$, that corresponds to $k > 10^{-5}$ M^{-1} s^{-1}. In summary, a polar organic reaction can be expected to work properly and with a predictable kinetics if $-5 < N + E < 9$ approximately. The majority of the most common polar organic reactions are in this range, as shown in Figure 8.

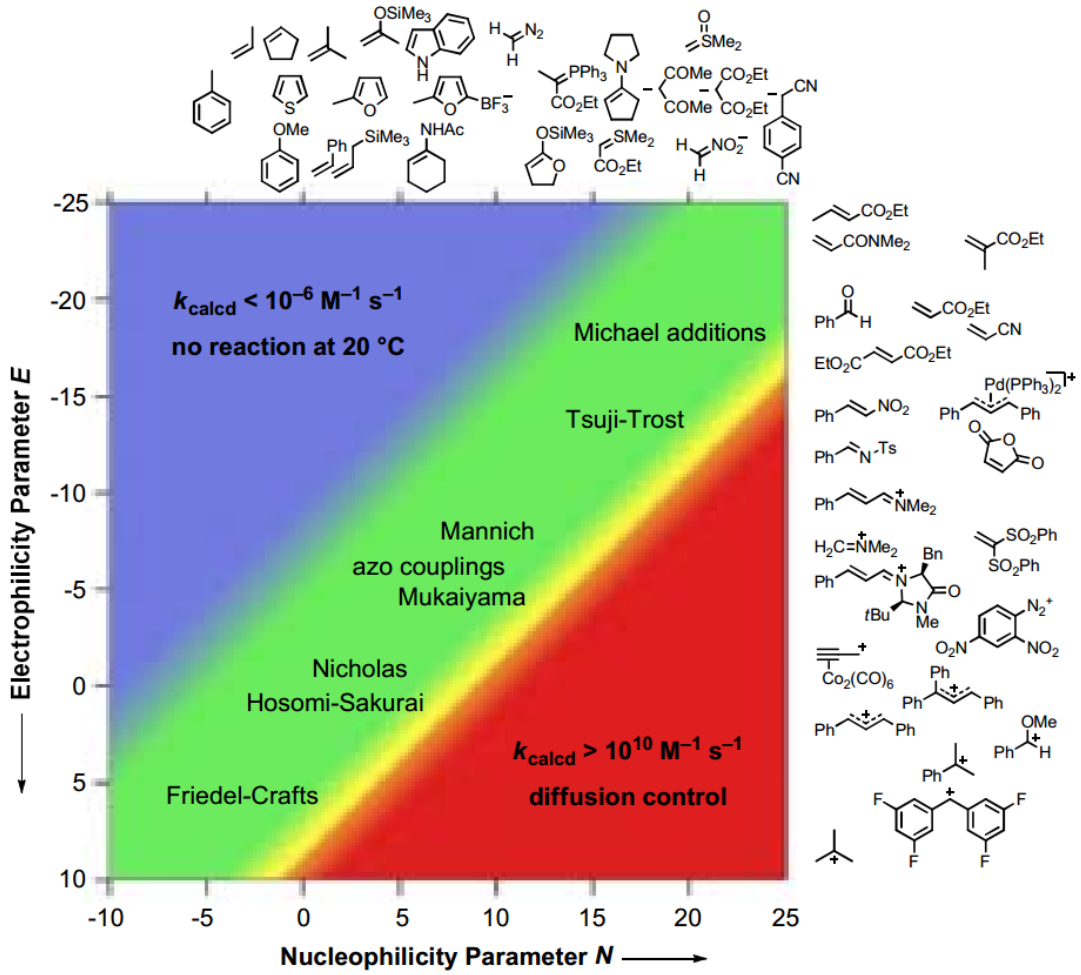


Figure 8. Source: *http://www.cup.lmu.de/oc/mayr/*

Bearing this condition in mind, one can select any of the reported nucleophiles and electrophiles (Figure 9) to know in advance the chances for the corresponding reaction and a rough prediction of the kinetics.

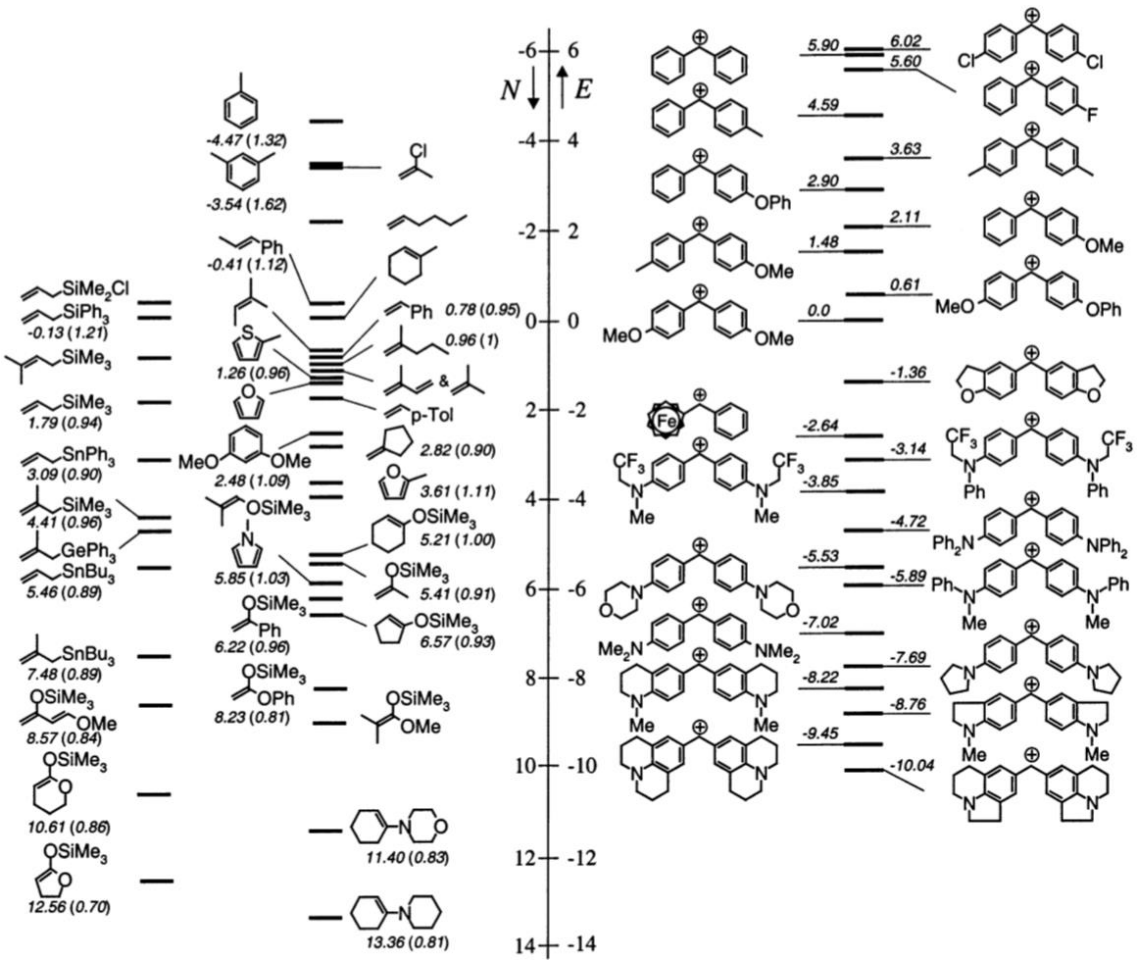


Figure 9. Source: *Acc. Chem. Res*. **2003**, *36*, 66.

5.3. A model for the prediction of the success of a Ni(II)-catalyzed alkylation reaction

The use of a wide array of electrophiles in our alkylation reaction had provided interesting qualitative information about the range of electrophiles able to react with the nickel(II) enolates. Indeed, highly electrophilic carbocations could have reacted efficiently, but their poor stability thwarted their activation by a mild Lewis acid such as TESOTf. In contrast, highly stabilized carbocations reacted smoothly with excellent yields despite their low electrophilic character. Thanks to this stabilization, which was produced by means of the introduction of π-electron donor groups, the activation was pretty easy.

This evidence is closely related to Mayr's scale of electrophilicity. As previously explained, this scale is obtained from an electrophilicity parameter (*E*), which directly

represents the kinetics of a polar organic reaction. Since the *E* factor depends intrinsically on the structure of the carbocation, there is a clear relationship between the stability of such species and the value of their *E* factor. The more stabilized is a carbocation, the lower is the electrophilicity parameter *E*. Assuming that our Ni(II) catalyzed alkylation reactions are also directly related to this stability, we could finally analyze the chances for any alkylation reaction by considering the parameter *E*. In Figure 10, the values of carbocations are shown.

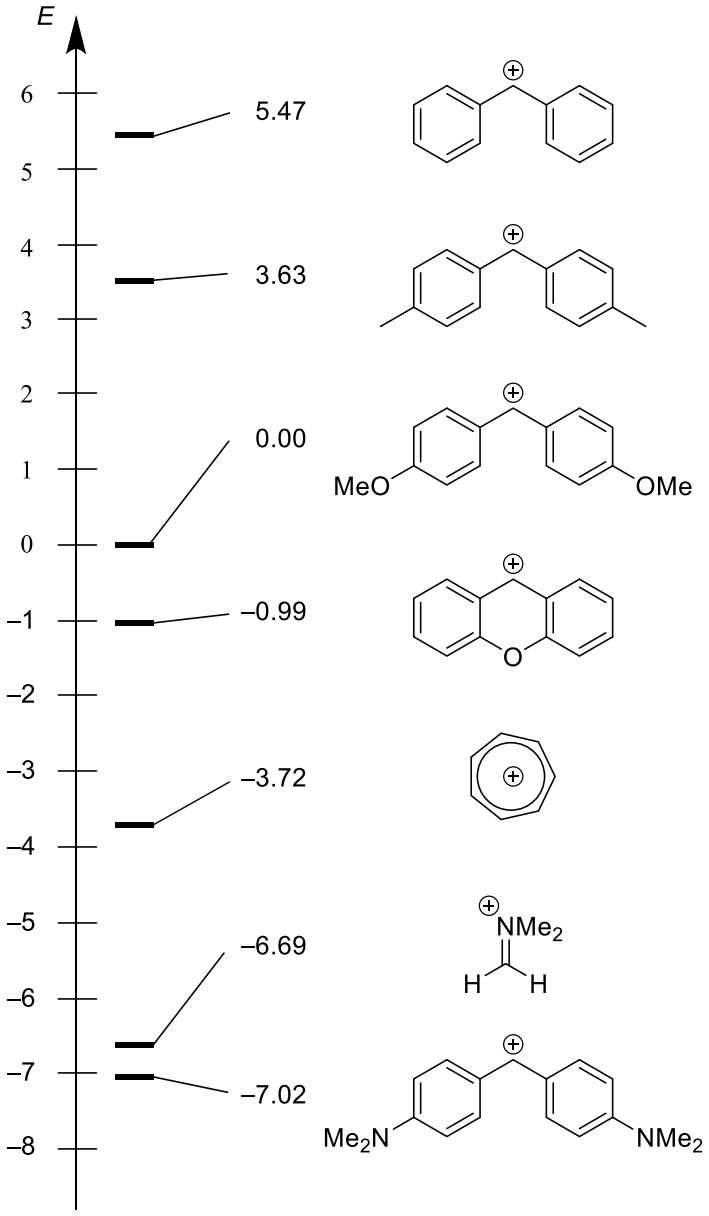


Figure 10

As far as our Ni(II) catalyzed alkylation reactions are concerned, all carbocations with *E* values smaller than the one described for di(*p*-methoxyphenyl)methylium cation (*E*=0) underwent the alkylation reaction and provided high yields. Otherwise, di(*p*-tolyl)methylium cation (*E*=3.63) only afforded traces of the alkylated product and benzhydryl cation (*E*=5.47) did not work at all, as could be expected from its high *E* value.

Thus, one could state that any carbocation with a negative value of electrophilicity parameter ($E \leq 0$) would be likely to react with our Ni(II) enolates ("*Safe Zone*"). Any carbocation with an *E* parameter between *E*=0 and $E \approx 3.6$ should be studied carefully ("*Danger Zone*"). Finally, those with an $E > 3.6$ would surely fail ("*Forbidden Zone*"). It is important to remember that this prediction will be valid as long as no side reactions concerning the cation exist or steric factors come into play. Further studies to confirm such a rule are in progress in our group.

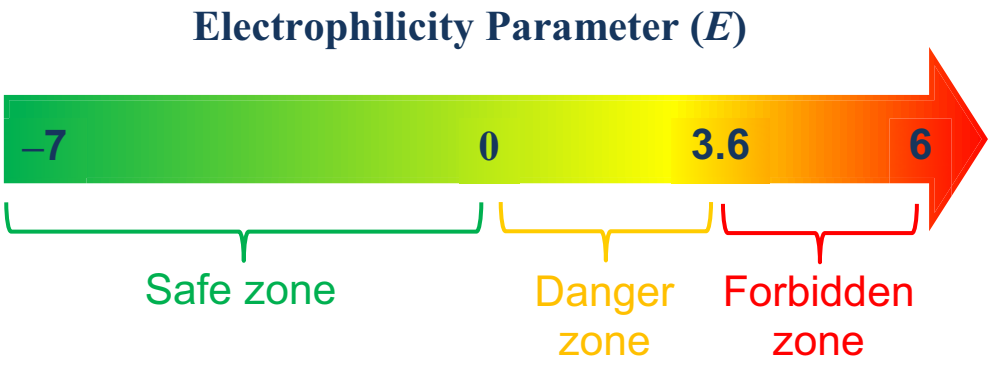
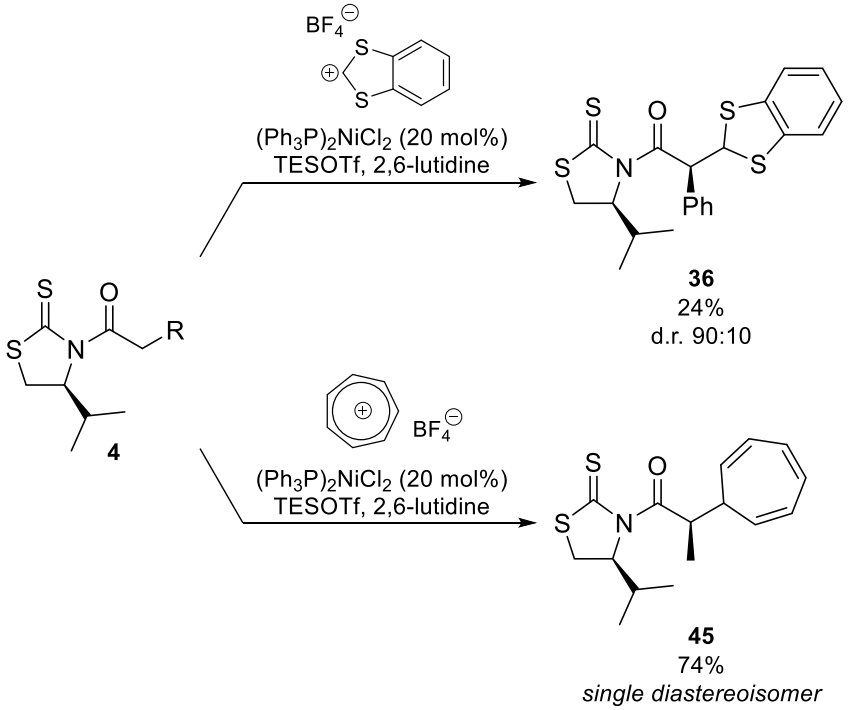


Figure 11

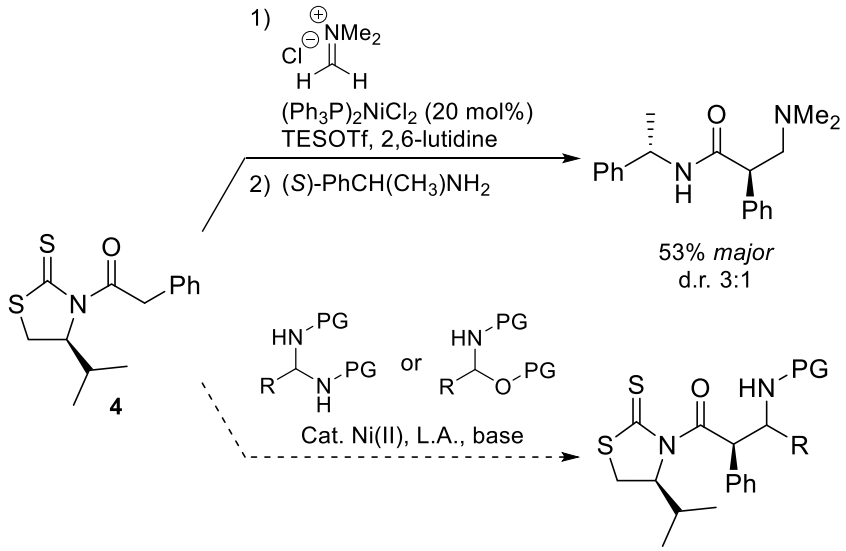
6. SUMMARY AND CONCLUSIONS

In this Chapter 2, the Ni(II) catalytic system previously developed has been used in S_N1–like alkylation reactions with commercially available carbocation salts (Scheme 120). The additions proceed with excellent diastereoselectivities. Unfortunately, these are plagued with several side reactions and some yields are low or moderate and/or require of high catalyst loadings.



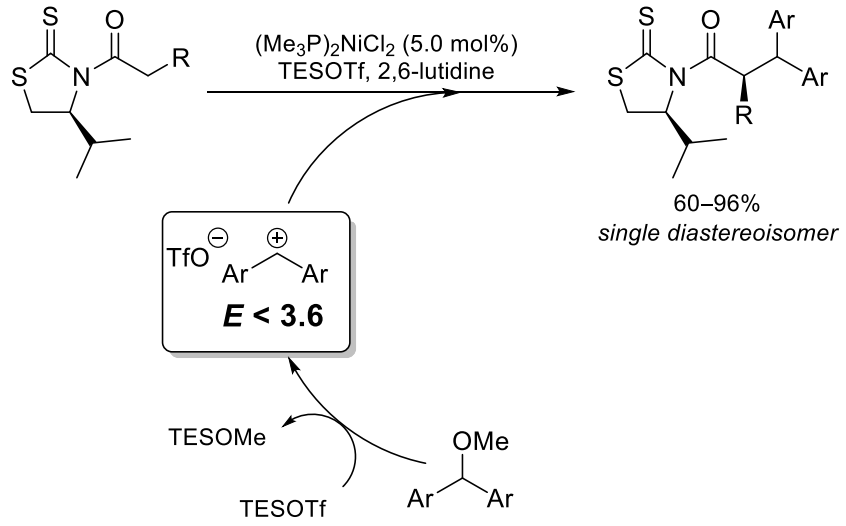
Scheme 120

Remarkably, a new β-amination method has been developed using the Eschenmoser's salt, but it was completely necessary to add a nucleophile to isolate the corresponding product. Primary amines resulted to be the best alternative. A chiral primary amine permitted to establish the diastereoselectivity of the process. This method opens a way for further applications to iminium ions generated *in situ* from aminals or hemiaminals.



Scheme 121

Furthermore, a new Ni(II)-catalyzed alkylation of *N*-acylthioimides with diarylcarbenium ethers has been developed (Scheme 122). Experimental data proved that the activation of these electrophiles plays a key role in the success of the reaction, concluding that the resulting carbocations need to be stabilized by π-donor groups to be produced efficiently. Mayr's scale of electrophilicity accounts for such results and can be used to predict which carbocations are likely to react. In our case, carbocations that fit into the "*Safe Zone*" ($E < 0$), while those into the "*Danger Zone*" ($0 < E < 3.6$) must be carefully studied.



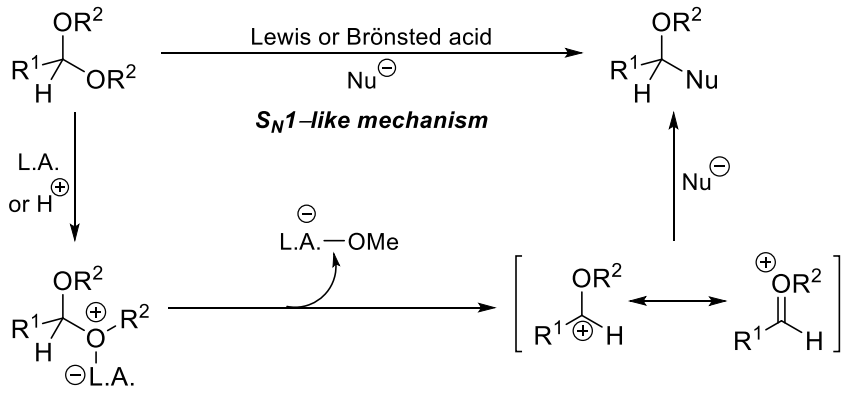
Scheme 122

CHAPTER 3

STEREOSELECTIVE Ni(II) CATALYZED REACTIONS OF *N*-ACYL THIAZOLIDINETHIONES WITH ACETALS

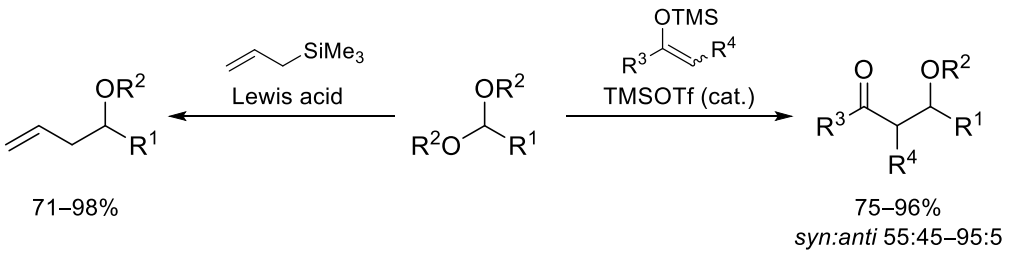
1. INTRODUCTION

Traditionally, acetals have been used for the protection of alcohols and diols, but they are also useful reagents for the construction of carbon–carbon bonds. As explained in the General Introduction, treatment of acetals with Lewis or Brönsted acids produces oxocarbenium ions, whose relative high stabilization confers them interesting electrophilic properties to undergo S_N1–like additions to *C*–nucleophiles and generate a new carbon–carbon bond (Scheme 123). Despite the undeniable potential of such an approach, just a few reports describe the use of *C*–nucleophiles in S_N1–like reactions with good levels of stereocontrol.



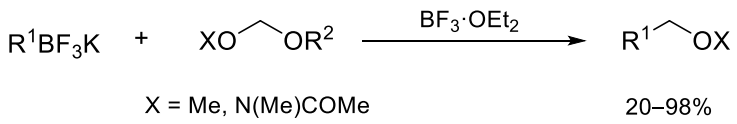
Scheme 123

The feasibility of such a transformation was early proved by Noyori and Sakurai in the Lewis acid-mediated addition of silyl enolates or allyl silanes to acetals.[34,35,134]



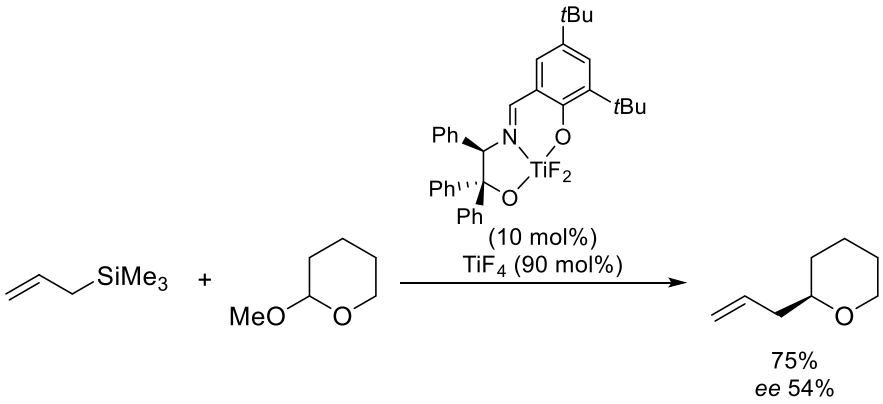
Scheme 124

More recently, potassium organofluoroborates have also been used as nucleophiles for their addition to heterosubstituted formaldehyde acetals activated with stoichiometric amounts of $F_3B \cdot OEt_2$, producing the corresponding oxygenated derivatives in low to excellent yields.[135,136]



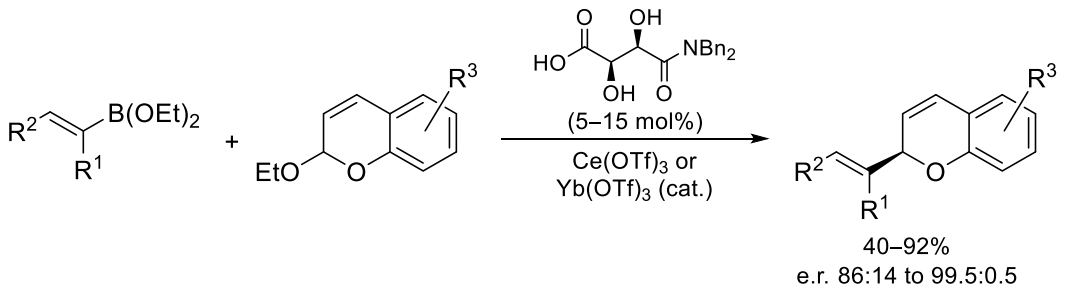
Scheme 125

The former examples do not involve any control on the absolute configuration of the new stereocenter. One of the earlier asymmetric reactions relied on the stereoselective addition of allyltrimethylsilane to 2-methoxytetrahydro-2*H*-pyran activated by catalytic amounts of a chiral Ti(IV) complex.[137]



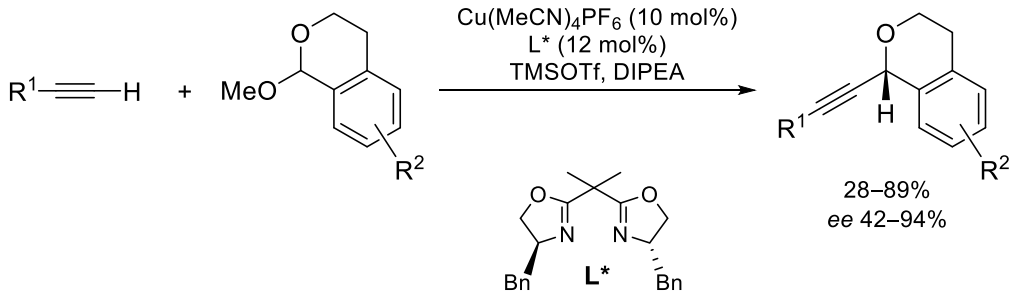
Scheme 126

It has also been reported an asymmetric transformation based on organoboron compounds. This employs catalytic amounts of an amide derived from tartaric acid for the *in situ* formation of chiral organoboronates and the subsequent asymmetric addition to chromene acetals activated by $Ce(OTf)_3$ or $Yb(OTf)_3$.[138]



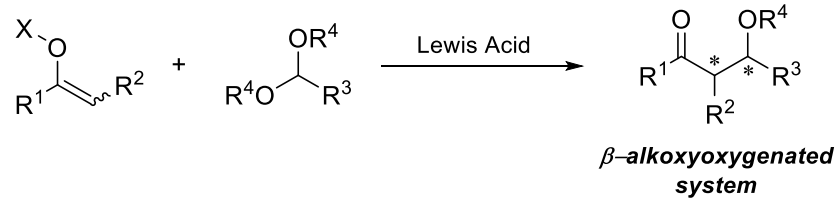
Scheme 127

A similar transformation was reported by Watson. As shown in Scheme 128, the asymmetric addition of chiral organocuprates from terminal alkynes to isochroman acetals activated with TMSOTf proceeds in low to high yields and enantiomeric excess up to 94%.[139]



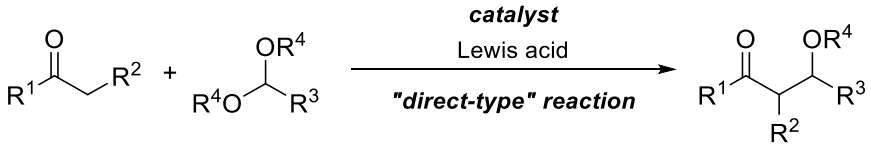
Scheme 128

In addition to these examples, the introduction of enolates as potential *C*–nucleophiles in the chemistry of acetals would be incredibly useful, since the coupling between an enolate and an oxonium cation would afford a β-alkoxyoxygenated system with a new carbon–carbon bond and up to two new stereogenic centers in a single step (Scheme 129). This is a challenging transformation for two main reasons. First, both the enolate and the oxonium intermediates are highly reactive species, so their formation and subsequent introduction must occur in a nicely orchestrated manner, as noted in previous Chapters. Secondly, this transformation usually proceeds through an open transition-state mechanism, which hinders the control on the configuration of the new stereocenters. Some successful examples involving preformed enolates such as Mukaiyama aldol-like reaction or coupling between metal enolates and acetals can be found in the Introduction of Chapter 1 and in Scheme 124.



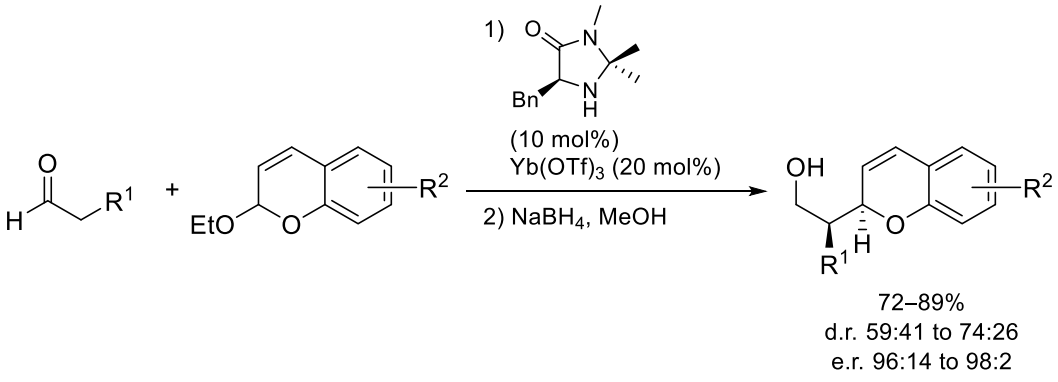
Scheme 129

Evidence for these challenges are found in recently reported "*Direct-type*" reactions. Indeed, the enolate or any other nucleophile species must be generated in catalytic amounts to undergo the electrophilic attack of the corresponding oxonium ion, which in turn is prepared *in situ* by the action of a Lewis acid on the acetal.



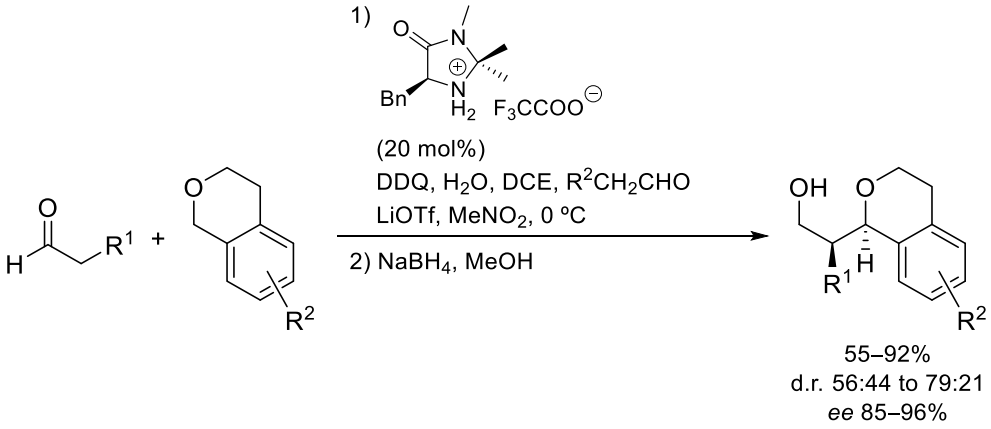
Scheme 130

Insightful organocatalytic approaches towards this kind of "*direct-type*" reactions have been published during the last decade. The results clearly prove the difficulty of combining high yields with high diastereomeric and enantiomeric ratios. For instance, the nucleophilic attack of aldehydes to oxonium ions from chromene acetals generated by $Yb(OTf)_3$ can be catalyzed by the MacMillan's imidazolidinone.[140] Importantly, a reducing agent required to obtain the corresponding alcohol derivatives with two new stereocenters in high yields, moderate to good diastereoselectivities and excellent enantiomeric ratios.



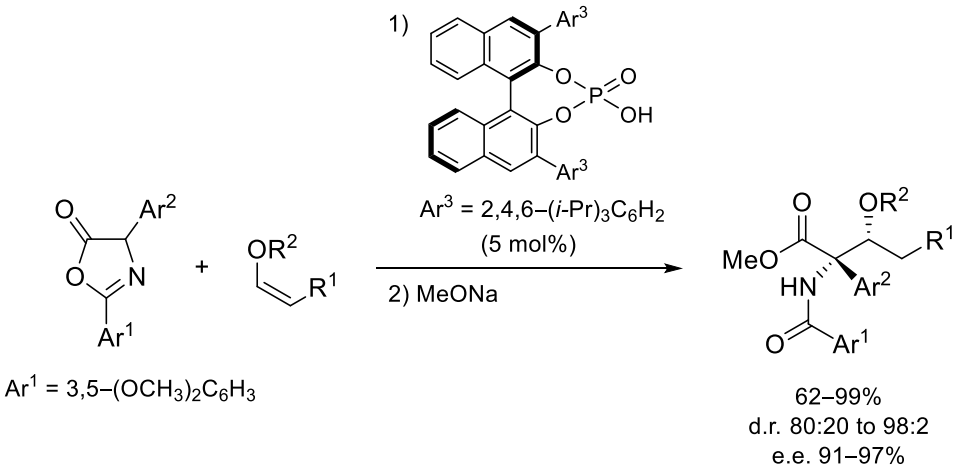
Scheme 131

Oxonium ions from isochromanes can also be produced *in situ* by oxidation with DDQ. Then, coupling of aldehydes and these oxonium ions catalyzed by MacMillan's imidazolidinones and subsequent reduction of the resultant aldehydes afford the corresponding alcohols in good to excellent yields and moderate diastereo- and enantioselectivities.[141]



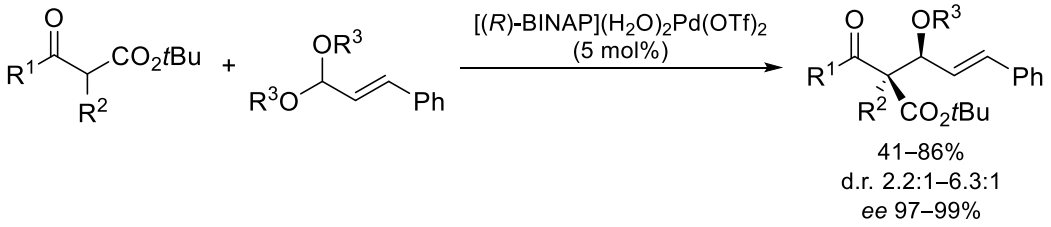
Scheme 132

Alternatively, other substrates prone to deliver oxonium ions have been used. For example, Terada use vinyl ethers, which can produce the required oxonium ions by protonation. Then, a chiral phosphoric acid provides the chiral environment that enables the nucleophilic attack of the oxazole tautomer of azlactones to oxonium ions with moderate to excellent stereoselectivities (Scheme 133).[142]



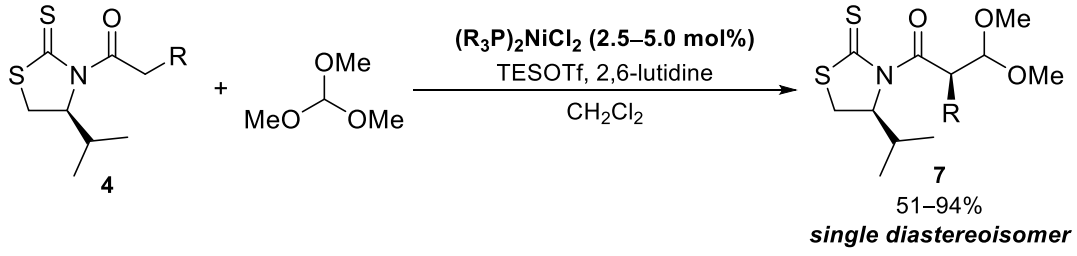
Scheme 133

Another option to carry out such a transformation relies on the addition of a metal enolate. As we explained in the General Introduction, the choice of the metal is crucial, since it must be able to react in a S_N1-like reaction with high levels of stereocontrol. Such an approach is rather difficult, so just only one example of "*direct-type*" metal-catalyzed reaction of carbonyl compounds with acetals has been reported so far. Thus, Sodeoka published the catalytic formation of β-ketoester Pd(II) enolates and subsequent nucleophilic attack to activated α,β-unsaturated acetals to yield *syn* α-(*tert*-butoxycarbonyl)-β-alkoxy carbonyl compounds (Scheme 134). The delivery of a protic acid during the enolate formation triggers the acetal activation and the resulting chelated enolate facilitates the stereocontrolled addition of the oxonium cation. Despite the success of this addition, it can only be applied to a very narrow scope of acetals.[30]



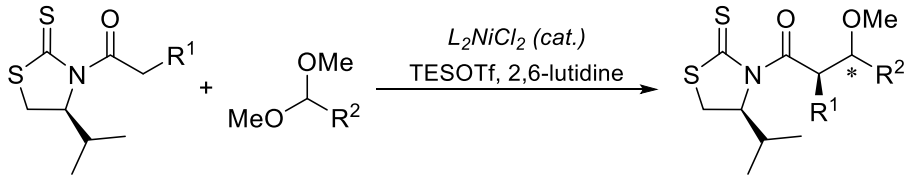
Scheme 134

As explained in Chapter 1, we were able to develop a new totally diastereoselective Ni(II) catalyzed β-formylation reaction of (*S*)-*N*-acyl-4-isopropyl-1,3-thiazolidine-2-thiones. In there, the oxonium ion from trimethyl orthoformate undergoes a nucleophilic attack of Ni(II) enolates from those chiral thioimides. Noteworthy, the resultant oxonium ion is not prochiral, which means that no stereocenter is produced at β position. Then, the process becomes completely stereoselective because the chiral auxiliary totally controls the configuration of the α stereocenter.



Scheme 135

Thus, taking advantage of our experience, we considered the possibility of developing a metal-catalyzed method for the production of β-alkoxyoxygenated systems from a variety of acyl chains and acetals. In this context, the Ni(II) catalytic system established in Chapter 1 was an excellent starting point for such a challenging objective. Indeed, following the results obtained with methyl orthoformate, the configuration of the α stereocenter would be controlled by the chiral auxiliary, whereas that of β stereocenter would be dependent on different structural features.

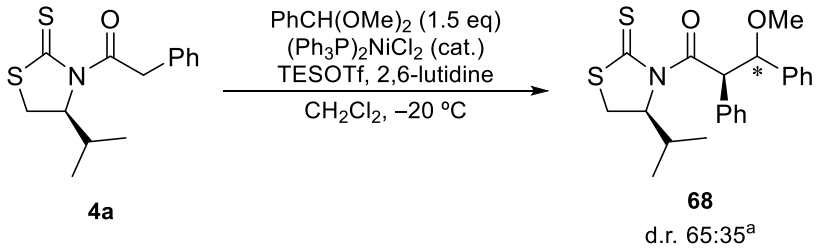


Scheme 136

2. OPTIMIZATION OF THE REACTION

2.1. Preliminary experiments with thioimide 4a

Initially, thioimide **4a** and benzaldehyde dimethyl acetal were chosen as model substrates. The reaction was examined using 10 mol% and 2.5 mol% of $(Ph_3P)_2NiCl_2$ at –20 ºC by taking some aliquots during the reaction and analyzing them by ^{1}H NMR. The results summarized in Table 16 show that the reaction is almost complete after 2.5 or 16 h, depending on the amount of catalyst. As for the stereoselectivity, only two of the four possible stereoisomers were observed since the configuration of the α stereocenter was totally controlled by the chiral auxiliary. The ratio between the two diastereomeric products was 65:35, which corresponded to a moderate stereocontrol of the configuration of the β stereocenter.



4a → **68**

d.r. 65:35[a]

Entry	Cat. (mol%)	t (h)	Conv (%)[b]
1[c]	10	0.3	61
2[c]	10	1	74
3[c]	10	2.5	94
4[d]	2.5	0.3	22
5[d]	2.5	1	38
6[d]	2.5	2.5	58
7[d]	2.5	7	81
8[d]	2.5	16	94

[a] Diastereomeric ratio established by ^{1}H NMR analysis of the crude product.

[b] Conversion established by ^{1}H NMR analysis of the crude product.

[c] 1.3 equivalents of TESOTf were used.

[d] 1.15 equivalents of TESOTf were used.

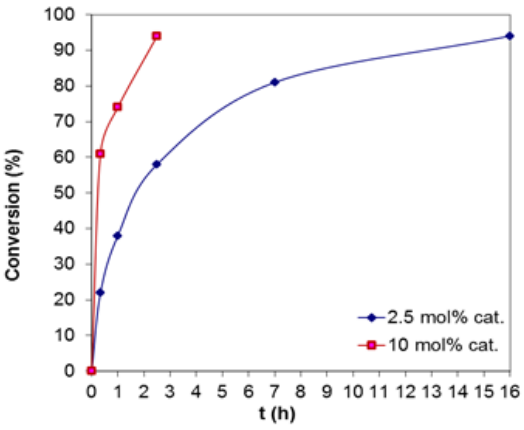
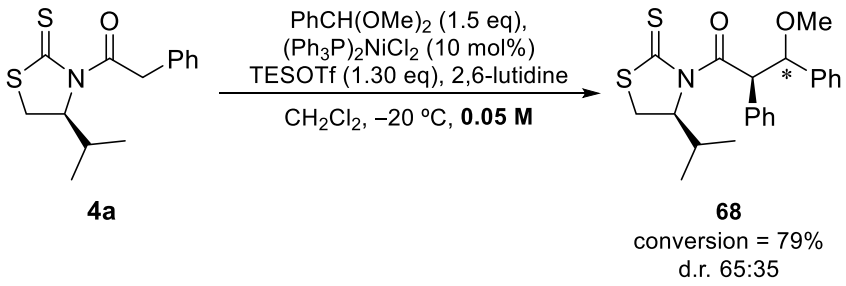


Table 16

Some of these results were confirmed by isolating adducts **68** as a 65:35 inseparable mixture of two diastereomers in 78% and 93% overall yields after 7 h and 16 h respectively (compare to entries 7 and 8 in Table 16).

The relatively low 65:35 diastereomeric ratio led us to look for new experimental conditions. First of all, we focused our attention on the temperature. We ran a reaction using 20 mol% of catalyst at –45 ºC and –78 ºC. Unfortunately, no traces of the expected adduct **68** were observed, which meant that the process was completely frozen at temperatures below –20 ºC.

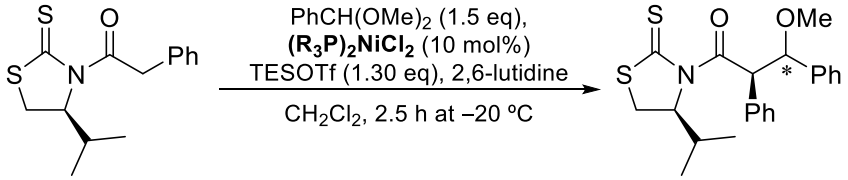
Since the use of low temperatures had to be ruled out, we focused our attention on the study of other conditions and reagents. Thus, we investigated the influence of more diluted conditions (0.05 M instead of 0.50 M). Such a modification did not alter the diastereomeric ratio either, and an overall conversion of 79% to the adducts **68** in a 65:35 diastereomeric ratio was observed by ^{1}H NMR of the crude.



Scheme 137

2.2. Further optimization with thioimide 4a

Having examined the influence of the temperature and the concentration, we centered our attention on the reagents that participate in the overall transformation: the nickel(II) catalyst, the Lewis acid, and the base. Therefore, we first assessed the influence of other commercially available catalysts. As summarized in Table 17, all the catalysts afforded very high conversions with the exception of bulky $(Cy_3P)_2NiCl_2$. However, none of them reached the 65:35 ratio, so $(Ph_3P)_2NiCl_2$ remained as the most stereoselective catalyst.



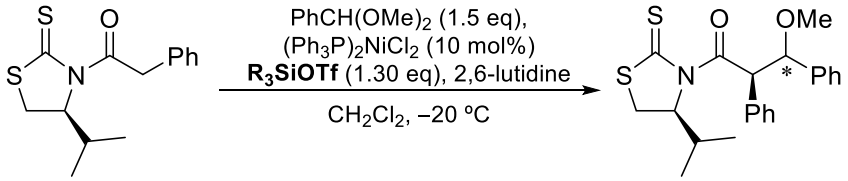
4a **68**

Entry	$(R_3P)_2NiCl_2$	d.r.[a]	Conversion (%)[a]
1	$(Ph_3P)_2NiCl_2$	65:35	94
2	(dppe)$NiCl_2$	60:40	100
3	(dppp)$NiCl_2$	55:45	100
4	$(Me_3P)_2NiCl_2$	60:40	89
5	$(Cy_3P)_2NiCl_2$	60:40	33

[a] Established by ^{1}H NMR analysis of the crude product.

Table 17

Using $(Ph_3P)_2NiCl_2$ as catalyst, we next evaluated the influence of the silyl triflate as Lewis acid. Both TMSOTf and TESOTf provided similar diastereomeric ratios, but TESOTf gave much better conversions (compare entries 1–4 in Table 18). In turn, TESOTf and TBSOTf afforded similar conversions after 2.5 h, but the diastereoselectivity using TESOTf was slightly better (compare entries 4 and 6 in Table 18). Thus, TESOTf turned out to be the most efficient Lewis acid.



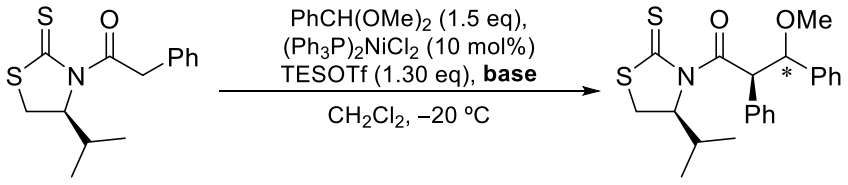
4a **68**

Entry	R_3SiOTf	t (h)	d.r.[a]	Conversion (%)[a]
1	TMSOTf	0.3	63:37	44
2	TMSOTf	2.5	64:36	45
3	TESOTf	0.3	65:35	61
4	TESOTf	2.5	65:35	94
5	TBSOTf	0.3	60:40	30
6	TBSOTf	2.5	62:38	80

[a] Established by ^{1}H NMR analysis of the crude product

Table 18

As for the effect of the base, simple tertiary amines such as triethylamine, trihexylamine or *N*-methylmorpholine afforded low conversions or even did not work (entries 1–3 in Table 19). More bulky amines proved to be more suitable: *i*-$PrNEt_2$ gave a conversion up to 84% (entry 4 in Table 19), which was higher than 2,2,6,6-tetramethylpiperidine (66%) (entry 5 in Table 19). On the other hand, aromatic bases such as the unhindered pyridine or the highly hindered 2,6-di(*tert*-butyl)-4-methylpyridine did not afford any product (compare entries 6–8 in Table 19). It can be concluded that relatively hindered bases (DIPEA, TMP, 2,6-lutidine) are the most appropriate bases and, particularly, 2,6-lutidine provides the best diastereomeric ratio and conversion, thus becoming the most suitable base.



4a **68**

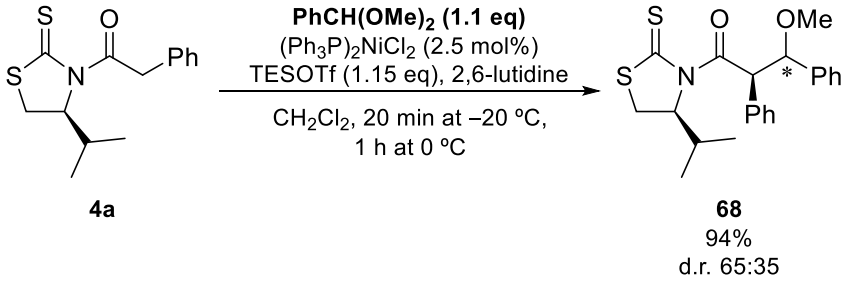
Entry	Base	t (h)	d.r.[a]	Conversion (%)[a]
1	Et_3N	2.5	55:45	39
2	Hex_3N	2.5	56:44	26
3	NMM[b]	1.0	–	n.r.
4	*i*-$PrNEt_2$	2.5	55:45	84
5	TMP[c]	2.5	57:43	66
6	Pyridine	1.0	–	n.r.
7	2,6-Lutidine	2.5	65:35	94
8	DTBMP[d]	1.0	–	n.r.

[a] Established by ^1H NMR analysis of the crude product.
[b] *N*-Methylmorpholine.
[c] Tetramethylpiperidine.
[d] 2,6-Di(*tert*-butyl)-4-methylpyridine.

Table 19

In conclusion, neither changing the reaction conditions nor the reactants the diastereoselectivity was improved. Actually, the diastereomeric ratio ranges from 55:45 to 65:35. Thus, the reaction between thioimide **4a** and benzaldehyde dimethyl acetal must be carried out in the conditions summarized in Scheme 138 (2.5 mol% of $(Ph_3P)_2NiCl_2$, 20 min at –20 ºC, 1 h at 0 ºC). Finally, we could also reduce the amount

of acetal to 1.1 equivalents, which rules out any unnecessary excess and makes the purification easier, and thus obtain a 94% yield of a mixture of the two diastereomeric products in a 65:35 ratio.



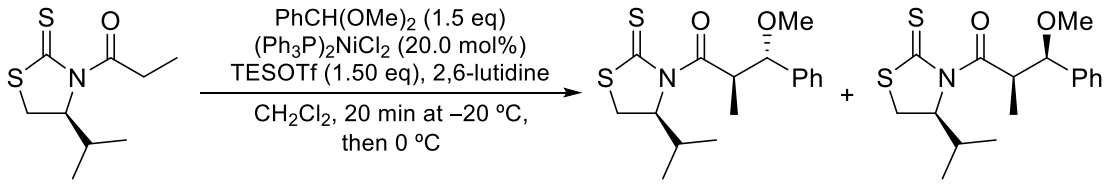
4a **68** 94% d.r. 65:35

Scheme 138

2.3. Preliminary experiments with thioimide 4f

The use of the conditions established for thioimide **4f** and trimethyl orthoformate in Chapter 1 (20 mol% $(Ph_3P)_2NiCl_2$, 20 min at –20 ºC, then 0 ºC) triggered a smooth but slow transformation and one day was necessary to isolate adduct **69** with an overall yield of 69% (Table 20). Clearly, the kinetics of the reaction with the *N*-propanoylthiazolidinethione **4f** was much slower than that with *N*-phenylacetylthiazolidinethione **4a**, likely due to the different acidity of the α proton.

Again, only two of the four possible stereoisomers were observed. The diastereomeric ratio by ^{1}H NMR of the crude was 60:40. To our pleasure, these diastereomers were totally separable by column chromatography, which allowed us to characterize each of them and, much more important, to compare and identify them with previously reported data.[31a,31h] This comparison confirmed that the α stereocenter was totally controlled, and the diastereomeric products arose from the moderate control of the configuration of the β stereocenter. The major adduct corresponded to the so-called *anti* diastereomer, while the minor one could be labeled as the *syn* diastereomer.



4f → **69** ***anti*** + **69m** ***syn***

d.r. 60:40[a]

Entry	t (h)	*Anti* (%)[b]	*Syn* (%)[c]
1	1	10	7
2	5	30	21
3	22	41	28

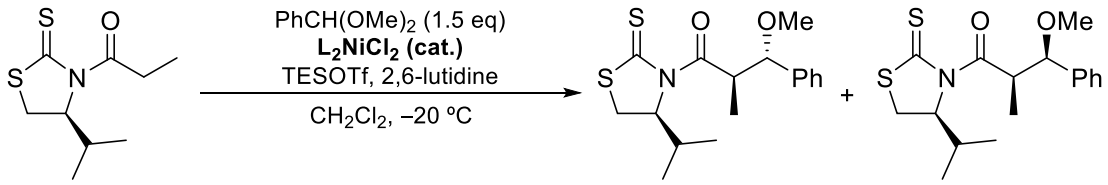
[a] Established by ^{1}H NMR analysis of the crude product

[b] Calculated yield over the isolated mixture of *anti* and benzaldehyde after column chromatography.

[c] Isolated yield after column chromatography.

Table 20

Next, we analyzed the diastereomeric ratio in reactions with commercially available catalysts at –20 ºC. At this temperature, $(Ph_3P)_2NiCl_2$ turned out to be almost inactive, whereas catalysts with chelated aromatic phosphines afforded very high yields (compare entries 1–3 in Table 21). As for catalysts with alkyl phosphines, the bulky $(Chx_3P)_2NiCl_2$ did not work, while $(Me_3P)_2NiCl_2$ showed to be very active. Remarkably, only 2.5 mol% of $(Me_3P)_2NiCl_2$ was necessary to achieve good yields, although the reaction lasted 22 h (compare entries 5–8 in Table 23). Unfortunately, the diastereomeric ratio did not go beyond 60:40 in any case. Further studies at lower temperatures demonstrated that no reaction took place. Therefore, the use of 2.5 mol% of catalyst $(Me_3P)_2NiCl_2$ would be selected for further optimizations and applications.



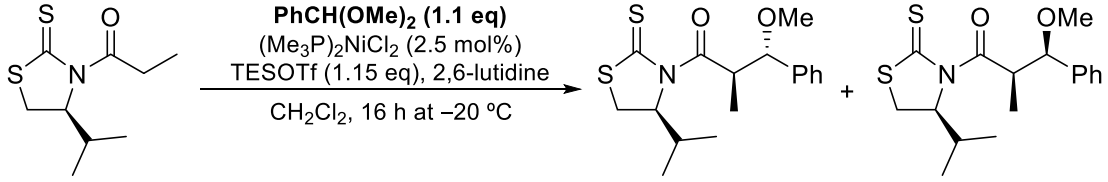
4f **69** ***anti*** **69m** ***syn***

Entry	L_2NiCl_2	mol%	t (h)	d.r.[a]	*Anti* (%)[b]	*Syn* (%)[c]
1	$(Ph_3P)_2NiCl_2$	20	22	60:40	7	4
2	$(dppe)NiCl_2$	20	22	60:40	58	38
3	$(dppp)NiCl_2$	20	22	55:45	49	42
4	$(Chx_3P)_2NiCl_2$	20	22	–	n.r.	n.r.
5	$(Me_3P)_2NiCl_2$	20	22	60:40	51	34
6	$(Me_3P)_2NiCl_2$	2.5	1.5	60:40	13	8
7	$(Me_3P)_2NiCl_2$	2.5	7	60:40	33	22
8	$(Me_3P)_2NiCl_2$	2.5	22	60:40	46	33

[a] Established by ^{1}H NMR analysis of the crude product
[b] Calculated yield over the isolated mixture of *anti* and benzaldehyde after column chromatography.
[c] Isolated yield after column chromatography.

Table 21

The amount of benzaldehyde dimethyl acetal was also reduced to 1.1 equivalents, which simplified the purification and facilitated the isolation of pure *anti* and *syn* diastereomers.



4f **69** ***anti*** 48% **69m** ***syn*** 31%

d.r. 60:40

Scheme 139

2.4. Influence of the chiral auxiliary

The failure to improve the stereocontrol both for **4a** and **4f** led us to examine the influence of the group at C4 of the chiral auxiliary. With this objective, *N*-propanoyl-1,3-thiazolidine-2-thiones **70–73** shown in Figure 12 were prepared by the standard procedure.

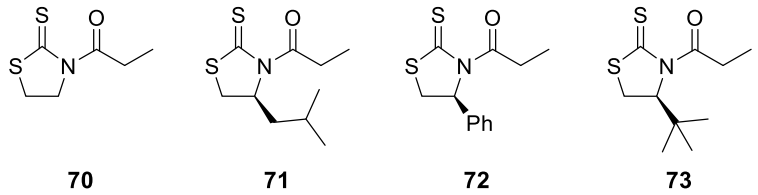
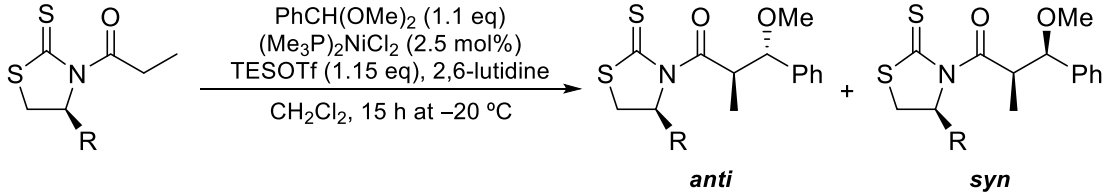


Figure 12

The diastereoselectivity turned out to depend on the steric bulk of the C4 group. Indeed, the most bulky *t*-Bu **73** afforded a 62:38 mixture of *anti/syn* diastereomers in 91% overall yield (entry 5 in Table 22), whereas the achiral thiazolidinethione **70** provided the poorest diastereomeric ratio (53:47 *anti/syn*) and lowest overall yield of 52% (entry 1 in Table 22). Thus, a *t*-Bu group could be a good choice to gain a higher diastereoselectivity, but the improvement is so poor (compare entries 4 and 5 in Table 22) and the price of the starting materials to prepare this chiral auxiliary is so expensive that it was not worth using it.



Entry	Subtrate	R	Adduct	d.r.[a]	*Anti* (%)[b]	*Syn* (%)[b]
1	**70**	H	**74**	53:47	26	26
2[c]	**71**	*i*-Bu	**75**	58:42	47	28
3[c]	**72**	Ph	**76**	58:42	51	36
4	**4f**	*i*-Pr	**69**	60:40	48	31
5	**73**	*t*-Bu	**77**	62:38	56	35

[a] Established by ^{1}H NMR analysis of the crude product.

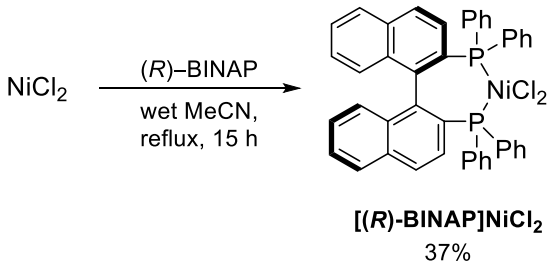
[b] Isolated yield after column chromatography.

[c] Carried out by Javier Fernández-Valparís.[53] Use of 1.5 equivalents of TESOTf.

Table 22

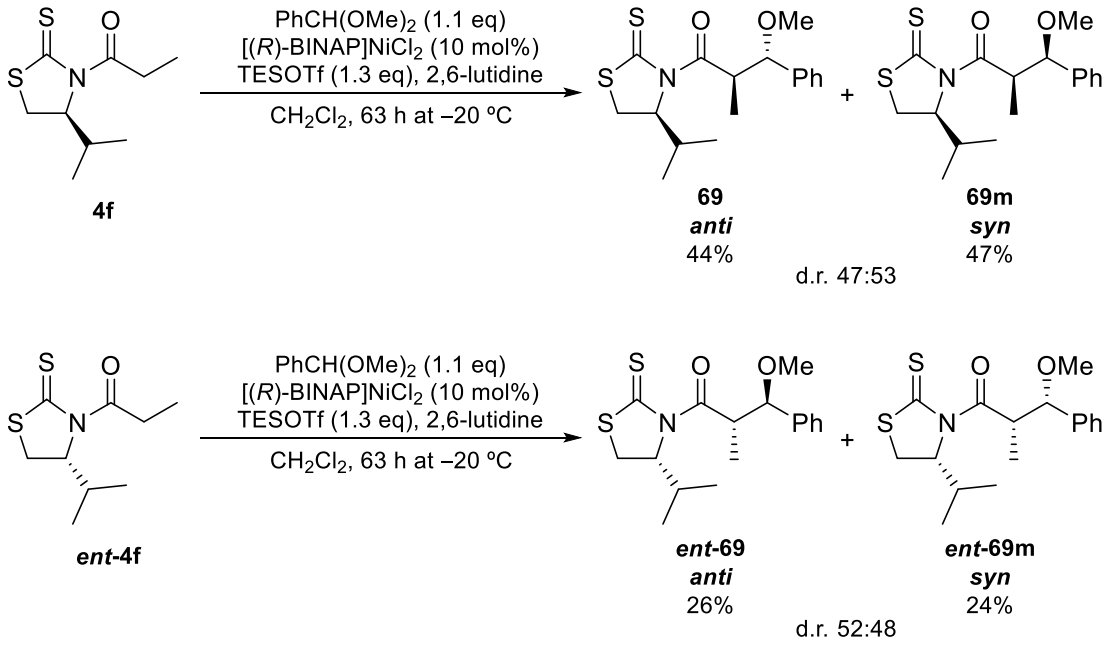
2.5. Influence of chiral ligands in the catalyst

As a final attempt to improve the diastereoselectivity, we examined the influence of a chiral Ni(II) catalyst such as [(*R*)-BINAP]$NiCl_2$, which was prepared by chelation of (*R*)-BINAP to nickel(II) chloride following a procedure described in the literature.[27]



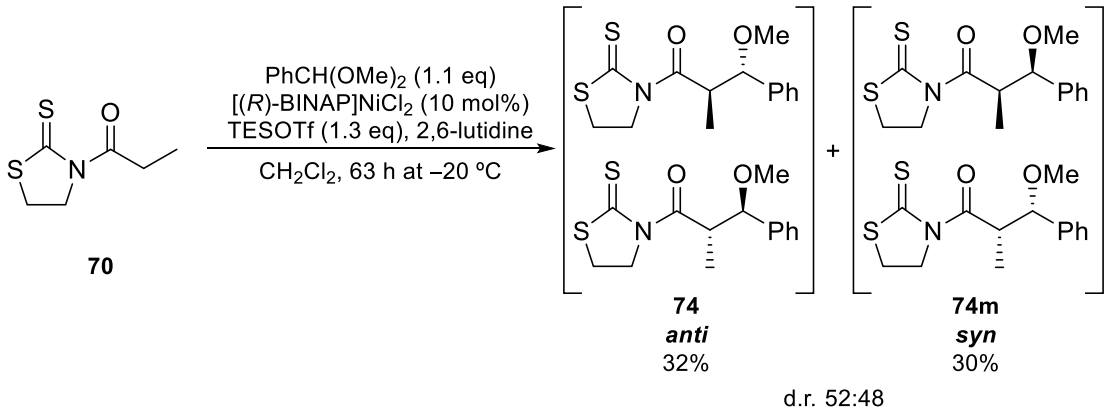
Scheme 140

This catalyst was employed either with thioimide **4f** and its enantiomer, ***ent*-4f**, to uncover the matched/mismatched pairs of catalyst and chiral auxiliary (Scheme 141). A good yield but very poor diastereoselectivity, slightly favoring the *syn* diastereomer, was obtained with **4f**. In turn, ***ent*-4f** gave a low yield of an almost equimolar mixture in which the *anti* diastereomer was the major one. Therefore, the influence of BINAP ligand was of little importance.



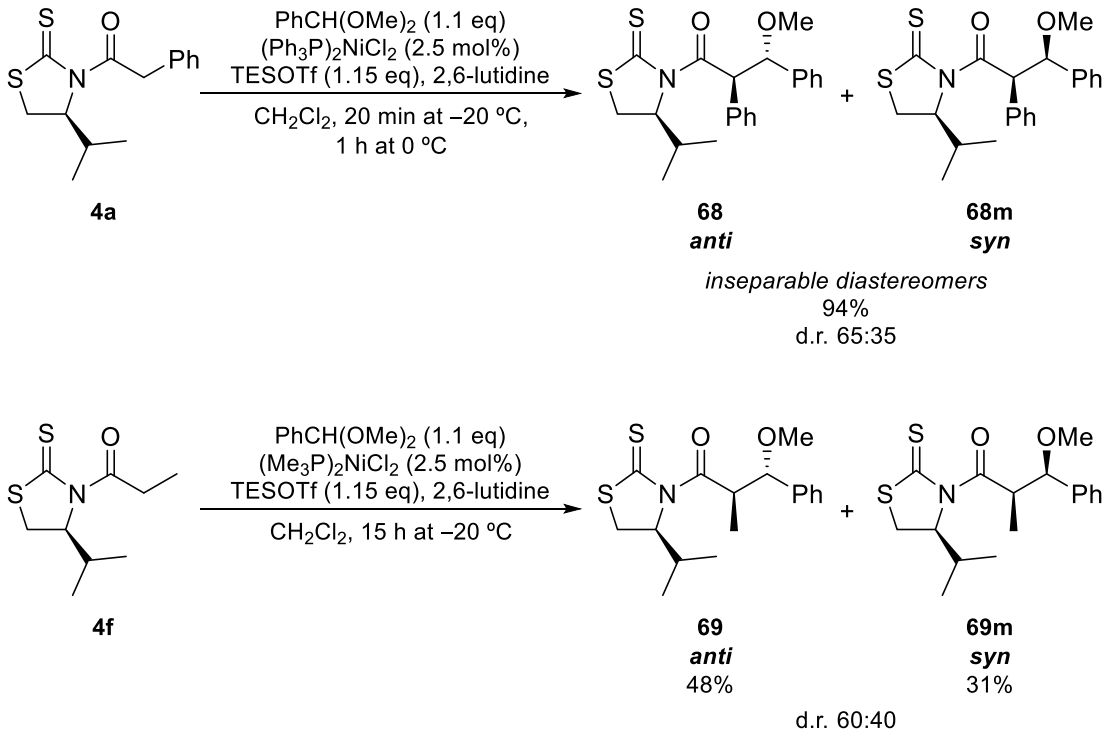
Scheme 141

Finally, we examined the reaction with the achiral thioimide **70**. Surprisingly, the results were quite similar to the reaction with ***ent*-4f** and also similar to those reported in entry 1 of Table 22. Thus, the chiral catalyst did not impart any influence on the configuration of the β stereocenter.



Scheme 142

In summary, we can conclude that the diastereomeric ratio of the process is practically unaltered by any change of the reaction conditions. The most appropriate catalyst for **4a** and **4f** turned out to be $(Ph_3P)_2NiCl_2$ and $(Me_3P)_2NiCl_2$, respectively.

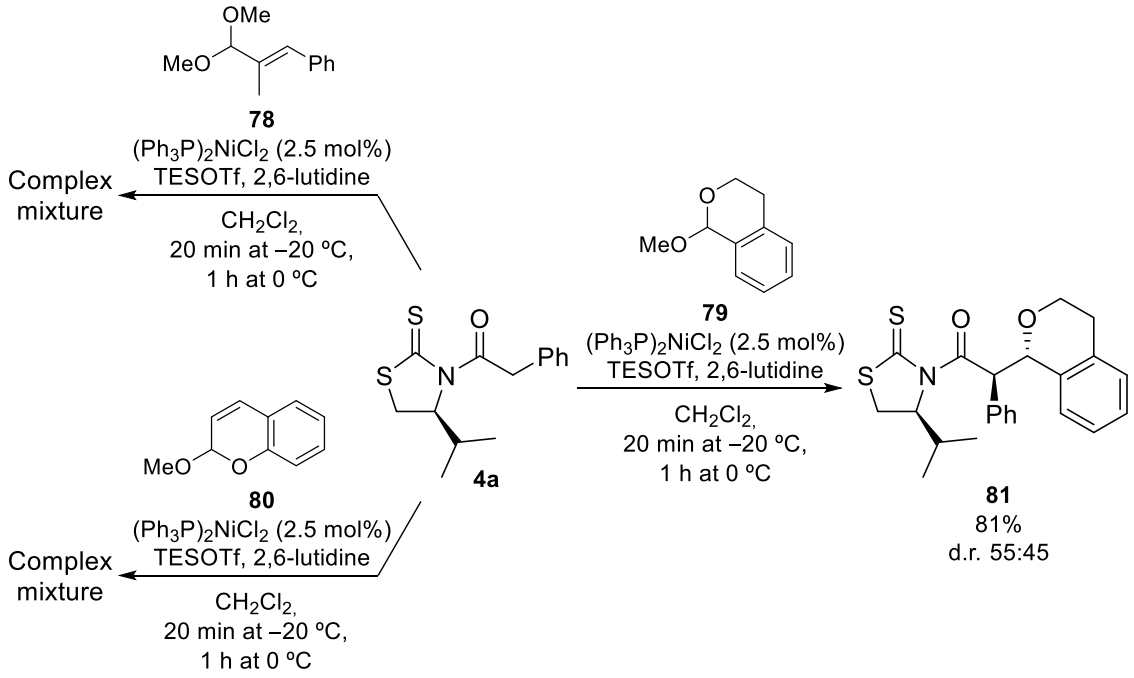


Scheme 143

3. SCOPE OF THE REACTION

3.1. Reaction of thioimide 4a with different acetals

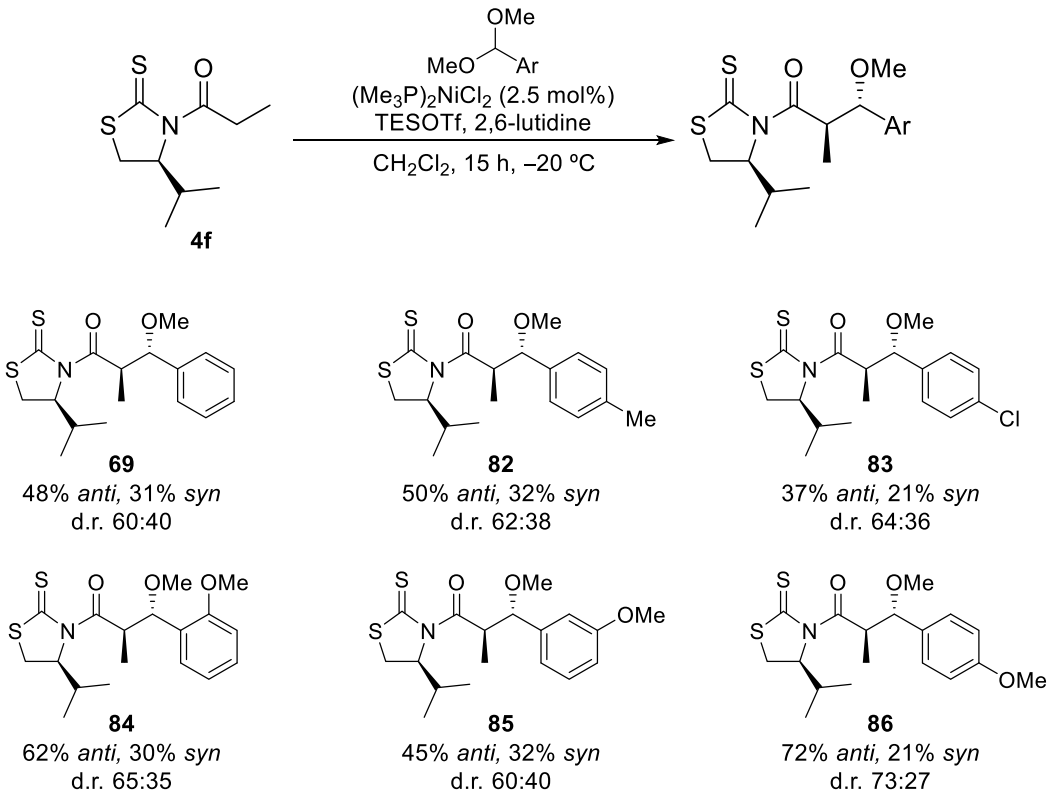
Once the experimental conditions had been established, we explored the scope of the reaction using a variety of acetals. Particularly, the addition of *N*-phenylacetylthiazolidinethione **4a** to acetals **78**, **79** and **80** was first assessed (Scheme 144). Unfortunately, only cyclic acetal **79** afforded the desired product in high yield but as an inseparable 55:45 mixture of two diastereomers. In turn, α,β-unsaturated acetal **78** and cyclic acetal **80** afforded complex mixtures, probably due to the low regio- and stereoselectivity of the processes. All these drawbacks indicated that the thioimide **4a** was not a good substrate for this kind of reaction.



Scheme 144

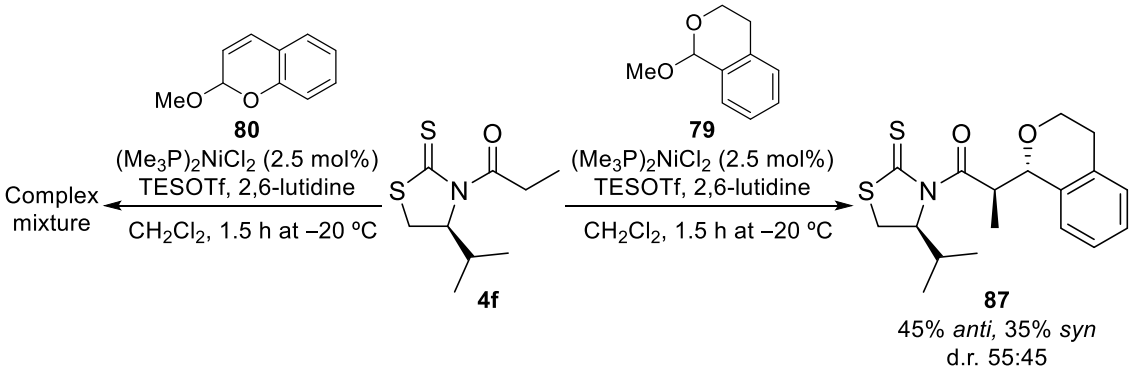
3.2. Reaction of thioimide 4f with different acetals

The addition of (*S*)-4-isopropyl-*N*-propanoyl-1,3-thiazolidine-2-thione (**4f**) to a wide set of acetals was next evaluated by Javier Fernández-Valparís.[53] We were pleased to observe that the experimental conditions optimized for $PhCH(OMe)_2$ proved to be suitable for aromatic acetals shown in Scheme 145. Indeed, *anti* diastereomers were isolated in moderate to good yields in diastereomeric ratios ranging from 60:40 to 73:27. The most diastereoselective addition (73:27) involved (*p*-MeO)$PhCH(OMe)_2$, whereas $PhCH(OMe)_2$ and (*m*-MeO)$PhCH(OMe)_2$ furnished the lowest diastereomeric ratios (60:40).



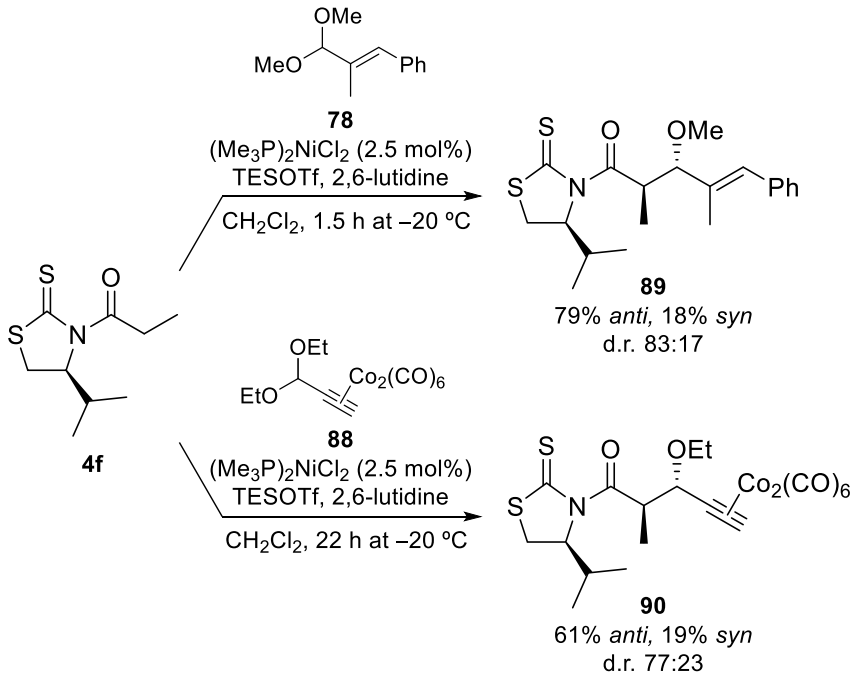
Scheme 145

The results of parallel additions to cyclic aromatic acetals **79** and **80** were rather different. Acetal **79** afforded *anti* adduct in 45% yield but a very poor diastereomeric ratio (55:45), whereas acetal **80** gave a complex mixture.



Scheme 146

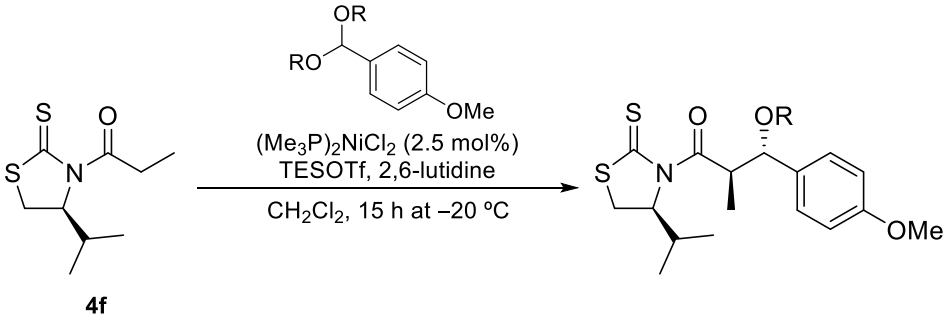
Otherwise, α,β–unsaturated acetal **78** and cobalted acetal **88** turned out to be the best substrates and afforded the corresponding pure *anti* adducts in yields up to 79% and diastereoselectivities higher than 77:23 (Scheme 147).



Scheme 147

Javier Fernández-Valparís also demonstrated that the method can also be applied to other *p*-anisaldehyde acetals (Table 23).[53] While the dibenzyl acetal showed the same stereoselectivity than the dimethyl acetal (compare entries 1 and 2 in Table 23), the diallyl acetal afforded a slightly higher one (78:22). In both cases the yields were excellent. Noteworthy, adducts **91** and **92** are highly valuable because they are protected

anti aldols that are generally difficult to obtain. Therefore, the Ni(II) catalytic method becomes an alternative to obtain adequately protected *anti* aldols.



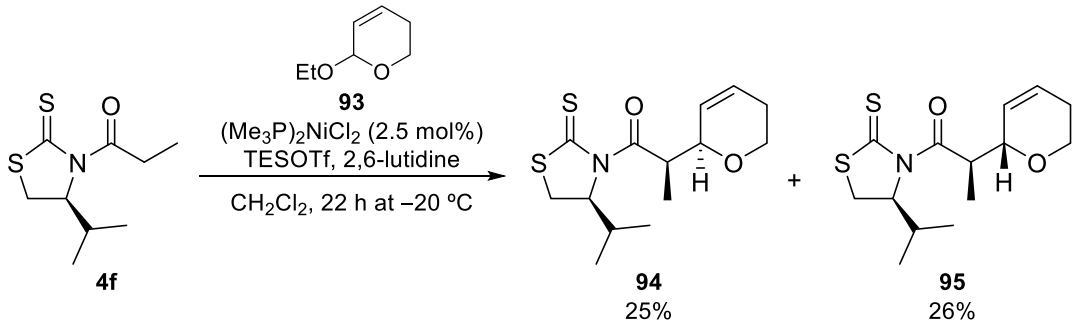
4f

Entry	R	Adduct	d.r.[a]	*Anti* (%)[b]	*Syn* (%)[b]
1	Me	**86**	73:27	72	21
2	Bn	**91**	73:27	87[c]	
3	$CH_2CH{=}CH_2$	**92**	78:22	67	22

[a] Established by ^{1}H NMR analysis of the crude product.
[b] Isolated yield after column chromatography.
[c] Isolated yield of the inseparable diastereomeric mixture after column chromatography.

Table 23

Finally, we examined the addition to pseudoglycal **93** (Scheme 148). Despite the lack of diastereocontrol and the moderate overall yield, the regioselectivity was excellent. Therefore, the resemblance between this reaction and *C*-glycosidation processes that occur *via* S_N1-like additions to glycals opens a new way to a future *C*-glycosidation reaction of *N*-propanoyl thiazolidinethiones with pseudoglycals.



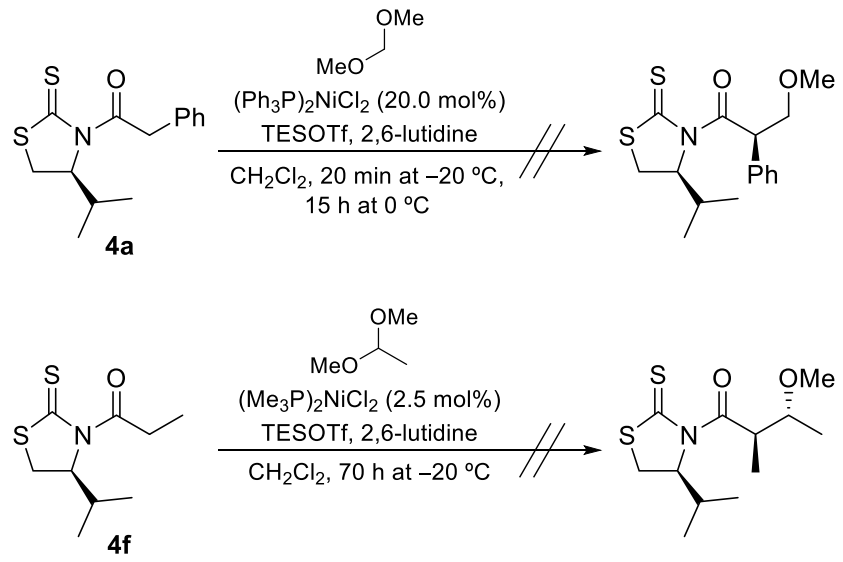
4f

94
25%

95
26%

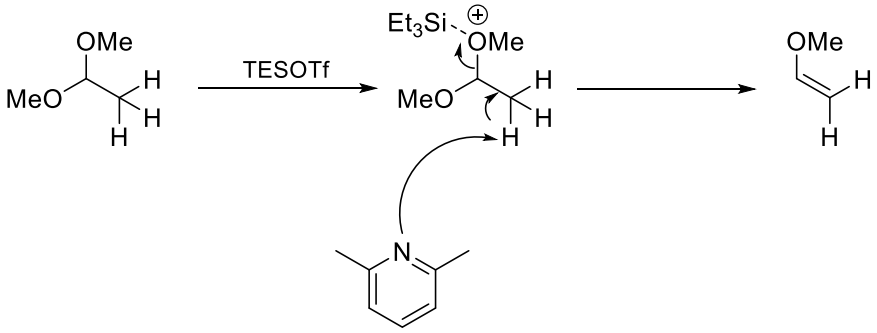
Scheme 148

Reaction with more reluctant acetals were also examined. Thus, two different reactions of formaldehyde and acetaldehyde dimethyl acetal with thioimides **4a** and **4f**, respectively, showed that the Ni(II) catalyzed rmethod is not suitable for aliphatic acetals.



Scheme 149

The failure of the acetaldehyde dimethyl acetal might be due to an α proton abstraction by action of 2,6-lutidine, which would produce a non–reactive enol ether (Scheme 150). A similar explanation was presented in Scheme 56 for the failure of trimethyl orthoacetate to react with nickel(II) enolates from **4**.



Scheme 150

This hypothesis is supported by the formation of 1-methoxy-2-methylpropene when isobutyraldehyde dimethyl acetal was treated with TESOTf and lutidine. The corresponding ^{1}H NMR spectrum is shown in Figure 13.

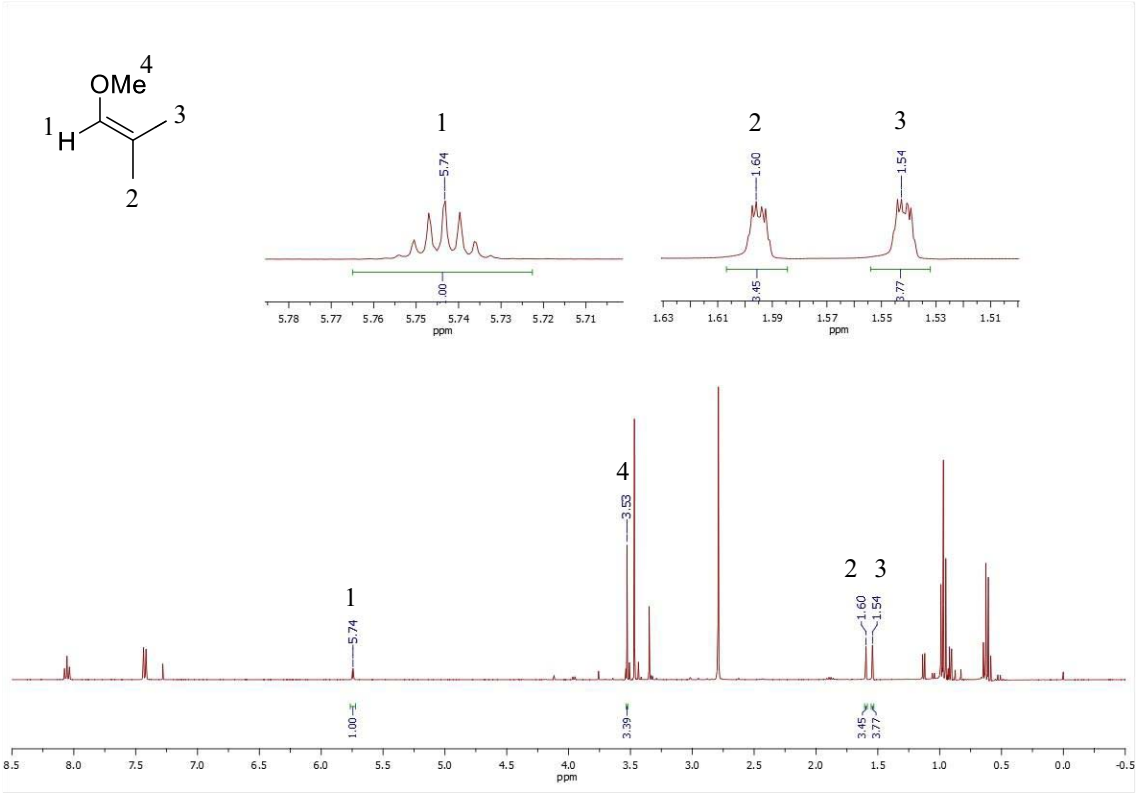
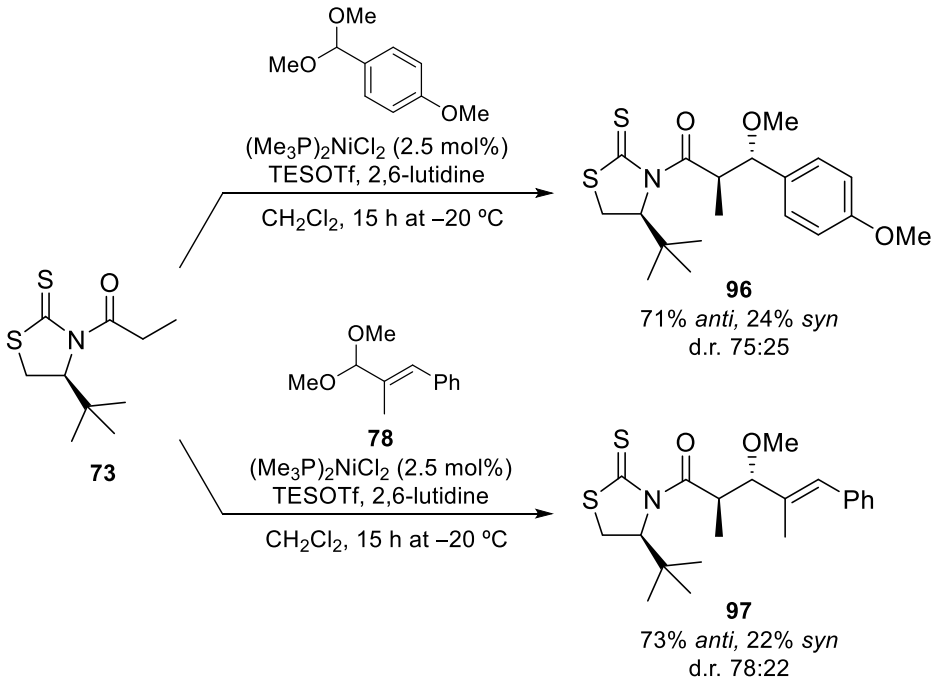


Figure 13

Therefore, acetals from aliphatic aldehydes with α protons are not suitable substrates for the reaction examined in this Chapter.

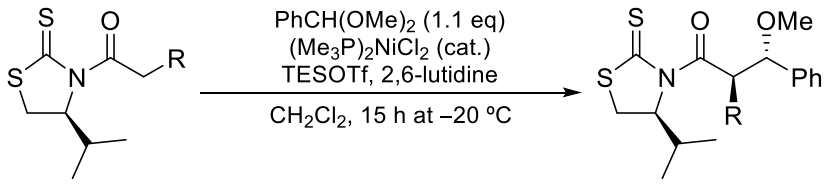
3.3. Other reactions with *N*-acylthiazolidinethiones

Aiming to improve the diastereoselectivity of such additions, (*S*)-4-(*tert*-butyl)-*N*-propanoyl-1,3-thiazolidine-2-thione (**73**) was used instead of thioimide **4f** with α,β–unsaturated acetal **78** and (*p*-MeO)PhCH(OMe)$_2$ (Scheme 151). Unexpectedly, the diastereoselectivities with (*p*-MeO)PhCH(OMe)$_2$ were quite similar to that with **4f**, whereas the addition to **78** resulted in a lower stereocontrol. It brought us to definitely rule out the use of this bulkier chiral auxiliary.



Scheme 151

Finally, the scope of different (*S*)-*N*-acyl-4-isopropyl-1,3-thiazolidine-2-thiones was analyzed using benzaldehyde dimethyl acetal. The results summarized in Table 24 proved the feasibility of the additions of such thioimides containing bulkier groups or other functional groups in the acyl chain. Indeed, thioimides **4i** and **4k** afforded good yields and similar diastereoselectivities (64:36, compare entries 2 and 3 in Table 24), whereas the glycolyl derivative **4m** gave *anti* adduct in 35% yield and a diastereomeric ratio surprisingly high (75:25) (entry 4 in Table 24). This result appeared to us as a blessing in disguise, since the possible use of acetals that already afforded better diastereomeric ratio could improve much more with the application to these glycolyl derivatives. These further studies will be thoroughly discussed in the next chapter.



4

Entry	**4**	R	Cat. (mol%)	Adduct	d.r.[a]	*Anti* (%)[b]	*Syn* (%)[b]
1	**f**	Me	2.5	**69**	60:40	48	31
2	**i**	*i*-Pr	5	**98**	64:36	53	28
3	**k**	$(CH_2)_2CO_2Me$	5	**99**	64:36	64	36
4	**m**	OPiv	20	**100**	75:25	35	11

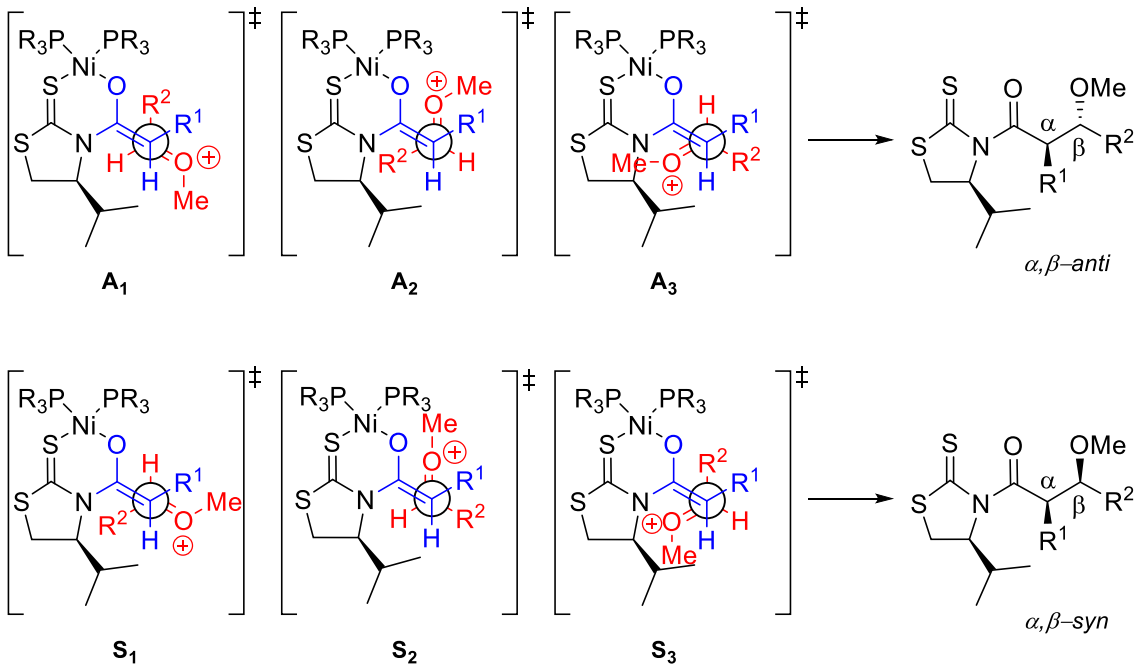
[a] Established by ^{1}H NMR analysis of the crude product.

[b] Isolated yield after column chromatography.

Table 24

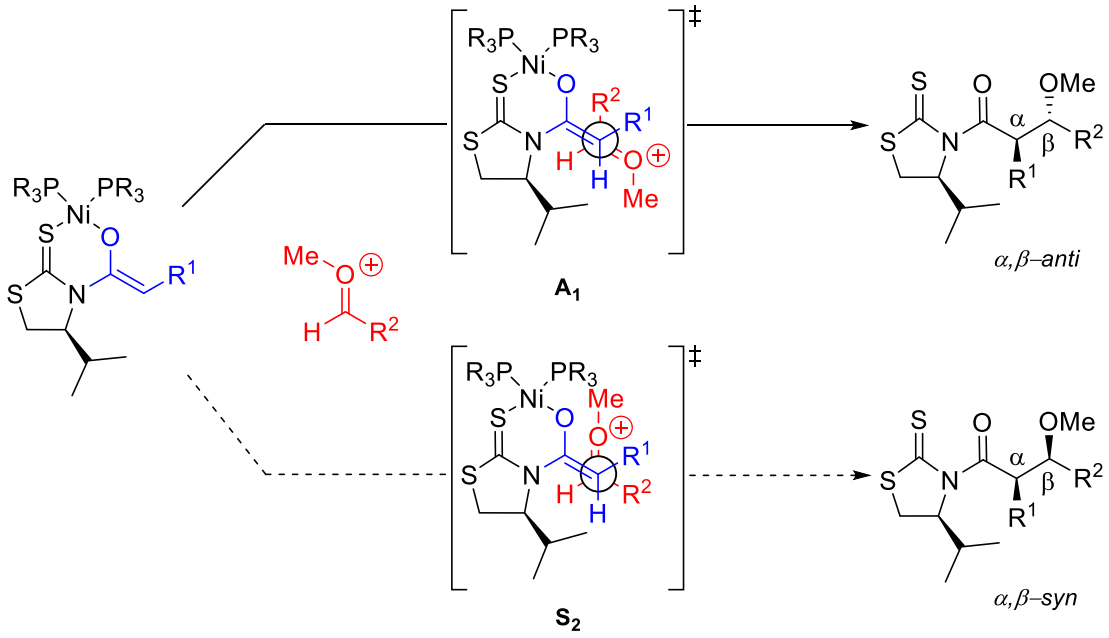
4. MECHANISTIC HYPOTHESIS

As discussed in former Chapters, the reaction with acetals must also proceed through a chelated *Z*-enolate bound to a distorsioned square-planar Ni(II) complex. The geometry of this enolate and the steric hindrance of the *Re* face of the putative nickel(II) enolate accounts for the total control of the α stereocenter. Thus, the partial control on the configuration at β center can be rationalized by a thorough analysis of the transition state. Taking advantage of our previous experience on additions of titanium enolates of chiral *N*-acyl thiazolidinethiones to oxonium ions,[32,33] an open transition state in which the oxonium ion approaches to the less hindered face (*Si* face) of the Ni(II) enolate could explain the stereochemical outcome. Assuming that the enolate adds to an oxonium cation, such a nucleophilic attack can affect both π–faces of the oxocarbenium intermediate, which involve up to six different transition states with a staggered conformation (Scheme 152). Three of them (A_1, A_2, A_3) produce the *anti* diastereomer, while the other three (S_1, S_2, S_3) lead to the *syn* one.



Scheme 152

The **A₂**, **A₃**, **S₁** and **S₃** transition states bring close the most bulky substituents (either R^2 or the methoxy group) to the thiazolidinethione scaffold. Therefore, they must be less stable than the two remaining transition states, **A₁** and **S₂**. These two display a *gauche* interaction between the enolate substituent R^1 and the oxonium ion substituent R^2, the only difference between them being the disposition of the C=O bond. This difference is crucial, because it allows the antiperiplanar transition state **A₁** to reduce the steric repulsions and, more importantly, to minimize the dipolar interactions between the oxonium ion and the C–O bond of the enolate. Such a disposition stabilizes the transition state **A₁** and, consequently, the *anti* diastereomer is finally favored.



Scheme 153

Another issue that attracted our attention was the diastereoselectivity provided by the acetals. The best result corresponds to the α,β-unsaturated acetal **78**, which afforded a 83:17 diastereomeric ratio. In turn, the simple benzaldehyde dimethyl acetal gives a poor 60:40. Besides these two examples, the diastereoselectivity seems to be directly correlated with the stability of the oxonium ion. Indeed, the presence of π donor substituents on the aromatic ring (such as methoxy groups) or π conjugated systems that facilitate the delocalization of the positive charge of the oxonium ion enhances the stability of the carbocation and, subsequently, the diastereoselectivity is increased as depicted in Figure 14.

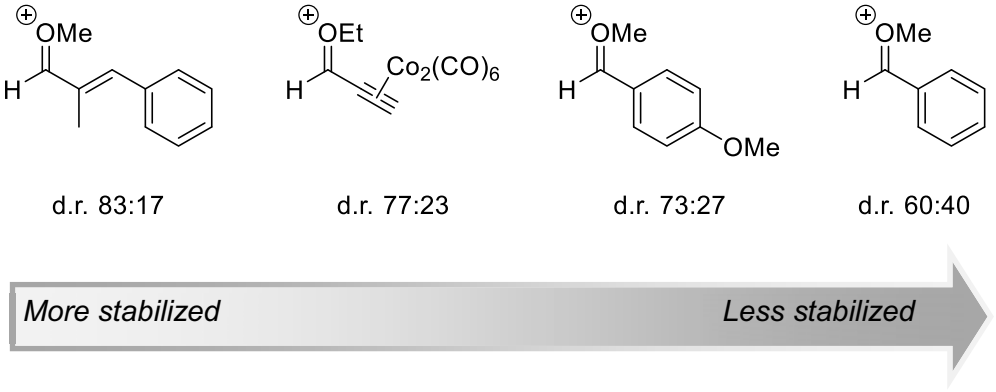
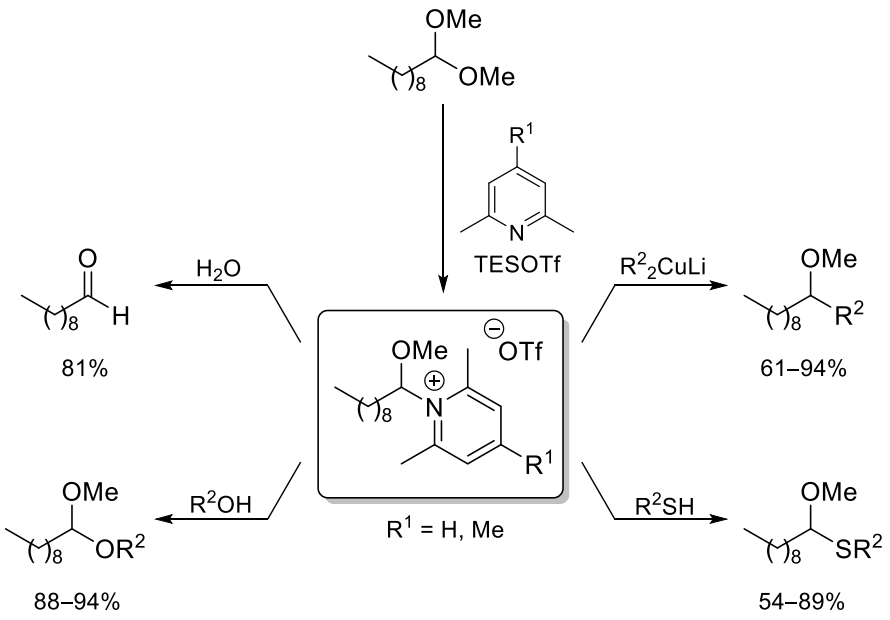


Figure 14

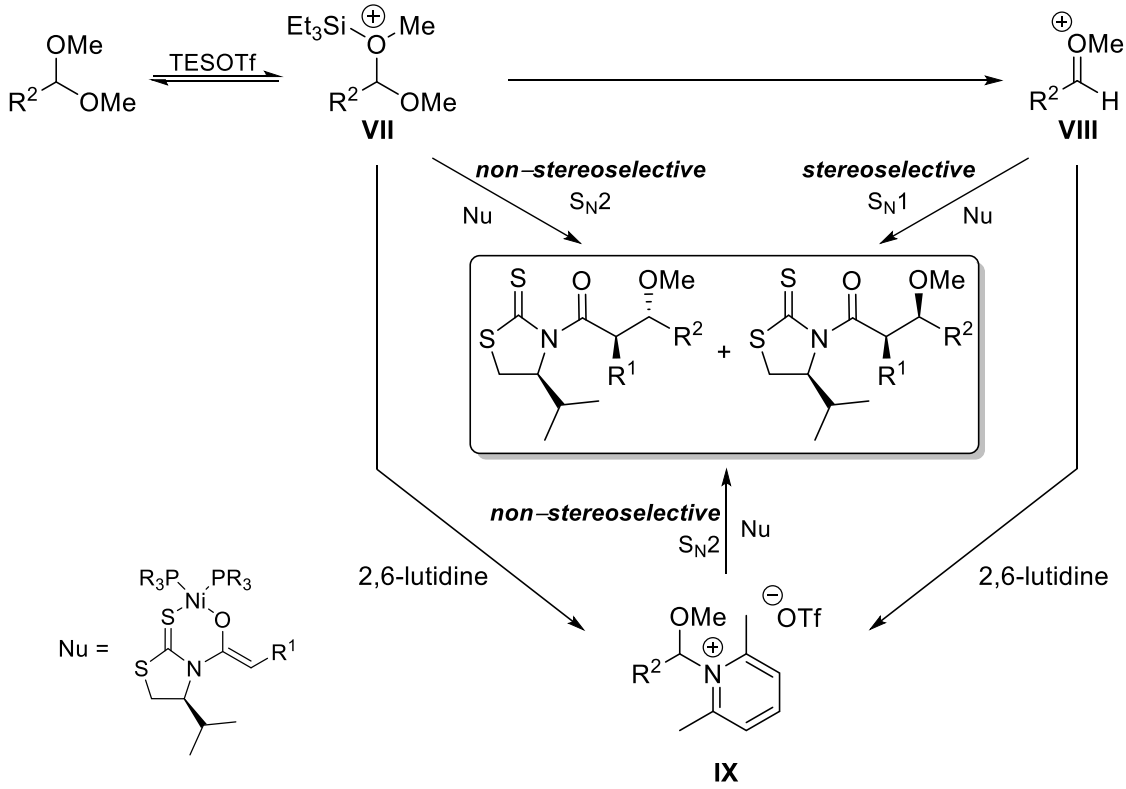
Despite the inherent difficulty for an enolate to differentiate both faces of planar oxocarbenium ions, the moderate diastereoselectivities achieved in most cases hints for alternative mechanisms. Indeed, parallel S_N2 processes might compete the main S_N1-like reaction, and reduce the control on the configuration of the β stereocenter.

The acetal reactivity reported by Fujioka and Kita might be the clue for such puzzling issues.[143] Apparently, the addition of TESOTf and a hindered aromatic base such 2,6-lutidine or 2,4,6-collidine to a dimethyl acetal produces a stable cationic intermediate, shown in Scheme 154, that can even be isolated and characterized.[144] Furthermore, it can be attacked by different nucleophiles to yield aldehydes, ethers, heteroacetals and *O,S*-acetals.[145–147]



Scheme 154

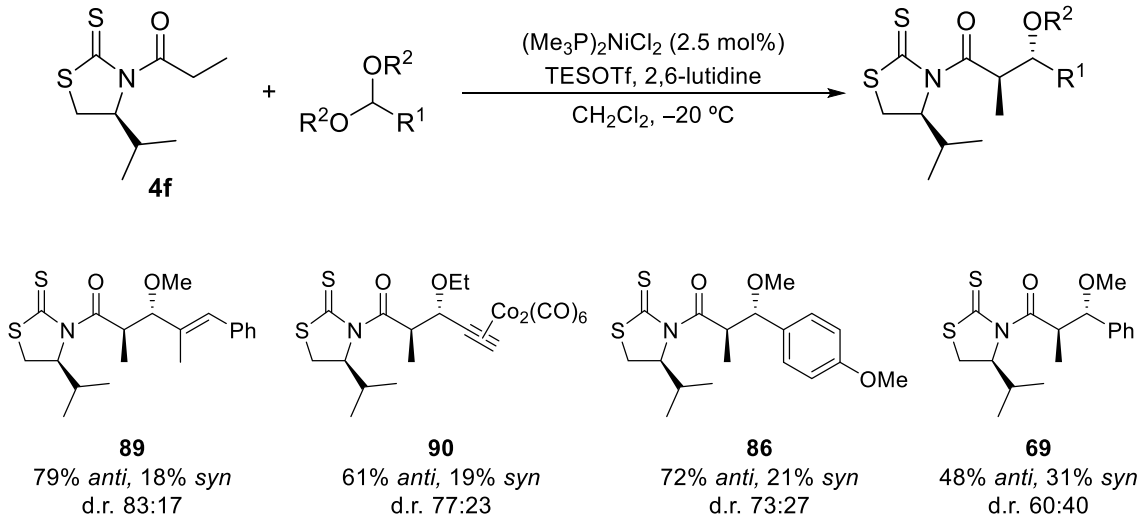
The reaction conditions in which Ni(II)-catalyzed reactions are carried out are a suitable scenario for the formation of such a cationic intermediate. These lutidinium salts could be especially formed if the Lewis acid is too weak to activate the acetal satisfactorily and the Ni(II)-catalyzed reaction lasts a long time. Then, the formation of such cationic intermediates (**IX**) is likely to occur by attack of 2,6-lutidine to either intermediates **VII** or **VIII** represented in Scheme 155. Addition of the enolate to intermediate **IX** by a S_N2-like pathway could afford the desired product with no stereocontrol over the β position. Alternatively, since the acetal is quite difficult to be activated, the Ni(II) enolate might also attack the intermediate **VII** also by means of a S_N2-like nucleophilic attack. The competence between these non-stereoselective processes and the desired stereoselective pathway would depend directly on the stability of the oxonium ion and, therefore, on the ease of its activation. A reaction with all these conditions would account for the low diastereoselectivity for the less stabilized oxonium ions.



Scheme 155

5. SUMMARY AND CONCLUSIONS

A new stereoselective reaction of catalytically generated Ni(II) enolates of chiral *N*-acyl-4-isopropyl-1,3-thiazolidine-2-thiones with acetals has been developed in this Chapter. The scope encompasses those acetals without hydrogens at α position, such as aromatic and α,β–unsaturated acetals. In this reaction, a new C–C bond and two new stereogenic centers are formed. The configuration of the α stereocenter is totally controlled, but that of the β position ranges from moderate (d.r. 60:40) to good diastereoselectivities (d.r. 83:17). The stereocontrol turned out to be closely related to the ease of activation of the acetal and the stability of the corresponding oxonium ion. Finally, it is worth recalling that steric effects can also play an important role in the stereochemical outcome of such reactions.



Scheme 156

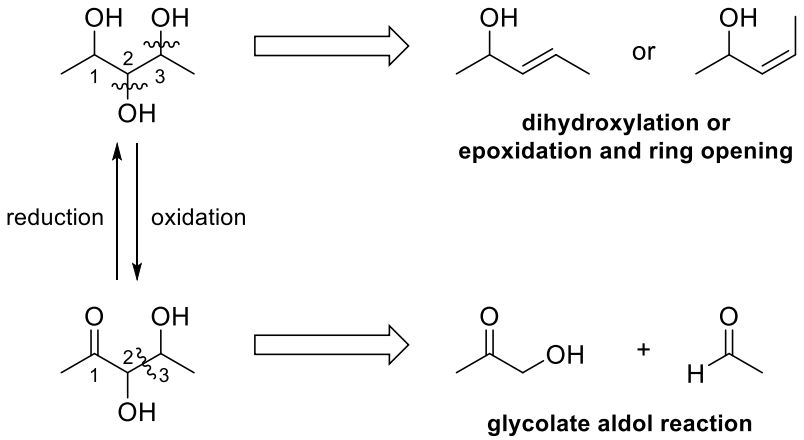
CHAPTER 4

STEREOSELECTIVE Ni(II) CATALYZED REACTIONS OF *N*-GLYCOLYL THIAZOLIDINETHIONES WITH ACETALS

1. INTRODUCTION

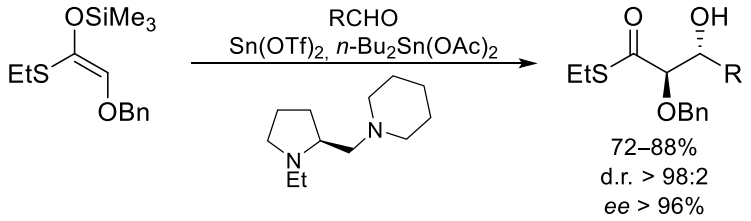
Polyoxygenated arrays are structural motifs common to a variety of natural products. Therefore, their stereoselective preparation has attracted much attention in recent decades. Particularly, the synthesis of 1,2,3-polyols and 2,3-carbonylic derivatives, which can be classified as 1,2,3-trioxygenated structures, has become an important target for the development of new synthetic methods.

Asymmetric catalytic dihydroxylation and epoxidation, followed by ring opening, of allylic alcohols represent some of the most successful approaches towards these substructures.[148–159] In turn, the stereoselective aldol reaction of an α-hydroxycarbonylic substrate with an aldehyde, named "*glycolate* aldol reaction", is an appealing alternative for the preparation of these polyoxygenated systems in which two new stereocenters are generated.[160,161]



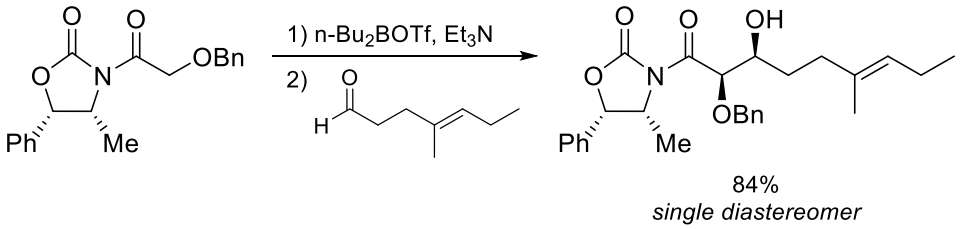
Scheme 157

Following the latter approach, Mukaiyama established that ketene thioacetals depicted in Scheme 158 reacted with aldehydes in the presence of a Lewis acid and a chiral ligand to produce the *anti* aldol products with high yields and stereoselectivities.[162]



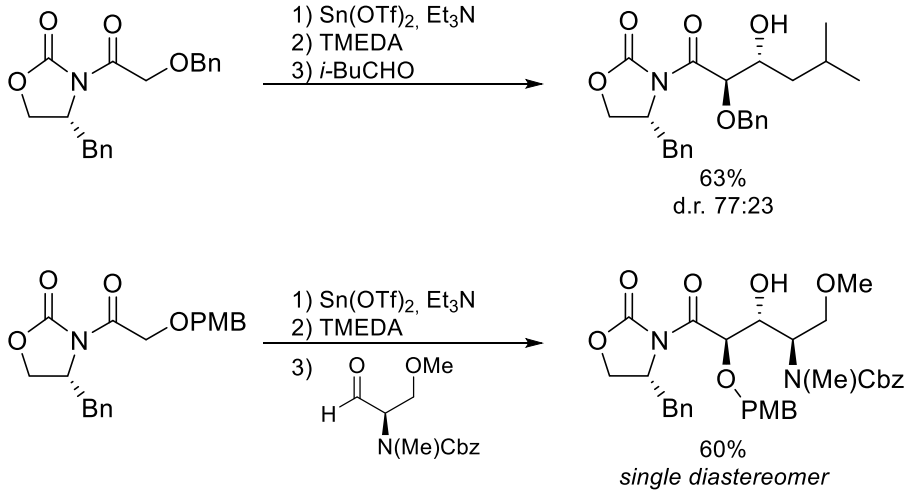
Scheme 158

Other highly stereoselective glycolate aldol reactions took advantage of chiral auxiliaries as the source of chirality. Indeed, the boron-mediated aldol reaction of chiral *N*-acylimides reported by Evans in 1981 has been one of the most successful and cited methods to obtain *syn* aldol adducts.[163] The glycolate aldol version was early exploited in the total synthesis of the polyether antibiotic X-206.[164]



Scheme 159

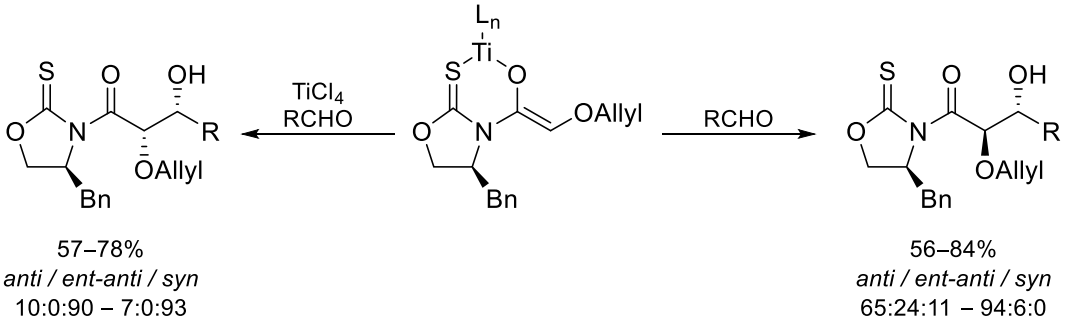
While *syn* glycolate adducts were available by using this excellent procedure, the *anti* counterparts have proved to be more reluctant. In this context, Evans, during the total synthesis of calyculin A, also reported that the aldol addition of tin enolates of a chiral α-hydroxyamide in the presence of TMEDA[165] produced the corresponding *anti* adducts in high to excellent diastereoselectivities.[166]



Scheme 160

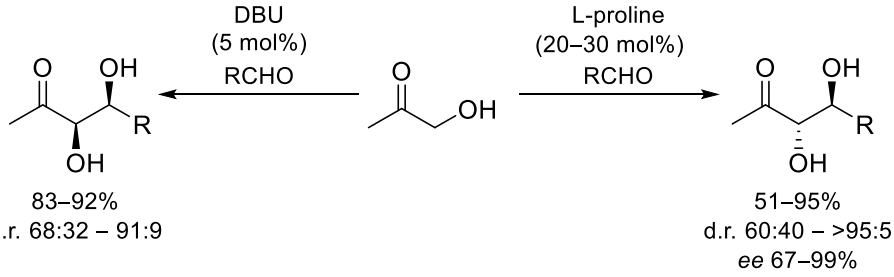
More recently, Crimmins has developed a general method based on the glycolate aldol reaction of titanium(IV) enolates of *N*-allyloxyacetyl-1,3-oxazolidine-2-thiones.[167]

As shown in Scheme 161, either *syn* or *anti* aldol products can be obtained, depending on the number of equivalents of Lewis acid ($TiCl_4$).



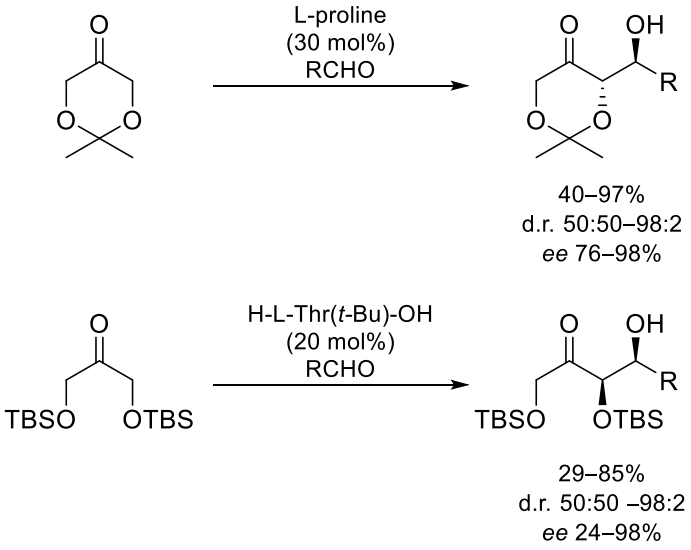
Scheme 161

Regarding the preparation of these polyoxygenated compounds by reaction of enolates or enamines prepared under catalytic premises, organocatalysis is at the forefront. Indeed, aldol additions of α-hydroxyacetone to aldehydes catalyzed by L-proline afford *anti*–α,β–hydroxyketones in good to excellent stereocontrol.[9] In turn, Mahrwald has also reported that these reactions can be promoted by DBU to yield the corresponding *syn* diastereomers.[168]



Scheme 162

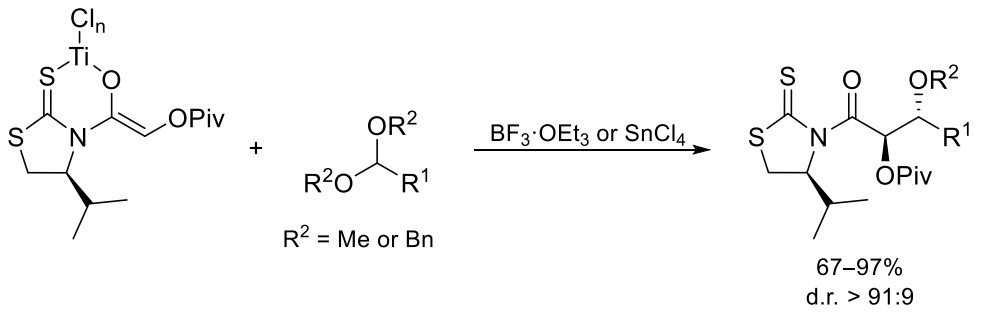
Apart from these methods, a variety of organocatalytic procedures have been published to provide higher stereoselectivities and to widen their applicability.[11,169,170] Interestingly, the introduction of dihydroxyacetone facilitated the asymmetric synthesis of a broad range of carbohydrates.[160,161] While the use of L-proline permits to obtain an *anti* disposition,[171] other catalysts such as threonine derivatives produce the *syn* counterparts (Scheme 163).[172]



Scheme 163

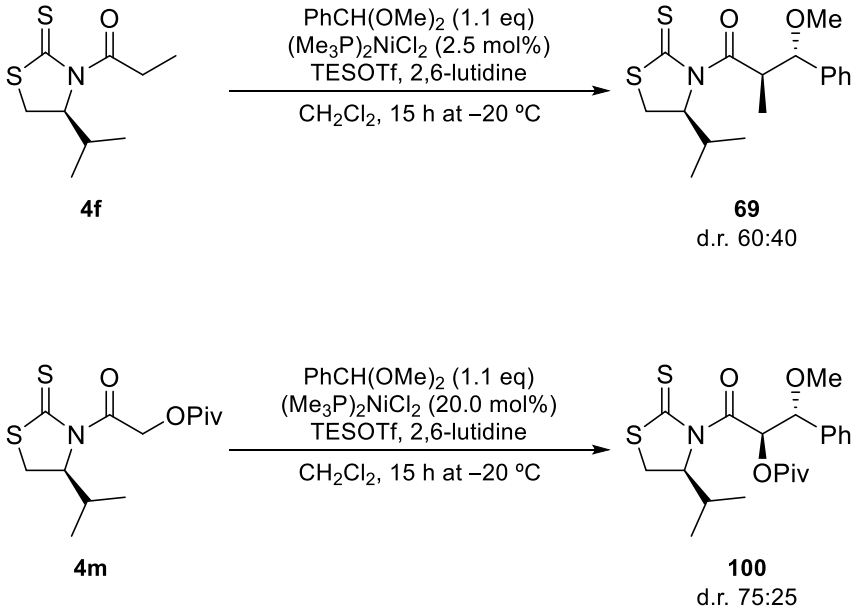
In spite of these accomplishments, there is a lack of methods for the synthesis of related β-alkoxy-α-hydroxycarboxylic moieties. These systems are usually prepared in a two-step process that involves the corresponding aldol reaction followed by an alkylation reaction. However, this second step is often troublesome due to possible epimerization of the α stereocenter and degradation processes.[173,174]

In this context, our research group recently disclosed a new method based on the stereoselective Lewis-acid mediated addition of titanium(IV) enolates from chiral *O*-protected *N*-glycolyl-1,3-thiazolidine-2-thiones to acetals to produce the enantiomerically pure β-alkoxy-α-hydroxycarboxylic adducts in a single step in high yields and excellent diastereoselectivities.[31i,33].



Scheme 164

Therefore, this was an obvious reaction to challenge the direct Ni(II) catalyzed method developed in this Thesis. As described in Chapter 3 (see Table 24), the catalytic reaction of benzaldehyde dimethyl acetal with *N*-pivaloyloxyacetyl thioimide **4m** afforded the corresponding adduct with a better stereocontrol than with *N*-propanoyl counterpart **4f** (75:25 versus 60:40, see Scheme 165), which suggested that oxygenated enolates might afford much higher diastereoselectivities.

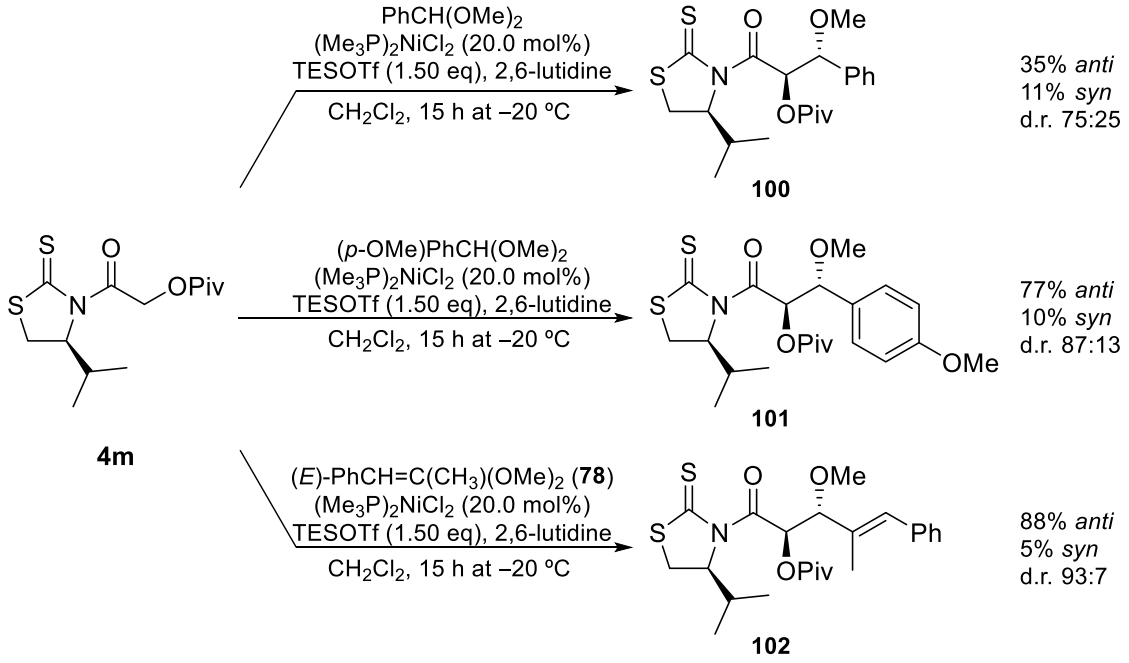


Scheme 165

Thus, the present Chapter will deal with the addition of *N*-glycolyl thiazolidinethiones to acetals in a glycolate aldol-like reaction catalyzed by nickel(II) complexes.

2. PRELIMINARY EXPERIMENTS

To explore the feasibility of such nickel(II)-mediated reactions, the addition of (*S*)-4-isopropyl-*N*-pivaloyloxyacetyl-1,3-thiazolidine-2-thione (**4m**) to a few acetals were tested using a 20 mol% of $(Me_3P)_2NiCl_2$ (Scheme 166). To our pleasure, *anti* adducts **101** and **102** were isolated in excellent yields and diastereomeric ratios. These results indicated that such an addition might become an straightforward entry to the stereoselective synthesis of diprotected *anti*–α,β–dihydroxy moieties. Thus, a comprehensive analysis was launched.

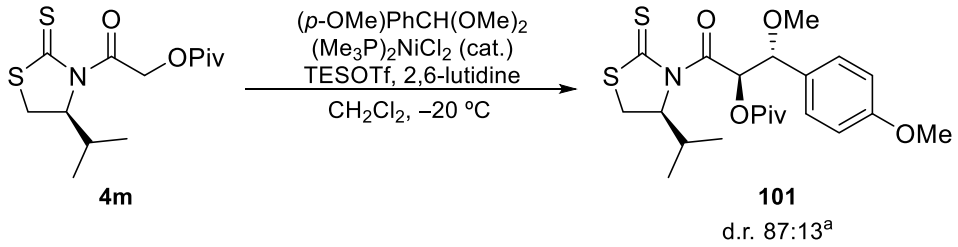


Scheme 166

3. REACTIONS WITH *p*-ANISALDEHYDE AND (*E*)-α-METHYLCINNAMALDEHYDE DIMETHYL ACETALS

3.1. Influence of the catalyst loading

Initially, we chose *p*-anisaldehyde dimethyl acetal as the model substrate to optimize the reaction conditions with *N*-pivaloyloxyacetylthiazolidinethione **4m**. Our main objective was to reduce the amount of $(Me_3P)_2NiCl_2$. As Table 25 shows, 2.5 mol% of catalyst afforded similar results to those of 20 mol%, as long as we took reaction times of 15 h. Although longer reaction times afforded a little improvement, we considered that this was negligible (compare entries 2 and 3 in Table 25).

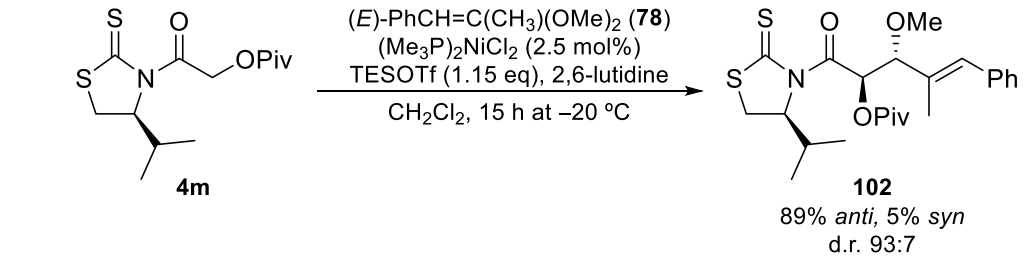


Entry	$(Me_3P)_2NiCl_2$ (mol%)	TESOTf (eq)	t (h)	*Anti* (%)[b]	*Syn* (%)[b]
1	20	1.50	15	77	10
2	2.5	1.15	90	81	10
3	2.5	1.15	15	77	10
4	2.5	1.15	4	71	10
5	2.5	1.15	1.5	57	8

[a] Established by HPLC analysis of the crude product
[b] Isolated yield after column chromatography.

Table 25

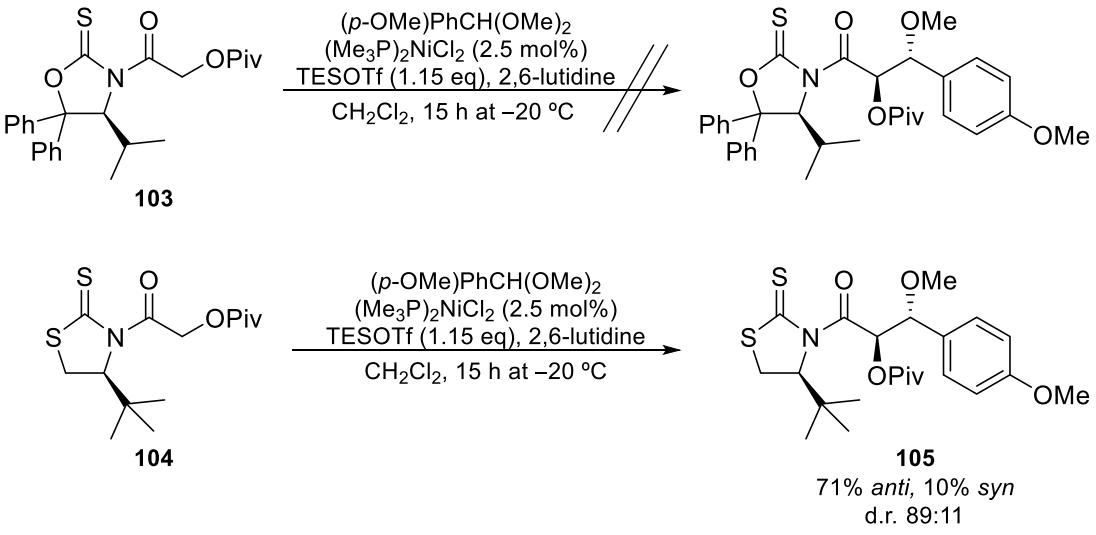
Such optimized conditions were next applied to the α,β–unsaturated acetal **78** (Scheme 167). The yield as well as the diastereoselectivity were again excellent, which proved that the addition proceeds smoothly provided that the corresponding oxonium ion is stable.



Scheme 167

3.2. Influence of the chiral auxiliary

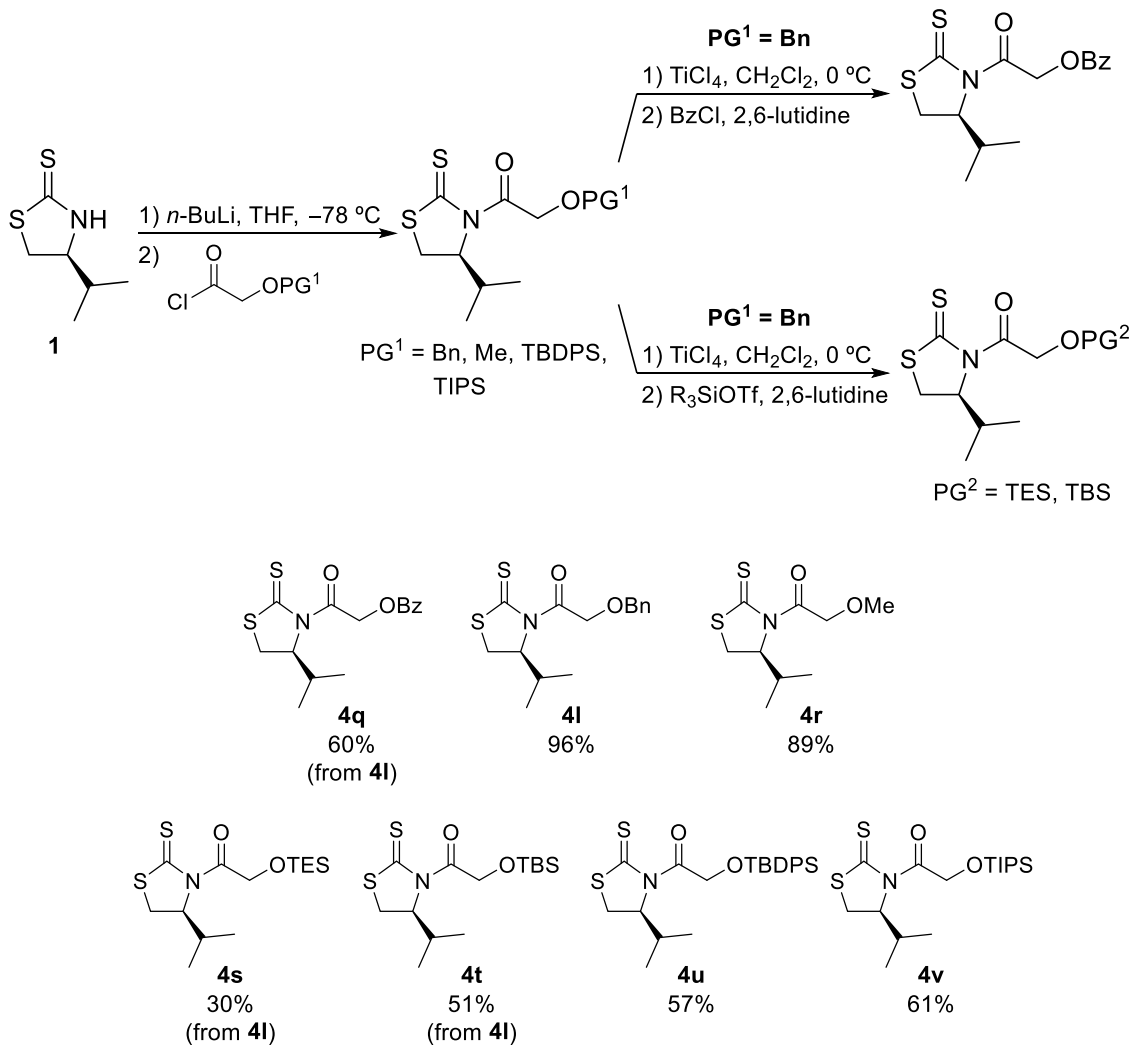
Having found the most appropriate catalyst loading and reaction time, the chiral auxiliary was next evaluated. Unfortunately, the Ni(II) catalyzed reaction using the oxazolidinethione-based substrate **103** afforded a complex mixture. In turn, 4-(*tert*-butyl)thiazolidinethione **104** produced adduct **105** in a slightly better diastereomeric ratio (89:11 vs 87:13) but in lower yields. Thus, none of these chiral auxiliaries led to a real improvement and 4-isopropylthiazolidinethiones remained as the most appropriate platform.



Scheme 168

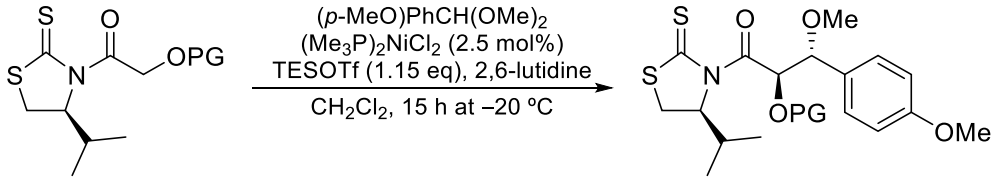
3.3. Influence of the hydroxyl protecting group

The influence of the protecting group over the hydroxyl group was also assessed. Three different types of *O*-protected (*S*)-*N*-glycolyl-4-isopropyl-1,3-thiazolidine-2-thiones were prepared. Thus, apart from the *O*-pivaloyl substrate **4m** described in Chapter 1, another thioimide with an ester-based protecting group, the *O*-benzoyl thioimide **4q,** as well as two other thioimides with ether groups (**4l** and **4r**) and other three substrates with silyl protecting groups (**4s**, **4t**, **4u**, and **4v**) in the glycolyl chain were prepared (Scheme 169). Most of these glycolic substrates were easily prepared by simple acylation of the chiral auxiliary, but three of them (PG = Bz (**4q**), TES (**4s**) and TBS (**4t**)) needed for a deprotection–protection sequence from *N*-benzyloxyacetyl thiazolidinethione **4l**.



Scheme 169

All these substrates were tested under the aforementioned optimized conditions. Either pivaloyl or benzoyl groups afforded high yields, but the second one produced a lower diastereoselectivity (entries 1 and 2 in Table 26). As for ether groups, the diastereoselectivity was quite similar to the initial one, but only the benzyl group permitted to obtain the *anti* diastereomer in a good yield (entries 3 and 4 in Table 26). In turn, silyl protecting groups gave complex mixtures (entries 6 and 7 in Table 26), except for *tert*-butyldiphenylsilyl (TBDPS) and triethylsilyl (TES) groups, which unfortunately afforded low yields (entries 5 and 8 in Table 26).

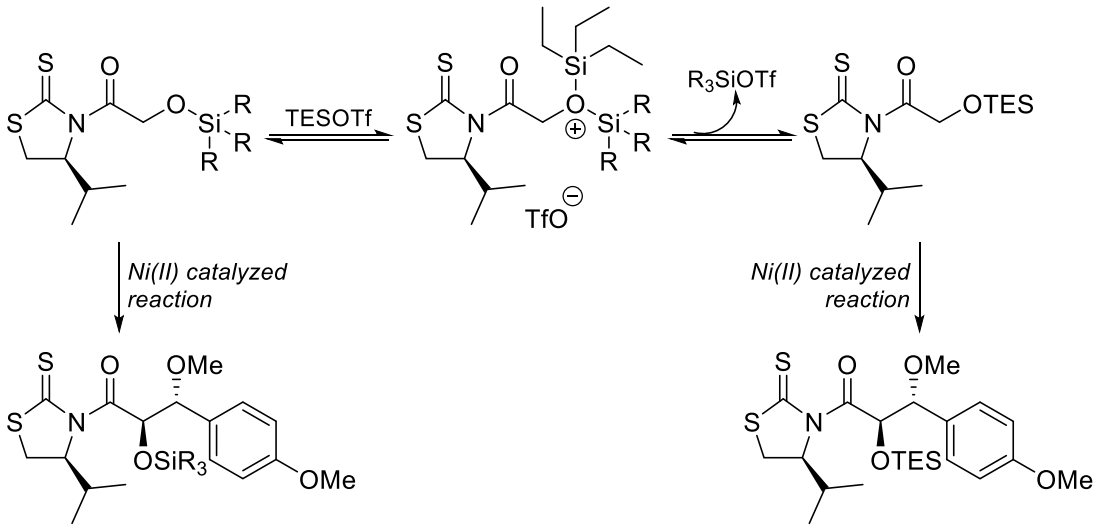


Entry	4	PG	d.r.	Adduct	*Anti* (%)[c]	*Syn* (%)[c]
1	**m**	Piv	87:13[a]	**101**	77	10
2	**q**	Bz	83:17[b]	**106**	80	17
3	**r**	Me	89:11[a]	**107**	36	5
4	**l**	Bn	88:12[a]	**108**	69	11
5	**u**	TBDPS	75:25[b]	**109**	19	6
6	**v**	TIPS	–	**–**	Complex mixture	
7	**t**	TBS	–	**–**	Complex mixture	
8	**s**	TES	90:10[b]	**110**	26	–

[a] Established by HPLC analysis of the crude product
[b] Established by ^{1}H NMR analysis of the crude product
[c] Isolated yield after column chromatography.

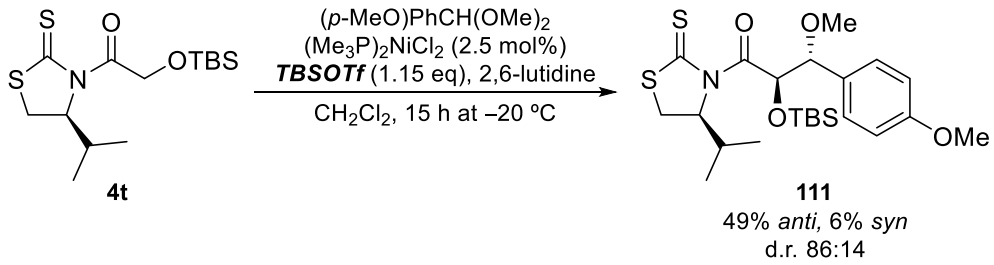
Table 26

Despite the complex mixtures obtained with TBS and TIPS protecting groups (**4t** and **4v**, respectively), we were able to identify the formation of the product with a TES group (**110**). Since some silyl ethers can undergo a transilylation process by TMSOTf,[175] we speculated that a similar process might occur for **4t** and **4v**, as represented in Scheme 170.



Scheme 170

For TBS-derived substrate **4t**, such a drawback was overcome by using TBSOTf, which avoided an overall change in the protecting group. Indeed, a reaction with thioimide **4t** afforded adduct **111** in a high diastereomeric ratio (86:14) and a moderate yield (see Scheme 171).

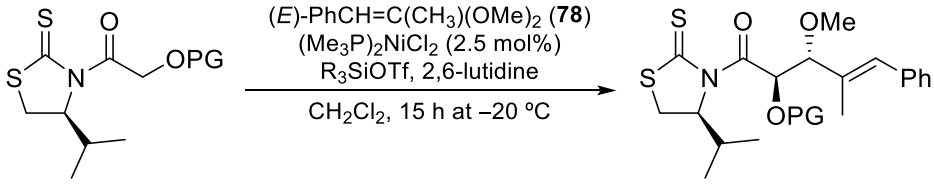


4t

111
49% *anti,* 6% *syn*
d.r. 86:14

Scheme 171

Since the Ni(II)-catalyzed reaction of *N*-glycolylthiazolidinethiones with acetals succeeded with a variety of *O*-protecting groups, either esters (Piv), ethers (Bn) or silyl ethers (TBS), we explored parallel additions to (*E*)-α-methylcinnamaldehyde dimethyl acetal (**78**). The results, summarized in Table 27, demonstrated that neither benzyl nor *tert*-butyldimethylsilyl groups were suitable due to the production of complex mixtures. Therefore, pivaloyl group turned out to be the most appropiate protecting group.



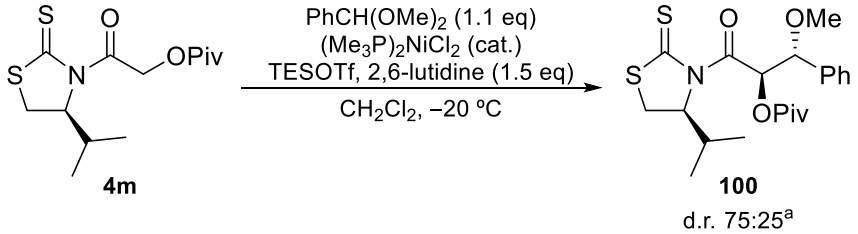
Entry	**4**	PG	R_3SiOTf	d.r.[a]	Adduct	*Anti* (%)[b]	*Syn* (%)[b]
1	**m**	Piv	TESOTf	93:7	**102**	89	5
2	**l**	Bn	TESOTf	–	–	Complex mixture	
3	**t**	TBS	TBSOTf	–	–	Complex mixture	

[a] Established by HPLC analysis of the crude product.
[b] Isolated yield after column chromatography.

Table 27

4. REACTIONS WITH BENZALDEHYDE DIMETHYL ACETAL

Having established the most appropriate conditions for the additions to *p*-anisaldehyde and (*E*)-α-methylcinnamaldehyde dimethyl acetals, we turned our attention to the less active benzaldehyde dimethyl acetal. A brief analysis of the influence of the catalyst on the conversion showed that both 20 mol% and 10 mol% loadings afforded similar results (entries 1 and 2 in Table 28), but the yield dropped dramatically with 2.5 mol% (entry 3 in Table 28). Furthermore, longer reaction times with 20 mol% did not afford any substantial improvement (entries 4 and 5 in Table 28).

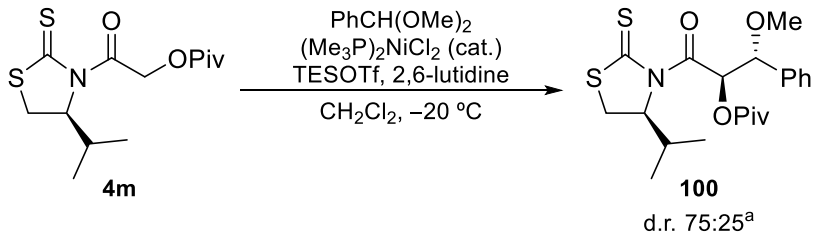


Entry	$(Me_3P)_2NiCl_2$ (mol%)	TESOTf (eq)	t (h)	Conversion (%)[a]
1	20	1.5	15	46
2	10	1.3	15	47
3	2.5	1.15	90	12
4	20	1.5	48	54
5	20	1.5	90	54

[a] Established by ^{1}H NMR analysis of the crude product.

Table 28

The moderate conversions achieved by using 10–20 mol% of $(Me_3P)_2NiCl_2$ led us to assess the influence of the stoichiometry of the reagents, that is, the acetal, TESOTf and 2,6-lutidine. The results are summarized in Table 29. A first attempt using a large excess of the three compounds (3.0 equivalents of each of them) with 2.5 mol% of $(Me_3P)_2NiCl_2$ gave a 28% conversion (entry 2 of Table 29), much better than that attained with the previous conditions (compare entries 1 and 2 in Table 29). This indicated that better results could be achieved with low catalyst loadings provided that a comprehensive analysis of the quantities of the reagents was carried out. Thus, the use of an excess of acetal or TESOTf (2.2 equivalents) showed conversions up to 38% (compare entries 3 and 4 in Table 29). However, excess of both reagents resulted in an important decrease of conversion (entry 5 in Table 29). Thus, considering that the Lewis acid was less important than the acetal, we fixed the quantities of 1.1 equivalents of acetal and 2.2 equivalents of TESOTf. With these reaction conditions in mind, longer reaction times were tried (70 h), which allowed to obtain a conversion of 48% (entry 6 in Table 29). Finally, the influence of the base was also assessed. It was observed that either decreasing or increasing the number of equivalents of 2,6-lutidine the yields were very low (entries 7 and 8 in Table 29). Fortunately, a conversion of 54% could be obtained when a catalyst loading of 5 mol% with the aforementioned excess of TESOTf were used (entry 9 in Table 29). Longer reaction times and a 10 mol% loading of catalyst did not increase the conversion value (compare entries 9–12 in Table 29).

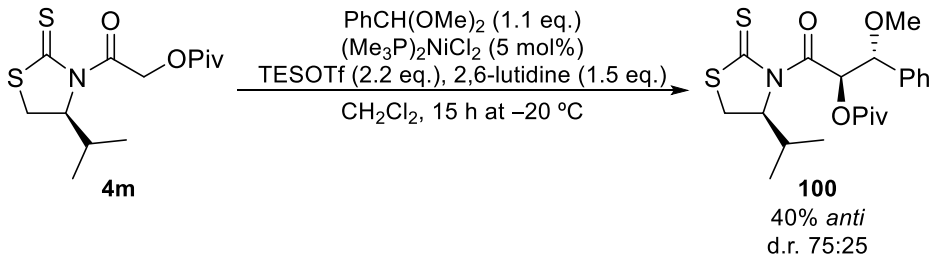


Entry	$(Me_3P)_2NiCl_2$ (mol%)	t (h)	Acetal (eq)	TESOTf (eq)	Base (eq)	Conv (%)[a]
1	2.5	90	1.1	1.15	1.5	12
2	2.5	15	3.0	3.0	3.0	28
3	2.5	15	2.2	1.15	1.5	35
4	2.5	15	1.1	2.2	1.5	38
5	2.5	15	2.2	2.2	1.5	5
6	2.5	70	1.1	2.2	1.5	48
7	2.5	15	1.1	2.2	1.1	8
8	2.5	15	1.1	2.2	3.0	8
9	5	15	1.1	2.2	1.5	54
10	5	70	1.1	2.2	1.5	51
11	10	15	1.1	2.2	1.5	45
12	10	90	1.1	2.2	1.5	50

[a] Established by ^{1}H NMR analysis of the crude product.

Table 29

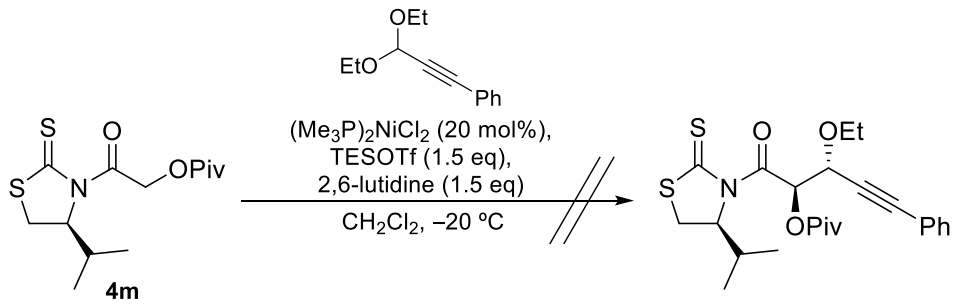
In conclusion, less reactive benzaldehyde dimethyl acetal required an excess of Lewis acid and a 5 mol% of the catalyst. Closely related with the kinetic aspects of Chapter 2 and 3, this requirement might be due to the difficult activation of the acetal. Finally, a reaction carried out using the conditions described in entry 9 in Table 29 permitted the isolation of the *anti* adduct in 40% yield (Scheme 172).



Scheme 172

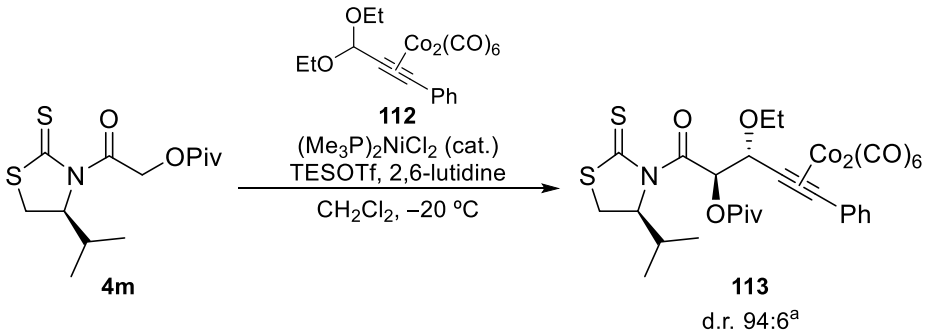
5. REACTIONS WITH PHENYLPROPARGYL DIETHYL ACETAL

Aiming to expand such a Ni(II) catalytic method to other acetals, we envisaged that propargylic acetals might be good candidates. Unfortunately, preliminary studies with 3-phenylpropynal diethyl acetal proved that the addition did not take place.



Scheme 173

Since this lack of reactivity could be due to the poor electrophilicity of the acetal, it was converted into the cobalt carbonyl derivative **112**. To our pleasure, the addition of thioimide **4m** to this new cobalted acetal **112** with a 5 mol% of $(Me_3P)_2NiCl_2$ afforded an outstanding diastereomeric ratio of 94:6 but in a low yield (36%) of the *anti* adduct. These results led us to perform a new optimization, as summarized in Table 30. First, it was observed that an increase of the catalyst loading and of the reaction time afforded worse results (compare entries 1 and 2 in Table 30). However, increasing the amount of reagents (acetal, TESOTf and 2,6-lutidine), either with 5 mol% or 20 mol% of catalyst, produced a dramatic improvement of the yield (compare entries 1–4 in Table 30), which brought us to attempt the previous optimized reaction conditions with an excess of TESOTf. The yield was not completely satisfactory (entry 5 in Table 30), but we uncovered that an increase of the quantity of acetal produced a significant improvement of the yield (entry 6 and 7 in Table 30). Considering that the most valuable component in a synthetic application of this reaction could be the acetal, we decided that experimental conditions of entry 6 in Table 30 may be the most appropriate to carry out the addition to acetal **112**.



Entry	$(Me_3P)_2NiCl_2$ (mol%)	t (h)	Acetal (eq)	TESOTf (eq)	Base (eq)	Yield (%)[b]
1	5.0	15	1.1	1.20	1.5	36
2	20.0	60	1.1	1.50	1.5	40
3	20.0	60	3.0	3.0	3.0	74
4	5.0	15	3.0	3.0	3.0	74
5	5.0	15	1.1	2.2	1.5	56
6	5.0	15	1.5	2.2	1.5	74
7	5.0	15	2.2	2.2	1.5	84

[a] Established by HPLC analysis of the crude product.
[b] Isolated yield of *anti* adduct after column chromatography.

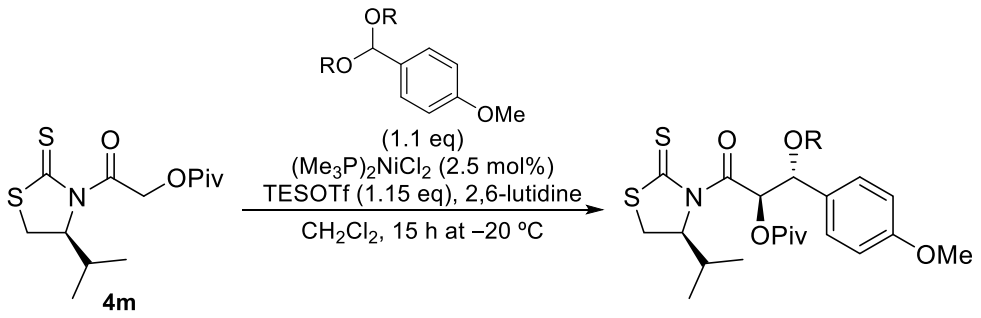
Table 30

All together, these results indicate that the glycolate addition to acetals can provide the corresponding *anti* adducts in good to high yields and diastereomeric ratios up to 94:6 by using 2.5–5 mol% of $(Me_3P)_2NiCl_2$, 1.1–1.5 equivalents of the acetal, 1.15–2.2 equivalents of TESOTf and 1.5 equivalents of 2,6-lutidine.

6. APPLICATION TO OTHER ACETALS

6.1. Reactions with different *p*-anisaldehyde acetals

The Ni(II) catalyzed reaction was first applied to diallyl and dibenzyl acetals from *p*-anisaldehyde using the conditions optimized for the corresponding dimethyl acetal. These reactions provided similar yields and diastereoselectivities than the parent dimethyl acetal (Table 31). Therefore, the Ni(II) catalytic method is useful to obtain adequately protected *anti* aldols, whose importance has been discussed in Chapter 3.



Entry	R	Adduct	d.r.[a]	Yield (%)[b]
1	Me	**101**	87:13	77
2	$-CH_2CH=CH_2$	**114**	84:16	73
3	Bn	**115**	83:17	69

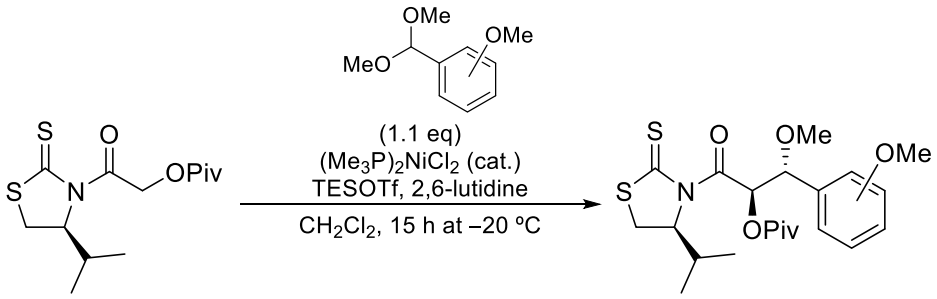
[a] Established by HPLC analysis of the crude product.
[b] Isolated yield of *anti* adduct after column chromatography.

Table 31

6.2. Reactions with aromatic dimethyl acetals

The scope of this Ni(II)-catalyzed reaction with other aromatic dimethyl acetals was also analyzed. First, the influence of the position of the methoxy group on the aromatic ring in different methoxybenzaldehyde dimethyl acetals was studied. Interestingly, the *meta* regioisomer did not react under the conditions established for *p*-$(MeO)PhCH(OMe)_2$ (entry 2 in Table 32). This problem was overcome using either 5 mol% of the catalyst and 2.2 equivalents of TESOTf or 20 mol% of catalyst and 1.5 equivalents of TESOTf. However, the yields were poor (entries 3 and 4 in Table 32). In

turn, the *ortho* regioisomer gave a higher diastereoselectivity (80:20), albeit a moderate yield (entry 5 in Table 32). It was also necessary to use 5 mol% of catalyst and 2.2 equivalents of TESOTf to attain a 60% yield (compare entries 5 and 6 in Table 32). These results proved the crucial role of activation of the acetal on the stereochemical outcome of the addition, as well as the poor performance of *ortho*- compared to the *para* isomer suggests that steric effects should also be considered.

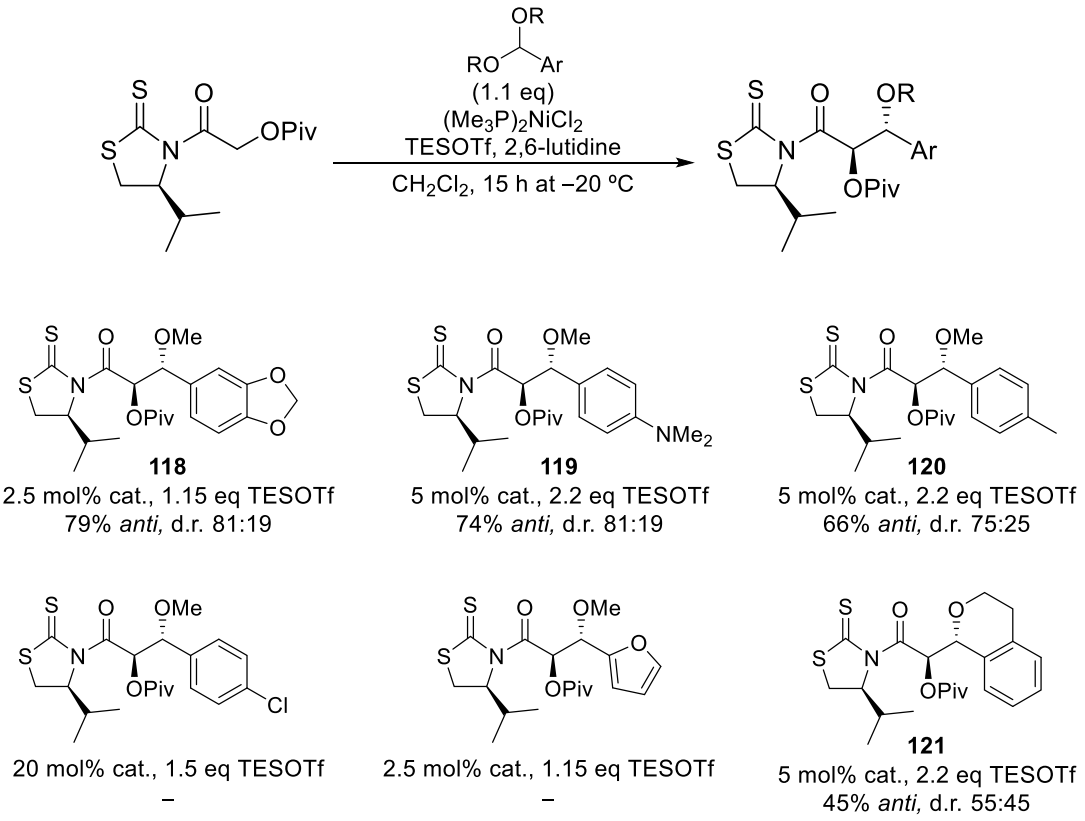


Entry	Acetal	$(Me_3P)_2NiCl_2$ (mol%)	TESOTf (eq)	Adduct	d.r.[a]	Yield (%)[b]
1	*p*-MeO	2.5	1.15	**101**	87:13[c]	77
2	*m*-MeO	2.5	1.15	**116**	–	n.r.
3	*m*-MeO	5	2.2	**116**	75:25	26
4	*m*-MeO	20	1.5	**116**	74:26	26
5	*o*-MeO	2.5	1.15	**117**	82:18	26
6	*o*-MeO	5	2.2	**117**	80:20	60

[a] Established by ^{1}H NMR analysis of the crude product.
[b] Isolated yield of *anti* adduct after column chromatography.
[c] Established by HPLC analysis of the crude product.

Table 32

Other aromatic dimethyl acetals were also assessed. The results are summarized in Scheme 174. While acetals containing π-electrodonating groups on the aromatic ring afforded the desired products in high yields and good diastereoselectivities (from 75:25 to 81:19), the *p*-chloro counterpart did not produce the expected adduct in spite of using up to 20 mol% of catalyst. This also happened with the furan–derived acetal. Finally, the addition to a semicyclic acetal afforded an equimolar mixture of *anti* and *syn* diastereomers in an excellent overall yield.

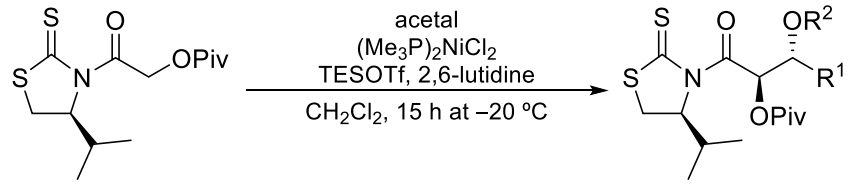


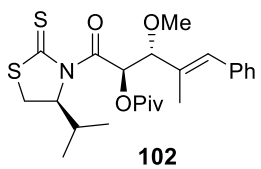
Scheme 174

6.3. Reactions with other dimethyl acetals

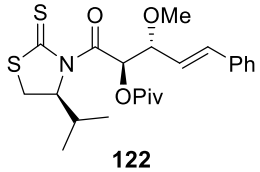
Once aromatic dimethyl acetals had been analyzed, non-aromatic acetals were examined. The results are summarized in Scheme 175. The most simple α,β-unsaturated acetal, (*E*)-cinnamaldehyde dimethyl acetal, gave a good yield (63%) and high diastereomeric ratio (78:22), but lower than (*E*)-α-methylcinnamaldehyde dimethyl acetal. This revealed that a methyl at the α position is crucial to obtain an excellent diastereoselectivity.

In turn, a coupling reaction of cobalt protected propargylic acetal **79** produced very good yields and diastereoselectivities, but not as outstanding as with the phenylpropargylic acetal **112**. Finally, a final attempt with an aliphatic dimethyl acetal failed, probably due to the difficult activation and a putative elimination of the proton at the α position.

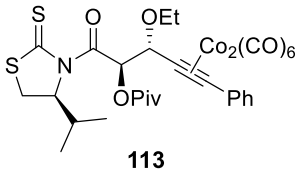




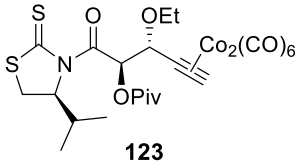
102
1.1 eq acetal
2.5 mol% cat., 1.15 eq TESOTf
89% *anti,* d.r. 93:7



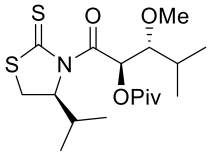
122
1.1 eq acetal
5 mol% cat., 1.20 eq TESOTf
63% *anti,* d.r. 78:22



113
1.5 eq acetal
5 mol% cat., 2.2 eq TESOTf
74% *anti,* d.r. 94:6



123
1.5 eq acetal
5 mol% cat., 2.2 eq TESOTf
79% *anti,* d.r. 85:15

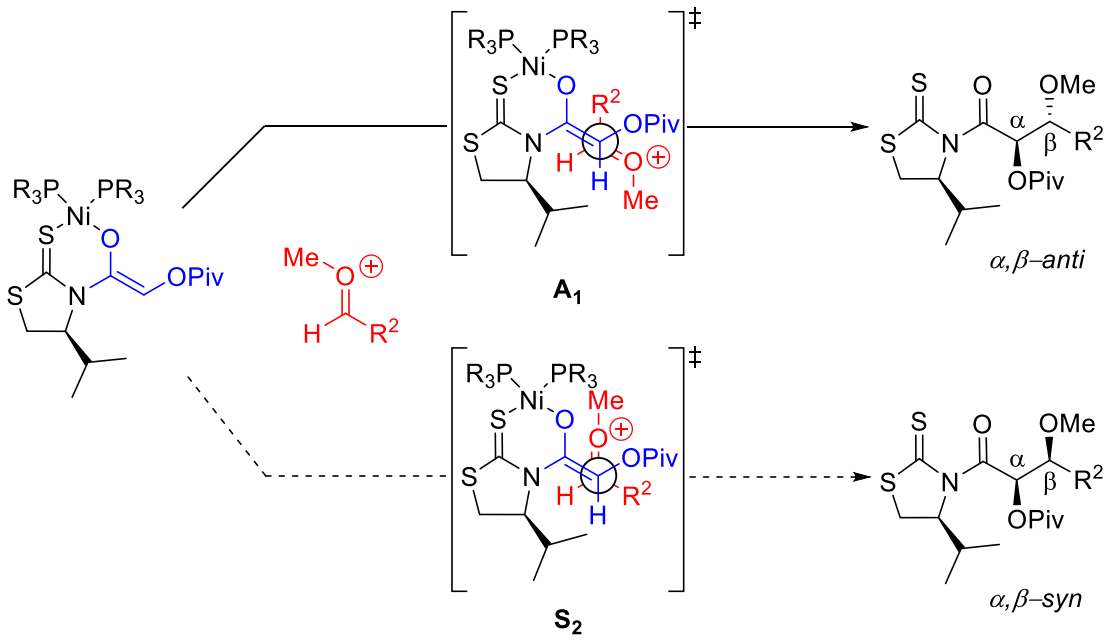


1.1 eq acetal
2.5 mol% cat., 1.15 eq TESOTf
–

Scheme 175

7. MECHANISTIC HYPOTHESIS

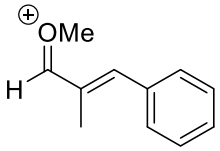
The mechanistic pathways that can be proposed for the Ni(II) catalyzed reaction of *N*-glycolylthiazolidinethiones with acetals are pretty similar to those proposed in Chapter 3. Thus, the less sterically hindered face of a chelated *Z*-enolate bound to a distorsioned square-planar Ni(II) complex would attack the oxonium ion, which allows us to speculate two different transition states that would end up in the *anti* and the *syn* diastereomers. The most stable transition state $\mathbf{A_1}$ would lead to the *anti* adduct.



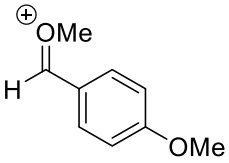
Scheme 176

However, both the yields and the diastereoselectivities cannot be easily explained through such a simple proposal. Indeed, all these results point out that other issues also play a crucial role on the yield and the stereochemical outcome of such reaction.

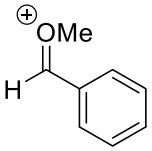
As observed in Chapter 3, the activation of the acetal is a key step. For instance, benzaldehyde acetal is more difficult to activate than *p*-anisaldehyde or (*E*)-α-methylcinnamaldehyde dimethyl acetal and it requires more nickel(II) complex and TESOTf to provide poorer diastereomeric ratios and yield (Scheme 177).



2.5 mol% cat., 1.15 eq TESOTf
89% *anti*
d.r. 93:7



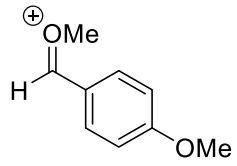
2.5 mol% cat., 1.15 eq TESOTf
77% *anti*
d.r. 87:13



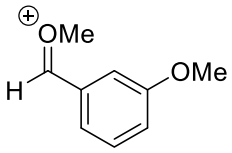
5.0 mol% cat., 2.2 eq TESOTf
40% *anti*
d.r. 75:25

Scheme 177

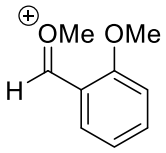
A similar trend has been observed for methoxybenzaldehyde dimethyl acetals. As summarized in Scheme 178, methoxy groups in *ortho* and *para* positions act as good π donors, thus facilitating the formation of the corresponding oxonium intermediate and giving diastereomeric ratios up to 87:13. Instead, the *meta* regioisomer, which cannot stabilize the positive charge so efficiently, affords a poor yield and low diastereoselectivity. Interestingly, the slightly low yield, poor stereocontrol and the need for an excess of TESOTf of the *ortho* regioisomer compared to *p*-(MeO)PhCH(OMe)$_2$ indicates that steric effects of the oxonium ion also play an important role in such additions.



2.5 mol% cat., 1.15 eq TESOTf
77% *anti*
d.r. 87:13



5.0 mol% cat., 2.2 eq TESOTf
26% *anti*
d.r. 75:25

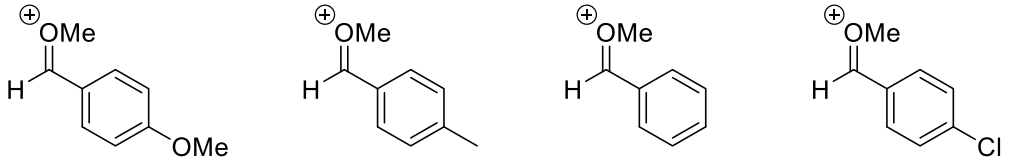


5.0 mol% cat., 2.2 eq TESOTf
60% *anti*
d.r. 80:20

Scheme 178

Regarding other aromatic dimethyl acetals, the electronic character of the substituents on the aromatic ring plays the same crucial role. Indeed, the less electrodonating the substituents are, the lower the yield and the diastereoselectivity are. Thus, aromatic dimethyl acetals with no π-electrodonating functional groups such as benzaldehyde and *p*-methylbenzaldehyde afforded worse results than *p*-(MeO)PhCH(OMe)$_2$, but their corresponding adducts were still isolated in moderate yields provided that an excess of Lewis acid is used (Scheme 179). In turn, a slightly electrowithdrawing group such as the *p*-chloro counterpart prevented the formation of

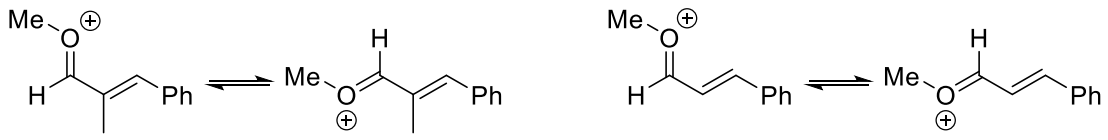
the adduct, even at high catalyst loadings (Scheme 179). In summary, the activation of the acetal and the proper stabilization of the resultant oxonium intermediates are critical issues, as had been already mentioned in former Chapters.



2.5 mol% cat., 1.15 eq TESOTf	5 mol% cat., 2.2 eq TESOTf	5 mol% cat., 2.2 eq TESOTf	20 mol% cat., 1.5 eq TESOTf
77% *anti*	66% *anti*	40% *anti*	–
d.r. 87:13	d.r. 75:25	d.r. 75:25	

Scheme 179

Steric effects are also very important for the stereochemical outcome of the process. Particularly, they play a crucial role on the control of the configuration of the β–stereocenters. This is clear for α,β-unsaturated acetals. As shown in Scheme 180, the presence of a methyl group in (*E*)-α-methylcinnamaldehyde dimethyl acetal ends up in a higher yield and better stereocontrol than those in parent (*E*)-cinnamaldehyde dimethyl acetal. Both oxonium intermediates are stabilized in the same extent, but the higher diastereoselectivity provided by the (*E*)-α-methylcinnamaldehyde dimethyl acetal might be due to the cisoid conformation; much more populated than for the (*E*)-cinnamaldehyde counterpart. Thus, the steric hindrance of the α-methyl group can impart a dramatic influence on the diastereoselectivity. Unfortunately, it is still difficult to forecast the stereochemical outcome of such additions by simple analysis of electronic and steric effects

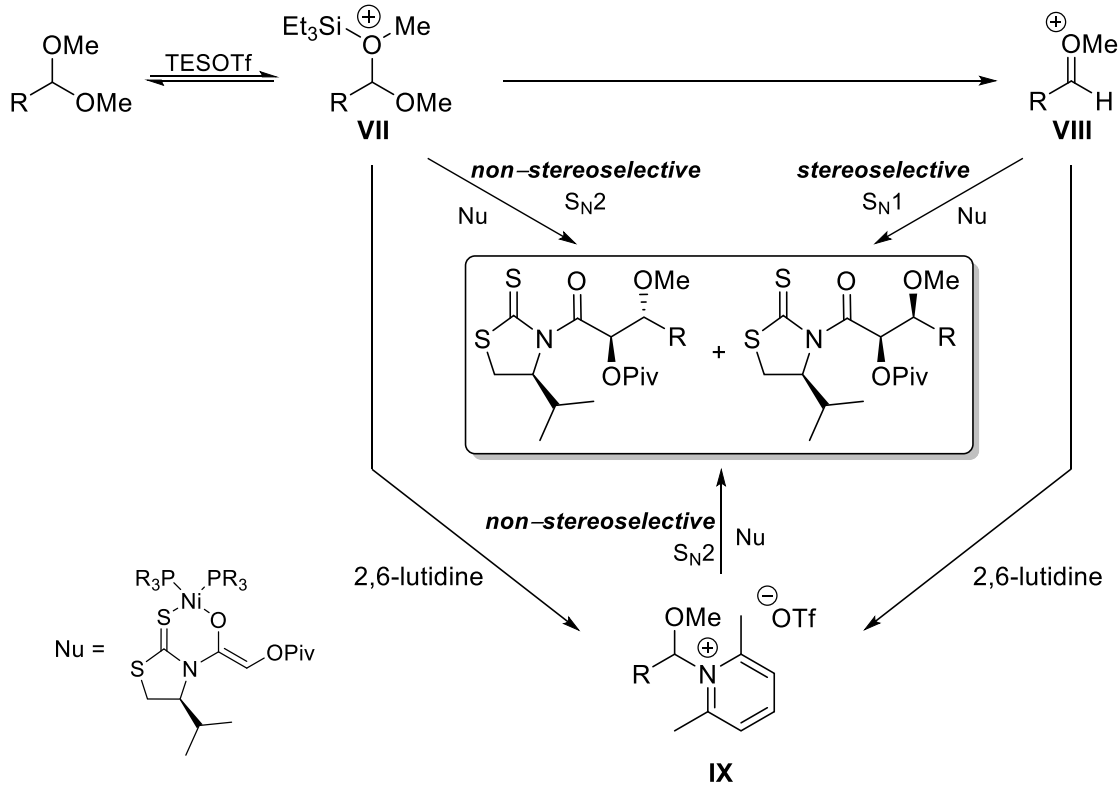


cisoid ⇌ *transoid*	*cisoid* ⇌ *transoid*
2.5 mol% cat., 1.15 eq TESOTf	5.0 mol% cat., 1.15 eq TESOTf
89% *anti*	63% *anti*
d.r. 93:7	d.r. 78:22

Scheme 180

Finally, some other questions remain unclear and deserve further studies. These concern to the reactivity of the putative nickel(II) enolates and the way to increase their nucleophilicity and the role of the metal atom in the overall process.

Furthermore, a parallel mechanism based on the formation of intermediates **IX** represented in Scheme 181 might account for the erosion of the diastereoselectivity observed for the less stabilized oxonium intermediates. This is the same model discussed in Chapter 3 (see Scheme 155).

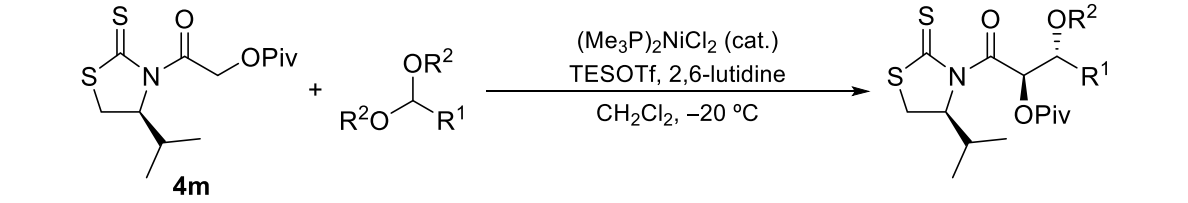


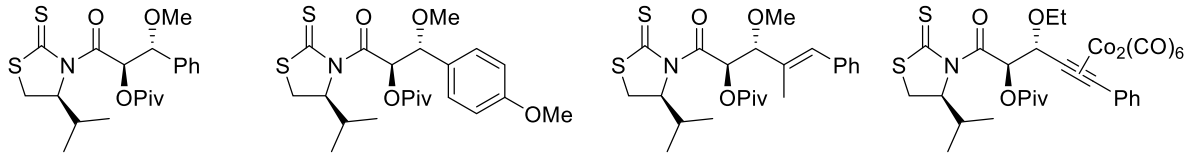
Scheme 181

8. SUMMARY AND CONCLUSIONS

This last Chapter deals with a new stereoselective addition of catalytically generated Ni(II) enolates of chiral *O*-protected *N*-glycolyl-4-isopropyl-1,3-thiazolidine-2-thiones to acetals, which provides *anti*-α,β-dioxygenated carboxylic systems in good yields and diastereomeric ratios ranging from 75:25 to 94:6. These results strongly depend on the electronic character of the acetals and the stabilization of the resultant oxonium cations.

Different reaction conditions have been established depending on the kind of acetal. Therefore, standard reaction conditions coming from Chapter 3 are applied to acetals that are very easy to activate, such as *p*-anisaldehyde dimethyl acetal. For more reluctant acetals, such as benzaldehyde dimethyl acetal, an excess of Lewis acid must be added. Finally, when cobalted propargyl acetals were used, an excess of Lewis acid and the acetal must be employed.





100
1.1 eq. acetal
5.0 mol% cat.
2.2 eq TESOTf
40% *anti*
d.r. 75:25

101
1.1 eq. acetal
2.5 mol% cat.
1.15 eq TESOTf
77% *anti*
d.r. 87:13

102
1.1 eq. acetal
2.5 mol% cat
1.15 eq TESOTf
89% *anti*
d.r. 93:7

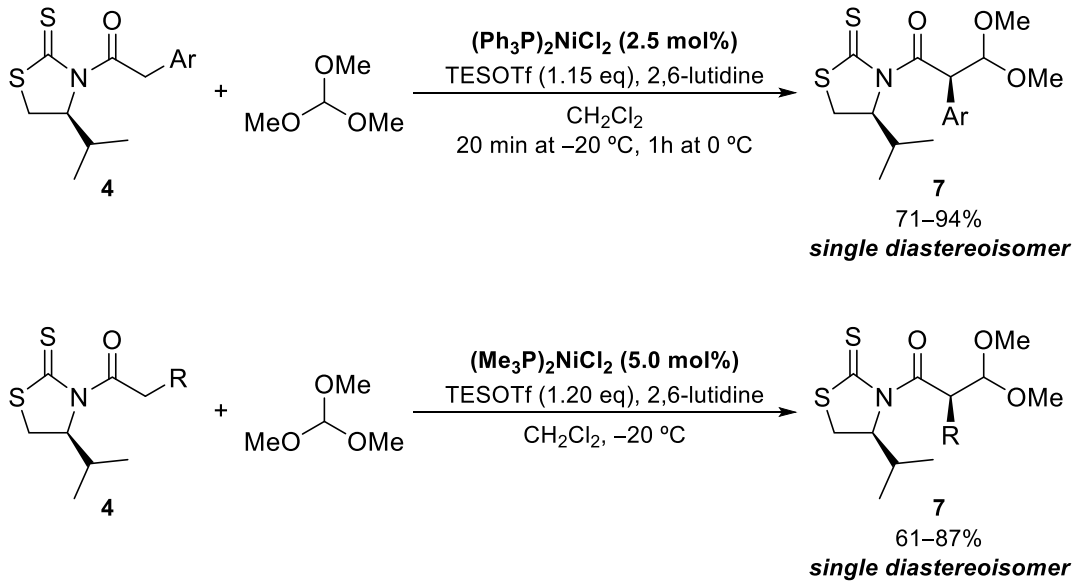
113
1.5 eq. acetal
5.0 mol% cat.
2.2 eq TESOTf
74% *anti*
d.r. 94:6

Scheme 182

SUMMARY AND CONCLUSIONS

In this Doctoral Thesis a new stereoselective Ni(II)-mediated catalytic system for the S_N1–like addition of chiral *N*-acyl thiazolidinethiones to electrophiles able to deliver cationic species under acidic conditions has been developed. Importantly, the nickel(II) complexes used along our studies are structurally simple, commercially available and easy to handle.

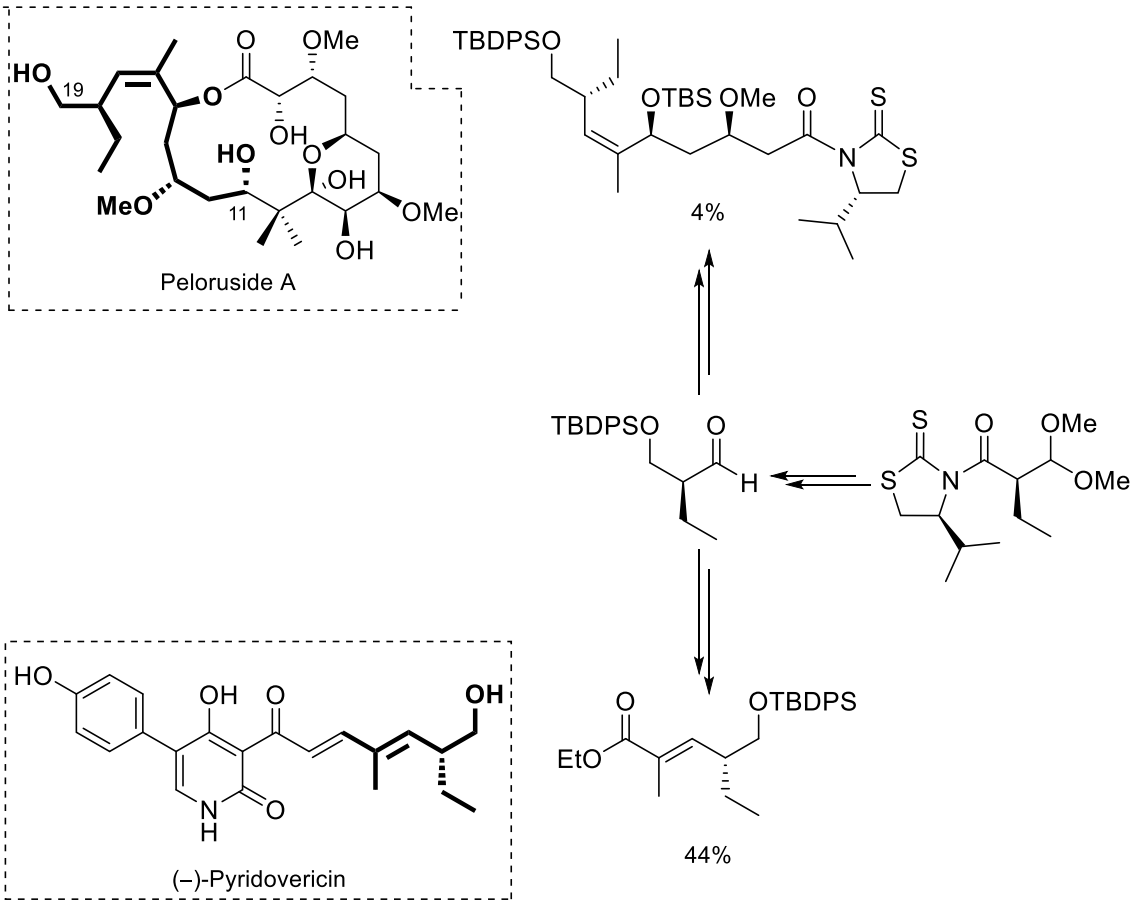
In Chapter 1, a totally stereoselective addition of *N*-acyl thiazolidinethiones to trimethyl orthoformate activated by TESOTf has been optimized. For *N*-arylacetyl thiazolidinethiones, a 2.5 mol% of $(Ph_3P)_2NiCl_2$ was required. Instead, when other *N*-acyl groups were used, up to 20 mol% of $(Ph_3P)_2NiCl_2$ was required. Alternatively, a 2.5–5 mol% of $(Me_3P)_2NiCl_2$ can be used. The resultant adducts can be converted easily in enantiomerically pure compounds with a wide array of different functional groups.



Scheme 183

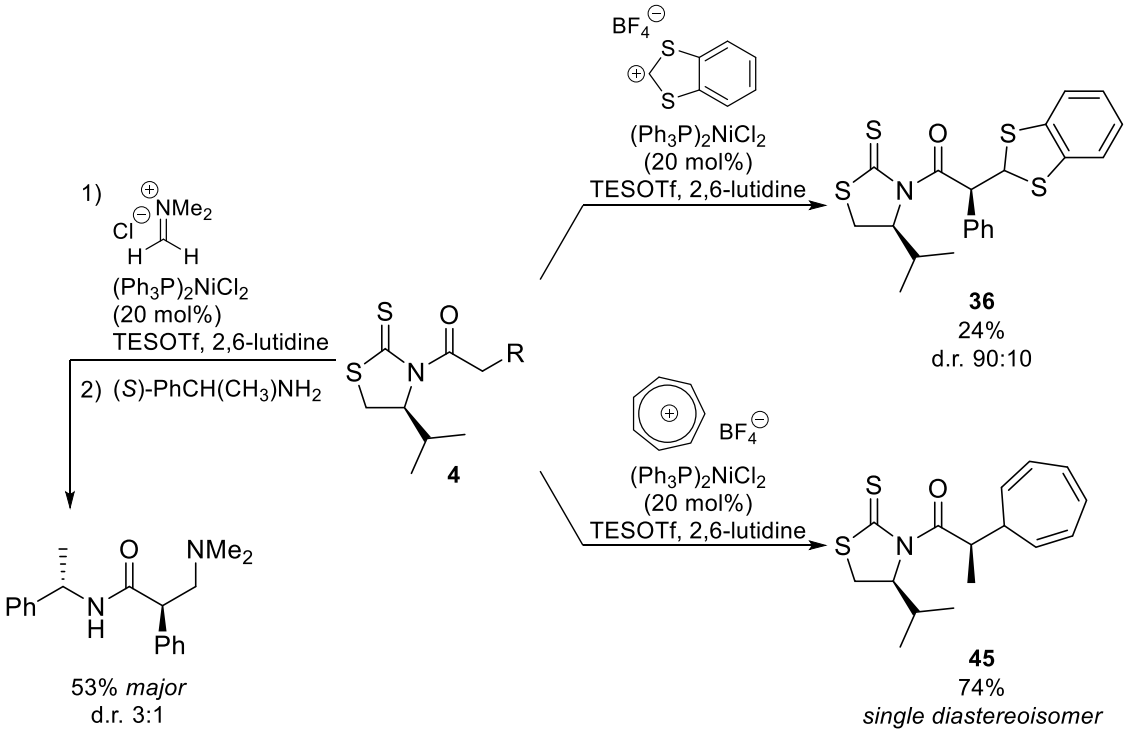
Most of these results have been published in the following communication: *"Diastereoselective Methyl Orthoformate Alkylations of Chiral N-Acylthiazolidinethiones Catalyzed by Nickel(II) Complexes"*, Romo, J. M.; Gálvez, E.; Nubiola, I.; Romea, P.; Urpí, F., Kindred, M. *Adv. Synth. Catal.* **2013**, *355*, 2781.

This method has been applied successfully to the stereoselective synthesis of the side chain of (–)-pyridovericin and the C11–C19 fragment of (+)-peloruside A, with overall yields of 44% and 4%, respectively.



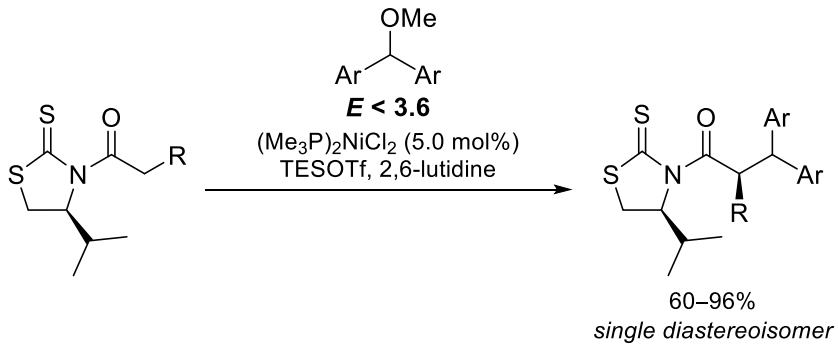
Scheme 184

In Chapter 2, the Ni(II)-mediated catalytic system was next applied to commercially available cationic salts such as 1,3-benzodithiolylium tetrafluoroborate, the Eschemoser's salt and the tropylium tetrafluoroborate.



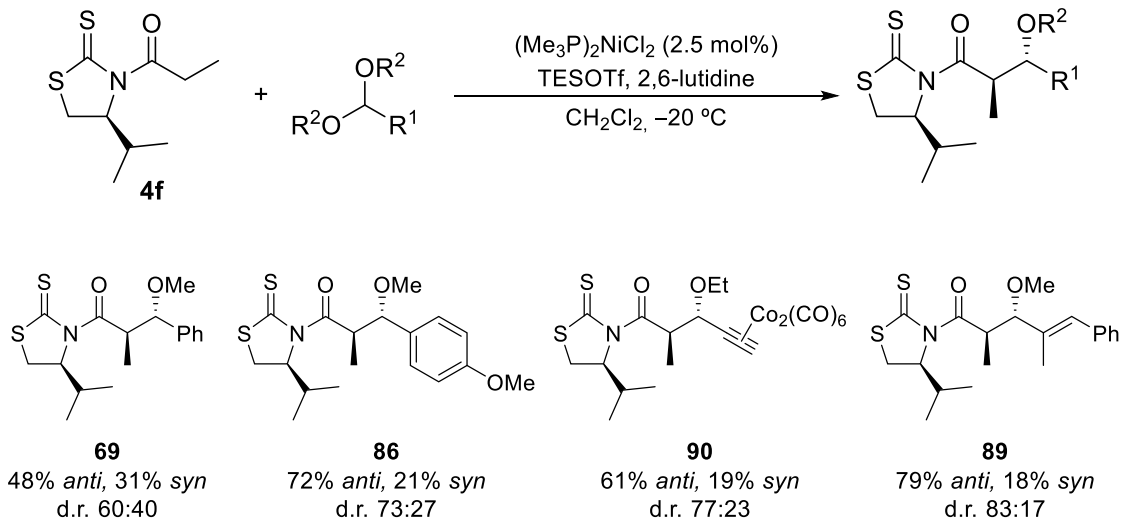
Scheme 185

Furthermore, a new stereoselective Ni(II) catalyzed alkylation reaction with diarylcarbenium methyl ethers has been developed. The reaction proceeds smoothly provided that the carbocationic intermediate is stable enough. Mayr's scale of electrophilicity accounts for the observed reactivity.



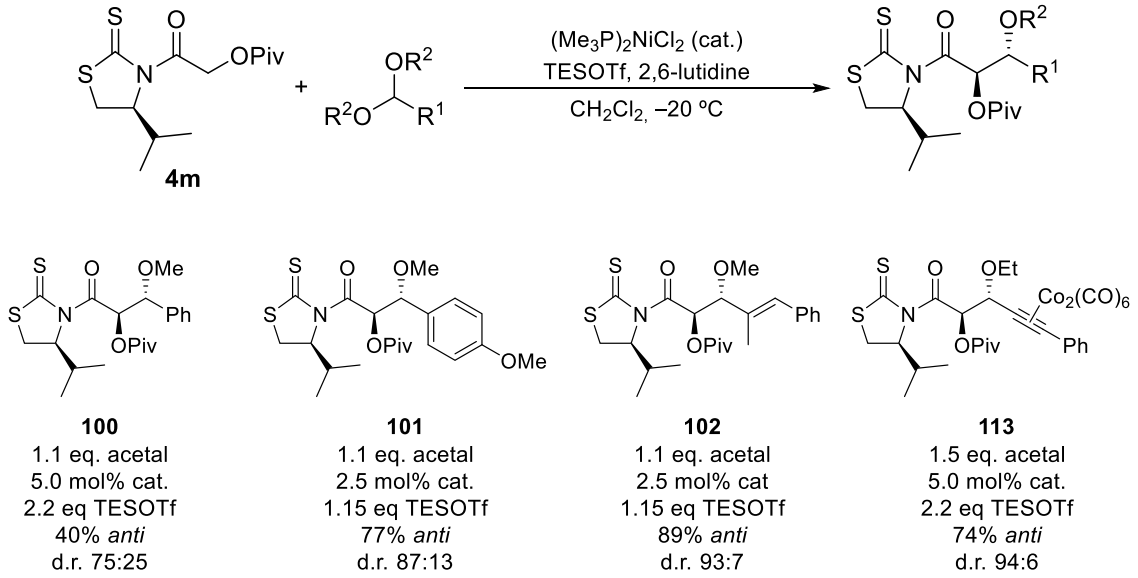
Scheme 186

In Chapter 3, the catalytic system has been applied to acetals, which involved the challenging construction of two new stereocenters in a single reaction. The reaction provides the corresponding *anti* adducts with aromatic, α,β-unsaturated and Co–propargylic acetals in low to moderate yields. The stereoselectivity of these additions strongly depends on the structure of the acetal. Particularly, acetals that furnish stable oxonium cations give the best stereocontrol, up to 83:17 diastereomeric ratio.



Scheme 187

Finally, Chapter 4 refers to our studies on the use of chiral *N*-glycolyl thiazolidinethiones in the Ni(II) catalyzed reaction to prepare *anti*-α,β-dihydroxycarboxyl compounds from aromatic, α,β-unsaturated cobalt–derived propargylic acetals in moderate to high yields. The diastereomeric ratios observed in these reactions resulted to be from good (75:25) to excellent (94:6). A thorough analysis of the reaction conditions uncovered that acetals difficult to be activated require an excess of Lewis acid or acetal.



Scheme 188

All together, these results proved that the Lewis acid–mediated addition of chiral *N*-acyl thiazolidinethiones to a wide range of electrophiles catalyzed by structurally simple, commercially available and easy to handle nickel(II) complexes is a very efficient method for the stereoselective construction of carbon–carbon bonds. Likely, such a transformation proceeds through a S_N1–like mechanism in which a putative nickel(II) enolate adds to a cationic intermediate generated *in situ* from orthoesters, acetals or ethers. The chiral auxiliary can be removed easily to afford an important number of enantiomerically pure compounds. The synthetic potential of this new method has been demonstrated in the preparation of the side chain of pyridovericin and the C11–C19 fragment of peloruside A.

EXPERIMENTAL SECTION

- Unless otherwise noted, resctions were conducted in ovendried glassware under inert atmosphere of nitrogen with anhydrous solvents. The solvents and reagents were dried and purified when necessary according to standard procedures.[176] All commercial reagents were used as received.

- Analytical thin-layer chromatography (TLC) were carried out on Merck silica gel 60 F254 plates and analyzed by UV (254 nm) and stained with phosphomolybdic acid and *p*-anisaldehyde. R_f values are approximate.

- Melting points (mp) were determined with a Stuart Scientific SMP10 or a Gallenkamp apparatus and are uncorrected.

- Specific rotations ($[\alpha]_D$) were determined at 20 ºC on a Perkin-Elmer 241 MC polarimeter.

- IR spectra were recorded on a Nicolet 6700 FT-IR Thermo Scientific spectrometer. The samples were analyzed as a compacted powder mixed with KBr (solids), over a NaCl tablet (liquid or oil) and using ATR technique (Attenuated Total Reflectance). Only the more representative frequencies (ν) are reported.

- ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Inova 300 spectrometer, on a Varian Mercury 400 spectrometer or on a Bruker 400. Chemical shifts (δ) are quoted in ppm and referenced to internal TMS (δ 0.00 for ^{1}H NMR) or $CDCl_3$ (δ 77.0 for ^{13}C NMR). Data are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; p, quintet; sext, sextuplet; hept, heptuplet; br or br s, broad (and their corresponding combinations); when necessary, 2D techniques (COSY, HSQC) were also used to assist on structure elucidation.

- High resolution mass spectra (HRMS) were obtained with an Agilent 1100 spectrometer by the Unitat d'Espectrometria de Masses, Universitat de Barcelona.

- Column chromatographies were carried out under low pressure (*flash*) conditions and performed on SDS silica gel 60 (35–70 μm).

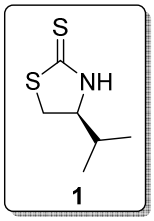
1. Stereoselective Ni(II) catalyzed reactions of *N*-acyl thiazolidinethiones with methyl orthoformate

1.1. PREPARATION OF STARTING MATERIALS

1.1.1. (*S*)-4-Isopropyl-1,3-thiazolidine-2-thione (1)[31h]

Carbon disulfide (12.3 mL, 203 mmol) was added to a solution of (*S*)-valinol (8.0 g, 78 mmol) in EtOH (25 mL) under N_2. To the yellow mixture, a solution of 2.25 M of KOH (11.8 g, 211 mmol) in 1:1 EtOH:H_2O (90 mL) was then added dropwise at room temperature over 20 min, turning to a red solution. After that, the reaction mixture was stirred and heated at reflux for 72 h.

After cooling, the volatiles were removed, and the resulting liquid was acidified with 0.5 M HCl (430 mL), appearing a yellow solid. The suspension was washed with CH_2Cl_2 (3 × 300 mL), and the combined organic layers were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give 11.6 g (72 mmol, 92%) of thiazolidinone **1**, which was used in the next step without further purification.



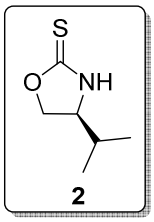
1

(*S*)-4-Isopropyl-1,3-thiazolidine-2-thione (**1**). Yellow solid; **mp** = 66–68 ºC [lit.[31h] **mp** = 68–69 ºC]; $\mathbf{R_f}$ = 0.30 (CH_2Cl_2); $\mathbf{[\alpha]_D}$ = –34.9 (*c* 1.14, $CHCl_3$) [lit.[31h] $\mathbf{[\alpha]_D}$ = –34.8 (*c* 1.10, $CHCl_3$)]; **IR** (KBr) 3190, 2965, 1500, 1410, 1385, 1030 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.99 (1H, br s, N$\underline{H}$), 4.06 (1H, td, *J* = 8.3, 6.7 Hz, NC$\underline{H}$), 3.51 (1H, dd, *J* = 11.1, 8.3 Hz, SC$\underline{H_a}H_b$), 3.33 (1H, dd, *J* = 11.1, 8.3 Hz, SC$H_a\underline{H_b}$), 1.91–2.06 (1H, m, C$\underline{H}$(CH_3)$_2$), 1.04 (3H, d, *J* = 6.8 Hz, CH(C$\underline{H_3}$)$_a$(CH_3)$_b$), 1.01 (3H, d, *J* = 6.8 Hz, CH(CH_3)$_a$(C$\underline{H_3}$)$_b$); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 201.2, 70.1, 36.0, 32.1, 18.9, 18.3; **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_6H_{11}NS_2$: 162.0406, found: 162.0402.

1.1.2. (*S*)-4-Isopropyl-1,3-oxazolidine-2-thione (2).[31e]

Anh Et_3N (5.4 mL, 38.7 mmol) was added dropwise to a solution of (*S*)-valinol (1.01 g, 9.8 mmol) and CS_2 (3.0 mL, 50 mmol) in THF (40 mL) at 0 ºC under N_2 and the resulting solution was heated to reflux for 16 h.

After cooling, the volatiles were removed, and the mixture partitioned with CH_2Cl_2 (150 mL) and water (50 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 100 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the resulting brown oil was purified by flash column chromatography on silica gel (CH_2Cl_2) to give 0.75 g (5.2 mmol, 53%) of oxazolidinethione **2**.



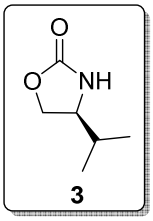
2

(*S*)-4-Isopropyl-1,3-oxazolidine-2-thione (**2**). White solid; **mp** = 45–47 ºC [lit.[31e] **mp** = 45–46 ºC]; $\mathbf{R_f}$ = 0.35 (CH_2Cl_2); $\mathbf{[\alpha]_D}$ = –28.0 (*c* 0.95, $CHCl_3$) [lit.[31e] $\mathbf{[\alpha]_D}$ = –27.4 (*c* 0.65, $CHCl_3$)]; **IR** (ATR) 3170, 2959, 2874, 1520, 1270, 1166 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.75 (1H, br s, N$\underline{H}$), 4.70 (1H, t, *J* = 9.1 Hz, OC$\underline{H_a}H_b$), 4.39 (1H, dd, *J* = 9.1, 6.7 Hz, OC$H_a\underline{H_b}$), 3.83 (1H, dt, *J* = 9.1, 6.7 Hz, NC$\underline{H}$), 1.82 (1H, m, C$\underline{H}$(CH_3)$_2$), 0.99 (3H, d, *J* = 6.7 Hz, CH(C$\underline{H_3}$)$_a$(CH_3)$_b$), 0.93 (3H, d, *J* = 6.7 Hz, CH(CH_3)$_a$(C$\underline{H_3}$)$_b$); **^{13}C NMR** ($CDCl_3$, 62.5 MHz) δ 189.5, 73.4, 62.4, 32.1, 17.9, 17.8.

1.1.3. (*S*)-4-Isopropyl-1,3-oxazolidin-2-one (3)[177]

Diethyl carbonate (8.3 mL, 70 mmol) was added to (*S*)-valinol (3.61 mg, 35 mmol) and potassium carbonate (0.265 g, 2.5 mmol) under N_2. The reaction mixture was then heated to 135 ºC and the resulting ethanol distilled for 2 h, then cooled to r.t.

Water (80 mL) was added to the resultant yellow oil and the aqueous layer extracted with CH_2Cl_2 (4 × 50 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated to afford a white solid, which was further purified by recrystallization (hexanes/EtOAc 2:1) to give 3.36 g (26.0 mmol, 75%) of oxazolidinone **3**.



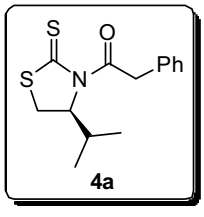
3

(*S*)-4-Isopropyl-1,3-oxazolidin-2-one (**3**). White solid; **mp** = 67–69 ºC [lit.[177] **mp** = 70–72 ºC]; $\mathbf{R_f}$ = 0.20 (CH_2Cl_2); $\mathbf{[\alpha]_D}$ = –14.7 (*c* 1.00, EtOH) [lit.[177] $\mathbf{[\alpha]_D}$ = –14.6 (*c* 1.10, EtOH)]; **IR** (ATR) 3259, 2960, 1721, 1241, 1006 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 5.75 (1H, br s, NH), 4.45 (1H, t, *J* = 8.6 Hz, OCH_aH_b), 4.11 (1H, dd, *J* = 8.6, 6.3 Hz, OCH_aH_b), 3.61 (1H, dt, *J* = 8.6, 6.3 Hz, NCH), 1.73 (1H, m, $CH(CH_3)_2$), 0.96 (3H, d, *J* = 6.7Hz, $CH(CH_3)_a(CH_3)_b$), 0.91 (3H, d, *J* = 6.7 Hz, $CH(CH_3)_a(CH_3)_b$).

1.1.4. (*S*)-4-Isopropyl-*N*-(2-phenylacetyl)-1,3-thiazolidine-2-thione (4a)

EDC·HCl (863 mg, 4.5 mmol) was added to a solution of phenylacetic acid (715 mg, 5.3 mmol), the thiazolidinethione **1** (484 mg, 3.0 mmol) and DMAP (18 mg, 0.15 mmol) in anh CH_2Cl_2 (5 mL) at 0 ºC under N_2. The mixture was purged with N_2 again. The ice bath was then removed and the reaction mixture was stirred for 16 h at r.t.

The resulting yellow reaction mixture was diluted in CH_2Cl_2 (30 mL) and washed with 0.5 M HCl (3 × 20 mL), 0.5 M NaOH (3 × 20 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography on silica gel (hexanes/CH_2Cl_2 1:1) to give 801 mg (2.9 mmol, 96%) of the thioimide **4a** as a yellow solid.



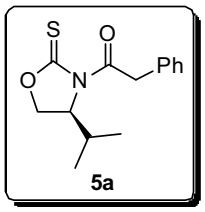
4a

(*S*)-4-Isopropyl-*N*-(2-phenylacetyl)-1,3-thiazolidine-2-thione (**4a**). Yellow solid; **mp** = 71–72 ºC [lit.[4] **mp**= 69–70 ºC]; $\mathbf{R_f}$ = 0.50 (hexanes/CH_2Cl_2 2:3); $\mathbf{[\alpha]_D}$ = +324.0 (*c* 1.10, $CHCl_3$); **IR** (ATR) 3022, 2954, 2924, 2872, 1703, 1339 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.35–7.22 (5H, m, ArH), 5.14 (1H, ddd, *J* = 7.8, 6.1, 1.1 Hz, NCH), 4.67 (1H, d, *J* = 17.0 Hz, CH_aH_bPh), 4.61 (1H, d, *J* = 17.0 Hz, CH_aH_bPh), 3.50 (1H, dd, *J* = 11.5, 7.8 Hz, SCH_aH_b), 3.03 (1H, dd, *J* = 11.5, 1.1 Hz, SCH_aH_b), 2.43–2.31 (1H, m, $CH(CH_3)_2$), 1.04 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(CH_3)_b$), 0.97 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 203.2 (C), 172.4 (C), 134.2 (C), 129.9 (CH), 128.7 (CH), 127.2 (CH), 72.2 (CH), 44.4 (CH), 31.0 (CH), 30.6 (CH_2), 19.3 (CH_3), 17.8 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{14}H_{18}NOS_2$: 280.0824, found: 280.0826.

1.1.5. (*S*)-4-Isopropyl-*N*-(2-phenylacetyl)-1,3-oxazolidine-2-thione (5a)

EDC·HCl (865 mg, 4.5 mmol) was added to a solution of phenylacetic acid (715 mg, 5.3 mmol), the oxazolidinethione **2** (436 mg, 3.0 mmol) and DMAP (18 mg, 0.15 mmol) in anh CH_2Cl_2 (5 mL) at 0 ºC under N_2. The mixture was purged with N_2 again. The ice bath was then removed and the reaction mixture was stirred for 16 h at r.t.

The resulting yellow reaction mixture was diluted in CH_2Cl_2 (30 mL) and washed with 0.5 M HCl (3 × 20 mL), 0.5 M NaOH (3 × 20 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography on silica gel (from hexanes/CH_2Cl_2 1:1 to CH_2Cl_2) to give 737 mg (2.8 mmol, 93%) of the thioimide **5a** as a clear oil.



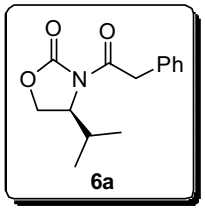
5a

(*S*)-4-Isopropyl-*N*-(2-phenylacetyl)-1,3-oxazolidine-2-thione (**5a**). Clear oil; $\mathbf{R_f}$ = 0.60 (CH_2Cl_2); $\mathbf{[\alpha]_D}$ = +99.4 (*c* 1.15, $CHCl_3$); **IR** (ATR) 2964, 1695, 1340, 1150, 1030 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.35–7.22 (5H, m, ArH), 4.81 (1H, d, *J* = 16.8 Hz, CH_aH_bPh), 4.72 (1H, td, *J* = 5.7, 3.9 Hz, NCH), 4.67 (1H, d, *J* = 16.8 Hz, CH_aH_bPh), 4.40 (2H, d, *J* = 5.7 Hz, OCH_2), 2.35 (1H, dsept, *J* = 7.0, 3.9 Hz, $CH(CH_3)_2$), 0.91 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_a(CH_3)_b$), 0.86 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 186.2, 172.2, 133.6, 129.8, 128.5, 127.1, 67.6, 63.5, 43.3, 28.9, 18.2, 14.9; **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{14}H_{18}NO_2S$: 264.1053, found: 264.1041.

1.1.6. (*S*)-4-Isopropyl-*N*-(2-phenylacetyl)-1,3-oxazolidin-2-one (6a)

Anh Et_3N (0.21 mL, 3.0 mmol) and pivaloyl chloride (0.35 mL, 3.0 mmol) were added to a solution of phenylacetic acid (408 mg, 3.0 mmol) in anh THF (25 mL) at 0 ºC under N_2 and the mixture was stirred for 1.5 h. Meanwhile, 1.6 M *n*-BuLi in hexanes (2.1 mL, 3.3 mmol) was added dropwise to a solution of oxazolidinone **3** (369 mg, 3.0 mmol) in anh THF (25 mL) at –78 ºC under N_2. The resulting brown solution was stirred for 40 min. The solution containing the mixed anhydride was cooled at –78 ºC and the solution of the anion of **3** added dropwise to it, avoiding the take up of the precipitate. The mixture was stirred at –78 ºC for 30 min and 2 h at r.t.

The reaction mixture was quenched with pH 7 buffer solution of $NaKHPO_4/KH_2PO_4$ (15 mL) and the organic solvent removed *in vacuo*. The resulting solution was diluted with the same buffer (160 mL) followed by extraction with Et_2O (3 × 40 mL). The combined organic layers were washed with sat $NaHCO_3$ (2 × 40 mL) and brine (40 mL), and then dried over $MgSO_4$, filtered and concentrated. The resulting crude oil was further purified by flash column chromatography on silica gel (hexanes/EtOAc 7:3) to yield 360 mg (1.47 mmol, 49%) of the imide **6a** as a clear oil.

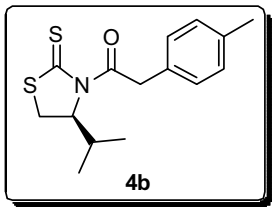


6a

(*S*)-4-Isopropyl-*N*-(2-phenylacetyl)-1,3-oxazolidin-2-one (**6a**). Clear oil; $\mathbf{R_f}$ = 0.75 (hexanes/EtOAc 7:3); $\mathbf{[\alpha]_D}$ = +67.2 (*c* 0.65, $CHCl_3$) [lit.[178] $\mathbf{[\alpha]_D}$ = +77.6 (*c* 2.05, $CHCl_3$)]; **IR** (ATR) 2962, 2360, 1772, 1698 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.42–7.15 (5H, m, Ar$\underline{H}$), 4.44 (1H, ddd, *J* = 9.0, 3.5, 3.1 Hz, NC$\underline{H}$), 4.36 (1H, d, *J* = 15.3 Hz, C$\underline{H_a}H_b$Ph), 4.27 (1H, t, *J* = 9.0 Hz, OC$\underline{H_a}H_b$), 4.23 (1H, d, *J* = 15.3 Hz, $CH_a\underline{H_b}$Ph), 4.20 (1H, dd, *J* = 9.0, 3.1 Hz, $OCH_a\underline{H_b}$), 2.35 (1H, dsept, *J* = 7.0, 3.5 Hz, C$\underline{H}(CH_3)_2$), 0.88 (3H, d, *J* = 7.0 Hz, CH(C$\underline{H_3}$)$_a$(CH$_3$)$_b$), 0.79 (3H, d, *J* = 7.0 Hz, CH(CH$_3$)$_a$(C$\underline{H_3}$)$_b$); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 171.2, 154.0, 133.7, 129.6, 128.5, 127.1, 63.3, 58.5, 41.5, 28.2, 17.9, 14.5; **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{14}H_{18}NO_3$: 248.1281, found: 248.1278.

1.1.7. (*S*)-4-Isopropyl-*N*-[2-(*p*-tolyl)acetyl]-1,3-thiazolidine-2-thione (4b)

The reaction was carried out as described in the section 1.1.4, but using EDC·HCl (1.44 g, 7.5 mmol), *p*-tolylacetic acid (1.31 g, 5.25 mmol), the thiazolidinethione **1** (806 mg, 5.0 mmol) and DMAP (31 mg, 0.25 mmol). A further purification by flash column chromatography on silica gel (CH_2Cl_2) afforded 1.21 g (4.12 mmol, 82%) of thioimide **4b** as a yellow solid.

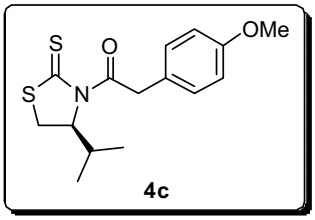


4b

(*S*)-4-Isopropyl-*N*-[2-(*p*-tolyl)acetyl]-1,3-thiazolidine-2-thione (**4b**). Yellow solid; **mp** = 93–94 ºC; $\mathbf{R_f}$ = 0.65 (CH_2Cl_2); $\mathbf{[\alpha]_D}$ = +303.4 (*c* 1.05, $CHCl_3$); **IR** (ATR) 2961, 2917, 2875, 1708, 1515, 1384, 1341 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.13 (2H, d, *J* = 8.5 Hz, Ar$\underline{H}$), 7.11 (2H, d, *J* = 8.5 Hz, Ar$\underline{H}$), 5.12 (1H, ddd, *J* = 8.7, 6.0, 1.2 Hz, NC$\underline{H}$), 4.62 (1H, d, *J* = 17.0 Hz, C$\underline{H_a}H_b$Ar), 4.56 (1H, d, *J* = 17.0 Hz, $CH_a\underline{H_b}$Ar), 3.48 (1H, dd, *J* = 11.5, 8.7 Hz, SC$\underline{H_a}H_b$), 3.01 (1H, dd, *J* = 11.5, 1.2 Hz, $SCH_a\underline{H_b}$), 2.43–2.32 (1H, m, C$\underline{H}(CH_3)_2$), 2.33 (3H, s, ArC$\underline{H_3}$), 1.03 (3H, d, *J* = 6.8 Hz, CH(C$\underline{H_3}$)$_a$(CH$_3$)$_b$), 0.96 (3H, d, *J* = 7.0 Hz, CH(CH$_3$)$_a$(C$\underline{H_3}$)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.9 (C), 172.4 (C), 136.6 (C), 130.9 (C), 129.5 (CH), 129.1 (CH), 72.0 (CH), 43.8 (CH_2), 30.8 (CH), 30.3 (CH_2), 21.1 (CH_3), 19.0 (CH_3), 17.6 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{15}H_{20}NOS_2$: 294.0981, found: 294.0979.

1.1.8. (*S*)-4-Isopropyl-*N*-[2-(*p*-methoxyphenyl)acetyl]-1,3-thiazolidine-2-thione (4c)

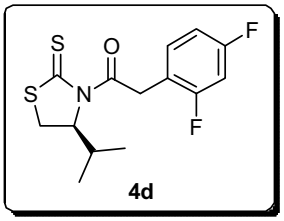
The reaction was carried out as described in the section 1.1.4, but using EDC·HCl (1.15 g, 6.0 mmol), *p*-methoxyphenylacetic acid (1.16 g, 7.0 mmol), the thiazolidinethione **1** (645 mg, 4.0 mmol) and DMAP (24 mg, 0.20 mmol). A further purification by flash column chromatography on silica gel (CH_2Cl_2) afforded 998 mg (3.23 mmol, 81%) of the thioimide **4c** as a yellow solid.



(*S*)-4-Isopropyl-*N*-[2-(*p*-methoxyphenyl)acetyl]-1,3-thiazolidine-2-thione (**4c**). Yellow solid; **mp** = 51–52 ºC; $\mathbf{R_f}$ = 0.70 (CH_2Cl_2); $\mathbf{[\alpha]_D}$ = +297.1 (*c* 1.00, $CHCl_3$); **IR** (ATR): 3007, 2960, 2912, 1705, 1614, 1513, 1389, 1241 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.15 (2H, d, *J* = 8.7 Hz, ArH), 6.86 (2H, d, *J* = 8.7 Hz, ArH), 5.12 (1H, ddd, *J* = 8.1, 6.0, 1.3 Hz, NCH), 4.61 (1H, d, *J* = 17.0 Hz, CH_aH_bAr), 4.54 (1H, d, *J* = 17.0 Hz, CH_aH_bAr), 3.79 (3H, s, OCH_3), 3.48 (1H, dd, *J* = 11.5, 8.1 Hz, SCH_aH_b), 3.01 (1H, dd, *J* = 11.5, 1.3 Hz, SCH_aH_b), 2.42–2.30 (1H, m, $CH(CH_3)_2$), 1.03 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(CH_3)_b$), 0.96 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.9 (C), 172.6 (C), 158.6 (C), 130.7 (CH), 126.0 (C), 113.9 (CH), 72.0 (CH), 55.2 (CH_3), 43.3 (CH_2), 30.8 (CH), 30.3 (CH_2), 19.0 (CH_3), 17.6 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{15}H_{20}NO_2S_2$: 310.0930, found: 310.0922.

1.1.9. (*S*)-*N*-[2-(2,4-Difluorophenyl)acetyl]-4-isopropyl-1,3-thiazolidine-2-thione (4d)

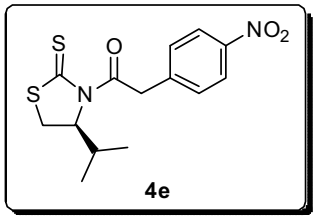
The reaction was carried out as described in the section 1.1.4, but using EDC·HCl (628 mg, 3.3 mmol), 2,4-difluorophenylacetic acid (658 mg, 3.8 mmol) and the thiazolidinethione **1** (352 mg, 2.2 mmol). No DMAP was added to the reaction. A further purification by flash column chromatography on silica gel (hexanes/CH_2Cl_2 2:3) afforded 287 mg (0.91 mmol, 42%) of the thioimide **4d** as a yellow solid.



(*S*)-*N*-[2-(2,4-Difluorophenyl)acetyl]-4-isopropyl-1,3-thiazolidine-2-thione (**4d**). Yellow solid; **mp** = 77–83 ºC; $\mathbf{R_f}$ = 0.35 (hexanes/CH_2Cl_2 3:2); $\mathbf{[\alpha]_D}$ = +253.7 (*c* 1.00, $CHCl_3$); **IR** (ATR) 2962, 2922, 2877, 2851, 1693, 1624, 1592, 1458, 1305, 1112 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 6.81–6.69 (3H, m, ArH), 5.15 (1H, ddd, *J* = 8.1, 6.0, 1.3 Hz, NCH), 4.70 (1H, d, *J* = 17.1 Hz, CH_aH_bAr), 4.54 (1H, d, *J* = 17.1 Hz, CH_aH_bAr), 3.54 (1H, dd, *J* = 11.5, 8.1 Hz, SCH_aH_b), 3.05 (1H, dd, *J* = 11.5, 1.3 Hz, SCH_aH_b), 2.44–2.31 (1H, m, $CH(CH_3)_2$), 1.06 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(CH_3)_b$), 0.98 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 203.1, 170.8, 164.1 (d, *J* = 12.9 Hz), 161.6 (d, *J* = 13.1 Hz), 137.6, 112.8 (d, *J* = 25.3 Hz), 112.8 (d, *J* = 11.7 Hz), 102.6 (t, *J* = 25.2 Hz), 71.9, 43.7, 30.8, 30.4, 19.0, 17.6; **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{14}H_{16}F_2NOS_2$: 316.0636, found: 316.0626.

1.1.10. (*S*)-4-Isopropyl-*N*-[2-(*p*-nitrophenyl)acetyl]-1,3-thiazolidine-2-thione (4e)

The reaction was carried out as described in the section 1.1.4, but using EDC·HCl (863 mg, 4.5 mmol), *p*-nitrophenylacetic acid (951 mg, 5.25 mmol) and the thiazolidinethione **1** (484 mg, 3.0 mmol). No DMAP was added to the reaction. A further purification by flash column chromatography on silica gel (CH_2Cl_2) afforded 168 mg (0.51 mmol, 17%) of the thioimide **4e** as an orange solid.

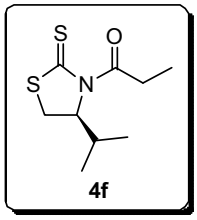


(*S*)-4-Isopropyl-*N*-[2-(*p*-nitrophenyl)acetyl]-1,3-thiazolidine-2-thione (**4e**). Orange solid; **mp** = 84–85 ºC; $\mathbf{R_f}$ = 0.65 (CH_2Cl_2); $\mathbf{[\alpha]_D}$ = +265.6 (*c* 0.55, $CHCl_3$); **IR** (ATR) 3067, 2964, 1690, 1600, 1510, 1389, 1342, 1154 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.20 (2H, d, *J* = 8.7 Hz, ArH), 7.41 (2H, d, *J* = 8.7 Hz, ArH), 5.16 (1H, ddd, *J* = 8.0, 6.1, 1.2 Hz, NCH), 4.86 (1H, d, *J* = 17.0 Hz, CH_aH_bAr), 4.65 (1H, d, *J* = 17.0 Hz, CH_aH_bAr), 3.55 (1H, dd, *J* = 11.5, 8.0 Hz, SCH_aH_b), 3.07 (1H, dd, *J* = 11.5, 1.2 Hz, SCH_aH_b), 2.43–2.32 (1H, m, $CH(CH_3)_2$), 1.07 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(CH_3)_b$), 0.98 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 203.2 (C), 170.5 (C), 147.1 (C), 141.6 (C), 130.7 (CH), 123.6 (CH), 71.9 (CH), 44.0 (CH_2), 30.8 (CH), 30.5 (CH_2), 19.0 (CH_3), 17.7 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{14}H_{17}N_2O_3S_2$: 325.0675, found: 325.0668.

1.1.11. (*S*)-4-Isopropyl-*N*-propanoyl-1,3-thiazolidine-2-thione (4f).

A 1.6 M solution of *n*-BuLi in hexanes (10.3 mL, 16.5 mmol) was added dropwise to a solution of the thiazolidinethione **1** (2.42 g, 15.0 mmol) in anh THF (10.0 mL) at –78 ºC under N_2. The reaction mixture was stirred for 15 min and propanoyl chloride (1.70 mL, 19.5 mmol) was carefully added. The resulting clear solution was stirred for 5 min at –78 ºC and 1.5 h at r.t.

The reaction mixture was cooled with an ice bath and quenched with sat NH_4Cl (6.0 mL) and water (15 mL). This mixture was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic layers were washed with 0.5 M NaOH (3 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The resultant oil was purified by flash column chromatography on silica gel (hexanes/CH_2Cl_2 1:1) to afford 3.20 g (14.7 mmol, 98%) of the thioimide **4f** as a yellow oil.

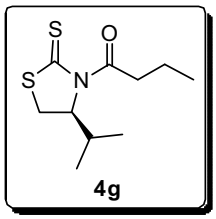


(*S*)-4-Isopropyl-*N*-propanoyl-1,3-thiazolidine-2-thione (**4f**). Yellow oil; $\mathbf{R_f}$ = 0.40 (hexanes/CH_2Cl_2 1:1); $\mathbf{[\alpha]_D}$ = +434.5 (*c* 1.00, $CHCl_3$) [lit.[1] $\mathbf{[\alpha]_D}$ = +420.8 (*c* 1.01, $CHCl_3$)]; **IR** (ATR) 2962, 2874, 1692, 1460, 1345, 1257, 1240 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.17 (1H, ddd, *J* = 8.0, 6.1, 1.2 Hz, NCH), 3.50 (1H, dd, *J* = 11.5, 8.0 Hz, SCH_aH_b), 3.37 (1H, dq, *J* = 18.0, 7.2 Hz, $COCH_aH_b$), 3.15 (1H, dq, *J* = 18.0, 7.2 Hz, $COCH_aH_b$), 3.01 (1H, dd, *J* = 11.5, 1.2 Hz, SCH_aH_b), 2.45–2.29 (1H, m, $CH(CH_3)_2$), 1.17 (3H, t, *J* = 7.2 Hz, CH_2CH_3), 1.06 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(CH_3)_b$), 0.97 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.6, 174.8, 71.6, 32.0, 30.7, 30.3, 19.0, 17.6, 8.9; **HRMS** (+ESI): *m/z* calculated for $[M+Na]^+$ $C_9H_{15}NNaOS_2$; 240.0487, found: 240.0486.

1.1.12. (*S*)-*N*-Butanoyl-4-isopropyl-1,3-thiazolidine-2-thione (4g).

Thioimide **4g** was prepared according to the procedure in section 1.1.11. from a 1.6 M solution of *n*-BuLi in hexanes (2.4 mL, 3.3 mmol), thiazolidinethione **1** (484 mg, 3.0 mmol), butanoyl chloride (405

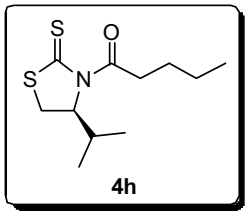
μL, 3.9 mmol) and anh THF (2.0 mL) for 1.5 h at r.t. Purification of the crude product by flash column chromatography (hexanes/EtOAc 9:1) afforded 512 mg (2.21 mmol, 74%) of **4g** as a yellow oil.



(*S*)-*N*-Butanoyl-4-isopropyl-1,3-thiazolidine-2-thione (**4g**). Yellow oil; $\mathbf{R_f}$ = 0.30 (hexanes/EtOAc 9:1); $[\alpha]_D$ = +407.0 (*c* 1.10, $CHCl_3$); **IR** (ATR) 2957, 2927, 2867, 1690, 1460, 1360, 1300, 1252 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 5.17 (1H, ddd, *J* = 8.0, 6.1, 1.3 Hz, NC<u>H</u>), 3.50 (1H, dd, *J* = 11.5, 8.0 Hz, SC<u>H$_a$</u>H$_b$), 3.33 (1H, ddd, *J* = 17.0, 8.4, 6.1 Hz, COC<u>H$_a$</u>H$_b$), 3.11 (1H, ddd, *J* = 17.0, 8.4, 6.5 Hz, COCH$_a$<u>H$_b$</u>), 3.01 (1H, dd, *J* = 11.5, 1.3 Hz, SCH$_a$<u>H$_b$</u>), 2.44–2.28 (1H, m, C<u>H</u>(CH$_3$)$_2$), 1.83–1.58 (2H, m, C<u>H$_2$</u>CH$_3$), 1.06 (3H, d, *J* = 7.0 Hz, CH(C<u>H$_3$</u>)$_a$(CH$_3$)$_b$), 0.97 (3H, d, *J* = 7.0 Hz, CH(CH$_3$)$_a$(C<u>H$_3$</u>)$_b$), 0.97 (3H, t, *J* = 7.4 Hz, CH$_2$C<u>H$_3$</u>); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.6 (C), 173.9 (C), 71.6 (CH), 40.0 (CH_2), 30.8 (CH), 30.4 (CH_2), 19.0 (CH_3), 18.3 (CH_2), 17.7 (CH_3), 13.6 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+Na]^+$ $C_{10}H_{17}NNaOS_2$: 254.0644, found: 254.0643.

1.1.13. (*S*)-4-Isopropyl-*N*-pentanoyl-1,3-thiazolidine-2-thione (4h).

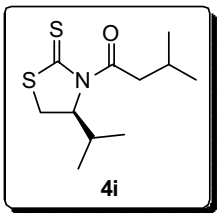
Thioimide **4h** was prepared according to the procedure in section 1.1.11. from a 1.6 M solution of *n*-BuLi in hexanes (2.4 mL, 3.3 mmol), thiazolidinethione **1** (484 mg, 3.0 mmol), pentanoyl chloride (474 μL, 3.9 mmol) and anh THF (2.0 mL) for 1.5 h at r.t. Purification of the crude product by flash column chromatography (hexanes/CH_2Cl_2 1:4) afforded 665 mg (2.71 mmol, 90%) of **4h** as a yellow oil.



(*S*)-4-Isopropyl-*N*-pentanoyl-1,3-thiazolidine-2-thione (**4h**). Yellow oil; $\mathbf{R_f}$ = 0.80 (CH_2Cl_2); $[\alpha]_D$ = +353.2 (*c* 1.10, $CHCl_3$); **IR** (ATR) 2957, 2930, 2869, 1693, 1463, 1247, 1152 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.16 (1H, ddd, *J* = 8.0, 6.5, 1.2 Hz, NC<u>H</u>), 3.50 (1H, dd, *J* = 11.5, 8.0 Hz, SC<u>H$_a$</u>H$_b$), 3.34 (1H, ddd, *J* = 17.0, 9.0, 5.8 Hz, COC<u>H$_a$</u>H$_b$), 3.14 (1H, ddd, *J* = 17.0, 9.0, 6.1, COCH$_a$<u>H$_b$</u>), 3.01 (1H, dd, *J* = 11.5, 1.2 Hz, SCH$_a$<u>H$_b$</u>), 2.42–2.29 (1H, m, C<u>H</u>(CH$_3$)$_2$), 1.76–1.57 (2H, m, COCH$_2$C<u>H$_2$</u>), 1.42–1.32 (2H, m, C<u>H$_2$</u>CH$_3$), 1.06 (3H, d, *J* = 6.8 Hz, CH(C<u>H$_3$</u>)$_a$(CH$_3$)$_b$), 0.97 (3H, d, *J* = 7.0 Hz, CH(CH$_3$)$_a$(C<u>H$_3$</u>)$_b$), 0.93 (3H, t, *J* = 7.4 Hz, CH$_2$C<u>H$_3$</u>); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.6 (C), 174.1 (C), 71.6 (CH), 37.9 (CH_2), 30.8 (CH), 30.4 (CH_2), 26.9 (CH_2), 22.1 (CH_2), 19.0 (CH_3), 17.7 (CH_3), 13.8 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{11}H_{20}NOS_2$: 246.0981, found: 246.0974.

1.1.14. (*S*)-4-Isopropyl-*N*-isovaleryl-1,3-thiazolidine-2-thione (4i).

Thioimide **4i** was prepared according to the procedure in section 1.1.11. from a 1.6 M solution of *n*-BuLi in hexanes (2.4 mL, 3.3 mmol), thiazolidinethione **1** (484 mg, 3.0 mmol), isovaleryl chloride (475 μL, 3.9 mmol) and anh THF (2.0 mL) for 1.5 h at r.t. Purification of the crude product by flash column chromatography (hexanes/CH_2Cl_2 3:7) afforded 656 mg (2.67 mmol, 89%) of **4i** as a yellow oil.

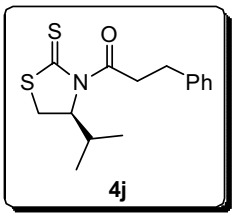


4i

(*S*)-4-Isopropyl-*N*-isovaleryl-1,3-thiazolidine-2-thione (**4i**). Yellow oil; $\mathbf{R_f}$ = 0.40 (hexanes/CH_2Cl_2 1:1); $\mathbf{[\alpha]_D}$ = +382.9 (*c* 1.05, $CHCl_3$); **IR** (ATR) 2955, 2930, 2870, 1688, 1464, 1359, 1293, 1255, 1154, 1086, 1033 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.17 (1H, ddd, *J* = 8.0, 6.2, 1.2 Hz, NC<u>H</u>), 3.49 (1H, dd, *J* = 11.5, 8.0 Hz, SC<u>H$_a$</u>H$_b$), 3.23 (1H, dd, *J* = 16.5, 6.1 Hz, COC<u>H$_a$</u>CH$_b$), 3.06 (1H, dd, *J* = 16.5, 7.4 Hz, COCH$_a$C<u>H$_b$</u>), 3.01 (1H, dd, *J* = 11.5, 1.2 Hz, SCH$_a$<u>H$_b$</u>), 2.43–2.31 (1H, m, NCHC<u>H</u>), 2.27–2.16 (1H, m, CH$_2$C<u>H</u>), 1.06 (3H, d, *J* = 6.8 Hz, CHCH(C<u>H$_3$</u>)$_a$(CH$_3$)$_b$), 0.99 (3H, d, *J* = 6.5 Hz, CH$_2$CH(C<u>H$_3$</u>)$_a$(CH$_3$)$_b$), 0.97 (3H, d, *J* = 6.6 Hz, CHCH(CH$_3$)$_a$(C<u>H$_3$</u>)$_b$), 0.96 (3H, d, *J* = 6.6 Hz, CH$_2$CH(CH$_3$)$_a$(C<u>H$_3$</u>)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.7 (C), 173.2 (C), 71.6 (CH), 46.5 (CH_2), 30.8 (CH), 30.4 (CH_2), 25.4 (CH), 22.5 (CH_3), 22.2 (CH_3), 19.1 (CH_3), 17.7 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{11}H_{20}NOS_2$: 246.0981, found: 246.0982.

1.1.15. (*S*)-*N*-Hydrocinammyl-4-isopropyl-1,3-thiazolidine-2-thione (4j).

Thioimide **4j** was prepared according to the procedure in section 1.1.11. from a 1.6 M solution of *n*-BuLi in hexanes (2.4 mL, 3.3 mmol), thiazolidinethione **1** (484 mg, 3.0 mmol), hydrocinammyl chloride (579 μL, 3.9 mmol) and anh THF (2.0 mL) for 1.5 h at r.t. Purification of the crude product by flash column chromatography (hexanes/CH_2Cl_2 1:4) afforded 684 mg (2.33 mmol, 78%) of **4j** as a yellow oil.

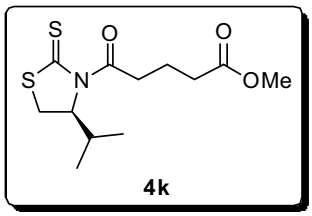


4j

(*S*)-*N*-Hydrocinammyl-4-isopropyl-1,3-thiazolidine-2-thione (**4j**). Yellow solid; **mp** = 84–85 ºC [lit.[4] **mp** = 84 ºC]; $\mathbf{R_f}$ = 0.65 (hexanes/CH_2Cl_2 1:4); $\mathbf{[\alpha]_D}$ = +321.6 (*c* 0.95, $CHCl_3$); **IR** (ATR) 3052, 3022, 2957, 2920, 2867, 1698, 1360, 1255, 1234 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.31–7.18 (5H, m, Ar<u>H</u>), 5.11 (1H, ddd, *J* = 8.0, 6.2, 1.2 Hz, NC<u>H</u>), 3.67 (1H, ddd, *J* = 17.1, 9.0, 5.9 Hz, COC<u>H$_a$</u>H$_b$), 3.52 (1H, ddd, *J* = 17.1, 8.9, 6.6 Hz, COCH$_a$<u>H$_b$</u>), 3.45 (1H, dd, *J* = 11.5, 8.0 Hz, SC<u>H$_a$</u>H$_b$), 3.10–2.93 (2H, m, C<u>H$_2$</u>Ph), 2.99 (1H, dd, *J* = 11.5, 1.2 Hz, SCH$_a$<u>H$_b$</u>), 2.40–2.28 (1H, m, C<u>H</u>(CH$_3$)$_2$), 1.04 (3H, d, *J* = 6.8 Hz, CH(C<u>H$_3$</u>)$_a$(CH$_3$)$_b$), 0.96 (3H, d, *J* = 7.0 Hz, CH(CH$_3$)$_a$(C<u>H$_3$</u>)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.7 (C), 173.1 (C), 140.5 (C), 128.5 (CH), 128.4 (CH), 126.2 (CH), 71.6 (CH), 39.6 (CH_2), 30.9 (CH_2), 30.7 (CH), 30.4 (CH_2), 19.0 (CH_3), 17.7 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{15}H_{20}NOS_2$: 294.0981, found: 294.0974.

1.1.16. (*S*)-4-Isopropyl-*N*-(4-methoxycarbonylbutanoyl)-1,3-thiazolidine-2-thione (4k).

Thioimide **4k** was prepared according to the procedure in section 1.1.11. from a 1.6 M solution of *n*-BuLi in hexanes (3.1 mL, 5.5 mmol), thiazolidinethione **1** (806 mg, 5.0 mmol), glutaric acid monomethyl ester chloride (898 μL, 6.5 mmol) and anh THF (3.3 mL) for 1.5 h at r.t. Purification of the crude product by flash column chromatography (hexanes/EtOAc 4:1) afforded 1.41 g (4.87 mmol, 97%) of **4k** as a yellow oil.

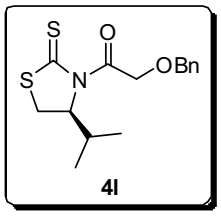


4k

(*S*)-4-Isopropyl-*N*-(4-methoxycarbonylbutanoyl)-1,3-thiazolidine-2-thione (**4k**). Yellow oil; $\mathbf{R_f}$ = 0.45 (hexanes/EtOAc 7:3); $\mathbf{[\alpha]_D}$ = +305.4 (*c* 1.05, $CHCl_3$); **IR** (ATR) 2957, 1872, 1732, 1690, 1434, 1363, 1307, 1252, 1139, 1088, 1030 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.16 (1H, ddd, *J* = 8.0, 6.2, 1.1 Hz, NC$\underline{H}$), 3.69 (3H, s, OC$\underline{H_3}$), 3.52 (1H, dd, *J* = 11.5, 8.0 Hz, SC$\underline{H_a}H_b$), 3.42 (1H, ddd, *J* = 17.6, 7.6, 6.5 Hz, NCOC$\underline{H_a}CH_b$), 3.20 (1H, ddd, *J* = 17.6, 7.8, 6.7 Hz, NCOCH$_a$C$\underline{H_b}$), 3.02 (1H, dt, *J* = 11.5, 1.1 Hz, SCH$_a\underline{H_b}$), 2.44–2.30 (1H, m, NCHC$\underline{H}$), 2.41 (2H, t, *J* = 7.3 Hz, OCOC$\underline{H_2}$), 2.12–1.90 (2H, m, COCH$_2$C$\underline{H_2}$), 1.06 (3H, d, *J* = 6.8 Hz, CHCH(C$\underline{H_3}$)$_a$(CH$_3$)$_b$), 0.97 (3H, d, *J* = 6.9 Hz, CHCH(CH$_3$)$_a$(C$\underline{H_3}$)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.7 (C), 173.4 (C), 173.1 (C), 71.5 (CH), 51.5 (CH_3), 37.4 (CH_2), 32.9 (CH_2), 30.8 (CH), 30.4 (CH_2), 20.1 (CH_2), 19.0 (CH_3), 17.7 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{12}H_{20}NO_3S_2$: 290.0879, found: 290.0887.

1.1.17. (*S*)-*N*-(2-Benzyloxyacetyl)-4-isopropyl-1,3-thiazolidine-2-thione (4l).

Thioimide **4l** was prepared according to the procedure in section 1.1.11. from a 1.6 M solution of *n*-BuLi in hexanes (2.4 mL, 3.3 mmol), thiazolidinethione **1** (484 mg, 3.0 mmol), benzyloxyacetyl chloride (606 µL, 3.9 mmol) and anh THF (2.0 mL) for 1.5 h at r.t. Purification of the crude product by flash column chromatography (from hexanes/EtOAc 9:1 to hexanes/EtOAc 7:3) afforded 684 mg (2.33 mmol, 78%) of **4l** as a yellow oil.



4l

(*S*)-*N*-(2-Benzyloxyacetyl)-4-isopropyl-1,3-thiazolidine-2-thione (**4l**). Yellow oil; $\mathbf{R_f}$ = 0.60 (hexanes/EtOAc 7:3); $\mathbf{[\alpha]_D}$ = +233.6 (*c* 1.10, $CHCl_3$); **IR** (ATR) 3059, 3025, 2959, 2872, 1701, 1463, 1363, 1307, 1260 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.42–7.28 (5H, m, Ar$\underline{H}$), 5.18 (1H, ddd, *J* = 8.1, 6.4, 1.0 Hz, NC$\underline{H}$), 5.05 (1H, d, *J* = 17.7 Hz, COC$\underline{H_a}H_b$), 4.97 (1H, d, *J* = 17.7 Hz, COCH$_a\underline{H_b}$), 4.67 (1H, d, *J* = 11.6 Hz, C$\underline{H_a}H_b$Ph), 4.63 (1H, d, *J* = 11.6 Hz, CH$_a\underline{H_b}$Ph), 3.59 (1H, dd, *J* = 11.5, 8.1 Hz, SC$\underline{H_a}H_b$), 3.08 (1H, dd, *J* = 11.5, 1.0 Hz, SCH$_a\underline{H_b}$), 2.45–2.32 (1H, m, C$\underline{H}$(CH$_3$)$_2$), 1.07 (3H, d, *J* = 6.8 Hz, CH(C$\underline{H_3}$)$_a$(CH$_3$)$_b$), 0.99 (3H, d, *J* = 6.9 Hz, CH(CH$_3$)$_a$(C$\underline{H_3}$)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.1 (C), 171.0 (C), 137.2 (C), 128.4 (CH), 128.0 (CH), 127.9 (CH), 73.4 (CH_2), 72.0 (CH_2), 71.3 (CH), 31.4 (CH_2), 30.7 (CH), 19.0 (CH_3), 17.6 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{15}H_{20}NO_2S_2$: 310.0930, found: 310.0930.

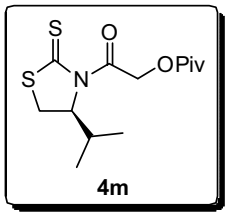
1.1.18. (*S*)-4-Isopropyl-*N*-(2-pivaloyloxyacetyl)-1,3-thiazolidine-2-thione (4m)

A mixture of pivaloyl chloride (4.4 mL, 36 mmol) and glycolic acid (1.52 g, 20 mmol) was stirred for 60 h at r.t. under N_2. Then, the volatiles were eliminated under vacuum and the crude product, 2-pivaloyloxy acetic acid, was used in the next step without further purification.

Thiazolidinethione **1** (2.74 mg, 17.0 mmol) and DMAP (104 mg, 0.85 mmol) were added to a solution of the previous crude in anh CH_2Cl_2 (27 mL) under N_2 at 0 ºC, and then EDC·HCl (4.89 g, 25.5

mmol) was also added. The mixture was purged with N_2 again. The reaction mixture was stirred for 16 h at r.t.

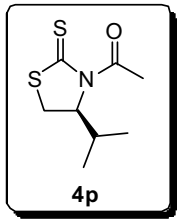
The resulting yellow reaction mixture was diluted in Et_2O (50 mL) and washed with 0.5 M HCl (3 × 40 mL), 0.5 M NaOH (3 × 40 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography on silica gel (hexanes/EtOAc 9:1) to give 4.11 g (13.5 mmol, 80%) of the thioimide **4m** as a dense yellow oil.



(*S*)-*N*-(2-Pivaloyloxyacetyl)-4-isopropyl-1,3-thiazolidine-2-thione (**4m**). Dense yellow oil; $\mathbf{R_f}$ = 0.50 (hexanes/CH_2Cl_2 7:3); $\mathbf{[\alpha]_D}$ = +232.8 (*c* 1.00, $CHCl_3$); **IR** (film) 2965, 2874, 1740, 1714, 1141 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.44 (2H, s, COC$\underline{H}_2$), 5.11 (1H, ddd, *J* = 8.1, 5.9, 1.1 Hz, NC$\underline{H}$), 3.63 (1H, dd, *J* = 11.5, 8.1 Hz, SC$\underline{H}_a$H$_b$), 3.09 (1H, dd, *J* = 11.5, 1.1 Hz, SCH$_a\underline{H}_b$), 2.43–2.32 (1H, m, C$\underline{H}$(CH$_3$)$_2$), 1.27 (9H, s, CH(C$\underline{H}_3$)$_3$), 1.06 (3H, d, *J* = 6.8 Hz, CH(C$\underline{H}_3$)$_a$(CH$_3$)$_b$), 0.98 (3H, d, *J* = 7.0 Hz, CH(CH$_3$)$_a$(C$\underline{H}_3$)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.5 (C), 177.9 (C), 168.1 (C), 71.4 (CH), 65.0 (CH_2), 38.7 (C), 31.4 (CH), 30.7 (CH_2), 27.1 (CH_3), 19.0 (CH_3), 17.5 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{13}H_{22}NO_3S_2$: 304.1036, found: 304.1037; calculated for $[M+Na]^+$ $C_{13}H_{21}NNaO_3S_2$: 326.0855, found: 326.0859.

1.1.19. (*S*)-*N*-Acetyl-4-isopropyl-1,3-thiazolidine-2-thione (4p).

The reaction was carried out as described in the section 1.1.11, but using a 1.6 M solution of *n*-BuLi in hexanes (15.0 mL, 24.0 mmol), thiazolidinethione **1** (3.22 g, 20.0 mmol), acetyl chloride (2.0 mL, 28 mmol) and anh THF (14 mL). A further purification by flash column chromatography on silica gel (from hexanes/CH_2Cl_2 1:1 to CH_2Cl_2) afforded 3.87 mg (19 mmol, 95%) of the thioimide **4p** as a yellow oil.



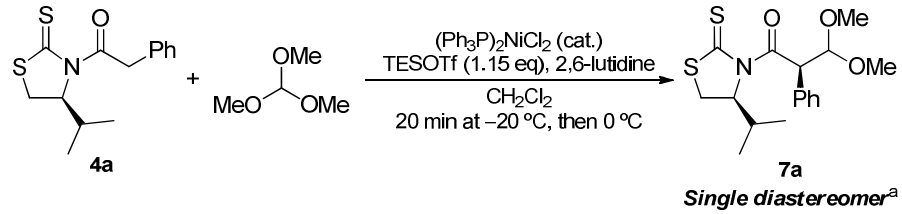
(*S*)-*N*-Acetyl-4-isopropyl-1,3-thiazolidine-2-thione (**4p**). Yellow oil; $\mathbf{R_f}$ = 0.75 (CH_2Cl_2); $\mathbf{[\alpha]_D}$ = +442.7 (*c* 2.67, $CHCl_3$); **IR** (film) 2970, 1690, 1480, 1395, 1375, 1285, 1205 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 5.15 (1H, ddd, *J* = 8.1, 6.3, 1.2 Hz, NC$\underline{H}$), 3.51 (1H, dd, *J* = 11.5, 8.1 Hz, SC$\underline{H}_a$H$_b$), 3.02 (1H, dd, *J* = 11.5, 1.2 Hz, SCH$_a\underline{H}_b$), 2.77 (3H, s, COC$\underline{H}_3$), 2.45–2.27 (1H, m, C$\underline{H}$(CH$_3$)$_2$), 1.06 (3H, d, *J* = 6.9 Hz, CH(C$\underline{H}_3$)$_a$(CH$_3$)$_b$), 0.98 (3H, d, *J* = 6.9 Hz, CH(CH$_3$)$_a$(C$\underline{H}_3$)$_b$); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 203.2, 170.7, 71.2, 30.7, 30.4, 26.9, 19.0, 17.7.

1.2. OPTIMIZATION USING (*S*)-4-ISOPROPYL-*N*-PHENYLACETYL-1,3-THIAZOLIDINE-2-THIONE (4a)

1.2.1. Optimization of theamount of catalyst and reaction time

Solid $(Ph_3P)_2NiCl_2$ was added to a solution of thioimide **4a** (279 mg, 1.00 mmol) and trimethyl orthoformate (165 μL, 1.50 mmol) in anh CH_2Cl_2 (2.0 mL) under N_2. The resulting black suspension was purged with N_2 again and then cooled to –20 ºC. TESOTf (260 μL, 1.15 mmol) and 2,6-lutidine (165 μL, 1.50 mmol) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred at –20 ºC for 20 min and then placed in an ice bath for a certain time.

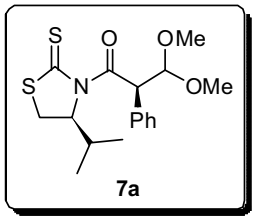
The reaction was quenched with sat NH_4Cl (2.5 mL) and then diluted in H_2O (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (70 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. ^{1}H NMR spectrum of the crude product revealed the presence of a single diastereoisomer of the desired formylated product. The crude product was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/CH_2Cl_2 2:3) to give the formylated product **7a** as a yellow solid. The yields obtained with different quantities of catalyst and reaction times are shown in Table 33.



Entry	Cat. (mol%)	reaction time (h)	Yield (%)[b]
1[c]	20.0	3	86
2	2.5	1	94
3	1.5	1	91
4	1.0	1	78
5	1.0	2	80
6	1.0	5	77
7	–	5	n.r.

[a] Observed by ^{1}H NMR of the crude product.
[b] Isolated yield after column chromatography.
[c] Carried out by Erik Gálvez. 1.50 eq of TESOTf was used.

Table 33



(*S*)-4-Isopropyl-*N*-[(*R*)-3,3-dimethoxy-2-phenylpropanoyl]-1,3-thiazolidine-2-thione (**7a**). Yellow solid; **mp** = 100–101 ºC; $\mathbf{R_f}$ = 0.65 (CH_2Cl_2); $\mathbf{[\alpha]_D}$ = +169.5 (*c* 1.05, $CHCl_3$); **IR** (ATR) 2928, 2825, 1692, 1338, 1313 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.43–7.41 (2H, m, ArH), 7.34–7.27 (3H, m, ArH), 6.77 (1H, d, *J* = 8.5 Hz, CHPh), 5.13 (1H, ddd, *J* = 8.0, 6.3, 1.0 Hz, NCH), 5.07 (1H,

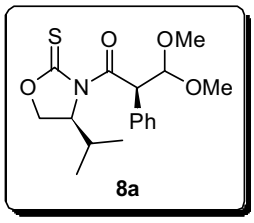
d, J = 8.5 Hz, C<u>H</u>$(OCH_3)_2$), 3.40 (3H, s, CH$(OC\underline{H_3})_a(OCH_3)_b$), 3.24 (1H, dd, J = 11.5, 8.0 Hz, $SC\underline{H_a}H_b$), 3.19 (3H, s, CH$(OCH_3)_a(OC\underline{H_3})_b$), 2.89 (1H, dd, J = 11.5, 1.0 Hz, $SCH_a\underline{H_b}$), 2.43–2.30 (1H, m, C<u>H</u>$(CH_3)_2$), 1.07 (3H, d, J = 6.8 Hz, CH$(C\underline{H_3})_a(CH_3)_b$), 1.01 (3H, d, J = 7.0 Hz, CH$(CH_3)_a(C\underline{H_3})_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 203.3 (C), 172.1 (C), 134.7 (C), 129.6 (CH), 128.8 (CH), 128.0 (CH), 106.4 (CH), 72.2 (CH), 55.1 (CH_3), 53.4 (CH_3), 51.5 (CH), 30.9 (CH), 29.8 (CH_2), 19.2 (CH_3), 18.0 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+Na]^+$ $C_{17}H_{23}NNaO_3S_2$: 376.1012, found: 376.1023.

1.2.2. Influence of the chiral auxiliary

1.2.2.1. Assessment of an oxazolidinethione scaffold

Solid $(Ph_3P)_2NiCl_2$ (8.2 mg, 12.5 μmol) was added to a solution of (*S*)-4-isopropyl-*N*-phenylacetyl-1,3-oxazolidine-2-thione **2** (132 mg, 0.50 mmol) and trimethyl orthoformate (83 μL, 0.75 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2. The resulting black suspension was purged with N_2 again and then cooled to –20 ºC. TESOTf (130 μL, 0.58 mmol) and 2,6-lutidine (88 μL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred at –20 ºC for 20 min and then placed in an ice bath for 1 h.

The reaction was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. ^{1}H NMR spectrum of the crude product revealed the presence of a single diastereoisomer of the desired formylated product. The crude product was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/CH_2Cl_2 1:9) to give 79 mg (0.23 mmol, 47%) of the formylated product **8a** as a white solid.



8a

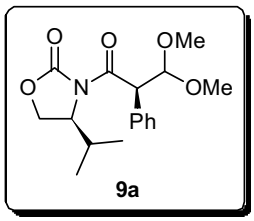
(*S*)-4-Isopropyl-*N*-[(*R*)-3,3-dimethoxy-2-phenylpropanoyl]-1,3-oxazolidine-2-thione (**8a**). White solid; **mp** = 75–78 ºC; **R_f** = 0.30 (CH_2Cl_2); **$[\alpha]_D$** = +22.1 (*c* 1.25, $CHCl_3$); **IR** (ATR) 2929, 2877, 2829, 1694, 1364 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.55–7.52 (2H, m, Ar<u>H</u>), 7.35–7.28 (3H, m, Ar<u>H</u>), 6.90 (1H, d, J = 8.6 Hz, C<u>H</u>Ph), 5.07 (1H, d, J = 8.6 Hz, C<u>H</u>$(OMe)_2$), 4.71 (1H, m, NC<u>H</u>), 4.32 (1H, dd, J = 9.4, 2.7 Hz, $OC\underline{H_a}H_b$), 4.24 (1H, dd, J = 9.4, 8.4 Hz, $OCH_a\underline{H_b}$), 3.42 (3H, s, CH$(OC\underline{H_3})_a(OCH_3)_b$), 3.22 (3H, s, CH$(OCH_3)_a(OC\underline{H_3})_b$), 2.41–2.27 (1H, m, C<u>H</u>$(CH_3)_2$), 0.96 (3H, d, J = 7.0 Hz, CH$(C\underline{H_3})_a(CH_3)_b$), 0.93 (3H, d, J = 7.0 Hz, CH$(CH_3)_a(C\underline{H_3})_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 185.8, 172.3, 134.2, 129.6, 128.5, 127.8, 106.4, 67.0, 63.2, 54.8, 52.9, 50.2, 28.9, 18.2, 14.8; **HRMS** (+ESI): *m/z* calculated for $[M–OMe]^+$ $C_{16}H_{20}NO_3S$: 306.1158, found: 306.1161.

1.2.2.2. Assessment of an oxazolidinone scaffold

Solid $(Ph_3P)_2NiCl_2$ (8.2 mg, 12.5 μmol) was added to a solution of (*S*)-4-isopropyl-*N*-phenylacetyl-1,3-oxazolidin-2-one **6a** (124 mg, 0.50 mmol) and trimethyl orthoformate (83 μL, 0.75 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2. The resulting black suspension was purged with N_2 again and

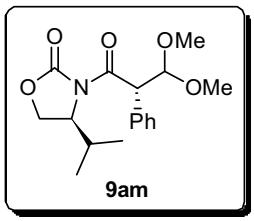
then cooled to –20 ºC. TESOTf (130 µL, 0.58 mmol) and 2,6-lutidine (88 µL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred at –20 ºC for 20 min and then placed in an ice bath for 1 h.

The reaction was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. ^{1}H NMR spectrum of the crude product revealed the presence of a single diastereoisomer of the desired formylated product. The crude product was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) (CH_2Cl_2) to give 97 mg (0.30 mmol, 60%) of the isolated *major* diastereomer of formylated product **9a** and 16 mg (0.05 mmol, 10%) of the isolated *minor* one (**9am**).



9a

(*S*)-4-Isopropyl-*N*-[(*R*)-3,3-dimethoxy-2-phenylpropanoyl]-1,3-oxazolidin-2-one (**9a**). White solid; **mp** = 83–86 ºC; $\mathbf{R_f}$ = 0.40 (hexanes/EtOAc 4:1); $\mathbf{[\alpha]_D}$ = +54.0 (*c* 0.80, $CHCl_3$); **IR** (ATR) 2956, 2930, 2830, 1775, 1695, 1105, 1059 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.51–7.48 (2H, m, ArH), 7.36–7.25 (3H, m, ArH), 5.64 (1H, d, *J* = 8.8 Hz, CHPh), 5.09 (1H, d, *J* = 8.8 Hz, $CH(OMe)_2$), 4.39 (1H, ddd, *J* = 6.5, 5.1, 4.0 Hz, NCH), 4.15–4.13 (2H, m, OCH_2), 3.42 (3H, s, $CH(OCH_3)_a(OCH_3)_b$), 3.20 (3H, s, $CH(OCH_3)_a(OCH_3)_b$), 2.49–2.34 (1H, m, $CH(CH_3)_2$), 0.94 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_a(CH_3)_b$), 0.92 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 171.4, 153.6, 134.3, 129.4, 128.5, 127.7, 105.9, 62.9, 58.5, 55.0, 52.5, 51.2, 28.4, 17.8, 14.6; **HRMS** (+ESI): *m/z* calculated for $[M–OMe]^+$ $C_{16}H_{20}NO_4$: 290.1387, found: 290.1392.



9am

(*S*)-4-Isopropyl-*N*-[(*S*)-3,3-dimethoxy-2-phenylpropanoyl]-1,3-oxazolidin-2-one (**9am**). Colorless oil; $\mathbf{R_f}$ = 0.20 (hexanes/EtOAc 4:1); $\mathbf{[\alpha]_D}$ = +6.2 (*c* 0.90, $CHCl_3$); **IR** (ATR) 2959, 2925, 1769, 1693, 1453, 1365, 1191, 1107, 1052 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.48–7.44 (2H, m, ArH), 7.35–7.24 (3H, m, ArH), 5.50 (1H, d, *J* = 8.8 Hz, CHPh), 5.11 (1H, d, *J* = 8.8 Hz, $CH(OMe)_2$), 4.48 (1H, ddd, *J* = 8.8, 3.8, 3.0 Hz, NCH), 4.25 (1H, t, *J* = 8.8 Hz, OCH_aH_b), 4.12 (1H, dd, *J* = 8.8, 3.0 Hz, OCH_aH_b), 3.44 (3H, s, $CH(OCH_3)_a(OCH_3)_b$), 3.17 (3H, s, $(OCH_3)_a(OCH_3)_b$), 2.25–2.09 (1H, m, $CH(CH_3)_2$), 0.79 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_a(CH_3)_b$), 0.46 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 171.1, 153.4, 134.2, 129.2, 128.5, 127.7, 105.0, 62.9, 58.0, 55.4, 52.7, 51.7, 27.9, 17.7, 14.0; **HRMS** (+ESI): *m/z* calculated for $[M–OMe]^+$ $C_{16}H_{20}NO_4$: 290.1387, found: 290.1392.

1.3. INFLUENCE OF THE *N*-ACYL GROUP

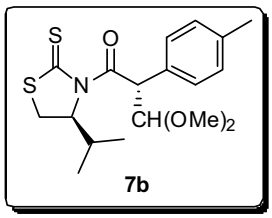
1.3.1. General Procedure

Solid $(Ph_3P)_2NiCl_2$ was added to a solution of the corresponding (*S*)-*N*-arylacetyl-4-isopropyl-1,3-thiazolidine-2-thione and trimethyl orthoformate in anh CH_2Cl_2 under N_2. The resulting black suspension was purged with N_2 again and then cooled to –20 ºC. TESOTf and 2,6-lutidine were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred at –20 ºC for 20 min and then placed in an ice bath for 1 h.

The reaction was quenched with sat NH_4Cl (2.4 mL) and then diluted in H_2O (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (70 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. ^{1}H NMR spectrum of the crude product revealed the presence of a single diastereoisomer of the corresponding desired formylated product. The crude product was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) to give the desired formylated product.

1.3.2. (*S*)-4-Isopropyl-*N*-[(*R*)-3,3-dimethoxy-2-(*p*-tolyl)propanoyl]-1,3-thiazolidine-2-thione (7b)

The formylated product **7b** was prepared according to the General Procedure in section 1.3.1. from thioimide **4b** (294 mg, 1.00 mmol), $(Ph_3P)_2NiCl_2$ (16.4 mg, 25.0 μmol), trimethyl orthoformate (164 μL, 1.50 mmol), TESOTf (260 μL, 1.15 mmol), 2,6-lutidine (174 μL, 1.50 mmol) and CH_2Cl_2 (2.0 mL) at –20 ºC for 20 min and at 0 ºC for 1 h. Purification of the crude product by flash column chromatography on deactivated silica gel (2.5% Et_3N) (CH_2Cl_2) afforded 322 mg (0.88 mmol, 88%) of **7b** as a yellow solid.

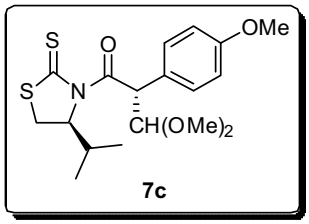


7b

(*S*)-4-Isopropyl-*N*-[(*R*)-3,3-dimethoxy-2-(*p*-tolyl)propanoyl]-1,3-thiazolidine-2-thione (**7b**). Yellow solid; **mp** = 105–107 ºC; $\mathbf{R_f}$ = 0.40 (CH_2Cl_2); $\mathbf{[\alpha]_D}$ = +166.1 (*c* 1.00, $CHCl_3$); **IR** (ATR) 2964, 2930, 1687, 1331, 1239 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.30 (2H, d, *J* = 8.0 Hz, ArH), 7.12 (2H, d, *J* = 8.0 Hz, ArH), 6.73 (1H, d, *J* = 8.5 Hz, CHAr), 5.12 (1H, ddd, *J* = 8.0, 6.3, 0.9 Hz, NCH), 5.06 (1H, d, *J* = 8.5 Hz, $CH(OCH_3)_2$), 3.42 (3H, s, $CH(OCH_3)_a(OCH_3)_b$), 3.24 (1H, dd, *J* = 11.4, 8.0 Hz, SCH_aH_b), 3.19 (3H, s, $CH(OCH_3)_a(OCH_3)_b$), 2.88 (1H, dd, *J* = 11.4, 0.9 Hz, SCH_aH_b), 2.42–2.29 (1H, m, $CH(CH_3)_2$), 2.31 (3H, s, $ArCH_3$), 1.07 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(CH_3)_b$), 1.01 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 203.6 (C), 172.1 (C), 137.5 (C), 131.4 (C), 129.3 (CH), 129.2 (CH), 106.1 (CH), 72.0 (CH), 54.9 (CH_3), 53.0 (CH_3), 50.8 (CH), 30.7 (CH), 29.6 (CH_2), 21.1 (CH_3), 19.0 (CH_3), 17.8 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OMe]^+$ $C_{17}H_{22}NO_2S_2$: 336.1086, found: 336.1079.

1.3.3. (*S*)-4-Isopropyl-*N*-[(*R*)-3,3-dimethoxy-2-(*p*-methoxyphenyl)propanoyl]-1,3-thiazolidine-2-thione (7c)

The formylated product **7c** was prepared according to the General Procedure in section 1.3.1. from thioimide **4c** (310 mg, 1.00 mmol), $(Ph_3P)_2NiCl_2$ (16.4 mg, 25.0 μmol), trimethyl orthoformate (164 μL, 1.50 mmol), TESOTf (260 μL, 1.15 mmol), 2,6-lutidine (174 μL, 1.50 mmol) and CH_2Cl_2 (2.0 mL) at –20 ºC for 20 min and at 0 ºC for 1 h. Purification of the crude product by flash column chromatography on deactivated silica gel (2.5% Et_3N) (CH_2Cl_2) afforded 351 mg (0.91 mmol, 91%) of **7c** as a yellow solid.

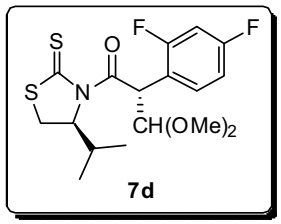


7c

(*S*)-4-Isopropyl-*N*-[(*R*)-3,3-dimethoxy-2-(*p*-methoxyphenyl)propanoyl]-1,3-thiazolidine-2-thione (**7c**). Yellow solid; **mp** = 106–109 ºC; $\mathbf{R_f}$ = 0.45 (CH_2Cl_2); $\mathbf{[\alpha]_D}$ = +185.8 (*c* 1.00, $CHCl_3$); **IR** (ATR) 2957, 2933, 1690, 1508, 1458, 1255, 1239 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.34 (2H, d, *J* = 8.8 Hz, Ar<u>H</u>), 6.85 (2H, d, *J* = 8.8 Hz, Ar<u>H</u>), 6.69 (1H, d, *J* = 8.5 Hz, ArC<u>H</u>), 5.13 (1H, ddd, *J* = 8.0, 6.3, 0.9 Hz, NC<u>H</u>), 5.03 (1H, d, *J* = 8.5 Hz, C<u>H</u>$(OCH_3)_2$), 3.79 (3H, s, ArOC<u>H$_3$</u>), 3.42 (3H, s, CH(OC<u>H$_3$</u>)$_a$(OCH$_3$)$_b$), 3.25 (1H, dd, *J* = 11.5, 8.0 Hz, SC<u>H$_a$</u>H$_b$), 3.19 (3H, s, CH(OCH$_3$)$_a$(OC<u>H$_3$</u>)$_b$), 2.89 (1H, dd, *J* = 11.5, 0.9 Hz, SCH$_a$<u>H$_b$</u>), 2.42–2.30 (1H, m, C<u>H</u>$(CH_3)_2$), 1.07 (3H, d, *J* = 6.8 Hz, CH(C<u>H$_3$</u>)$_a$(CH$_3$)$_b$), 1.01 (3H, d, *J* = 7.0 Hz, CH(CH$_3$)$_a$(C<u>H$_3$</u>)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 203.1 (C), 172.2 (C), 159.1 (C), 130.4 (CH), 126.5 (C), 114.0 (CH), 106.1 (CH), 72.0 (CH), 55.2 (CH_3), 54.9 (CH_3), 53.1 (CH_3), 50.4 (CH), 30.7 (CH), 29.6 (CH_2), 19.0 (CH_3), 17.8 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OMe]^+$ $C_{17}H_{22}NO_3S_2$: 352.1036, found: 352.1034.

1.3.4. (*S*)-*N*-[(*R*)-2-(2,4-Difluorophenyl)-3,3-dimethoxypropanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (7d)

The formylated product **7d** was prepared according to the General Procedure in section 1.3.1. from thioimide **4d** (95 mg, 0.30 mmol), $(Ph_3P)_2NiCl_2$ (4.9 mg, 7.5 μmol), trimethyl orthoformate (49 μL, 0.45 mmol), TESOTf (78 μL, 0.35 mmol), 2,6-lutidine (52 μL, 0.45 mmol) and CH_2Cl_2 (0.6 mL) at –20 ºC for 20 min and at 0 ºC for 1 h. Purification of the crude product by flash column chromatography (from hexanes/CH_2Cl_2 7:3 to 1:1) afforded 86 mg (0.22 mmol, 74%) of **7d** as a yellow solid.



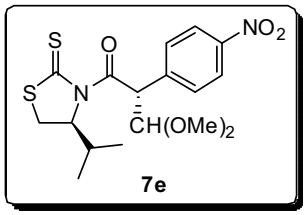
7d

(*S*)-*N*-[(*R*)-2-(2,4-Difluorophenyl)-3,3-dimethoxypropanoyl]-4-isopropyl -1,3-thiazolidine-2-thione (**7d**). Yellow solid; **mp** = 68–69 ºC; $\mathbf{R_f}$ = 0.55 (hexanes/CH_2Cl_2 3:7); $\mathbf{[\alpha]_D}$ = +96.9 (*c* 1.05, $CHCl_3$); **IR** (ATR) 3091, 2958, 2838, 1698, 1619, 1590, 1309, 1170, 1104, 1067, 1046 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.01–6.94 (2H, m, Ar<u>H</u>), 6.81 (1H, d, *J* = 8.3 Hz, ArC<u>H</u>), 6.73 (1H, tt, *J* = 8.9, 2.3 Hz, Ar<u>H</u>), 5.23 (1H, ddd, *J* = 8.1, 6.1, 1.3 Hz, NC<u>H</u>), 4.99 (1H, d, *J* = 8.3 Hz, C<u>H</u>$(OCH_3)_2$), 3.42 (3H, s, CH(OC<u>H$_3$</u>)$_a$(OCH$_3$)$_b$), 3.33 (1H, dd, *J* = 11.5, 8.1 Hz, SC<u>H$_a$</u>H$_b$), 3.22 (3H,

s, $CH(OCH_3)_a(OC\underline{H_3})_b$), 2.93 (1H, dd, *J* = 11.5, 1.3 Hz, $SCH_a\underline{H_b}$), 2.41–2.29 (1H, m, $C\underline{H}(CH_3)_2$), 1.08 (3H, d, *J* = 6.8 Hz, $CH(C\underline{H_3})_a(CH_3)_b$), 1.01 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_a(C\underline{H_3})_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 203.2 (C), 170.9 (C), 164.0 (C, d, *J* = 12.9 Hz), 161.6 (C, d, *J* = 12.9 Hz), 138.0 (C, t, *J* = 9.7 Hz), 112.5 (CH, d, *J* = 25.7 Hz), 112.5 (CH, d, *J* = 11.7 Hz), 106.0 (CH), 103.4 (CH, d, *J* = 25.3 Hz), 71.8 (CH), 55.0 (CH_3), 53.5 (CH_3), 50.9 (CH), 30.6 (CH), 29.3 (CH_2), 18.9 (CH_3), 17.5 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OMe]^+$ $C_{16}H_{18}F_2NO_2S_2$: 358.0742, found: 358.0742.

1.3.5. (*S*)-4-Isopropyl-*N*-[(R)-3,3-dimethoxy-2-(*p*-nitrophenyl)propanoyl]-1,3-thiazolidine-2-thione (7e)

The formylated product **7e** was prepared according to the General Procedure in section 1.3.1. from thioimide **4e** (97 mg, 0.30 mmol), $(Ph_3P)_2NiCl_2$ (4.9 mg, 7.5 μmol), trimethyl orthoformate (49 μL, 0.45 mmol), TESOTf (78 μL, 0.35 mmol), 2,6-lutidine (52 μL, 0.45 mmol) and CH_2Cl_2 (0.6 mL) at –20 ºC for 20 min and at 0 ºC for 1 h. Purification of the crude product by flash column chromatography (hexanes/CH_2Cl_2 1:1) afforded 85 mg (0.21 mmol, 71%) of **7e** as an orange solid.



7e

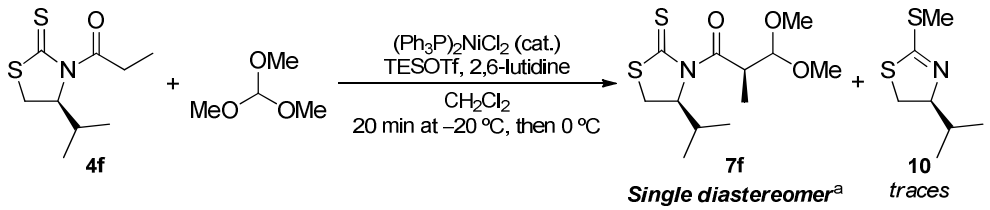
(*S*)-4-Isopropyl-*N*-[(R)-3,3-dimethoxy-2-(*p*-nitrophenyl)propanoyl]-1,3-thiazolidine-2-thione (**7e**). Orange solid; **mp** = 114–116 ºC; **R_f** = 0.55 (CH_2Cl_2); **$[\alpha]_D$** = +148.3 (*c* 0.55, $CHCl_3$); **IR** (ATR) 2959, 2930, 1685, 1603, 1516, 1344, 1154, 1107, 1064, 1030 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.18 (2H, d, *J* = 8.8 Hz, Ar$\underline{H}$), 7.61 (2H, d, *J* = 8.8 Hz, Ar$\underline{H}$), 6.91 (1H, d, *J* = 8.1 Hz, ArC$\underline{H}$), 5.24 (1H, ddd, *J* = 8.3, 6.1, 1.2 Hz, NC$\underline{H}$), 5.05 (1H, d, *J* = 8.2 Hz, $C\underline{H}(OCH_3)_2$), 3.44 (3H, s, $CH(OC\underline{H_3})_a(OCH_3)_b$), 3.31 (1H, dd, *J* = 11.5, 8.3 Hz, $SC\underline{H_a}H_b$), 3.21 (3H, s, $CH(OCH_3)_a(OC\underline{H_3})_b$), 2.94 (1H, dd, *J* = 11.5, 1.2 Hz, $SCH_a\underline{H_b}$), 2.42–2.30 (1H, m, $C\underline{H}(CH_3)_2$), 1.09 (3H, d, *J* = 6.8 Hz, $CH(C\underline{H_3})_a(CH_3)_b$), 1.02 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_a(C\underline{H_3})_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 203.2 (C), 170.8 (C), 147.4 (C), 141.7 (C), 130.5 (CH), 123.5 (CH), 106.0 (CH), 71.8 (CH), 55.1 (CH_3), 53.7 (CH_3), 51.6 (CH), 30.6 (CH), 29.2 (CH_2), 18.9 (CH_3), 17.4 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OMe]^+$ $C_{16}H_{19}N_2O_4S_2$: 367.0781, found: 367.0781.

1.4. OPTIMIZATION USING (*S*)-4-ISOPROPYL-*N*-PROPANOYL-1,3-THIAZOLIDINE-2-THIONE (4f)

1.4.1. Influence of the amount of catalyst and the reaction time

Solid $(Ph_3P)_2NiCl_2$ was added to a solution of thioimide **4f** (217 mg, 1.00 mmol) and trimethyl orthoformate (165 μL, 1.50 mmol) in anh CH_2Cl_2 (2.0 mL) under N_2. The resulting black suspension was purged with N_2 again and then cooled to –20 ºC. TESOTf and 2,6-lutidine (165 μL, 1.50 mmol) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred at –20 ºC for 20 min and then placed in an ice bath for a certain time.

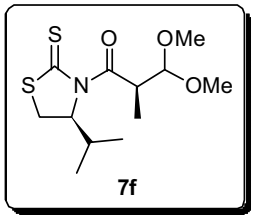
The reaction was quenched with sat NH_4Cl (2.5 mL) and then diluted in H_2O (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (70 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. ^{1}H NMR spectrum of the crude product revealed the presence of a single diastereoisomer of the desired formylated product. The crude product was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/CH_2Cl_2 1:4) to give the formylated product **7f** as a yellow oil and traces of the isolated *S*-methylated byproduct **10**.



Entry	Cat. (mol%)	TESOTf (eq)	reaction time	Yield (%)[b]
1	2.5	1.15	15 h	12
2	10.0	1.30	15 h	46
3	20.0	1.50	15 min	46
4	20.0	1.50	30 min	68
5	20.0	1.50	1 h	72
6	20.0	1.50	15 h	75

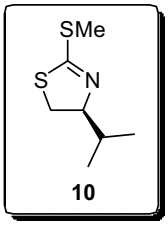
[a] Observed by ^{1}H NMR of the crude product.
[b] Isolated yield after column chromatography.

Table 34



(*S*)-4-Isopropyl-*N*-[(*R*)-3,3-dimethoxy-2-methylpropanoyl]-1,3-thiazolidine-2-thione (**7f**). Yellow oil; $\mathbf{R_f}$ = 0.20 (CH_2Cl_2); $\mathbf{[\alpha]_D}$ = +173.6 (*c* 1.00, $CHCl_3$); **IR** (ATR) 2959, 2930, 1690, 1453, 1368, 1310, 1247 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.31–5.21 (2H, m, NC<u>H</u>, COC<u>H</u>), 4.68 (1H, d, *J* = 7.8 Hz, C<u>H</u>(OMe)$_2$), 3.44 (1H, dd, *J* = 11.5, 8.7 Hz, SC<u>H$_a$</u>H$_b$), 3.35 (3H, s, CH(OC<u>H$_3$</u>)$_a$(OCH$_3$)$_b$), 3.32 (3H, s, CH(OCH$_3$)$_a$(OC<u>H$_3$</u>)$_b$), 2.98 (1H, dd, *J* = 11.5, 1.9 Hz, SCH$_a$<u>H$_b$</u>), 2.36–2.24 (1H, m, C<u>H</u>(CH$_3$)$_2$), 1.18 (3H, d, *J* = 6.9 Hz, COCHC<u>H$_3$</u>), 1.06 (3H, d, *J* = 6.8 Hz, CH(C<u>H$_3$</u>)$_a$(CH$_3$)$_b$), 0.98 (3H, d, *J* = 7.0 Hz,

$CH(CH_3)_a(C\underline{H}_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.6 (C), 175.4 (C), 105.9 (CH), 71.6 (CH), 55.0 (CH_3), 52.1 (CH_3), 41.6 (CH), 30.5 (CH), 28.8 (CH_2), 18.9 (CH_3), 16.9 (CH_3), 13.0 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{12}H_{22}NO_3S_2$: 292.1036, found: 292.1040.

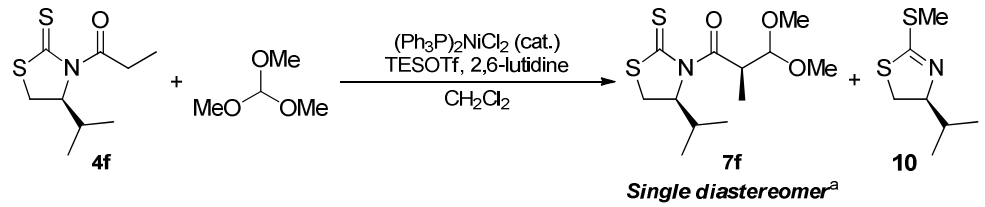


(*S*)-4-Isopropyl-2-(methylthio)-4,5-dihydrothiazole (**10**). Colorless oil; **R_f** = 0.30 (CH_2Cl_2); **$[\alpha]_D$** = +7.2 (*c* 0.73, $CHCl_3$); **IR** (film) 2957, 2926, 2869, 1568, 1462, 943 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 4.18 (1H, ddd, *J* = 9.0, 8.3, 6.6 Hz, NC$\underline{H}$), 3.39 (1H, dd, *J* = 10.7, 8.3 Hz, SC$\underline{H}_a$H$_b$), 3.14 (1H, dd, *J* = 10.7, 9.0 Hz, SCH$_a\underline{H}_b$), 2.53 (3H, s, SC$\underline{H}_3$), 2.01–1.93 (1H, m, C$\underline{H}(CH_3)_2$), 1.06 (3H, d, *J* = 6.8 Hz, $CH(C\underline{H}_3)_a(CH_3)_b$), 0.97 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(C\underline{H}_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 163.8, 83.3, 37.4, 33.1, 19.8, 19.0, 15.3; **MS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{12}H_{22}NO_3S_2$: 175.05, found: 175.08.

1.4.2. Influence of the temperature

Solid $(Ph_3P)_2NiCl_2$ was added to a solution of thioimide **4f** (109 mg, 1.00 mmol) and trimethyl orthoformate (83 μL, 0.75 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2. The resulting black suspension was purged with N_2 again and then cooled to certain temperature. TESOTf and 2,6-lutidine (88 μL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred at the temperature and during the reaction time indicated at Table 35.

The reaction was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. ^{1}H NMR spectrum of the crude product revealed the presence of a single diastereoisomer of the desired formylated product. The crude product was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/CH_2Cl_2 1:4) to give the formylated product **7f** as a yellow oil and the isolated *S*-methylated byproduct **10** as a volatile clear oil.



Entry	Cat. (mol%)	TESOTf (eq)	t (h)	T (ºC)	Yield (%)[b]	r.s.m.[c] (%)	**10** (%)[b]
1[d]	20.0	1.50	1.0	0	72	21	6
2	20.0	1.50	1.5	0	66	–	14
3	20.0	1.50	1.5	–20	73	23	–
4	20.0	1.50	3.0	–20	84	16	–
5	20.0	1.50	5.0	–20	88	5	–
6	20.0	1.50	15.0	–20	82	4	3
7	10.0	1.30	5.0	–20	60	32	–
8	10.0	1.30	15.0	–20	58	35	6
9	5.0	1.20	15.0	–20	47	56	–
10	20.0	1.50	5.0	–40	n.r.	–	–

[a] Observed by ^{1}H NMR of the crude product.

[b] Isolated yield after column chromatography.

[c] r.s.m.: Recovered Starting Material. Obtained after column chromatography.

[d] The additions of TESOTf and 2,6-lutidine were done at –20 ºC, and the resulting reaction mixture was previously stirred for 20 min at –20 ºC.

Table 35

1.4.3. Influence of the concentration

Solid $(Ph_3P)_2NiCl_2$ (65.4 mg, 0.10 mmol) was added to a solution of thioimide **4f** (217 mg, 1.00 mmol) and trimethyl orthoformate (164 µL, 1.50 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2. The resulting black suspension was purged with N_2 again and then cooled to –20 ºC. TESOTf (294 µL, 1.30 mmol) and 2,6-lutidine (174 µL, 1.50 mmol) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred for 20 min at –20 ºC and then placed in an ice bath for 1 h.

The reaction was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (70 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. ^{1}H NMR spectrum of the crude product revealed the presence of a single diastereoisomer of the desired formylated product. The crude product was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/CH_2Cl_2 1:4) to give 149 mg (0.51 mmol, 51%) of the formylated product **7f** as a yellow oil.

1.4.4. The effect of changing the way of adding reagents

1.4.4.1. A time gap between the addition of TESOTf and 2,6-lutidine

Solid $(Ph_3P)_2NiCl_2$ (65.4 mg, 0.10 mmol) was added to a solution of **4f** (109 mg, 0.50 mmol) and trimethyl orthoformate (83 µL, 0.75 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2. The resulting black suspension was purged with N_2 again and then cooled to –20 ºC. TESOTf (170 µL, 0.75 mmol) was added dropwise and the mixture stirred for 1 h. Then, 2,6-lutidine (88 µL, 0.75 mmol) was added and the reaction mixture stirred for 20 min at –20 ºC and then placed in an ice bath for 1 h.

The reaction was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/CH_2Cl_2 1:4) to give 108 mg (0.37 mmol, 74%) of the desired product **7f** and 20 mg (0.12 mmol, 23%) of the *S*-methylated byproduct **10**.

1.4.4.2. Reaction without base

Solid $(Ph_3P)_2NiCl_2$ (65.4 mg, 0.10 mmol) was added to a solution of **4f** (109 mg, 0.50 mmol) and trimethyl orthoformate (83 µL, 0.75 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2. The resulting black suspension was purged with N_2 again and then cooled to –20 ºC. TESOTf (170 µL, 0.75 mmol) was added dropwise and the reaction mixture stirred for 20 min at –20 ºC and placed in an ice bath for 1 h.

The reaction was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo*. The ^1H NMR spectrum of the crude showed a complex mixture derived from decomposition of the starting material.

1.4.4.3. Reaction without base nor catalyst

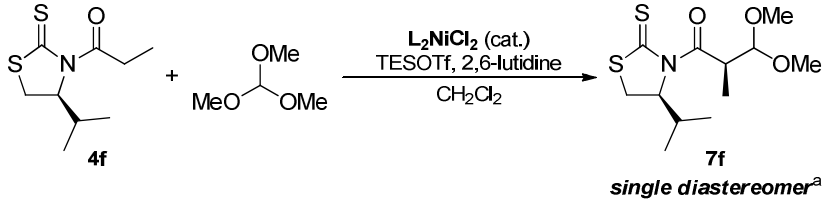
TESOTf (170 µL, 0.75 mmol) was added dropwise to a solution of **4f** (109 mg, 0.50 mmol) and trimethyl orthoformate (83 µL, 0.75 mmol) in anh CH_2Cl_2 (1.0 mL) at –20 ºC under N_2. The reaction mixture was stirred for 20 min at –20 ºC and then placed in an ice bath for 1 h.

The reaction was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The ^1H NMR spectrum of the crude showed a complex mixture derived from the total decomposition of the starting material.

1.4.5. Assessment of different catalysts

Solid Ni(II) catalyst was added to a solution of thioimide **4f** (109 mg, 1.00 mmol) and trimethyl orthoformate (83 μL, 0.75 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2. The resulting suspension was purged with N_2 again and then cooled to –20 ºC. TESOTf and 2,6-lutidine (88 μL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred for a certain time at a certain temperature.

The reaction was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. ^1H NMR spectrum of the crude product revealed the presence of a single diastereoisomer of the desired formylated product. The crude product was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/CH_2Cl_2 1:4) to give the formylated product **7f** as a yellow oil.



Entry	Catalyst	Cat. (mol%)	TESOTf (eq)	t (h)	T (ºC)	Yield (%)[b]
1[c]	$(Ph_3P)_2NiCl_2$	20.0	1.50	1.0	0	72
2[c,d]	(dppe)$NiCl_2$	20.0	1.50	3.0	0	80
3[c,d]	(dppp)$NiCl_2$	20.0	1.50	3.0	0	79
4[c,d]	$(Cy_3P)_2NiCl_2$	20.0	1.50	1.0	0	n.r.
5[c,d]	$(Bu_3P)_2NiCl_2$	20.0	1.50	3.0	0	79
6[c,d]	$(Me_3P)_2NiCl_2$	20.0	1.50	1.0	0	70
7	$(Ph_3P)_2NiCl_2$	5.0	1.20	15	–20	47
8[d]	$(Bu_3P)_2NiCl_2$	5.0	1.20	1.5	–20	78
9	$(Me_3P)_2NiCl_2$	5.0	1.20	1.5	–20	87
10	$(Me_3P)_2NiCl_2$	2.5	1.15	1.5	–20	81
11	(DME)$NiCl_2$	20.0	1.50	4.0	0	n.r.

[a] Observed by ^1H NMR of the crude product.
[b] Isolated yield after column chromatography.
[c] The reaction mixture was previously stirred for 20 min at –20 ºC.
[d] Carried out by Ignasi Nubiola.

Table 36

1.5. APPLICATION TO OTHER *N*-ACYL THIOIMIDES

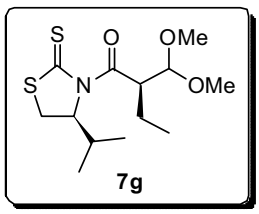
1.5.1. General Procedure with $(Ph_3P)_2NiCl_2$

Solid $(Ph_3P)_2NiCl_2$ was added to a solution of the corresponding (*S*)-*N*-acyl-4-isopropyl-1,3-thiazolidine-2-thione and trimethyl orthoformate in anh CH_2Cl_2 under N_2. The resulting black suspension was purged with N_2 again and then cooled to –20 ºC. TESOTf and 2,6-lutidine were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred for 20 min at –20 ºC and then placed in an ice bath for 1 h.

The reaction was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. ^{1}H NMR spectrum of the crude product revealed the presence of a single diastereoisomer of the desired formylated product. The crude product was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) to give the desired formylated product.

1.5.2. (*S*)-*N*-[(*R*)-2-Ethyl-3,3-dimethoxypropanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (7g)

The formylated product **7g** was prepared according to the General Procedure in section 1.5.1. from thioimide **4g** (116 mg, 0.50 mmol), $(Ph_3P)_2NiCl_2$ (65.4 mg, 0.10 mmol), trimethyl orthoformate (83 μL, 0.75 mmol), TESOTf (170 μL, 0.75 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and anh CH_2Cl_2 (1.0 mL). Purification of the crude product by flash column chromatography on deactivated silica gel (2.5% Et_3N) (from hexanes/CH_2Cl_2 3:7 to CH_2Cl_2) afforded 85 mg (0.27 mmol, 54%) of **7g** as a yellow oil.

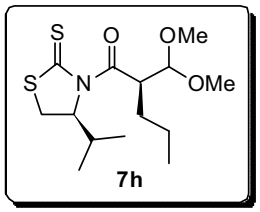


7g

(*S*)-*N*-[(*R*)-2-Ethyl-3,3-dimethoxypropanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**7g**). Yellow oil; $\mathbf{R_f}$ = 0.40 (CH_2Cl_2); $\mathbf{[\alpha]_D}$ = +215.3 (*c* 1.05, $CHCl_3$); **IR** (ATR) 2959, 2930, 1687, 1460, 1241, 1104, 1088 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.51 (1H, dt, *J* = 8.0, 6.7 Hz , C<u>H</u>CO), 5.32 (1H, ddd, *J* = 8.3, 6.0, 1.3 Hz, NC<u>H</u>), 4.66 (1H, d, *J* = 8.0 Hz, C<u>H</u>$(OCH_3)_2$), 3.43 (1H, dd, *J* = 11.5, 8.3 Hz, SC<u>H$_a$</u>H$_b$), 3.35 (3H, s, CH(OC<u>H$_3$</u>)$_a$$(OCH_3)_b$), 3.33 (3H, s, CH$(OCH_3)_a$(OC<u>H$_3$</u>)$_b$), 2.97 (1H, dd, *J* = 11.5, 1.3 Hz, SCH$_a$<u>H$_b$</u>), 2.37–2.25 (1H, m, C<u>H</u>$(CH_3)_2$), 1.76–1.67 (2H, m, C<u>H$_2$</u>CH_3), 1.07 (3H, d, *J* = 6.8 Hz, CH(C<u>H$_3$</u>)$_a$$(CH_3)_b$), 0.99 (3H, d, *J* = 7.0 Hz, CH$(CH_3)_a$(C<u>H$_3$</u>)$_b$), 0.92 (3H, t, *J* = 7.5 Hz, CH_2C<u>H$_3$</u>); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 203.0 (C), 174.2 (C), 105.6 (CH), 71.5 (CH), 55.1 (CH_3), 52.2 (CH_3), 46.6 (CH), 30.6 (CH), 29.4 (CH_2), 22.3 (CH_2), 18.9 (CH_3), 17.5 (CH_3), 10.9 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OMe]^+$ $C_{12}H_{20}NO_2S_2$: 274.0930, found: 274.0934.

1.5.3. (*S*)-4-Isopropyl-*N*-[(*R*)-3,3-dimethoxy-2-propylpropanoyl]-1,3-thiazolidine-2-thione (7h)

The formylated product **7h** was prepared according to the General Procedure in section 1.5.1. from thioimide **4h** (123 mg, 0.50 mmol), $(Ph_3P)_2NiCl_2$ (65.4 mg, 0.10 mmol), trimethyl orthoformate (83 μL, 0.75 mmol), TESOTf (170 μL, 0.75 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and anh CH_2Cl_2 (1.0 mL). Purification of the crude product by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/CH_2Cl_2 2:3) afforded 140 mg (0.44 mmol, 88%) of **7h** as a yellow oil.

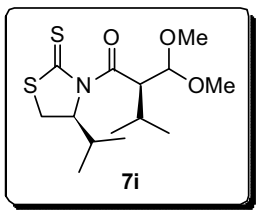


7h

(*S*)-4-Isopropyl-*N*-[(*R*)-3,3-dimethoxy-2-propylpropanoyl]-1,3-thiazolidine-2-thione (**4h**). Yellow oil; $\mathbf{R_f}$ = 0.50 (hexanes/CH_2Cl_2 3:7); $[\boldsymbol{\alpha}]_\mathbf{D}$ = +219.5 (*c* 1.15, $CHCl_3$); **IR** (ATR) 2954, 2924, 1687, 1460, 1358, 1310, 1244, 1152, 1107, 1052 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.55 (1H, ddd, *J* = 9.3, 7.8, 4.4 Hz, C<u>H</u>CO), 5.31 (1H, ddd, *J* = 8.2, 6.1, 1.1 Hz, NC<u>H</u>), 4.63 (1H, d, *J* = 7.8 Hz, C<u>H</u>$(OCH_3)_2$), 3.44 (1H, dd, *J* = 11.5, 8.2 Hz, SC<u>H$_a$</u>H$_b$), 3.35 (3H, s, CH(OC<u>H$_3$</u>)$_a$$(OCH_3)_b$), 3.34 (3H, s, $CH(OCH_3)_a$(OC<u>H$_3$</u>)$_b$), 2.97 (1H, dd, *J* = 11.5, 1.1 Hz, SCH$_a$<u>H$_b$</u>), 2.37–2.25 (1H, m, C<u>H</u>$(CH_3)_2$), 1.74–1.56 (2H, m, COCHC<u>H$_2$</u>), 1.41–1.21 (2H, m, C<u>H$_2$</u>CH_3), 1.07 (3H, d, *J* = 6.8 Hz, CH(C<u>H$_3$</u>)$_a$$(CH_3)_b$), 0.98 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_a$(C<u>H$_3$</u>)$_b$), 0.89 (3H, t, *J* = 7.3 Hz, CH_2C<u>H$_3$</u>); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.9 (C), 174.4 (C), 105.9 (CH), 71.5 (CH), 55.2 (CH_3), 52.2 (CH_3), 45.5 (CH), 31.4 (CH_2), 30.6 (CH), 29.4 (CH_2), 19.9 (CH_2), 18.9 (CH_3), 17.5 (CH_3), 14.4 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OMe]^+$ $C_{13}H_{22}NO_2S_2$: 288.1086, found: 288.1091.

1.5.4. (*S*)-4-Isopropyl-*N*-[(*R*)-2-isopropyl-3,3-dimethoxypropanoyl]-1,3-thiazolidine-2-thione (7i)

The formylated product **7i** was prepared according to the General Procedure in section 1.5.1. from thioimide 4i (123 mg, 0.50 mmol), $(Ph_3P)_2NiCl_2$ (65.4 mg, 0.10 mmol), trimethyl orthoformate (83 μL, 0.75 mmol), TESOTf (170 μL, 0.75 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and anh CH_2Cl_2 (1.0 mL). Purification of the crude product by flash column chromatography on deactivated silica gel (2.5% Et_3N) (from hexanes/CH_2Cl_2 1:1 to CH_2Cl_2) afforded 110 mg (0.34 mmol, 69%) of **7i** as a yellow oil.



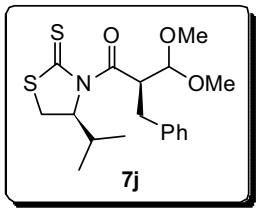
7i

(*S*)-4-Isopropyl-*N*-[(*R*)-2-isopropyl-3,3-dimethoxypropanoyl]-1,3-thiazolidine-2-thione (**7i**). Yellow oil; $\mathbf{R_f}$ = 0.20 (hexanes/CH_2Cl_2 1:1); $[\boldsymbol{\alpha}]_\mathbf{D}$ = +228.4 (*c* 1.05, $CHCl_3$); **IR** (ATR) 2958, 2933, 2870, 2825, 1686, 1461, 1363, 1302, 1245, 1147, 1109, 1087, 1055 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.60 (1H, dd, *J* = 8.4, 5.5 Hz, COC<u>H</u>), 5.27 (1H, ddd, *J* = 7.9, 6.5, 1.1 Hz, NC<u>H</u>), 4.75 (1H, d, *J* = 8.4 Hz, C<u>H</u>$(OMe)_2$), 3.41 (1H, dd, *J* = 11.5, 7.9 Hz, SC<u>H$_a$</u>H$_b$), 3.35 (3H, s, CH(OC<u>H$_3$</u>)$_a$$(OCH_3)_b$), 3.35 (3H, s, $CH(OCH_3)_a$(OC<u>H$_3$</u>)$_b$), 2.97 (1H, dd, *J* = 11.5, 1.1 Hz, SCH$_a$<u>H$_b$</u>), 2.37–2.29 (1H, m, NCHC<u>H</u>), 2.12–2.04 (1H, m, COCHC<u>H</u>$(CH_3)_2$), 1.07 (3H, d, *J* = 6.8 Hz, NCHCH(C<u>H$_3$</u>)$_a$$(CH_3)_b$), 1.01 (3H, d, *J* = 7.0 Hz, COCHCH(C<u>H$_3$</u>)$_a$$(CH_3)_b$), 0.99 (3H, d, *J* = 7.0 Hz,

NCHCH$(CH_3)_a(C\underline{H}_3)_b$), 0.98 (3H, d, *J* = 6.8 Hz, COCHCH$(CH_3)_a(C\underline{H}_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 203.4 (C), 172.9 (C), 105.0 (CH), 71.5 (CH), 55.0 (CH_3), 52.2 (CH_3), 49.0 (CH), 30.5 (CH), 29.9 (CH_2), 29.1 (CH), 19.9 (CH_3), 19.4 (CH_3), 18.9 (CH_3), 17.8 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OMe]^+$ $C_{13}H_{22}NO_2S_2$: 288.1086, found: 288.1088.

1.5.5. (*S*)-*N*-[(*R*)-2-Benzyl-3,3-dimethoxypropanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (7j)

The formylated product **7j** was prepared according to the General Procedure in section 1.5.1. from thioimide **4j** (147 mg, 0.50 mmol), $(Ph_3P)_2NiCl_2$ (65.4 mg, 0.10 mmol), trimethyl orthoformate (83 μL, 0.75 mmol), TESOTf (170 μL, 0.75 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and anh CH_2Cl_2 (1.0 mL). Purification of the crude product by flash column chromatography on deactivated silica gel (2.5% Et_3N) (from hexanes/CH_2Cl_2 2:3 to 1:4) afforded 125 mg (0.34 mmol, 68%) of **7j** as a yellow oil.

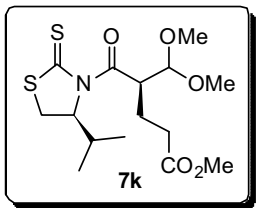


7j

(*S*)-4-Isopropyl-*N*-[(*R*)-2-dimethoxymethyl-3-phenylpropanoyl]-1,3-thiazolidine-2-thione (**7j**). Yellow oil; $\mathbf{R_f}$ = 0.40 (CH_2Cl_2); $\mathbf{[\alpha]_D}$ = +265.2 (*c* 1.05, $CHCl_3$); **IR** (ATR) 2951, 2930, 1687, 1450, 1387, 1329, 1244, 1086 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.29–7.16 (5H, m, Ar$\underline{H}$), 5.79 (1H, ddd, *J* = 11.1, 7.7, 5.1 Hz, NC$\underline{H}$), 4.76 (1H, d, *J* = 7.7 Hz, C$\underline{H}(OMe)_2$), 4.76–4.72 (1H, m, COC$\underline{H}$), 3.43 (3H, s, CH$(OC\underline{H}_3)_a(OCH_3)_b$), 3.41 (3H, s, CH$(OCH_3)_a(OC\underline{H}_3)_b$), 3.07 (1H, dd, *J* = 13.2, 5.1 Hz, SC$\underline{H}_aH_b$), 2.80 (1H, dd, *J* = 13.2, 11.1 Hz, $SCH_a\underline{H}_b$), 2.67–2.65 (2H, m, PhC$\underline{H}_2$), 2.18 (1H, m, C$\underline{H}(CH_3)_2$), 0.96 (3H, d, *J* = 6.8 Hz, CH$(C\underline{H}_3)_a(CH_3)_b$), 0.90 (3H, d, *J* = 6.9 Hz, CH$(CH_3)_a(C\underline{H}_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 203.4 (C), 173.3 (C), 137.7 (C), 128.8 (CH), 128.4 (CH), 126.5 (CH), 105.8 (CH), 71.4 (CH), 55.7 (CH_3), 52.7 (CH_3), 46.7 (CH), 36.4 (CH_2), 30.6 (CH_2), 30.3 (CH), 18.8 (CH_3), 18.2 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{17}H_{22}NO_2S_2$: 336.1086, found: 336.1084.

1.5.6. (*S*)-4-Isopropyl-*N*-[(*R*)-4-methoxycarbonyl-2-dimethoxymethylbutanoyl]-1,3-thiazolidine-2-thione (7k)

The formylated product **7k** was prepared according to the General Procedure in section 1.5.1. from thioimide **4k** (145 mg, 0.50 mmol), $(Ph_3P)_2NiCl_2$ (65.4 mg, 0.10 mmol), trimethyl orthoformate (83 μL, 0.75 mmol), TESOTf (170 μL, 0.75 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and anh CH_2Cl_2 (1.0 mL). Purification of the crude product by flash column chromatography on deactivated silica gel (2.5% Et_3N) (CH_2Cl_2) afforded 109 mg (0.30 mmol, 60%) of **7k** as a yellow oil.



(*S*)-4-Isopropyl-*N*-[(*R*)-4-methoxycarbonyl-2-dimethoxymethylbutanoyl]-1,3-thiazolidine-2-thione (**7k**). Yellow oil; $\mathbf{R_f}$ = 0.30 (CH_2Cl_2); $[\alpha]_D$ = +163.4 (*c* 0.95, $CHCl_3$); **IR** (ATR) 2955, 2829, 1733, 1686, 1432, 1363, 1612, 1245, 1144, 1116, 1087, 1062 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.57 (1H, td, *J* = 7.8, 4.8 Hz, COC<u>H</u>), 5.31 (1H, ddd, *J* = 8.4, 6.0, 1.3 Hz, NC<u>H</u>), 3.66 (3H, s, COOC<u>H$_3$</u>), 4.67 (1H, d, *J* = 7.8 Hz, C<u>H</u>(OCH$_3$)$_2$), 3.49 (1H, dd, *J* = 11.4, 8.4 Hz, SC<u>H$_a$</u>H$_b$), 3.35 (3H, s, CH(OC<u>H$_3$</u>)$_a$(OCH$_3$)$_b$), 3.34 (3H, s, CH(OCH$_3$)$_a$(OC<u>H$_3$</u>)$_b$), 2.97 (1H, dd, *J* = 11.4, 1.3 Hz, SCH$_a$<u>H$_b$</u>), 2.45–2.24 (3H, m, NCHC<u>H</u>, COC<u>H$_2$</u>), 2.10–1.94 (2H, m, COCHC<u>H$_2$</u>), 1.06 (3H, d, *J* = 6.8 Hz, CH(CH$_3$)$_a$(C<u>H$_3$</u>)$_b$), 0.98 (3H, d, *J* = 7.0 Hz, CH(CH$_3$)$_a$(C<u>H$_3$</u>)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 203.1 (C), 173.7 (C), 173.4 (C), 105.5 (CH), 71.6 (CH), 55.3 (CH_3), 52.3 (CH_3), 51.6 (CH_3), 44.9 (CH), 31.1 (CH_2), 30.5 (CH), 29.3 (CH_2), 23.8 (CH_2), 18.9 (CH_3), 17.4 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OMe]^+$ $C_{14}H_{22}NO_4S_2$: 332.0985, found: 332.0985.

1.5.7. Attempt with *N*-glycolylthioimide 4l

The reaction was carried out according to the General Procedure in section 1.5.1. from thioimide **4l** (155 mg, 0.50 mmol), $(Ph_3P)_2NiCl_2$ (65.4 mg, 0.10 mmol), trimethyl orthoformate (83 μL, 0.75 mmol), TESOTf (170 μL, 0.75 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and anh CH_2Cl_2 (1.0 mL). The ^{1}H NMR spectrum of the crude showed the only presence of starting material.

1.5.8. General Procedure with $(Me_3P)_2NiCl_2$

Solid $(Me_3P)_2NiCl_2$ was added to a solution of the corresponding (*S*)-*N*-acyl-4-isopropyl-1,3-thiazolidine-2-thione and trimethyl orthoformate in anh CH_2Cl_2 under N_2. The resulting suspension was purged with N_2 again and then cooled to –20 ºC. TESOTf and 2,6-lutidine were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred at –20 ºC.

The reaction was quenched with sat NH_4Cl (2.4 mL) and then diluted in H_2O (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (70 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. ^{1}H NMR spectrum of the crude product revealed the presence of a single diastereoisomer of the desired formylated product. The crude product was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) to give the desired formylated product.

1.5.9. (*S*)-*N*-[(*R*)-2-Ethyl-3,3-dimethoxypropanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (7g)

The formylated product **7g** was prepared according to the General Procedure in section 1.5.8. from thioimide **4g** (231 mg, 1.00 mmol), $(Me_3P)_2NiCl_2$ (14.1 mg, 50 μmol), trimethyl orthoformate (165 μL, 1.50 mmol), TESOTf (275 μL, 1.20 mmol), 2,6-lutidine (175 μL, 1.50 mmol) and CH_2Cl_2 (2.0 mL) at –20 ºC for 1.5 h. Purification of the crude product by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/CH_2Cl_2 1:4) afforded 266 mg (0.87 mmol, 87%) of **7g** as a yellow oil.

1.5.10. (*S*)-4-Isopropyl-*N*-[(*R*)-3,3-dimethoxy-2-propylpropanoyl]-1,3-thiazolidine-2-thione (7h)

The formylated product **7h** was prepared according to the General Procedure in section 1.5.8. from thioimide **4h** (231 mg, 0.94 mmol), $(Me_3P)_2NiCl_2$ (13.3 mg, 47 μmol), trimethyl orthoformate (154 μL, 1.41 mmol), TESOTf (255 μL, 1.13 mmol), 2,6-lutidine (163 μL, 1.41 mmol) and CH_2Cl_2 (2.0 mL) at –20 ºC for 1.5 h. Purification of the crude product by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/CH_2Cl_2 2:3) afforded 244 mg (0.76 mmol, 81%) of **7h** as a yellow oil.

1.5.11. (*S*)-4-Isopropyl-*N*-[(*R*)-2-isopropyl-3,3-dimethoxypropanoyl]-1,3-thiazolidine-2-thione (7i)

The formylated product **7i** was prepared according to the General Procedure in section 1.5.8. from thioimide **4i** (245 mg, 1.00 mmol), $(Me_3P)_2NiCl_2$ (14.1 mg, 50 μmol), trimethyl orthoformate (165 μL, 1.50 mmol), TESOTf (275 μL, 1.20 mmol), 2,6-lutidine (175 μL, 1.50 mmol) and CH_2Cl_2 (2.0 mL) at –20 ºC for 1.5 h. Purification of the crude product by flash column chromatography on deactivated silica gel (2.5% Et_3N) (from hexanes/CH_2Cl_2 1:1 to CH_2Cl_2) afforded 210 mg (0.66 mmol, 66%) of **4i** as a yellow oil.

1.5.12. (*S*)-*N*-[(*R*)-2-Benzyl-3,3-dimethoxypropanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (7j)

The formylated product **7j** was prepared according to the General Procedure in section 1.5.8. from thioimide **4j** (293 mg, 1.00 mmol), $(Me_3P)_2NiCl_2$ (14.1 mg, 50 μmol), trimethyl orthoformate (165 μL, 1.50 mmol), TESOTf (275 μL, 1.20 mmol), 2,6-lutidine (175 μL, 1.50 mmol) and CH_2Cl_2 (2.0 mL) at –20 ºC for 1.5 h. Purification of the crude product by flash column chromatography on deactivated silica gel (2.5% Et_3N) (from hexanes/CH_2Cl_2 2:3 to 1:4) afforded 268 mg (0.73 mmol, 73%) of **7j** as a yellow oil.

1.5.13. (*S*)-4-Isopropyl-*N*-[(*R*)-4-methoxycarbonyl-2-dimethoxymethylbutanoyl]-1,3-thiazolidine-2-thione (7k)

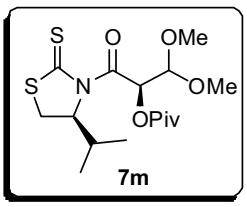
The formylated product **7k** was prepared according to the General Procedure in section 1.5.8. from thioimide **4k** (289 mg, 1.00 mmol), $(Me_3P)_2NiCl_2$ (14.1 mg, 50 μmol), trimethyl orthoformate (165 μL, 1.50 mmol), TESOTf (275 μL, 1.20 mmol), 2,6-lutidine (175 μL, 1.50 mmol) and CH_2Cl_2 (2.0 mL) at –20 ºC for 1.5 h. Purification of the crude product by flash column chromatography on deactivated silica gel

(2.5% Et_3N) (from hexanes/CH_2Cl_2 1:4 to CH_2Cl_2) afforded 244 mg (0.67 mmol, 67%) of **7k** as a yellow oil.

1.5.14. (*S*)-4-Isopropyl-*N*-[(*R*)-3,3-dimethoxy-2-pivaloyloxypropanoyl]-1,3-thiazolidine-2-thione (7m)

1.5.14.1. Reaction time of 1.5 h

The formylated product **7m** was prepared according to the General Procedure in section 1.5.8. from thioimide **4m** (152 mg, 0.50 mmol) at –20 ºC for 1.5 h. Purification of the crude product by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/CH_2Cl_2 3:2) afforded 136 mg (0.36 mmol, 72%) of **7m** as a yellow oil.



(*S*)-4-Isopropyl-*N*-[(*R*)-3,3-dimethoxy-2-pivaloyloxypropanoyl]-1,3-thiazolidine-2-thione (**7m**). Yellow oil; $\mathbf{R_f}$ = 0.30 (CH_2Cl_2); $\mathbf{[\alpha]_D}$ = +206.2 (*c* 1.00, $CHCl_3$); **IR** (ATR) 2964, 2930, 2869, 1735, 1693, 1474, 1458, 1363, 1268, 1249, 1149, 1070 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.24 (1H, d, *J* = 5.4 Hz, COC<u>H</u>), 5.31 (1H, ddd, *J* = 8.5, 5.5, 1.2 Hz, NC<u>H</u>), 4.92 (1H, d, *J* = 5.4 Hz, C<u>H</u>$(OCH_3)_2$), 3.58 (1H, dd, *J* = 11.5, 8.5 Hz, SC<u>H$_a$</u>H$_b$), 3.44 (3H, s, CH(OC<u>H$_3$</u>)$_a$(OCH$_3$)$_b$), 3.42 (3H, s, CH(OCH$_3$)$_a$(OC<u>H$_3$</u>)$_b$), 3.01 (1H, dd, *J* = 11.5, 1.2 Hz, SCH$_a$<u>H$_b$</u>), 2.33–2.24 (1H, m, C<u>H</u>$(CH_3)_2$), 1.25 (9H, s, $(C\underline{H_3})_3$), 1.06 (3H, d, *J* = 6.8 Hz, CH(C<u>H$_3$</u>)$_a$(CH$_3$)$_b$), 0.98 (3H, d, *J* = 6.9 Hz, CH(CH$_3$)$_a$(C<u>H$_3$</u>)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.4 (C), 177.7 (C), 168.5 (C), 102.6 (CH), 71.5 (CH), 71.0 (CH), 56.0 (CH_3), 53.6 (CH_3), 38.5 (C), 30.5 (CH_2), 30.0 (CH), 26.9 (CH_3), 18.8 (CH_3), 17.2 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OMe]^+$ $C_{15}H_{24}NO_4S_2$: 346.1141, found: 346.1143.

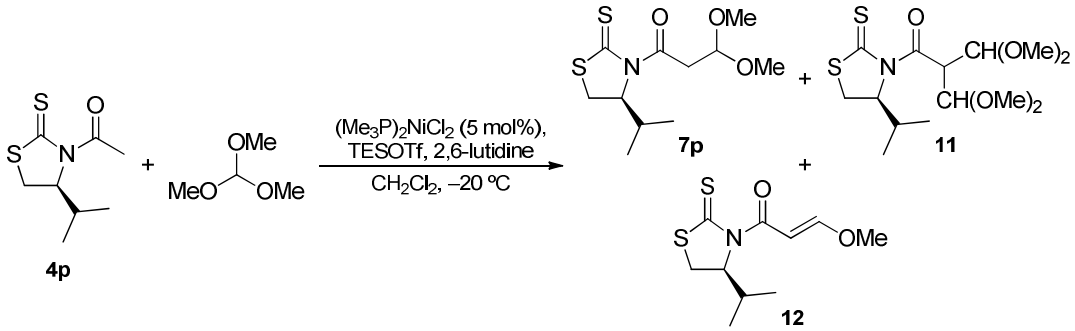
1.5.14.2. Reaction time of 3.0 h

The formylated product **7m** was prepared according to the General Procedure in section 1.5.8. from thioimide **4m** (152 mg, 0.50 mmol) at –20 ºC for 3.0 h. Purification of the crude product by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/CH_2Cl_2 3:2) afforded 155 mg (0.41 mmol, 82%) of **4m** as a yellow oil.

1.5.15. Reactions with thioimide 4p

Solid $(Me_3P)_2NiCl_2$ (7.0 mg, 12.5 μmol) was added to a solution of thioimide **4p** (102 mg, 0.50 mmol) and trimethyl orthoformate in anh CH_2Cl_2 (1.0 mL) under N_2. The resulting suspension was purged with N_2 again and then cooled to –20 ºC. TESOTf and 2,6-lutidine (88 μL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred at –20 ºC.

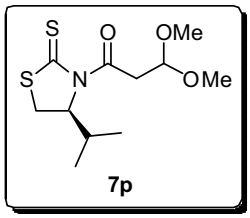
The reaction was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. ^1H NMR spectrum of the crude product revealed the presence of three different diastereomerically pure products. The crude product was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) (from hexanes/CH_2Cl_2 1:4 to CH_2Cl_2/EtOAc 92:8) to give separately the desired formylated product **7p**, the diformylated product **11** and the unsaturated product **12**.



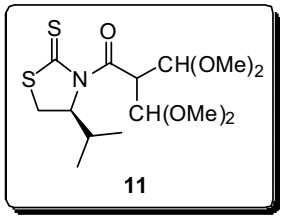
Entry	$CH(OMe)_3$ (eq)	TESOTf (eq)	t (h)	**7p** (%)[a]	**11** (%)[a]	**12** (%)[a]	r.s.m.(%)[a,b]
1	1.5	1.5	1.5	23	21	11	38
2	1.5	1.5	20	24	27	9	29
3	3.0	2.2	1.5	9	68	16	4

[a] Isolated yield after column chromatography.
[b] r.s.m.: Recovered Starting Material.

Table 37

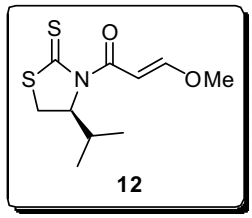


(*S*)-4-Isopropyl-*N*-(3,3-dimethoxypropanoyl)-1,3-thiazolidine-2-thione (**7p**). Yellow oil; $\mathbf{R_f}$ = 0.25 (CH_2Cl_2); $\mathbf{[\alpha]_D}$ = +259.2 (*c* 1.10, $CHCl_3$); **IR** (ATR) 2959, 2927, 2830, 1693, 1463, 1370, 1360, 1310, 1255, 1160, 1110, 1081, 1049, 1038 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.14 (1H, ddd, *J* = 8.0, 6.1, 1.2 Hz, NC<u>H</u>), 4.96 (1H, t, *J* = 5.5 Hz, C<u>H</u>$(OCH_3)_2$), 3.62 (2H, d, *J* = 5.5 Hz, COC<u>H_2</u>), 3.51 (1H, dd, *J* = 11.5, 8.0 Hz, SC<u>H_a</u>H_b), 3.39 (3H, s, CH(OC<u>H_3</u>)$_a$$(OCH_3)_b$), 3.37 (3H, s, $CH(OCH_3)_a$(OC<u>H_3</u>)$_b$), 3.03 (1H, dd, *J* = 11.5, 1.2 Hz, SCH_a<u>H_b</u>), 2.43–2.31 (1H, m, C<u>H</u>$(CH_3)_2$), 1.06 (3H, d, *J* = 6.8 Hz, CH(C<u>H_3</u>)$_a$$(CH_3)_b$), 0.98 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_a$(C<u>H_3</u>)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.9 (C), 170.0 (C), 101.3 (CH), 71.5 (CH), 54.1 (CH_3), 53.3 (CH_3), 42.2 (CH_2), 30.7 (CH), 30.4 (CH_2), 19.0 (CH_3), 17.6 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OMe]^+$ $C_{10}H_{16}NO_2S_2$: 246.0617, found: 246.0623.



11

(*S*)-4-Isopropyl-*N*-(3,3,3',3'-tetramethoxyisovaleroyl)-1,3-thiazolidine-2-thione (**11**). Yellow oil; $\mathbf{R_f}$ = 0.10 (CH_2Cl_2); $\mathbf{[\alpha]_D}$ = +227.5 (*c* 1.18, $CHCl_3$); **IR** (ATR) 2959, 2930, 2827, 1690, 1463, 1442, 1360, 1313, 1252, 1162, 1059 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.98 (1H, dd, *J* = 7.7, 5.9 Hz, COC<u>H</u>), 5.18 (1H, ddd, *J* = 7.7, 6.5, 1.0 Hz, NC<u>H</u>), 4.79 (1H, d, *J* = 7.5 Hz, CH(C<u>H</u>$(OCH_3)_2)_a$($CH(OCH_3)_2)_b$), 4.60 (1H, d, *J* = 5.9 Hz, $CH(CH(OCH_3)_2)_a$(C<u>H</u>$(OCH_3)_2)_b$), 3.46 (1H, dd, *J* = 11.3, 7.7 Hz, SC<u>H</u>$_a$H$_b$), 3.42 (3H, s, $CH(CH(OC\underline{H}_3)_x(OCH_3)_y)_a(CH(OCH_3)_x(OCH_3)_y)_b$), 3.41 (3H, s, $CH(CH(OCH_3)_x(OC\underline{H}_3)_y)_a(CH(OCH_3)_x(OCH_3)_y)_b$), 3.40 (3H, s, $CH(CH(OCH_3)_x(OCH_3)_y)_a(CH(OC\underline{H}_3)_x(OCH_3)_y)_b$), 3.39 (3H, s, $CH(CH(OCH_3)_x(OCH_3)_y)_a(CH(OCH_3)_x(OC\underline{H}_3)_y)_b$), 2.96 (1H, dd, *J* = 11.3, 1.0 Hz, SCH$_a$<u>H</u>$_b$), 2.40–2.28 (1H, m, C<u>H</u>$(CH_3)_2$), 1.05 (3H, d, *J* = 6.8 Hz, $CH(C\underline{H}_3)_a(CH_3)_b$), 0.98 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_a(C\underline{H}_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 204.0 (C), 169.8 (C), 104.9 (CH), 104.2 (CH), 72.2 (CH), 56.1 (CH_3), 55.5 (CH_3), 55.3 (CH_3), 54.4 (CH_3), 49.0 (CH), 30.6 (CH), 30.4 (CH_2), 19.0 (CH_3), 17.9 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OMe]^+$ $C_{13}H_{22}NO_4S_2$: 230.0985, found: 320.0985; *m/z* calculated for $[M+Na]^+$ $C_{14}H_{25}NNaO_5S_2$: 374.1066, found: 374.1069.



12

(*S*)-4-Isopropyl-*N*-(3-methoxyacryloyl)-1,3-thiazolidine-2-thione (**12**). Yellow oil; $\mathbf{R_f}$ = 0.55 (hexanes/CH_2Cl_2 1:4); $\mathbf{[\alpha]_D}$ = +295.8 (*c* 0.73, $CHCl_3$); **IR** (ATR) 3107, 2957, 2930, 2869, 1669, 1592, 1463, 1437, 1331, 1305, 1228, 1125, 1088, 1046 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.76 (1H, d, *J* = 12.1 Hz, COCH=C<u>H</u>), 7.12 (1H, d, *J* = 12.1 Hz, COC<u>H</u>=CH), 5.14 (1H, ddd, *J* = 8.2, 5.7, 2.4 Hz, NC<u>H</u>), 3.76 (3H, s, OC<u>H</u>$_3$), 3.48 (1H, dd, *J* = 11.4, 8.2 Hz, SC<u>H</u>$_a$H$_b$), 3.05 (1H, dd, *J* = 11.4, 2.4 Hz, SCH$_a$<u>H</u>$_b$), 2.49–2.40 (1H, m, C<u>H</u>$(CH_3)_2$), 1.05 (3H, d, *J* = 6.8 Hz, $CH(C\underline{H}_3)_a(CH_3)_b$), 0.99 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_a(C\underline{H}_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.5 (C), 166.9 (C), 165.0 (CH), 99.1 (CH), 72.1 (CH), 57.9 (CH_3), 30.9 (CH), 30.1 (CH_2), 19.0 (CH_3), 17.3 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{10}H_{16}NO_2S_2$: 246.0617, found: 246.0614.

1.6. REACTIONS WITH OTHER ORTHOESTERS

1.6.1. Reaction with trimethyl orthobenzoate and thioimide 4a

Solid $(Ph_3P)_2NiCl_2$ (8.2 mg, 12.5 μmol) was added to a solution of thioimide **4a** (140 mg, 0.50 mmol) and trimethyl orthobenzoate (129 μL, 0.75 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2. The resulting suspension was purged with N_2 again and then cooled to –20 ºC. TESOTf (130 μL, 0.58 mmol) and 2,6-lutidine (88 μL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred for at –20 ºC for 20 min and 1 h at 0 ºC.

The reaction was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. ^{1}H NMR spectrum of the crude product showed that the reaction had not taken place.

1.6.2. Reaction with trimethyl orthobenzoate and thioimide 4f

Solid $(Ph_3P)_2NiCl_2$ (65.4 mg, 0.20 mmol) was added to a solution of thioimide **4f** (109 mg, 0.50 mmol) and trimethyl orthobenzoate (129 μL, 0.75 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2. The resulting suspension was purged with N_2 again and then cooled to –20 ºC. TESOTf (170 μL, 0.75 mmol) and 2,6-lutidine (88 μL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred for at –20 ºC for 20 min and 15 h at r.t.

The reaction was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. ^1H NMR spectrum of the crude product showed the only formation of thiazole **10**.

1.6.3. Reaction with trimethyl orthoacetate and thioimide 4a

Solid $(Ph_3P)_2NiCl_2$ (65.4 mg, 0.20 mmol) was added to a solution of thioimide **4a** (140 mg, 0.50 mmol) and trimethyl orthoacetate (191 μL, 0.75 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2. The resulting suspension was purged with N_2 again and then cooled to –20 ºC. TESOTf (170 μL, 0.75 mmol) and 2,6-lutidine (88 μL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred for at –20 ºC for 20 min and 0 ºC for 1 h.

The reaction was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. ^1H NMR spectrum of the crude product showed that no reaction had taken place.

1.6.4. Reaction with trimethyl orthoacetate and thioimide 4f

Solid $(Ph_3P)_2NiCl_2$ (65.4 mg, 0.20 mmol) was added to a solution of thioimide **4f** (109 mg, 0.50 mmol) and trimethyl orthoacetate (191 μL, 0.75 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2. The resulting suspension was purged with N_2 again and then cooled to –20 ºC. TESOTf (170 μL, 0.75 mmol) and 2,6-lutidine (88 μL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred for at –20 ºC for 20 min and 0 ºC for 1 h.

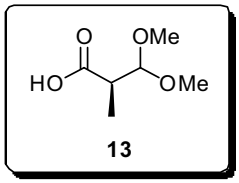
The reaction was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. ^1H NMR spectrum of the crude product showed that no reaction had taken place.

1.7. ELUCIDATION OF THE ABSOLUTE CONFIGURATION

1.7.1. Elucidation for formylated product 7f. [27]

Solid LiOH (96 mg, 4.0 mmol) was added to a solution of thioimide **7f** (583 mg, 2.0 mmol) in THF/water 4:1 (10 mL) at 0 ºC. The resulting reaction mixture was stirred for 5.5 h at 0 ºC until the color faded.

The incolor reaction mixture was acidified with 1.0 M HCl until acid pH and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with sat $NaHCO_3$ (3 × 40 mL) and the combined aqueous extracts acidified to pH = 1 with concentrated HCl solution. Extraction of the aqueous layer with EtOAc (3 × 80 mL), drying of the combined organic layers over $MgSO_4$, filtration and concentration *in vacuo* afforded 260 mg (1.75 mmol, 88%) of the carboxylic acid **13** as a colorless oil, which is pure by 400 MHz ^{1}H NMR.

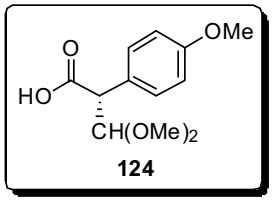


13

(*R*)-3,3-Dimethoxy-2-methylpropanoic acid (**13**). Colorless oil; $\mathbf{R_f}$ = 0.5 (EtOAc); $\mathbf{[\alpha]_D}$ = –20.0 (*c* 0.70, $CHCl_3$) [lit.[27] $\mathbf{[\alpha]_D}$ = –19.4 (*c* 0.50, $CHCl_3$)] [lit.[40] $\mathbf{[\alpha]_D}$ = –16.0 (*c* 0.50, $CHCl_3$)]; **IR** (ATR) 3087 (br), 2937, 2830, 1705, 1453, 1188, 1105, 1046 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 10.07 (1H, br, COOH), 4.53 (1H, d, *J* = 7.2 Hz, CH(OCH$_3$)$_2$), 3.41 (3H, s, CH(OCH$_3$)$_a$(OCH$_3$)$_b$), 3.38 (3H, s, CH(OCH$_3$)$_a$(OCH$_3$)$_b$), 2.81 (1H, p, *J* = 7.2 Hz, COCH), 1.22 (3H, d, *J* = 7.2 Hz, CHCH$_3$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 179.3 (C), 105.1 (CH), 54.9 (CH_3), 53.3 (CH_3), 43.2 (CH), 12.3 (CH_3).

1.7.2. Elucidation for formylated product 7d. [27]

Carboxylic acid **124** was prepared according to section 1.7.1. from LiOH (39 mg, 1.62 mmol) and a solution of thioimide **7d** (311 mg, 0.81 mmol) in THF/water 4:1 (4.0 mL) during 5.5 h at 0 ºC. Treatment of the reaction mixture as in section 1.7.1 afforded 190 mg (0.79 mmol, 97%) of carboxylic acid **124**, which was used into the next step without further purification.

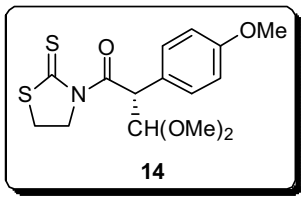


124

(*R*)-3,3-Dimethoxy-2-(*p*-methoxyphenyl)propanoic acid (**124**). Colorless solid; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.31–7.29 (2H, m, ArH), 6.88–6.86 (2H, m, ArH), 4.90 (1H, d, *J* = 8.4 Hz, CH(OCH$_3$)$_2$), 3.85 (1H, d, *J* = 8.4 Hz, ArCH), 3.79 (3H, s, ArOCH$_3$), 3.46 (3H, s, CH(OCH$_3$)$_a$(OCH$_3$)$_b$), 3.20 (3H, s, CH(OCH$_3$)$_a$(OCH$_3$)$_b$).

EDC (172 µL, 0.97 mmol) was added dropwise over a solution of carboxylic acid **124** (156 mg, 0.65 mmol), 1,3-thiazolidine-2-thione (85 mg, 0.72 mmol) and DMAP (4 mg, 32 µmol) in anh CH_2Cl_2 (1.1 mL) at 0 ºC under N_2. The reaction mixture was stirred for 15 h at r.t.

After this time, the yellow solution was diluted in CH_2Cl_2 (20 mL) and washed with 0.5 M NaOH (3 × 30 mL) and brine (40 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (hexanes/CH_2Cl_2 1:4) to give 95 mg (0.28 mmol, 43%) of thioimide **14**. An enantiomeric excess of 78% was determined by HPLC of the pure product.



14

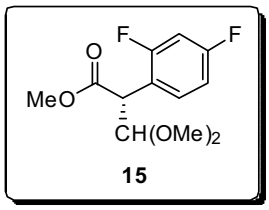
(*R*)-*N*-[3,3-Dimethoxy-2-(4-methoxyphenyl)propanoyl]-1,3-thiazolidine-2-thione (**14**). Yellow solid; **mp** = 104–105 ºC; $\mathbf{R_f}$ = 0.50 (CH_2Cl_2); **HPLC** (Chiralcel OD-H column, 10% of *i*-PrOH in hexanes, 0.9 mL/min, 310 nm), $t_{R,\ major}$ = 18.0 min, $t_{R,\ minor}$ = 14.7 min; $\mathbf{[\alpha]_D}$ = –23.3 (*c* 1.00, $CHCl_3$); calculated for major (*R*)-enantiomer: $\mathbf{[\alpha]_D}$ = –41.6 (*c* 1.00, $CHCl_3$) [lit.[27] $\mathbf{[\alpha]_D}$ = –47.4 (*c* 1.00, $CHCl_3$)]; **IR** (ATR) 2928, 2829, 1681, 1606, 1509, 1249, 1108, 1041 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.41–7.39 (2H, m, ArH), 6.87–6.85 (2H, m, ArH), 6.27 (1H, d, *J* = 8.4 Hz, CHAr), 4.96 (1H ,d, *J* = 8.4 Hz, $CH(OCH_3)_2$), 4.61 (1H, ddd, *J* = 12.2, 7.8, 6.9 Hz, NCH_aH_b), 4.48 (1H, dt, *J* = 12.2, 7.8 Hz, NCH_aH_b), 3.79 (3H, s, $ArOCH_3$), 3.41 (3H, s, $CH(OCH_3)_a(OCH_3)_b$), 3.26 (1H, dt, *J* = 11.1, 7.8 Hz, SCH_aH_b), 3.17 (3H, s, $CH(OCH_3)_a(OCH_3)_b$), 3.16 (1H, ddd, *J* = 11.1, 7.8, 6.9 Hz, SCH_aH_b); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 201.5 (C), 173.1 (C), 159.1 (C), 130.6 (CH), 126.1 (C), 113.8 (CH), 106.5 (CH), 56.4 (CH_2), 55.1 (CH_3), 55.1 (CH_3), 53.5 (CH_3), 51.7 (CH), 28.0 (CH_2).

1.8. CHIRAL AUXILIARY REMOVAL

1.8.1. Preparation of ester 15 in a formylation-derivatization one-pot reaction

Solid $(Ph_3P)_2NiCl_2$ (4.9 mg, 7.5 μmol) was added to a solution of thioimide **4d** (94 mg, 0.30 mmol) and trimethyl orthoformate (49 μL, 0.45 mmol) in anh CH_2Cl_2 (0.6 mL) under N_2. The resulting black suspension was purged with N_2 again and then cooled to –20 ºC. TESOTf (78 μL, 0.35 mmol) and 2,6-lutidine (52 μL, 0.45 mmol) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred at –20 ºC for 20 min and then placed in an ice bath for 1.5 h. Then, a solution of DMAP (126 mg, 1.05 mmol) in anh MeOH (3 mL) was added *via cannula*, obtaining a yellow solution. The reaction was stirred for 15 h at r.t.

The reaction was quenched with sat NH_4Cl (2.5 mL) and then diluted in H_2O (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (70 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) (from hexanes/CH_2Cl_2 1:1 to CH_2Cl_2) to give 57 mg (0.22 mmol, 73%) of methyl ester **15**. An enantiomeric excess of 52% was determined by HPLC of the pure product.



15

(*R*)-Methyl 2-(2,4-difluorophenyl)-3,3-dimethoxypropanoate (**15**). White solid; **mp** = 44–45 ºC; $\mathbf{R_f}$ = 0.30 (hexanes/CH_2Cl_2 3:7); **HPLC** (Chiralcel OD-H column, 2% of EtOAc in hexanes, 0.9 mL/min, 254 nm), $t_{R,\,major}$ = 11.7 min, $t_{R,\,minor}$ = 12.3 min; $\mathbf{[\alpha]_D}$ = +17.6 (*c* 1.00, $CHCl_3$); **IR** (ATR) 2952, 2838, 1733, 1622, 1597, 1461, 1435, 1312, 1112, 1062 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 6.97–6.91 (2H, m, ArH), 6.74 (1H, tt, *J* = 8.9, 2.3 Hz, ArH), 4.88 (1H, d, *J* = 8.5 Hz, CH(OCH_3)$_2$), 3.86 (1H, d, *J* = 8.5 Hz, ArCH), 3.71 (3H, s, COOCH_3), 3.45 (3H, s, CH(OCH_3)$_a$(OCH_3)$_b$), 3.23 (3H, s, CH(OCH_3)$_a$(OCH_3)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 170.6 (C), 164.1 (C, d, *J* = 12.9 Hz), 161.6 (C, d, *J* = 12.9 Hz), 138.0 (C, t, *J* = 9.6 Hz), 111.8 (CH, d, *J* = 25.9 Hz), 111.8 (CH, d, *J* = 11.7 Hz), 104.9 (CH), 103.3 (CH, t, *J* = 25.2 Hz), 55.3 (CH_3), 55.0 (CH), 54.0 (CH_3), 52.4 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OMe]^+$ $C_{11}H_{11}F_2O_3$: 229.0671, found: 229.0670

1.8.2. Preparation of thioester 16

1.8.2.1. Using DMAP

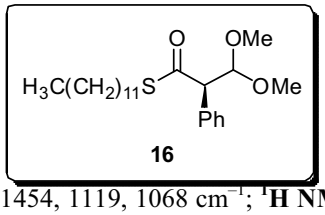
1-Dodecanethiol (359 µL, 1.50 mmol) was added to a solution of the thioimide **7a** (177 mg, 0.50 mmol) and DMAP (214 mg, 1.75 mmol) in anh CH_2Cl_2 (5 mL) at 0 ºC under N_2. The reaction mixture was stirred for 20 min at 0 ºC and 15 h at r.t.

The volatiles were removed *in vacuo* and the crude product purified by flash column chromatography on silica gel (hexanes/CH_2Cl_2 1:1) to give 177 mg (0.45 mmol, 90%) of thioester **16**. An enantiomeric excess of 63% was determined by HPLC of the pure product.

1.8.2.2. Using catalytic amounts of n-BuLi

A 1.55 M solution of *n*-BuLi in hexanes (97 µL, 0.15 mmol) was added dropwise to a solution of 1-dodecanethiol (360 µL, 1.5 mmol) in anh THF (1.5 mL) under N_2 at 0 ºC. After 15 min, a solution of the thioimide **7a** (177 mg, 0.50 mmol) in anh THF (2.8 mL) was added *via cannula*. The resulting solution was stirred for 45 min at 0 ºC.

The reaction was quenched with sat NH_4Cl (1.4 mL) and then diluted in H_2O (15 mL). The aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the product was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/CH_2Cl_2 1:1) to give 151 mg (0.38 mmol, 77%) of the thioester **16**. An enantiomeric excess of 98% was determined by HPLC of the pure product.



16

(*R*)-*S*-Dodecyl 3,3-dimethoxy-2-phenylpropanethioate (**16**). Colorless oil; $\mathbf{R_f}$ = 0.65 (hexanes/CH_2Cl_2 3:7); **HPLC** (Chiralcel OD-H column, 1.5% of EtOAc in hexanes, 0.9 mL/min, 254 nm), $t_{R,\,minor}$ = 10.5 min, $t_{R,\,major}$ = 9.8 min; $\mathbf{[\alpha]_D}$ = +74.1 (*c* 1.00, $CHCl_3$); **IR** (film) 3030, 2923, 2853, 1687, 1454, 1119, 1068 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.38–7.26 (5H, m, Ar<u>H</u>), 5.02 (1H, d, *J* = 8.6 Hz, C<u>H</u>$(OCH_3)_2$), 4.06 (1H, d, *J* = 8.6 Hz, C<u>H</u>Ar), 3.44 (3H, s, CH$(OC\underline{H_3})_a(OCH_3)_b$), 3.16 (3H, s, CH$(OCH_3)_a(OC\underline{H_3})_b$), 2.90–2.78 (2H, m, S<u>CH_2</u>), 1.55–1.48 (2H, m, SCH_2<u>CH_2</u>), 1.35–1.18 (18H, m, CH_3(<u>CH_2</u>)$_9$), 0.88 (3H, t, *J* = 6.9 Hz, <u>CH_3</u>$(CH_2)_9$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 197.4 (C), 134.5 (C), 128.7 (CH), 128.6 (CH), 127.7 (CH), 104.9 (CH), 63.3 (CH), 55.3 (CH_3), 53.2 (CH_3), 31.9 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 28.7 (CH_2), 22.7 (CH_2), 14.1 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+Na]^+$ $C_{23}H_{38}NaO_3S$: 417.2434, found: 417.2443.

1.9. SYNTHETIC STUDIES

1.9.1. Side chain of (–)-pyridovericin

*1.9.1.1. Formylation reaction of **4g** in a large scale*

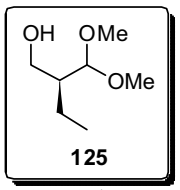
Solid $(Me_3P)_2NiCl_2$ (141 mg, 0.50 mmol) was added to a solution of (*S*)-*N*-butanoyl-4-isopropyl-1,3-thiazolidine-2-thione (**4g**) (2.31 g, 10.0 mmol) and trimethyl orthoformate (1.64 mL, 15.0 mmol) in anh CH_2Cl_2 (20 mL) under N_2. The resulting red solution was purged with N_2 again and then cooled to –20 ºC. TESOTf (2.71 mL, 12.0 mmol) and 2,6-lutidine (1.74 mL, 15.0 mmol) were added dropwise after 5 and 10 min respectively. The reaction mixture was stirred at –20 ºC for 1.5 h.

The reaction was quenched with sat NH_4Cl (22 mL) and then diluted in H_2O (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (70 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the product was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/EtOAc 9:1) to give 2.50 g (8.18 mmol, 82%) of pure (*S*)-*N*-[(*R*)-2-ethyl-3,3-dimethoxypropanoyl]-4-isopropyl-1,3-thiazolidine-2-thione **7g**.

1.9.1.2. Removal of the chiral auxiliary by reduction with $NaBH_4$ and protection of the alcohol

A solution of **7g** (153 mg, 0.50 mmol) in THF (7.8 mL) was added *via cannula* to a suspension of $NaBH_4$ (95 mg, 2.5 mmol) in THF (10 mL) and water (185 μL) at 0 ºC under N_2. The reaction mixture was stirred for 30 min at 0 ºC and 3 h at r.t.

The reaction was quenched with NH_4Cl (20 mL) at 0 ºC. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with 2 M NaOH (3 × 20 mL), and the combined basic fraction was extracted with CH_2Cl_2 (3 × 25 mL). The final combined organic layers were dried over $MgSO_4$ and filtered. The resulting crude oil containing the alcohol **125** was used into the next step without further purification.

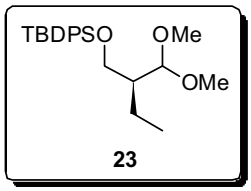


125

(*S*)-2-Ethyl-3,3-dimethoxypropanol (**125**). Colorless oil; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 4.31 (1H, d, *J* = 6.0 Hz, C<u>H</u>$(OCH_3)_2$), 3.68 (1H, ddd, *J* = 11.1, 7.7, 3.1 Hz, OC<u>H$_a$</u>H$_b$), 3.60 (1H, ddd, *J* = 11.1, 7.4, 4.0 Hz, OCH$_a$<u>H$_b$</u>), 3.44 (3H, s, CH(OC<u>H$_3$</u>)$_a$(OCH$_3$)$_b$), 3.38 (3H, s, CH(OCH$_3$)$_a$(OC<u>H$_3$</u>)$_b$), 2.78 (1H, dd, *J* = 7.7, 4.0 Hz, O<u>H</u>), 1.80–1.74 (1H, m, OCH$_2$C<u>H</u>), 1.50–1.43 (1H, m, C<u>H$_a$</u>H$_b$CH$_3$), 1.33–1.20 (1H, m, CH$_a$<u>H$_b$</u>CH$_3$), 0.95 (3H, t, *J* = 7.5 Hz, CH$_2$C<u>H$_3$</u>).

TBDPSCl (130 μL, 0.5 mmol) was added to a solution of the previous crude and imidazole (44 mg, 0.65 mmol) in anh CH_2Cl_2 (0.6 mL) at 0ºC under N_2. The reaction mixture was stirred for 12 h at r.t.

The reaction solution was quenched with sat $NaHCO_3$ (0.5 mL) and diluted in CH_2Cl_2 (10 mL) and H_2O (10 mL). The layers were separated and the aqueous one was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The crude was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/CH_2Cl_2 2:3) to afford 128 mg (0.34 mmol, 67%) of dimethyl acetal **23**.



23

(*S*)-2-(*tert*-Butyldiphenylsilyloxymethyl)butyraldehyde dimethyl acetal (**23**). Colorless oil; $\mathbf{R_f}$ = 0.55 (hexanes/CH_2Cl_2 3:7); $\mathbf{[\alpha]_D}$ = +9.4 (*c* 1.00, $CHCl_3$); **IR** (ATR) 3070, 2959, 2929, 2851, 1472, 1427, 1101, 1045 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.69–7.66 (4H, m, ArH), 7.44–7.36 (6H, m, ArH), 4.46 (1H, d, *J* = 6.8 Hz, CH$(OCH_3)_2$), 3.77 (1H, dd, *J* = 10.1, 4.3 Hz, OCH_aH_b), 3.68 (1H, dd, *J* = 10.1, 4.4 Hz, OCH_aH_b), 3.34 (3H, s, $CH(OCH_3)_a(OCH_3)_b$), 3.33 (3H, s, $CH(OCH_3)_a(OCH_3)_b$), 1.69–1.64 (1H, m, OCH_2CH), 1.60–1.43 (2H, m, CH_2CH_3), 1.06 (9H, s, $C(CH_3)_3$), 0.86 (3H, t, *J* = 7.5 Hz, CH_2CH_3); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 135.6, 133.8, 133.8, 129.5, 129.5, 127.6, 127.6, 105.5, 61.7, 54.3, 53.6, 44.9, 26.9, 19.3, 18.5, 11.7; **HRMS** (+ESI): *m/z* calculated for $[M–OCH_3]^+$ $C_{22}H_{31}O_2Si$: 355.2088, found: 355.2101; *m/z* calculated for $[M+Na]^+$ $C_{23}H_{34}NaO_3Si$: 409.2169, found: 409.2180.

1.9.1.3. Removal of the chiral auxiliary by reduction with $LiBH_4$ and protection of the alcohol

A 2 M solution of $LiBH_4$ in THF (21.0 mL, 42.0 mmol) was added to a solution of thioimide **7g** (4.28 g, 14.0 mmol) in anh THF (88 mL) at –78 ºC under N_2. The solution was stirred for 30 min at –78 ºC and 2 h at r.t.

The mixture was carefully quenched with NH_4Cl (70 mL) at 0 ºC. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with 2 M NaOH (3 × 75 mL) and the basic layers extracted with CH_2Cl_2 (3 × 100 mL). The final combined organic layers were dried over $MgSO_4$ and filtered. The resulting crude oil containing the alcohol **125** was used into the next step without further purification.

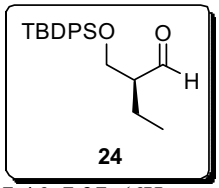
TBDPSCl (3.7 mL, 14.0 mmol) was added to a solution of the previous crude and imidazole (1.30 g, 18.2 mmol) in anh CH_2Cl_2 (12.0 mL) at 0ºC under N_2. The reaction mixture was stirred for 12 h at r.t.

The reaction solution was quenched with sat $NaHCO_3$ (15 mL) and diluted in CH_2Cl_2 (40 mL) and H_2O (40 mL). The layers were separated and the aqueous one was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The crude was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/CH_2Cl_2 2:3) to afford 4.35 g (11.3 mmol, 80%) of dimethyl acetal **23**.

1.9.1.4. Deprotection of the formyl group[62]

SiO_2 (28.0 g) and a 10% aqueous solution of oxalic acid (4.2 mL) were added to a solution of the acetal **23** (4.35 g, 11.3 mmol) in CH_2Cl_2 (80 mL). The resulting slurry was stirred for 24 h at r.t.

After this time, solid $NaHCO_3$ (10 g) was added and the mixture was stirred for 10 min. Then, the mixture was dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the product was purified by flash column chromatography on silica gel (hexanes/CH_2Cl_2 1:1) to give 3.14 g (9.22 mmol, 82%) of aldehyde **24**.



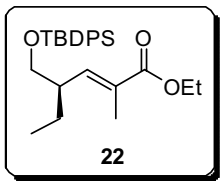
24

(*S*)-3-(*tert*-Butyldiphenylsilyloxymethyl)butyraldehyde (**24**). Colorless oil; $\mathbf{R_f}$ = 0.60 (hexanes/CH_2Cl_2 1:1); $\mathbf{[\alpha]_D}$ = +16.0 (*c* 1.30, $CHCl_3$); **IR** (ATR) 3066, 2962, 2929, 2855, 1709, 1472, 1457, 1423, 1375, 1210, 1105, 1086 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.73 (1H, d, *J* = 2.4 Hz, C<u>H</u>O), 7.65–7.63 (4H, m, Ar<u>H</u>), 7.46–7.37 (6H, m, Ar<u>H</u>), 3.89–3.88 (2H, OC<u>H</u>$_2$), 2.40–2.33 (1H, m, C<u>H</u>CHO), 1.78–1.67 (1H, m, C<u>H</u>$_a$H$_b$CH$_3$), 1.57–1.46 (1H, m, CH$_a$<u>H</u>$_b$CH$_3$), 1.03 (9H, s, C(C<u>H</u>$_3$)$_3$), 0.88 (3H, t, *J* = 7.5 Hz, CH$_2$C<u>H</u>$_3$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 204.6 (C), 135.6 (CH), 133.2 (C), 133.1 (C), 129.8 (CH), 122.7 (CH), 62.3 (CH_2), 55.8 (CH), 26.8 (CH_3), 19.2 (C), 18.5 (CH_2), 11.4 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–C_6H_5]^+$ $C_{15}H_{23}O_2Si$: 263.1462, found: 263.1472; *m/z* calculated for $[M+H]^+$ $C_{21}H_{29}O_2Si$: 341.1931, found: 341.1944; *m/z* calculated for $[M+Na]^+$ $C_{21}H_{28}NaO_2Si$: 363.1751, found: 363.1759.

*1.9.1.5. Synthesis of the ethyl ester **22** via a Witting olefination*[59]

(Carbethoxyethylidene)triphenylphosphorane (877 mg, 2.42 mmol) in anh CH_2Cl_2 (0.25 + 0.25 mL) was added *via cannula* to a solution of **24** in anh CH_2Cl_2 (0.5 mL). The reaction mixture was stirred for 24 h at r.t.

After this time, the volatiles were removed *in vacuo* and the crude oil was purified by flash column chromatography on silica gel (hexanes/CH_2Cl_2 3:1) to afford 419 mg (0.99 mmol, 82%) of ethyl ester **22**.



22

(*R, E*)-Ethyl 4-(*tert*-butyldiphenylsilyloxymethyl)-2-methylhex-2-enoate (**22**). Colorless oil; $\mathbf{R_f}$ = 0.40 (hexanes/CH_2Cl_2 1:1); $\mathbf{[\alpha]_D}$ = –6.2 (*c* 1.20, $CHCl_3$); **IR** (ATR) 2955, 2925, 2851, 1705, 1460, 1423, 1275, 1227, 1105, 1090 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.68–7.61 (4H, m, Ar<u>H</u>), 7.44–7.35 (6H, m, Ar<u>H</u>), 6.59 (1H, dq, *J* = 10.3, 1.4 Hz, C=C<u>H</u>), 4.25–4.14 (2H, m, OC<u>H</u>$_2$CH$_3$), 3.61 (1H, dd, *J* = 9.9, 6.0 Hz, C<u>H</u>$_a$H$_b$OSi), 3.55 (1H, dd, *J* = 9.9, 6.2 Hz, CH$_a$<u>H</u>$_b$OSi), 2.60–2.49 (1H, m, C=CHC<u>H</u>), 1.81 (3H, d, *J* = 1.4 Hz, HC=CC<u>H</u>$_3$), 1.72–1.60 (1H, m, CHC<u>H</u>$_a$H$_b$CH$_3$), 1.37–1.24 (1H, m, CHCH$_a$<u>H</u>$_b$CH$_3$), 1.29 (3H, t, *J* = 7.1 Hz, OCH$_2$C<u>H</u>$_3$), 1.04 (9H, s, C(CH$_3$)$_3$), 0.84 (3H, t, *J* = 7.5 Hz, CHCH$_2$C<u>H</u>$_3$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 168.2 (C), 143.7 (CH), 135.6 (CH), 135.6 (CH), 133.7 (C), 133.6 (C), 129.6 (CH), 129.6 (CH),

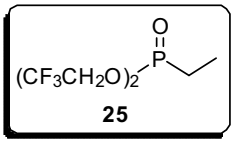
129.0 (C), 127.6 (2 × CH), 66.3 (CH_2), 60.4 (CH_2), 43.4 (CH), 26.8 (CH_3), 24.1 (CH_2), 19.2 (C), 14.3 (CH_3), 12.9 (CH_3), 11.7 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+NH_4]^+$ $C_{26}H_{40}O_3Si$: 442.2772, found: 442.2784.

1.9.2. Synthesis of the C11–C19 fragment of (+)-peloruside A

*1.9.2.1. Preparation of phosphonate **26*** [88]

A solution of ethylphosphonic dichloride (5.00 g, 34.0 mmol) in anh THF (64 mL) was added *via cannula* over a solution of 2,2,2-trifluoroethanol (5.1 mL, 69.7 mmol) and triethylamine (9.5 mL, 68 mmol) in anh THF (4.0 mL) at 0 ºC under N_2. The reaction solution was stirred for 2 h at r.t.

The mixture was filtered and the volatiles were removed *in vacuo*, obtaining 8.79 g of an oil containing phosphonate **25** that was used into the next step without further purification.

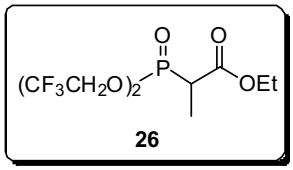


25

Bis(2,2,2-trifluoroethyl)ethylphosphonate (**25**). Colorless oil; **IR** (ATR) 1462, 1419, 1288, 1255, 1174, 1109, 1080, 1036, 1016 cm^{-1}; $\mathbf{R_f}$ = 0.25 (hexanes/EtOAc4:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 4.49–4.29 (4H, m, $(CF_3C\underline{H}_2O)_2$), 1.94 (2H, dq, *J* = 18.8, 7.7 Hz, $PC\underline{H}_2$), 1.23 (3H, dt, *J* = 21.6, 7.7 Hz, $C\underline{H}_3$); **^{19}F NMR** ($CDCl_3$, 376.3 MHz) –75.4 (6F, t, *J* = 8.1 Hz, $C\underline{F}_3$).

A solution of the previous crude oil and ethyl chloroformate (3.4 mL, 35.7 mmol) in anh THF (120 mL) was added dropwise *via cannula* over a 1.0 M solution of LiHMDS in THF (71.4 mL, 71.4 mmol) at –78 ºC under N_2. Once added, the reaction solution was stirred for 10 min at –78 ºC and 30 min at 0 ºC.

The mixture was quenched with 2 M HCl (100 mL). The layers were separated and the aqueous layer washed with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and the volatiles removed *in vacuo*. The product was purified by flash column chromatography on silica gel (hexanes/EtOAc 7:3) to give 10.4 g (30.0 mmol, 89%) of the β–ketophosphonate **26**.



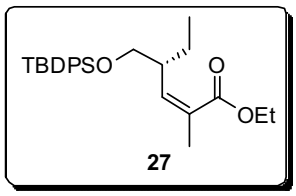
26

Ethyl 2-[bis(2,2,2-trifluoroethoxy)phosphinyl]propanoate (**26**). Colorless oil; $\mathbf{R_f}$ = 0.45 (hexanes/EtOAc 65:35); **IR** (ATR) 2977, 1731, 1286, 1260, 1156, 1064 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ4.49–4.36 (4H, m, $(CF_3C\underline{H}_2O)_2$), 4.23 (2H, qd, *J* = 7.1, 1.9 Hz, $OC\underline{H}_2CH_3$), 3.19 (1H, dq, *J* = 22.3, 7.4 Hz, $\underline{H}CP{=}O$), 1.52 (3H, dd, *J* = 19.4, 7.4 Hz, $\underline{H}_3CCHP{=}O$), 1.30 (3H, t, *J* = 7.1 Hz, $OCH_2C\underline{H}_3$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 168.4 (C, d, *J* = 3.2 Hz), 122.5 (CF_3, qd, *J* = 277.4, 2.9 Hz), 122.4 (CF_3, qd, *J* = 276.8, 2.0 Hz), 62.5 (CH_2, qd, *J* = 38.0, 5.8 Hz), 62.1 (CH_2), 39.5 (CH, d, *J* = 140.7 Hz), 13.8 (CH_3), 11.5 (CH_3, d, *J* = 6.5 Hz).

*1.9.2.2. Synthesis of ester **27** via a Still–Gennari olefination*[77]

A 0.5 M solution of KHMDS in toluene (7.18 mL, 3.59 mmol) was added dropwise to a solution of the β-ketophosphonate **26** (1.11 g, 3.26 mmol) and 18–crown–6 (3.02 g, 11.4 mmol) in anh THF (15.4 mL) at –78 ºC under N_2. After the addition, the reaction mixture was stirred for 15 min at r.t. and cooled again at –78 ºC. A solution of the aldehyde **24** (1.11 g, 3.26 mmol) in anh THF (1.5 + 1.5 mL) was added *via cannula*, and the reaction mixture was stirred for 2 h at –78 ºC.

The reaction was quenched with sat NH_4Cl (14 mL). The layers were separated and the aqueous phase extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The product was purified by flash column chromatography on silica gel (hexanes/CH_2Cl_2 65:35) to give 1.24 g (2.92 mmol, 89%) of pure ethyl ester **27**.



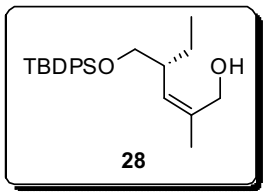
27

(*R, Z*)-Ethyl 4-(*tert*-butyldiphenylsilyloxymethyl)-2-methylhex-2-enoate (**27**). Colorless oil; $\mathbf{R_f}$ = 0.65 (hexanes/CH_2Cl_2 1:1); $\mathbf{[\alpha]_D}$ = –40.0 (*c* 1.15, $CHCl_3$); **IR** (ATR) 3070, 2959, 2925, 2855, 1724, 1472, 1457, 1423, 1104 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.66–7.62 (4H, m, ArH), 7.44–7.34 (6H, m, ArH), 5.75 (1H, ddd, *J* = 10.2, 2.9, 1.4 Hz, C=CH), 4.16 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 3.62 (1H, dd, *J* = 8.6, 4.3 Hz, CH_aH_bOSi), 3.58 (1H, dd, *J* = 8.6, 4.4 Hz, CH_aH_bOSi), 3.28–3.18 (1H, m, C=CHCH), 1.92 (3H, d, *J* = 1.4 Hz, $HC=CCH_3$), 1.70–1.53 (1H, m, $CHCH_aH_bCH_3$), 1.37–1.24 (1H, m, $CHCH_aH_bCH_3$), 1.27 (3H, t, *J* = 7.1 Hz, OCH_2CH_3), 1.03 (9H, s, $C(CH_3)_3$), 0.85 (3H, t, *J* = 7.5 Hz, $CHCH_2CH_3$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 168.0, 144.3, 135.6, 135.6, 133.8 (2C), 129.5, 129.5, 128.3, 127.5 (2C), 66.7, 60.0, 42.9, 26.8, 24.4, 21.0, 19.3, 14.2, 11.6; **HRMS** (+ESI): *m/z* calculated for $[M–C_6H_5]^+$ $C_{15}H_{23}O_2Si$: 263.1462, found: 263.1472; *m/z* calculated for $[M+H]^+$ $C_{26}H_{37}O_3Si$:425.2506, found: 425.2499.

*1.9.2.3. Reduction of the α,β–unsaturated ester **27***[72]

A 1.0 M solution of DIBALH in toluene (6.7 mL, 6.7 mmol) was added dropwise to a solution of the ethyl ester **27** (1.14 g, 2.69 mmol) in anh CH_2Cl_2 (27 mL) at –78 ºC under N_2. The reaction mixture was stirred for 45 min at –78 ºC.

The reaction mixture was quenched with a 20% sodium potassium tartrate solution (27 mL) and stirred for 2 h at r.t. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography on silica gel (hexanes/EtOAc 88:12) to give 1.06 g (2.77 mmol, 99%) of allylic alcohol **28**.

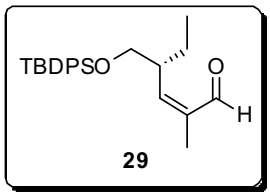


(*R, Z*)-4-(*tert*-Butyldiphenylsilyloxymethyl)-2-methylhex-2-en-1-ol (**28**). Colorless oil; $\mathbf{R_f}$ = 0.50 (hexanes/EtOAc85:15); $\mathbf{[\alpha]_D}$ = –21.2 (*c* 1.00, $CHCl_3$); **IR** (ATR) 3346 (br), 3066, 2954, 2928, 2850, 1468, 1424, 1108 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.68–7.64 (4H, m, ArH), 7.43–7.35 (6H, m, ArH), 5.00 (1H, dt, *J* = 10.2, 1.4 Hz, C=CH), 4.15 (1H, dd, *J* = 11.8, 1.4 Hz, CH_aH_bOH), 3.93 (1H, d, *J* = 11.8 Hz, CH_aH_bOH), 3.57 (1H, dd, *J* = 9.7, 5.4 Hz, CH_aH_bOSi), 3.35 (1H, dd, *J* = 9.7, 8.1 Hz, CH_aH_bOSi), 2.59–2.50 (1H, m, C=CHCH), 1.84 (3H, d, *J* = 1.4 Hz, HC=CCH_3), 1.50–1.40 (1H, m, $CH_aH_bCH_3$), 1.15–1.02 (1H, m, $CH_aH_bCH_3$), 1.05 (9H, s, $C(CH_3)_3$), 0.81 (3H, t, *J* = 7.4 Hz, $CHCH_2CH_3$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 137.1, 135.6, 135.6, 133.4, 133.4, 130.6, 129.6 (2C), 127.6, 127.6, 67.5, 62.1, 42.3, 26.8, 24.5, 22.0, 19.1, 11.7; **HRMS** (+ESI): *m/z* calculated for $[M+Na]^+$ $C_{24}H_{34}NaO_2Si$: 405.2220, found: 405.2218.

*1.9.2.4. Oxidation of the allylic alcohol **28***[72]

Solid MnO_2 (1.11 g, 12.8 mmol) was added to a solution of allylic alcohol **28** (334 mg, 0.87 mmol) in anh CH_2Cl_2 (6.0 mL) under N_2. The system was purged again with N_2 and stirred for 20 h at r.t.

The mixture was filtrated through a sintered glass funnel and the volatiles removed *in vacuo*. The crude oil was immediately purified by flash column chromatography on silica gel (hexanes/EtOAc 9:1) to give 259 mg (0.68 mmol, 78%) of aldehyde **29**.



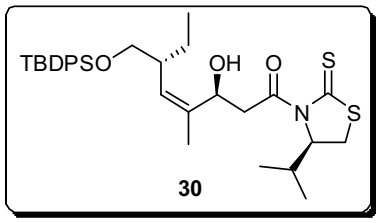
(*R, Z*)-4-(*tert*-Butyldiphenylsilyloxymethyl)-2-methylhex-2-enal (**29**). Colorless oil; $\mathbf{R_f}$ = 0.65 (hexanes/EtOAc9:1); $\mathbf{[\alpha]_D}$ = –45.2 (*c* 0.86, $CHCl_3$); **IR** (ATR) 3066, 2959, 2925, 2851, 1676, 1468, 1427, 1375, 1108 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 10.03 (1H, s, CHO), 7.64–7.60 (4H, m, ArH), 7.46–7.36 (6H, m, ArH), 6.23 (1H, dq, *J* = 10.9, 1.4 Hz, C=CH), 3.69 (1H, dd, *J* = 10.0, 5.2 Hz, CH_aH_bOSi), 3.52 (1H, dd, *J* = 10.0, 7.3 Hz, CH_aH_bOSi), 3.22–3.12 (1H, m, C=CHCH), 1.80 (3H, d, *J* = 1.4 Hz, HC=CCH_3), 1.65–1.53 (1H, m, $CH_aH_bCH_3$), 1.31–1.19 (1H, m, $CH_aH_bCH_3$), 1.02 (9H, s, $C(CH_3)_3$), 0.85 (3H, t, *J* = 7.5 Hz, $CHCH_2CH_3$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 191.8, 151.2, 137.7, 135.6, 135.5, 133.4, 133.4, 129.7 (2C), 127.7, 127.7, 66.7, 41.0, 26.8, 24.3, 19.1, 16.6, 11.7; **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{24}H_{33}O_2Si$: 381.2244, found: 381.2247; *m/z* calculated for $[M+Na]^+$ $C_{24}H_{32}NaO_2Si$:403.2064, found: 403.2062.

*1.9.2.5. Titanium(IV)–mediated acetate aldol reaction with aldehyde **29***[89]

Neat $TiCl_4$ (190 µL, 1.74 mmol) was added dropwise to a solution of *N*-acetylthioimide ***ent*-4p** (333 mg, 1.64 mmol) in anh CH_2Cl_2 (3.4 mL) at 0 ºC under N_2. The resulting mixture was stirred for 5 min and cooled at –78 ºC. DIPEA (302 µL, 1.74 mmol) was added dropwise. The resulting solution was

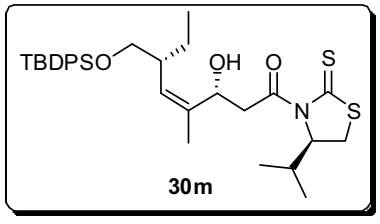
stirred for 2 h at –40 ºC and then cooled again at –78 ºC. A solution of aldehyde **29** (367 mg, 0.97 mmol) in anh CH_2Cl_2 (0.8 + 0.8 mL) was added *via cannula* and the reaction mixture was stirred for 1 h at –78 ºC.

The reaction was quenched with sat NH_4Cl (6.0 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. HPLC of the reaction crude revealed a d.r. of 94:6. Purification by flash column chromatography on silica gel (hexanes/EtOAc 90:10 to 88:12) afforded 431 mg (0.74 mmol, 76%) of the pure major diastereomer aldol **30** and 33 mg (0.06 mmol, 6%) of the minor diastereomer **30m**.



30

(3*S*, 6*R*, *Z*)-*N*-[6-(t*ert*-Butyldiphenylsilyloxymethyl)-3-hydroxy-4-methyloct-4-enoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**30**). Yellow oil; $\mathbf{R_f}$ = 0.40 (hexanes/EtOAc4:1); **HPLC** (Tracer Spherisorb S3W (N4184) column, 8% of EtOAc in hexanes, 0.9 mL/min, 254 nm), t_R = 29.9 min; $[\alpha]_D$ = –212.0 (*c* 0.80, $CHCl_3$); **IR** (ATR) 3459 (br), 3067, 2959, 2925, 2850, 1730, 1687, 1641, 1422, 1366, 1358, 1256, 1153, 1105, 1034 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.67–7.64 (4H, m, ArH), 7.44–7.36 (6H, m, ArH), 5.16 (1H, ddd, *J* = 8.0, 6.1, 1.0 Hz, NCH), 5.10 (1H, dd, *J* = 9.9, 3.0 Hz, CHOH), 5.00 (1H, dd, *J* = 11.1, 1.3 Hz, C=CH), 3.56 (1H, dd, *J* = 9.6, 5.6 Hz, CH_aH_bOSi), 3.55 (1H, dd, *J* = 17.5, 9.9 Hz, $COCH_aH_b$), 3.52 (1H, dd, *J* = 11.4, 8.0 Hz, SCH_aH_b), 3.43 (1H, dd, *J* = 9.6, 7.1 Hz, CH_aH_bOSi), 3.35 (1H, dd, *J* = 17.5, 3.0 Hz, $COCH_aH_b$), 3.02 (1H, dd, *J* = 11.4, 1.0 Hz, SCH_aH_b), 2.63–2.53 (1H, m, C=CHCH), 2.45–2.34 (1H, m, $CH(CH_3)_2$), 1.76 (3H, d, *J* = 1.3 Hz, $HC=CCH_3$), 1.58–1.47 (1H, m, $CH_aH_bCH_3$), 1.19–1.04 (1H, m, $CH_aH_bCH_3$), 1.08 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(CH_3)_b$), 1.04 (9H, s, $C(CH_3)_3$), 1.00 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_a(CH_3)_b$), 0.81 (3H, t, *J* = 7.4 Hz, CH_2CH_3); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.9, 172.5, 137.2, 135.6, 135.6, 133.6, 133.6, 130.7, 129.6 (2C), 127.6 (2C), 71.6, 67.4, 65.9, 43.5, 41.9, 30.9, 30.6, 26.9, 24.5, 19.2, 19.1, 18.4, 17.8, 11.8; **HRMS** (+ESI): *m/z* calculated for $[M–OH]^+$ $C_{32}H_{44}NO_2S_2Si$: 566.2577, found: 566.2586; *m/z* calculated for $[M+Na]^+$ $C_{32}H_{45}NNaO_3S_2Si$: 606.2502, found: 606.2499.



30m

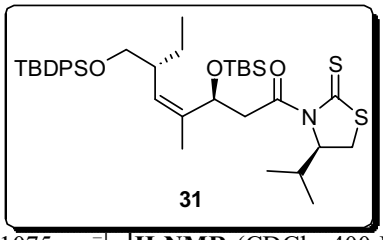
(*R*)-*N*-[(3*R*, 6*R*, *Z*)-6-(t*ert*-Butyldiphenylsilyloxymethyl)-3-hydroxy-4-methyloct-4-enoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**30m**). Yellow oil; $\mathbf{R_f}$ = 0.40 (hexanes/EtOAc4:1); **HPLC** (Tracer Spherisorb S3W (N4184) column, 8% of EtOAc in hexanes, 0.9 mL/min, 254 nm), t_R = 15.2 min; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.66–7.60 (4H, m, ArH), 7.44–7.34 (6H, m, ArH), 5.13 (1H, ddd, *J* = 7.9, 6.1, 1.2 Hz, NCH), 5.02 (1H, dd, *J* = 10.4, 1.6 Hz, C=CH), 4.95 (1H, dd, *J* = 10.2, 2.6 Hz, CHOH), 3.81 (1H, dd, *J* = 17.4, 10.2 Hz, $COCH_aH_b$), 3.51 (1H, dd, *J* = 9.7, 5.8 Hz, CH_aH_bOSi), 3.45 (1H, dd, *J* = 11.5, 7.9 Hz, SCH_aH_b), 3.43 (1H, dd, *J* = 9.7, 6.5 Hz, CH_aH_bOSi), 3.06 (1H, dd, *J* = 17.4, 2.6 Hz, SCH_aH_b), 3.01 (1H, dd, *J* = 11.5, 1.2 Hz, SCH_aH_b), 2.65–2.55 (1H, m, C=CHCH), 2.43–2.30 (1H, m, $CH(CH_3)_2$),1.78 (3H, d, *J* = 1.3 Hz,

HC=CC$\underline{H}_3$), 1.62–1.51 (1H, m, C$\underline{H}_a$H$_b$CH$_3$), 1.22–1.11 (1H, m, CH$_a\underline{H}_b$CH$_3$), 1.06 (3H, d, *J* = 6.8 Hz, CH(C$\underline{H}_3$)$_a$(CH$_3$)$_b$), 1.02 (9H, s, C(C$\underline{H}_3$)$_3$), 0.98 (3H, d, *J* = 7.0 Hz, CH(CH$_3$)$_a$(C$\underline{H}_3$)$_b$), 0.87 (3H, t, *J* = 7.4 Hz, CH$_2$C$\underline{H}_3$).

*1.9.2.6. Protection of aldol **30***

2,6-Lutidine (180 µL, 1.55 mmol) and TBSOTf (165 µL, 0.72 mmol) were added to a solution of aldol **30** (334 mg, 0.58 mmol) in anh CH_2Cl_2 (5.4 mL) at 0 ºC under N_2. The reaction mixture was stirred for 1 h at 0 ºC.

A pH 7 buffer solution of $NaKHPO_4/KH_2PO_4$ (6.0 mL) was added to quench the reaction. After stirring for 10 min, the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with sat $NaHCO_3$ (30 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography on silica gel (hexanes/EtOAc 95:5) afforded 317 mg (0.45 mmol, 79%) of pure protected aldol **31**.



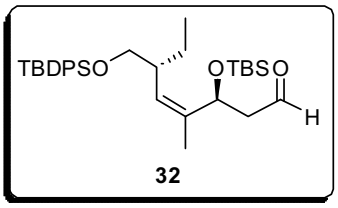
31

(*R*)-*N*-[(3*S*, 6*R*, *Z*)-3-(*tert*-Butyldimethylsilyloxy)-6-(*tert*-butyldiphenylsilyloxymethyl)-4-methyloct-4-enoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**31**). Yellow oil; $\mathbf{R_f}$ = 0.50 (hexanes/EtOAc 95:5); $\mathbf{[\alpha]_D}$ = –190.2 (*c* 1.00, $CHCl_3$); **IR** (ATR) 3070, 2947, 2922, 2851, 1692, 1464, 1357, 1279, 1249, 1156, 1108, 1075 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.68–7.64 (4H, m, Ar$\underline{H}$), 7.43–7.34 (6H, m, Ar$\underline{H}$), 5.18 (1H, dd, *J* = 9.8, 2.0 Hz, C$\underline{H}$OTBS), 5.06–4.98 (2H, m, NC$\underline{H}$, C=C$\underline{H}$), 4.05 (1H, dd, *J* = 16.6, 9.8 Hz, COC$\underline{H}_a$H$_b$), 3.62 (1H, dd, *J* = 9.8, 4.2 Hz, C$\underline{H}_a$H$_b$OTBDPS), 3.47 (1H, dd, *J* = 11.5, 7.8 Hz, SC$\underline{H}_a$H$_b$), 3.46 (1H, dd, *J* = 9.8, 7.1 Hz, CH$_a\underline{H}_b$OTBDPS), 3.03 (1H, dd, *J* = 11.5, 0.8 Hz, SCH$_a\underline{H}_b$), 2.69 (1H, dd, *J* = 16.6, 2.0 Hz, COCH$_a\underline{H}_b$), 2.63–2.54 (1H, m, C=CHC$\underline{H}$), 2.48–2.36 (1H, m, C$\underline{H}$(CH$_3$)$_2$), 1.85–1.73 (1H, m, C$\underline{H}_a$H$_b$CH$_3$), 1.69 (1H, d, *J* = 1.3 Hz, HC=CC$\underline{H}_3$), 1.33–1.21 (1H, m, CH$_a\underline{H}_b$CH$_3$), 1.07 (3H, d, *J* = 6.8 Hz, CH(C$\underline{H}_3$)$_a$(CH$_3$)$_b$), 1.06 (9H, s, Ph$_2$SiC(C$\underline{H}_3$)$_3$), 0.99 (3H, d, *J* = 7.0 Hz, CH(CH$_3$)$_a$(C$\underline{H}_3$)$_b$), 0.82 (3H, t, *J* = 7.4 Hz, CH$_2$C$\underline{H}_3$), 0.80 (9H, s, (H$_3$C)$_2$SiC(C$\underline{H}_3$)$_3$), –0.02 (3H, s, Si(C$\underline{H}_3$)$_a$(CH$_3$)$_b$), –0.10 (3H, s, Si(CH$_3$)$_a$(C$\underline{H}_3$)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.8 (C), 171.5 (C), 137.9 (C), 135.5 (CH), 135.5 (CH), 133.7 (C), 133.7 (C), 129.5 (CH), 129.4 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 71.7 (CH), 67.5 (CH), 66.5 (CH_2), 44.6 (CH_2), 41.4 (CH), 30.9 (CH_2), 30.8 (CH), 26.8 (CH_3), 25.6 (CH_3), 24.9 (CH_2), 19.3 (C), 19.1 (CH_3), 18.2 (CH_3), 17.9 (C), 17.9 (CH_3), 11.7 (CH_3), –5.0 (CH_3), –5.1 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OTBS]^+$ $C_{32}H_{44}NO_2S_2Si$: 566.2577, found: 566.2585; *m/z* calculated for $[M+Na]^+$ $C_{38}H_{59}NNaO_3S_2Si_2$: 720.3367, found: 720.3355.

*1.9.2.7. Synthesis of aldehyde **32***

1 M DIBALH in toluene (330 µL, 0.33 mmol) was added dropwise to a solution of silylated aldol **31** (105 mg, 0.15 mmol) in anh CH_2Cl_2 (1.0 mL) at –78 ºC under N_2.

After stirring 10 min, the reaction mixture was quenched with anh MeOH (0.1 mL) and allowed to be warmed to r.t. Then, a 20% solution of sodium potassium tartrate (4.2 mL) was added and the mixture was stirred for 2.5 h. The mixture was diluted in CH_2Cl_2 (10 mL) and water (10 mL) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2(3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*.Purification by flash column chromatography on silica gel (hexanes/EtOAc 7:3) afforded 74 mg (0.14 mmol, 89%) of pure **32**.



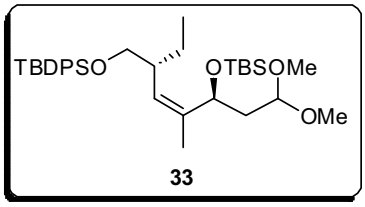
32

(3*S*, 6*R*, *Z*)-3-(*tert*-Butyldimethylsilyloxy)-6-(*tert*-butyldiphenylsilyl oxymethyl)-4-methyloct-4-enal (**32**). Colorless oil; $\mathbf{R_f}$ = 0.35 (hexanes/EtOAc7:3); $\mathbf{[\alpha]_D}$= –35.5 (*c* 1.25, $CHCl_3$); **IR** (ATR):3070, 2951, 2922, 2851, 1724, 1468, 1427, 1249, 1108, 1071 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.77 (1H, dd, *J* = 3.0, 1.9 Hz, C<u>H</u>O), 7.67–7.63 (4H, m, Ar<u>H</u>), 7.45–7.34 (6H, m, Ar<u>H</u>), 5.04 (1H, dd, *J* = 9.6, 3.2 Hz,C<u>H</u>OTBS), 5.01 (1H, dd, *J* = 10.6, 1.2 Hz, C=C<u>H</u>), 3.62 (1H, dd, *J* = 9.8, 4.3 Hz, C<u>H$_a$</u>H$_b$OTBDPS), 3.46 (1H, dd, *J* = 9.8, 7.4 Hz, CH$_a$<u>H$_b$</u>OTBDPS), 2.76 (1H, ddd, *J* = 15.4, 9.6, 3.0 Hz, COC<u>H$_a$</u>H$_b$), 2.54–2.44 (1H, m, C=CHC<u>H</u>), 2.28 (1H, ddd, *J* = 15.4, 3.2, 1.9 Hz, COCH$_a$<u>H$_b$</u>), 1.86–1.75 (1H, m, C<u>H$_a$</u>H$_b$CH$_3$), 1.69 (1H, d, *J* = 1.2 Hz, HC=CC<u>H$_3$</u>), 1.33–1.21 (1H, m, CH$_a$<u>H$_b$</u>CH$_3$), 1.06 (9H, s, Ph$_2$SiC(C<u>H$_3$</u>)$_3$), 0.81 (3H, m, CH$_2$C<u>H$_3$</u>), 0.81 (9H, s, (H$_3$C)$_2$SiC(C<u>H$_3$</u>)$_3$), –0.04 (3H, s, Si(C<u>H$_3$</u>)$_a$(CH$_3$)$_b$), –0.12 (3H, s, Si(CH$_3$)$_a$(C<u>H$_3$</u>)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 201.7 (C), 137.6 (C), 135.6 (CH), 135.6 (CH), 133.8 (C), 133.7 (C), 129.6 (CH), 129.5 (CH), 127.6 (CH), 127.6 (CH), 127.6 (CH), 127.6 (CH), 66.5 (CH_2), 66.3 (CH), 50.3 (CH_2), 41.4 (CH), 26.9 (CH_3), 25.6 (CH_3), 24.9 (CH_2), 19.3 (C), 18.0 (C), 17.9 (CH_3), 11.7 (CH_3), –4.8 (CH_3), –5.1 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OTBS]^+$ $C_{26}H_{35}O_2Si$: 407.2401, found: 407.2400; *m/z* calculated for $[M+NH_4]^+$ $C_{32}H_{54}NO_3Si_2$: 556.3637, found: 556.3647; *m/z* calculated for $[M+Na]^+$ $C_{32}H_{50}NaO_3Si_2$: 561.3191, found: 561.3188.

*1.9.2.8. Synthesis of dimethyl acetal **33***

A suspension of aldehyde **32** (74 mg, 0.14 mmol) and catalytic amounts of PPTS in anh MeOH (20 µL, 0.49 mmol) and methyl orthoformate (20 µL, 0.18 mmol) under N_2 was stirred for 70 h at r.t.

The reaction mixture was diluted in Et_2O (20 mL) and washed with sat $NaHCO_3$ (3 × 10 mL) and brine (15 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to afford 73 mg (0.12 mmol, 91%) of pure dimethyl acetal **33**.



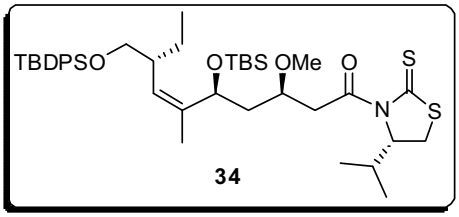
33

(2*R*, 5*S*, *Z*)-3-(*tert*-Butyldimethylsilyloxy)-6-(*tert*-butyldiphenyl silyloxymethyl)-4-methyloct-4-enaldehyde dimethyl acetal (**33**). Colorless oil; $\mathbf{R_f}$ = 0.30 (hexanes/CH_2Cl_2 7:3); $\mathbf{[\alpha]_D}$ = –42.3 (*c* 0.97, $CHCl_3$); **IR** (ATR) 2954, 2919, 2852, 1472, 1459, 1424, 1375, 1361, 1246, 1108, 1072, 1050 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.68–7.64 (4H, m, ArH), 7.43–7.34 (6H, m, ArH), 4.97 (1H, d, *J* = 10.0 Hz, C=CH), 4.61 (1H, dd, *J* = 10.1, 3.0 Hz, CHOTBS), 4.51 (1H, dd, *J* = 8.4, 3.1 Hz, $CH(OCH_3)_2$), 3.62 (1H, dd, *J* = 9.8, 4.2 Hz, $CH_aH_bOTBDPS$), 3.46 (1H, dd, *J* = 9.8, 7.2 Hz, $CH_aH_bOTBDPS$), 3.34 (3H, s, $CH(OCH_3)_a(OCH_3)_b$), 3.30 (3H, s, $CH(OCH_3)_a(OCH_3)_b$), 2.55–2.45 (1H, m, C=CHCH), 1.90–1.72 (2H, m, $CH_aH_bCH(OCH_3)_2$, $CH_aH_bCH_3$), 1.66 (1H, d, *J* = 1.3 Hz, $HC=CCH_3$), 1.64–1.57 (1H, m, $CH_aH_bCH(OCH_3)_2$), 1.35–1.24 (1H, m, $CH_aH_bCH_3$), 1.06 (9H, s, $Ph_2SiC(CH_3)_3$), 0.84 (3H, t, *J* = 7.4 Hz, CH_2CH_3), 0.84 (9H, s, $(H_3C)_2SiC(CH_3)_3$), –0.04 (3H, s, $Si(CH_3)_a(CH_3)_b$), –0.15 (3H, s, $Si(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 138.7 (C), 135.6 (CH), 135.6 (CH), 133.9 (C), 133.8 (C), 129.5 (CH), 129.5 (CH), 127.6 (CH), 127.6 (CH), 126.7 (CH), 102.2 (CH), 67.1 (CH), 66.5 (CH_2), 52.8 (CH_3), 52.5 (CH_3), 41.1(CH), 39.3 (CH_2), 26.9 (CH_3), 25.8 (CH_3), 24.9 (CH_2), 19.4 (C), 18.1 (C), 17.8 (CH_3), 11.6 (CH_3), –4.8 (CH_3), –5.1 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+Na]^+$ $C_{34}H_{56}NaO_4Si_2$: 607.3609, found: 607.3602.

*1.9.2.9. Addition of a titanium(IV) enolate to dimethyl acetal **33*** [31]

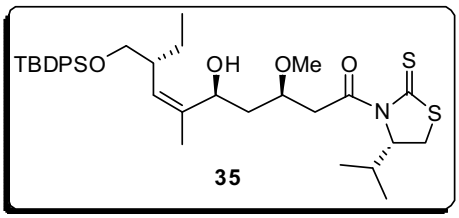
A 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (369 µL, 0.37 mmol) was added dropwise to a solution of thioimide **4p** (72 mg, 0.35 mmol) in anh CH_2Cl_2 (2.5 mL) at 0 ºC under N_2. The resulting mixture was stirred for 5 min and cooled at –78 ºC. A solution of DIPEA (65 µL, 0.37 mmol) in anh CH_2Cl_2 (0.20 + 0.15 mL) was added dropwise *via cannula*. The resulting solution was stirred for 30 min at –78 ºC and 2 h at –50 ºC and then cooled again at –78 ºC. A 1.0 M solution of $SnCl_4$ in CH_2Cl_2 (195 µL, 0.20 mmol) was then added. After stirring for 3 min, a solution of dimethyl acetal **33** (103 mg, 0.18 mmol) in CH_2Cl_2 (0.20 + 0.20 mL) was added *via cannula* and the reaction mixture was stirred for 2 h at –78 ºC.

The reaction was quenched with sat NH_4Cl (2.6 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography on silica gel (hexanes/EtOAc from 90:10 to 88:12) afforded 28 mg (37 µmol, 21%) of pure thioimide **34** and 59 mg (92 µmol, 52%) of a 4:1 mixture of the two diastereomers of the desilylated products **35** and **35m**.



34

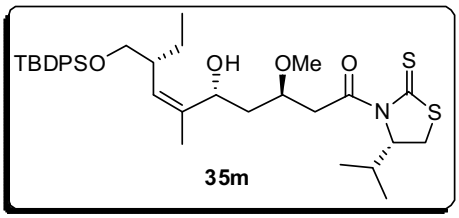
(*S*)-*N*-[(3*R*, 5*S*, 8*R*, *Z*)-5-(*tert*-Butyldimethylsilyloxy)-8-(*tert*-butyldiphenylsilyloxymethyl)-3-methoxy-6-methyl-dec-6-enoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**34**). Yellow oil; $\mathbf{R_f}$ = 0.40 (hexanes/EtOAc9:1); $\mathbf{[\alpha]_D}$ = +57.8 (*c* 1.40, $CHCl_3$); **IR** (ATR) 2955, 2925, 2851, 1698, 1468, 1460, 1431, 1371, 1357, 1301, 1257, 1153, 1108, 1067 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.67–7.65 (4H, m, ArH), 7.43–7.34 (6H, m, ArH), 5.17 (1H, ddd, *J* = 8.1, 5.9, 1.8 Hz, NCH), 5.04 (1H, d, *J* = 9.8 Hz, C=CH), 4.51 (1H, dd, *J* = 8.8, 4.0 Hz, CHOTBS), 3.82 (1H, tt, *J* = 7.8, 4.5 Hz, CHOCH$_3$), 3.68 (1H, dd, *J* = 17.2, 7.8 Hz, COCH$_a$H$_b$), 3.62 (1H, dd, *J* = 10.0, 4.2 Hz, CH$_a$H$_b$OTBDPS), 3.48 (1H, dd, *J* = 10.0, 3.2 Hz, CH$_a$H$_b$OTBDPS), 3.47 (1H, dd, *J* = 11.5, 8.1 Hz, SCH$_a$H$_b$), 3.40 (1H, dd, *J* = 17.2, 4.5 Hz, COCH$_a$H$_b$), 3.34 (3H, s, OCH$_3$), 3.02 (1H, dd, *J* = 11.5, 1.8 Hz, SCH$_a$H$_b$), 2.50–2.41 (1H, m, C=CHCH), 2.41–2.32 (1H, m, CH(CH$_3$)$_2$), 2.00 (1H, ddd, *J* = 13.8, 8.8, 4.5 Hz, CH$_a$H$_b$CHOTBS), 1.85–1.73 (1H, m, CH$_a$H$_b$CH$_3$), 1.68 (3H, d, *J* = 1.3 Hz, HC=CCH$_3$), 1.50 (1H, ddd, *J* = 13.8, 7.8, 4.0 Hz, CH$_a$H$_b$CHOTBS), 1.38–1.24 (1H, m, CH$_a$H$_b$CH$_3$), 1.06 (9H, s, Ph$_2$SiC(CH$_3$)$_3$), 1.05 (3H, d, *J* = 7.6 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$), 0.98 (3H, d, *J* = 7.0 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$), 0.85 (3H, t, *J* = 7.5 Hz, CH$_2$CH$_3$), 0.84 (9H, s, (H$_3$C)$_2$SiC(CH$_3$)$_3$), –0.05 (3H, s, Si(CH$_3$)$_a$(CH$_3$)$_b$), –0.17 (3H, s, Si(CH$_3$)$_a$(CH$_3$)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.6 (C), 172.2 (C), 138.27 (C), 135.6 (CH), 135.6 (CH), 133.9 (C), 133.8 (C), 129.5 (CH), 129.5 (CH), 127.6 (CH), 127.6 (CH), 127.3 (CH), 74.9 (CH), 71.8 (CH), 67.5 (CH), 66.2 (CH_2), 56.3 (CH_3), 43.1 (CH_2), 41.1 (CH), 40.4 (CH_2), 30.6 (CH), 30.1 (CH_2), 26.9 (CH_3), 25.8 (CH_3), 24.9 (CH_2), 19.4 (C), 19.1 (CH_3), 18.0 (C), 17.9 (CH_3), 17.3 (CH_3), 11.7 (CH_3), –4.8 (CH_3), –4.9 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OTBS–OCH_3]^+$ $C_{34}H_{46}NO_2S_2Si$: 592.2734, found: 592.2727; *m/z* calculated for $[M–OTBS]^+$ $C_{35}H_{50}NO_3S_2Si$: 624.2996, found: 624.2990; *m/z* calculated for $[M+Na]^+$ $C_{41}H_{65}NNaO_4S_2Si_2$: 778.3786, found: 778.3803.



35

(*S*)-*N*-[(3*R*, 5*S*, 8*R*, *Z*)-8-(*tert*-Butyldiphenylsilyloxy methyl)-5-hydroxy-3-methoxy-6-methyl-dec-6-enoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**35**). Yellow oil; $\mathbf{R_f}$ = 0.30 (hexanes/EtOAc9:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.69–7.62 (4H, m, ArH), 7.45–7.35 (6H, m, ArH), 5.21–5.14 (1H, m, CHOH), 5.16 (1H, ddd, *J* = 8.1, 6.0, 1.3 Hz, NCH), 5.07 (1H, dd, *J* = 10.2, 1.2 Hz, C=CH), 4.10–4.02 (1H, m, CHOCH$_3$), 3.75 (1H, dd, *J* = 17.2, 5.0 Hz, COCH$_a$H$_b$), 3.54–3.49 (2H, m, CH$_2$OSi), 3.48 (1H, dd, *J* = 11.5, 8.1 Hz, SCH$_a$H$_b$), 3.41 (3H, s, OCH$_3$), 3.21 (1H, dd, *J* = 17.2, 7.2 Hz, COCH$_a$H$_b$), 3.02 (1H, dd, *J* = 11.5, 1.3 Hz, SCH$_a$H$_b$), 2.60–2.46 (1H, m, C=CHCH), 2.45–2.30 (1H, m, CH(CH$_3$)$_2$), 2.03 (1H, ddd, *J* = 13.7, 10.8, 2.6 Hz, HOCHCH$_a$H$_b$), 1.79 (3H, d, *J* = 1.2 Hz, HC=CCH$_3$), 1.71–1.58 (2H, m, HOCHCH$_a$H$_b$, CH$_a$H$_b$CH$_3$), 1.37–1.19 (1H, m, CH$_a$H$_b$CH$_3$), 1.07 (3H, d, *J* = 6.8 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$), 1.05 (9H, s, C(CH$_3$)$_3$), 0.99 (3H, d, *J* = 7.0 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$),0.89 (3H, t, *J* = 7.4 Hz, CH$_2$CH$_3$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.7 (C), 171.4 (C), 135.6 (CH), 135.6 (CH), 135.4 (C), 133.8 (C), 133.8 (C), 131.4 (CH), 129.5 (CH), 129.5 (CH), 127.6 (CH), 127.6 (CH), 74.6 (CH), 71.5 (CH), 67.1 (CH_2), 57.9 (CH), 57.7 (CH_3), 42.5 (CH_2), 42.2 (CH_2), 42.1 (CH), 30.7 (CH), 30.3 (CH_2), 26.9 (CH_3), 24.5

(CH_2), 19.3 (C), 19.0 (CH_3), 18.1 (CH_3), 17.6 (CH_3), 11.7 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OH]^+$ $C_{35}H_{50}NO_3S_2Si$: 624.2996, found: 624.2989.



35m

(*S*)-*N*-[(3*S*, 5*S*, 8*R*, *Z*)-8-(*tert*-Butyldiphenylsilyloxy methyl)-5-hydroxy-3-methoxy-6-methyl-dec-6-enoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**35m**). Yellow oil; $\mathbf{R_f}$ = 0.30 (hexanes/EtOAc9:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.15–5.10 (1H, m, NC<u>H</u>), 3.64 (1H, dd, *J* = 13.5, 5.2 Hz, COC<u>H</u>$_a$H$_b$), 3.33 (3H, s, OC<u>H</u>$_3$), 2.60–2.46 (1H, m, C=CHC<u>H</u>), 2.45–2.30 (1H, m, C<u>H</u>$(CH_3)_2$), 2.16–1.99 (1H, m, HOCHC<u>H</u>$_a$H$_b$), 1.82 (3H, d, *J* = 1.2 Hz, HC=CC<u>H</u>$_3$), 1.71–1.58 (2H, m, HOCHCH$_a$<u>H</u>$_b$, C<u>H</u>$_a$H$_b$CH$_3$), 1.37–1.19 (1H, m, CH$_a$<u>H</u>$_b$CH$_3$), 1.07 (9H, s, C(C<u>H</u>$_3$)$_3$), 0.86 (3H, t, *J* = 6.3 Hz, CH$_2$C<u>H</u>$_3$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.8, 171.6, 134.8, 132.7, 129.5, 75.1, 71.6, 66.3, 56.6, 56.5, 41.9, 41.7, 41.1, 30.5, 25.8, 24.6.

2. Stereoselective Ni(II) catalyzed alkylation reactions of *N*-acyl thiazolidinethiones

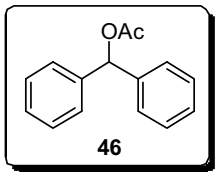
2.1. PREPARATION OF STARTING MATERIALS

2.1.1. Preparation of diarylmethyl acetates

*2.1.1.1. Benzhydryl acetate (**46**)*

Anh triethylamine (2.2 mL, 16.0 mmol) and acetic anhydride (1.50 mL, 16.0 mmol) were added to a solution of diphenylmethanol (1.47 g, 8.0 mmol) and DMAP (98 mg, 0.8 mmol) in anh CH_2Cl_2 (40 mL) under N_2 at r.t. The reaction was stirred for 45 min at r.t.

The solvent was then removed *in vacuo* and the resulting pale yellow oil was further purified by flash column chromatography on silica gel (CH_2Cl_2) to give 1.80 g (8.0 mmol, 99%) of acetate **46**.



Benzhydryl acetate (**46**). White solid; **mp** = 42–43 ºC; $\mathbf{R_f}$ = 0.75 (CH_2Cl_2); **IR** (KBr) 3066, 3032, 2968, 2696, 2483, 2345, 1961, 1734, 1495, 1373, 1245 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.34–7.25 (10H, m, ArH), 6.88 (1H, s, OCH), 2.16 (3H, s, CH_3); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 169.7 (C), 140.1 (C), 128.3 (CH), 127.7 (CH), 126.9 (CH), 76.7 (CH), 21.0 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+Na]^+$ $C_{15}H_{14}NaO_2$: 249.0886, found: 249.0895.

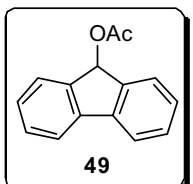
*2.1.1.2. 9H-fluoren-9-yl acetate (**49**)*

A mixture of 9-fluorenone (901 mg, 5.0 mmol) and $NaBH_4$ (378 mg, 10 mmol) in THF/H_2O 30:1 (15.5 mL) was heated at reflux under N_2 for 20 min.

Water (15 mL) was added and the mixture was stirred for 10 min. After that, the layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo*.

The resulting white solid crude and a small amount of DMAP (53 mg, 0.43 mmol) were dissolved in anh CH_2Cl_2 (22 mL). Anh triethylamine (1.2 mL, 8.7 mmol) and acetic anhydride (810 µL, 8.7 mmol) were added to the solution, and the reaction mixture was stirred for 45 min at r.t.

The solvent was then removed *in vacuo*. The resulting pale yellow oil was further purified by flash column chromatography on silica gel (CH_2Cl_2) to give 1.06 g (4.7 mmol, 94%) of acetate **49**.



9*H*-Fluoren-9-yl acetate (**49**).White solid; **mp** = 68–69 ºC; $\mathbf{R_f}$ = 0.55 (CH_2Cl_2); **IR** (KBr) 3070, 3040, 2923, 1955, 1924, 1738, 1448, 1368, 1231, 1026 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.66 (2H, d, *J* = 7.5 Hz, ArH), 7.55 (2H, d, *J* = 7.5 Hz, ArH), 7.41 (2H, t, *J* = 7.5 Hz, ArH), 7.29 (2H, t, *J* = 7.5 Hz, ArH), 6.80 (1H, s, OCH), 2.19 (3H, s, CH_3); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 171.5 (C), 141.9 (C), 140.9 (C), 129.3 (CH), 127.7 (CH),

125.7 (CH), 119.9 (CH), 74.99 (CH), 21.1 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+Na]^+$ $C_{15}H_{12}NaO_2$: 247.0730, found: 247.0725.

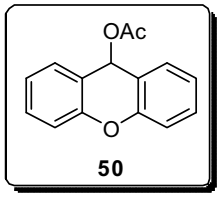
*2.1.1.3. 9H-xanthen-9-yl acetate (**50**)*

A mixture of xanthone (981 mg, 5.0 mmol) and $NaBH_4$ (1.13 g, 30 mmol) in MeOH (20 mL) was heated at 65 ºC under N_2 for 30 min.

The mixture was allowed to cool at r.t. during 15 min. Then, the solvent was removed *in vacuo*. The resulting white solid was mixed with Et_2O (50 mL), filtered and the solvent removed *in vacuo*.

The resulting white solid and a small amount of DMAP (61 mg, 0.25 mmol) were dissolved in anh CH_2Cl_2 (35 mL). Anh triethylamine (1.39 mL, 10 mmol) and acetic anhydride (0.95 mL, 10 mmol) were added to the solution, and the reaction was allowed to proceed for 45 min at r.t.

The solvent was then removed *in vacuo*. The crude was dissolved in Et_2O (40 mL) and washed with water (3 × 30 mL) and sat $NaHCO_3$ (3 × 30 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to afford 1.04 g (4.3 mmol, 87%) of acetate **50**, which was used without further purification.



50

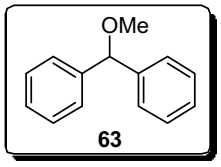
9*H*-Xanthen-9-yl acetate (**50**). White solid; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.53 (2H, dd, *J* = 7.7, 1.7 Hz, ArH), 7.40 (2H, ddd, *J* = 8.4, 7.2, 1.7 Hz, ArH), 7.23 (1H, s, OCH), 7.22 (2H, dd, *J* = 8.4, 1.3 Hz, ArH), 7.16 (2H, td, *J* = 7.7, 1.3 Hz, ArH), 2.00 (3H, s, CH_3).

2.1.2. Preparation of diarylmethyl methyl ethers

*2.1.2.1. Benzhydryl methyl ether (**63**)*

Methyl orthoformate (440 μL, 4.0 mmol) was added to a solution of diphenylmethanol (740 mg, 4.0 mmol) and camphorsulfonic acid (93 mg, 0.40 mmol) in anh MeOH (4.0 mL) under N_2. The resulting mixture was heated to reflux for 2 h, and after cooling, stirred for 16 h at r.t.

Triethylamine (5.6 mL, 0.40 mmol) was then added and the solvent removed *in vacuo*. The resulting oil was further purified by flash column chromatography on silica gel (hexanes/EtOAc 9:1) to give 767 mg (3.8 mmol, 95%) of methyl ether **63**.

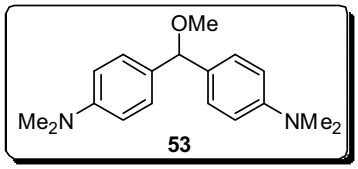


Benzhydryl methyl ether (**63**). Colorless oil; $\mathbf{R_f}$ = 0.70 (hexanes/EtOAc 9:1); **IR** (ATR) 3059, 3025, 2981, 2929, 2818, 1946, 1887, 1809, 1490, 1453, 1190, 1093, 1075 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.37–7.23 (10H, m, ArH), 5.25 (1H, s, OCH), 3.39 (3H, s, OCH_3); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 142.1 (C), 128.3 (CH), 127.4 (CH), 126.9 (CH), 85.4 (CH), 57.0 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OMe]^+$ $C_{13}H_{11}$: 167.0855, found: 167.0851.

*2.1.2.2. 4,4'-Bis(dimethylamino)benzhydryl methyl ether (**53**)*

A suspension of 4,4'-bis(dimethylamino)benzhydrol (811 mg, 3.0 mmol) and catalytic amounts of Amberlyst® 15 resin in trimethyl orthoformate (1.2 mL, 11.1 mmol) and anh MeOH (0.75 mL, 18.6 mmol) under N_2 was stirred for 15 h at r.t.

Then, the reaction mixture was filtered and the solid was washed with MeOH. The solid was dried under reduced pressure to afford 812 mg (2.86 mmol, 95%) of ether **53**, which was pure by ^{1}H NMR.

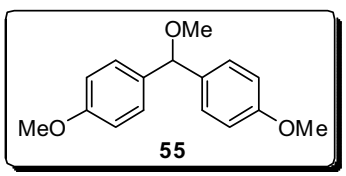


4,4'-Bis(dimethylamino)benzhydryl methyl ether (**53**). Green solid; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.19–7.17 (4H, m, ArH), 6.69–6.67 (4H, m, ArH), 5.11 (1H, s, CHOCH$_3$), 3.33 (3H, s, OCH_3), 2.90 (12H, s, $N(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 149.9 (C), 130.7 (C), 127.8 (CH), 112.4 (CH), 84.9 (CH), 56.6 (CH_3), 40.7 (CH_3).

*2.1.2.3. 4,4'-Dimethoxybenzhydryl methyl ether (**55**)*

A suspension of 4,4'-bis(dimethoxy)benzhydrol (733 mg, 3.0 mmol) and catalytic amounts of Amberlyst® 15 resin in trimethyl orthoformate (1.2 mL, 11.1 mmol) and anh MeOH (0.75 mL, 18.6 mmol) under N_2 was stirred for 15 h at r.t.

Then, the reaction mixture was filtered and the solid was washed with MeOH. The solid was dried under reduced pressure to afford 702 mg (2.72 mmol, 91%) of ether **55**, which was pure by ^{1}H NMR.

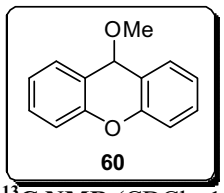


4,4'-Dimethoxybenzhydryl methyl ether (**55**). White solid; **mp** = 33–35 ºC; **IR** (ATR) 3004, 2985, 2936, 2896, 2829, 1601, 1583, 1505, 1464, 1301, 1234, 1161, 1086, 1027 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.25–7.23 (4H, m, ArH), 6.86–6.84 (4H, m, ArH), 5.16 (1H, s, CHOCH$_3$), 3.78 (6H, s, ArOCH_3), 3.34 (3H, s, CHOCH_3), **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 158.8, 134.4, 128.0, 113.6, 84.4, 56.6, 55.1.

*4.1.2.4. 9H-Xanthen-9-yl methyl ether (**60**)*

A suspension of xanthydrol (595 mg, 3.0 mmol) and catalytic amounts of Amberlyst® 15 resin in trimethyl orthoformate (1.2 mL, 11.1 mmol) and anh MeOH (0.75 mL, 18.6 mmol) under N_2 was stirred for 15 h at r.t.

Then, the reaction mixture was filtered and the solid was washed with MeOH. The solid was dried under reduced pressure to afford 626 mg (2.95 mmol, 98%) of ether **60**, which was pure by ^{1}H NMR.



60

9*H*-Xanthen-9-yl methyl ether (**60**). Colorless oil; **IR** (ATR) 3040, 2977, 2929, 2888, 2814, 1605, 1572, 1475, 1453, 1249, 1208, 1056 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.52 (2H, dd, *J* = 7.5, 1.7 Hz, ArH), 7.37 (2H, ddd, *J* = 8.5, 7.2, 1.7 Hz, ArH), 7.20–7.15 (4H, m, ArH), 5.73 (1H, s, C<u>H</u>OCH$_3$), 2.96 (3H, s, CHOC<u>H</u>$_3$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 152.4, 130.0, 129.6, 123.1, 119.5, 116.5, 70.7, 51.5.

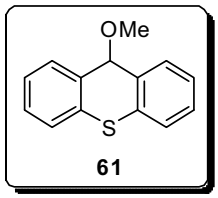
*4.1.2.5. 9H-Thioxanthen-9-yl methyl ether (**61**)*

A 1.0 M solution of DIBALH in toluene (2.83 mL, 2.83 mmol) was added to a solution of thioxanthone (500 mg, 2.36 mmol) in anh CH_2Cl_2 (24 mL) under N_2 at –78 ºC. After 1.5 h, the reaction mixture was heated to –20 ºC and stirred for 1.5 h.

The reaction was quenched with a 20% w/w sodium potassium tartrate solution (25 mL) and the resulting mixture stirred for 2 h at r.t. After this time, the layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the volatiles removed *in vacuo*. The crude product was used into the next step without further purification.

A solution of the previous crude product and a catalytic amounts of Amberlyst® 15 resin in methyl orthoformate (1.9 mL, 17.4 mmol) and anh MeOH (1.2 mL, 29.2 mmol) under N_2 was stirred for 15 h at r.t..

After this time, the reaction mixture was filtered and the solid was dried under reduced pressure to afford 500 mg (2.19 mmol, 93%) of methyl ether **61**, which was pure by ^{1}H NMR.



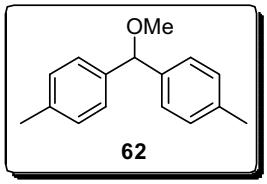
61

9*H*-Thioxanthen-9-yl methyl ether (**61**). Yellow oil; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.62–7.24 (8H, m, Ar<u>H</u>), 5.14 (1H, s, C<u>H</u>OCH$_3$), 3.33 (3H, s, OC<u>H</u>$_3$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 133.7 (C), 133.2 (C), 128.7 (CH), 127.7 (CH), 126.9 (CH), 126.2 (CH), 81.0 (CH), 56.6 (CH_3).

*4.1.2.6. 4,4'-Dimethylbenzhydryl methyl ether (**62**)*

Anh CH_2Cl_2 (22 mL) was added to a suspension of 4,4'-dimethylbenzhydrol (470 mg, 2.22 mmol) and camphorsulfonic acid (77 mg, 0.33 mmol) in anh MeOH (4.5 mL, 111 mmol). The reaction mixture was stirred for 70 h at r.t.

The reaction was quenched with sat $NaHCO_3$ (30 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic fractions were dried over $MgSO_4$ and filtrated. The removal of the volatiles at reduced pressure afforded 495 mg (2.19 mmol, 99%) of methyl esther **62**, which was pure by ^{1}H NMR.



62

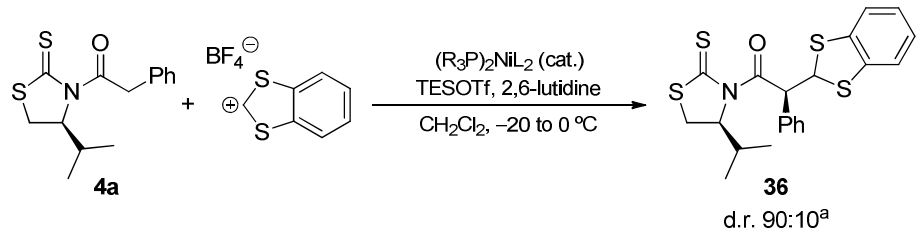
4,4'-Dimethylbenzhydryl methyl ether (**62**). White solid; **mp** = 44–46 ºC; **IR** (ATR) 3018, 2977, 2922, 2884, 2810, 1505, 1320, 1175, 1090 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.22–7.20 (4H, m, Ar<u>H</u>), 7.12–7.10 (4H, m, Ar<u>H</u>), 5.17 (1H, s, C<u>H</u>OCH_3), 3.35 (3H, s, O<u>C</u>H_3), 2.30 (6H, s, 2 × Ar<u>C</u>H_3); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 139.3 (C), 136.9 (C), 129.00 (CH), 126.8 (CH), 85.1 (CH), 56.8 (CH_3), 21.1 (CH_3).

2.2. REACTIONS WITH CATIONIC SALTS

2.2.1. Reactions with 1,3-benzodithiolylium tetrafluoroborate

Solid Ni(II) catalyst was added to a solution of thioimide **4a** (140 mg, 0.50 mmol) and 1,3-benzodithiolylium tetrafluoroborate (180 mg, 0.75 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2 at r.t.. The resulting dark red suspension was purged with N_2 again and then cooled to –20 ºC. TESOTf and 2,6-lutidine (88 µL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred at –20 ºC and then placed at 0 ºC (see Table 38 for stirring times at these temperatures).

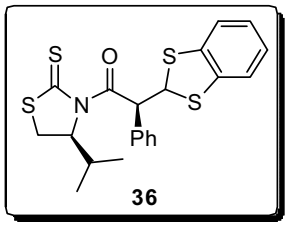
The reaction was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/CH_2Cl_2 4:1) to give undetermined amounts of tetrathiofulvalene **37** and an inseparable mixture of the two diastereomers **36** and **36m** in a 9:1 ratio observed by ^{1}H NMR. The yields of the mixtures of the two diastereomers of the alkylation product are shown in Table 38.



Entry	Catalyst	mol%	TESOTf (eq)	Time at –20 ºC	Time at 0 ºC (h)	Yield (%)[b]
1	$(Ph_3P)NiCl_2$	2.5	0.15	20 min	1	3
2	$(Ph_3P)NiCl_2$	20.0	0.50	3 h	1	24
3	$(Ph_3P)NiCl_2$	20.0	0.50	20 min	86	22
4	$(Ph_3P)NiCl_2$	40.0	0.90	20 min	5	29
5	$(Me_3P)NiCl_2$	20.0	0.50	20 min	5	3

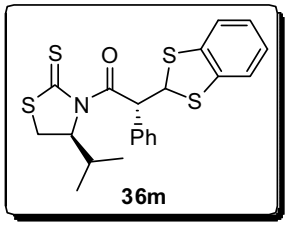
[a] Established by ^{1}H NMR analysis of the crude product.
[b] Isolated yield after column chromatography.

Table 38



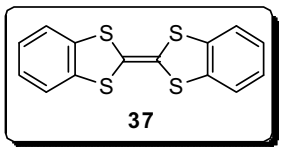
(*S*)-*N*-[(*R*)-2-(Benzo[*d*][1,3]dithiol-2-yl)-2-phenylacetyl]-4-isopropyl-1,3-thiazolidine-2-thione (**36**). Yellow solid; **mp** = 62–64 ºC; $\mathbf{R_f}$ = 0.65 (hexanes/CH_2Cl_2 7:3); $\mathbf{[\alpha]_D}$ = +275.9 (*c* 1.00, $CHCl_3$); **IR** (KBr) 3058, 2962, 2871, 1678, 1443, 1333,1276, 1240, 1156, 1034 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.45–7.00 (9H, m, ArH), 6.68 (1H, d, *J* = 10.5 Hz, CHPh), 5.41 (1H, d, *J* = 10.5 Hz, CHS_2), 5.02 (1H, ddd, *J* = 7.7, 6.5, 1.0 Hz, NCH), 3.16 (1H, dd, *J* = 11.5, 7.7 Hz, SCH_aH_b), 2.87 (1H, dd, *J* = 11.5, 1.0 Hz, SCH_aH_b), 2.50–2.38 (1H, m, $CH(CH_3)_2$), 1.09 (3H, d, *J* = 6.9 Hz,$CH(CH_3)_a(CH_3)_b$), 1.07 (3H, d, *J* = 7.1 Hz, $CH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.7

(C), 172.9 (C), 136.9 (C), 136.3 (C), 134.8 (C), 129.7 (CH), 128.6 (CH),128.4 (CH), 125.6 (CH), 125.5 (CH), 122.6 (CH), 122.5 (CH), 72.4 (CH), 56.7 (CH), 56.2 (CH), 30.7 (CH), 30.3 (CH_2), 19.3 (CH_3), 18.0 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{21}H_{22}NOS_4$: 432.0579, found: 432.0583.



36m

(*S*)-*N*-[(*S*)-2-(Benzo[*d*][1,3]dithiol-2-yl)-2-phenylacetyl]-4-isopropyl-1,3-thiazolidine-2-thione (**36m**). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 6.28 (1H, d, *J* = 10.7 Hz, C<u>H</u>Ph), 5.35 (1H, d, *J* = 10.7 Hz, C<u>H</u>S_2), 5.25 (1H, ddd, *J* = 8.1, 6.0, 1.5 Hz, NC<u>H</u>), 3.56 (1H, dd, *J* = 11.4, 8.1 Hz, SC<u>H$_a$</u>H$_b$), 2.99 (1H, dd, *J* = 11.4, 1.5 Hz, SCH$_a$<u>H$_b$</u>), 2.19–2.10 (1H, m, C<u>H</u>$(CH_3)_2$), 0.84 (3H, d, *J* = 6.9 Hz, CH(C<u>H$_3$</u>)$_a$$(CH_3)_b$), 0.77 (3H, d, *J* = 6.8 Hz, CH$(CH_3)_a$(C<u>H$_3$</u>)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.2 (C), 173.0 (C), 136.9 (C), 136.3 (C), 134.8 (C), 130.0 (CH), 128.3 (CH), 128.2 (CH), 125.8 (CH), 125.7 (CH), 122.6 (CH), 122.6 (CH), 71.8 (CH), 58.0 (CH), 56.2 (CH), 30.4 (CH), 30.3 (CH_2), 18.9 (CH_3), 17.0 (CH_3).



37

2,2'-Bibenzo[d][1,3]dithiolylidene (**37**). Yellow solid. **LRMS** (+ESI): *m/z* calculated for $[M]^+$ $C_{14}H_8S_4$: 303.9509, found: 303.9586.

2.2.2. Reactions with the Eschenmoser's salt

*2.2.2.1. Application of the standard procedure with thioimide **4f** using $(Ph_3P)_2NiCl_2$*

Solid $(Ph_3P)_2NiCl_2$ (65.4 mg, 0.10 mmol) was added to a solution of thioimide **4f** (109 mg, 0.50 mmol) and *N,N*-dimethylmethyleneiminium chloride (70 mg, 0.75 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2 at r.t.. The resulting dark suspension was purged with N_2 again and then cooled to –20 ºC. TESOTf (57 μL, 0.25 mmol) and 2,6-lutidine (88 μL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred at –20 ºC for 45 min and then placed at 0 ºC for 15 h.

The reaction was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/CH_2Cl_2 2:3) to give 105 mg (0.48 mmol, 96%) of the recovered starting material **4f**.

*2.2.2.2. Application of the standard procedure with thioimide **4f** using $(Me_3P)_2NiCl_2$*

Solid $(Me_3P)_2NiCl_2$ (28.2 mg, 0.10 mmol) was added to a solution of thioimide **4f** (109 mg, 0.50 mmol) and *N,N*-dimethylmethyleneiminium chloride (70 mg, 0.75 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2 at r.t.. The resulting dark suspension was purged with N_2 again and then cooled to –20 ºC. TESOTf (57 μL, 0.25 mmol) and 2,6-lutidine (88 μL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred at –20 ºC for 45 min and then placed at 0 ºC for 15 h.

The reaction was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/CH_2Cl_2 2:3) to give 106 mg (0.48 mmol, 97%) of the recovered starting material **4f**.

*2.2.2.3. Application of the standard procedure with thioimide **4a** using $(Ph_3P)_2NiCl_2$*

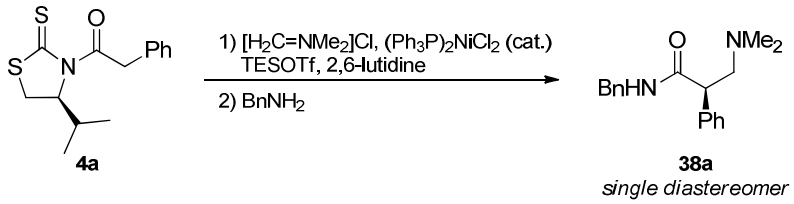
Solid $(Ph_3P)_2NiCl_2$ (65.4 mg, 0.10 mmol) was added to a solution of thioimide **4a** (140 mg, 0.50 mmol) and *N,N*-dimethylmethyleneiminium chloride (70 mg, 0.75 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2 at r.t.. The resulting dark suspension was purged with N_2 again and then cooled to –20 ºC. TESOTf (57 μL, 0.25 mmol) and 2,6-lutidine (88 μL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred at –20 ºC for 1.5 h and then placed at 0 ºC for 20 h.

The reaction was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. ^1H NMR of the crude revealed the only presence of (*S*)-4-isopropyl-1,3-thiazolidine-2-thione (**1**).

2.2.2.4.Quench with benzylamine

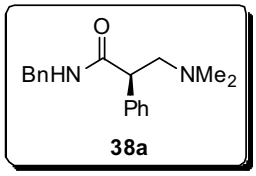
Solid $(Ph_3P)_2NiCl_2$ was added to a solution of thioimide **4a** (140 mg, 0.50 mmol) and *N,N*-dimethylmethyleneiminium chloride (70 mg, 0.75 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2 at r.t. The resulting suspension was purged with N_2 again and then cooled to –20 ºC. TESOTf and 2,6-lutidine (88 μL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The mixture was stirred at –20 ºC for 45 min and placed in an ice bath for 15 h. Benzylamine (273 μL, 2.5 mmol) was then added and the reaction mixture was stirred for 50 min at 0 ºC and 1.5 h at r.t.

The reaction mixture was diluted in CH_2Cl_2 (40 mL), washed with 1 M NaOH (3 × 30 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) (from CH_2Cl_2 to EtOAc and then EtOAc/MeOH 9:1) to give **38a**. The results are shown in Table 39.



Entry	$(Ph_3P)_2NiCl_2$ (mol%)	TESOTf (eq)	Yield (%)
1	2.5	0.07	54
2	5	0.20	84
3	20	0.50	92

Table 39

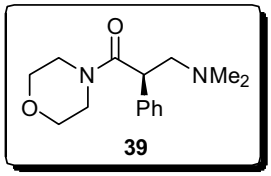


(*R*)-3-(Dimethylamino)-2-phenyl-*N*-benzylpropanamide (**38a**). Pale brown solid; **mp** = 63–65 ºC; $\mathbf{R_f}$ = 0.15 (EtOAc/MeOH 9:1); **IR** (KBr) 3303, 3064, 2940, 2778, 1952, 1880, 1809, 1651, 1546, 1455, 1264, 1039 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.84 (1H, br s, NH), 7.35–7.22 (10H, m, ArH), 4.49 (1H, dd, *J* = 14.0, 4.8 Hz, $PhCH_aH_b$), 4.44 (1H, dd, *J* = 14.0, 4.7 Hz, $PhCH_aH_b$), 3.66 (1H, dd, *J* = 10.2, 4.8 Hz, COCH), 3.12 (1H, dd, *J* = 12.6, 10.2 Hz, $COCHCH_aH_b$), 2.51 (1H, dd, *J* = 12.6, 4.8 Hz, $COCHCH_aH_b$), 2.28 (6H, s, $N(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 172.7 (C), 139.0 (C), 138.7 (C), 128.6 (CH), 128.5 (CH), 128.3 (CH), 127.4 (CH), 127.1 (CH), 62.8 (CH_2), 50.0 (CH), 45.1 (CH_3), 43.3 (CH_2); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{18}H_{23}N_2O$: 283.1805, found: 283.1803.

2.2.2.5. Quench with morpholine

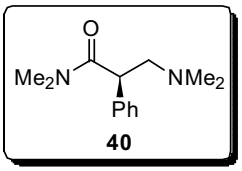
Solid $(Ph_3P)_2NiCl_2$ (65.4 mg, 0.10 mmol) was added to a solution of thioimide **4a** (140 mg, 0.50 mmol) and *N,N*-dimethylmethyleneiminium chloride (70 mg, 0.75 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2 at r.t. The resulting suspension was purged with N_2 again and then cooled to –20 ºC. TESOTf and 2,6-lutidine (88 µL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The mixture was stirred at –20 ºC for 45 min and placed in an ice bath for 15 h. Morpholine (216 µL, 2.5 mmol) was then added and the reaction mixture was stirred for 50 min at 0 ºC and 1.5 h at r.t.

The reaction mixture was diluted in CH_2Cl_2 (40 mL), washed with 1 M NaOH (3 × 30 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) (from CH_2Cl_2 to EtOAc and then EtOAc/MeOH 9:1) to give 94 mg of a 3.45:1 mixture of amides **39** (57%) and **40** (17%) determined by ^{1}H NMR integration.



39

(*R*)-3-(Dimethylamino)-2-phenyl-*N*-morpholinopropanamide (**39**). Pale brown solid; $\mathbf{R_f}$ = 0.15 (EtOAc); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.34–7.22 (5H, m, Ar<u>H</u>), 3.98 (1H, dd, *J* = 8.9, 4.5 Hz, COC<u>H</u>), 3.84–3.77 (1H, m, $N(C\underline{H_a}H_b)_x(CH_aH_b)_y$), 3.70–3.63 (1H, m, $O(C\underline{H_a}H_b)_x(CH_aH_b)_y$), 3.57–3.43 (4H, m, $N(CH_a\underline{H_b})_x(CH_aH_b)_y$, $N(CH_aH_b)_x(C\underline{H_a}H_b)_y$, $O(CH_a\underline{H_b})_x(CH_aH_b)_y$, $O(CH_aH_b)_x(C\underline{H_a}H_b)_y$), 3.43–3.34 (1H, m, $N(CH_aH_b)_x(CH_a\underline{H_b})_y$), 3.33 (1H, dd, *J* = 12.5, 8.9 Hz, $COCHC\underline{H_a}H_b$), 3.15–3.06 (1H, m, $O(CH_aH_b)_x(CH_a\underline{H_b})_y$), 2.43 (1H, dd, *J* = 12.5, 4.5 Hz, $COCHCH_a\underline{H_b}$), 2.30 (6H, s, $N(C\underline{H_3})_2$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 170.4 (C), 138.2 (C), 128.9 (CH), 127.6 (CH), 127.1 (CH), 66.6 (CH_2), 66.2 (CH_2), 63.5 (CH_2), 47.0 (CH), 45.9 (CH_2), 45.8 (CH_3), 42.4 (CH_2); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{15}H_{23}N_2O_2$: 263.1754, found: 263.1754.



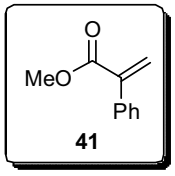
40

(*R*)-3-(Dimethylamino)-*N,N*-dimethyl-2-phenylpropanamide (**40**). Pale brown solid; $\mathbf{R_f}$ = 0.15 (EtOAc); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.34–7.22 (5H, m, Ar<u>H</u>), 4.05 (1H, dd, *J* = 8.9, 4.5 Hz, COC<u>H</u>), 3.33 (1H, dd, *J* = 12.5, 8.9 Hz, $COCHC\underline{H_a}H_b$), 2.97 (3H, s, $CON(C\underline{H_3})_a(CH_3)_b$), 2.95 (3H, s, $CON(CH_3)_a(C\underline{H_3})_b$), 2.43 (1H, dd, *J* = 12.5, 4.5 Hz, $COCHCH_a\underline{H_b}$), 2.30 (6H, s, $CH_2N(C\underline{H_3})_2$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 171.8 (C), 138.2 (C), 128.7 (CH), 127.8 (CH), 127.0 (CH), 63.7 (CH_2), 47.1 (CH), 45.7 (CH_3), 37.0 (CH_3), 35.9 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{13}H_{21}N_2O$: 221.1648, found: 221.1643.

2.2.2.6. Quench with methanol

Solid $(Ph_3P)_2NiCl_2$ (65.4 mg, 0.10 mmol) was added to a solution of thioimide **4a** (140 mg, 0.50 mmol) and *N,N*-dimethylmethyleneiminium chloride (70 mg, 0.75 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2 at r.t. The resulting suspension was purged with N_2 again and then cooled to –20 ºC. TESOTf and 2,6-lutidine (88 μL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The mixture was stirred at –20 ºC for 45 min and placed in an ice bath for 20 h. Anhydrous MeOH (1.5 mL) was then added and the reaction mixture was stirred for 50 min at 0 ºC and 4 days at r.t.

The reaction mixture was diluted in CH_2Cl_2 (40 mL), washed with 1 M NaOH (3 × 30 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) (from hexanes/CH_2Cl_2 1:1 to CH_2Cl_2) to give 34 mg (0.21 mmol, 42%) of ester **41**.



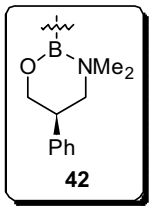
41

Methyl 2-phenylacrylate (**41**). Colorless oil; $\mathbf{R_f}$ = 0.45 (hexanes/CH_2Cl_2 3:7); **IR** (ATR) 3057, 3022, 2999, 2949, 1724, 1445, 1431, 1202 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.43–7.30 (5H, m, Ar<u>H</u>), 6.36 (1H, d, *J* = 1.2 Hz, $COCC\underline{H}aH_b$), 5.89 (1H, d, *J* = 1.2 Hz, $COCCHa\underline{H_b}$), 3.82 (3H, s, $OC\underline{H_3}$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 167.2 (C), 141.3 (C), 136.7 (C), 128.3 (CH), 128.1 (CH), 128.1 (CH), 126.9 (CH_2), 52.2 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[2M+NH_4]^+$ $C_{20}H_{24}NO_4$: 342.1700, found: 342.1700.

2.2.2.7. Quench with $LiBH_4$

Solid $(Ph_3P)_2NiCl_2$ (65.4 mg, 0.10 mmol) was added to a solution of thioimide **4a** (140 mg, 0.50 mmol) and *N,N*-dimethylmethyleneiminium chloride (70 mg, 0.75 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2 at r.t. The resulting suspension was purged with N_2 again and then cooled to –20 ºC. TESOTf and 2,6-lutidine (88 μL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The mixture was stirred at –20 ºC for 45 min and placed in an ice bath for 15 h. It was cooled to –78 ºC and a 2.0 M solution of $LiBH_4$ in THF (0.50 mL, 1.0 mmol) was added. After 5 min the reaction mixture was placed at 0 ºC and stirred for 30 min. Then, it was cooled to –78 ºC. More 2.0 M solution of $LiBH_4$ in THF (0.75 mL, 1.5 mmol) was added, and the mixture stirred for 5 min at – 78 ºC, 1 h at 0 ºC and 30 min at r.t.

The reaction mixture was quenched with MeOH (1.2 mL), diluted in CH_2Cl_2 (40 mL), washed with 1 M NaOH (3 × 30 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) (from hexanes/CH_2Cl_2 8:2 to CH_2Cl_2 and then to AcOEt) to give 95 mg of the partially characterized compound **42**.



42

42. Dark oil; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 3.73 (1H, dd, *J* = 10.8, 6.4 Hz, OCH_aH_b), 3.66 (1H, dd, *J* = 10.8, 7.1 Hz, OCH_aH_b), 3.54–3.47 (1H, m, CHPh), 3.34 (1H, dd, *J* = 13.3, 2.5 Hz, NCH_aH_b), 3.20 (1H, dd, *J* = 13.3, 8.4 Hz, NCH_aH_b), 2.49 (3H, s, $N(CH_3)_a(CH_3)_b$), 2.41 (3H, s, $N(CH_3)_a(CH_3)_b$).

2.2.2.7.1. Attempt to release aminoalcohol **43**: H_2O_2 dissolved in NaOH[90]

42 (95 mg) was dissolved in a mixture of 30% v/v H_2O_2 (2.0 mL) and 1 M NaOH (8.0 mL). The solution was stirred for 16 h at r.t.

After this time, the products were extracted with Et_2O (3 × 20 mL), the organic layer dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. ^{1}H NMR analysis of the crude product revealed the only presence of starting material **42**.

2.2.2.7.2. Attempt to release aminoalcohol **43**: dissolved in THF/NaOH[90]

42 (95 mg) was dissolved in a mixture of 30% v/v H_2O_2 (1.0 mL), THF (10 mL) and 2 M NaOH (5.0 mL). The solution was stirred for 16 h at r.t.

After this time, the products were extracted with CH_2Cl_2 (5 × 20 mL), the organic layer dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. ^{1}H NMR analysis of the crude product revealed the only presence of starting material **42**.

2.2.2.7.3. Attempt to release aminoalcohol **43**: dissolved in THF/LiOH[90]

42 (95 mg) was dissolved in a mixture of 30% v/v H_2O_2 (1.0 mL), THF (8.0 mL) and 2.5 M LiOH in water (1.0 mL). The solution was stirred for 16 h at r.t.

After this time, the mixture was diluted with H_2O (4.0 mL), the products were extracted with Et_2O (4 × 20 mL), the organic layer dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. ^{1}H NMR analysis of the crude product revealed the only presence of starting material **42**.

2.2.2.7.4. Attempt to release aminoalcohol **43**: H_2O_2 dissolved in MeOH/NaOH[90]

42 (95 mg) was dissolved in a mixture of 30% v/v H_2O_2 (2.5 mL), MeOH (3.0 mL) and 2 M NaOH (3.0 mL). The solution was stirred for 16 h at r.t.

After this time, the mixture was diluted with H_2O (4.0 mL) the products were extracted with CH_2Cl_2 (5 × 20 mL), the organic layer dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. ^{1}H NMR analysis of the crude product revealed the only presence of starting material **42**.

2.2.2.7.5. Attempt to release aminoalcohol **43**: H_2O_2 and NaOAc dissolved in THF/H_2O[90]

42 (95 mg) was dissolved in a mixture of 30% v/v H_2O_2 (0.65 mL) and NaOAc (83 mg), THF (1.9 mL) and H_2O (0.6 mL). The solution was stirred for 16 h at r.t.

After this time, the mixture was quenched with saturated Na_2SO_3 (10 mL) and extracted with Et_2O (3 × 20 mL) and EtOAc (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. ^{1}H NMR analysis of the crude product revealed the only presence of starting material **42**.

2.2.2.7.6. Attempt to release aminoalcohol **43**: Na_3BO_4 dissolved in THF/H_2O[90]

42 (95 mg) was dissolved in 3:2 THF/H_2O (2.5 mL) and $Na_3BO_4 \cdot 4H_2O$ (40 mg) was added. The reaction mixture was stirred for 24 h at r.t.

After this time, it was filtered and the filtrate extracted with Et_2O (4 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. ^{1}H NMR analysis of the crude product revealed the only presence of starting material **42**.

2.2.2.7.7. Attempt to release aminoalcohol **43**: Na_3BO_4 dissolved in THF/H_2O[90]

42 (15 mg) was dissolved in 3:2 THF/H_2O (1.2 mL) and $Na_3BO_4 \cdot 4H_2O$ (112 mg) were added. The reaction mixture was stirred for 65 h at r.t.

After this time, it was diluted with H_2O (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers weredried over $MgSO_4$ and the solvent removed *in vacuo*. ^1H NMR analysis of the crude product revealed the only presence of starting material **42**.

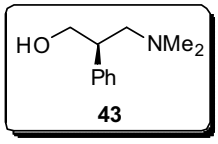
2.2.2.7.8. Release of aminoalcohol **43**: displacement by equilibrium with ethanolamine [128]

Solid $(Ph_3P)_2NiCl_2$ (65.4 mg, 0.10 mmol) was added to a solution of thioimide **4a** (140 mg, 0.50 mmol) and *N,N*-dimethylmethyleneiminium chloride (70 mg, 0.75 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2 at r.t. The resulting suspension was purged with N_2 again and then cooled to –20 ºC. TESOTf and 2,6-lutidine (88 µL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The mixture was stirred at –20 ºC for 45 min and placed in an ice bath for 15 h. It was cooled to –78 ºC and a 2.0 M solution of $LiBH_4$ in THF (0.50 mL, 1.0 mmol) was added. After 5 min the reaction mixture was placed at 0 ºC and stirred for 30 min. Then, it was cooled to –78 ºC. More 2.0 M solution of $LiBH_4$ in THF (0.75 mL, 1.5 mmol) was added, and the mixture stirred for 5 min at – 78 ºC, 1 h at 0 ºC and 30 min at r.t.

The reaction mixture was quenched with MeOH (1.2 mL), diluted in CH_2Cl_2 (40 mL), washed with 1 M NaOH (3 × 30 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) (from hexanes/CH_2Cl_2 8:2 to CH_2Cl_2 and then to AcOEt) to give 95 mg of the partially characterized compound **42**.

Ethanolamine (272 µL, 4.5 mmol) was added to a solution of **42** (95 mg) in Et_2O (0.5 mL) at 0 ºC. The reaction mixture was stirred 1 h at 0 ºC and 65 h at r.t.

The volatiles were removed *in vacuo* and the residue redissolved again in Et_2O (20 mL). The solutionwas washed with 0.01 M NaOH (4 × 20 mL) and the organic layer weredried over $MgSO_4$, filtered and the solvent removed *in vacuo* to give 28 mg (0.16 mmol, 31%) of **43**.



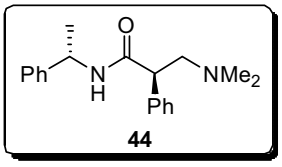
43

(*R*)-3-(Dimethylamino)-2-phenylpropan-1-ol (**43**). Colorless oil; $[\alpha]_D$ = +7.4 (*c* 1.35, $CHCl_3$); **IR** (film) 3430, 2953, 2098, 1640 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.32–7.16 (5H, m, ArH), 4.36 (1H, br s, OH), 3.96 (1H, t, *J* = 10.4 Hz, OCH_aH_b), 3.84 (1H, ddd, *J* = 10.4, 3.7, 2.5 Hz, OCH_aH_b), 3.25–3.16 (1H, m, CHPh), 3.01 (1H, t, *J* = 12.0 Hz, NCH_aH_b), 2.57 (1H, ddd, *J* = 12.0, 3.1, 2.5 Hz, NCH_aH_b), 2.37 (6H, s, $N(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 140.3 (C), 128.6 (CH), 127.5 (CH), 126.9 (CH), 70.4 (CH_2), 66.5 (CH_2), 45.7 (2 × CH_3), 43.4 (CH); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{11}H_{18}NO$: 180.1383, found: 180.1388.

2.2.3.8. Quench with (S)-1-phenylethylamine: elucidation of the diastereoselectivity

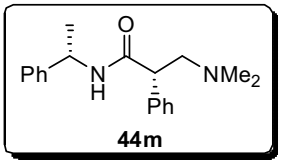
Solid $(Ph_3P)_2NiCl_2$ (65.4 mg, 0.10 mmol) was added to a solution of thioimide **4a** (140 mg, 0.50 mmol) and *N,N*-dimethylmethyleneiminium chloride (70 mg, 0.75 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2 at r.t. The resulting suspension was purged with N_2 again and then cooled to –20 ºC. TESOTf and 2,6-lutidine (88 μL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The mixture was stirred at –20 ºC for 45 min and placed in an ice bath for 15 h. (*S*)-1-Phenylethylamine (322 μL, 2.5 mmol) was then added and the reaction mixture was stirred for 50 min at 0 ºC and 1.5 h at r.t.

The reaction mixture was diluted in CH_2Cl_2 (40 mL), washed with 1 M NaOH (3 × 30 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the 1H NMR spectrum of the crude product revealed the presence of two diastereomeric products in a 3:1 ratio. The crude product was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) (from CH_2Cl_2/EtOAc 4:1 to EtOAc and then to EtOAc/MeOH 99:1) to give 78 mg (0.26 mmol, 53%) of the major amide **44** and 24 mg (0.08 mmol, 16%) of the minor amide **44m**.



44

(*R*)-3-(Dimethylamino)-2-phenyl-*N*-((*S*)-1-phenylethyl)propanamide (**44**). Pale brown solid; **mp** = 85–86 ºC**;** $\mathbf{R_f}$ = 0.20 (CH_2Cl_2/MeOH 95:5); $\mathbf{[\alpha]_D}$= –54.9 (*c* 1.25, $CHCl_3$); **IR** (KBr) 3430, 2977, 1819, 2779, 1645, 1544, 1281 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.98–7.89 (1H, br s, NH), 7.39–7.10 (10H, m, ArH), 5.11 (1H, p, *J* = 7.0 Hz, NCH), 3.67 (1H, dd, *J* = 10.1, 4.6 Hz, COCH), 3.15 (1H, dd, *J* = 12.7, 10.1 Hz, $COCHCH_aH_b$), 2.53 (1H, dd, *J* = 12.7, 4.6 Hz, $COCHCH_aH_b$), 2.33 (6H, s, $N(CH_3)_2$), 1.48 (3H, d, *J* = 7.0 Hz, $CHCH_3$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 171.7 (C), 143.7 (C), 139.0 (C), 128.5 (CH), 128.3 (CH), 128.3 (CH), 127.0 (CH), 126.8 (CH), 125.8 (CH), 62.7 (CH_2), 49.8 (CH), 48.5 (CH), 45.0 (CH_3), 22.4 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{19}H_{25}N_2O$: 297.1961, found: 297.1958.



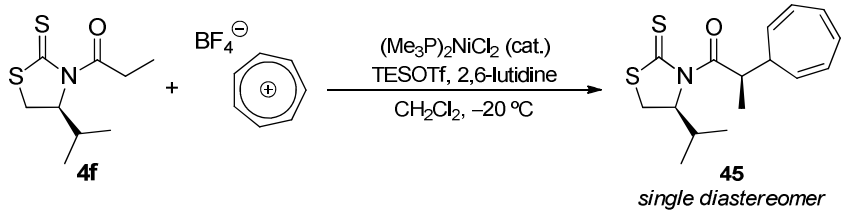
44m

(*S*)-3-(Dimethylamino)-2-phenyl-*N*-((*S*)-1-phenylethyl)propanamide (**44m**). Pale brown solid; **mp** = 132–133 ºC; $\mathbf{R_f}$ = 0.10 (EtOAc); $\mathbf{[\alpha]_D}$= –44.5 (*c* 1.05, $CHCl_3$); **IR** (KBr) 3430, 2973, 2817, 2776, 1645, 1547, 1285 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.91–7.76 (1H, br s, NH), 7.39–7.19 (10H, m, ArH), 5.10 (1H, p, *J* = 7.0 Hz, NCH), 3.82 (1H, dd, *J* = 9.8, 4.3 Hz, COCH), 3.19 (1H, dd, *J* = 12.7, 9.8 Hz, $COCHCH_aH_b$), 2.61 (1H, dd, *J* = 12.7, 4.3 Hz, $COCHCH_aH_b$), 2.33 (6H, s, $N(CH_3)_2$), 1.43 (3H, d, *J* = 7.0 Hz, $CHCH_3$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 171.9 (C), 143.8 (C), 139.1 (C), 128.6 (CH), 128.5 (CH), 128.4 (CH), 127.0 (2 × CH), 126.0 (CH), 62.9 (CH_2), 49.9 (CH), 48.6 (CH), 45.1 (2 × CH_3), 22.1 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{19}H_{25}N_2O$: 297.1961, found: 297.1961.

2.2.3. Reactions with tropylium tetrafluoroborate

Solid $(Me_3P)NiCl_2$ was added to a solution of thioimide **4f** (109 mg, 0.50 mmol) and tropylium tetrafluoroborate in anh CH_2Cl_2 (1.0 mL) under N_2 at r.t.. The resulting dark red suspension was purged with N_2 again and then cooled to –20 ºC. TESOTf and 2,6-lutidine (88 µL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred at –20 ºC for the time indicated in Table 40.

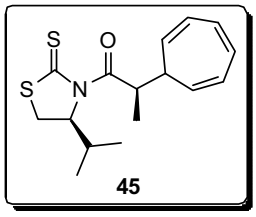
The reaction was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo*. ^{1}H NMR analysis of the crude product showed the presence of a single diastereomer of the alkylation product. The crude was purified by flash column chromatography on silica gel (hexanes/CH_2Cl_2 from 3:7 to 1:4) to afford the pure alkylation adduct **45**.



Entry	mol%	Cation (eq)	TESOTf (eq)	t (h)	Yield (%)[a]
1	5	1.5	0.20	20	29
2	5	0.5	0.20	2.5	40[b]
3	5	1.1	0.20	2	19
4	5	3.0	0.20	2	n.r.
5	10	1.5	0.30	2	47
6	20	1.5	0.50	2	74

[a] Isolated yield after column chromatography.
[b] Calculated yield based on the amount of tropylium tetrafluoroborate.

Table 40



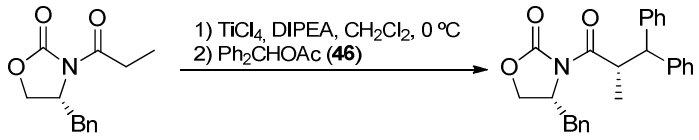
(*S*)-*N*-[(*R*)-2-(Cyclohepta-2,4,6-trien-1-yl)propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**45**). Yellow oil; $\mathbf{R_f}$ = 0.70 (hexanes/CH_2Cl_2 3:7); $\mathbf{[\alpha]_D}$ = +225.0 (*c* 1.00, $CHCl_3$); **IR** (ATR) 3011, 2959, 2925, 2870, 1683, 1457, 1360, 1253, 1231, 1145 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 6.68–6.62 (2H, m, COCHCHCH=CHC<u>H</u>=C<u>H</u>), 6.27–6.15 (2H, m, C<u>H</u>=CHCHCH=C<u>H</u>), 5.32 (2H, dt, *J* = 9.5, 5.8 Hz, CH=C<u>H</u>CHC<u>H</u>=CH), 5.21 (1H, ddd, *J* = 8.1, 6.0, 1.2 Hz, NC<u>H</u>), 5.09 (1H, dq, *J* = 8.4, 6.9 Hz, COC<u>H</u>), 3.47 (1H, dd, *J* = 11.5, 8.1 Hz, SC<u>H$_a$</u>H$_b$), 2.98 (1H, dd, *J* = 11.5, 1.2 Hz, SCH$_a$<u>H$_b$</u>), 2.38–2.32 (1H, m, C<u>H</u>(CH$_3$)$_2$), 2.23 (1H, dtt, *J* = 8.4, 5.8, 1.2 Hz, COCHC<u>H</u>), 1.27 (3H, d, *J* = 6.9 Hz, COCHC<u>H$_3$</u>), 1.04 (3H, d, *J* = 6.8 Hz, CH(C<u>H$_3$</u>)$_a$(CH$_3$)$_b$), 0.97 (3H, d, *J* = 7.0 Hz, CH(CH$_3$)$_a$(C<u>H$_3$</u>)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.7 (C), 176.9 (C), 131.0 (CH), 130.6 (CH), 125.4 (CH), 125.0 (CH), 124.6 (CH), 122.6 (CH), 71.9 (CH), 42.0 (CH), 39.6 (CH), 30.8 (CH), 29.7 (CH_2), 19.2 (CH_3), 17.6 (CH_3), 15.1 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{16}H_{22}NOS_2$: 308.1137, found: 308.1139.

2.3. REACTIONS WITH DIARYLCARBENIUM SUBSTRATES

2.3.1. Study of the effect of the Lewis Acid in the activation of benzhydryl acetate (46)

Neat $TiCl_4$ (60 μL, 0.55 mmol) was added dropwise to a solution of (*R*)-benzyl-*N*-propanoyl-1,3-oxazolidin-2-one (117 mg, 0.5 mmol) in anh CH_2Cl_2 (2 mL) at 0 °C under N_2. The yellow suspension was stirred for 5 min at 0 ºC and DIPEA (95 μL, 0.55 mmol) was added. The dark red solution was stirred for 1 h at 0 ºC. The corresponding Lewis acid (0.55 mmol) (see Table 41) was added and the reaction mixture stirred for 5 min. Then, a solution of benzhydryl acetate **46** (124 mg, 0.55 mmol) in anh CH_2Cl_2 (0.28 + 0.28 mL) was added *via cannula*. The resulting mixture was stirred at 0 ºC during the times displayed in Table 41.

The reaction mixture was quenched with sat NH_4Cl (4.5 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with water (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography on deactivated silica gel (hexanes/EtOAc 90:10 to 1:1) to afford the desired alkylation product in the yields shown in Table 41.

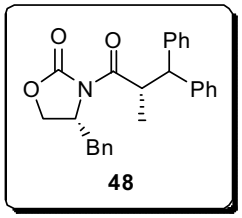


48
single diastereomer

Entry	Lewis acid	t (h)	Yield (%)[a]
1	$TiCl_4$	2	71
2	$BF_3{\cdot}OEt_2$	4.5	25
3	TESOTf	4.5	13

[a] Isolated yield after column chromatography.

Table 41



48

(*R*)-4-Benzyl-*N*-[(*S*)-2-methyl-3,3-diphenylpropanoyl]-1,3-oxazolidin-2-one (**48**). White solid; **mp** = 178–179 ºC; $\mathbf{R_f}$ = 0.30 (hexanes/EtOAc 7:3); $[\alpha]_D$= –359.6 (*c* 1.00, $CHCl_3$); **IR** (ATR) 3057, 3022, 3957, 2925, 1767, 1693, 1397, 1384, 1210 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.42–6.94 (15H, m, ArH), 5.04 (1H, dq, *J* = 12.4, 6.7 Hz, COCH), 4.50 (1H, ddt, *J* = 10.6, 7.8, 3.2 Hz, NCH), 4.25 (1H, d, *J* = 12.4 Hz, COCHCH), 4.00 (1H, dd, *J* = 8.9, 7.8 Hz, OCH_aH_b), 3.93 (1H, dd, *J* = 8.9, 3.2 Hz, OCH_aH_b), 2.56 (1H, dd, *J* = 13.5, 3.2 Hz, CH_aH_bPh), 1.93 (1H, dd, *J* = 13.5, 10.6 Hz, CH_aH_bPh), 1.15 (6H, d, *J* = 6.7 Hz, CH_3); **^{13}C NMR** ($CDCl_3$, 100.4 MHz) δ 176.3 (C), 153.1 (C), 143.2 (C), 142.0 (C), 135.4 (C), 129.1 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 128.1 (CH), 128.0 (CH), 127.0 (CH), 126.6

(CH), 126.5 (CH), d65.6 (CH_2), 56.0 (CH), 54.9 (CH), 41.1 (CH), 36.9 (CH_2), 17.0 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{26}H_{26}NO_3$: 400.1907, found: 400.1915.

2.3.2. Study of the effect of TESOTf as Lewis Acid in the activation of fluorenyl acetate (49)

Neat $TiCl_4$ (60 μL, 0.55 mmol) was added dropwise to a solution of (*R*)-benzyl-*N*-propanoyl-1,3-oxazolidin-2-one (117 mg, 0.5 mmol) in anh CH_2Cl_2 (2 mL) at 0 °C under N_2. The yellow suspension was stirred for 5 min at 0 ºC and DIPEA (95 μL, 0.55 mmol) was added. The dark red enolate solution was stirred for 1 h at 0 ºC. TESOTf (125 μL, 0.55 mmol) was added and the reaction mixture stirred for 5 min. Then, a solution of fluorenyl acetate **49** (123 mg, 0.55 mmol) in anh CH_2Cl_2 (0.28 + 0.28 mL) was added *via cannula*. The resulting mixture was stirred for 4.5 h at 0 ºC.

The reaction mixture was quenched with sat NH_4Cl (4.5 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with water (50 mL), dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. ^1H NMR of the crude product revealed that no reaction took place.

2.3.3. Study of the effect of $TiCl_4$ as Lewis Acid in the activation of fluorenyl acetate (49)

Neat $TiCl_4$ (60 μL, 0.55 mmol) was added dropwise to a solution of (*R*)-benzyl-*N*-propanoyl-1,3-oxazolidin-2-one (117 mg, 0.5 mmol) in anh CH_2Cl_2 (2 mL) at 0 °C under N_2. The yellow suspension was stirred for 5 min at 0 ºC and DIPEA (95 μL, 0.55 mmol) was added. The dark red enolate solution was stirred for 1 h at 0 ºC. Neat $TiCl_4$ (60 μL, 0.55 mmol) was added and the reaction mixture stirred for 5 min. Then, a solution of fluorenyl acetate **49** (123 mg, 0.55 mmol) in anh CH_2Cl_2 (0.28 + 0.28 mL) was added *via cannula*. The resulting mixture was stirred for 24 h at 0 ºC.

The reaction mixture was quenched with sat NH_4Cl (4.5 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with water (50 mL), dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. ^1H NMR of the crude product revealed that no reaction took place.

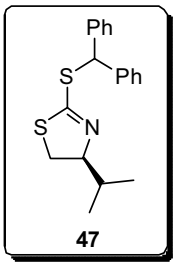
2.3.4. Reactions with (*S*)-*N*-phenylacetyl-4-isopropyl-1,3-thiazolidine-2-thione (4a)

*2.3.4.1. With benzhydryl acetate (**46**)*

Solid $(Ph_3P)_2NiCl_2$ (32.7 mg, 0.05 mmol) was added to a solution of thioimide **4a** (140 mg, 0.50 mmol) and benzhydryl acetate (**46**) (170 mg, 0.75 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2 at r.t. The resulting black suspension was purged with N_2 again and then cooled to –20 ºC. TESOTf (147 μL, 0.65 mmol) and 2,6-lutidine (88 μL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred at –20 ºC for 20 min and then placed at 0 ºC for 4.5 h.

The reaction was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with

brine (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude was purified by flash column chromatography on deactivated silica gel (from hexanes/EtOAc 95:5 to 70:30) to give 97 mg (0.30 mmol, 59%) of thiazole **47** and 53 mg (0.19 mmol, 38%) of the starting material **4a**.



47

(*S*)-2-(Benzhydrylthio)-4-isopropyl-4,5-dihydrothiazole (**47**). Colorless oil; $\mathbf{R_f}$ = 0.50 (hexanes/EtOAc 4:1); $\mathbf{[\alpha]_D}$ = –11.9 (*c* 0.90, $CHCl_3$); **IR** (ATR) 3054, 3022, 2957, 2864, 1943, 1880, 1803, 1740, 1693, 1566, 1489, 1447, 1226, 954 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.46–7.20 (10H, m, ArH), 6.15 (1H, s, SCH), 4.12 (1H, td, *J* = 8.5, 6.4 Hz, NCH), 3.31 (1H, dd, *J* = 10.7, 8.5 Hz, SCH_aH_b), 3.04 (1H, dd, *J* = 10.7, 8.5 Hz, SCH_aH_b), 1.78 (1H, m, $CH(CH_3)_2$), 0.82 (6H, d, *J* = 6.7 Hz, CH_3); **^{13}C NMR** ($CDCl_3$, 100.4 MHz) δ 161.4 (C), 140.7 (C), 140.3 (C), 128.5 (CH), 128.4 (CH), 128.4 (CH), 128.3 (CH), 127.3 (CH), 127.1 (CH), 83.1 (CH), 55.1 (CH), 37.3 (CH_2), 33.1 (CH), 19.1 (2 × CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{19}H_{22}NS_2$: 328.1188, found: 328.1199.

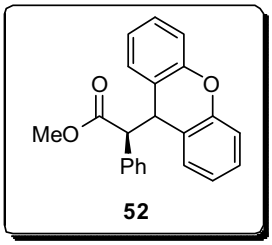
*2.3.4.2. With 9-xanthen-9-yl acetate (**50**)*

Solid $(Ph_3P)_2NiCl_2$ (32.7 mg, 0.05 mmol) was added to a solution of thioimide **4a** (140 mg, 0.50 mmol) and xanthydryl acetate **50** (180 mg, 0.75 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2 at r.t. The resulting black suspension was purged with N_2 again and then cooled to –20 ºC. TESOTf (147 µL, 0.65 mmol) and 2,6-lutidine (88 µL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred at –20 ºC for 20 min and then placed at 0 ºC for 2 h.

The reaction was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude was purified by flash column chromatography on deactivated silica gel (from hexanes/CH_2Cl_2 2:3 to CH_2Cl_2) to give 99 mg of the impure alkylation product, which was used into the next step without further purification.

A solution of the previous impure product and DMAP (25 mg, 0.22 mmol) in anh MeOH (2.0 mL) under N_2 was stirred for 21 h at r.t.

The volatiles were removed *in vacuo* and the residue was dissolved in Et_2O (40 mL). The organic solution was washed with 0.5 M NaOH (3 × 30 mL), 0.5 M HCl (3 × 30 mL), sat $NaHCO_3$ (30 mL) and brine (30 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography on silica gel (hexanes/CH_2Cl_2 2:3) to give 54 mg (0.17 mmol, 33%) of ester **52**.



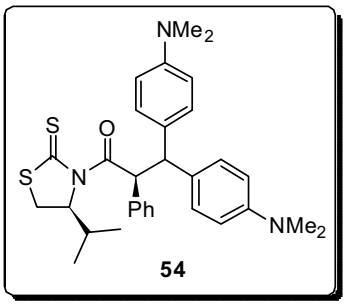
52

(*S*)-Methyl 2-phenyl-2-(9*H*-xanthen-9-yl)acetate (**52**). White solid; **mp** = 130–132 ºC; $\mathbf{R_f}$ = 0.45 (hexanes/CH_2Cl_2 7:3); $\mathbf{[\alpha]_D}$ = –63.0 (*c* 1.05, $CHCl_3$); **IR** (KBr) 3061, 3027, 2940, 1729, 1474, 1459, 1255, 1244, 1156 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.34 (1H, dd, *J* = 7.5, 1.5 Hz, ArH), 7.26–6.99 (10H, m, ArH), 6.69 (1H, td, *J* = 7.5, 1.5 Hz, ArH), 6.48 (1H, dd, *J* = 7.5, 1.5 Hz, ArH), 4.57 (1H, d, *J* = 9.5 Hz, COCHCH), 3.64 (1H, d, *J* = 9.5 Hz, COCH), 3.51 (3H ,s, OCH_3); **^{13}C NMR** ($CDCl_3$, 100.4 MHz) δ 172.8 (C), 153.1 (C), 153.0 (C), 135.7 (C), 129.4 (CH), 129.0 (CH), 128.9 (CH), 128.1 (CH), 128.1 (CH), 127.8 (CH), 127.5 (CH), 124.2 (C), 123.1 (CH), 122.9 (C), 122.4 (CH), 116.5 (CH), 116.1 (CH), 59.7 (CH), 51.9 (CH_3), 44.4 (CH); **HRMS** (+ESI): *m/z* calculated for $[M+NH_4]^+$ $C_{22}H_{22}NO_3$: 348.1594, found: 348.1601.

*2.3.4.3. With 4,4'-bis(dimethylamino)benzhydryl methyl ether (**53**)*

Solid $(Me_3P)_2NiCl_2$ (7.0 mg, 25 μmol) was added to a solution of thioimide **4a** (140 mg, 0.50 mmol) and diaryl methyl ether **53** (213 mg, 0.75 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2 at r.t. The resulting solution was purged with N_2 again and then cooled to –20 ºC. TESOTf (136 μL, 0.60 mmol) and 2,6-lutidine (88 μL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred at –20 ºC for 15 h.

The reaction was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude was purified by flash column chromatography on silica gel (from hexanes/EtOAc 85:15 to 80:20) to afford 256 mg (0.48 mmol, 96%) of alkylation product **54**.



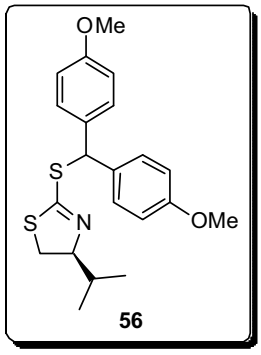
54

(*S*)-*N*-[(*S*)-3,3-Bis(4-dimethylaminophenyl)-2-phenylpropanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**54**). Yellow solid; **mp** = 202–203 ºC; $\mathbf{R_f}$ = 0.30 (hexanes/EtOAc 4:1); $\mathbf{[\alpha]_D}$ = +317.2 (*c* 0.95, $CHCl_3$); **IR** (ATR) 2955, 2925, 2788, 1698, 1676, 1606, 1516, 1342, 1238, 1145, 1123 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.41 (1H, d, *J* = 11.7 Hz, COCH), 7.39 (2H, d, *J* = 8.7 Hz, ArH), 7.35–7.31 (2H, m, ArH), 7.15–7.05 (3H, m, ArH), 6.89 (2H, d, *J* = 8.7 Hz, ArH), 6.64 (2H, d, *J* = 8.7 Hz, ArH), 6.42 (2H, d, *J* = 8.7 Hz, ArH), 5.00 (1H, ddd, *J* = 8.3, 5.4, 0.9 Hz, NCH), 4.58 (1H, d, *J* = 11.7 Hz, COCHCH), 3.01 (1H, dd, *J* = 11.4, 8.3 Hz, SCH_aH_b), 2.83 (6H, s, $N(CH_3)_2$), 2.74 (6H, s, $N(CH_3)_2$), 2.65 (1H, dd, *J* = 11.4, 0.9 Hz, SCH_aH_b), 1.87–1.75 (1H, m, $CH(CH_3)_2$), 0.79 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(CH_3)_b$), 0.65 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.4 MHz) δ 203.4 (C), 173.6 (C), 149.0 (C), 148.6 (C), 137.4 (C), 132.5 (C), 130.9 (C), 129.4 (CH), 128.7 (CH), 128.6 (CH), 128.1 (CH), 127.0 (CH), 113.2 (CH), 112.5 (CH), 72.1 (CH), 55.2 (CH), 52.0 (CH), 40.8 (2 ×CH_3), 40.5 (2 ×CH_3), 30.6 (CH), 28.4 (CH_2), 18.7 (CH_3), 17.4 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{31}H_{38}N_3OS_2$: 532.2451, found: 532.2468.

*2.3.4.4. With 4,4'-dimethoxybenzhydryl methyl ether (**55**)*

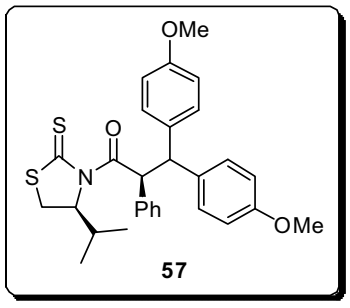
Solid $(Me_3P)_2NiCl_2$ (7.0 mg, 25 μmol) was added to a solution of thioimide **4a** (140 mg, 0.50 mmol) and diaryl methyl ether **55** (194 mg, 0.75 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2 at r.t. The resulting solution was purged with N_2 again and then cooled to –20 ºC. TESOTf (136 μL, 0.60 mmol) and 2,6-lutidine (88 μL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred at –20 ºC for 15 h.

The reaction was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude was purified by flash column chromatography on silica gel (hexanes/EtOAc 85:15) to afford a first fraction of 66 mg of a 3:1 mixture of the desired alkylation product **57** (53 mg, 0.10 mmol, 21%) and the methyl ester **58** (13 mg, 0.40 mmol, 7%) and a second fraction of 102 mg of a 1:14.3 mixture of the desired product **57** (8 mg, 0.02 mmol, 3%) and the *S*-alkylated product **56** (94 mg, 0.25 mmol, 49%).



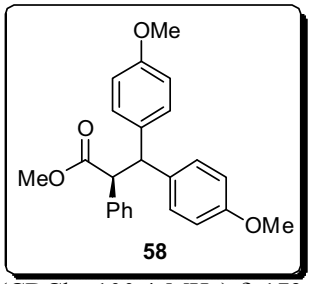
56

(*S*)-2-[(Bis(4-methoxyphenyl)methyl)thio]-4-isopropyl-4,5-dihydrothiazole (**56**). Yellow oil; $\mathbf{R_f}$ = 0.15 (hexanes/EtOAc 85:15); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.40–7.38 (1H, m, ArH), 7.29–7.26 (1H, m, ArH), 7.16–7.13 (2H, m, ArH), 6.93–6.90 (2H, m, ArH), 6.87–6.85 (2H, m, ArH), 4.14 (1H, ddd, *J* = 9.5, 2.7, 1.5 Hz, NCH), 3.83 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.44 (1H, dd, *J* = 11.5, 9.5 Hz, SCH_aH_b), 3.01 (1H, dd, *J* = 11.5, 1.5 Hz, SCH_aH_b), 1.38–1.30 (1H, m, $CH(CH_3)_2$), 0.94 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(CH_3)_b$), 0.64 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_a(CH_3)_b$).



57

(*S*)-*N*-[(*S*)-3,3-Bis(4-methoxyphenyl)-2-phenylpropanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**57**). Yellow solid; $\mathbf{R_f}$ = 0.25 (hexanes/EtOAc 85:15); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.48–7.46 (2H, m, ArH), 7.41 (1H, d, *J* = 11.8 Hz, COCH), 7.30–7.27 (2H, m, ArH), 7.20–7.10 (3H, m, ArH), 6.95–6.91 (2H, m, ArH), 6.84–6.81 (2H, m, ArH), 6.60–6.58 (2H, m, ArH), 5.01 (1H, ddd, *J* = 8.2, 5.7, 0.9 Hz, NCH), 4.68 (1H, d, *J* = 11.8 Hz, COCHCH), 3.74 (3H, s, OCH_3), 3.64 (3H, s, OCH_3), 3.12 (1H, dd, *J* = 11.5, 8.2 Hz, SCH_aH_b), 2.76 (1H, dd, *J* = 11.5, 0.9 Hz, SCH_aH_b), 1.92–1.83 (1H, m, $CH(CH_3)_2$), 0.84 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(CH_3)_b$), 0.68 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.4 MHz) δ 203.7 (C), 173.4 (C), 158.0 (C), 157.7 (C), 137.0 (C), 136.0 (C), 134.5 (C), 129.4 (CH), 129.2 (CH), 129.1 (CH),128.3 (CH), 127.3 (CH), 114.0 (CH), 114.0 (CH), 72.3 (CH), 55.3 (CH), 55.2 (CH_3), 55.0 (CH_3), 52.2 (CH), 30.6 (CH), 28.9 (CH_2), 18.7 (CH_3), 17.5 (CH_3).



58

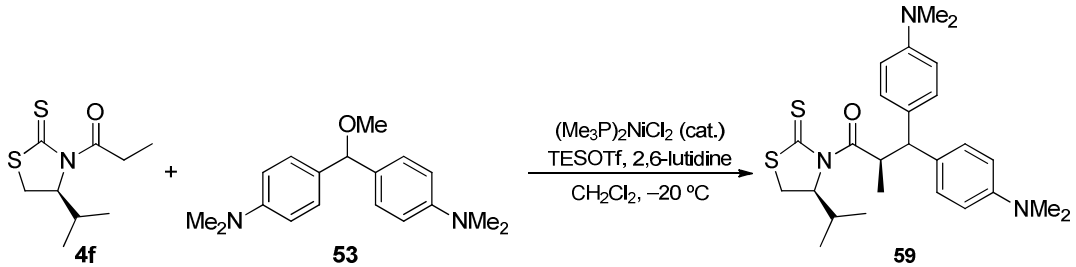
(*S*)-Methyl 3,3-bis(4-methoxyphenyl)-2-phenylpropanoate (**58**). Yellow solid; $\mathbf{R_f}$ = 0.25 (hexanes/EtOAc 85:15); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.30–7.27 (4H, m, ArH), 7.20–7.10 (3H, m, ArH), 6.95–6.91 (2H, m, ArH), 6.84–6.81 (2H, m, ArH), 6.60–6.58 (2H, m, ArH), 4.61 (1H, d, *J* = 12.3 Hz, COCHCH), 4.35 (1H, d, *J* = 12.3 Hz, COCH), 3.76 (3H, s, $ArOCH_3$), 3.64 (3H, s, $ArOCH_3$), 3.47 (3H, s, $COOCH_3$); **^{13}C NMR** ($CDCl_3$, 100.4 MHz) δ 173.3 (C), 158.1 (C), 157.7 (C), 137.1 (C), 135.4 (C), 134.1 (C), 129.1 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 127.2 (CH), 114.0 (CH), 113.5 (CH), 57.1 (CH), 55.3 (CH_3), 55.2 (CH_3), 53.0 (CH), 51.9 (CH_3).

2.3.5. With (*S*)-*N*-propanoyl-4-isopropyl-1,3-thiazolidine-2-thione (4f)

*2.3.5.1. Optimization with 4,4'-bis(dimethylamino)benzhydryl methyl ether (**53**)*

Solid $(Me_3P)_2NiCl_2$ was added to a solution of thioimide **4f** (109 mg, 0.50 mmol) and diaryl methyl ether **53** (213 mg, 0.75 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2 at r.t. The resulting solution was purged with N_2 again and then cooled to –20 ºC. TESOTf and 2,6-lutidine (88 μL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred at –20 ºC during the time displayed in Table 42.

The reaction was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude was purified by flash column chromatography on silica gel (from hexanes/EtOAc 90:10 to 80:20) to afford the alkylation product **59** in the yields shown in Table 42.

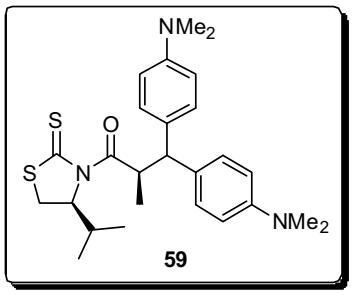


4f **53** **59**
single diastereomer

Entry	$(Me_3P)_2NiCl_2$ (mol%)	TESOTf (eq)	t (h)	Yield (%)[a]
1	2.5	1.15	1.5	62
2	5.0	1.2	1.5	65
3	20.0	1.5	1.5	77
4	2.5	1.15	15	67
5	5.0	1.2	15	96

[a] Isolated yield after column chromatography.

Table 42



59

(*S*)-*N*-[(*R*)-3,3-Bis(4-dimethylaminophenyl)-2-methylpropanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**59**). Blue solid; **mp** = 159–160 ºC; $\mathbf{R_f}$ = 0.60 (hexanes/EtOAc 7:3); $[\alpha]_D$ = +167.3 (*c* 0.011, $CHCl_3$); **IR** (ATR) 2955, 2925, 2788, 1698, 1675, 1605, 1516, 1342, 1238, 1145, 1123 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.25–7.23 (2H, m, ArH), 7.16–7.14 (2H, m, ArH), 6.67–6.65 (2H, m, ArH), 6.63–6.60 (2H, m, ArH), 6.01 (1H, dq, *J* = 11.4, 6.8 Hz, COCH), 5.20 (1H, ddd, *J* = 8.7, 5.0, 1.0 Hz, NCH), 4.09 (1H, d, *J* = 11.4 Hz, COCHCH), 3.36 (1H, dd, *J* = 11.4, 8.7 Hz, SCH_aH_b), 2.88 (6H, s, $N(CH_3)_2$), 2.83 (1H, dd, *J* = 11.4, 1.0 Hz, SCH_aH_b), 2.83 (6H, s, $N(CH_3)_2$), 1.68–1.56 (1H, m, $CH(CH_3)_2$), 1.08 (3H, d, *J* = 6.8 Hz, $COCHCH_3$), 0.77 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(CH_3)_b$), 0.65 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.4 MHz) δ 202.9 (C), 177.4 (C), 149.1 (2 ×C), 133.2 (C), 131.6 (C), 128.7 (CH), 128.3 (CH), 113.3 (CH), 113.0 (CH), 71.5 (CH), 54.2 (CH), 42.1 (CH), 40.9 (2 ×CH_3), 40.7 (2 ×CH_3), 30.7 (CH), 28.0 (CH_2), 18.8 (CH_3), 17.2 (CH_3), 17.0 (CH_3).; **HRMS** (+ESI): *m/z* calculated for $[M–C_8H_{11}N]^+$ $C_{18}H_{25}N_2OS_2$: 349.1403, found: 349.1412; *m/z* calculated for $[M+H]^+$ $C_{26}H_{36}N_3OS_2$: 470.2294, found: 470.2299.

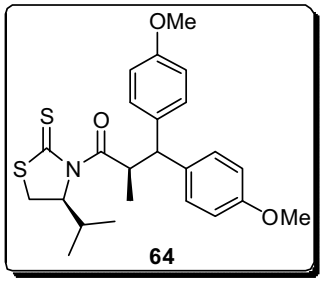
2.3.6. General Procedure for the catalytic alkylation reaction

Solid $(Me_3P)_2NiCl_2$ (7.0 mg, 25 μmol) was added to a solution of thioimide **4f** (109 mg, 0.50 mmol) and the corresponding diaryl methyl ether (0.75 mmol) in CH_2Cl_2 (1.0 mL) under N_2 at r.t. The resulting mixture was purged with N_2 again and then cooled to –20 ºC. TESOTf (136 μL, 0.60 mmol) and 2,6-lutidine (88 μL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred at –20 ºC for 15 h.

The reaction was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude was purified by flash column chromatography on silica gel to afford the corresponding alkylated product.

2.3.7. (*S*)-*N*-[(*R*)-3,3-Bis(4-methoxyphenyl)-2-methylpropanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (64)

The alkylation product **64** was prepared according to the General Procedure in section 2.3.6. from thioimide **4f** (109 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (7.0 mg, 25 μmol), 4,4'-dimethoxybenzhydryl methyl ether (**55**) (194 mg, 0.75 mmol), TESOTf (136 μL, 0.60 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and anh CH_2Cl_2 (1.0 mL). Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc 85:15) afforded 209 mg (0.47 mmol, 94%) of alkylation product **64** as a yellow solid.

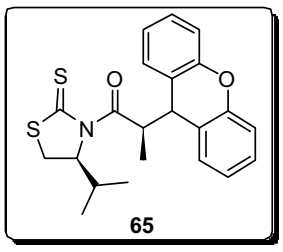


64

(*S*)-*N*-[(*R*)-3,3-Bis(4-methoxyphenyl)-2-methylpropanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**64**). Yellow solid; **mp** = 175–176 ºC; $\mathbf{R_f}$ = 0.30 (hexanes/EtOAc 85:15); $\mathbf{[\alpha]_D}$ = +316.7 (*c* 1.00, $CHCl_3$); **IR** (ATR) 2959, 2925, 2829, 1683, 1601, 1501, 1464, 1360, 1238, 1145, 1030 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.32–7.18 (4H, m, ArH), 6.83–6.73 (4H, m, ArH), 6.07 (1H, dq, *J* = 11.5, 6.8 Hz, COCH), 5.18 (1H, ddd, *J* = 8.5, 5.2, 1.1 Hz, NCH), 4.19 (1H, d, *J* = 11.5 Hz, COCHCH), 3.74 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.36 (1H, dd, *J* = 11.5, 8.5 Hz, SCH_aH_b), 2.84 (1H, dd, *J* = 11.5, 1.1 Hz, SCH_aH_b), 1.69–1.61 (1H, m, $CH(CH_3)_2$), 1.07 (3H, d, *J* = 6.8 Hz, $COCHCH_3$), 0.78 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(CH_3)_b$), 0.64 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.4 MHz) δ 203.2 (C), 176.9 (C), 158.1 (C), 157.9 (C), 136.5 (C), 135.1 (C), 129.0 (CH), 128.8 (CH), 114.0 (CH), 113.9 (CH), 71.5 (CH), 55.2 (CH_3), 55.2 (CH_3), 54.2 (CH), 42.0 (CH), 30.7 (CH), 28.3 (CH_2), 18.7 (CH_3), 17.2 (CH_3), 17.1 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{24}H_{30}NO_3S_2$: 444.1662, found: 444.1672.

2.3.8. (*S*)-*N*-4-Isopropyl-[(*R*)-2-methyl-3-(9*H*-xanthen-9-yl)propanoyl]-1,3-thiazolidine-2-thione (65)

The alkylation product **65** was prepared according to the General Procedure in section 2.3.6. from thioimide **4f** (109 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (7.0 mg, 25 μmol), 9*H*-xanthen-9-yl methyl ether (**60**) (159 mg, 0.75 mmol), TESOTf (136 μL, 0.60 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and anh CH_2Cl_2 (1.0 mL). Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc 85:15) afforded 190 mg (0.48 mmol, 95%) of alkylation product **65** as a yellow solid.

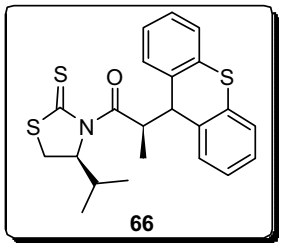


65

(*S*)-*N*-4-Isopropyl-[(*R*)-2-methyl-3-(9*H*-xanthen-9-yl)propanoyl]-1,3-thiazolidine-2-thione (**65**). Yellow solid; **mp** = 92–93 ºC; $\mathbf{R_f}$ = 0.60 (hexanes/EtOAc 4:1); $\mathbf{[\alpha]_D}$ = +163.4 (*c* 1.00, $CHCl_3$); **IR** (ATR): 2962, 2922, 2866, 1676, 1472, 1449, 1249, 1238, 1153 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.34–6.98 (8H, m, ArH), 5.08 (1H, dd, *J* = 8.2, 5.5, 0.9 Hz, NCH), 4.94 (1H, dq, *J* = 7.7, 6.9 Hz, COCH), 4.50 (1H, d, *J* = 7.7 Hz, COCHCH), 3.34 (1H, dd, *J* = 11.5, 8.2 Hz, SCH_aH_b), 2.89 (1H, dd, *J* = 11.5, 0.9 Hz, SCH_aH_b), 2.29–2.17 (1H, m, $CH(CH_3)_2$), 1.00 (3H, d, *J* = 6.9 Hz, $COCHCH_3$), 0.91 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_a(CH_3)_b$), 0.90 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.4 MHz) δ 202.5 (C), 175.9 (C), 153.6 (2 × C), 130.1 (CH), 128.9 (CH), 128.0 (CH), 127.9 (CH), 124.6 (C), 123.1 (CH), 122.9 (C), 122.6 (CH), 116.6 (CH), 116.4 (CH), 71.9 (CH), 45.0 (CH), 42.2 (CH), 30.8 (CH), 29.1 (CH_2), 19.1 (CH_3), 17.0 (CH_3), 15.6 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{22}H_{24}NO_2S_2$: 398.1243, found: 398.1260; *m/z* calculated for $[M+Na]^+$ $C_{22}H_{23}NNaO_2S_2$: 420.1062, found: 420.1077.

2.3.9. (*S*)-*N*-4-Isopropyl-[(*R*)-2-methyl-3-(9*H*-thioxanthen-9-yl)propanoyl]-1,3-thiazolidine-2-thione (66)

The alkylation product **66** was prepared according to the General Procedure in section 2.3.6. from thioimide **4f** (109 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (7.0 mg, 25 μmol), 9*H*-thioxanthen-9-yl methyl ether (**61**) (171 mg, 0.75 mmol), TESOTf (136 μL, 0.60 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and anh CH_2Cl_2 (1.0 mL). Purification of the crude product by flash column chromatography on silica gel (from hexanes/EtOAc 95:5 to 90:10) afforded 125 mg (0.30 mmol, 60%) of **66** as a yellow solid.

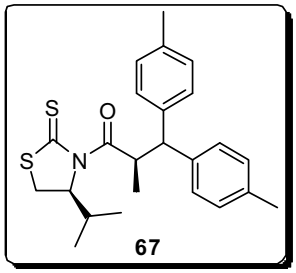


66

(*S*)-*N*-4-Isopropyl[(*R*)-2-methyl-3-(9*H*-thioxanthen-9-yl)propanoyl]-1,3-thiazolidine-2-thione (**66**). Yellow solid; **mp** = 160–162 ºC; $\mathbf{R_f}$ = 0.35 (hexanes/EtOAc 9:1); $\mathbf{[\alpha]_D}$ = +112.5 (*c* 1.30, $CHCl_3$); **IR** (ATR) 2959, 2925, 2866, 1683, 1457, 1349, 1242, 1153 cm^{-1}; **^{1}H NMR**($CDCl_3$, 400 MHz) δ 7.45–7.11 (8H, m, Ar<u>H</u>), 5.36 (1H, dq, *J* = 10.6, 6.9 Hz, COC<u>H</u>), 5.08 (1H, ddd, *J* = 8.4, 5.8, 0.9 Hz, NC<u>H</u>), 4.51 (1H, d, *J* = 10.6 Hz, COCHC<u>H</u>), 3.26 (1H, ddd, *J* = 11.5, 8.4, 1.0 Hz, SC<u>H</u>$_a$H$_b$), 2.79 (1H, dt, *J* = 11.5, 1.1 Hz, SCH$_a$<u>H</u>$_b$) 1.84–1.75 (1H, m, C<u>H</u>$(CH_3)_2$), 0.94 (3H, d, *J* = 6.9 Hz, COCHC<u>H</u>$_3$), 0.70 (3H, d, *J* = 7.0 Hz, CH$(C\underline{H}_3)_a(CH_3)_b$), 0.67 (3H, d, *J* = 6.8 Hz, CH$(CH_3)_a(C\underline{H}_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.4 MHz) δ 201.8 (C), 176.4 (C), 136.2 (C), 135.5 (C), 133.6 (C), 133.3 (C), 130.6 (CH), 130.5 (CH), 127.3 (CH), 127.1 (CH), 126.8 (CH), 126.6 (CH), 126.0 (CH), 126.0 (CH), 71.3 (CH), 51.9 (CH), 37.6 (CH), 30.6 (CH), 28.7 (CH_2), 18.9 (CH_3), 17.4 (CH_3), 16.8 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+Na]^+$ $C_{22}H_{23}NNaOS_3$: 436.0834, found: 436.0834.

2.3.10. (*S*)-*N*-4-Isopropyl-[(*R*)-2-methyl-3,3-bis(*p*-tolyl)propanoyl]-1,3-thiazolidine-2-thione (67)

The alkylation product **67** was prepared according to the General Procedure in section 2.3.6. from thioimide **4f** (109 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (7.0 mg, 25 μmol), 3,3'-dimethylbenzhydryl methyl ether (**62**) (170 mg, 0.75 mmol), TESOTf (136 μL, 0.60 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and anh CH_2Cl_2 (1.0 mL). Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc 9:1) afforded 18 mg of a first mixture of desired alkylation product **67** and ether **62** in a 1:2.51 ratio determined by ^{1}H NMR, and 120 mg of a second mixture of starting material **4f** and desired alkylation product **67** in a 1:0.07 ratio determined by ^{1}H NMR. The calculated mass of desired alkylation product **67** in these mixtures was about 20 mg (0.05 mmol, 10%).



67

(*S*)-*N*-4-Isopropyl-[(*R*)-2-Methyl-3,3-bis(*p*-tolyl)propanoyl]-1,3-thiazolidine-2-thione (**67**). Yellow oil; $\mathbf{R_f}$ = 0.55 (hexanes/EtOAc 85:15); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.28–6-99 (8H, m, Ar<u>H</u>), 6.10 (1H, dq, *J* = 12.3, 6.6 Hz, COC<u>H</u>), 4.21 (1H, d, *J* = 12.3 Hz, COCHC<u>H</u>), 4.15–4.10 (1H, m, NC<u>H</u>), 3.04 (1H, dd, *J* = 11.1, 8.6 Hz, SC<u>H$_a$</u>H$_b$), 2.84 (1H, dd, *J* = 11.1, 1.0 Hz, SCH$_a$<u>H$_b$</u>), 2.31 (6H, s, 2 × ArC<u>H$_3$</u>), 1.84–1.76 (1H, m,C<u>H</u>$(CH_3)_2$), 1.08 (3H, d, *J* = 6.6 Hz, , CH(C<u>H$_3$</u>)$_a$$(CH_3)_b$), 0.77 (3H, d, *J* = 6.8 Hz,), 0.63 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_a$(C<u>H$_3$</u>)$_b$).

2.3.11. Attempt with benzhydryl methyl ether (63)

The alkylation reaction was carried out according to the General Procedure in section 2.3.6. from thioimide **4f** (109 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (7.0 mg, 25 μmol), benzhydryl methyl ether (**63**) (149 mg, 0.75 mmol), TESOTf (136 μL, 0.60 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and anh CH_2Cl_2 (1.0 mL). ^{1}H NMR spectrum of the crude product showed a complex mixture in which thiazole **47** was detected.

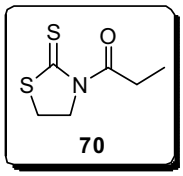
3. Stereoselective Ni(II) catalyzed reactions of *N*-acyl thiazolidinethiones with acetals

3.1. PREPARATION OF STARTING MATERIALS

3.1.1. *N*-Propanoyl-1,3-thiazolidine-2-thione (70)

A 1.6 M solution of *n*-BuLi in hexanes (3.0 mL, 4.8 mmol) was added dropwise to a solution of 1,3-thiazolidine-2-thione (477 mg, 4.0 mmol) in anh THF (2.8 mL) at –78 ºC under N_2. The reaction mixture was stirred for 15 min and propanoyl chloride (490 µL, 5.6 mmol) was carefully added. The resulting clear solution was stirred for 5 min at –78 ºC and for 1 h at r.t.

The reaction mixture was cooled with an ice bath and quenched with sat NH_4Cl (2.8 mL) and diluted with water (20 mL). This mixture was extracted with CH_2Cl_2 (3 ×20 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated. The resultant oil was purified by flash column chromatography on silica gel (hexanes/CH_2Cl_2 3:7) to afford 597 mg (3.41 mmol, 85%) of thioimide **70**.



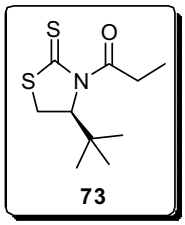
70

N-Propanoyl-1,3-thiazolidine-2-thione (**70**). Yellow oil; $\mathbf{R_f}$ = 0.65 (CH_2Cl_2); **IR** (film) 2930, 1516, 1450, 1296, 1250, 1087, 1050 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 4.59 (2H, t, *J* = 7.6 Hz, NC$\underline{H}_2$), 3.28 (2H, t, *J* = 7.6 Hz, SC$\underline{H}_2$), 3.26 (2H, q, *J* = 7.3 Hz, C$\underline{H}_2$CH$_3$). 1.18 (3H, t, *J* = 7.3 Hz, C$\underline{H}_3$); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 201.5, 175.6, 56.0, 32.2, 28.2, 8.7.

3.1.2. (*S*)-4-(*tert*-Butyl)-*N*-propanoyl-1,3-thiazolidine-2-thione (73)

A 1.6 M solution of *n*-BuLi in hexanes (1.1 mL, 1.7 mmol) was added dropwise to a solution of (*S*)-4-(*tert*-butyl)-1,3-thiazolidine-2-thione (274 mg, 1.56 mmol) in anh THF (1.1 mL) at –78 ºC under N_2. The reaction mixture was stirred for 15 min and propanoyl chloride (177 µL, 2.0 mmol) was carefully added. The resulting clear solution was stirred for 5 min at –78 ºC and for 1 h at r.t.

The reaction mixture was cooled with an ice bath and quenched with sat NH_4Cl (2.8 mL) and diluted with water (20 mL). This mixture was extracted with CH_2Cl_2 (3 ×20 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated. The resultant oil was purified by flash column chromatography on silica gel (hexanes/CH_2Cl_2 2:3) to afford 334 mg (1.44 mmol, 93%) of thioimide **73**.



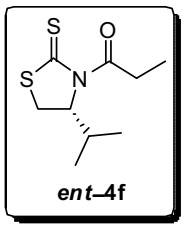
73

(*S*)-4-(*tert*-Butyl)-*N*-propanoyl-1,3-thiazolidine-2-thione (**73**). Yellow solid; **mp** = 29–30 °C; $\mathbf{R_f}$ = 0.50 (hexanes/CH_2Cl_2 1:1); $\mathbf{[\alpha]_D}$ = +602.4 (*c* 0.85, $CHCl_3$); **IR** (KBr) 2964, 1703, 1353, 1325, 1250, 1156, 1045 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 5.35 (1H, dd, *J* = 8.4, 0.7 Hz, NC$\underline{H}$), 3.54 (1H, dd, *J* = 11.4, 8.4 Hz, SC$\underline{H}_a$H$_b$), 3.36 (1H, dq, *J* = 17.9, 7.2 Hz, COC$\underline{H}_a$H$_b$), 3.21 (1H, dq, *J* = 17.9, 7.2 Hz, COCH$_a$$\underline{H}_b$), 3.10 (1H, dd, *J* = 11.4, 0.7 Hz, SCH$_a$$\underline{H}_b$), 1.18 (3H, t, *J* = 7.2 Hz, COCH$_2$C$\underline{H}_3$), 1.03 (9H, s, C(C$\underline{H}_3$)$_3$); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 204.7, 174.5, 72.4, 37.9, 31.8, 30.5, 26.8, 9.2.

3.1.3. (*R*)-4-Isopropyl-*N*-propanoyl-1,3-thiazolidine-2-thione (*ent*–4f)

A 1.6 M solution of *n*-BuLi in hexanes (11.8 mL, 18.8 mmol) was added dropwise to a solution of (*R*)-4-isopropyl-1,3-thiazolidine-2-thione (2.53 g, 15.7 mmol) in anh THF (8.6 mL) at –78 ºC under N_2. The reaction mixture was stirred for 15 min and propanoyl chloride (1.77 mL, 20.4 mmol) was carefully added. The resulting clear solution was stirred for 5 min at –78 ºC and for 1 h at r.t.

The reaction mixture was cooled with an ice bath and quenched with sat NH_4Cl (6.3 mL) and diluted with water (20 mL). This mixture was extracted with CH_2Cl_2 (3 ×50 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated. The resultant oil was purified by flash column chromatography on silica gel (hexanes/CH_2Cl_2 1:1) to afford 3.30 g (15.2 mmol, 97%) of thioimide ***ent*–4f**.

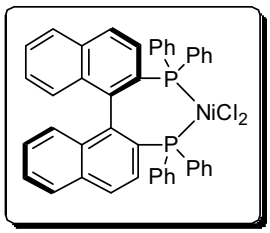


(*R*)-4-Isopropyl-*N*-propanoyl-1,3-thiazolidine-2-thione (***ent*-4f**). Yellow oil; $[\alpha]_D$ = –430.7 (*c* 0.20, $CHCl_3$).

3.1.4. (*R*)-(2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl)nickel(II) dichloride[27]

Nickel(II) chloride (64.8 mg, 0.50 mmol) and water (9 μL) were added to a solution of (*R*)-BINAP (311 mg, 0.50 mmol) in acetonitrile (9 mL) at r.t. The reaction mixture was purged with N_2 and heated to reflux with vigorous stirring for 15 h.

After this time, the resulting purple solution was filtered through Celite® and the volatiles evaporated under vacuum to afford 138 mg (0.18 mmol, 37%) of [(*R*)-BINAP]$NiCl_2$.

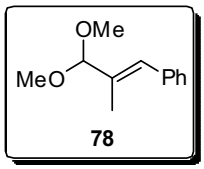


(*R*)-(2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl)nickel(II) dichloride. Grey solid; **^{31}P NMR** ($CDCl_3$, 121.4 MHz) δ –15.6 (s); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 10.79 (4H, br s), 9.51 (2H, br s), 8.74–8.51 (2H, br s), 8.68 (2H, d, *J* = 8.1 Hz), 8.06 (2H, br s), 7.89–6.81 (10H, m), 6.32 (2H, br s), 6.06 (2H, br s), 4.69–4.58 (4H, m), 4.47 (2H, br s).

3.1.5. (*E*)-α-methylcinnamaldehyde dimethyl acetal (78)

Trimethyl orthoformate (5.3 mL, 48 mmol) and anh MeOH (0.90 mL, 22 mmol) were added to a mixture of (*E*)-2-methyl-3-phenylpropenal (5.6 mL, 40 mmol) and catalytic amounts of Amberlyst® 15 resin at 0 ºC under N_2. The reaction mixture was stirred for 36 h at r.t.

After this time, it was filtered and the volatiles removed *in vacuo*. Further purification by distillation under reduced pressure afforded 4.0 g (20.8 mmol, 52%) of dimethyl acetal **78**.



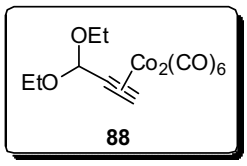
78

(*E*)-α-methylcinnamaldehyde dimethyl acetal (**78**). Yellow liquid; **bp** = 120–130 ºC (2.7 mmHg); **IR** (film) 2987, 2932, 2827, 1601, 1445, 1347, 1196, 1073 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.24–7.36 (5H, m, ArH), 6.63 (1H, br s, C=CH), 4.65 (1H, d, *J* = 1.2 Hz, CH(OCH$_3$)$_2$), 3.38 (6H, s, CH(OCH$_3$)$_2$), 1.89 (3H, d, *J* = 1.2 Hz, HC=CCH$_3$); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 137.0, 134.4, 129.1, 128.5, 128.1, 126.8, 107.7, 53.6, 13.0; **HRMS** (+ESI): *m/z* calculated for $[M+Na]^+$ $C_{12}H_{16}NaO_2$: 215.1043, found: 215.1041.

3.1.6. Hexacarbonyl μ-[η^4-(1,1-diethoxypropyne)dicobalt (88)[90]

A solution of propiolaldehyde diethyl acetal (0.8 mL, 5.6 mmol) in anh pentane (3.0 mL) under N_2 was added *via cannula* to a solution of $Co_2(CO)_8$ (2.01 g, 5.9 mmol) in anh pentane (27 mL) under N_2 at r.t. After having stirred for 1.5 h, vacuum was applied and the system purged again with N_2. This process was repeated for four times. Then, the reaction mixture was stirred for 1.5 h.

After this time, the solution was bubbled with a N_2 flux until the volume of solvent was reduced by half. The resulting solution was purified by flash column chromatography on silica gel (hexanes/Et_2O 95:5) to give 1.48 g (3.58 mmol, 64%) of cobalted diethyl acetal **88**.



88

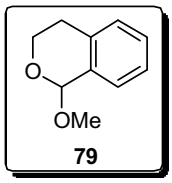
Hexacarbonyl μ-[η^4-(1,1-diethoxypropyne)dicobalt (**88**). Dark red solid; **R_f** = 0.75 (hexanes/Et_2O 9:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 6.01 (1H, s, C[$Co_2(CO)_6$]CH), 5.47 (1H, s, CH(OCH$_2$CH$_3$)$_2$), 3.82–3.59 (4H, m, CH(OCH$_2$CH$_3$)$_2$), 1.25 (6H, t, *J* = 7.0 Hz, CH(OCH$_2$CH$_3$)$_2$).

3.1.7. 1-Methoxyisochroman (79)[38]

Anh MeOH (0.39 mL, 9.6 mmol) followed by isochroman (1.01 mL, 8.0 mmol) were added to a solution of DDQ (2.18 g, 9.6 mmol) in anh CH_2Cl_2 (50 mL) under N_2. The bright red heterogeneous mixture was stirred under N_2 at r.t. for 24 h.

The reaction mixture was quenched by addition of sat $NaHCO_3$ (60 mL), filtered through Celite® and rinsed with an additional CH_2Cl_2 (50 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed once with sat $NaHCO_3$ (30 mL) and

brine (30 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude oil was purified by flash column chromatography on silica gel (CH_2Cl_2) to give 787 mg (4.8 mmol, 60%) of acetal **79**.



79

1-Methoxyisochroman (**79**). Colorless oil; $\mathbf{R_f}$ = 0.50 (CH_2Cl_2); **IR** (ATR) 3065, 2933, 2877, 2825, 1492, 1493, 1381, 1339, 1183, 1088, 1070, 1044 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.25–7.10 (4H, m, ArH), 5.45 (1H, s, CHOCH$_3$), 4.12 (1H, ddd, *J* = 11.9, 11.3, 3.4 Hz, OCH$_a$H$_b$), 3.91 (1H, ddd, *J* = 11.3, 5.9, 1.7 Hz, OCH$_a$H$_b$), 3.55 (3H, s, OCH$_3$), 3.03 (1H, ddd, *J* = 17.0, 11.9, 5.9 Hz, ArCH$_a$H$_b$), 2.62 (1H, ddd, *J* = 17.0, 3.4, 1.7 Hz, ArCH$_a$H$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 134.1 (C), 134.0 (C), 128.4 (CH), 128.1 (CH), 127.4 (CH), 126.3 (CH), 97.8 (CH), 57.7 (CH_2), 55.3 (CH_3), 27.9 (CH_2); **HRMS** (+ESI): *m/z* calculated for $[M–OMe]^+$ C_9H_9O: 133.0648, found: 133.0650.

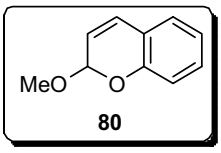
3.1.8. 2-Methoxy-2*H*-chromene (80)[138]

A 1 M solution of DIBALH in toluene (21.0 mL, 21.0 mmol) was added dropwise during 1 h to a solution of coumarin (2.92 g, 20 mmol) in anh CH_2Cl_2 (30 mL) at –78 ºC under N_2. The yellow reaction mixture was stirred for 1 h at –78 ºC and 15 min at 0 ºC.

EtOAc (100 mL) and water (100 mL) were added and the mixture was stirred vigorously. Then, it was filtered through Celite®. The aqueous layer was separated and washed with EtOAc (2 × 100 mL). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*.

The crude oil was then dissolved with anh MeOH (15.0 mL) under N_2 and trifluoroacetic acid (46 μL, 0.6 mmol) was added over this solution at r.t. The maroon reaction mixture was stirred for 3 h at r.t.

The reaction solution was quenched with solid K_2CO_3 (110 mg), filtered and concentrated *in vacuo*. The yellow crude oil was purified by flash column chromatography on silica gel (hexanes/EtOAc 95:5) to give 2.39 g (14.8 mmol, 74%) of acetal **80**.



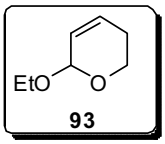
80

2-Methoxy-2*H*-chromene (**80**). Colorless oil; $\mathbf{R_f}$ = 0.30 (hexanes/EtOAc 9:1); **IR** (ATR): 3041, 2906, 2825, 1640, 1603, 1484, 1453, 1205, 1081, 1030, 1017 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.24–7.19 (1H, m, ArH), 7.14 (1H, dd, *J* = 7.5, 1.6 Hz, ArH), 7.00–6.94 (2H, m, ArH), 6.74 (1H, d, *J* = 9.7 Hz, ArCH), 5.86 (1H, dd, *J* = 9.7, 3.7 Hz, ArCHCH), 5.60 (1H, d, *J* = 3.7 Hz, OCH), 3.50 (3H, s, OCH$_3$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 151.2, 129.2, 126.9, 126.4, 121.3, 120.5, 119.5, 116.3, 95.7, 54.7; **HRMS** (+ESI): *m/z* calculated for $[M–OMe]^+$ C_9H_7O: 131.0491, found: 131.0493.

3.1.9. 2-Ethoxy-5,6-dihydro-2H-pyran (93)[180]

To a solution of 3,4-dihydro-2*H*-pyran (3.64 mL, 40 mmol) in absolute EtOH (32 mL) at 0 ºC under N_2, *N*-bromosuccinimide (7.12 g, 40 mmol) in 18 portions of 396 mg with a 10 min lapse between was added. Having the additions finished, the reaction mixture was stirred for 30 min at 0 ºC and solid KOH (8.98 g, 160 mmol) was added. Then, it was heated to reflux for 13 h.

The mixture was filtered though a sintered glass funnel. The filtrate was evaporated to obtain an oil residue, which was redissolved in Et_2O (80 mL) and washed with water (3 × 50 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude oil was purified by flash column chromatography on silica gel (hexanes/EtOAc 95:5) to give 209 mg (1.63 mmol, 4%) of **93**.



93

6-Ethoxy-3,6-dihydro-2*H*-pyran (**93**). Colorless oil; $\mathbf{R_f}$ = 0.55 (hexanes/EtOAc 9:1); **IR** (ATR) 2972, 2928, 2870, 1383, 1317, 1183, 1099, 1053, 1038, 1008 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 6.03 (1H, dddt, *J* = 10.2, 5.7, 2.3, 1.2 Hz, OCHCH=C<u>H</u>), 5.74 (1H, dtd, *J* = 10.2, 2.8, 1.4 Hz, OCHC<u>H</u>=CH), 4.94–4.91 (1H, m, OC<u>H</u>CH=CH), 3.94 (1H, td, *J* = 11.2, 3.7 Hz, CH=CHCH$_2$C<u>H$_a$</u>H$_b$O), 3.84 (1H, dq, *J* = 9.6, 7.1 Hz, OC<u>H$_a$</u>H$_b$CH$_3$), 3.72 (1H, ddt, *J* = 11.2, 6.1, 1.2 Hz, CH=CHCH$_2$CH$_a$<u>H$_b$</u>O), 3.52 (1H, dq, *J* = 9.6, 7.1 Hz, OCH$_a$<u>H$_b$</u>CH$_3$), 2.36–2.24 (1H, m, CH=CHC<u>H$_a$</u>H$_b$), 1.95–1.86 (1H, m, CH=CHCH$_a$<u>H$_b$</u>), 1.24 (3H, t, *J* = 7.1 Hz, C<u>H$_3$</u>); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 129.0 (CH), 125.9 (CH), 93.7 (CH), 63.2 (CH_2), 57.2 (CH_2), 24.7 (CH_2), 15.3 (CH_3).

3.2. GENERAL PROCEDURE FOR OPTIMIZATION REACTIONS

Solid Ni(II) catalyst was added to a solution of *N*-acyl thioimide (0.50 mmol) and benzaldehyde dimethyl acetal in anh CH_2Cl_2 (1.0 mL) under N_2. The resulting mixture was purged with N_2 again and then cooled to –20 ºC. TESOTf and 2,6-lutidine were added dropwise after 3 and 7 min respectively and then the reaction mixture was stirred for a certain time at a given temperature.

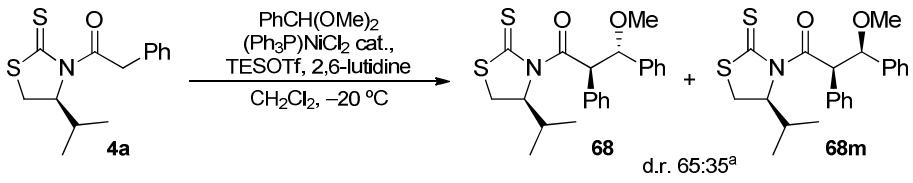
The reaction was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) to give the desired products.

3.3. OPTIMIZATION OF THE REACTION

3.3.1. Preliminary experiments with thioimide 4a

3.3.1.1. Kinetic study of the reaction progress by ^{1}H NMR

Thioimides **68** and **68m** were prepared according to the General Procedure in section 3.2. from thioimide **4a** (140 mg, 0.50 mmol), variable quantities of $(Ph_3P)_2NiCl_2$ as shown in Table 43, benzaldehyde dimethyl acetal (113 µL, 0.75 mmol), variable quantities of TESOTf as shown in Table 43, 2,6-lutidine (88 µL, 0.75 mmol) and anh CH_2Cl_2 (1.0 mL) at –20 ºC during the reaction times displayed in Table 43. Some aliquots were taken from the reaction mixture, treated with the same *work up* as in Section 3.2. and analyzed by ^{1}H NMR spectroscopy to calculate the conversion of the reaction. A 65:35 ratio of *anti/syn* diastereomers **68** and **68m** was detected by ^{1}H NMR spectroscopy in all aliquots.



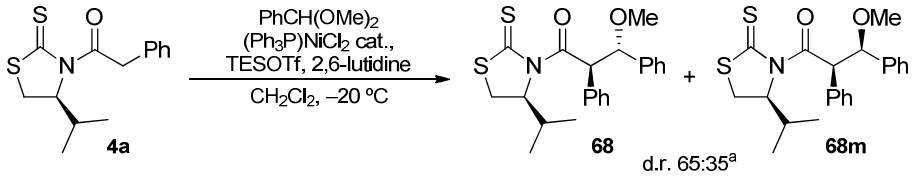
Entry	$(Ph_3P)_2NiCl_2$ (mol%)	TESOTf (eq)	t (h)	Conversion (%)[a]
1	10	1.3	0	0
2	10	1.3	0.3	61
3	10	1.3	1	74
4	10	1.3	2.5	94
5	2.5	1.15	0	0
6	2.5	1.15	0.3	22
7	2.5	1.15	1	38
8	2.5	1.15	2.5	58
9	2.5	1.15	7	81
10	2.5	1.15	16	94

[a] Established by ^{1}H NMR analysis of the crude product.

Table 43

3.3.1.2. Reactions with isolation of the products

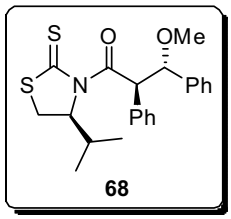
The thioimides **68** and **68m** were prepared according to the General Procedure in section 3.2. from thioimide **4a** (140 mg, 0.50 mmol), variable quantities of $(Ph_3P)_2NiCl_2$ as shown in Table 44, benzaldehyde dimethyl acetal (113 μL, 0.75 mmol), variable quantities of TESOTf as shown in Table 44, 2,6-lutidine (88 μL, 0.75 mmol) and anh CH_2Cl_2 (1.0 mL) taking temperature and reaction times displayed in Table 44. ^{1}H NMR spectra of the crude reaction mixtures revealed a 65:35 ratio of *anti/syn* diastereomers in all cases. Purification of the crude products by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/EtOAc 95:5) afforded a non separable 65:35 mixture of the two diastereomeric adducts **68** and **68m**. The corresponding yields are shown in Table 44.



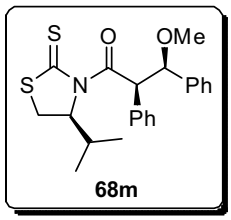
Entry	T (ºC)	Cat. (mol%)	TESOTf (eq)	t (h)	Yield (%)[b]
1[c]	0	10	1.30	24 h	86
2[c]	0	10	1.30	5 h	87
3[c]	0	10	1.30	1 h	90
4[c]	0	2.5	1.15	1 h	94
5	–20	2.5	1.15	10 min	n.r.
6	–20	2.5	1.15	7 h	78
7	–20	2.5	1.15	16 h	93
8	–45[d]	20	1.50	4 h	n.r.
9	–78[d]	20	1.50	8 h	n.r.

[a] Established by ^{1}H NMR analysis of the crude product.
[b] Isolated yield after column chromatography.
[c] The reaction mixture was previously stirred at –20 ºC for 20 min.
[d] This temperature was also employed during the addition of TESOTf and 2,6-lutidine.

Table 44



(*S*)-4-Isopropyl-*N*-[(*2R*, *3S*)-3-methoxy-2,3-diphenylpropanoyl]-1,3-thiazolidine-2-thione (**68**). Yellow solid; $\mathbf{R_f}$ = 0.45 (hexanes/EtOAc 90:10); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.55–7.04 (10H, m, ArH), 6.73 (1H, d, *J* = 10.2 Hz, COCH), 5.25 (1H, ddd, *J* = 8.0, 6.5, 1.4 Hz, NCH), 4.78 (1H, d, *J* = 10.2 Hz, $CHOCH_3$), 3.24 (1H, dd, *J* = 11.4, 8.0. Hz, SCH_aH_b), 3.20 (3H, s, OCH_3), 2.90 (1H, dd, *J* = 11.4, 1.4 Hz, SCH_aH_b), 2.50–2.41 (1H, m, $CH(CH_3)_2$), 1.12 (3H, d, *J* = 6.8 Hz, $NCH(CH_3)_a(CH_3)_b$), 1.08 (3H, d, *J* = 7.0 Hz, $NCH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 203.0 (C), 173.7 (C), 138.6 (C), 134.4 (C), 129.7 (CH), 128.2 (CH), 128.1 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 87.3 (CH), 72.3 (CH), 56.8 (CH_3), 55.4 (CH), 30.7 (CH), 29.7 (CH_2), 19.1 (CH_3), 17.9 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OMe]^+$ $C_{21}H_{22}NOS_2$: 368.1137, found: 368.1119.



(*S*)-4-Isopropyl-*N*-[(*2R*, *3R*)-3-methoxy-2,3-diphenylpropanoyl]-1,3-thiazolidine-2-thione (**68m**). Yellow solid; $\mathbf{R_f}$ = 0.40 (hexanes/EtOAc 90:10); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.55–7.04 (10H, m, ArH), 6.94 (1H, d, *J* = 9.4 Hz, COCH), 4.94 (1H, ddd, *J* = 8.0, 6.1, 1.1 Hz, NCH), 4.78 (1H, d, *J* = 9.4 Hz, CHOCH$_3$), 3.12 (1H, dd, *J* = 11.5, 8.0. Hz, SCH$_a$H$_b$), 3.01 (3H, s, OCH$_3$), 2.73 (1H, dd, *J* = 11.5, 1.1 Hz, SCH$_a$H$_b$), 0.70 (3H, d, *J* = 6.8 Hz, NCH(CH$_3$)$_a$(CH$_3$)$_b$), 0.56 (3H, d, *J* = 7.0 Hz, NCH(CH$_3$)$_a$(CH$_3$)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.8 (C), 171.8 (C), 139.2 (C), 136.3 (C), 129.5 (CH), 128.7 (CH), 128.4 (CH), 128.1 (CH), 127.6 (CH), 127.4 (CH), 86.0 (CH), 71.7 (CH), 56.8 (CH_3), 54.3 (CH), 30.4 (CH), 29.2 (CH_2), 18.5 (CH_3), 17.4 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OMe]^+$ $C_{21}H_{22}NOS_2$: 368.1137, found: 368.1119.

3.3.1.3. Attempts to use a temperature below –20 ºC

Attempt 1

Solid $(Ph_3P)_2NiCl_2$ (65.4 mg, 0.10 mmol) was added to a solution of **4a** (140 mg, 0.50 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2 at r.t. The resulting mixture was purged with N_2 again and then cooled to –20 ºC. TESOTf (170 µL, 0.75 mmol) and 2,6-lutidine (88 µL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The resulting black reaction mixture was stirred for 20 min at –20 ºC. After that time, the reaction mixture was cooled at –78 ºC and benzaldehyde dimethyl acetal (113 µL, 0.75 mmol) was added after 3 min. The reaction was stirred for 4 h at –78 ºC.

After carrying out the same *work up* described in General Procedure in Section 3.2, ^{1}H NMR spectrum of the crude product showed the only presence of starting material **4a**.

Attempt 2

Solid $(Ph_3P)_2NiCl_2$ (65.4 mg, 0.10 mmol) was added to a solution of **4a** (140 mg, 0.50 mmol) and benzaldehyde dimethyl acetal (113 µL, 0.75 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2 at r.t. The resulting black suspension was purged with N_2 again and then cooled to –20 ºC. TESOTf (170 µL, 0.75 mmol) was added and then the reaction mixture was cooled to –78 ºC. After 4 min, 2,6-lutidine (88 µL, 0.75 mmol) was added dropwise. The resulting black reaction mixture was stirred for 15 min. After that time, the reaction was gradually heated during 1 h to 0 ºC. The reaction mixture was stirred for 15 min more at this temperature.

After carrying out the same *work up* as described in General Procedure in Section 3.2., ^{1}H NMR spectrum of the crude showed a conversion of 88% with a d.r. of 65:35.

Attempt 3

Solid $(Ph_3P)_2NiCl_2$ (65.4 mg, 0.10 mmol) was added to a solution of **4a** (140 mg, 0.50 mmol) and benzaldehyde dimethyl acetal (113 µL, 0.75 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2 at r.t. The resulting

black suspension was purged with N_2 again and then cooled to –78 ºC. TESOTf (170 µL, 0.75 mmol) and 2,6-lutidine (88 µL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The resulting black reaction mixture was stirred for 15 min. After that time, the reaction is gradually heated during 1 h to 0 ºC. The reaction was stirred for 15 min more at this temperature.

After carrying out the same *work up* as described in General Procedure in Section 3.2, ^{1}H NMR spectrum of the crude showed a conversion of 94% with a d.r. of 65:35.

Attempt 4

Solid $(Ph_3P)_2NiCl_2$ (65.4 mg, 0.10 mmol) was added to a solution of **4a** (140 mg, 0.50 mmol) and benzaldehyde dimethyl acetal (113 µL, 0.75 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2 at r.t. The resulting black suspension was purged with N_2 again and then cooled to –78 ºC. TESOTf (57 µL, 0.25 mmol), $BF_3{\cdot}OEt_2$ (70 µL, 0.55 mmol) and 2,6-lutidine (88 µL, 0.75 mmol) were added dropwise after 3 min, 5 min and 9 min respectively. The resulting black reaction mixture was stirred for 2 h at –78 ºC and then stirred for 1 h at 0 ºC.

After carrying out the same *work up* as described in General Procedure in Section 3.2, ^{1}H NMR spectrum of the crude showed a conversion of 19% with a d.r. of 60:40.

Attempt 5

Solid $(Ph_3P)_2NiCl_2$ (65.4 mg, 0.10 mmol) was added to a solution of **4a** (140 mg, 0.50 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2 at r.t. The resulting black suspension was purged with N_2 again and then cooled to –20 ºC. TESOTf (170 µL, 0.75 mmol) and 2,6-lutidine (88 µL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred for 20 min at –20 ºC. After that time, it was cooled at –45 ºC and benzaldehyde dimethyl acetal (113 µL, 0.75 mmol) was added after 3 min. The reaction was stirred for 1 h at –45 ºC.

After carrying out the same *work up* as described in General Procedure in Section 3.2, ^{1}H NMR spectrum of the crude showed only starting material **4a**.

Attempt 6

Solid $(Ph_3P)_2NiCl_2$ (65.4 mg, 0.10 mmol) was added to a solution of **4a** (140 mg, 0.50 mmol) and benzaldehyde dimethyl acetal (113 µL, 0.75 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2 at r.t. The resulting black suspension was purged with N_2 again and then cooled to –20 ºC. TESOTf (170 µL, 0.75 mmol) was added and then the reaction mixture was cooled to –45 ºC. After 4 min, 2,6-lutidine (88 µL, 0.75 mmol) was added dropwise. The reaction mixture was stirred for 1 h at –45 ºC.

After carrying out the same *work up* as described in General Procedure in Section 3.2, ^{1}H NMR spectrum of the crude showed only starting material **4a**.

3.3.1.4. Effect of the concentration

The reaction was carried out according to the General Procedure in section 3.2. from thioimide **4a** (140 mg, 0.50 mmol), $(Ph_3P)_2NiCl_2$ (32.7 mg, 0.05 mmol), benzaldehyde dimethyl acetal (113 μL, 0.75 mmol), TESOTf (147 μL, 0.65 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and anh CH_2Cl_2 (10 mL) at –20 ºC for 2.5 h.

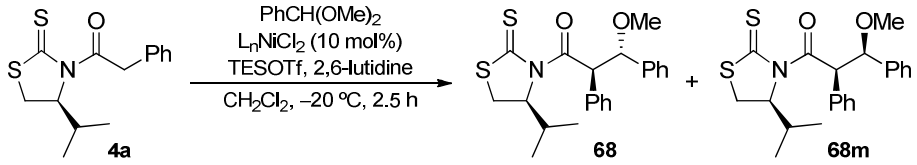
After the usual reaction mixture treatment described in General Procedure in section 3.2, the ^1H NMR spectrum of the crude showed a conversion of 79% with a d.r. of 65:35.

3.3.2. Further optimization with thioimide 4a

3.3.2.1. Effect of the catalyst

The reactions were carried out according to the General Procedure in section 3.2. from thioimide **4a** (140 mg, 0.50 mmol), 10 mol% of the corresponding nickel(II) catalyst (0.05 mmol) shown in Table 45, benzaldehyde dimethyl acetal (113 μL, 0.75 mmol), TESOTf (147 μL, 0.65 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and anh CH_2Cl_2 (1.0 mL) at –20 ºC for 2.5 h.

After the usual reaction mixture treatment described in General Procedure in section 3.2, the crudes were analyzed by ^1H NMR without further purification.



Entry	L_nNiCl_2	d.r.[a]	Conversion (%)[a]
1	$(Ph_3P)_2NiCl_2$	65:35	94
2	$(dppe)NiCl_2$	60:40	100
3	$(dppp)NiCl_2$	55:45	100
4	$(Me_3P)_2NiCl_2$	60:40	89
5	$(Chx_3P)_2NiCl_2$	60:40	33

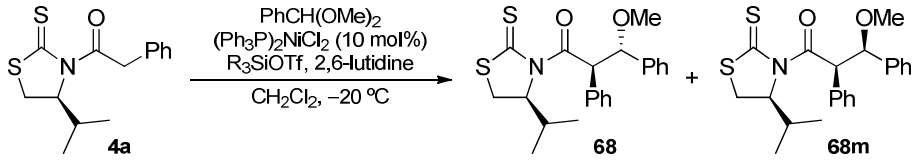
[a] Established by ^1H NMR analysis of the crude product.

Table 45

3.3.2.2. Effect of the silyl triflate

The reactions were carried out according to the General Procedure in section 3.2. from thioimide **4a** (140 mg, 0.50 mmol), $(Ph_3P)_2NiCl_2$ (32.7 mg, 0.05 mmol), benzaldehyde dimethyl acetal (113 μL, 0.75 mmol), the corresponding silyl triflate (0.65 mmol) shown in Table 46, 2,6-lutidine (88 μL, 0.75 mmol) and anh CH_2Cl_2 (1.0 mL) at –20 ºC during the reaction times displayed in Table 46.

After the usual reaction mixture treatment described in General Procedure in section 3.2, the crudes were analyzed by ^1H NMR without further purification.



Entry	Lewis acid	t (h)	d.r.[a]	Conversion (%)[a]
1	TMSOTf	0.3	63:37	44
2	TMSOTf	2.5	64:36	45
3	TESOTf	0.3	65:35	61
4	TESOTf	2.5	65:35	94
5	TBSOTf	0.3	60:40	30
6	TBSOTf	2.5	62:38	80

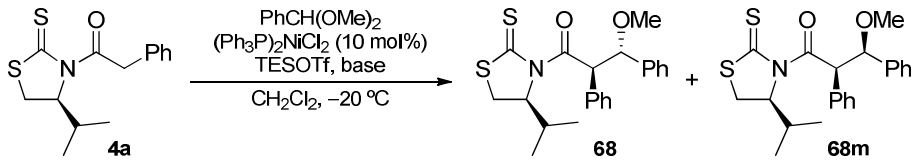
[a] Established by ^{1}H NMR analysis of the crude product.

Table 46

3.3.2.3. Effect of the base

The reactions were carried out according to the General Procedure in section 3.2. from thioimide **4a** (140 mg, 0.50 mmol), $(Ph_3P)_2NiCl_2$ (32.7 mg, 0.05 mmol), benzaldehyde dimethyl acetal (113 μL, 0.75 mmol), TESOTf (147 μL, 0.65 mmol), the corresponding base (0.75 mmol) shown in Table 47 and anh CH_2Cl_2 (1.0 mL) at –20 ºC during the reaction times displayed in Table 47.

After the usual reaction mixture treatment described in General Procedure in section 3.2, the crudes were analyzed by ^{1}H NMR without further purification.



Entry	Base	t (h)	d.r.[a]	Conversion (%)[a]
1	Et_3N	0.3	55:45	35
2	Et_3N	1.0	55:45	37
3	Et_3N	2.5	55:45	39
4	Hex_3N	0.3	56:44	22
5	Hex_3N	1.0	56:44	25
6	Hex_3N	2.5	56:44	26
7	DIPEA[b]	0.3	55:45	79
8	DIPEA[b]	1.0	55:45	80
9	DIPEA[b]	2.5	55:45	84
10	NMM[c]	0.3	–	n.r.
11	NMM[c]	1.0	–	n.r.
12	TMP[d]	0.3	57:43	55
13	TMP[d]	1.0	57:43	61
14	TMP[d]	2.5	57:43	66
15	Pyridine	0.3	–	n.r.
16	Pyridine	1.0	–	n.r.
17	2,6-Lutidine	2.5	65:35	94
18	DTBMP[e]	0.3	–	n.r.
19	DTBMP[e]	1.0	–	n.r.

[a] Established by ^{1}H NMR analysis of the crude product.
[b] Diisopropylethylamine.
[c] *N*-Methylmorpholine.
[d] 2,2,6,6-Tetramethylpiperidine.
[e] 2,6-Di(*tert*-butyl)-4-methylpyridine.

Table 47

3.3.2.4. Attempt to use DIPEA with a temperature of –78 ºC

Solid $(Ph_3P)_2NiCl_2$ (32.7 mg, 0.05 mmol) was added to a solution of **4a** (140 mg, 0.50 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2 at r.t. The resulting black suspension was purged with N_2 again and then cooled to –78 ºC. TESOTf (147 µL, 0.65 mmol) and DIPEA (131 µL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred for 1 h at –78 ºC.

After the usual reaction mixture treatment described in General Procedure in Section 3.2, ^{1}H NMR spectrum of the crude product showed a conversion of 18% with a d.r. of 1:1.

3.3.2.5. Use of 1.1 equivalents of benzaldehyde dimethyl acetal

Thioimides **68** and **68m** were prepared according to the General Procedure in section 3.2. from thioimide **4a** (140 mg, 0.50 mmol), $(Ph_3P)_2NiCl_2$ (8.2 mg, 12.5 µmol), benzaldehyde dimethyl acetal (83

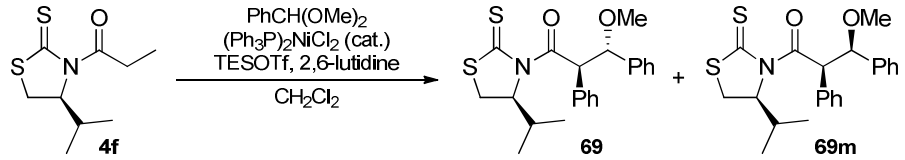
μL, 0.55 mmol), TESOTf (130 μL, 0.58 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and anh CH_2Cl_2 (1.0 mL) and stirring the reaction mixture for 20 min at –20 ºC and 1 h at 0 ºC. ^{1}H NMR spectrum of the crude product revealed a 65:35 ratio of the *anti/syn* diastereomers. Purification of the crude product by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/EtOAc 95:5) afforded 188 mg (0.47 mmol, 94%) of a non separable 65:35 mixture of the two diastereomeric adducts **68** and **68m**.

3.3.3. Preliminary experiments with thioimide 4f

3.3.3.1. Influence of catalyst and different reaction conditions

The reactions were carried out according to the General Procedure in section 3.2. from thioimide **4f** (109 mg, 0.50 mmol), the corresponding nickel(II) complex depicted in Table 48, benzaldehyde dimethyl acetal (113 μL, 0.75 mmol), the corresponding quantity of TESOTf shown in Table 48, 2,6-lutidine (88 μL, 0.75 mmol) and anh CH_2Cl_2 (1.0 mL) taking the temperature and reaction time shown in Table 48.

After the usual reaction mixture treatment described in General Procedure in section 3.2, the crude products were purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/CH_2Cl_2 1:1) to afford the pure *syn* adduct **69m** and an inseparable mixture of the *anti* adduct **69** and benzaldehyde dimethyl acetal. The yields of the *anti* adduct **69** shown in Table 48 were calculated from the weight of the mixture and the molar ratio determined by ^{1}H NMR between the *anti* adduct and benzaldehyde.



Entry	Catalyst	Cat. (mol%)	TESOTf (eq)	t (h)	T (ºC)	d.r.[a]	*Anti* **69** (%)[b]	*Syn* **69** (%)[c]
1	$(Ph_3P)_2NiCl_2$	20	1.5	1	0	60:40	10	7
2	$(Ph_3P)_2NiCl_2$	20	1.5	5	0	60:40	30	21
3	$(Ph_3P)_2NiCl_2$	20	1.5	22	0	60:40	41	28
4	$(Ph_3P)_2NiCl_2$	20	1.5	22	–20	60:40	7	4
5	$(dppe)NiCl_2$	20	1.5	22	–20	60:40	58	38
6	$(dppp)NiCl_2$	20	1.5	22	–20	55:45	49	42
7	$(Chx_3P)_2NiCl_2$	20	1.5	22	–20	60:40	n.r.	n.r.
8	$(Me_3P)_2NiCl_2$	20	1.5	22	–20	60:40	51	34
9	$(Me_3P)_2NiCl_2$	20	1.5	1.5	–78	60:40	n.r.	n.r.
10	$(Me_3P)_2NiCl_2$	2.5	1.15	1.5	–20	60:40	13	8
11	$(Me_3P)_2NiCl_2$	2.5	1.15	7	–20	60:40	33	22
12	$(Me_3P)_2NiCl_2$	2.5	1.15	22	–20	60:40	46	33

[a] Established by ^{1}H NMR analysis of the crude product.

[b] Calculated yield over the isolated mixture of *anti* adduct and benzaldehyde after column chromatography.

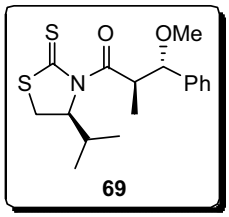
[c] Isolated yield after column chromatography.

Table 48

3.3.3.2. Use of 1.1 equivalents of benzaldehyde dimethyl acetal

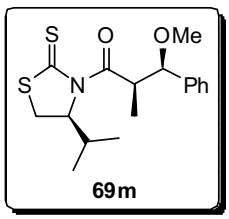
The reactions were carried out according to the General Procedure in section 3.2. from thioimide **4f** (109 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol), benzaldehyde dimethyl acetal (83 μL, 0.55 mmol), TESOTf (130 μL, 0.58 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and anh CH_2Cl_2 (1.0 mL) at –20 ºC during 22 h.

After the usual reaction mixture treatment described in General Procedure in section 3.2, the crude product was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/CH_2Cl_2 1:1) to afford 52 mg of the pure *syn* adduct **69m** (0.15 mmol, 31%) and 81 mg of the pure *anti* adduct **69** (0.24 mmol, 48%).



69

(*S*)-4-Isopropyl-*N*-[(*2R*, *3S*)-3-methoxy-2-methyl-3-phenylpropanoyl]-1,3-thiazolidine-2-thione (**69**). Yellow solid; **mp** = 82–83 ºC; $\mathbf{R_f}$ = 0.60 (CH_2Cl_2); $\mathbf{[\alpha]_D}$ = +120.0 (*c* 1.90, $CHCl_3$); **IR** (KBr) 2927, 1670, 1458, 1363, 1250, 1154 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.36–7.22 (5H, m, ArH), 5.36 (1H, ddd, *J* = 8.9, 5.5, 2.1 Hz, NCH), 5.26 (1H, dq, *J* = 9.8, 7.0 Hz, COCHCH$_3$), 4.35 (1H, d, *J* = 9.8 Hz, CHOCH$_3$), 3.46 (1H, dd, *J* = 11.5, 8.9 Hz, SCH$_a$H$_b$), 3.08 (3H, s, OCH$_3$), 3.01 (1H, dd, *J* = 11.5, 2.1 Hz, SCH$_a$H$_b$), 2.45–2.30 (1H, m, CH(CH$_3$)$_2$), 1.11 (3H, d, *J* = 6.7 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$), 1.03 (3H, d, *J* = 6.7 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$). 0.86 (3H, d, *J* = 7.0 Hz, COCHCH$_3$); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 202.6 (C), 177.7 (C), 139.1 (C), 128.3 (CH), 128.2 (CH), 128.1 (CH), 87.7 (CH), 71.9 (CH), 56.4 (CH_3), 45.1 (CH), 30.4 (CH), 28.8 (CH_2), 19.0 (CH_3),17.0 (CH_3), 14.3 (CH_3); **HRMS** (+FAB): *m/z* calculated for $[M+H]^+$ $C_{17}H_{24}NO_2S_2$: 338.1243, found: 338.1251.



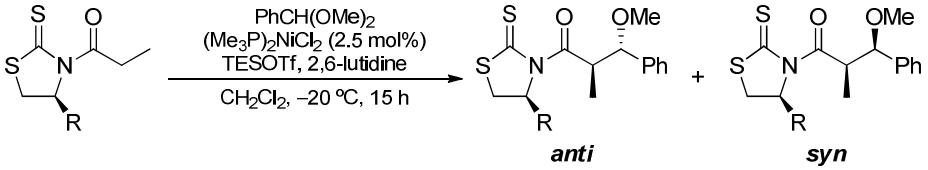
69m

(*S*)-4-Isopropyl-*N*-[(*2R*, *3R*)-3-methoxy-2-methyl-3-phenylpropanoyl]-1,3-thiazolidine-2-thione (**69m**). Yellow solid; **mp** = 61–63 ºC; $\mathbf{R_f}$ = 0.45 (CH_2Cl_2); $\mathbf{[\alpha]_D}$ = +302.1 (*c* 2.30, $CHCl_3$); **IR** (KBr) 2966, 1696, 1457, 1364, 1259, 1156 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.40–7.24 (5H, m, ArH), 5.27 (1H, dq, *J* = 6.9, 6.8 Hz, COCHCH$_3$), 5.24 (1H, ddd, *J* = 8.7, 5.2, 1.5 Hz, NCH), 4.63 (1H, d, *J* = 6.9 Hz, CHOCH$_3$), 3.29 (1H, dd, *J* = 11.5, 8.7 Hz, SCH$_a$H$_b$), 3.19 (3H, s, OCH$_3$), 2.87 (1H, dd, *J* = 11.5, 1.5 Hz, SCH$_a$H$_b$), 1.83 (1H, heptd, *J* = 6.9, 5.2 Hz, CH(CH$_3$)$_2$), 1.24 (3H, d, *J* = 6.8 Hz, COCHCH$_3$), 0.80 (3H, d, *J* = 6.9 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$), 0.71 (3H, d, *J* = 6.9 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 202.3 (C), 175.0 (C), 139.3 (C), 128.1 (CH), 127.8 (CH), 127.7 (CH), 84.1 (CH), 71.4 (CH), 56.7 (CH_3), 45.3 (CH), 30.6 (CH), 28.5 (CH_2), 18.6 (CH_3), 16.9 (CH_3), 13.3 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{17}H_{24}NO_2S_2$: 338.1243, found: 338.1233.

3.3.4. Influence of the chiral auxiliary

The reactions were carried out according to the General Procedure in section 3.2. from the corresponding thioimide shown in Table 49 (0.50 mmol), $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol), benzaldehyde dimethyl acetal (83 μL, 0.55 mmol), TESOTf (130 μL, 0.58 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and anh CH_2Cl_2 (1.0 mL) at –20 ºC during 15 h.

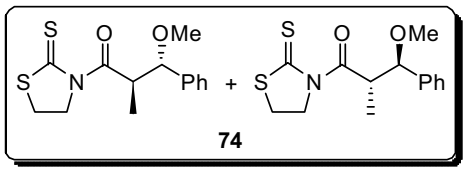
After the usual reaction mixture treatment described in General Procedure in section 3.2, the crude product was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/CH_2Cl_2 1:1) to afford the isolated pure *anti* adduct and the isolated pure *syn* adduct.



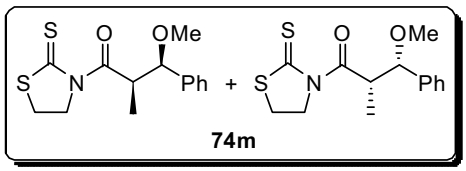
Entry	R	d.r.[a]	*Anti* (%)[b]	*Syn* (%)[b]
1	H	53:47	26	26
2[c]	Ph	58:42	51	36
3[c]	*i*-Bu	58:42	47	28
4	*i*-Pr	60:40	48	31
5	*t*-Bu	62:38	56	35

[a] Established by ^{1}H NMR analysis of the crude product.
[b] Isolated yield after column chromatography.
[c] Carried out by Javier Fernández-Valparís.[53] Use of 1.5 equivalents of TESOTf.

Table 49

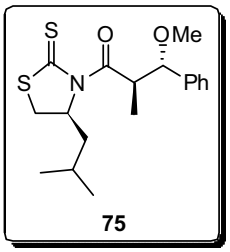


Anti-N-(3-Methoxy-2-methyl-3-phenylpropanoyl)-1,3-thiazolidine-2-thione (**74**). Yellow oil; $\mathbf{R_f}$ = 0.68 (CH_2Cl_2); **IR** (film) 2981, 2934, 1700, 1453, 1364, 1278, 1153 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.41–7.27 (5H, m, ArH), 4.73–4.60 (2H, m, NCH_aH_b, COCH), 4.46 (1H, ddd, J = 11.9, 11.3, 7.5 Hz, NCH_aH_b), 4.34 (1H, d, J = 9.8 Hz, $CHOCH_3$), 3.43 (1H, td, J =11.3, 7.5 Hz, SCH_aH_b), 3.21 (1H, ddd, J = 11.9, 7.5, 3.2 Hz, SCH_aH_b), 3.11 (3H, s, OCH_3), 0.95 (3H, d, J = 6.8 Hz, $CHCH_3$); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 201.6, 178.6, 138.8, 128.5, 128.3, 127.9, 87.6, 56.8, 56.5, 46.2, 28.9, 14.1; **MS–CI** (NH_3): *m/z* (%) 295.9 $[M+H]^+$ (100).



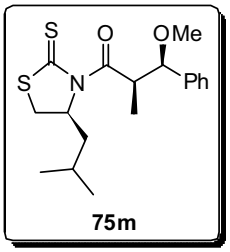
Syn-N-(3-Methoxy-2-methyl-3-phenylpropanoyl)-1,3-thiazolidine-2-thione (**74m**). Yellow oil; $\mathbf{R_f}$ = 0.71 (CH_2Cl_2); **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.40–7.27 (5H, m, ArH), 4.78 (1H, dq, J = 8.4, 6.6 Hz, COCH), 4.27 (1H, d, J = 8.4 Hz, $CHOCH_3$), 4.07 (1H, td, J = 12.0, 7.2 Hz, NCH_aH_b), 3.88 (1H, ddd, J = 12.0, 7.5, 2.3 Hz, NCH_aH_b),

3.20 (3H, s, OC$\underline{H}_3$), 2.87 (1H, ddd, *J* = 10.8, 7.2, 2.3 Hz, SC$\underline{H}_a$H$_b$), 2.65 (1H, ddd, *J* = 12.0, 10.8, 7.5 Hz, SCH$_a\underline{H}_b$), 1.38 (3H, d, *J* = 6.6 Hz, CHC$\underline{H}_3$); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 201.3, 177.2, 139.8, 128.3, 128.1, 127.5, 86.1, 56.9, 56.3, 47.5, 28.8, 13.4.



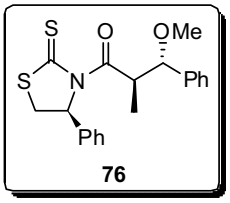
75

(*S*)-4-Isobutyl-*N*-[(*2R*, *3S*)-3-methoxy-2-methyl-3-phenylpropanoyl]-1,3-thiazolidine-2-thione (**75**). Yellow solid; **mp** = 92–94 ºC; **R$_f$** = 0.45 (hexanes/CH_2Cl_2 3:7); **IR** (ATR) 2955, 1703, 1453, 1366, 1288, 1215 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.39–7.29 (5H, m, Ar$\underline{H}$), 5.39 (1H, ddt, *J* = 10.3, 7.6, 2.7 Hz, NC$\underline{H}$), 5.08 (1H, dq, *J* = 9.9, 6.9 Hz, COC$\underline{H}$CH$_3$), 4.36 (1H, d, *J* = 9.9 Hz, C$\underline{H}$OCH$_3$), 3.53 (1H, ddd, *J* = 11.2, 7.6, 0.5 Hz, SC$\underline{H}_a$H$_b$), 3.10 (3H, s, OC$\underline{H}_3$), 2.93 (1H, dd, *J* = 11.2, 2.7 Hz, SCH$_a\underline{H}_b$), 1.93–1.84 (1H, m, CH$_2$C$\underline{H}$(CH$_3$)$_2$), 1.74–1.63 (2H, m, C$\underline{H}_2$CH(CH$_3$)$_2$), 1.02 (3H, d, *J* = 6.1 Hz, CH$_2$CH(C$\underline{H}_3$)$_a$(CH$_3$)$_b$), 1.01 (3H, d, *J* = 6.2 Hz, CH$_2$CH(CH$_3$)$_a$(C$\underline{H}_3$)$_b$), 0.88 (3H, d, *J* = 6.9 Hz, COCHC$\underline{H}_3$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 201.5, 171.9, 139.0, 128.4, 128.2, 128.0, 87.7, 66.5, 56.5, 45.5, 40.7, 33.0, 25.3, 23.6, 21.3, 14.4.



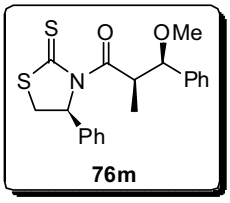
75m

(*S*)-4-Isobutyl-*N*-[(*2R*, *3R*)-3-methoxy-2-methyl-3-phenylpropanoyl]-1,3-thiazolidine-2-thione (**75m**). Yellow solid; **mp** = 97–99 ºC; **R$_f$** = 0.35 (hexanes/CH_2Cl_2 3:7); **IR** (KBr) 2956, 1691, 1452, 1336, 1289, 1251 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.40–7.20 (5H, m, Ar$\underline{H}$), 5.35–5.25 (1H, m, NC$\underline{H}$), 5.19 (1H, p, *J* = 7.0 Hz, COC$\underline{H}$CH$_3$), 4.58 (1H, d, *J* = 7.0 Hz, C$\underline{H}$OCH$_3$), 3.45 (1H, ddd, *J* = 11.2, 7.6, 1.0 Hz, SC$\underline{H}_a$H$_b$), 3.20 (3H, s, OC$\underline{H}_3$), 2.78 (1H, dd, *J* = 11.2, 1.8 Hz, SCH$_a\underline{H}_b$), 2.00–1.60 (3H, m, C$\underline{H}_2$C$\underline{H}$(CH$_3$)), 1.25 (3H, d, *J* = 7.0 Hz, COCHC$\underline{H}_3$), 0.86 (3H, d, *J* = 6.6 Hz, CH(C$\underline{H}_3$)$_a$(CH$_3$)$_b$), 0.86 (3H, d, *J* = 7.0 Hz, CH(CH$_3$)$_a$(C$\underline{H}_3$)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 201.0, 175.3, 139.4, 128.2, 128.0, 127.8, 84.1, 65.9, 56.8, 45.7, 40.0, 32.4, 25.1, 23.5, 21.1, 13.2.



76

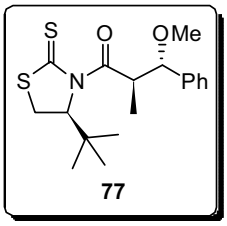
(*S*)-*N*-[(*2R*, *3S*)-3-Methoxy-2-methyl-3-phenylpropanoyl]-4-phenyl-1,3-thiazolidine-2-thione (**76**). Yellow oil; **R$_f$** = 0.25 (hexanes/CH_2Cl_2 2:3); **IR** (film) 2933, 1670, 1595, 1455, 1300, 1254, 1151 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.50–7.20 (10H, m, Ar$\underline{H}$), 6.34 (1H, dd, *J* = 8.2, 3.3 Hz, NC$\underline{H}$), 5.09 (1H, dq, *J* = 9.8, 6.9 Hz, COC$\underline{H}$CH$_3$), 4.19 (1H, d, *J* = 9.8 Hz, C$\underline{H}$OCH$_3$), 3.84 (1H, dd, *J* = 11.2, 8.2 Hz, SC$\underline{H}_a$H$_b$), 3.14 (1H, dd, *J* = 11.2, 3.3 Hz, SCH$_a\underline{H}_b$), 2.86 (3H, s, OC$\underline{H}_3$), 0.85 (1H, d, *J* = 6.9 Hz, COCHC$\underline{H}_3$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 203.3, 177.3, 139.0, 138.9, 128.7, 128.4, 128.2, 128.2, 128.0, 126.0, 87.7, 70.3, 56.5, 45.5, 36.2, 14.4.



76m

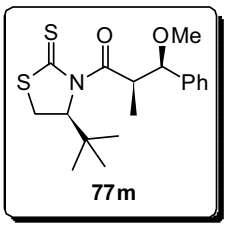
(*S*)-*N*-[(*2R*, *3R*)-3-Methoxy-2-methyl-3-phenylpropanoyl]-4-phenyl-1,3-thiazolidine-2-thione (**76m**). Yellow oil; **R$_f$** = 0.20 (hexanes/CH_2Cl_2 2:3); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.35–7.20 (8H, m, Ar$\underline{H}$), 7.10–7.03 (2H, m, Ar$\underline{H}$), 6.24 (1H, dd, *J* = 8.3, 2.1 Hz, NC$\underline{H}$), 5.22 (1H, p, *J* = 6.7 Hz, COC$\underline{H}$CH$_3$), 4.54 (1H, d, *J* = 6.6 Hz, C$\underline{H}$OCH$_3$), 3.80 (1H, dd, *J* = 11.3, 8.3 Hz, SC$\underline{H}_a$H$_b$), 3.03 (1H, s, OC$\underline{H}_3$), 3.03–2.97 (1H, m, SCH$_a\underline{H}_b$), 1.23 (3H, d, *J* = 6.7 Hz, COCHC$\underline{H}_3$); **^{13}C NMR** ($CDCl_3$, 100.6

MHz) δ 201.8, 174.9, 139.3, 138.7, 128.8, 128.1, 128.1, 127.7, 127.6, 125.4, 83.3, 69.7, 56.7, 45.8, 35.8, 13.2.



77

(*S*)-4-(*tert*-Butyl)-*N*-[(*2R*, *3S*)-3-methoxy-2-methyl-3-phenylpropanoyl]-1,3-thiazolidine-2-thione (**77**). Yellow solid; **mp** = 105–106 ºC; $\mathbf{R_f}$ = 0.50 (hexanes/CH_2Cl_2 3:7); $\mathbf{[\alpha]_D}$ = +333.4 (*c* 1.00, $CHCl_3$); **IR** (ATR) 2933, 2818, 1690, 1446, 1353, 1316, 1238, 1123, 1093, 1053, 1012 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.38–7.29 (5H, m, ArH), 5.53 (1H, dd, *J* = 8.5, 0.9 Hz, NCH), 5.42 (1H, dq, *J* = 10.0, 6.9 Hz, COCHCH$_3$), 4.37 (1H, d, *J* = 10.0 Hz, CHOCH$_3$), 3.49 (1H, dd, *J* = 11.7, 8.5 Hz, SCH$_a$H$_b$), 3.09 (1H, s, OCH$_3$), 3.07 (1H, dd, *J* = 11.7, 0.9 Hz, SCH$_a$H$_b$), 1.10 (9H, s, C(CH$_3$)$_3$), 0.80 (3H, d, *J* = 6.9 Hz, COCHCH$_3$); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 205.0, 176.3, 139.3, 128.4, 128.2, 128.1, 87.2, 72.5, 56.5, 44.1, 37.9, 29.5, 26.7, 14.3; **HRMS** (+ESI): *m/z* calculated for $[M–OMe]^+$ $C_{17}H_{22}NOS_2$: 320.1137, found: 320.1149; *m/z* calculated for $[M+H]^+$ $C_{18}H_{26}NO_2S_2$: 352.1399, found: 352.1408.



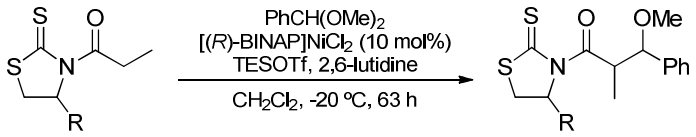
77m

(*S*)-4-(t*ert*-Butyl)-*N*-[(*2R*, *3R*)-3-methoxy-2-methyl-3-phenylpropanoyl]-1,3-thiazolidine-2-thione (**77m**). Yellow solid; **mp** = 103–104 ºC; $\mathbf{R_f}$ = 0.40 (hexanes/CH_2Cl_2 3:7); $\mathbf{[\alpha]_D}$ = +491.8 (*c* 1.10, $CHCl_3$); **IR** (ATR) 2962, 2870, 2818, 1694, 1446, 1353, 1242, 1138, 1086 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.45–7.42 (2H, m, ArH), 7.33–7.22 (3H, m, ArH), 5.35 (1H, dd, *J* = 8.4, 0.7 Hz, NCH), 5.20 (1H, p, *J* = 6.8 Hz, COCHCH$_3$), 4.69 (1H, d, *J* = 6.8 Hz, CHOCH$_3$), 3.42 (1H, dd, *J* = 11.8, 8.4 Hz, SCH$_a$H$_b$), 3.18 (1H, s, OCH$_3$), 3.02 (1H, dd, *J* = 11.8, 0.7 Hz, SCH$_a$H$_b$), 1.22 (3H, d, *J* = 6.8 Hz, COCHCH$_3$), 0.80 (9H, s, C(CH$_3$)$_3$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 205.0, 173.9, 139.4, 128.1, 128.0, 127.7, 84.0, 72.1, 56.6, 44.4, 37.4, 29.7, 26.4, 13.4.

3.3.5. Influence of chiral ligands in the catalyst

The reactions were carried out according to the General Procedure in section 3.2. from the corresponding thioimide shown in Table 50 (0.50 mmol), [(*R*)-BINAP]$NiCl_2$ (see Section 3.1.4 for its preparation) (37.7 mg, 0.05 mmol), benzaldehyde dimethyl acetal (83 µL, 0.55 mmol), TESOTf (147 µL, 0.65 mmol), 2,6-lutidine (88 µL, 0.75 mmol) and anh CH_2Cl_2 (1.0 mL) at –20 ºC during 63 h.

After the usual reaction mixture treatment described in General Procedure in section 3.2, the crude was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) to afford the isolated pure *anti* and *syn* adducts separately. The results are summarized in Table 50.



Entry	Substrate	R	d.r.[a]	*Anti* adduct	*Syn* adduct	*Anti* (%)[b]	*Syn* (%)[b]
1	**74**	H	52:48	**74**	**74m**	32	30
2	**4f**	(*S*)-*i*Pr	47:53	**69**	**69m**	44	47
3	**ent–4f**	(*R*)-*i*Pr	52:48	**ent–69**	**ent–69m**	26	24

[a] Established by ^{1}H NMR analysis of the crude product.
[b] Isolated yield after column chromatography.

Table 50

3.4. SCOPE OF THE REACTION WITH 4a

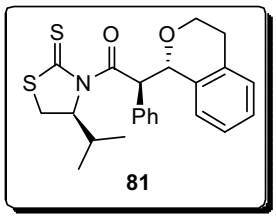
3.4.1. General procedure

Solid $(Ph_3P)_2NiCl_2$ (8.2 mg, 12.5 μmol) was added to a solution of the *N*-phenylacetyl thioimide **4a** (140 mg, 0.50 mmol) and the corresponding dimethyl acetal (0.55 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2 at r.t. The resulting mixture was purged with N_2 again and then cooled to –20 ºC. TESOTf (130 μL, 0.58 mmol) and 2,6-lutidine (88 μL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred for 20 min at –20 ºC and then stirred for 1 h at 0 ºC.

The reaction was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) to give the desired products.

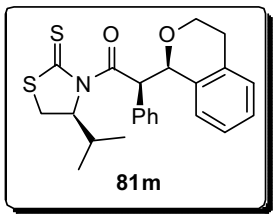
3.4.2. (*S*)-*N*-[(*R*)-2-[(*S*)-Isochroman-1-yl]-2-phenylacetyl]-4-isopropyl-1,3-thiazolidine-2-thione (81)

The β–methoxycarboxylic product **81** was prepared according to the General Procedure in Section 3.4.1. from thioimide **4a** (140 mg, 0.50 mmol), $(Ph_3P)_2NiCl_2$ (8.2 mg, 12.5 μmol), 1-methoxyisochroman **79** (90 mg, 0.55 mmol), TESOTf (130 μL, 0.58 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 20 min and at 0 ºC for 1 h. A 65:35 diastereomeric ratio of the *anti/syn* diastereomers was established by ^{1}H NMR of the crude product. Purification of the crude product by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/CH_2Cl_2 2:3) afforded 180 mg of a mixture of *anti* adduct **81**, *syn* adduct **81m** and acetal **79** in a 1.85:1.00:1.06 molar ratio. The overall calculated yield of the *anti* and *syn* diastereomers was 81% (0.40 mmol).



81

(*S*)-*N*-[(*R*)-2-[(*S*)-Isochroman-1-yl]-2-phenylacetyl]-4-isopropyl-1,3-thiazolidine-2-thione (**81**). Yellow solid; $\mathbf{R_f}$ = 0.25 (hexanes/CH_2Cl_2 3:7); **IR** (ATR) 3022, 2959, 2867, 1687, 1453, 1352, 1331, 1239, 1141, 1088 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.29–7.04 (7H, m, ArH), 6.87 (1H, d, *J* = 9.5 Hz, COCH), 6.74–6.70 (1H, m, ArH), 5.96 (1H, d, *J* = 7.8 Hz, ArH), 5.48 (1H, d, *J* = 9.5 Hz, COCHCH), 5.25 (1H, ddd, *J* = 7.0, 5.8, 1.2 Hz, NCH), 4.31 (1H, ddd, *J* = 11.4, 7.2, 4.9 Hz, OCH_aH_b), 3.85 (1H, dt, *J* = 11.4, 5.5 Hz, OCH_aH_b), 3.21 (1H, dd, *J* = 11.5, 8.2 Hz, SCH_aH_b), 3.06–2.84 (3H, m, SCH_aH_b, OCH_2CH_2), 2.50–2.38 (1H, m, $CH(CH_3)_2$), 1.07 (3H, d, *J* = 6.8 Hz, $NCHCH(CH_3)_a(CH_3)_b$), 1.01 (3H, d, *J* = 7.0 Hz, $NCHCH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 203.1 (C), 172.6 (C), 134.7 (C), 134.4 (C), 134.1 (C), 130.2 (CH), 128.4 (CH), 128.4 (CH), 127.9 (CH), 126.6 (CH), 125.9 (CH), 124.7 (CH), 77.9 (CH), 72.2 (CH), 61.8 (CH_2), 54.0 (CH), 30.7 (CH), 29.0 (CH_2), 28.8 (CH_2), 19.0 (CH_3), 17.5 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+C_{23}H_{26}NO_2S_2$: 412.1399, found: 412.1394.



81m

(*S*)-*N*-[(*R*)-2-[(*R*)-isochroman-1-yl]-2-phenylacetyl]-4-isopropyl-1,3-thiazolidine-2-thione (**81m**). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.29–6.95 (9H, m, ArH), 6.78 (1H, d, *J* = 4.9 Hz, COCH), 5.75 (1H, d, *J* = 4.9 Hz, COCHCH), 5.19 (1H, ddd, *J* = 8.5, 5.3, 1.7 Hz, NCH), 4.11–4.07 (1H, m, OCH_aH_b), 3.67 (1H, ddd, *J* = 11.0, 10.0, 3.7 Hz, OCH_aH_b), 3.31 (1H, dd, *J* = 11.4, 8.5 Hz, SCH_aH_b), 3.06–2.84 (1H, m, SCH_aH_b), 2.74 (1H, ddd, *J* = 15.7, 10.0, 5.4 Hz, $OCH_2CH_aH_b$), 2.53 (1H, dt, *J* = 15.7, 3.7 Hz, $OCH_2CH_aH_b$), 2.50–2.38 (1H, m, $CH(CH_3)_2$), 1.04 (3H, d, *J* = 6.8 Hz, $NCHCH(CH_3)_a(CH_3)_b$), 1.01 (3H, d, *J* = 7.0 Hz, $NCHCH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.7 (C), 173.0 (C), 135.2 (C), 134.8 (C), 134.5 (C), 130.6 (CH), 128.5 (CH), 127.6 (CH), 127.1 (CH), 126.6 (CH), 126.4 (CH), 125.5 (CH), 76.2 (CH), 72.7 (CH), 63.5 (CH_2), 55.1 (CH), 30.7 (CH), 29.2 (CH_2), 28.6 (CH_2), 19.0 (CH_3), 17.0 (CH_3)

3.4.3. Attempt with (*E*)-α-methylcinnamaldehyde dimethyl acetal (78)

The reaction was carried out according to the General Procedure in section 3.4.1. from thioimide **4a** (140 mg, 0.50 mmol), $(Ph_3P)_2NiCl_2$ (8.2 mg, 12.5 μmol), (*E*)-α-methylcinnamaldehyde dimethyl acetal **78** (106 mg, 0.55 mmol), TESOTf (130 μL, 0.58 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 20 min and at 0 ºC for 1 h.

After the usual reaction mixture treatment indicated in the General Procedure in section 3.4.1, ^{1}H NMR analysis of the crude product showed the presence of a complex mixture.

3.4.4. Attempt with 2-methoxy-2*H*-chromene (80)

The reaction was carried out according to the General Procedure in section 3.4.1. from thioimide **4a** (140 mg, 0.50 mmol), $(Ph_3P)_2NiCl_2$ (8.2 mg, 12.5 μmol), 2-methoxy-2*H*-chromene **80** (89 mg, 0.55

mmol), TESOTf (130 μL, 0.58 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 20 min and at 0 ºC for 1 h.

After the usual reaction mixture treatment indicated in the General Procedure in section 3.4.1, ^1H NMR analysis of the crude product showed the presence of a complex mixture.

3.4.5. Attempt to use formaldehyde dimethyl acetal

The reaction was carried out according to the General Procedure in section 3.4.1. from thioimide **4a** (140 mg, 0.50 mmol), $(Ph_3P)_2NiCl_2$ (0.10 mg, 0.20 mmol), formaldehyde dimethyl acetal (67 μL, 0.75 mmol), TESOTf (170 μL, 0.75 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 20 min and at 0 ºC for 16 h.

After the usual reaction mixture treatment indicated in the General Procedure in section 3.4.1, ^1H NMR analysis of the crude product showed the presence of a complex mixture.

3.5. SCOPE OF THE REACTION WITH 4f

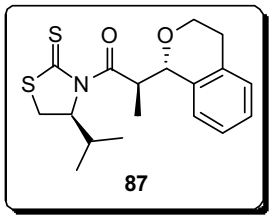
3.5.1. General procedure

Solid $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol) was added to a solution of thioimide **4f** (109 mg, 0.50 mmol) and the corresponding dimethyl acetal (0.55 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2 at r.t. The resulting mixture was purged with N_2 again and then cooled to –20 ºC. TESOTf (130 μL, 0.58 mmol) and 2,6-lutidine (88 μL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred for a certain time at –20 ºC.

The reaction was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) to give the desired products.

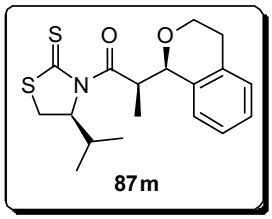
3.5.2. (*S*)-*N*-[(*R*)-2-[(*S*)-Isochroman-1-yl]propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (87)

The thioimide **87** was prepared according to the General Procedure in section 3.5.1. from thioimide **4f** (109 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol), 1-methoxyisochroman (**79**) (90 mg, 0.55 mmol), TESOTf (130 μL, 0.58 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 1.5 h. A 55:45 diastereomeric ratio of the *anti/syn* diastereomers was established by ^{1}H NMR of the crude product. Purification of the crude product by flash column chromatography on deactivated silica gel (2.5% Et_3N) (from hexanes/CH_2Cl_2 1:1 to CH_2Cl_2) afforded 78 mg of the pure *anti* adduct **87** (0.23 mmol, 45%) and 61 mg of the *syn* adduct **87m** (0.17 mmol, 35%).



87

(*S*)-*N*-[(*R*)-2-[(*S*)-Isochroman-1-yl]propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**87**). Yellow oil; $\mathbf{R_f}$= 0.15 (hexanes/CH_2Cl_2 7:3); $[\boldsymbol{\alpha}]_\mathbf{D}$ = +195.2 (*c* 1.95, $CHCl_3$); **IR** (ATR) 2959, 2974, 2869, 1693, 1450, 1352, 1236, 1144, 1086 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.20–7.11 (4H, m, ArH), 5.53 (1H, p, *J* = 7.1 Hz, COCH), 5.27 (1H, ddd, *J* = 8.6, 5.3, 1.5 Hz, NCH), 5.04 (1H, d, *J* = 7.1 Hz, COCHCH), 4.24 (1H, dt, *J* = 11.1, 4.7 Hz, OCH_aH_b), 3.75 (1H, ddd, *J* = 11.1, 8.4, 4.7 Hz, OCH_aH_b), 3.42 (1H, dd, *J* = 11.5, 8.6 Hz, SCH_aH_b), 3.02 (1H, ddd, *J* = 16.1, 8.4, 4.7 Hz, $OCH_2CH_aH_b$), 2.93 (1H, dd, *J* = 11.5, 1.5 Hz, SCH_aH_b), 2.75 (1H, dt, *J* = 16.1, 4.7 Hz, $OCH_2CH_aH_b$), 2.23–2.15 (1H, m, $CH(CH_3)_2$), 1.26 (3H, d, *J* = 7.1 Hz, COCHCH$_3$), 0.98 (3H, d, *J* = 6.8 Hz, NCHCH(CH_3)$_a$(CH_3)$_b$), 0.87 (3H, d, *J* = 7.0 Hz, NCHCH(CH_3)$_a$(CH_3)$_b$); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 202.8 (C), 175.7 (C), 135.6 (C), 134.6 (C), 128.7 (CH), 126.7 (CH), 126.0 (CH), 125.6 (CH), 77.6 (CH), 71.8 (CH), 62.8 (CH_2), 43.4 (CH), 30.7 (CH), 28.8 (CH_2), 28.6 (CH_2), 18.9 (CH_3), 17.0 (CH_3), 14.7 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{18}H_{24}NO_2S_2$: 350.1243, found: 350.1240.



(*S*)-*N*-[(*R*)-2-[(*R*)-Isochroman-1-yl]propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**87m**). Yellow oil; $\mathbf{R_f}$ = 0.35 (hexanes/CH_2Cl_2 7:3); $\mathbf{[\alpha]_D}$ = +152.0 (*c* 1.55, $CHCl_3$); **IR** (ATR) 2957, 2930, 2848, 1706, 1450, 1368, 1249, 1149, 1125, 1112, 1075 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.33–7.31 (1H, dd, *J* = 7.3, 2.0 Hz, ArH), 7.22–7.14 (2H, m, ArH), 7.09–7.07 (1H, dd, *J* = 7.1, 2.1 Hz, ArH), 5.54 (1H, d, *J* = 2.6 Hz, COCHCH), 5.50 (1H, ddd, *J* = 9.4, 4.4, 2.5 Hz, NCH), 5.37 (1H, qd, *J* = 6.8, 2.6 Hz, COCH), 4.15 (1H, ddd, *J* = 11.3, 5.8, 1.5 Hz, OCH_aH_b), 3.66 (1H, td, *J* = 11.3, 3.0 Hz, OCH_aH_b), 3.49 (1H, dd, *J* = 11.5, 9.4 Hz, SCH_aH_b), 3.11–3.02 (1H, m, $OCH_2CH_aH_b$), 3.04 (1H, dd, *J* = 11.5, 2.5 Hz, SCH_aH_b), 2.54 (1H, m, $OCH_2CH_aH_b$), 2.39 (1H, m, $CH(CH_3)_2$), 1.05 (3H, d, *J* = 6.8 Hz, $COCHCH_3$), 0.99 (3H, d, *J* = 7.0 Hz, $NCHCH(CH_3)_a(CH_3)_b$), 0.96 (3H, d, *J* = 6.7 Hz, $NCHCH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 202.0 (C), 175.6 (C), 135.3 (C), 134.7 (C), 128.8 (CH), 126.5 (CH), 126.4 (CH), 125.0 (CH), 76.6 (CH), 72.3 (CH), 64.4 (CH_2), 45.6 (CH), 30.6 (CH), 28.8 (CH_2), 28.3 (CH_2), 18.9 (CH_3), 16.2 (CH_3), 9.2 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{18}H_{24}NO_2S_2$: 350.1243, found: 350.1239.

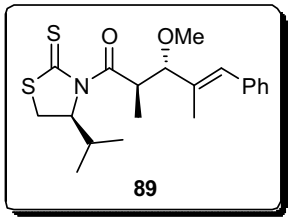
3.5.3. Attempt with 2-methoxy-2*H*-chromene (80)

The reaction was carried out according to the General Procedure in section 3.5.1. from thioimide **4f** (109 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol), 2-methoxy-2*H*-chromene (**80**) (89 mg, 0.55 mmol), TESOTf (130 μL, 0.58 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 1.5 h.

After the usual reaction mixture treatment indicated in the General Procedure in section 3.5.1, ^{1}H NMR analysis of the crude product showed the presence of a complex mixture.

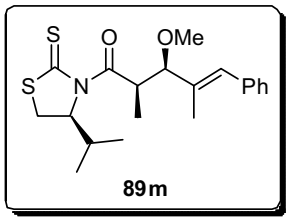
3.5.4. (*S*)-4-Isopropyl-*N*-[(*2R*, *3S*)-3-methoxy-2,4-dimethyl-5-phenylpent-4-enoyl]-1,3-thiazolidine-2-thione (89)

The thioimide **89** was prepared according to the General Procedure in section 3.5.1. from thioimide **4f** (109 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol), (*E*)-α-methylcinnamaldehyde dimethyl acetal (**78**) (106 mg, 0.55 mmol), TESOTf (130 μL, 0.58 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 1.5 h. A 83:17 diastereomeric ratio of the *anti/syn* diastereomers was established by ^{1}H NMR of the crude product. Purification of the crude product by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/CH_2Cl_2 1:1) afforded 149 mg of the pure *anti* adduct **89** (0.40 mmol, 79%) and 34 mg of the *syn* adduct **89m** (0.09 mmol, 18%).



89

(*S*)-4-Isopropyl-*N*-[(*2R*, *3S*)-3-methoxy-2,4-dimethyl-5-phenylpent-4-enoyl]-1,3-thiazolidine-2-thione (**89**).Yellow oil; $\mathbf{R_f}$ = 0.75 (CH_2Cl_2); $\mathbf{[\alpha]_D}$ = +178.7 (*c* 1.20, $CHCl_3$); **IR** (film) 2940, 1690, 1440, 1365, 1240, 1150 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.37–7.22 (5H, m, ArH), 6.53 (1H, br s, C=CHPh), 5.34 (1H, ddd, *J* = 8.7, 5.4, 2.1 Hz, NCH), 5.21 (1H, dq, *J* = 9.9, 6.8 Hz, COCH), 3.93 (1H, d, *J* = 9.9 Hz, $CHOCH_3$), 3.44 (1H, dd, *J* = 11.4, 8.7 Hz, SCH_aH_b), 3.17 (3H, s, OCH_3), 2.98 (1H, dd, *J* = 11.4, 2.1 Hz, SCH_aH_b), 2.40–2.32 (1H, m, $CH(CH_3)_2$), 1.82 (3H, d, *J* = 1.4 Hz, CH_3C=CH), 1.08 (3H, d, *J* = 6.6 Hz, $CH(CH_3)_a(CH_3)_b$), 1.03 (3H, d, *J* = 6.8 Hz, $COCHCH_3$), 1.01 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.6 (C), 177.8 (C), 137.0 (C), 135.0 (C), 131.1 (CH), 129.0 (CH), 128.1 (CH), 126.7 (CH), 91.8 (CH), 71.9 (CH), 55.9 (CH_3), 41.3 (CH), 30.3 (CH), 28.7 (CH_2), 19.0 (CH_3), 16.8 (CH_3), 14.2 (CH_3), 12.1 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OMe]^+$ $C_{19}H_{24}NOS_2$: 346.1294, found: 346.1284.

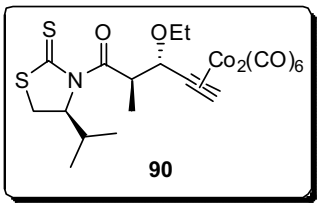


89m

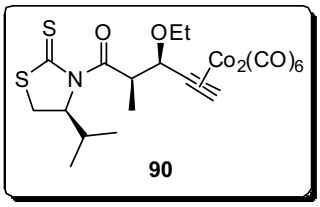
(*S*)-4-Isopropyl-*N*-[(*2R*, *3S*)-3-methoxy-2,4-dimethyl-5-phenylpent-4-enoyl]-1,3-thiazolidine-2-thione (**89m**). Yellow oil; $\mathbf{R_f}$ = 0.50 (hexanes/CH_2Cl_2 1:4); $\mathbf{[\alpha]_D}$ = +163.2 (*c* 0.60, $CHCl_3$); **IR** (ATR) 2959, 2925, 1690, 1442, 1363, 1244, 1146, 1086 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.34–7.19 (5H, m, ArH), 6.51 (1H, br s, C=CHPh), 5.31–5.24 (2H, m, NCH, COCH), 4.07 (1H, d, *J* = 8.1 Hz, $CHOCH_3$), 3.43 (1H, dd, *J* = 11.5, 8.6 Hz, SCH_aH_b), 3.28 (3H, s, OCH_3), 2.91 (1H, dd, *J* = 11.5, 1.3 Hz, SCH_aH_b), 2.21–2.11 (1H, m, $CH(CH_3)_2$), 1.87 (3H, d, *J* = 1.3 Hz, CH_3C=CH), 1.27 (3H, d, *J* = 6.8 Hz, $COCHCH_3$), 0.89 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(CH_3)_b$), 0.84 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.6 (C), 175.3 (C), 137.4 (C), 135.0 (C), 129.8 (CH), 129.0 (CH), 128.0 (CH), 126.5 (CH), 87.8 (CH), 71.5 (CH), 56.4 (CH_3), 41.8 (CH), 30.8 (CH), 28.7 (CH_2), 19.0 (CH_3), 17.0 (CH_3), 14.1 (CH_3), 13.8 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OMe]^+$ $C_{19}H_{24}NOS_2$: 346.1294, found: 346.1300.

3.5.5. (*S*)-*N*-[(*2R*,*3S*)-Hexacarbonyl[μ-η^4-(3-ethoxy-2-methyl-4-pentynoyl)dicobalt (*Co-Co*)]-4-isopropyl -1,3-thiazolidine-2-thione (90)

The thioimide **90** was prepared according to the General Procedure in section 3.5.1. from thioimide **4f** (109 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol), hexacarbonyl μ-[η^4-(1,1-diethoxypropyne)dicobalt (**88**) (228 mg, 0.55 mmol), TESOTf (130 μL, 0.58 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 22 h. A 77:23 diastereomeric ratio of the *anti/syn* diastereomers was established by ^{1}H NMR of the crude product. Purification of the crude product by flash column chromatography on silica gel (hexanes/CH_2Cl_2 3:2) afforded 179 mg of the pure *anti* adduct **90** (0.31 mmol, 61%) and 69 mg of a 1.46:1 mixture of starting material **4f** and the *syn* adduct **90m** (0.09 mmol, 19%).



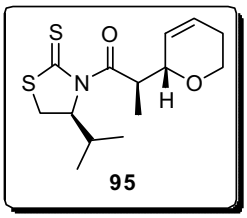
(*S*)-*N*-[(*2R, 3S*)-Hexacarbonyl[μ-η^4-(3-ethoxy-2-methyl-4-pentynoyl)dicobalt (*Co-Co*)]-4-isopropyl-1,3-thiazolidine-2-thione (**90**). Red oil; $\mathbf{R_f}$ = 0.40 (hexanes/CH_2Cl_2 1:1); $\mathbf{[\alpha]_D}$ = +849.0 (c 0.01, CH_2Cl_2); **IR** (film) 2920, 2070, 2030, 2000, 1680, 1340, 1240, 1140 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 6.05 (1H, br s, C[$Co_2(CO)_6$]H), 5.31 (1H, ddd, *J* = 8.5, 6.0, 1.2 Hz, NCH), 5.03 (1H, dq, *J* = 9.8, 6.9 Hz, COCHCH$_3$), 4.67 (1H, d, *J* = 9.8 Hz, CHOCH$_2$CH$_3$), 3.82 (1H, p, *J* = 7.2 Hz, OCH$_a$H$_b$CH$_3$), 3.61 (1H, p, *J* = 7.2 Hz, OCH$_a$H$_b$CH$_3$), 3.47 (1H, dd, *J* = 11.5, 8.5 Hz, SCH$_a$H$_b$), 2.98 (1H, dd, *J* = 11.5, 1.2 Hz, SCH$_a$H$_b$), 2.42–2.30 (1H, m, CH(CH$_3$)$_2$), 1.22 (3H, d, *J* = 6.9 Hz, COCHCH$_3$), 1.12 (3H, t, *J* = 7.2 Hz, OCH$_2$CH$_3$), 1.09 (3H, d, *J* = 6.8 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$), 1.02 (3H, d, *J* = 7.0 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.4, 199.5, 175.7, 93.4, 82.3, 73.0, 71.6, 66.6, 45.7, 30.6, 29.0, 19.1, 17.3, 14.9, 14.7; **HRMS** (+FAB): *m/z* calculated for $[M–6CO]^+$ $C_{16}H_{21}NO_4S_2Co_2$: 472.7576, found: 472.9565.



(*S*)-*N*-[(*2R, 3R*)-Hexacarbonyl[μ-η^4-(3-ethoxy-2-methyl-4-pentynoyl)dicobalt (*Co-Co*)]-4-isopropyl-1,3-thiazolidine-2-thione (**90**). Red oil; $\mathbf{R_f}$ = 0.30 (hexanes/CH_2Cl_2 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.88 (1H, br s, C[$Co_2(CO)_6$]H), 5.16 (1H, ddd, *J* = 8.2, 5.7, 1.0 Hz, NCH), 4.95–4.86 (2H, m, COCHCH), 3.88 (1H, dq, *J* = 13.9, 7.0 Hz, OCH$_a$H$_b$CH$_3$), 3.63 (1H, dq, *J* = 13.9, 7.0 Hz, OCH$_a$H$_b$CH$_3$), 3.49 (1H, dd, *J* = 11.5, 8.2 Hz, SCH$_a$H$_b$), 3.02 (1H, dd, *J* = 11.5, 1.0 Hz, SCH$_a$H$_b$), 2.44–2.31 (1H, m, CH(CH$_3$)$_2$), 1.33 (3H, d, *J* = 6.3 Hz, COCHCH$_3$), 1.23 (3H, t, *J* = 7.0 Hz, OCH$_2$CH$_3$), 1.10 (3H, d, *J* = 6.8 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$), 1.04 (3H, d, *J* = 6.9 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$).

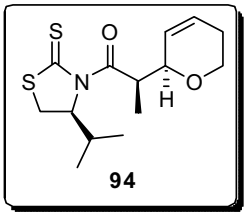
3.5.6. (*R*)- and (*S*)-*N*-[(*R*)-2-[(*S*)-5,6-Dihydro-2*H*-pyran-2-yl]propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (94 and 95)

The thioimides **94** and **95** were prepared according to the General Procedure in section 3.5.1. from thioimide **4f** (109 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol), 2-ethoxy-5,6-dihydro-2H-pyran (**93**) (71 mg, 0.55 mmol), TESOTf (130 μL, 0.58 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 22 h. A 1:1 diastereomeric ratio of the diastereomers **94** and **95** was established by ^{1}H NMR of the crude product. Purification of the crude product by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/CH_2Cl_2 3:7) afforded 35 mg of the pure *anti* adduct **95** (0.13 mmol, 25%) and 37 mg of the pure *syn* adduct **94** (0.13 mmol, 26%).



95

(*S*)-*N*-[(*R*)-2-[(*S*)-5,6-Dihydro-2*H*-pyran-2-yl]propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**95**). Yellow oil; $\mathbf{R_f}$= 0.35 (CH_2Cl_2); $\mathbf{[\alpha]_D}$ = +272.0 (*c* 1.00, $CHCl_3$); **IR** (film) 2964, 2927, 1710, 1374, 1258, 1158, 1079 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.96–5.91 (1H, m, OCHCH=C<u>H</u>), 5.65–5.61 (1H, m, OCHC<u>H</u>=CH), 5.37 (1H, ddd, *J* = 8.8, 5.3, 2.0 Hz, NC<u>H</u>), 4.87 (1H, qd, *J* = 6.8, 4.0 Hz, COC<u>H</u>CH_3), 4.72–4.68 (1H, m, OC<u>H</u>CH=CH), 3.96 (1H, dddd, *J* = 11.1, 5.7, 2.0, 1.1 Hz, OC<u>H$_a$</u>H$_b$), 3.61 (1H, ddd, *J* = 11.1, 10.4, 3.7, OCH$_a$<u>H$_b$</u>), 3.47 (1H, dd, *J* = 11.4, 8.8 Hz, SC<u>H$_a$</u>H$_b$), 3.00 (1H, dd, *J* = 11.4, 2.0 Hz, SCH$_a$<u>H$_b$</u>), 2.39–2.23 (2H, m, C<u>H</u>$(CH_3)_2$, CH=CHC<u>H$_a$</u>H$_b$), 1.91–1.83 (1H, m, CH=CHCH$_a$<u>H$_b$</u>), 1.15 (3H, d, *J* = 6.8 Hz, COCHC<u>H$_3$</u>), 1.04 (3H, d, *J* = 6.8 Hz, CH(C<u>H$_3$</u>)$_a$$(CH_3)_b$), 0.97 (3H,d, *J* = 7.0 Hz, CH$(CH_3)_a$(C<u>H$_3$</u>)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.3 (C), 175.5 (C), 127.9 (CH), 126.5 (CH), 74.8 (CH), 72.0 (CH), 63.7 (CH_2), 43.3 (CH), 30.7 (CH), 29.0 (CH_2), 24.8 (CH_2), 18.9 (CH_3), 16.9 (CH_3), 10.6 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{14}H_{22}NO_2S_2$: 300.1086, found: 300.1096.



94

(*S*)-*N*-[(*R*)-2-[(*R*)-5,6-Dihydro-2*H*-pyran-2-yl]propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**94**). Yellow solid; **mp** = 61–62 ºC; $\mathbf{R_f}$= 0.30 (CH_2Cl_2); **IR** (ATR) 2959, 2925, 1676, 1468, 1353, 1249, 1145, 1082 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.95 (1H, ddt, *J* = 10.2, 4.8, 2.5 Hz, OCHCH=C<u>H</u>), 5.79 (1H, ddd, *J* = 10.2, 3.9, 2.0 Hz, OCHC<u>H</u>=CH), 5.28 (1H, ddd, *J* = 8.6, 5.4, 1.9 Hz, NC<u>H</u>), 4.95 (1H, p, *J* = 6.8 Hz, COC<u>H</u>CH_3), 4.50–4.47 (1H, m, OC<u>H</u>CH=CH), 3.95–3.90 (1H, m, OC<u>H$_a$</u>H$_b$), 3.65 (1H, ddd, *J* = 11.2, 8.4, 4.2 Hz, OCH$_a$<u>H$_b$</u>), 3.46 (1H, dd, *J* = 11.4, 8.6 Hz, SC<u>H$_a$</u>H$_b$), 2.99 (1H, dd, *J* = 11.4, 1.9 Hz, SCH$_a$<u>H$_b$</u>), 2.40–2.30 (1H, m, C<u>H</u>$(CH_3)_2$), 2.26–2.16 (1H, m, CH=CHC<u>H$_a$</u>H$_b$), 2.02–1.93 (1H, m, CH=CHCH$_a$<u>H$_b$</u>), 1.15 (3H, d, *J* = 6.8 Hz, COCHC<u>H$_3$</u>), 1.05 (3H, d, *J* = 6.8 Hz, CH(C<u>H$_3$</u>)$_a$$(CH_3)_b$), 0.97 (3H, d, *J* = 7.0 Hz, CH$(CH_3)_a$(C<u>H$_3$</u>)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.4 (C), 176.4 (C), 126.8 (CH), 126.5 (CH), 75.3 (CH), 71.9 (CH), 62.9 (CH_2), 43.0 (CH), 30.5 (CH), 29.1 (CH_2), 25.1 (CH_2), 19.1 (CH_3), 17.0 (CH_3), 12.8 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{14}H_{22}NO_2S_2$: 300.1086, found: 300.1091.

3.5.7. Attempt to use acetaldehyde dimethyl acetal

The reaction was carried out according to the General Procedure in section 3.5.1. from thioimide **4f** (109 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol), acetaldehyde dimethyl acetal (58 μL, 0.55 mmol), TESOTf (130 μL, 0.58 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 70 h.

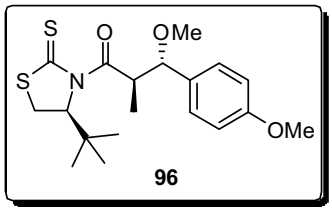
After the usual reaction mixture treatment indicated in the General Procedure in section 3.5.1, ^{1}H NMR analysis of the crude product showed the only presence of starting material **4f**.

3.6. SCOPE OF THE REACTION WITH THIOIMIDE 73

3.6.1. (*S*)-4-(*tert*-Butyl)-*N*-[(*2R*, *3S*)-3-methoxy-3-(*p*-methoxyphenyl)-2-methylpropanoyl]-1,3-thiazolidine-2-thione (96)

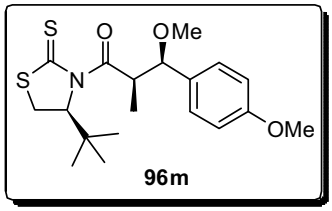
Solid $(Me_3P)_2NiCl_2$ (2.7 mg, 9.7 μmol) was added to a solution of thioimide **73** (90 mg, 0.39 mmol) and *p*-anisaldehyde dimethyl acetal (73 μL, 0.43 mmol) in anh CH_2Cl_2 (0.8 mL) under N_2 at r.t. The resulting mixture was purged with N_2 again and then cooled to –20 ºC. TESOTf (101 μL, 0.45 mmol) and 2,6-lutidine (68 μL, 0.58 mmol) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred at –20 ºC for 15 h.

The reaction was quenched with sat NH_4Cl (1.0 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) (from hexanes/CH_2Cl_2 2:3 to 1:4) to afford 108 mg of the pure *anti* diastereomer **96** (0.28 mmol, 71%) and 36 mg of the pure *syn* diastereomer **96m** (0.09 mmol, 24%).



96

(*S*)-4-(*tert*-Butyl)-*N*-[(*2R*, *3S*)-3-methoxy-3-(4-methoxyphenyl)-2-methylpropanoyl]-1,3-thiazolidine-2-thione (**96**). Yellow solid; **mp** = 93–94 ºC; $\mathbf{R_f}$ = 0.55 (hexanes/CH_2Cl_2 1:9); $[\alpha]_D$ = +298.7 (*c* 0.95, $CHCl_3$); **IR** (ATR) 2959, 2821, 1687, 1605, 1509, 1364, 1353, 1308, 1260, 1230, 1134 cm^{-1}; ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 7.29–7.27 (2H, m, ArH), 6.91–6.89 (2H, m, ArH), 5.53 (1H, dd, *J* = 8.5, 0.9 Hz, NCH), 5.39 (1H, dq, *J* = 9.9, 7.0 Hz, COCHCH$_3$), 4.32 (1H, d, *J* = 9.9 Hz, CHOCH$_3$), 3.81 (3H, s, ArOCH$_3$), 3.48 (1H, dd, *J* = 11.8, 8.5 Hz, SCH$_a$H$_b$), 3.07 (1H, dd, *J* = 11.8, 0.9 Hz, SCH$_a$H$_b$), 3.07 (3H, s, CHOCH$_3$), 1.10 (9H, s, C(CH$_3$)$_3$), 0.79 (3H, d, *J* = 7.0 Hz, CHCH$_3$); ^{13}**C NMR** ($CDCl_3$, 100.6 MHz) δ 204.9 (C), 176.3 (C), 159.4 (C), 131.2 (C), 129.2 (CH), 113.7 (CH), 86.6 (CH), 72.4 (CH), 56.3 (CH_3), 55.1 (CH_3), 44.1 (CH), 37.8 (C), 29.5 (CH_2), 26.7 (CH_3), 14.5 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OCH_3]^+$ $C_{18}H_{24}NO_2S_2$: 350.1243, found: 350.1258; *m/z* calculated for $[M+Na]^+$ $C_{19}H_{27}NNaO_3S_2$: 404.1325, found: 404.1341.



96m

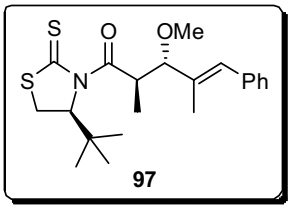
(*S*)-4-(*tert*-Butyl)-*N*-[(*2R*, *3R*)-3-methoxy-3-(4-methoxyphenyl)-2-methylpropanoyl]-1,3-thiazolidine-2-thione (**96m**). Yellow solid; **mp** = 125–126 ºC; $\mathbf{R_f}$ = 0.35 (hexanes/CH_2Cl_2 1:9); $[\alpha]_D$ = +500.1 (*c* 0.75, $CHCl_3$); **IR** (ATR) 2955, 2866, 2814, 1716, 1605, 1505, 1349, 1323, 1239, 1116 cm^{-1}; ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 7.36–7.33 (2H, m, ArH), 6.87–6.84 (2H, m, ArH), 5.34 (1H, dd, *J* = 8.4, 0.8 Hz, NCH), 5.19 (1H, p, *J* = 6.9 Hz, COCHCH$_3$), 4.61 (1H, d, *J* = 6.9 Hz, CHOCH$_3$), 3.79 (3H, s, ArOCH$_3$), 3.42 (1H, dd, *J* = 11.8, 8.4 Hz, SCH$_a$H$_b$), 3.16 (3H, s, CHOCH$_3$), 3.01 (1H, dd, *J* = 11.8, 0.8 Hz, SCH$_a$H$_b$), 1.22 (3H, d, *J* = 6.9 Hz, CHCH$_3$), 1.10 (9H, s, C(CH$_3$)$_3$); ^{13}**C NMR** ($CDCl_3$, 100.6 MHz) δ 205.0 (C), 174.1 (C), 159.2 (C), 131.6

(C), 129.2 (CH), 113.5 (CH), 83.7 (CH), 72.1 (CH), 56.4 (CH_3), 55.2 (CH_3), 44.5 (CH), 37.4 (C), 29.7 (CH_2), 26.4 (CH_3), 13.6 (CH_3).

3.6.2. (*S*)-4-(*tert*-Butyl)-*N*-[(*2R*, *3S*)-3-methoxy-2,4-dimethyl-5-phenylpent-4-enoyl]-1,3-thiazolidine-2-thione (97)

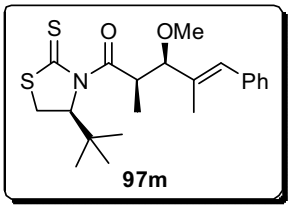
Solid $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol) was added to a solution of thioimide **73** (116 mg, 0.50 mmol) and (*E*)-α-methylcinnamaldehyde dimethyl acetal (106 μL, 0.55 mmol) in anh CH_2Cl_2 (1.0 mL) under N_2 at r.t. The resulting mixture was purged with N_2 again and then cooled to –20 ºC. TESOTf (130 μL, 0.58 mmol) and 2,6-lutidine (88 μL, 0.75 mmol) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred at –20 ºC for 1.5 h.

The reaction was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/CH_2Cl_2 1:1) to afford 142 mg of the pure *anti* diastereomer **97** (0.37 mmol, 73%) and 45 mg of a 1:0.14 mixture of the *syn* diastereomer (0.11 mmol, 22%) and (*E*)-α-methylcinnamaldehyde dimethyl acetal.



97

(*S*)-4-(*tert*-Butyl)-*N*-[(*2R*, *3S*)-3-methoxy-2,4-dimethyl-5-phenylpent-4-enoyl]-1,3-thiazolidine-2-thione (**97**). Yellow solid; **mp** = 75–76 ºC; $\mathbf{R_f}$ = 0.60 (hexanes/CH_2Cl_2 2:3); $\mathbf{[\alpha]_D}$ = +372.8 (*c* 1.05, $CHCl_3$); **IR** (ATR) 2951, 2922, 2888, 2810, 1694, 1446, 1342, 1323, 1249, 1130 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.40–7.31 (4H, m, ArH), 7.53–7.22 (1H, m, ArH), 6.53 (1H, br s, C=CHPh), 5.51 (1H, dd, *J* = 8.5, 0.7 Hz, NCH), 5.37 (1H, dq, *J* = 10.0, 7.0 Hz, COCHCH$_3$), 3.96 (1H, d, *J* = 10.0 Hz, CHOCH$_3$), 3.48 (1H, *J* = 11.8, 8.5 Hz, SCH$_a$H$_b$), 3.18 (3H, s, OCH$_3$), 3.06 (1H, dd, *J* = 11.8, 0.7 Hz, SCH$_a$H$_b$), 1.84 (3H, d, *J* = 1.3 Hz, CH$_3$C=CH), 1.08 (9H, s, C(CH$_3$)$_3$), 0.98 (3H, d, *J* = 7.0 Hz, COCHCH$_3$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 205.1 (C), 176.3 (C), 137.1 (C), 135.1 (C), 131.1 (CH), 129.0 (CH), 128.2 (CH), 126.7 (CH), 91.2 (CH), 72.4 (CH), 56.1 (CH_3), 40.4 (CH), 37.9 (C), 29.4 (CH_2), 26.7 (CH_3), 14.4 (CH_3), 12.2 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OCH_3]^+$ $C_{20}H_{26}NOS_2$: 360.1450, found: 360.1459.



97m

(*S*)-4-(*tert*-Butyl)-*N*-[(*2R*, *3R*)-3-methoxy-2,4-dimethyl-5-phenylpent-4-enoyl]-1,3-thiazolidine-2-thione (**97m**). Yellow solid; $\mathbf{R_f}$ = 0.45 (hexanes/CH_2Cl_2 2:3); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.33–7.19 (5H, m, ArH), 6.56 (1H, br s, C=CHPh), 5.37 (1H, dd, *J* = 8.4, 0.7 Hz, NCH), 5.22 (1H, dq, *J* = 8.3, 6.8 Hz, COCHCH$_3$), 4.09 (1H, d, *J* = 8.3 Hz, OCH), 3.46 (1H, *J* = 11.9, 8.4 Hz, SCH$_a$H$_b$), 3.28 (3H, s, OCH$_3$), 3.05 (1H, dd, *J* = 11.9, 0.7 Hz, SCH$_a$H$_b$), 1.89 (3H, d, *J* = 1.3 Hz, CH$_3$C=CH), 1.24 (3H, d, *J* = 6.8 Hz, COCHCH$_3$), 0.94 (9H, s, C(CH$_3$)$_3$); **^{13}C NMR**

($CDCl_3$, 100.6 MHz) δ 205.3 (C), 174.1 (C), 137.3 (C), 134.9 (C), 130.2 (CH), 129.0 (CH), 128.0 (CH), 126.4 (CH), 87.8 (CH), 72.1 (CH), 56.3 (CH_3), 40.8 (CH), 37.6 (C), 29.8 (CH_2), 26.8 (CH_3), 14.5 (CH_3), 13.7 (CH_3).

3.7. APPLICATION TO OTHER *N*-ACYL THIAZOLIDINETHIONES

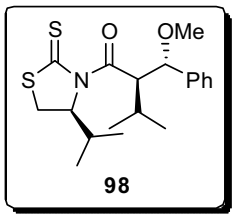
3.7.1. General Procedure

Solid $(Me_3P)_2NiCl_2$ was added to a solution of the corresponding thioimide and benzaldehyde dimethyl acetal in anh CH_2Cl_2 under N_2 at r.t. The resulting mixture was purged with N_2 again and then cooled to –20 ºC. TESOTf and 2,6-lutidine were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred at –20 ºC for 15 h.

The reaction was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude was purified by flash column chromatography to afford the isolated pure *syn* and *anti* adducts.

3.7.2. Preparation of (*S*)-4-isopropyl-*N*-[(*2R*, *3S*)-2-isopropyl-3-methoxy-3-phenylpropanoyl]-1,3-thiazolidine-2-thione (98) with 2.5 mol% of $(Me_3P)_2NiCl_2$

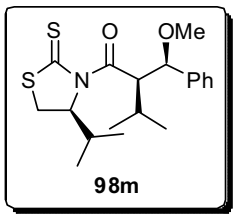
The thioimide **98** was prepared according to the General Procedure in section 3.7.1. from thioimide **4i** (123 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol), benzaldehyde dimethyl acetal (83 μL, 0.55 mmol), TESOTf (130 μL, 0.58 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. A 63:37 diastereomeric ratio of the *anti/syn* diastereomers was established by ^{1}H NMR of the crude product. Purification of the crude product by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/CH_2Cl_2 from 3:2 to 2:3) afforded 69 mg of the pure *anti* adduct **98** (0.18 mmol, 38%) and 37 mg of the pure *syn* adduct **98m** (0.10 mmol, 20%).



98

(*S*)-4-Isopropyl-*N*-[(*2R*, *3S*)-2-isopropyl-3-methoxy-3-phenylpropanoyl]-1,3-thiazolidine-2-thione (**98**). Yellow solid; **mp** = 125–127 ºC; $\mathbf{R_f}$= 0.45 (hexanes/CH_2Cl_2 1:1); $[\alpha]_D$ = +205.3 (*c* 0.67, $CHCl_3$); **IR** (ATR) 2959, 2918, 1687, 1460, 1394, 1357, 1301, 1238, 1149, 1090 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.43–7.30 (5H, m, ArH), 5.81 (1H, dd, *J* = 10.1, 4.8 Hz, COCH), 5.33 (1H, ddd, *J* = 7.8, 6.8, 0.9 Hz, NCH), 4.45 (1H, d, *J* = 10.1 Hz, CHOCH$_3$), 3.43 (1H, dd, *J* = 11.5, 7.8 Hz, SCH$_a$H$_b$), 3.07 (3H, s, OCH$_3$), 2.97 (1H, dd, *J* = 11.5, 0.9 Hz, SCH$_a$H$_b$), 2.44–2.32 (1H, m, NCHCH(CH$_3$)$_2$), 1.60–1.50 (1H, m, COCHCH(CH$_3$)$_2$), 1.09 (3H, d, *J* = 6.8 Hz, NCHCH(CH$_3$)$_a$(CH$_3$)$_b$), 1.03 (3H, d, *J* = 6.9 Hz, NCHCH(CH$_3$)$_a$(CH$_3$)$_b$), 0.88 (3H, d, *J* = 6.8 Hz, COCHCH(CH$_3$)$_a$(CH$_3$)$_b$), 0.80 (3H, d, *J* = 7.0 Hz, COCHCH(CH$_3$)$_a$(CH$_3$)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 203.6 (C), 174.6 (C), 139.5 (C), 128.4 (CH), 128.3 (CH), 128.2 (CH), 85.5 (CH), 71.8 (CH), 56.5 (CH_3), 52.5 (CH), 30.5 (CH), 30.3 (CH_2), 28.5 (CH), 20.5 (CH_3), 19.0 (CH_3), 18.4 (CH_3), 18.1 (CH_3); **HRMS** (+ESI): *m/z* calculated

for $[M–OCH_3]^+$ $C_{18}H_{24}NOS_2$: 334.1294, found: 334.1297; *m/z* calculated for $[M+Na]^+$ $C_{19}H_{27}NNaO_2S_2$: 388.1375, found: 388.1384.



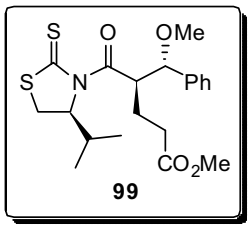
(*S*)-*N*-[(*2R*, *3R*)-3-Methoxy-3-phenyl-2-isopropylpropanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**98m**). Yellow oil; $\mathbf{R_f}$ = 0.50 (hexanes/CH_2Cl_2 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.42–7.40 (2H, m, ArH), 7.29–7.19 (3H, m, ArH), 5.80 (1H, dd, *J* = 9.9, 4.4 Hz, COCH), 5.04 (1H, ddd, *J* = 7.8, 6.5, 0.9 Hz, NCH), 4.44 (1H, d, *J* = 9.9 Hz, $CHOCH_3$), 3.28 (1H, dd, *J* = 11.5, 7.8 Hz, SCH_aH_b), 3.15 (3H, s, OCH_3), 2.80 (1H, dd, *J* = 11.5, 0.9 Hz, SCH_aH_b), 2.44–2.36 (1H, m, $NCHCH(CH_3)_2$), 1.76–1.68 (1H, m, $COCHCH(CH_3)_2$), 1.08 (3H, d, *J* = 7.1 Hz, $COCHCH(CH_3)_a(CH_3)_b$), 1.06 (3H, d, *J* = 7.4 Hz, $COCHCH(CH_3)_a(CH_3)_b$), 0.67 (3H, d, *J* = 6.8 Hz, $NCHCH(CH_3)_a(CH_3)_b$), 0.47 (3H, d, *J* = 7.0 Hz, $NCHCH(CH_3)_a(CH_3)_b$).

3.7.3. Preparation of (*S*)-4-isopropyl-*N*-[(*2R*, *3S*)-2-isopropyl-3-methoxy-3-phenylpropanoyl]-1,3-thiazolidine-2-thione (98) with 5.0 mol% of $(Me_3P)_2NiCl_2$

The thioimide **98** was prepared according to the General Procedure in section 3.7.1. from thioimide **4i** (87 mg, 0.35 mmol), $(Me_3P)_2NiCl_2$ (4.9 mg, 17.5 μmol), benzaldehyde dimethyl acetal (58 μL, 0.39 mmol), TESOTf (120 μL, 0.53 mmol), 2,6-lutidine (61 μL, 0.53 mmol) and CH_2Cl_2 (0.7 mL) at –20 ºC for 15 h. A 64:36 diastereomeric ratio of the *anti/syn* diastereomers was established by ^{1}H NMR of the crude product. Purification of the crude product by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/CH_2Cl_2 1:1) afforded 67 mg of the pure *anti* adduct **98** (0.18 mmol, 53%) and 28 mg of the pure *syn* adduct **98m** (0.10 mmol, 28%).

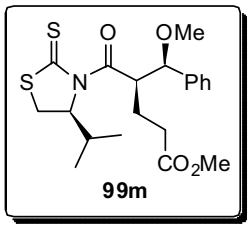
3.7.4. (*S*)-4-Isopropyl-*N*-[(*2R*, *3S*)-3-methoxy-2-[1-methoxycarbonylprop-3-yl]-3-phenylpropanoyl]-1,3-thiazolidine-2-thione (99) with 2.5 mol% of $(Me_3P)_2NiCl_2$

The thioimide **99** was prepared according to the General Procedure in section 3.7.1. from thioimide **4k** (145 mg, 0.35 mmol), $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol), benzaldehyde dimethyl acetal (83 μL, 0.55 mmol), TESOTf (130 μL, 0.58 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. A 64:36 diastereomeric ratio of the *anti/syn* diastereomers was established by ^{1}H NMR of the crude product. Purification of the crude product by flash column chromatography on deactivated silica gel (2.5% Et_3N) (from hexanes/CH_2Cl_2 75:25 to CH_2Cl_2, then from CH_2Cl_2 to CH_2Cl_2/MeOH 98:2) afforded 56 mg of the pure *anti* adduct **99** (0.14 mmol, 28%) and 30 mg of the pure *syn* adduct **99m** (0.07 mmol, 15%).



99

(*S*)-4-Isopropyl-*N*-[(*2R*, *3S*)-3-methoxy-2-[1-methoxycarbonylprop-3-yl]-3-phenylpropanoyl]-1,3-thiazolidine-2-thione (**99**). Yellow oil; $\mathbf{R_f}$ = 0.65 (CH_2Cl_2); $\mathbf{[\alpha]_D}$ = +123.9 (*c* 1.15, $CHCl_3$); **IR** (ATR) 3018, 2959, 2925, 2870, 1731, 1683, 1434, 1360, 1238, 1145, 1086 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.40–7.31 (5H, m, ArH), 5.69 (1H, td, *J* = 9.5, 4.1 Hz, COCH), 5.38 (1H, ddd, *J* = 8.2, 6.2, 1.1 Hz, NCH), 4.30 (1H, d, *J* = 9.5 Hz, CHOCH$_3$), 3.58 (3H, s, COOCH$_3$), 3.50 (1H, dd, *J* = 11.4, 8.2 Hz, SCH$_a$H$_b$), 3.06 (3H. s, CHOCH$_3$), 2.99 (1H, dd, *J* = 11.4, 1.1 Hz, SCH$_a$H$_b$), 2.43–2.32 (1H, m, CH(CH$_3$)$_2$), 2.15 (2H, t, *J* = 7.7 Hz, CH$_2$COOCH$_3$), 1.78 (1H, ddt, *J* = 14.3, 9.5, 7.7 Hz, COCHCH$_a$H$_b$), 1.78 (1H, dtd, *J* = 14.3, 7.7, 4.1 Hz, COCHCH$_a$H$_b$), 1.10 (3H, d, *J* = 6.8 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$), 1.03 (3H, d, *J* = 7.0 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 203.2 (C), 175.9 (C), 173.1 (C), 138.9 (C), 128.5 (CH), 128.5 (CH), 128.2 (CH), 87.3 (CH), 71.9 (CH), 56.4 (CH_3), 51.6 (CH_3), 48.0 (CH), 31.1 (CH_2), 30.5 (CH), 29.5 (CH_2), 24.7 (CH_2), 19.0 (CH_3), 17.5 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OCH_3]^+$ $C_{19}H_{24}NO_3S_2$: 378.1192, found: 378.1199; *m/z* calculated for $[M+Na]^+$ $C_{20}H_{27}NNaO_4S_2$: 432.1274, found: 432.1274.



99m

(*S*)-4-Isopropyl-*N*-[(*2R*, *3R*)-3-methoxy-2-[1-methoxycarbonylprop-3-yl]-3-phenylpropanoyl]-1,3-thiazolidine-2-thione (**99m**). Yellow oil; $\mathbf{R_f}$ = 0.60 (CH_2Cl_2); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.41–7.22 (5H, m, ArH), 5.55 (1H, td, *J* = 7.9, 4.3 Hz, COCH), 5.18 (1H, ddd, *J* = 8.4, 5.7, 1.2 Hz, NCH), 4.57 (1H, d, *J* = 7.9 Hz, CHOCH$_3$), 3.64 (3H, s, COOCH$_3$), 3.42 (1H, dd, *J* = 11.4, 8.4 Hz, SCH$_a$H$_b$), 3.17 (3H. s, CHOCH$_3$), 2.85 (1H, dd, *J* = 11.4, 1.2 Hz, SCH$_a$H$_b$), 2.46–2.32 (1H, m, CH(CH$_3$)$_2$), 2.24–2.06 (2H, m, CH$_2$COOCH$_3$), 1.86–1.73 (1H, m, COCHCH$_a$H$_b$), 1.61–1.49 (1H, m, COCHCH$_a$H$_b$), 1.75 (3H, d, *J* = 6.8 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$), 0.65 (3H, d, *J* = 7.0 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$).

3.7.5. (*S*)-4-Isopropyl-*N*-[(*2R*, *3S*)-3-methoxy-2-[1-methoxycarbonylprop-3-yl]-3-phenylpropanoyl]-1,3-thiazolidine-2-thione (99) with 5.0 mol% of $(Me_3P)_2NiCl_2$

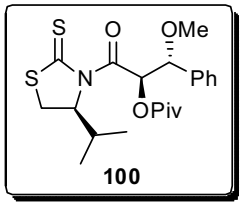
The thioimide **99** was prepared according to the General Procedure in section 3.7.1. from thioimide **4k** (145 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (7.0 mg, 25 μmol), benzaldehyde dimethyl acetal (83 μL, 0.55 mmol), TESOTf (170 μL, 0.75 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. A 64:36 diastereomeric ratio of the *anti/syn* diastereomers was established by ^{1}H NMR of the crude product. Purification of the crude product by flash column chromatography on deactivated silica gel (2.5% Et_3N) (from hexanes/CH_2Cl_2 75:25 to CH_2Cl_2, then from CH_2Cl_2 to CH_2Cl_2/MeOH 98:2) afforded 131 mg of the pure *anti* adduct **99** (0.32 mmol, 64%) and 74 mg of the pure *syn* adduct **99m** (0.18 mmol, 36%).

3.7.6. (*S*)-4-Isopropyl-*N*-[(*2R*, *3R*)-3-methoxy-2-pivaloyloxy-3-phenylpropanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (100) with 2.5 mol% of $(Me_3P)_2NiCl_2$

The reaction was carried out according to the General Procedure in section 3.7.1. from thioimide **4m** (152 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol), benzaldehyde dimethyl acetal (83 μL, 0.55 mmol), TESOTf (130 μL, 0.58 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. After the usual treatment, ^{1}H NMR spectrum of the crude product showed a conversion of 12% with a ratio of the *anti/syn* diastereomers of 75:25.

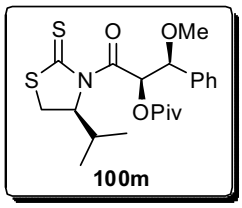
3.7.7. (*S*)-4-Isopropyl-*N*-[(*2R*, *3R*)-3-methoxy-2-pivaloyloxy-3-phenylpropanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (100) with 20 mol% of $(Me_3P)_2NiCl_2$

The thioimide **100** was prepared according to the General Procedure in section 3.7.1. from thioimide **4m** (152 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (28.2 mg, 0.10 mmol), benzaldehyde dimethyl acetal (83 μL, 0.55 mmol), TESOTf (170 μL, 0.75 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. A 75:25 diastereomeric ratio of the *anti/syn* diastereomers was established by ^{1}H NMR of the crude product. Purification of the crude product by flash column chromatography on silica gel (from hexanes/EtOAc 93:7 to 85:15) afforded 22 mg of the pure *syn* diastereomer **100m** (0.06 mmol, 11%) and a mixture of the *anti* diastereomer **100** and the starting material **4m**. Another purification of this last mixture by flash column chromatography on silica gel (from hexanes/CH_2Cl_2 7:3 to CH_2Cl_2) afforded 72 mg of the pure *anti* diastereomer **100** (0.19 mmol, 35%).



100

(*S*)-4-Isopropyl-*N*-[(*2R*, *3R*)-3-methoxy-2-pivaloyloxy-3-phenylpropanoyl]-1,3-thiazolidine-2-thione (**100**). Yellow solid; **mp** = 142–143 ºC. $\mathbf{R_f}$ = 0.45 (hexanes/EtOAc 85:15), $\mathbf{R_f}$ = 0.50 (hexanes/CH_2Cl_2 1:4); $[\alpha]_D$ = +210.7 (*c* 1.15, $CHCl_3$); **IR** (KBr) 2962, 1728, 1707, 1368, 1178, 1149 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.47–7.44 (2H, m, ArH), 7.38–7.30 (3H, m, ArH), 7.15 (1H, d, *J* = 7.6 Hz, COCH), 5.30 (1H, ddd, *J* = 8.3, 5.9, 1.0 Hz, NCH), 4.64 (1H, d, *J* = 7.6 Hz, CHOCH$_3$), 3.60 (1H, dd, *J* = 11.4, 8.3 Hz, SCH$_a$H$_b$), 3.20 (3H, s, OCH$_3$), 3.02 (1H, dd, *J* = 11.4, 1.0 Hz, SCH$_a$H$_b$), 2.39–2.27 (1H, m, CH(CH$_3$)$_2$), 1.12 (3H, d, *J* = 6.8 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$), 1.08 (9H, s, C(CH$_3$)$_3$), 1.02 (3H, d, *J* = 6.9 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 202.6 (C), 177.5 (C), 170.3 (C), 137.5 (C), 128.5 (CH), 128.2 (CH), 128.1 (CH), 83.9 (CH), 73.0 (CH), 71.7 (CH), 56.9 (CH_3), 38.3 (C), 30.6 (CH), 30.3 (CH_2), 26.8 (CH_3), 18.9 (CH_3), 17.5 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{21}H_{30}NO_4S_2$: 424.1611, found: 424.1625.



(*S*)-4-Isopropyl-*N*-[(*2R*, *3S*)-3-Methoxy-2-pivaloyloxy-3-phenylpropanoyl]-1,3-thiazolidine-2-thione (**100m**). Yellow solid; $\mathbf{R_f}$ = 0.35 (hexanes/EtOAc 85:15), $\mathbf{R_f}$ = 0.50 (hexanes/CH_2Cl_2 1:4); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.52–7.50 (2H, m, Ar<u>H</u>), 7.37–7.29 (3H, m, Ar<u>H</u>), 7.00 (1H, d, *J* = 2.7 Hz, COC<u>H</u>), 5.50 (1H, ddd, *J* = 8.9, 5.1, 1.5 Hz, NC<u>H</u>), 5.38 (1H, d, *J* = 2.7 Hz, C<u>H</u>OCH$_3$), 3.61 (1H, dd, *J* = 11.5, 8.9 Hz, SC<u>H$_a$</u>H$_b$), 3.26 (3H, s, OC<u>H$_3$</u>), 3.06 (1H, dd, *J* = 11.5, 1.5 Hz, SCH$_a$<u>H$_b$</u>), 2.42–2.31 (1H, m, C<u>H</u>(CH$_3$)$_2$), 1.10 (9H, s, C(C<u>H$_3$</u>)$_3$), 1.09 (3H, d, *J* = 6.8 Hz, CH(C<u>H$_3$</u>)$_a$(CH$_3$)$_b$), 1.01 (3H, d, *J* = 7.0 Hz, CH(CH$_3$)$_a$(C<u>H$_3$</u>)$_b$).

4. Stereoselective Ni(II) catalyzed reactions of N-glycolyl thiazolidinethiones with acetals

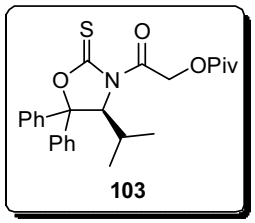
4.1. PREPARATION OF STARTING MATERIALS

4.1.1. (*S*)-4-Isopropyl-5,5-diphenyl-*N*-pivaloyloxyacetyl-1,3-oxazolidine-2-thione (103)

A mixture of pivaloyl chloride (4.4 mL, 36 mmol) and glycolic acid (1.52 g, 20 mmol) was stirred for 60 h at r.t. under N_2. Then, the volatiles were eliminated under vacuum and the crude product, 2-pivaloyloxy acetic acid, was used in the next step without further purification.

EDC·HCl (576 mg, 3.0 mmol) was added to a solution of previously prepared 2-pivaloyloxy acetic acid (368 mg, 2.30 mmol), (*S*)-4-isopropyl-5,5-diphenyl-1,3-oxazolidine-2-thione (595 mg, 2.0 mmol) and DMAP (12 mg, 0.10 mmol) in anh CH_2Cl_2 (3 mL) at 0 ºC. The mixture was purged with N_2 again. The ice bath was then removed and the reaction was stirred for 16 h at r.t.

The resulting reaction mixture was diluted in Et_2O (50 mL) and washed with 0.5 M HCl (3 × 20 mL), 0.5 M NaOH (3 × 20 mL) and brine (40 mL). The organic layer was dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography on silica gel (hexanes/CH_2Cl_2 1:1) to afford 427 mg (0.97 mmol, 49%) of **103** as a white solid.



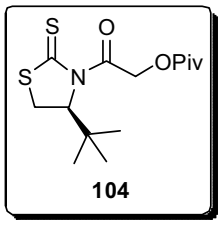
103

(*S*)-4-Isopropyl-5,5-diphenyl-*N*-pivaloyloxyacetyl-1,3-oxazolidine-2-thione (**103**). White solid; **mp** = 136–137 ºC; $\mathbf{R_f}$ = 0.30 (hexanes/CH_2Cl_2 1:4). $\mathbf{[\alpha]_D}$ = –217.5 (*c* 1.00, $CHCl_3$); **IR** (film) 2973, 2955, 1735, 1720, 1446, 1401, 1375, 1331, 1190, 1138, 1104 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.46–7.26 (10H, m, Ar<u>H</u>), 5.63 (1H, d, *J* = 17.0 Hz, COC<u>H</u>$_a$H$_b$), 5.57 (1H, d, *J* = 3.7 Hz, NC<u>H</u>), 5.19 (1H, d, *J* = 17.0 Hz, COCH$_a$<u>H</u>$_b$), 2.08–1.97 (1H, m, C<u>H</u>(CH$_3$)$_2$), 0.86 (3H, d, *J* = 7.0 Hz, CH(C<u>H</u>$_3$)$_a$(CH$_3$)$_b$), 0.80 (3H, d, *J* = 6.8 Hz, CH(CH$_3$)$_a$(C<u>H</u>$_3$)$_b$); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 184.1 (C), 177.4 (C), 168.1 (C), 141.2 (C), 137.3 (C), 129.0 (CH), 128.8 (CH), 128.4 (CH), 128.2 (CH), 126.1 (CH), 125.5 (CH), 94.5 (C), 68.3 (CH), 64.2 (CH_2), 38.7 (C), 30.1 (CH), 27.1 (CH_3), 21.5 (CH_3), 16.8 (CH_3).

4.1.2. (*S*)-4-(*tert*-Butyl)-*N*-pivaloyloxyacetyl-1,3-thiazolidine-2-thione (104)

EDC·HCl (1.44 g, 7.5 mmol) was added to a solution of previously prepared 2-pivaloyloxy acetic acid (921 mg, 5.75 mmol) (see section 4.1.1), (*S*)-4-(*tert*-butyl)-1,3-thiazolidine-2-thione (877 mg, 5.0 mmol) and DMAP (31 mg, 0.25 mmol) in anh CH_2Cl_2 (8.0 mL) at 0 ºC. The mixture was purged with N_2 again. The ice bath was then removed and the reaction was stirred for 16 h at r.t.

The resulting yellow reaction mixture was diluted in Et_2O (50 mL) and washed with 0.5 M HCl (3 × 20 mL), 0.5 M NaOH (3 × 20 mL) and brine (40 mL). The organic layer was dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography on silica gel (hexanes/CH_2Cl_2 2:3) to give 1.07 g (3.38 mmol, 67%) of thioimide **104** as a yellow solid.



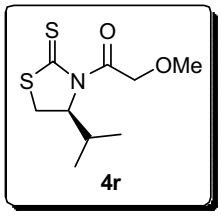
104

(*S*)-4-(*tert*-Butyl)-*N*-pivaloyloxyacetyl-1,3-thiazolidine-2-thione (**104**). Yellow solid; **mp** = 70–71 ºC; $\mathbf{R_f}$ = 0.50 (hexanes/CH_2Cl_2 7:3); $\mathbf{[\alpha]_D}$= +334.2 (*c* 1.40, $CHCl_3$); **IR** (ATR) 2962, 2866, 1731, 1702, 1475, 1397, 1364, 1312, 1253, 1182, 1134 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.48 (1H, d, *J* = 16.7 Hz, $COCH_aH_b$), 5.41 (1H, d, *J* = 16.7 Hz, $COCH_aH_b$), 5.24 (1H, dd, *J* = 8.4, 0.9 Hz, NCH), 3.66 (1H, dd, *J* = 11.8, 8.4 Hz, SCH_aH_b), 3.17 (1H, dd, *J* = 11.8, 0.9 Hz, SCH_aH_b), 1.27 (9H, s, $C(CH_3)_3$), 1.04 (9H, s, $C(CH_3)_3$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 204.4 (C), 177.7 (C), 167.5 (C), 72.3 (CH), 64.6 (CH_2), 38.7 (C), 37.9 (C), 31.6 (CH_2), 27.1 (CH_3), 26.8 (CH_3).

4.1.3. (*S*)-4-Isopropyl-*N*-methoxyacetyl-1,3-thiazolidine-2-thione (4r)

An 1.55 M solution of *n*-BuLi in hexanes (2.1 mL, 3.3 mmol) was added dropwise to a solution of thiazolidinethione **1** (484 mg, 3.0 mmol) in THF (2.0 mL) at –78 ºC under N_2. The reaction mixture was stirred for 15 min and methoxyacetyl chloride (357 μL, 3.9 mmol) was carefully added. The resulting clear solution was stirred for 5 min and the solution warmed to r.t. and stirred for 1.5 h.

The reaction mixture was cooled with an ice bath and quenched with sat NH_4Cl (1.2 mL) and water (3 mL). This mixture was extracted with CH_2Cl_2 (3 ×20 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated. The resultant oil was purified through flash column chromatography on silica gel (hexanes/EtOAc 95:5) to afford 625 mg (2.68 mmol, 89%) of thioimide **4r** as a yellow oil.



4r

(*S*)-4-Isopropyl-*N*-methoxyacetyl-1,3-thiazolidine-2-thione (**4r**). Yellow oil; $\mathbf{R_f}$ = 0.30 (hexanes/CH_2Cl_2 1:4). $\mathbf{[\alpha]_D}$ = +312.6 (*c* 1.65, $CHCl_3$); **IR** (film) 2963, 1709, 1368, 1313, 1264, 1176, 1120 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.19 (1H, ddd, *J* = 8.2, 6.2, 1.2 Hz, NCH), 4.98 (1H, d, *J* = 17.7 Hz, $COCH_aH_b$), 4.87 (1H, d, *J* = 17.7 Hz, $COCH_aH_b$), 3.61 (1H, dd, *J* = 11.6, 8.2 Hz, SCH_aH_b), 3.48 (3H, s, OCH_3), 3.09 (1H, dd, *J* = 11.6, 1.2 Hz, SCH_aH_b), 2.44–2.33 (1H, m, $CH(CH_3)_2$), 1.07 (3H, d, *J* = 6.7 Hz, $CH(CH_3)_a(CH_3)_b$), 0.99 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 202.1 (C), 171.0 (C), 74.5 (CH_2), 71.3 (CH), 59.3 (CH_3), 31.5 (CH_2), 30.7 (CH), 19.0 (CH_3), 17.7 (CH_3).

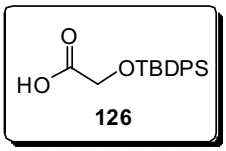
4.1.4. *tert*-Butyldiphenylsilyloxyacetic acid (126)[33]

TBDPSCl (2.6 mL, 10.0 mmol) was added to a suspension of methyl glycolate (0.78 mL, 8.4 mmol) and imidazole (1.36 g, 20.0 mmol) in anh CH_2Cl_2 (10 mL) at 0 ºC under N_2. The reaction mixture was stirred for 36 h

The reaction mixture was diluted in Et_2O (50 mL) and washed with water (2 × 30 mL), 2 M HCl (2 × 30 mL) and brine (30 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated.

1 M solution of KOH in water/MeOH 2:1 *v/v* (4.2 mL) was added over a solution of the previous crude in THF (7.5 mL) at 0 ºC. The reaction mixture was stirred at 0 ºC for 3 h.

The reaction mixture was diluted in Et_2O (70 mL) and washed with water (2 × 50 mL). The aqueous layer was acidified at ºC with 2 M HCl until pH = 1. Then, it was extracted with Et_2O (2 × 80 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to obtain 862 mg (2.74 mmol, 33%) of carboxylic acid **126**, which was pure by ^{1}H NMR analysis.



126

tert-Butyldiphenylsilyloxyacetic acid (**126**). Colorless oil; $\mathbf{R_f}$ = 0.10 (CH_2Cl_2); **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.66–7.63 (4H, m, Ar<u>H</u>), 7.50–7.38 (6H, m, Ar<u>H</u>), 4.23 (2H, s, C<u>H</u>$_2$), 1.11 (9H, s, C(C<u>H</u>$_3$)$_3$).

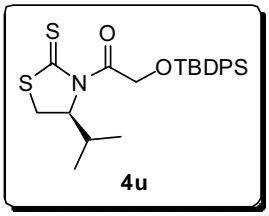
4.1.5. (*S*)-*N*-(*tert*-Butyl)diphenylsilyloxyacetyl-4-isopropyl-1,3-thiazolidine-2-thione (4u) [33]

The carboxylic acid **126** (1.23 g, 3.9 mmol) was dissolved in benzene (6.0 mL) and the solvent removed *in vacuo*. The process was repeated once again. Then, oxalyl chloride (0.56 mL, 6.6 mmol) was added dropwise to a solution of the previous washed carboxylic acid in benzene (6.6 mL). The resulting mixture was stirred for 30 min at r.t. and 30 min at reflux.

The solution was concentrated and the crude product used into the next step without further purification.

The next reaction step was carried out as in 4.1.3., using a solution of thiazolidinethione **1** in anh THF (1.5 mL) and a solution of the previous crude in anh THF (1.5 mL) as the acid chloride.

The final crude product was purified by flash column chromatography on silica gel (hexanes/EtOAc 95:5) to give 783 mg (1.71 mmol, 57%) of thioimide **4u**.



4u

(*S*)-*N*-(t*ert*-Butyldiphenylsilyloxyacetyl)-4-isopropyl-1,3-thiazolidine-2-thione (**4u**). Yellow oil; $\mathbf{R_f}$ = 0.60 (hexanes/EtOAc 85:15); **[α]$_D$** = +140.5 (*c* 0.95, $CHCl_3$); **IR** (film) 2961, 1716, 1364, 1313, 1114 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.73–7.66 (5H, m, Ar<u>H</u>), 7.43–7.34 (5H, m, Ar<u>H</u>), 5.20 (1H, d, *J* = 18.0 Hz, COC<u>H$_a$</u>H$_b$), 5.12 (1H, d, *J* = 18.0 Hz, COCH$_a$<u>H$_b$</u>), 5.10 (1H, ddd, *J* = 8.1, 6.2, 1.2 Hz, NC<u>H</u>), 3.46 (1H, dd, *J* = 11.6, 8.1 Hz, SC<u>H$_a$</u>H$_b$), 2.99 (1H, dd, *J* = 11.6, 1.2 Hz, SCH$_a$<u>H$_b$</u>), 2.44–2.33 (1H, m, C<u>H</u>(CH$_3$)$_2$), 1.11 (9H, s, C(C<u>H</u>$_3$)$_3$), 0.98 (3H, d, *J* = 6.9 Hz, CH(C<u>H</u>$_3$)$_a$(CH$_3$)$_b$), 0.90 (3H, d, *J* = 6.9 Hz, CH(CH$_3$)$_a$(C<u>H</u>$_3$)$_b$), 0.93 (9H, s, C(C<u>H</u>$_3$)$_3$), 0.12 (3H, s, Si(C<u>H</u>$_3$)$_a$(CH$_3$)$_b$), 0.11 (3H, s, Si(CH$_3$)$_a$(C<u>H</u>$_3$)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.0 (C), 172.1 (C), 135.9 (CH), 135.6 (CH), 133.1 (C), 133.0 (C), 129.8 (CH), 129.7 (CH), 127.7 (CH), 127.6 (CH), 71.4 (CH), 66.8 (CH_2), 31.3 (CH_2), 30.6 (CH), 26.8 (C), 19.3 (CH_3), 19.0 (CH_3), 17.5 (CH_3).

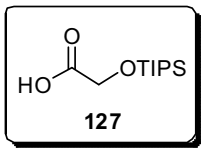
4.1.6. Triisopropylsilyloxyacetic acid 127[33]

TIPSCl (2.2 mL, 10.3 mmol) was added to a suspension of methyl glycolate (0.78 mL, 8.4 mmol) and imidazole (1.36 g, 20.0 mmol) in anh CH_2Cl_2 (10 mL) at 0 ºC under N_2. The reaction mixture was stirred for 72 h.

The reaction mixture was diluted in Et_2O (50 mL) and washed with water (2 × 30 mL), 2 M HCl (2 × 30 mL) and brine (30 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated.

A 1 M solution of KOH in water/MeOH 2:1 *v/v* (10 mL) was added over a solution of the previous crude in THF (16 mL) at 0 ºC. The reaction mixture was stirred at 0 ºC for 72 h.

The reaction mixture was diluted in Et_2O (70 mL) and washed with water (2 × 50 mL). The aqueous layer was acidified at ºC with 2 M HCl until pH = 1. Then, it was extracted with Et_2O (2 × 80 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to obtain 1.60 mg (6.9 mmol, 82%) of carboxylic acid **127**, which was pure by ^{1}H NMR analysis.



127

Triisopropylsilyloxyacetic acid (**127**). Colorless oil; $\mathbf{R_f}$ = 0.15 (CH_2Cl_2); **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 4.20 (2H, s, C<u>H</u>$_2$), 1.21–1.05 (21H, m, Si(C<u>H</u>(C<u>H</u>$_3$)$_2$)$_3$).

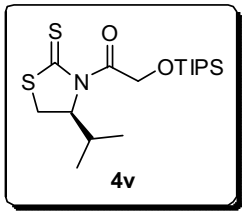
4.1.7. (*S*)-4-Isopropyl-*N*-triisopropylsilyloxyacetyl-1,3-thiazolidine-2-thione (4v) [33]

The carboxylic acid **127** (906 mg, 3.9 mmol) was dissolved in benzene (6.0 mL) and the solvent removed *in vacuo*. The process was repeated once again. Then, oxalyl chloride (0.56 mL, 6.6 mmol) was added dropwise to a solution of the previous washed carboxylic acid in benzene (6.6 mL). The resulting mixture was stirred for 30 min at r.t. and 30 min at reflux.

The solution was concentrated and the crude product used into the next step without further purification.

The next reaction step was carried out as in 4.1.3., using a solution of **1** in anh THF (1.5 mL) and a solution of the previous crude in anh THF (1.5 mL) as the acid chloride.

The final crude product was purified by flash column chromatography on silica gel (hexanes/EtOAc 95:5) to give 684 mg (1.82 mmol, 61%) of thioimide **4v**.



4v

(*S*)-4-Isopropyl-*N*-triisopropylsilyloxyacetyl-1,3-thiazolidine-2-thione (**4v**). Yellow oil; $\mathbf{R_f}$ = 0.60 (CH_2Cl_2); $\mathbf{[\alpha]_D}$ = +183.7 (*c* 0.95, $CHCl_3$); **IR** (film) 2943, 2866, 1716, 1367, 1264, 1177, 1145 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.24 (1H, d, *J* = 18.0 Hz, $COCH_aH_b$), 5.19 (1H, ddd, *J* = 8.3, 6.0, 1.2 Hz, NCH), 5.17 (1H, d, *J* = 18.0 Hz, $COCH_aH_b$), 3.59 (1H, dd, *J* = 11.4, 8.3 Hz, SCH_aH_b), 3.07 (1H, dd, *J* = 11.4, 1.2 Hz, SCH_aH_b), 2.45–2.34 (1H, m, $CH(CH_3)_2$), 1.14–1.05 (24H, m, $Si(CH(CH_3)_2)_3$, $CH(CH_3)_a(CH_3)_b$, 0.98 (3H, d, *J* = 6.9 Hz, $CH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 202.5 (C), 172.6 (C), 71.6 (CH), 66.9 (CH_2), 31.3 (CH_2), 30.7 (CH), 19.0 (CH_3), 17.8 (CH_3), 17.8 (CH_3), 17.7 (CH_3), 17.5 (CH_3), 12.0 (CH).

4.1.8. General procedure for the preparation of some (*S*)-4-isopropyl-*N*-(*O*-protected)glicolyl-1,3-thiazolidine-2-thiones[33]

Neat $TiCl_4$ (0.5 mL, 4.6 mmol) was added to a solution of (*S*)-*N*-benzyloxyacetyl-4-isopropyl-1,3-thiazolidine-2-thione (**4l**) (707 mg, 2.3 mmol) in anh CH_2Cl_2 (18 mL) at 0 ºC. The resulting mixture was stirred for 30 min at r.t.

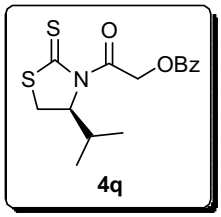
Then, sat NH_4Cl (30 mL) was added and the layers were separated. The aqueous phase was washed with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The resulting crude was used into the next reaction without further purification.

2,6-Lutidine and the corresponding hydroxyl protecting agent were added to a solution of the previous crude in anh CH_2Cl_2 (9.2 mL) at 0 ºC. The reaction mixture was stirred for 40 min at r.t.

MeOH (2.3 mL) was added to the reaction mixture and then it was diluted in Et_2O (30 mL) and washed with sat $NaHCO_3$ (3 × 20 mL), sat $KHSO_4$ (3 × 20 mL) and brine (40 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography on silica gel to give the corresponding pure product.

4.1.9. (*S*)-*N*-Benzoyloxyacetyl-4-isopropyl-1,3-thiazolidine-2-thione (4q)

The thioimide **4q** was prepared according to the General Procedure in section 4.1.8. from thioimide **4l** (707 mg, 2.3 mmol), $TiCl_4$ (0.5 mL, 4.6 mmol), 2,6-lutidine (1.3 mL, 11.3 mmol), benzoyl chloride (1.3 mL, 11.4 mmol) as the hydroxyl protecting agent, anh CH_2Cl_2 (18 mL) at the first step and anh CH_2Cl_2 (9.2 mL) at the second step. Purification of the crude product by flash column chromatography (from hexanes/CH_2Cl_2 1:1 to 1:5) afforded 446 mg (1.38 mmol, 60%) of thioimide **4q**.



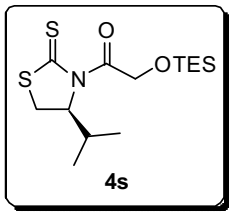
4q

(*S*)-*N*-Benzoyloxyacetyl-4-isopropyl-1,3-thiazolidine-2-thione (**4q**). Yellow solid; **mp** = 93–95 ºC; $\mathbf{R_f}$ = 0.40 (hexanes/CH_2Cl_2 1:4); $\mathbf{[\alpha]_D}$ = +211.8 (*c* 1.10, $CHCl_3$); **IR** (KBr) 2960, 1726, 1376, 1260, 1183, 1115 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.12–8.09 (2H, m, ArH), 7.61–7.43 (3H, m, ArH), 5.75 (1H, d, *J* = 16.7 Hz, $COCH_aH_b$), 5.68 (1H, d, *J* = 16.7 Hz, $COCH_aH_b$), 5.14 (1H, ddd, *J* = 8.2, 5.9, 1.2

Hz, NC<u>H</u>), 3.66 (1H, dd, *J* = 11.6, 8.2 Hz, SC<u>H</u>$_a$H$_b$), 3.11 (1H, dd, *J* = 11.6, 1.2 Hz, SCH$_a$<u>H</u>$_b$), 2.45–2.34 (1H, m, C<u>H</u>(CH$_3$)$_2$), 1.08 (3H, d, *J* = 6.7 Hz, CH(C<u>H</u>$_3$)$_a$(CH$_3$)$_b$), 0.98 (3H, d, *J* = 6.9 Hz, CH(CH$_3$)$_a$(C<u>H</u>$_3$)$_b$); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 202.5 (C), 167.9 (C), 166.0 (C), 133.3 (CH), 129.9 (CH), 129.3 (C), 128.4 (CH), 71.5 (CH), 65.6 (CH_2), 31.5 (CH_2), 30.7 (CH), 19.0 (CH_3), 17.5 (CH_3).

4.1.10. (*S*)-4-Isopropyl-*N*-(triethylsilyloxy)acetyl-1,3-thiazolidine-2-thione (4s)

The thioimide **4s** was prepared according to the General Procedure in section 4.1.8. from thioimide **4l** (707 mg, 2.3 mmol), $TiCl_4$ (0.5 mL, 4.6 mmol), 2,6-lutidine (0.35 mL, 3.0 mmol), triethylsilyl trifluoromethanesulfonate (0.65 mL, 2.86 mmol) as the hydroxyl protecting agent, anh CH_2Cl_2 (18 mL) at the first step and anh CH_2Cl_2 (9.2 mL) at the second step. Purification of the crude product by flash column chromatography (hexanes/EtOAc 9:1) afforded 234 mg (0.70 mmol, 30%) of thioimide **4s**.

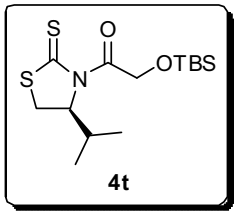


4s

(*S*)-4-Isopropyl-*N*-(triethylsilyloxy)acetyl-1,3-thiazolidine-2-thione (**4s**). Yellow oil; **R_f** = 0.35 (hexanes/EtOAc 9:1); **$[\alpha]_D$** = +180.5 (*c* 0.67, $CHCl_3$); **IR** (ATR) 2951, 2870, 1705, 1679, 1464, 1405, 1364, 1264, 1175, 1119 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.18 (1H, ddd, *J* = 8.2, 6.2, 1.2 Hz, NC<u>H</u>), 5.16 (1H, d, *J* = 18.2 Hz, COC<u>H</u>$_a$H$_b$), 5.10 (1H, d, *J* = 18.2 Hz, COCH$_a$<u>H</u>$_b$), 3.59 (1H, dd, *J* = 11.5, 8.2 Hz, SC<u>H</u>$_a$H$_b$), 3.08 (1H, dd, *J* = 11.5, 1.2 Hz, SCH$_a$<u>H</u>$_b$), 2.45–2.33 (1H, m, C<u>H</u>(CH$_3$)$_2$), 1.06 (3H, d, *J* = 6.8 Hz, CH(C<u>H</u>$_3$)$_a$(CH$_3$)$_b$), 0.98 (3H, d, *J* = 7.1 Hz, CH(CH$_3$)$_a$(C<u>H</u>$_3$)$_b$), 0.98 (9H, t, *J* = 7.8 Hz, Si(CH$_2$C<u>H</u>$_3$)$_3$), 0.66 (6H, q, *J* = 7.8 Hz, Si(C<u>H</u>$_2$CH$_3$)$_3$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.0 (C), 172.8 (C), 71.6 (CH), 66.3 (CH_2), 31.4 (CH_2), 30.7 (CH), 19.0 (CH_3), 17.5 (CH_3), 6.7 (CH_3), 4.4 (CH_2).

4.1.11. (*S*)-*N*-(tert-Butyl)dimethylsilyloxyacetyl-4-isopropyl-1,3-thiazolidine-2-thione (4t)

The thioimide **4t** was prepared according to the General Procedure in section 4.1.8. from thioimide **4l** (707 mg, 2.3 mmol), $TiCl_4$ (0.5 mL, 4.6 mmol), 2,6-lutidine (0.35 mL, 3.0 mmol), *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.65 mL, 2.86 mmol) as the hydroxyl protecting agent, anh CH_2Cl_2 (18 mL) at the first step and anh CH_2Cl_2 (9.2 mL) at the second step. Purification of the crude product by flash column chromatography (hexanes/EtOAc 95:5) afforded 391 mg (1.17 mmol, 51%) of thioimide **4t**.



4t

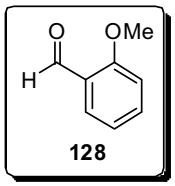
(*S*)-*N*-(*tert*-Butyldimethylsilyloxyacetyl)-4-isopropyl-1,3-thiazolidine-2-thione (**4t**). Yellow oil; **R_f** = 0.70 (CH_2Cl_2); **$[\alpha]_D$** = +227.1 (*c* 0.98, $CHCl_3$); **IR** (film) 2958, 2857, 1715, 1373, 1263, 1178, 1142 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.17 (1H, ddd, *J* = 8.2, 6.0, 1.2 Hz, NC<u>H</u>), 5.14 (1H, d, *J* = 18.3 Hz, COC<u>H</u>$_a$H$_b$), 5.13 (1H, d, *J* = 18.3 Hz, COCH$_a$<u>H</u>$_b$), 3.59 (1H, dd, *J* = 11.5, 8.2 Hz, SC<u>H</u>$_a$H$_b$), 3.08 (1H, dd, *J* = 11.6, 1.2 Hz, SCH$_a$<u>H</u>$_b$), 2.43–2.35 (1H, m, C<u>H</u>(CH$_3$)$_2$), 1.06 (3H, d, *J* = 6.8 Hz,

$CH(C\underline{H}_3)_a(CH_3)_b$), 0.98 (3H, d, J = 6.9 Hz, $CH(CH_3)_a(C\underline{H}_3)_b$), 0.93 (9H, s, $C(C\underline{H}_3)_3$), 0.12 (3H, s, $Si(C\underline{H}_3)_a(CH_3)_b$), 0.11 (3H, s, $Si(CH_3)_a(C\underline{H}_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.9, 172.9, 71.6, 66.7, 31.4, 30.7, 25.8, 19.0, 18.5, 17.5, –5.3, –5.4.

4.1.12. 2-Methoxybenzaldehyde (128)

A solution of iodomethane (2.5 mL, 40 mmol) in THF (20 mL) was added dropwise to a suspension of NaH (480 mg, 20 mmol) and salicylaldehyde (2.44 g, 20 mmol) in 4:1 DMF/THF (30 mL) at 0 ºC under N_2. The reaction mixture was stirred for 3 h at r.t.

The mixture was diluted in Et_2O (30 mL) and washed with water (3 × 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography (hexanes/EtOAc 9:1) to afford 1.04 g (7.6 mmol, 38%) of aldehyde **128**.



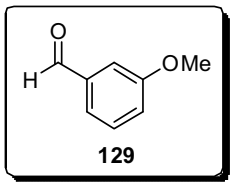
128

2-Methoxybenzaldehyde (**128**). Colorless Oil; $\mathbf{R_f}$ = 0.50 (hexanes/EtOAc 9:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 10.48 (1H, s, C$\underline{H}$O), 7.84 (1H, dd, J = 7.7, 1.9 Hz, Ar$\underline{H}$), 7.56 (1H, ddd, J = 8.5, 7.3, 1.9 Hz, Ar$\underline{H}$), 7.10–6.96 (2H, m, Ar$\underline{H}$), 3.94 (1H, s, $OC\underline{H}_3$).

4.1.13. 3-Methoxybenzaldehyde (129)

A solution of iodomethane (3.75 mL, 60 mmol) in acetone (18 mL) was added to a solution of 3-hydroxybenzaldehyde (3.66 g, 30 mmol) in acetone (18 mL) at 0 ºC under N_2. Then, solid K_2CO_3 (8.29 g, 60 mmol) was added, the mixture purged with N_2 again and heated to reflux for 2 h and stirred for 10 h at r.t.

The reaction mixture was filtered and concentrated. A further purification by flash column chromatography on silica gel (hexanes/EtOAc 85:15) afforded 2.81 g (20.6 mmol, 69%) of aldehyde **129**.



129

3-Methoxybenzaldehyde (**129**). Colorless oil; $\mathbf{R_f}$ = 0.40 (hexanes/EtOAc 9:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.98 (1H, s, C$\underline{H}$O), 7.48–7.39 (3H, m, Ar$\underline{H}$), 7.21–7.16 (1H, m, Ar$\underline{H}$), 3.87 (1H, s, $OC\underline{H}_3$).

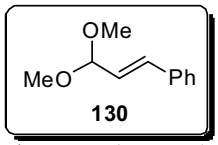
4.1.14. General procedure for the preparation of dimethyl acetals[33]

Trimethyl orthoformate (1.2 eq) and anh MeOH (0.2 eq) were added to a mixture of the corresponding aldehyde (1.0 eq) and catalytic amounts of Amberlyst® 15 resin under N_2 at r.t. The suspension was stirred at r.t. for a certain time.

The mixture was filtered and the solvent was removed *in vacuo*. The residue was then purified to afford the corresponding dimethyl acetal.

4.1.15. (*E*)-Cinnamaldehyde dimethyl acetal (130)

The dimethyl acetal **130** was prepared according to the General Procedure in section 4.1.11. from cinnamaldehyde (3.8 mL, 30 mmol), trimethyl orthoformate (4.0 mL, 36 mmol), anh MeOH (0.3 mL, 6 mmol) at r.t. for 70 h. The crude residue was purified by distillation at reduced pressure, followed by a further purification of the impurified fractions by flash column chromatography on silica gel (hexanes/EtOAc 85:15) to afford 3.73 g (20.9 mmol, 70%) of dimethyl acetal **130**.

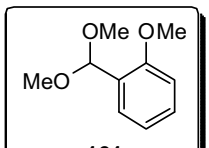


130

(*E*)-Cinnamaldehyde dimethyl acetal (**130**). Colorless oil; **bp**= 71–73 ºC (10 mmHg); $\mathbf{R_f}$ = 0.50 (hexanes/EtOAc 85:15); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.44–7.38 (2H, m, ArH), 7.35–7.24 (3H, m, ArH), 6.73 (1H, dd, *J* = 16.2, 1.3 Hz, PhCH=CH), 6.16 (1H, dd, *J* = 16.2, 4.9 Hz, PhCH=CH), 4.96 (1H, dd, *J* = 4.9, 1.3 Hz, CH$(OCH_3)_2$), 3.38 (6H, s, CH$(OCH_3)_2$).

4.1.16. 2-Methoxybenzaldehyde dimethyl acetal (131)

The dimethyl acetal **131** was prepared according to the General Procedure in section 4.1.11. from 2-methoxybenzaldehyde (1.0 g, 7.5 mmol), trimethyl orthoformate (1.0 mL, 9 mmol), anh MeOH (60 µL, 1.5 mmol) at r.t. for 3 h. The crude residue was purified by distillation under reduced pressure to afford 442 mg (2.4 mmol, 32%) of dimethyl acetal **131**.

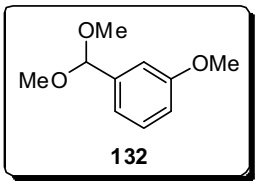


131

2-Methoxybenzaldehyde dimethyl acetal (**131**). Colorless liquid; **bp** = 129–131 ºC (15 mmHg); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.53 (1H, dd, *J* = 7.6, 1.8 Hz, ArH), 7.31 (1H, ddd, *J* = 8.3, 7.6, 1.8 Hz, ArH), 6.97 (1H, td, *J* = 7.6, 0.7 Hz, ArH), 6.90 (1H, d, *J* = 8.3 Hz, ArH), 5.68 (1H, s, CH$(OCH_3)_2$), 3.85 (3H, s, ArOCH$_3$), 3.36 (6H, s, CH$(OCH_3)_2$).

4.1.17. 3-Methoxybenzaldehyde dimethyl acetal (132)

The dimethyl acetal **132** was prepared according to the General Procedure in section 4.1.11. from 2-methoxybenzaldehyde (2.0 g, 14.5 mmol), trimethyl orthoformate (1.9 mL, 17.4 mmol), anh MeOH (0.1 mL, 2.5 mmol) at r.t. for 70 h. The crude residue was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/EtOAc 95:5 to 1:1) to give 2.15 g (11.8 mmol, 82%) of dimethyl acetal **132**.

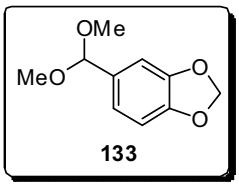


132

3-Methoxybenzaldehyde dimethyl acetal (**132**). Colorless oil; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.30–7.26 (1H, m, ArH), 7.04–7.01 (2H, m, ArH), 6.88–6.86 (1H, m, ArH), 5.36 (1H, s, CH$(OCH_3)_2$), 3.82 (3H, s, ArOCH_3), 3.34 (6H, s, CH(OCH_3)$_2$).

4.1.18. Piperonal dimethyl acetal (133)

The dimethyl acetal **133** was prepared according to the General Procedure in section 4.1.11. from piperonal (5.5 g, 36.5 mmol), trimethyl orthoformate (4.8 mL, 43.8 mmol), anh MeOH (0.3 mL, 7.3 mmol) at r.t. for 70 h. The crude residue was purified by flash column chromatography on silica gel (hexanes/EtOAc 9:1) to give 3.9 g (20 mmol, 55%) of dimethyl acetal **133**.

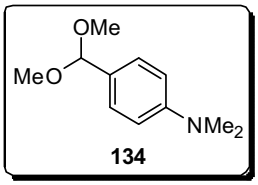


133

Piperonal dimethyl acetal (**133**). Colorless oil; $\mathbf{R_f}$ = 0.55 (hexanes/EtOAc 85:15); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 6.95 (1H, d, *J* = 1.7 Hz, ArH), 6.92 (1H, dd, *J* = 8.0, 1.7 Hz, ArH), 6.79 (1H, d, *J* = 8.0 Hz, ArH), 5.96 (2H, s, OCH_2O), 5.29 (1H, s, CH$(OCH_3)_2$), 3.31 (6H, s, CH(OCH_3)$_2$).

4.1.19. 4-(*N,N*-Dimethylamino)benzaldehyde dimethyl acetal (134)

The dimethyl acetal **134** was prepared according to the General Procedure in section 4.1.11. from 4-(*N,N*-dimethylamino)benzaldehyde (4.5 g, 30 mmol), trimethyl orthoformate (4.0 mL, 36 mmol), anh MeOH (0.25 mL, 6 mmol) at r.t. for 110 h. The crude residue was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/EtOAc 9:1) to give 2.0 g (10.5 mmol, 35%) of dimethyl acetal **134**.

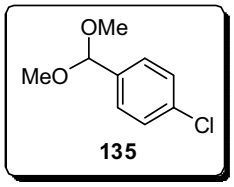


134

4-(*N,N*-Dimethylamino)benzaldehyde dimethyl acetal (**134**). Colorless oil; $\mathbf{R_f}$ = 0.50 (hexanes/EtOAc 85:15); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.31–7.29 (2H, m, ArH), 6.73–6.70 (2H, m, ArH), 5.32 (1H, s, CH$(OCH_3)_2$),3.31 (6H, s, CH$(OCH_3)_2$), 2.95 (6H, s, N$(CH_3)_2$).

4.1.20. 4-Chlorobenzaldehyde dimethyl acetal (135)

The dimethyl acetal **135** was prepared according to the General Procedure in section 4.1.11. from 4-chlorobenzaldehyde (5.1 g, 36.5 mmol), trimethyl orthoformate (4.8 mL, 43.8 mmol), anh MeOH (0.3 mL, 7.3 mmol) at r.t. for 70 h. The crude residue was purified by distillation under reduced pressure to afford 4.5 g (24.4 mmol, 67%) of dimethyl acetal **135**.



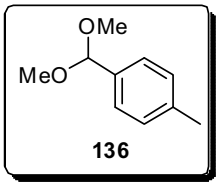
135

4-Chlorobenzaldehyde dimethyl acetal (**135**). Colorless liquid; **bp** = 49−51 ºC (10 mmHg); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.43–7.26 (4H, m, Ar<u>H</u>), 5.38 (1H, s, C<u>H</u>$(OCH_3)_2$),3.31 (6H, s, CH$(OC\underline{H}_3)_2$).

4.1.21. 4-Methylbenzaldehyde dimethyl acetal (136)[179]

A solution of 4-methylbenzaldehyde (1.2 mL, 10 mmol) and CSA (340 mg, 1.5 mmol) in 2:1 MeOH/CH_2Cl_2 (30 mL) was stirred for 3 days at r.t. under N_2.

The mixture was washed with sat $NaHCO_3$ (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The resultant oil was purified through flash column chromatography on deactivated silica gel (hexanes/EtOAc 10:1) to give 935 mg (5.6 mmol, 56%) of dimethyl acetal **136**.



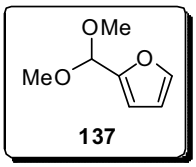
136

4-Methylbenzaldehyde dimethyl acetal (**136**). Colorless oil; $\mathbf{R_f}$ = 0.50 (hexanes/EtOAc 10:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.33 (2H, d, *J* = 8.2 Hz, Ar<u>H</u>), 7.17 (2H, d, *J* = 8.2 Hz, Ar<u>H</u>), 5.36 (1H, s, C<u>H</u>$(OCH_3)_2$), 3.32 (6H, s, CH$(OC\underline{H}_3)_2$), 2.35 (3H, s, Ar$C\underline{H}_3$)

4.1.22. 2-Furfural dimethyl acetal (137) [128]

2-Furfural (15.3 g, 160 mmol) was added to a suspension of NH_4Cl (0.43 g, 8.0 mmol) in anh MeOH (19.4 mL, 480 mmol). Then, it was cooled to 0 ºC and trimethyl orthoformate (19.7 mL, 180 mmol) was added. The resulting mixture was heated to reflux for 3 h.

After this time, it was filtered and the volatiles removed *in vacuo*. The resulting crude was purified by distillation under reduced pressure to afford 14.3 g (100 mmol, 63%) of dimethyl acetal **137**.



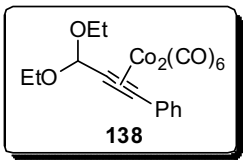
137

4-Furfural dimethyl acetal (**137**). Colorless liquid; **bp** = 27−29 ºC (10 mmHg); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.42–7.41 (1H, m, ArH), 6.42 (1H, dt, *J* = 3.3, 0.9 Hz, ArH), 6.37 (1H, dd, *J* = 3.3, 1.8 Hz, ArH), 5.44 (1H, d, *J* = 0.9 Hz, CH(OCH_3)$_2$), 3.31 (6H, s, CH(OCH_3)$_2$).

4.1.23. Hexacarbonyl μ-[η^4-(1,1-diethoxy-3-phenylpropyne)dicobalt (138)] [128]

Under N_2, a solution of phenylpropiolaldehyde diethyl acetal (0.80 mL, 3.9 mmol) in anh pentane (2.3 mL) was added *via cannula* to a solution of $Co_2(CO)_8$ (1.40 g, 4.1 mmol) in anh pentane (18.7 mL). The reaction mixture was stirred for 1.5 h at r.t. Vacuum was applied and the system purged again with N_2. This process was repeated for four times. Then, the reaction mixture was stirred for 1.5 h at r.t.

After this time, the solution was bubbled with a N_2 flux until the volume of solvent was reduced by half. The resulting solution was purified by flash column chromatography on silica gel (hexanes/Et_2O 98:2 to 94:6) to give 1.82 g (3.71 mmol, 95%) of cobalted acetal **138**.



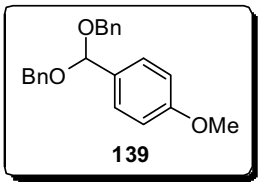
138

Hexacarbonyl μ-[η^4-(1,1-diethoxy-3-phenylpropyne)dicobalt (**138**). Black solid; **R_f** = 0.55 (hexanes/Et_2O 95:5); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.65–7.58 (2H, m, ArH), 7.38–7.28 (3H, m, ArH), 5.73 (1H, s, CH(OCH_2CH_3)$_2$), 3.87–3.69 (4H, m,CH(OCH_2CH_3)$_2$), 1.26 (6H, t, *J* = 7.0 Hz, CH(OCH_2CH_3)$_2$).

4.1.24. *p*-Anisaldehyde dibenzyl acetal (139)

A solution of *p*-anisaldehyde dimethyl acetal (1.7 mL, 10 mmol), benzyl alcohol (2.1 mL, 21 mmol) and CSA (116 mg, 0.5 mmol) in cyclohexane (50 mL) under N_2 was equipped with a Dean-Stark apparatus containing 5 Å molecular sieves and heated to reflux for 1.5 h.

After cooling, the mixture was diluted with Et_2O (25 mL) and washed with 0.5 M NaOH (3 × 30 mL) and brine (30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude oil was purified by flash column chromatography on deactivated silica gel (2.5% Et_3N) (hexanes/EtOAc 9:1) to afford 2.47 g (7.39 mmol, 74%) of dibenzyl acetal **139**.



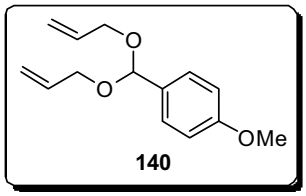
139

p-Anisaldehyde dibenzyl acetal (**139**). White solid; **R_f** = 0.45 (hexanes/EtOAc 9:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.53–7.46 (2H, m, ArH), 7.37–7.25 (10H, m, ArH), 6.96–6.89 (2H, m, ArH), 5.73 (1H, s, CH(OCH_2Ph)$_2$), 4.59 (4H, s, CH(OCH_2Ph)$_2$), 3.82 (3H, s, ArOCH_3).

4.1.25. *p*-Anisaldehyde diallyl acetal (140)

A mixture of *p*-anisaldehyde dimethyl acetal (2.55 mL, 15.0 mmol), allyl alcohol (31 mL, 450 mmol) and catalytic amounts of Amerlyst® 15 resin was stirred at r.t. for 70 h.

Then, it was filtered and the volatiles removed *in vacuo*. The resulting crude oil was purified by distillation under reduced pressure to afford 243 mg (1.04 mmol, 7%) of diallyl acetal **140**.



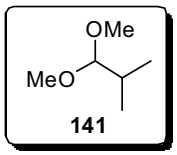
140

p-Anisaldehyde diallyl acetal (**140**). Colorless liquid; **bp** = 100–105 ºC (20 mmHg); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.44–7.38 (2H, m, ArH), 6.92–6.87 (2H, m, ArH), 5.93 (2H, ddt, *J* = 17.2, 10.6, 5.5 Hz, 2 × CH=CH_2), 5.59 (1H, s, CH($OCH_2CH=CH_2$)$_2$), 5.30 (2H, dq, *J* = 17.2, 1.7 Hz, 2 × CH=CH_EH_Z), 5.20–5.13 (2H, m, 2 × CH=CH_EH_Z), 4.05 (4H, dt, *J* = 5.5, 1.5 Hz, 2 × OCH_2), 3.81 (3H, s, OCH_3).

4.1.26. Isobutyraldehyde dimethyl acetal (141)

Trimethyl orthoformate (7.6 mL, 69 mmol) and anh MeOH (0.85 mL, 20.7 mmol) were added to a mixture of isobutyraldehyde (5.5 mL, 60 mmol) and catalytic amounts of Amberlyst® 15 resin under N_2. The suspension was stirred at r.t. for 24 h.

The mixture was filtered and the solvent was removed *in vacuo*. The residue was then purified by distillation to afford 3.52 g (29.8 mmol, 50%) of dimethyl acetal **141**.



141

Isobutyraldehyde dimethyl acetal (**141**). Colorless liquid; **bp** = 63−65 ºC; **IR** (film) 2959, 2930, 2830, 1767, 1716, 1108 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 3.96 (1H, d, *J* = 6.8 Hz, CH(OCH_3)$_2$), 3.35 (6H, s, CH(OCH_3)$_2$), 1.93–1.84 (1H, m, CH(CH_3)$_2$), 0.91 (6H, d, *J* = 6.7 Hz, CH(CH_3)$_2$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 109.6 (CH), 53.6 (CH_3), 30.6 (CH), 17.6 (CH_3).

4.2. GENERAL PROCEDURE FOR OPTIMIZATION REACTIONS

Solid $(Me_3P)_2NiCl_2$ was added to a solution of the corresponding *N*-glycolylthioimide (0.50 mmol) and the corresponding dimethyl acetal in anh CH_2Cl_2 (1.0 mL) under N_2. The resulting mixture was purged with N_2 again and then cooled to –20 ºC. Silyl triflate and 2,6-lutidine were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred at –20 ºC.

The reaction was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude was purified by flash column chromatography on silica gel to give the desired products.

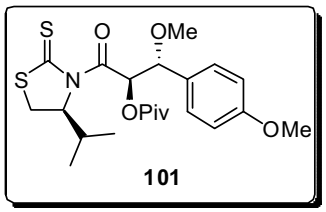
4.3. PRELIMINARY EXPERIMENTS

4.3.1. With benzaldehyde dimethyl acetal

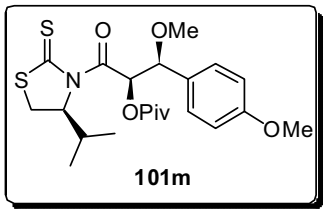
The thioimide **100** was prepared according to the General Procedure in section 4.2. from thioimide **4m** (152 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (28.2 mg, 0.10 mmol), benzaldehyde dimethyl acetal (83 µL, 0.55 mmol), TESOTf (170 µL, 0.75 mmol), 2,6-lutidine (88 µL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. A 75:25 diastereomeric ratio of the *anti/syn* diastereomers was established by ^{1}H NMR of the crude product. Purification of the crude product by flash column chromatography on silica gel (from hexanes/EtOAc 93:7 to 85:15) afforded 22 mg of the pure *syn* diastereomer **100m** (0.06 mmol, 11%) and a mixture of the *anti* diastereomer **100** and the starting material **4m**. Another purification of this last mixture by flash column chromatography on silica gel (from hexanes/CH_2Cl_2 7:3 to CH_2Cl_2) afforded 72 mg of the pure *anti* diastereomer **100** (0.19 mmol, 35%).

4.3.2. With *p*-anisaldehyde dimethyl acetal

The thioimide **101** was prepared according to the General Procedure in section 4.2. from thioimide **4m** (152 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (28.2 mg, 0.10 mmol), *p*-anisaldehyde dimethyl acetal (94 µL, 0.55 mmol), TESOTf (170 µL, 0.75 mmol), 2,6-lutidine (88 µL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. A 87:13 diastereomeric ratio of the *anti/syn* diastereomers was established by HPLC of the crude product. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc 85:15) afforded 175 mg of the pure *anti* diastereomer **101** (0.39 mmol, 77%) and 22 mg of the pure *syn* diastereomer **101m** (0.05 mmol, 10%).



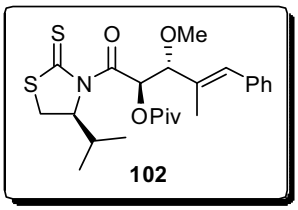
(*S*)-4-Isopropyl-*N*-[(*2R*, *3R*)-3-methoxy-3-(4-methoxyphenyl)-2-pivaloyloxypropanoyl]-1,3-thiazolidine-2-thione (**101**). Yellow solid; **mp** = 129–130 ºC; $\mathbf{R_f}$ = 0.40 (hexanes/EtOAc 85:15); $\mathbf{R_f}$ = 0.50 (CH_2Cl_2); **HPLC** (Tracer Spherisorb S3W (N4184) column, 5% of EtOAc in hexanes, 0.9 mL/min, 254 nm), t_R = 23.3 min; $\mathbf{[\alpha]_D}$ = +171.9 (*c* 1.00, $CHCl_3$); **IR** (ATR) 2966, 2929, 2862, 2825, 1727, 1701, 1606, 1512, 1360, 1245, 1171, 1145 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.39–7.37 (2H, m, ArH), 7.13 (1H, *J* = 7.4 Hz, COCH), 6.90–6.88 (2H, m, ArH), 5.29 (1H, ddd, *J* = 8.3, 5.9, 1.0 Hz, NCH), 4.60 (1H, d, *J* = 7.4 Hz, CHOCH$_3$), 3.81 (3H, s, ArOCH$_3$), 3.60 (1H, dd, *J* = 11.4, 8.3 Hz, SCH$_a$H$_b$), 3.17 (3H, s, CHOCH$_3$), 3.01 (1H, dd, *J* = 11.4, 1.0 Hz, SCH$_a$H$_b$), 2.36–2.27 (1H, m, CH(CH$_3$)$_2$), 1.11 (3H, d, *J* = 6.8 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$), 1.10 (9H, s, C(CH$_3$)$_3$), 1.01 (3H, d, *J* = 6.9 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.6 (C), 177.5 (C), 170.3 (C), 159.7 (C), 129.4 (CH), 129.4 (C), 113.5 (CH), 83.4 (CH), 73.1 (CH), 71.6 (CH), 56.7 (CH_3), 55.2 (CH_3), 38.3 (C), 30.5 (CH), 30.2 (CH_2), 26.8 (CH_3), 18.9 (CH_3), 17.4 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OCH_3]^+$ $C_{21}H_{28}NO_4S_2$: 422.1454, found: 422.1445; *m/z* calculated for $[M+Na]^+$ $C_{22}H_{31}NNaO_5S_2$: 476.1536, found: 476.1531.



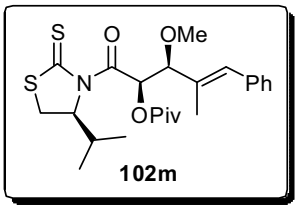
(*S*)-4-isopropyl-*N*-[(*2R*, *3S*)-3-methoxy-3-(4-methoxyphenyl)-2-pivaloyloxypropanoyl]-1,3-thiazolidine-2-thione (**101m**). Yellow solid; $\mathbf{R_f}$ = 0.30 (hexanes/EtOAc 85:15), $\mathbf{R_f}$ = 0.50 (CH_2Cl_2); **HPLC** (Tracer Spherisorb S3W (N4184) column, 5% of EtOAc in hexanes, 0.9 mL/min, 254 nm), t_R = 40.5 min; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.44–7.41 (2H, m, ArH), 6.97 (1H, *J* = 2.6 Hz, COCH), 6.89–6.87 (2H, m, ArH), 5.49 (1H, ddd, *J* = 9.0, 5.1, 1.5 Hz, NCH), 5.30 (1H, d, *J* = 2.6 Hz, CHOCH$_3$), 3.81 (3H, s, ArOCH$_3$), 3.60 (1H, dd, *J* = 11.5, 9.0 Hz, SCH$_a$H$_b$), 3.22 (3H, s, CHOCH$_3$), 3.05 (1H, dd, *J* = 11.5, 1.5 Hz, SCH$_a$H$_b$), 2.39–2.29 (1H, m, CH(CH$_3$)$_2$), 1.14 (9H, s, C(CH$_3$)$_3$), 1.08 (3H, d, *J* = 6.8 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$), 1.00 (3H, d, *J* =7.0 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.3, 177.9, 167.9, 159.5, 128.9, 128.9, 113.4, 80.5, 75.6, 71.7, 57.2, 55.2, 38.6, 30.8, 29.7, 26.9, 18.9, 17.0.

4.3.3. With (*E*)-α-methylcinnamaldehyde dimethyl acetal (78)

The thioimide **102** was prepared according to the General Procedure in section 4.2. from thioimide **4m** (152 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (28.2 mg, 0.10 mmol), dimethyl acetal **78** (106 mg, 0.55 mmol), TESOTf (170 μL, 0.75 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 48 h. A 93:7 diastereomeric ratio of the *anti/syn* diastereomers was established by HPLC of the crude product. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc 92:8) afforded 201 mg of the pure *anti* diastereomer **102** (0.44 mmol, 88%) and 15 mg of the pure *syn* diastereomer **102m** (0.03 mmol, 5%).



(*S*)-4-Isopropyl-*N*-[(*2R*, *3R*)-3-methoxy-4-methyl-5-phenyl-2-pivaloyloxypent-4-enoyl]-1,3-thiazolidine-2-thione (**102**). Yellow oil; $\mathbf{R_f}$ = 0.45 (hexanes/EtOAc 85:15), $\mathbf{R_f}$ = 0.30 (hexanes/$CH_2Cl_2$1:4); **HPLC** (Tracer Spherisorb S3W (N4184) column, 5% of EtOAc in hexanes, 0.9 mL/min, 254 nm), t_R = 14.3 min; $\mathbf{[\alpha]_D}$ = +222.0 (*c* 2.10, $CHCl_3$); **IR** (film) 2966, 2874, 1732, 1700, 1364, 1176, 1149 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.37–7.19 (5H, m, ArH), 7.20 (1H, d, *J* = 7.5 Hz, COCH), 6.54 (1H, br s, C=CHPh), 5.31 (1H, ddd, *J* = 8.5, 5.7, 1.1 Hz, NCH), 4.26 (1H, d, *J* = 7.5 Hz, CHOCH$_3$), 3.57 (1H, dd, *J* = 11.5, 8.5, Hz, SCH$_a$H$_b$), 3.25 (3H, s, OCH$_3$), 2.99 (1H, dd, *J* = 11.5, 1.1 Hz, SCH$_a$H$_b$), 2.32–2.22 (1H, m, CH(CH$_3$)$_2$), 1.66 (3H, d, *J* = 1.3 Hz, CH$_3$C=CH), 1.19 (9H, s, C(CH$_3$)$_3$), 1.05 (3H, d, *J* = 6.8 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$), 0.96 (3H, d, *J* = 6.9 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.5 (C), 177.6 (C), 170.3 (C), 136.8 (C), 134.5 (C), 131.4 (CH), 128.9 (CH), 128.1 (CH), 126.8 (CH), 87.5 (CH), 71.6 (CH), 70.8 (CH), 56.3 (CH_3), 38.4 (C), 30.5 (CH), 29.9 (CH_2), 26.9 (CH_3), 18.8 (CH_3), 17.1 (CH_3), 13.2 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+Na]^+$ $C_{24}H_{33}NNaO_4S_2$: 486.1744, found: 486.1742.



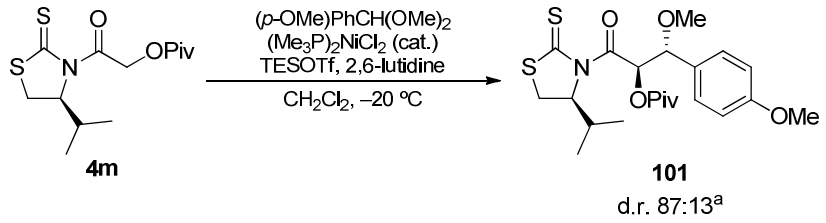
(*S*)-4-isopropyl-*N*-[(*2R*, *3S*)-3-methoxy-4-methyl-5-phenyl-2-pivaloyloxypent-4-enoyl]-1,3-thiazolidine-2-thione (**102m**). Yellow oil; $\mathbf{R_f}$ = 0.45 (hexanes/EtOAc 85:15), $\mathbf{R_f}$ = 0.30 (hexanes/$CH_2Cl_2$1:4); **HPLC** (Tracer Spherisorb S3W (N4184) column, 5% of EtOAc in hexanes, 0.9 mL/min, 254 nm), t_R = 27.9 min; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.36–7.18 (5H, m,ArH), 7.09 (1H, d, *J* = 2.8 Hz, COCH), 6.68 (1H, br s, C=CHPh), 5.48 (1H, ddd,*J* = 9.0, 4.9, 1.5 Hz, NCH), 4.79 (1H, d, *J* = 2.8 Hz, CHOCH$_3$), 3.60 (1H, dd, *J* = 11.5, 9.0 Hz, SCH$_a$H$_b$), 3.31 (3H, s, OCH$_3$), 3.05 (1H, dd, *J* = 11.5, 1.5 Hz, SCH$_a$H$_b$), 2.38–2.30 (1H, m, CH(CH$_3$)$_2$), 1.96 (3H, d, *J* = 1.3 Hz, CH$_3$C=CH), 1.23 (9H, s, C(CH$_3$)$_3$),1.08 (3H, d, *J* = 6.8 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$), 1.00 (3H,d, *J* = 7.0 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$).

4.4. REACTIONS WITH *p*-ANISALDEHYDE AND (*E*)-α-METHYLCINNAMALDEHYDE DIMETHYL ACETAL

4.4.1. Influence of the catalyst loading

4.4.1.1. With p-anisaldehyde dimethyl acetal

The reactions were carried out according to the General Procedure in section 4.2. from thioimide **4m** (152 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ in the loadings shown in Table 51, *p*-anisaldehyde dimethyl acetal (94 µL, 0.55 mmol), TESOTf in the quantities shown in Table 51, 2,6-lutidine (88 µL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. A 87:13 diastereomeric ratio of the *anti/syn* diastereomers was established by HPLC of the crude product. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc 85:15) afforded the isolated pure *anti* diastereomer **101** and *syn* diastereomer **101m**. The results are shown in Table 51.



Entry	$(Me_3P)_2NiCl_2$ (mol%)	TESOTf (eq)	t (h)	*Anti* (%)[b]	*Syn* (%)[b]
1	20	1.5	15	77	10
2	2.5	1.15	1.5	57	8
3	2.5	1.15	4	71	10
4	2.5	1.15	15	77	10
5	2.5	1.15	90	81	10

[a] Established by HPLC analysis of the crude products.
[b] Isolated yield after column chromatography.

Table 51

*4.4.1.2. With (E)-2-methylcinnamaldehyde dimethyl acetal (**78**)*

The thioimide **102** was prepared according to the General Procedure in section 4.2. from thioimide **4m** (152 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 µmol), dimethyl acetal **78** (106 mg, 0.55 mmol), TESOTf (130 µL, 0.58 mmol), 2,6-lutidine (88 µL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. A 93:7 diastereomeric ratio of the *anti/syn* diastereomers was established by HPLC of the crude product. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc 92:8) afforded 203 mg of the pure *anti* diastereomer **102** (0.45 mmol, 89%) and 15 mg of the pure *syn* diastereomer **102m** (0.03 mmol, 5%).

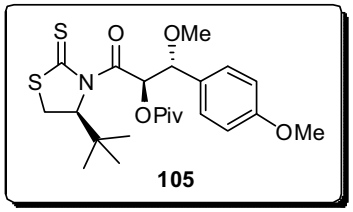
4.4.2. Influence of the chiral auxiliary

*4.4.2.1. With (S)-4-isopropyl-5,5-Diphenyl-N-pivaloyloxyacetyl-1,3-oxazolidine-2-thione (**103**)*

The reaction was carried out according to the General Procedure in section 4.2. from thioimide **103** (132 mg, 0.30 mmol), $(Me_3P)_2NiCl_2$ (2.1 mg, 7.5 μmol), *p*-anisaldehyde dimethyl acetal (56 μL, 0.33 mmol), TESOTf (78 μL, 0.35 mmol), 2,6-lutidine (52 μL, 0.45 mmol) and CH_2Cl_2 (0.6 mL) at –20 ºC for 15 h. ^{1}H NMR spectrum of the crude product revealed a complex mixture.

*4.4.2.2. With (S)-4-(tert-butyl)-N-pivaloyloxyacetyl-1,3-thiazolidine-2-thione (**104**)*

The thioimide **105** was prepared according to the General Procedure in section 4.2. from thioimide **104** (159 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol), *p*-anisaldehyde dimethyl acetal (94 μL, 0.55 mmol), TESOTf (130 μL, 0.58 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. A 89:11 diastereomeric ratio of the *anti/syn* diastereomers was established by HPLC of the crude product. Purification of the crude product by flash column chromatography on silica gel (from hexanes/EtOAc 9:1 to 7:3) afforded 167 mg of the pure *anti* diastereomer **105** (0.45 mmol, 71%) and 23 mg of the pure *syn* diastereomer **105m** (0.05 mmol, 10%).



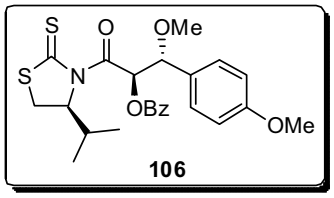
105

(*S*)-4-(*tert*-Butyl)-*N*-[(*2R*, *3R*)-3-methoxy-3-(4-methoxyphenyl)-2-pivaloyloxypropanoyl]-1,3-thiazolidine-2-thione (**105**). Yellow solid; **mp** = 129–130 ºC; $\mathbf{R_f}$ = 0.35 (hexanes/EtOAc 85:15); **HPLC** (Tracer Spherisorb S3W (N4184) column, 10% of EtOAc in hexanes, 0.9 mL/min, 254 nm), $t_{R,major}$ = 8.7 min, $t_{R,minor}$ = 12.7 min; $\mathbf{[\alpha]_D}$ = +261.5 (*c* 0.83, $CHCl_3$); **IR** (ATR) 2962, 2925, 2858, 2821, 1727, 1705, 1605, 1512, 1349, 1323, 1249, 1134 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.42–7.40 (2H, m, ArH), 7.01–6.99 (2H, m, ArH), 7.00 (1H, *J* = 8.0 Hz, COCH), 5.38 (1H, dd, *J* = 8.3, 0.6 Hz, NCH), 4.56 (1H, d, *J* = 8.0 Hz, CHOCH$_3$), 3.82 (3H, s, ArOCH$_3$), 3.65 (1H, dd, *J* = 11.7, 8.3 Hz, SCH$_a$H$_b$), 3.16 (3H, s, CHOCH$_3$), 3.12 (1H, dd, *J* = 11.7, 0.6 Hz, SCH$_a$H$_b$), 1.09 (9H, s, C(CH$_3$)$_3$), 1.07 (9H, s, C(CH$_3$)$_3$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 205.4 (C), 177.5 (C), 170.1 (C), 159.7 (C), 129.8 (C), 129.4 (CH), 113.5 (CH), 83.6 (CH), 72.5 (CH), 72.5 (CH), 56.7 (CH_3), 55.2 (CH_3), 38.3 (C), 37.7 (C), 31.1 (CH_2), 26.8 (CH_3), 26.7 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OCH_3]^+$ $C_{22}H_{30}NO_4S_2$: 436.1611, found: 436.1626.

4.4.3. Influence of the hydroxyl protecting group with *p*-anisaldehyde dimethyl acetal

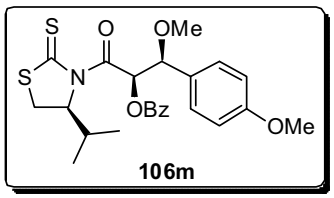
*4.4.3.1. With thioimide **4q***

The thioimide **106** was prepared according to the General Procedure in section 4.2. from thioimide **4q** (162 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol), *p*-anisaldehyde dimethyl acetal (94 μL, 0.55 mmol), TESOTf (130 μL, 0.58 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. A 83:17 diastereomeric ratio of the *anti/syn* diastereomers was established by ^{1}H NMR of the crude product. Purification of the crude product by flash column chromatography on silica gel (hexanes/CH_2Cl_2 2:3) afforded 190 mg of the pure *anti* diastereomer **106** (0.40 mmol, 80%) and 40 mg of the pure *syn* diastereomer **106m** (0.09 mmol, 17%).



106

(*S*)-*N*-[(*2R*, *3R*)-2-Benzoyloxy-3-methoxy-3-(4-methoxyphenyl) propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**106**). Yellow oil; $\mathbf{R_f}$ = 0.60 (hexanes/CH_2Cl_2 1:4); $\mathbf{[\alpha]_D}$ = +128.6 (*c* 0.93, $CHCl_3$). **IR** (ATR) 2962, 2925, 2825, 1716, 1694, 1605, 1512, 1449, 1360, 1245, 1171, 1108, 1090, 1026 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.93–7.90 (2H, m, ArH), 7.55–7.46 (3H, m, ArH), 7.43 (1H, *J* = 7.4 Hz, COCH), 7.41–7.37 (2H, m, ArH), 6.94–6.92 (2H, m, ArH), 5.32 (1H, ddd, *J* = 8.1, 6.0, 1.0 Hz, NCH), 4.75 (1H, d, *J* = 7.4 Hz, CHOCH$_3$), 3.81 (3H, s, ArOCH$_3$), 3.65 (1H, dd, *J* = 11.5, 8.1 Hz, SCH$_a$H$_b$), 3.21 (3H, s, CHOCH$_3$), 3.04 (1H, dd, *J* = 11.5, 1.0 Hz, SCH$_a$H$_b$), 2.41–2.29 (1H, m, CH(CH$_3$)$_2$), 1.13 (3H, d, *J* = 6.8 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$), 1.03 (3H, d, *J* = 7.0 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.8 (C), 170.2 (C), 165.8 (C), 159.8 (C), 133.3 (CH), 129.8 (CH), 129.5 (C), 129.4 (CH), 129.0 (C), 128.3 (CH), 113.7 (CH), 83.5 (CH), 73.6 (CH), 71.7 (CH), 56.8 (CH_3), 55.2 (CH_3), 30.5 (CH), 30.5 (CH_2), 18.9 (CH_3), 17.6 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OCH_3]^+$ $C_{23}H_{24}NO_4S_2$: 442.1141, found: 442.1134; *m/z* calculated for $[M+Na]^+$ $C_{24}H_{27}NNaO_5S_2$: 496.1223, found: 496.1224.

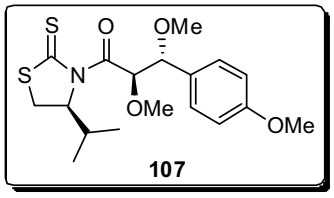


106m

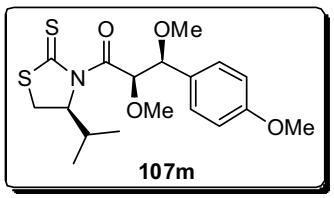
(*S*)-*N*-[(*2R*, *3S*)-2-Benzoyloxy-3-methoxy-3-(4-methoxyphenyl) propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**106m**). Yellow oil; $\mathbf{R_f}$ = 0.50 (hexanes/CH_2Cl_2 1:4); $\mathbf{[\alpha]_D}$ = +128.6 (*c* 0.93, $CHCl_3$). **IR** (ATR) 2962, 2925, 2825, 1716, 1694, 1605, 1512, 1449, 1360, 1245, 1171, 1108, 1090, 1026 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.04–8.02 (2H, m, ArH), 7.57–7.52 (3H, m, ArH), 7.44–7.40 (2H, m, ArH), 7.21 (1H, *J* = 2.6 Hz, COCH), 6.90–6.88 (2H, m, ArH), 5.51 (1H, ddd, *J* = 8.9, 5.2, 1.5 Hz, NCH), 5.40 (1H, d, *J* = 2.6 Hz, CHOCH$_3$), 3.78 (3H, s, ArOCH$_3$), 3.64 (1H, dd, *J* = 11.5, 8.9 Hz, SCH$_a$H$_b$), 3.28 (3H, s, CHOCH$_3$), 3.08 (1H, dd, *J* = 11.5, 1.5 Hz, SCH$_a$H$_b$), 2.42–2.31 (1H, m, CH(CH$_3$)$_2$), 1.09 (3H, d, *J* = 6.8 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$), 1.01 (3H, d, *J* = 6.9 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.4 (C), 167.8 (C), 166.0 (C), 159.6 (C), 133.3 (CH), 129.9 (CH), 129.1 (C), 128.8 (CH), 128.3 (CH), 128.1 (C), 113.7 (CH), 80.6 (CH), 76.4 (CH), 71.9 (CH), 57.2 (CH_3), 55.2 (CH_3), 30.8 (CH), 30.0 (CH_2), 18.9 (CH_3), 17.1 (CH_3).

*4.4.3.2. With thioimide **4r***

The thioimide **107** was prepared according to the General Procedure in section 4.2. from thioimide **4r** (117 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol), *p*-anisaldehyde dimethyl acetal (94 μL, 0.55 mmol), TESOTf (130 μL, 0.58 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. A 89:11 diastereomeric ratio of the *anti/syn* diastereomers was established by HPLC of the crude product. Purification of the crude product by flash column chromatography on silica gel (from hexanes/CH_2Cl_2 2:3 to CH_2Cl_2) afforded 70 mg of the pure *anti* diastereomer **107** (0.18 mmol, 36%) and 9 mg of *syn* diastereomer **107m** (0.02 mmol, 5%).



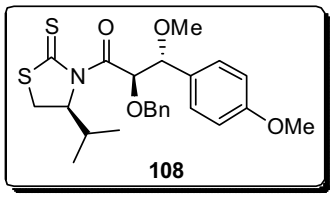
(*S*)-4-Isopropyl-*N*-[(*2R*, *3R*)-2,3-dimethoxy-3-(4-methoxyphenyl) propanoyl]-1,3-thiazolidine-2-thione (**107**). Yellow oil; $\mathbf{R_f}$ = 0.40 (CH_2Cl_2); **HPLC** (Tracer Spherisorb S3W (N4184) column, 15% of EtOAc in hexanes, 0.9 mL/min, 254 nm), t_R = 12.5 min; $\mathbf{[\alpha]_D}$ = +160.7 (*c* 1.04, $CHCl_3$); **IR** (ATR) 2959, 2929, 2821, 1690, 1608, 1509, 1360, 1238, 1160, 1093 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.39–7.37 (2H, m, ArH), 6.91–6.89 (2H, m, ArH), 6.48 (1H, *J* = 7.7 Hz, COCH), 5.39 (1H, ddd, *J* = 8.5, 5.5, 1.2 Hz, NCH), 4.37 (1H, d, *J* = 7.7 Hz, CHOCH$_3$), 3.81 (3H, s, ArOCH$_3$), 3.53 (1H, dd, *J* = 11.5, 8.5 Hz, SCH$_a$H$_b$), 3.15 (3H, s, OCH$_3$), 3.11 (3H, s, OCH$_3$), 3.04 (1H, dd, *J* = 11.5, 1.2 Hz, SCH$_a$H$_b$), 2.38–2.26 (1H, m, CH(CH$_3$)$_2$), 1.11 (3H, d, *J* = 6.8 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$), 1.10 (3H, d, *J* = 6.9 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.9 (C), 173.3 (C), 159.6 (C), 130.3 (C), 129.6 (CH), 113.6 (CH), 84.7 (CH), 80.4 (CH), 71.8 (CH), 58.8 (CH_3), 56.4 (CH_3), 55.2 (CH_3), 30.6 (CH), 29.8 (CH_2), 19.0 (CH_3), 17.2 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OCH_3]^+$ $C_{17}H_{22}NO_3S_2$: 352.1036, found: 352.1031; *m/z* calculated for $[M+Na]^+$ $C_{18}H_{25}NNaO_4S_2$: 406.1117, found: 406.1105.



(*S*)-4-Isopropyl-*N*-[(*2R*, *3S*)-2,3-dimethoxy-3-(4-methoxyphenyl) propanoyl]-1,3-thiazolidine-2-thione (**107m**). Yellow oil; $\mathbf{R_f}$ = 0.40 (CH_2Cl_2); **HPLC** (Tracer Spherisorb S3W (N4184) column, 15% of EtOAc in hexanes, 0.9 mL/min, 254 nm), t_R = 25.2 min; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.45–7.43 (2H, m, ArH), 6.89–6.87 (2H, m, ArH), 6.05 (1H, *J* = 3.1 Hz, COCH), 5.50 (1H, ddd, *J* = 9.1, 4.9, 1.8 Hz, NCH), 4.95 (1H, d, *J* = 3.1 Hz, CHOCH$_3$), 3.81 (3H, s, ArOCH$_3$), 3.56 (1H, dd, *J* = 11.5, 9.1 Hz, SCH$_a$H$_b$), 3.29 (3H, s, OCH$_3$), 3.14 (3H, s, OCH$_3$), 3.05 (1H, dd, *J* = 11.5, 1.8 Hz, SCH$_a$H$_b$), 2.30–2.19 (1H, m, CH(CH$_3$)$_2$), 1.01 (3H, d, *J* = 7.0 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$), 0.94 (3H, d, *J* = 7.0 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$).

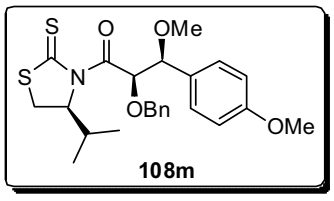
*4.4.3.3. With thioimide **4l***

The thioimide **108** was prepared according to the General Procedure in section 4.2. from thioimide **4l** (155 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol), *p*-anisaldehyde dimethyl acetal (94 μL, 0.55 mmol), TESOTf (130 μL, 0.58 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. A 88:12 diastereomeric ratio of the *anti/syn* diastereomers was established by HPLC of the crude product. Purification of the crude product by flash column chromatography on silica gel (from hexanes/CH_2Cl_2 3:7 to CH_2Cl_2) afforded 142 mg of the pure *anti* diastereomer **108** (0.31 mmol, 61%) and 23 mg of *syn* diastereomer **108m** (0.05 mmol, 10%).



108

(*S*)-*N*-[(*2R*, *3R*)-2-Benzyloxy-3-methoxy-3-(4-methoxyphenyl) propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**108**). Yellow oil; $\mathbf{R_f}$ = 0.50 (CH_2Cl_2); **HPLC** (Tracer Spherisorb S3W (N4184) column, 10% of EtOAc in hexanes, 0.9 mL/min, 254 nm), t_R = 12.0 min; $\mathbf{[\alpha]_D}$ = +151.0 (*c* 1.00, $CHCl_3$); **IR** (ATR) 2959, 2925, 2866, 1694, 1606, 1509, 1245, 1168, 1093, 1027 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.44–7.41 (2H, m, ArH), 7.26–7.24 (3H, m, ArH), 7.14–7.12 (2H, m, ArH), 6.92–6.90 (2H, m, ArH), 6.54 (1H, *J* = 8.2 Hz, COCH), 5.03 (1H, ddd, *J* = 8.1, 6.1, 1.1 Hz, NCH), 4.40 (1H, d, *J* = 12.1 Hz, CH_aH_bPh), 4.37 (1H, d, *J* = 8.2 Hz, $CHOCH_3$), 4.17 (1H, d, *J* = 12.1 Hz, CH_aH_bPh), 3.84 (3H, s, $ArOCH_3$), 3.18 (1H, dd, *J* = 11.3, 8.1 Hz, SCH_aH_b), 3.10 (3H, s, $CHOCH_3$), 2.88 (1H, dd, *J* = 11.3, 1.1 Hz, SCH_aH_b), 2.30–2.22 (1H, m, $CH(CH_3)_2$), 1.03 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(CH_3)_b$), 0.96 (3H, d, *J* = 6.9 Hz, $CH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.6 (C), 173.5 (C), 159.6 (C), 137.4 (C), 130.7 (C), 129.6 (CH), 128.4 (CH), 128.1 (CH), 127.8 (CH), 113.6 (CH), 85.0 (CH), 78.1 (CH), 73.7 (CH_2), 71.5 (CH), 56.6 (CH_3), 55.2 (CH_3), 30.5 (CH), 30.3 (CH_2), 18.8 (CH_3), 17.5 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OCH_3]^+$ $C_{23}H_{26}NO_3S_2$: 428.1349, found: 428.1346; *m/z* calculated for $[M+Na]^+$ $C_{24}H_{29}NNaO_4S_2$: 482.1430, found: 482.1425.

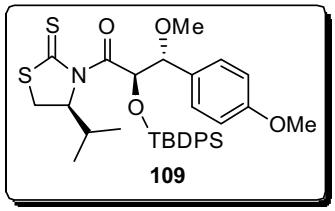


108m

(*S*)-*N*-[(*2R*, *3S*)-2-Benzyloxy-3-methoxy-3-(4-methoxyphenyl) propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**108m**). Yellow oil; $\mathbf{R_f}$ = 0.25 (CH_2Cl_2); **HPLC** (Tracer Spherisorb S3W (N4184) column, 10% of EtOAc in hexanes, 0.9 mL/min, 254 nm), t_R = 24.5 min; $\mathbf{[\alpha]_D}$ = +185.1 (*c* 1.00, $CHCl_3$); **IR**(ATR) 2959, 2925, 2873, 2833, 1709, 1605, 1512, 1468, 1242, 1090, 1030 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.42–7.40 (2H, m, ArH), 7.20–7.18 (3H, m, ArH), 7.07–7.05 (2H, m, ArH), 6.88–6.86 (2H, m, ArH), 6.23 (1H, *J* = 3.4 Hz, COCH), 5.33 (1H, ddd, *J* = 9.0, 4.8, 1.8 Hz, NCH), 4.96 (1H, d, *J* = 3.4 Hz, $CHOCH_3$), 4.54 (1H, d, *J* = 12.0 Hz, CH_aH_bPh), 4.37 (1H, d, *J* = 12.0 Hz, CH_aH_bPh), 3.82 (3H, s, $ArOCH_3$), 3.40 (1H, dd, *J* = 11.4, 9.0 Hz, SCH_aH_b), 3.19 (3H, s, $CHOCH_3$), 2.97 (1H, dd, *J* = 11.4, 1.8 Hz, SCH_aH_b), 2.24–2.16 (1H, m, $CH(CH_3)_2$), 0.95 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(CH_3)_b$), 0.91 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.1 (C), 171.0 (C), 159.4 (C), 137.2 (C), 129.5 (CH), 128.8 (C), 128.2 (CH), 128.0 (CH), 127.6 (CH), 113.4 (CH), 82.7 (CH), 81.0 (CH), 73.6 (CH_2), 71.8 (CH), 56.8 (CH_3), 55.3 (CH_3), 30.7 (CH), 29.4 (CH_2), 18.8 (CH_3), 16.8 (CH_3).

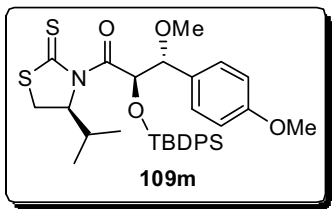
*4.4.3.4. With thioimide **4u***

The thioimide **109** was prepared according to the General Procedure in section 4.2. from thioimide **4u** (229 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol), *p*-anisaldehyde dimethyl acetal (94 μL, 0.55 mmol), TESOTf (130 μL, 0.58 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. A 75:25 diastereomeric ratio of the *anti/syn* diastereomers was established by ^{1}H NMR of the crude product. Purification of the crude product by flash column chromatography on silica gel (hexanes/CH_2Cl_2 3:2) afforded 58 mg of the pure *anti* diastereomer **109** (0.10 mmol, 19%) and 18 mg of *syn* diastereomer **109m** (0.03 mmol, 6%).



109

(*S*)-*N*-[(*2R*, *3R*)-2-(*tert*-Butyldiphenylsilyloxy)-3-methoxy-3-(4-methoxyphenyl)propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**109**). Yellow oil; $\mathbf{R_f}$ = 0.45 (hexanes/CH_2Cl_2 2:3); $\mathbf{[\alpha]_D}$ = +119.4 (*c* 0.90, $CHCl_3$); **IR** (ATR) 2955, 2925, 2851, 1694, 1609, 1505, 1360, 1234, 1164, 1112 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.62–7.60 (2H, m, ArH), 7.48–7.45 (2H, m, ArH), 7.42–7.29 (4H, m, ArH), 7.16–7.12 (2H, m, ArH), 7.00–6.98 (2H, m, ArH), 6.95–6.93 (2H, m, ArH), 6.80 (1H, *J* = 7.6 Hz, COCH), 4.71 (1H, ddd, *J* = 8.3, 5.7, 1.2 Hz, NCH), 4.36 (1H, d, *J* = 7.6 Hz, $CHOCH_3$), 3.87(3H, s, $ArOCH_3$), 3.09 (3H, s, $CHOCH_3$), 2.78 (1H, dd, *J* = 11.2, 8.3 Hz, SCH_aH_b), 2.67 (1H, dd, *J* = 11.2, 1.2 Hz, SCH_aH_b), 2.20–2.12 (1H, m, $CH(CH_3)_2$), 0.95 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(CH_3)_b$), 0.93 (9H, s, $C(CH_3)_3$), 0.90 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 201.6 (C), 174.06 (C), 159.8 (C), 136.1 (CH), 135.7 (CH), 133.3 (C), 132.5 (C), 131.1 (C), 130.1 (CH), 129.7 (CH), 129.4 (CH), 127.3 (CH), 127.2 (CH), 113.6 (CH), 87.4 (CH), 72.0 (CH), 71.2 (CH), 56.5 (CH_3), 55.3 (CH_3), 30.4 (CH), 29.2 (CH_2), 26.8 (CH_3), 19.0 (C), 18.8 (CH_3), 17.1 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OCH_3]^+$ $C_{32}H_{38}NO_3S_2Si$: 576.2057, found: 576.2052; *m/z* calculated for $[M+Na]^+$ $C_{33}H_{41}NNaO_4S_2Si$: 630.2138, found: 630.2141.



109m

(*S*)-*N*-[(*2R*, *3S*)-2-(*tert*-Butyldiphenylsilyloxy)-3-methoxy-3-(4-methoxyphenyl)propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**109m**). Yellow oil; $\mathbf{R_f}$ = 0.40 (hexanes/CH_2Cl_2 2:3); $\mathbf{[\alpha]_D}$ = +195.2 (*c* 0.67, $CHCl_3$); **IR** (ATR) 2955, 2925, 2851, 1709, 1609, 1509, 1245, 1086 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.61–7.59 (2H, m, ArH), 7.43–7.41 (2H, m, ArH), 7.38–7.29 (4H, m, ArH), 7.18–7.15 (2H, m, ArH), 7.07–7.04 (2H, m, ArH), 6.89–6.87 (2H, m, ArH), 6.54 (1H, *J* = 3.5 Hz, COCH), 4.95 (1H, d, *J* = 3.5 Hz, $CHOCH_3$), 4.88 (1H, ddd, *J* = 8.5, 5.8, 1.2 Hz, NCH), 3.84(3H, s, $ArOCH_3$),3.17 (3H, s, $CHOCH_3$), 2.97(1H, dd, *J* = 11.3, 8.5 Hz, SCH_aH_b), 2.74 (1H, dd, *J* = 11.3, 1.2 Hz, SCH_aH_b), 2.13–2.01 (1H, m, $CH(CH_3)_2$), 0.99 (9H, s, $C(CH_3)_3$), 0.86 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(CH_3)_b$), 0.83 (3H, d, *J* = 6.9 Hz, $CH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 201.7 (C), 170.7 (C), 159.5 (C), 136.3 (CH), 135.8 (CH), 133.4 (C), 133.0 (C), 129.6 (CH), 129.4 (CH), 129.3 (C), 129.2 (CH), 127.3 (CH), 127.2 (CH), 113.5 (CH), 83.0 (CH), 74.5 (CH), 71.1 (CH), 57.0 (CH_3), 55.3 (CH_3), 30.5 (CH), 29.8 (CH_2), 26.9 (CH_3), 19.2(C), 18.7 (CH_3), 17.3 (CH_3).

*4.4.3.5. With thioimide **4v***

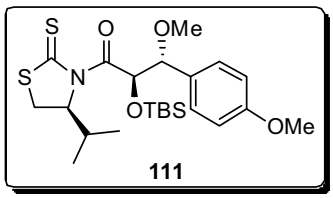
The reaction was carried out according to the General Procedure in section 4.2. from thioimide **4v** (188 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol), *p*-anisaldehyde dimethyl acetal (94 μL, 0.55 mmol), TESOTf (130 μL, 0.58 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. ^{1}H NMR spectrum of the crude product revealed a complex mixture.

*4.4.3.6. With thioimide **4t***

The reaction was carried out according to the General Procedure in section 4.2. from thioimide **4t** (167 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol), *p*-anisaldehyde dimethyl acetal (94 μL, 0.55 mmol), TESOTf (130 μL, 0.58 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. ^{1}H NMR spectrum of the crude product revealed a complex mixture.

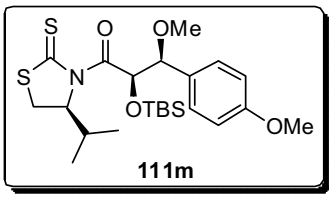
*4.4.3.7. With thioimide **4t** and TBSOTf as Lewis acid*

The thioimide **111** was prepared according to the General Procedure in section 4.2. from thioimide **4t** (138 mg, 0.41 mmol), $(Me_3P)_2NiCl_2$ (2.9 mg, 10 μmol), *p*-anisaldehyde dimethyl acetal (78 μL, 0.46 mmol), TBSOTf as Lewis acid (110 μL, 0.48 mmol), 2,6-lutidine (72 μL, 0.62 mmol) and CH_2Cl_2 (0.8 mL) at –20 ºC for 15 h. A 86:14 diastereomeric ratio of the *anti/syn* diastereomers was established by HPLC of the crude product. Purification of the crude product by flash column chromatography on silica gel (from hexanes/CH_2Cl_2 1:1 to 2:3) afforded 96 mg of the pure *anti* diastereomer **111** (0.20 mmol, 49%) and 18 mg of *syn* diastereomer **111m** (0.04 mmol, 9%).



111

(*S*)-*N*-[(*2R*, *3R*)-2-(*tert*-Butyldimethylsilyloxy)-3-methoxy-3-(4-methoxyphenyl)propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**111**). Yellow oil; $\mathbf{R_f}$ = 0.65 (CH_2Cl_2); **HPLC** (Tracer Spherisorb S3W (N4184) column, 5% of EtOAc in hexanes, 0.9 mL/min, 254 nm), t_R = 9.4 min; $\mathbf{[\alpha]_D}$ = +141.0 (*c* 0.96, $CHCl_3$); **IR** (film) 2930, 2858, 1704, 1512, 1364, 1250, 1163, 1121 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.39–7.37 (2H, m, ArH), 6.89–6.87 (2H, m, ArH), 6.75 (1H, *J* = 8.2 Hz, COCH), 5.39 (1H, ddd, *J* = 8.2, 6.2, 1.2 Hz, NCH), 4.26 (1H, d, *J* = 8.2 Hz, CHOCH$_3$), 3.81 (3H, s, ArOCH$_3$), 3.50 (1H, dd, *J* = 11.5, 8.2 Hz, SCH$_a$H$_b$), 3.10 (3H, s, CHOCH$_3$), 3.03 (1H, dd, *J* = 11.5, 1.2 Hz, SCH$_a$H$_b$), 2.42–2.30 (1H, m, CH(CH$_3$)$_2$), 1.11 (3H, d, *J* = 6.8 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$), 1.03 (3H, d, *J* = 6.9 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$), 0.72 (9H, s, C(CH$_3$)$_3$), –0.22 (3H, s, Si(CH$_3$)$_a$(CH$_3$)$_b$), –0.39 (3H, s, Si(CH$_3$)$_a$(CH$_3$)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.6 (C), 174.8 (C), 159.6 (C), 131.0 (C), 129.8 (CH), 113.4 (CH), 86.9 (CH), 71.8 (CH), 71.7 (CH), 56.6 (CH_3), 55.3 (CH_3), 30.6 (CH), 30.4 (CH_2), 25.5 (CH_3), 18.9 (CH_3), 17.9 (C), 17.7 (CH_3), –5.2 (CH_3), –5.4 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OMe]^+$ $C_{22}H_{34}NO_3S_2Si$: 452.1744, found: 452.1741; calculated for $[M+Na]^+$ $C_{23}H_{37}NNaO_4S_2Si$: 506.1825, found:506.1825.

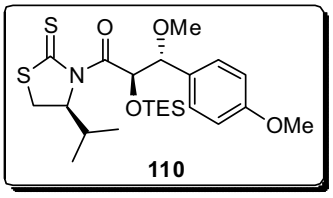


111m

(*S*)-*N*-[(*2R*, *3S*)-2-(*tert*-Butyldimethylsilyloxy)-3-methoxy-3-(4-methoxyphenyl)propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**111m**). Yellow oil; $\mathbf{R_f}$ = 0.55 (CH_2Cl_2); **HPLC** (Tracer Spherisorb S3W (N4184) column, 5% of EtOAc in hexanes, 0.9 mL/min, 254 nm), t_R = 18.1 min; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.44–7.34 (2H, m, ArH), 6.92–6.84 (2H, m, ArH), 6.59 (1H, *J* = 2.8 Hz, COCH), 5.57 (1H, ddd, *J* = 9.5, 4.1, 1.9 Hz, NCH), 4.99 (1H, d, *J* = 2.8 Hz, CHOCH$_3$), 3.81 (3H, s, ArOCH$_3$), 3.56 (1H, dd, *J* = 11.5, 9.5 Hz, SCH$_a$H$_b$), 3.16 (3H, s, CHOCH$_3$), 3.05 (1H, dd, *J* = 11.5, 1.9 Hz, SCH$_a$H$_b$), 2.41–2.28 (1H, m, CH(CH$_3$)$_2$), 1.05 (3H, d, *J* = 6.8 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$), 0.96 (3H, d, *J* = 6.9 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$), 0.75 (9H, s, C(CH$_3$)$_3$), –0.24 (3H, s, Si(CH$_3$)$_a$(CH$_3$)$_b$), –0.33 (3H, s, Si(CH$_3$)$_a$(CH$_3$)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.2, 172.8, 159.7, 129.6, 129.2, 113.7, 83.2, 76.7, 72.5, 56.9, 55.5, 31.0, 29.1, 25.9, 19.4, 18.7, 16.8, –5.2, –5.7.

*4.4.3.8. With thioimide **4s***

The thioimide **110** was prepared according to the General Procedure in section 4.2. from thioimide **4s** (167 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol), *p*-anisaldehyde dimethyl acetal (94 μL, 0.55 mmol), TESOTf (130 μL, 0.58 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. A 90:10 diastereomeric ratio of the *anti/syn* diastereomers was established by ^{1}H NMR of the crude product. Purification of the crude product by flash column chromatography on silica gel (from hexanes/CH_2Cl_2 1:1 to CH_2Cl_2) afforded 46 mg of the pure *anti* diastereomer **110** (0.13 mmol, 26%).



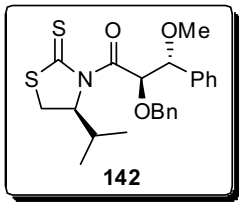
110

(*S*)-*N*-[(*2R*, *3R*)-2-(Triethylsilyloxy)-3-methoxy-3-(4-methoxyphenyl)propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**110**). Yellow oil; $\mathbf{R_f}$ = 0.60 (hexanes/CH_2Cl_2 1:4); $\mathbf{[\alpha]_D}$ = +138.2 (*c* 1.00, $CHCl_3$); **IR** (ATR) 2951, 2870, 1694, 1605, 1509, 1360, 1238, 1156, 1108 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.39–7.37 (2H, m, ArH), 6.89–6.87 (2H, m, ArH), 6.70 (1H, *J* = 8.1 Hz, COCH), 5.36 (1H, ddd, *J* = 8.0, 6.4, 0.9 Hz, NCH), 4.27 (1H, d, *J* = 8.1 Hz, CHOCH$_3$), 3.81 (3H, s, ArOCH$_3$), 3.50 (1H, dd, *J* = 11.5, 8.0 Hz, SCH$_a$H$_b$), 3.10 (3H, s, CHOCH$_3$), 3.03 (1H, dd, *J* = 11.5, 0.9 Hz, SCH$_a$H$_b$), 2.40–2.31 (1H, m, CH(CH$_3$)$_2$), 1.11 (3H, d, *J* = 6.8 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$), 1.03 (3H, d, *J* = 6.9 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$), 0.70 (9H, t, *J* = 7.9 Hz, Si(CH$_2$CH$_3$)$_3$), 0.39–0.22 (6H, m, Si(CH$_2$CH$_3$)$_3$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.6 (C), 174.8 (C), 159.6 (C), 131.0 (C), 129.7 (CH), 113.4 (CH), 86.8 (CH), 71.8 (CH), 71.3 (CH), 56.6 (CH_3), 55.3 (CH_3), 30.6 (CH), 30.5 (CH_2), 18.9 (CH_3), 17.8 (CH_3), 6.4 (CH_3), 4.4 (CH_2); **HRMS** (+ESI): *m/z* calculated for $[M–OCH_3]^+$ $C_{22}H_{34}NO_3S_2Si$: 452.1744, found: 452.1733; *m/z* calculated for $[M+NH_4]^+C_{23}H_{41}N_2O_4S_2Si$: 501.2272, found: 501.2277; *m/z* calculated for $[M+Na]^+$ $C_{23}H_{37}NNaO_4S_2Si$: 506.1825, found: 506.1834.

4.4.4. Influence of the hydroxyl protecting group with other acetals

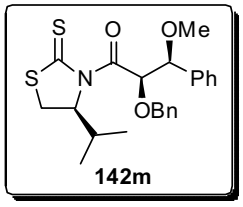
*4.4.4.1. Reaction of **4l** with benzaldehyde dimethyl acetal*

The thioimide **142** was prepared according to the General Procedure in section 4.2. from thioimide **4l** (155 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (28.2 mg, 0.10 mmol), benzaldehyde dimethyl acetal (83 μL, 0.55 mmol), TESOTf (170 μL, 0.58 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. A 64:36 diastereomeric ratio of the *anti/syn* diastereomers was established by ^{1}H NMR of the crude product. Purification of the crude product by flash column chromatography on silica gel (from hexanes/CH_2Cl_2 3:2 to 15:85) afforded 39 mg of the pure *anti* diastereomer **142** (0.09 mmol, 18%) and 26 mg of the pure *syn* diastereomer **142m** (0.06 mmol, 12%).



142

(*S*)-*N*-[(*2R*, *3R*)-2-Benzyloxy-3-methoxy-3-phenylpropanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**142**). Yellow oil; $\mathbf{R_f}$ = 0.75 (CH_2Cl_2); $\mathbf{[\alpha]_D}$ = +141.9 (*c* 1.00, $CHCl_3$). **IR** (ATR) 3028, 2956, 2922, 2869, 2819, 1693, 1450, 1358, 1236, 1160, 1088 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.52–7.50 (2H, m, Ar<u>H</u>), 7.40–7.34 (3H, m, Ar<u>H</u>), 7.25–7.23 (3H, m, Ar<u>H</u>), 7.12–7.10 (2H, m, Ar<u>H</u>), 6.56 (1H, *J* = 8.3 Hz, COC<u>H</u>), 5.03 (1H, ddd, *J* = 8.0, 6.2, 1.0 Hz, NC<u>H</u>), 4.42 (1H, d, *J* = 8.3 Hz, C<u>H</u>OCH$_3$), 4.38 (1H, d, *J* = 12.1 Hz, C<u>H$_a$</u>H$_b$Ph), 4.16 (1H, d, *J* = 12.1 Hz, CH$_a$<u>H$_b$</u>Ph), 3.17 (1H, dd, *J* = 11.3, 8.0 Hz, SC<u>H$_a$</u>H$_b$), 3.12 (3H, s, CHOC<u>H$_3$</u>), 2.89 (1H, dd, *J* = 11.3, 1.0 Hz, SCH$_a$<u>H$_b$</u>), 2.33–2.21 (1H, m, C<u>H</u>(CH$_3$)$_2$), 1.04 (3H, d, *J* = 6.8 Hz, CH(C<u>H$_3$</u>)$_a$(CH$_3$)$_b$), 0.97 (3H, d, *J* = 6.9 Hz, CH(CH$_3$)$_a$(C<u>H$_3$</u>)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.6 (C), 173.5 (C), 138.7 (C), 137.3 (C), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 127.8 (CH), 85.4 (CH), 78.0 (CH), 73.7 (CH_2), 71.5 (CH), 56.8 (CH_3), 30.5 (CH), 30.3 (CH_2), 18.8 (CH_3), 17.5 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OCH_3]^+$ $C_{22}H_{24}NO_2S_2$: 398.1243, found: 398.1260; *m/z* calculated for $[M+H]^+$ $C_{23}H_{28}NO_3S_2$: 430.1505, found: 430.1513.



142m

(*S*)-*N*-[(*2R*, *3S*)-2-Benzyloxy-3-methoxy-3-phenylpropanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**142m**). Yellow oil; $\mathbf{R_f}$ = 0.40 (CH_2Cl_2); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.50–7.48 (2H, m, Ar<u>H</u>), 7.38–7.29 (3H, m, Ar<u>H</u>), 7.22–7.17 (3H, m, Ar<u>H</u>), 7.07–6.98 (2H, m, Ar<u>H</u>), 6.23 (1H, *J* = 3.3 Hz, COC<u>H</u>), 5.36 (1H, ddd, *J* = 8.0, 4.9, 1.2 Hz, NC<u>H</u>), 5.04 (1H, d, *J* = 3.3 Hz, C<u>H</u>OCH$_3$), 4.53 (1H, d, *J* = 12.1 Hz, C<u>H$_a$</u>H$_b$Ph), 4.32 (1H, d, *J* = 12.1 Hz, CH$_a$<u>H$_b$</u>Ph), 3.42 (1H, dd, *J* = 11.5, 8.0 Hz, SC<u>H$_a$</u>H$_b$), 3.22 (3H, s, CHOC<u>H$_3$</u>), 2.99 (1H, dd, *J* = 11.5, 1.2 Hz, SCH$_a$<u>H$_b$</u>), 2.28–2.17 (1H, m, C<u>H</u>(CH$_3$)$_2$), 0.97 (3H, d, *J* = 6.7 Hz, CH(C<u>H$_3$</u>)$_a$(CH$_3$)$_b$), 0.92 (3H, d, *J* = 6.8 Hz, CH(CH$_3$)$_a$(C<u>H$_3$</u>)$_b$).

*4.4.4.2. Reaction of **4l** with (E)-α-methylcinnamaldehyde dimethyl acetal (**78**)*

The reaction was carried out according to the General Procedure in section 4.2. from thioimide **4l** (155 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol), (*E*)-α-methylcinnamaldehyde dimethyl acetal (**78**) (106 mg, 0.55 mmol), TESOTf (130 μL, 0.58 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. ^{1}H NMR spectrum of the crude product showed a complex mixture.

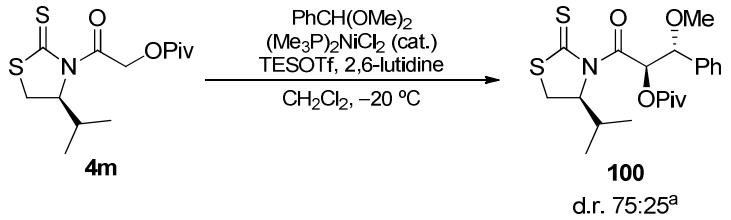
*4.4.4.3. Reaction of **4t** with (E)-α-methylcinnamaldehyde dimethyl acetal (**78**)*

The reaction was carried out according to the General Procedure in section 4.2. from thioimide **4t** (79 mg, 0.24 mmol), $(Me_3P)_2NiCl_2$ (1.7 mg, 6.0 μmol), (*E*)-α-methylcinnamaldehyde dimethyl acetal (**78**) (50 mg, 0.26 mmol), TBSOTf as Lewis acid (63 μL, 0.27 mmol), 2,6-lutidine (41 μL, 0.36 mmol) and CH_2Cl_2 (0.5 mL) at –20 ºC for 15 h. ^{1}H NMR spectrum of the crude product showed a complex mixture.

4.5. REACTIONS WITH BENZALDEHYDE DIMETHYL ACETAL

4.5.1. Optimization by ^{1}H NMR conversion

The reactions were carried out according to the General Procedure in section 4.2. from thioimide **4m** (152 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$, benzaldehyde dimethyl acetal, TESOTf and 2,6-lutidine. The quantities of these last four reagents are shown in Table 52. The reactions were carried out in CH_2Cl_2 (1.0 mL) at –20 ºC for the time reactions indicated in Table 52. With no further purification, the crudes were analyzed by ^{1}H NMR spectroscopy. ^{1}H NMR of the crude products showed a d.r. of 75:25 in all cases. The results are shown in the following Table 52.



4m → **100**, d.r. 75:25[a]

Entry	$(Me_3P)_2NiCl_2$ (mol%)	t (h)	Acetal (eq)	TESOTf (eq)	Base (eq)	Conversion (%)[a]
1	2.5	90	1.1	1.15	1.5	12
2	10	15	1.1	1.3	1.5	47
3	20	15	1.1	1.5	1.5	46
4	20	48	1.1	1.5	1.5	54
5	20	90	1.1	1.5	1.5	54
6	2.5	15	2.2	1.15	1.5	35
7	2.5	15	1.1	2.2	1.5	38
8	2.5	70	1.1	2.2	1.5	48
9	2.5	15	1.1	2.2	1.1	8
10	2.5	15	1.1	2.2	3.0	8
11	2.5	15	2.2	2.2	1.5	5
12	2.5	15	3.0	3.0	3.0	28
13	5	15	1.1	2.2	1.5	54
14	5	70	1.1	2.2	1.5	51
15	10	15	1.1	2.2	1.5	45
16	10	90	1.1	2.2	1.5	50

[a] Established by ^{1}H NMR analysis of the crude products.

Table 52

4.5.2. Reaction with 5 mol% $(Me_3P)_2NiCl_2$ and 2.2 equivalents of TESOTf

The thioimide **100** was prepared according to the General Procedure in section 4.2. from thioimide **4m** (152 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (7.0 mg, 25 μmol), benzaldehyde dimethyl acetal (83 μL, 0.55 mmol), TESOTf (249 μL, 1.1 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. A 75:25 diastereomeric ratio of the *anti/syn* diastereomers was established by ^{1}H NMR of the crude product. A first purification of the crude product by flash column chromatography on silica gel (from hexanes/EtOAc 93:7 to 85:15) afforded 29 mg of the pure *syn* diastereomer **100m** (0.07 mmol, 14%) and a mixture of *anti* diastereomer **100** and starting material **4m**. This mixture was further purified by flash column chromatography on silica gel (from hexanes/CH_2Cl_2 7:3 to 15:85) to afford 84 mg of *anti* diastereomer **100** (0.20 mmol, 40%) and 57 mg of starting material **4m** (0.19 mmol, 38%).

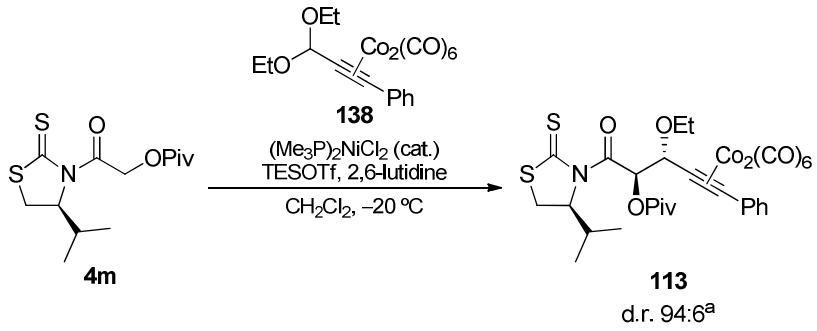
4.6. REACTIONS WITH PHENYLPROPARGYL DIETHYL ACETAL

4.6.1. With phenylpropiolaldehyde diethyl acetal

The reaction was carried out according to the General Procedure in section 4.2. from thioimide **4m** (152 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (28.2 mg, 0.10 mmol), phenylpropiolaldehyde diethyl acetal (114 μL, 0.55 mmol), TESOTf (170 μL, 0.75 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. ^{1}H NMR spectrum of the crude product showed that no reaction had taken place.

4.6.2. With hexacarbonyl(μ-η^4-3,3-diethoxy-1-phenyl-1-propyne)dicobalt (Co-Co) (138)

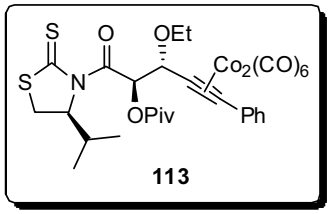
The reactions were carried out according to the General Procedure in section 4.2. from thioimide **4m** (152 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$, cobalted acetal **138**, TESOTf and 2,6-lutidine in the quantities shown in Table 53, and CH_2Cl_2 (1.0 mL) at –20 ºC for the reaction times indicated in Table 53. A 94:6 diastereomeric ratio of the *anti/syn* diastereomers was established by HPLC of the crude products in all cases. Purification of the crude products by flash column chromatography on silica gel (from hexanes/CH_2Cl_2 1:1 to 3:7) the pure *anti* diastereomer **113** and another fraction of the *syn* diastereomer **113m** impurified with a small part of the *anti* one. The results are shown in the following Table.



Entry	$(Me_3P)_2NiCl_2$ (mol%)	t (h)	Acetal (eq)	TESOTf (eq)	Base (eq)	*Anti* (%)[b]
1	5.0	15	1.1	1.2	1.5	36
2	20.0	60	1.1	1.5	1.5	40
3	20.0	60	3.0	3.0	3.0	74
4	5.0	15	3.0	3.0	3.0	74
5	5.0	15	1.1	2.2	1.5	56
6	5.0	15	1.5	2.2	1.5	74
7	5.0	15	2.2	2.2	1.5	84

[a] Established by HPLC analysis of the crude products.
[b] Isolated yield after column chromatography.

Table 53



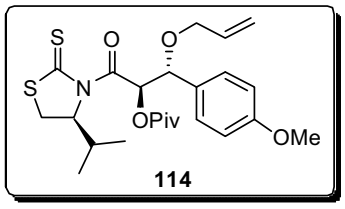
113

(*S*)-*N*-[(*2R,3R*)-Hexacarbonyl[μ-η^4-(3-ethoxy-5-phenyl-2-pivaloyloxy pent-4-ynoyl)dicobalt (*Co-Co*)]-4-isopropyl-1,3-thiazolidine-2-thione (**113**). Deep maroon solid; **mp** = 109–111 ºC; $\mathbf{R_f}$ = 0.50 (hexanes/CH_2Cl_2 3:7); **HPLC** (Tracer Spherisorb S3W (N4184) column, 4% of EtOAc in hexanes, 0.9 mL/min, 254 nm), $t_{R,major}$ = 23.2 min, $t_{R,minor}$ = 17.0 min; **IR** (ATR) 2960, 2922, 2090, 2045, 2011, 1727, 1706, 1362, 1169, 1122 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.76–7.74 (2H, m, ArH), 7.35–7.26 (2H, m, ArH), 6.56 (1H, *J* = 1.9 Hz, COCH), 5.88 (1H, d, *J* = 1.9 Hz, COCHCH), 5.20 (1H, ddd, *J* = 8.5, 5.4, 1.2 Hz, NCH), 3.80 (1H, dq, *J* = 8.7, 7.0 Hz, OCH_aH_b), 3.66 (1H, dd, *J* = 11.5, 8.5 Hz, SCH_aH_b), 3.56 (1H, dq, *J* = 8.7, 7.0 Hz, OCH_aH_b), 3.07 (1H, dd, *J* = 11.5, 1.2 Hz, SCH_aH_b), 2.44–2.32 (1H, m, $CH(CH_3)_2$), 1.21 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 1.11 (3H, d, *J* = 6.9 Hz, $CH(CH_3)_a(CH_3)_b$), 1.04 (9H, s, $C(CH_3)_3$), 1.01 (3H, d, *J* = 6.9 Hz, $CH(CH_3)_a(CH_3)_b$), 0.89 (9H, s, $C(CH_3)_3$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 203.1 (C), 199.3 (C), 178.9 (C), 167.7 (C), 137.7 (C), 130.4 (CH), 128.6 (CH), 127.7 (CH), 93.6 (C), 91.1 (C), 79.5 (CH), 75.5 (CH), 72.5 (CH), 68.2 (CH_2), 38.5 (C), 30.7(CH), 30.5 (CH_2), 26.5 (CH_3), 19.1 (CH_3), 17.1 (CH_3), 15.0 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OC_2H_5–CO]^+$ $C_{22}H_{26}Co_2NO_3S_2$: 534.0013, found: 534.0000; *m/z* calculated for $[M–OC_2H_5]^+$ $C_{28}H_{26}Co_2NO_9S_2$: 701.9707, found: 701.9704.

4.7. APPLICATION TO OTHER ACETALS

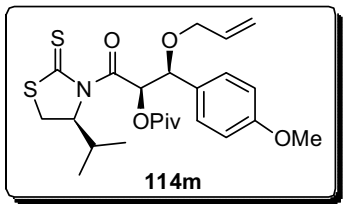
4.7.1.(*S*)-*N*-[(*2R*, *3R*)-3-Allyloxy-3-(4-methoxyphenyl)-2-pivaloyloxypropanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (114)

The thioimide **114** was prepared according to the General Procedure in section 4.2. from thioimide **4m** (152 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (7.0 mg, 25 μmol), benzaldehyde diallyl acetal (129 mg, 0.55 mmol), TESOTf (130 μL, 0.58 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. A 84:16 diastereomeric ratio of the *anti/syn* diastereomers was established by HPLC of the crude product. Purification of the crude product by flash column chromatography on silica gel (from hexanes/CH_2Cl_2 4:1 to 2:3) afforded 179 mg of pure *anti* diastereomer **114** (0.36 mmol, 73%) and 45 mg of pure *syn* diastereomer **114m** (0.09 mmol, 19%).



114

(*S*)-*N*-[(*2R*, *3R*)-3-Allyloxy-3-(4-methoxyphenyl)-2-pivaloyloxy propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**114**). Yellow solid; **mp** = 89–90 ºC; $\mathbf{R_f}$ = 0.35 (hexanes/CH_2Cl_2 1:4); **HPLC** (Tracer Spherisorb S3W (N4184) column, 15% of EtOAc in hexanes, 0.9 mL/min, 254 nm), t_R = 18.5 min; $\mathbf{[\alpha]_D}$ = +240.8 (*c* 1.00, $CHCl_3$); **IR** (ATR) 2962, 2929, 2873, 1720, 1702, 1609, 1509, 1357, 1257, 1175, 1149 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.40–7.38 (2H, m, ArH), 7.07 (1H, d, *J* = 7.4 Hz, COCH), 6.89–6.87 (2H, m, ArH), 5.82–5.72 (1H, m, CH=CH_2), 5.25 (1H, ddd, *J* = 8.2, 6.0, 0.9 Hz, NCH), 5.21 (1H, dq, *J* = 17.2, 1.6 Hz, CH=C$H_E$$H_Z$), 5.10 (1H, dq, *J* = 10.5, 1.6 Hz, CH=C$H_E$$H_Z$), 4.80 (1H, d, *J* = 7.4 Hz, COCHCH), 3.91 (1H, ddt, *J* = 12.9, 4.7, 1.6 Hz, OC$H_a$$H_b$CH=$CH_2$), 3.81 (3H, s, ArOC$H_3$), 3.75 (1H, ddt, *J* = 12.9, 6.1, 1.6 Hz, OC$H_a$$H_b$CH=$CH_2$), 3.61 (1H, dd, *J* = 11.4, 8.2 Hz, SC$H_a$$H_b$), 3.01 (1H, dd, *J* = 11.4, 0.9 Hz, SC$H_a$$H_b$), 2.37–2.25 (1H, m, CH$(CH_3)_2$), 1.09 (9H, s, C$(CH_3)_3$), 1.08 (3H, d, *J* = 6.5 Hz, CH$(CH_3)_a(CH_3)_b$), 1.00 (3H, d, *J* = 6.9 Hz, CH$(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.6 (C), 177.6 (C), 170.2 (C), 159.7 (C), 134.1 (CH), 129.7 (C), 129.5 (CH), 117.0 (CH_2), 113.5 (CH), 80.6 (CH), 73.1 (CH), 71.7 (CH), 69.2 (CH_2), 55.2 (CH_3), 38.4 (C), 30.6 (CH), 30.4 (CH_2), 26.8 (CH_3), 19.1 (CH_3), 17.7 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OC_3H_5]^+$ $C_{21}H_{28}NO_4S_2$: 422.1454, found: 422.1442; *m/z* calculated for $[M+Na]^+$ $C_{24}H_{33}NNaO_5S_2$: 502.1692, found: 502.1687.



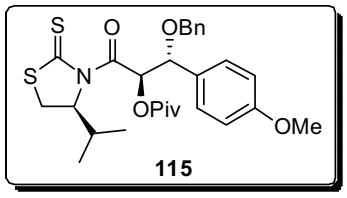
114m

(*S*)-*N*-[(*2R*, *3S*)-3-Allyloxy-3-(4-methoxyphenyl)-2-pivaloyloxy propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**114m**). Yellow oil; $\mathbf{R_f}$ = 0.30 (hexanes/CH_2Cl_2 1:4); **HPLC** (Tracer Spherisorb S3W (N4184) column, 5% of EtOAc in hexanes, 0.9 mL/min, 254 nm), t_R = 23.8 min; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.44–7.42 (2H, m, ArH),6.90–6.86 (3H, m, COCH, ArH), 5.85–5.72 (1H, m, CH=CH_2), 5.43 (1H, d, *J* = 2.8 Hz, COCHCH), 5.43 (1H, ddd, *J* = 8.9, 4.6, 1.3 Hz, NCH), 5.23–5.19 (1H, m, CH=C$H_E$$H_Z$), 5.14 (1H, dq, *J* = 10.4, 1.4 Hz, CH=C$H_E$$H_Z$), 4.00 (1H, ddt, *J* = 12.6, 4.9, 1.4 Hz, OC$H_a$$H_b$CH=$CH_2$), 3.80 (3H, s, ArOC$H_3$), 3.68 (1H, ddt, *J* = 12.6, 6.4, 1.4 Hz, OC$H_a$$H_b$CH=$CH_2$), 3.59 (1H, dd, *J* = 11.5, 8.9 Hz, SC$H_a$$H_b$), 3.02 (1H, dd, *J* =

11.5, 1.3Hz, $SCH_a\underline{H}_b$), 2.37–2.25 (1H, m, $C\underline{H}(CH_3)_2$), 1.16 (9H, s, $C(C\underline{H}_3)_3$), 1.04 (3H, d, J = 6.5 Hz, $CH(C\underline{H}_3)_a(CH_3)_b$), 0.98 (3H, d, J = 7.4 Hz, $CH(CH_3)_a(C\underline{H}_3)_b$).

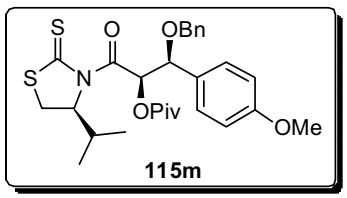
4.7.2.(*S*)-*N*-[(*2R*, *3R*)-3-Benzyloxy-3-(4-methoxyphenyl)-2-pivaloyloxypropanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (115)

The thioimide **115** was prepared according to the General Procedure in section 4.2. from thioimide **4m** (152 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (7.0 mg, 25 μmol), benzaldehyde dibenzyl acetal (184 mg, 0.55 mmol), TESOTf (130 μL, 0.58 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. A 83:17 diastereomeric ratio of the *anti/syn* diastereomers was established by HPLC of the crude product. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc 9:1) afforded 183 mg of pure *anti* diastereomer **115** (0.35 mmol, 69%) and 34 mg of pure *syn* diastereomer **115m** (0.07 mmol, 13%).



115

(*S*)-*N*-[(*2R*, *3R*)-3-Benzyloxy-3-(4-methoxyphenyl)-2-pivaloyloxy propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**115**). Yellow oil; $\mathbf{R_f}$ = 0.40 (hexanes/EtOAc 85:15); **HPLC** (Tracer Spherisorb S3W (N4184) column, 5% of EtOAc in hexanes, 0.9 mL/min, 254 nm), t_R = 26.5 min; $\mathbf{[\alpha]_D}$ = +137.5 (*c* 1.00, $CHCl_3$); **IR** (ATR) 2962, 2870, 1724, 1690, 1605, 1509, 1357, 1249, 1171, 1142 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.44–7.42 (2H, m, Ar$\underline{H}$), 7.30–7.21 (5H, m, Ar$\underline{H}$), 7.04 (1H, d, J = 7.1 Hz, COC$\underline{H}$), 6.91–6.87 (2H, m, Ar$\underline{H}$), 5.19 (1H, ddd, J = 8.2, 5.9, 0.8 Hz, NC$\underline{H}$), 4.88 (1H, d, J = 7.1 Hz, COCHC$\underline{H}$), 4.46 (1H, d, J = 11.9 Hz, $C\underline{H}_aH_bPh$), 4.25 (1H, d, J = 11.9 Hz, $CH_a\underline{H}_bPh$), 3.81 (3H, s, $ArOC\underline{H}_3$), 3.57 (1H, dd, J = 11.4, 8.2 Hz, $SC\underline{H}_aH_b$), 2.96 (1H, dd, J = 11.4, 0.8 Hz, $SCH_a\underline{H}_b$), 2.25–2.14 (1H, m, $C\underline{H}(CH_3)_2$), 1.10 (9H, s, $C(C\underline{H}_3)_3$), 0.91 (3H, d, J = 6.8 Hz, $CH(C\underline{H}_3)_a(CH_3)_b$), 0.88 (3H, d, J = 6.9 Hz, $CH(CH_3)_a(C\underline{H}_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.6 (C), 177.6 (C), 169.8 (C), 159.7 (C), 137.7 (C), 129.6 (CH), 129.3 (C), 128.0 (CH), 127.4 (CH), 127.3 (CH), 113.5 (CH), 80.9 (CH), 73.2 (CH), 71.6 (CH), 70.3 (CH_2), 55.2 (CH_3), 38.3 (C), 30.6 (CH), 30.4 (CH_2), 26.8 (CH_3), 18.9 (CH_3), 17.3 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OBn]^+$ $C_{21}H_{28}NO_4S_2$: 422.1454, found: 422.1447; *m/z* calculated for $[M+Na]^+$ $C_{28}H_{35}NNaO_5S_2$: 552.1849, found: 552.1849.



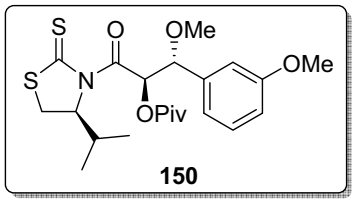
115m

(*S*)-*N*-[(*2R*, *3S*)-3-Benzyloxy-3-(4-methoxyphenyl)-2-pivaloyloxy propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**115m**). Yellow oil; $\mathbf{R_f}$ = 0.40 (hexanes/EtOAc 85:15); **HPLC** (Tracer Spherisorb S3W (N4184) column, 5% of EtOAc in hexanes, 0.9 mL/min, 254 nm), t_R = 30.1 min; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.48–7.46 (2H, m, Ar$\underline{H}$), 7.31–7.23 (5H, m, Ar$\underline{H}$), 6.93 (1H, d, J = 3.2 Hz, COC$\underline{H}$), 6.89–6.87 (2H, m, Ar$\underline{H}$), 5.43 (1H, d, J = 3.2 Hz, COCHC$\underline{H}$), 5.35 (1H, ddd, J = 8.3, 4.9, 1.4 Hz, NC$\underline{H}$), 4.54 (1H, d, J = 12.1 Hz, $C\underline{H}_aH_bPh$), 4.23 (1H, d, J = 12.1 Hz, $CH_a\underline{H}_bPh$), 3.81 (3H, s, $ArOC\underline{H}_3$), 3.56 (1H, dd, J = 12.1, 8.3 Hz, $SC\underline{H}_aH_b$), 2.96 (1H, dd, J =

12.1, 1.4Hz, SCH_aH_b), 2.24–2.11 (1H, m, $CH(CH_3)_2$), 1.18 (9H, s, $C(CH_3)_3$), 0.87 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(CH_3)_b$), 0.84 (3H, d, *J* = 6.9 Hz, $CH(CH_3)_a(CH_3)_b$).

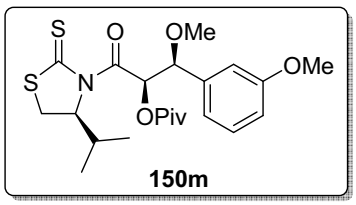
4.7.3. (*S*)-4-Isopropyl-*N*-[(*2R*, *3R*)-3-methoxy-3-(3-methoxyphenyl)-2-pivaloyloxypropanoyl]-1,3-thiazolidine-2-thione (116) with 20 mol% of $(Me_3P)_2NiCl_2$

The thioimide **116** was prepared according to the General Procedure in section 4.2. from thioimide **4m** (30 mg, 0.10 mmol), $(Me_3P)_2NiCl_2$ (5.6 mg, 20 µmol), 3-methoxybenzaldehyde dimethyl acetal (**132**) (20 mg, 0.11 mmol), TESOTf (34 µL, 0.15 mmol), 2,6-lutidine (17 µL, 0.15 mmol) and CH_2Cl_2 (0.2 mL) at –20 ºC for 65 h. A 74:26 diastereomeric ratio of the *anti/syn* diastereomers was established by ^{1}H NMR of the crude product. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc 85:15) afforded 12 mg of pure *anti* diastereomer **116** (26 µmol, 26%) and 4 mg of *syn* diastereomer **116m** (9 µmol, 9%).



150

(*S*)-4-Isopropyl-*N*-[(*2R*, *3R*)-3-methoxy-3-(3-methoxyphenyl)-2-pivaloyloxypropanoyl]-1,3-thiazolidine-2-thione (**116**). Yellow solid; **mp** = 85–88 ºC; $\mathbf{R_f}$ = 0.35 (hexanes/EtOAc 85:15); $\mathbf{[\alpha]_D}$ = +247.4 (*c* 0.90, $CHCl_3$); **IR** (KBr) 3005, 2968, 2868, 1735, 1698, 1486, 1145, 1095 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.28–7.22 (1H, m, ArH), 7.14 (1H, d, *J* = 7.6 Hz, COCH), 7.14 (1H, dd, *J* = 2.6, 1.5 Hz, ArH), 7.02 (1H, dt, *J* = 7.6, 1.5 Hz, ArH), 6.86 (1H, ddd, *J* = 8.3, 2.6, 1.0 Hz, ArH), 5.30 (1H, ddd, *J* = 8.4, 5.9, 1.1 Hz, NCH), 4.61 (1H, d, *J* = 7.6 Hz, $CHOCH_3$), 3.82 (3H, s, $ArOCH_3$), 3.60 (1H, dd, *J* = 11.4, 8.4 Hz, SCH_aH_b), 3.20 (3H, s, $CHOCH_3$), 3.02 (1H, dd, *J* = 11.4, 1.1 Hz, SCH_aH_b), 2.39–2.27 (1H, m, $CH(CH_3)_2$), 1.12 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(CH_3)_b$), 1.10 (9H, s, $C(CH_3)_3$), 1.02 (3H, d, *J* = 6.9 Hz, $CH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.6 (C), 177.5 (C), 170.3 (C), 159.6 (C), 139.2 (C), 129.0 (CH), 120.7 (CH), 114.5 (CH), 113.0 (CH), 83.9 (CH), 72.9 (CH), 71.7 (CH), 56.9 (CH_3), 55.2 (CH_3), 38.3 (C), 30.5 (CH), 30.3 (CH_2), 26.8 (CH_3), 19.0 (CH_3), 17.5 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{22}H_{32}NO_5S_2$: 422.1454, found: 422.1453; m/*z*calculated for $[M+Na]^+$ $C_{22}H_{31}NNaO_5S_2$: 476.1536, found: 476.1539.



150m

(*S*)-*N*-[(*2R*, *3S*)-3-Methoxy-3-(3-methoxyphenyl)-2-pivaloyloxy propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**116m**). Yellow oil; $\mathbf{R_f}$ = 0.30 (hexanes/EtOAc 85:15); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.28–7.24 (1H, m, ArH), 7.10–7.08 (2H, m, ArH), 7.00 (1H, d, *J* = 2.8 Hz, COCH), 6.85–6.82 (1H, m, ArH), 5.49 (1H, ddd, *J* = 8.9, 5.1, 1.5 Hz, NCH), 5.35 (1H, d, *J* = 2.8 Hz, $CHOCH_3$), 3.81 (3H, s, $ArOCH_3$), 3.61 (1H, dd, *J* = 11.5, 8.9 Hz, SCH_aH_b), 3.28 (3H, s, $CHOCH_3$), 3.06 (1H, dd, *J* = 11.5, 1.5 Hz, SCH_aH_b), 2.41–2.29 (1H, m, $CH(CH_3)_2$), 1.12 (9H, s, $C(CH_3)_3$), 1.09 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(CH_3)_b$), 1.01 (3H, d, *J* = 6.9 Hz, $CH(CH_3)_a(CH_3)_b$).

4.7.4. (*S*)-4-Isopropyl-*N*-[(*2R*, *3R*)-3-methoxy-3-(3-methoxyphenyl)-2-pivaloyloxypropanoyl]-1,3-thiazolidine-2-thione (116) with 5 mol% of $(Me_3P)_2NiCl_2$

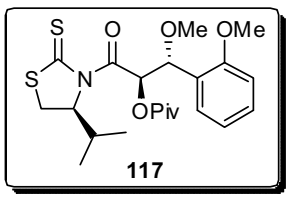
The thioimide **116** was prepared according to the General Procedure in section 4.2. from thioimide **4m** (152 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (7.0 mg, 25 μmol), 3-methoxybenzaldehyde dimethyl acetal (**132**) (101 mg, 0.55 mmol), TESOTf (249 μL, 1.1 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. A 75:25 diastereomeric ratio of the *anti/syn* diastereomers was established by ^{1}H NMR of the crude product. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc 85:15) afforded 60 mg of pure *anti* diastereomer **116** (0.13 mmol, 26%) and 21 mg of *syn* diastereomer **116m** (0.05 mmol, 9%).

4.7.5. Attempt with 3-methoxybenzaldehyde dimethyl acetal and 2.5 mol% of $(Me_3P)_2NiCl_2$

The reaction was carried out according to the General Procedure in section 4.2. from thioimide **4m** (152 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol), 3-methoxybenzaldehyde dimethyl acetal (**132**) (101 mg, 0.55 mmol), TESOTf (130 μL, 0.58 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. ^{1}H NMR spectrum of the crude product showed the only presence of starting materials.

4.7.6. (*S*)-4-Isopropyl-*N*-[(*2R*, *3R*)-3-methoxy-3-(2-methoxyphenyl)-2-pivaloyloxypropanoyl]-1,3-thiazolidine-2-thione (117) with 2.5 mol% of $(Me_3P)_2NiCl_2$

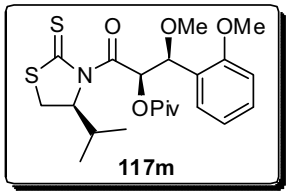
The thioimide **117** was prepared according to the General Procedure in section 4.2. from thioimide **4m** (152 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol), 2-methoxybenzaldehyde dimethyl acetal (**131**) (100 mg, 0.55 mmol), TESOTf (130 μL, 0.58 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. A 82:18 diastereomeric ratio of the *anti/syn* diastereomers was established by ^{1}H NMR of the crude product. Purification of the crude product by flash column chromatography on silica gel (from hexanes/CH_2Cl_2 1:1 to 1:4) afforded 58 mg of pure *anti* diastereomer **117** (0.13 mmol, 26%) and 13 mg of *syn* diastereomer **117m** (0.03 mmol, 6%).



117

(*S*)-4-Isopropyl-*N*-[(*2R*, *3R*)-3-methoxy-3-(2-methoxyphenyl)-2-pivaloyloxypropanoyl]-1,3-thiazolidine-2-thione (**117**). Yellow solid; **mp** = 125–126 ºC; $\mathbf{R_f}$ = 0.45 (hexanes/CH_2Cl_2 1:4); $\mathbf{[\alpha]_D}$ = +143.0 (*c* 1.00, $CHCl_3$); **IR** (ATR) 2955, 2929, 2870, 1724, 1698, 1598, 1586, 1486, 1457, 1360, 1264, 1242, 1160 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.62 (1H, dd, *J* = 7.5, 1.8 Hz, ArH), 7.29 (1H, ddd, *J* = 8.3, 7.5, 1.8 Hz, ArH), 7.01 (1H, td, *J* = 7.5, 1.1 Hz, ArH), 6.96 (1H, *J* = 5.8 Hz, COCH), 6.85 (1H, dd, *J* = 8.3, 1.1 Hz, ArH), 5.43 (1H, d, *J* = 5.8 Hz, CHOCH$_3$), 5.16 (1H, ddd, *J* = 8.4, 5.3, 1.0 Hz, NCH), 3.78 (3H, s, ArOCH$_3$), 3.61 (1H, dd, *J* = 11.4, 8.4 Hz, SCH$_a$H$_b$), 3.22 (3H, s, CHOCH$_3$), 3.01 (1H, dd, *J* = 11.4, 1.0 Hz, SCH$_a$H$_b$), 2.39–2.28 (1H, m, CH(CH$_3$)$_2$), 1.11 (3H, d, *J* = 6.8 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$), 1.08 (9H, s, C(CH$_3$)$_3$), 1.00 (3H, d, *J* = 7.0 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.6 (C), 177.9 (C), 169.6 (C), 157.8 (C), 129.5 (CH), 129.3 (CH), 125.0 (C),

120.5 (CH), 110.0 (CH), 75.5 (CH), 73.4 (CH), 72.0 (CH), 56.9 (CH_3), 55.3 (CH_3), 38.5 (C), 30.8 (CH), 30.1 (CH_2), 26.8 (CH_3), 19.0 (CH_3), 17.2 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+Na]^+$ $C_{22}H_{31}NNaO_5S_2$: 476.1536, found: 476.1536.



117m

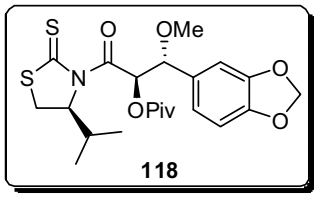
(*S*)-*N*-[(*2R*, *3S*)-3-Methoxy-3-(2-methoxyphenyl)-2-pivaloyloxy propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**117m**). Yellow solid; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.54–7.52 (1H, m, ArH), 7.25–7.23 (1H, m, ArH), 7.03–6.95 (2H, m, COCH, ArH), 6.85–6.83 (1H, m, ArH), 5.70 (1H, d, *J* = 3.9 Hz, CHOCH$_3$), 5.45–5.41 (1H, ddd, *J* = 9.0, 4.8, 1.6 Hz, NCH), 3.81 (3H, s, ArOCH$_3$), 3.59 (1H, dd, *J* = 11.4, 9.0 Hz, SCH$_a$H$_b$), 3.26 (3H, s, CHOCH$_3$), 3.06 (1H, dd, *J* = 11.4, 1.6 Hz, SCH$_a$H$_b$), 2.44–2.28 (1H, m, CH(CH$_3$)$_2$), 1.10 (3H, d, *J* = 6.8 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$), 1.01 (3H, d, *J* = 7.0 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$), 1.01 (9H, s, C(CH$_3$)$_3$).

4.7.7. (*S*)-4-Isopropyl-*N*-[(*2R*, *3R*)-3-methoxy-3-(2-methoxyphenyl)-2-pivaloyloxypropanoyl]-1,3-thiazolidine-2-thione (117) with 5.0 mol% of $(Me_3P)_2NiCl_2$

The thioimide **117** was prepared according to the General Procedure in section 4.2. from thioimide **4m** (152 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (7.0 mg, 25 μmol), 2-methoxybenzaldehyde dimethyl acetal (**131**) (100 mg, 0.55 mmol), TESOTf (249 μL, 1.1 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. A 80:20 diastereomeric ratio of the *anti/syn* diastereomers was established by ^{1}H NMR of the crude product. Purification of the crude product by flash column chromatography on silica gel (from hexanes/CH_2Cl_2 1:1 to 1:4) afforded 120 mg of pure *anti* diastereomer **117** (0.30 mmol, 60%) and 32 mg of *syn* diastereomer **117m** (0.08 mmol, 16%).

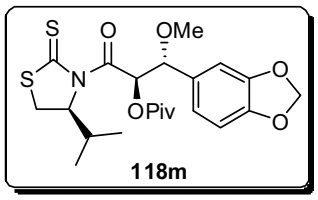
4.7.8. (*S*)-*N*-[(*2R*, *3R*)-3-(Benzo[*d*][1,3]dioxol-5-yl)-3-methoxy-2-pivaloyloxypropanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (118)

The thioimide **118** was prepared according to the General Procedure in section 4.2. from thioimide **4m** (152 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol), piperonal dimethyl acetal (**133**) (108 mg, 0.55 mmol), TESOTf (130 μL, 0.58 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. A 81:19 diastereomeric ratio of the *anti/syn* diastereomers was established by ^{1}H NMR of the crude product. Purification of the crude product by flash column chromatography on silica gel (from hexanes/EtOAc 88:12 to 84:16) afforded 186 mg of pure *anti* diastereomer **118** (0.40 mmol, 79%) and 47 mg of *syn* diastereomer **118m** (0.10 mmol, 19%).



118

(*S*)-*N*-[(*2R*, *3R*)-3-(Benzo[*d*][1,3]dioxol-5-yl)-3-methoxy-2-pivaloyloxy propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**118**). Yellow solid; **mp** = 132–133 ºC; $\mathbf{R_f}$ = 0.45 (hexanes/EtOAc 4:1); $\mathbf{[\alpha]_D}$ = +186.8 (*c* 1.25, $CHCl_3$); **IR** (ATR) 2959, 2925, 2870, 1724, 1705, 1480, 1438, 1337, 1249, 1156, 1030 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.11 (1H, d, *J* = 7.4 Hz, COC$\underline{H}$), 7.03 (1H, d, *J* = 1.6 Hz, ArH), 6.86 (1H, dd, *J* = 7.9, 1.6 Hz, ArH), 6.77 (1H, d, *J* = 7.9 Hz, ArH), 5.97 (1H, d, *J* = 1.5 Hz, OC$\underline{H_a}H_bO$), 5.96 (1H, d, *J* = 1.5 Hz, OC$H_a\underline{H_b}$O), 5.29 (1H, ddd, *J* = 8.3, 5.9, 1.0 Hz, NC$\underline{H}$), 4.57 (1H, d, *J* = 7.4 Hz, C$\underline{H}$OCH$_3$), 3.60 (1H, dd, *J* = 11.5, 8.3 Hz, SC$\underline{H_a}H_b$), 3.18 (3H, s, CHOC$\underline{H_3}$), 3.02 (1H, dd, *J* = 11.5, 1.0 Hz, SC$H_a\underline{H_b}$), 2.37–2.25 (1H, m, C$\underline{H}$(CH$_3$)$_2$), 1.12 (9H, s, C(C$\underline{H_3}$)$_3$), 1.09 (3H, d, *J* = 6.9 Hz, CH(C$\underline{H_3}$)$_a$(CH$_3$)$_b$), 1.01 (3H, d, *J* = 6.9 Hz, CH(CH$_3$)$_a$(C$\underline{H_3}$)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.6 (C), 177.5 (C), 170.1 (C), 147.7 (2 × C), 131.3 (C), 122.1 (CH), 108.1 (CH), 107.6 (CH), 101.0 (CH_2), 83.6 (CH), 72.9 (CH), 71.6 (CH), 56.7 (CH_3), 38.3 (C), 30.5 (CH), 30.2 (CH_2), 26.8 (CH_3), 18.8 (CH_3), 17.4 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OCH_3]^+$ $C_{21}H_{26}NO_5S_2$: 436.1247, found: 436.1247.

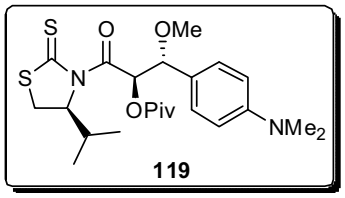


118m

(*S*)-*N*-[(*2R*, *3S*)-3-(Benzo[*d*][1,3]dioxol-5-yl)-3-methoxy-2-pivaloyloxy propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**118m**). Yellow solid; $\mathbf{R_f}$ = 0.40 (hexanes/EtOAc 4:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.03 (1H, d, *J* = 1.6 Hz, ArH), 6.97 (1H, dd, *J* = 8.0, 1.6 Hz, ArH), 6.94 (1H, d, *J* = 2.7 Hz, COC$\underline{H}$), 6.78 (1H, d, *J* = 8.0 Hz, ArH), 5.96–5.95 (1H, m, OC$\underline{H_2}$O), 5.49 (1H, ddd, *J* = 8.9, 5.1, 1.5 Hz, NC$\underline{H}$), 5.26 (1H, d, *J* = 2.7 Hz, C$\underline{H}$OCH$_3$), 3.61 (1H, dd, *J* = 11.5, 8.9 Hz, SC$\underline{H_a}H_b$), 3.23 (3H, s, CHOC$\underline{H_3}$), 3.05 (1H, dd, *J* = 11.5, 1.5 Hz, SC$H_a\underline{H_b}$), 2.38–2.26 (1H, m, C$\underline{H}$(CH$_3$)$_2$), 1.16 (9H, s, C(C$\underline{H_3}$)$_3$), 1.08 (3H, d, *J* = 6.8 Hz, CH(C$\underline{H_3}$)$_a$(CH$_3$)$_b$), 1.00 (3H, d, *J* = 7.0 Hz, CH(CH$_3$)$_a$(C$\underline{H_3}$)$_b$).

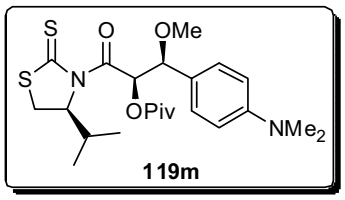
4.7.9. (*S*)-4-Isopropyl-*N*-[(*2R*, *3R*)-3-methoxy-3-(4-dimethylaminophenyl)-2-pivaloyloxypropanoyl]-1,3-thiazolidine-2-thione (119) with 2.5 mol% of $(Me_3P)_2NiCl_2$

The thioimide **119** was prepared according to the General Procedure in section 4.2. from thioimide **4m** (152 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol), 4-dimethylaminobenzaldehyde dimethyl acetal (**134**) (107 mg, 0.55 mmol), TESOTf (130 μL, 0.58 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. A 83:17 diastereomeric ratio of the *anti/syn* diastereomers was established by ^{1}H NMR of the crude product. Purification of the crude product by flash column chromatography on silica gel (from hexanes/EtOAc 9:1 to 4:1) afforded 132 mg of pure *anti* diastereomer **119** (0.28 mmol, 57%) and 28 mg of *syn* diastereomer **119m** (0.06 mmol, 12%).



119

(*S*)-4-Isopropyl-*N*-[(*2R*, *3R*)-3-methoxy-3-(4-dimethylaminophenyl)-2-pivaloyloxypropanoyl]-1,3-thiazolidine-2-thione (**119**). Yellow solid; **mp** = 136–137 ºC; $\mathbf{R_f}$ = 0.45 (hexanes/EtOAc 4:1); $\mathbf{[\alpha]_D}$ = +164.8 (*c* 1.00, $CHCl_3$); **IR** (ATR) 2973, 2954, 2870, 1720, 1702, 1613, 1523, 1360, 1182, 1149 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.32–7.30 (2H, m, ArH), 7.13 (1H, *J* = 7.4 Hz, COCH), 6.71–6.69 (2H, m, ArH), 5.30 (1H, ddd, *J* = 8.4, 5.7, 1.0 Hz, NCH), 4.54 (1H, d, *J* = 7.4 Hz, CHOCH$_3$), 3.59 (1H, dd, *J* = 11.4, 8.4 Hz, SCH$_a$H$_b$), 3.16 (3H, s, CHOCH$_3$), 3.00 (1H, dd, *J* = 11.4, 1.0 Hz, SCH$_a$H$_b$), 2.96 (6H, s, N(CH$_3$)$_2$), 2.37–2.26 (1H, m, CH(CH$_3$)$_2$), 1.11 (3H, d, *J* = 6.6 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$), 1.11 (9H, s, C(CH$_3$)$_3$), 1.01 (3H, d, *J* = 6.9 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.4 (C), 177.6 (C), 170.5 (C), 150.5 (C), 129.1 (CH), 124.8 (C), 111.8 (CH), 83.7 (CH), 73.3 (CH), 71.6 (CH), 56.5 (CH_3), 40.4 (CH_3), 38.3 (C), 30.5 (CH), 30.1 (CH_2), 26.8 (CH_3), 18.9 (CH_3), 17.4 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OCH_3]^+$ $C_{22}H_{31}N_2O_3S_2$: 435.1771, found: 435.1784; *m/z* calculated for $[M+H]^+$ $C_{23}H_{35}N_2O_4S_2$: 467.2033, found: 467.2047.



119m

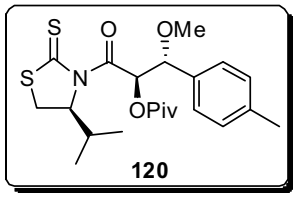
(*S*)-4-Isopropyl-*N*-[(*2R*, *3S*)-3-Methoxy-3-(4-dimethylaminophenyl)-2-pivaloyloxypropanoyl]-1,3-thiazolidine-2-thione (**119m**). Yellow solid; $\mathbf{R_f}$ = 0.35 (hexanes/EtOAc 4:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.37–7.35 (2H, m, ArH), 6.97 (1H, *J* = 2.7 Hz, COCH), 6.75–6.69 (2H, m, ArH), 5.49 (1H, ddd, *J* = 9.1, 5.1, 1.6 Hz, NCH), 5.23 (1H, d, *J* = 2.7 Hz, CHOCH$_3$), 3.59 (1H, dd, *J* = 11.4, 9.1 Hz, SCH$_a$H$_b$), 3.21 (3H, s, CHOCH$_3$), 3.04 (1H, dd, *J* = 11.4, 1.6 Hz, SCH$_a$H$_b$), 2.95 (6H, s, N(CH$_3$)$_2$), 2.40–2.26 (1H, m, CH(CH$_3$)$_2$), 1.17 (9H, s, C(CH$_3$)$_3$), 1.07 (3H, d, *J* = 6.8 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$), 1.00 (3H, d, *J* = 6.9 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$).

4.7.10. (*S*)-4-Isopropyl-*N*-[(*2R*, *3R*)-3-methoxy-3-(4-dimethylaminophenyl)-2-pivaloyloxypropanoyl]-1,3-thiazolidine-2-thione (119) with 5.0 mol% of $(Me_3P)_2NiCl_2$

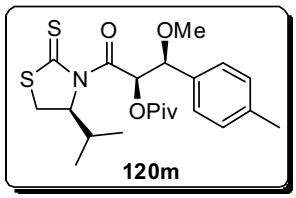
The thioimide **119** was prepared according to the General Procedure in section 4.2. from thioimide **4m** (152 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (7.0 mg, 25 μmol), 4-dimethylaminobenzaldehyde dimethyl acetal (**134**) (107 mg, 0.55 mmol), TESOTf (249 μL, 1.1 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. A 83:17 diastereomeric ratio of the *anti/syn* diastereomers was established by ^{1}H NMR of the crude product. Purification of the crude product by flash column chromatography on silica gel (from hexanes/EtOAc 9:1 to 4:1) afforded 172 mg of pure *anti* diastereomer **119** (0.37 mmol, 74%) and 39 mg of *syn* diastereomer **119m** (0.09 mmol, 17%).

4.7.11. (*S*)-4-Isopropyl-*N*-[(*2R*, *3R*)-3-methoxy-3-(4-tolyl)-2-pivaloyloxypropanoyl]-1,3-thiazolidine-2-thione (120)

The thioimide **120** was prepared according to the General Procedure in section 4.2. from thioimide **4m** (152 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (7.0 mg, 25 μmol), 4-methylbenzaldehyde dimethyl acetal (**136**) (91 mg, 0.55 mmol), TESOTf (249 μL, 1.1 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. A 75:25 diastereomeric ratio of the *anti/syn* diastereomers was established by ^{1}H NMR of the crude product. Purification of the crude product by flash column chromatography on silica gel (from hexanes/CH_2Cl_2 1:1 to 1:9) afforded 145 mg of pure *anti* diastereomer **120** (0.33 mmol, 66%) and 45 mg of *syn* diastereomer **119m** (0.10 mmol, 21%).



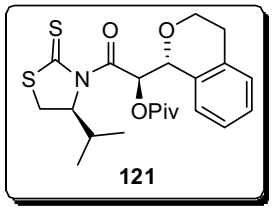
(*S*)-4-Isopropyl-*N*-[(*2R*, *3R*)-3-methoxy-2-pivaloyloxy-3-(4-tolyl)propanoyl]-1,3-thiazolidine-2-thione (**120**). Yellow solid; **mp** = 139–140 ºC; $\mathbf{R_f}$ = 0.60 (hexanes/CH_2Cl_2 1:9); $\mathbf{[\alpha]_D}$ = +196.3 (*c* 0.75, $CHCl_3$); **IR** (ATR) 2959, 2928, 1724, 1694, 1464, 1357, 1305, 1257, 1171, 1145 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.35–7.33 (2H, m, ArH), 7.17–7.15 (2H, m, ArH), 7.12 (1H, *J* = 7.3 Hz, COCH), 5.29 (1H, ddd, *J* = 8.4, 5.6, 1.1 Hz, NCH), 4.62 (1H, d, *J* = 7.3 Hz, CHOCH$_3$), 3.59 (1H, dd, *J* = 11.4, 8.4 Hz, SCH$_a$H$_b$), 3.18 (3H, s, CHOCH$_3$), 3.01 (1H, dd, *J* = 11.4, 1.1 Hz, SCH$_a$H$_b$), 2.37–2.28 (1H, m, CH(CH$_3$)$_2$), 2.35 (3H, s, ArCH$_3$), 1.11 (3H, d, *J* = 7.0 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$), 1.10 (9H, s, C(CH$_3$)$_3$), 1.02 (3H, d, *J* = 6.9 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.5 (C), 177.5 (C), 170.2 (C), 138.2 (C), 134.3 (C), 128.8 (CH), 128.1 (CH), 83.6 (CH), 73.1 (CH), 71.6 (CH), 56.8 (CH_3), 38.3 (C), 30.5 (CH), 30.2 (CH_2), 26.8 (CH_3), 21.2 (CH_3), 18.9 (CH_3), 17.4 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M+H]^+$ $C_{22}H_{32}NO_4S_2$: 438.1767, found: 438.1772; *m/z* calculated for $[M+Na]^+$ $C_{22}H_{31}NNaO_4S_2$: 460.1587, found: 460.1595; *m/z* calculated for $[2M+Na]^+$ $C_{44}H_{62}N_2NaO_8S_4$: 897.3281, found: 897.3289.



(*S*)-4-Isopropyl-*N*-[(*2R*, *3S*)-3-methoxy-2-pivaloyloxy-3-(4-tolyl)propanoyl]-1,3-thiazolidine-2-thione (**120m**). Yellow solid; $\mathbf{R_f}$ = 0.45 (hexanes/CH_2Cl_2 1:9);**^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.41–7.38 (2H, m, ArH), 7.16–7.14 (2H, m, ArH), 6.98 (1H, *J* = 2.7 Hz, COCH), 5.49 (1H, ddd, *J* = 8.9, 5.0, 1.1 Hz, NCH), 5.31 (1H, d, *J* = 2.7 Hz, CHOCH$_3$), 3.60 (1H, dd, *J* = 11.4, 8.9 Hz, SCH$_a$H$_b$), 3.23 (3H, s, CHOCH$_3$), 3.01 (1H, dd, *J* = 11.4, 1.1 Hz, SCH$_a$H$_b$), 2.37–2.28 (1H, m, CH(CH$_3$)$_2$), 2.34 (3H, s, ArCH$_3$),1.13 (9H, s, C(CH$_3$)$_3$), 1.08 (3H, d, *J* = 6.8 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$), 1.00 (3H, d, *J* = 7.4 Hz, CH(CH$_3$)$_a$(CH$_3$)$_b$).

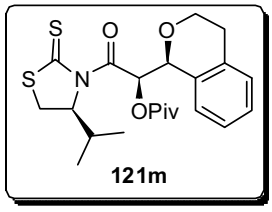
4.7.12. (*S*)-*N*-[(*R*)-2-[(*R*)-Isochroman-1-yl]-1-pivaloyloxyacetyl]-4-isopropyl-1,3-thiazolidine-2-thione (121)

The thioimide **121** was prepared according to the General Procedure in section 4.2. from thioimide **4m** (152 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (28.2 mg, 0.10 mmol), 1-methoxyisochroman (**79**) (90 mg, 0.55 mmol), TESOTf (170 μL, 0.75 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. A 55:45 diastereomeric ratio of the *anti/syn* diastereomers was established by ^{1}H NMR of the crude product. Purification of the crude product by flash column chromatography on silica gel (hexanes/CH_2Cl_2 3:7) afforded 200 mg of a 5.6:4.4:1.0:1.3 mixture of *anti* diastereomer **121** (98 mg, 0.22 mmol, 45%), *syn* diastereomer **121m** (76 mg, 0.17 mmol, 33%), starting material **4m** (12 mg, 0.04 mmol, 8%) and acetal **79** (9 mg, 0.05 mmol, 10%).



121

(*S*)-*N*-[(*R*)-2-[(*R*)-Isochroman-1-yl]-1-pivaloyloxyacetyl]-4-isopropyl-1,3-thiazolidine-2-thione (**121**). Yellow solid; $\mathbf{R_f}$ = 0.45 (CH_2Cl_2); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.27–7.12 (4H, m, ArH), 7.04 (1H, d, *J* = 7.0 Hz, COC<u>H</u>), 5.33 (1H, ddd, *J* = 8.4, 5.5, 1.2 Hz, NC<u>H</u>), 5.25 (1H, d, *J* = 7.0 Hz, COCHC<u>H</u>), 4.12 (1H, ddd, *J* = 10.8, 5.3, 2.8 Hz, OC<u>H$_a$</u>H$_b$), 3.69 (1H, td, *J* = 10.8, 3.0 Hz, OCH$_a$<u>H$_b$</u>), 3.59 (1H, dd, *J* = 11.4, 8.4 Hz, SC<u>H$_a$</u>H$_b$), 3.17–3.10 (1H, m, ArC<u>H$_a$</u>H$_b$), 3.00 (1H, dd, *J* = 11.4, 1.2 Hz, SCH$_a$<u>H$_b$</u>), 2.60 (1H, dt, *J* = 15.9, 2.8 Hz, ArCH$_a$<u>H$_b$</u>), 2.47–2.31 (1H, C<u>H</u>(CH$_3$)$_2$), 1.26 (9H, s, C(C<u>H$_3$</u>)$_3$), 1.09 (3H, d, *J* = 6.8 Hz, CH(C<u>H$_3$</u>)$_a$(CH$_3$)$_b$), 1.03 (3H, d, *J* = 6.9 Hz, CH(CH$_3$)$_a$(C<u>H$_3$</u>)$_b$).



121m

(*S*)-*N*-[(*R*)-2-[(*S*)-Isochroman-1-yl]-1-pivaloyloxyacetyl]-4-isopropyl-1,3-thiazolidine-2-thione (**121m**). Yellow solid; $\mathbf{R_f}$ = 0.45 (CH_2Cl_2); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.48 (1H, d, *J* = 2.6 Hz, COC<u>H</u>), 7.27–7.12 (4H, m, ArH), 5.93 (1H, d, *J* = 2.6 Hz, COCHC<u>H</u>), 5.49 (1H, ddd, *J* = 9.1, 4.8, 1.9 Hz, NC<u>H</u>), 4.28 (1H, dt, *J* = 11.0, 4.8 Hz, OC<u>H$_a$</u>H$_b$), 3.84–3.76 (1H, m, OCH$_a$<u>H$_b$</u>), 3.61 (1H, td, *J* = 11.5, 9.0 Hz, SC<u>H$_a$</u>H$_b$), 3.17–2.94 (1H, m, ArC<u>H$_a$</u>H$_b$), 3.08 (1H, dd, *J* = 11.5, 1.9 Hz, SCH$_a$<u>H$_b$</u>),2.74 (1H, dt, *J* = 9.4, 4.8 Hz, ArCH$_a$<u>H$_b$</u>), 2.47–2.31 (1H, C<u>H</u>(CH$_3$)$_2$), 1.07 (3H, d, *J* = 6.9 Hz, CH(C<u>H$_3$</u>)$_a$(CH$_3$)$_b$), 1.03 (3H, d, *J* = 6.9 Hz, CH(CH$_3$)$_a$(C<u>H$_3$</u>)$_b$), 0.94 (9H, s, C(C<u>H$_3$</u>)$_3$).

4.7.13. Attempt with *p*-chlorobenzaldehyde dimethyl acetal (135)

The reaction was carried out according to the General Procedure in section 4.2. from thioimide **4m** (152 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (28.2 mg, 0.10 mmol), 4-chlorobenzaldehyde dimethyl acetal (**135**) (103 mg, 0.55 mmol), TESOTf (170 μL, 0.75 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. ^{1}H NMR spectrum of the crude product showed the only presence of starting materials.

4.7.14. Attempt with furfural dimethyl acetal (135)

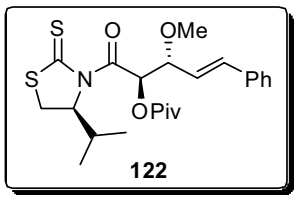
The reaction was carried out according to the General Procedure in section 4.2. from thioimide **4m** (152 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol), furfural dimethyl acetal (**137**) (78 mg, 0.55 mmol), TESOTf (130 μL, 0.75 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. ^{1}H NMR spectrum of the crude product only showed the unaltered starting material **4m** and decomposition products coming from the acetal.

4.7.15. (*S*)-4-Isopropyl-*N*-[(*2R*, *3R*)-3-methoxy-5-phenyl-2-pivaloyloxypent-4-enoyl]-1,3-thiazolidine-2-thione (122) with 2.5 mol% of $(Me_3P)_2NiCl_2$

The reaction was carried out according to the General Procedure in section 4.2. from thioimide **4m** (152 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol), (*E*)-cinnamaldehyde dimethyl acetal (**130**) (98 mg, 0.55 mmol), TESOTf (130 μL, 0.58 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. ^{1}H NMR of the crude product showed a conversion of 45% with a diastereomeric ratio of 78:22.

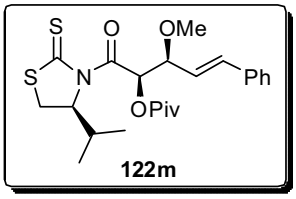
4.7.16. (*S*)-4-Isopropyl-*N*-[(*2R*, *3R*)-3-methoxy-5-phenyl-2-pivaloyloxypent-4-enoyl]-1,3-thiazolidine-2-thione (122) with 5 mol% of $(Me_3P)_2NiCl_2$

The thioimide **122** was prepared according to the General Procedure in section 4.2. from thioimide **4m** (152 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (7.0 mg, 25 μmol), (*E*)-cinnamaldehyde dimethyl acetal (**130**) (98 mg, 0.55 mmol), TESOTf (136 μL, 0.60 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. A 78:22 diastereomeric ratio of the *anti/syn* diastereomers was established by ^{1}H NMR of the crude product. Purification of the crude product by flash column chromatography on silica gel (hexanes/CH_2Cl_2 3:7) afforded 142 mg of *anti* diastereomer **122** (0.31 mmol, 63%) and 38 mg of the *syn* diastereomer **122m** (0.08 mmol, 17%).



122

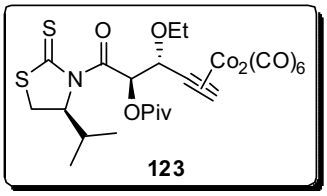
(*S*)-4-Isopropyl-*N*-[(*2R*, *3R*)-3-methoxy-5-phenyl-2-pivaloyloxypent-4-enoyl]-1,3-thiazolidine-2-thione (**122**). Yellow oil; $\mathbf{R_f}$ = 0.45 (CH_2Cl_2); $\mathbf{[\alpha]_D}$ = +197.3 (*c* 1.00, $CHCl_3$); **IR** (ATR) 2962, 2925, 2866, 1731, 1698, 1475, 1460, 1360, 1260, 1175, 1145 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.40–7.25 (5H, m, ArH), 6.96 (1H, d, *J* = 4.8 Hz, COCH), 6.60 (1H, d, *J* = 16.0 Hz, CH=CHPh), 6.25 (1H, dd, *J* = 16.0, 8.4 Hz, CH=CHPh), 5.23 (1H, ddd, *J* = 8.4, 6.0, 1.1 Hz, NCH), 4.41 (1H, dd, *J* = 8.4, 4.8 Hz, $CHOCH_3$), 3.61 (1H, dd, *J* = 11.5, 8.4 Hz,SCH_aH_b), 3.35 (3H, s, OCH_3), 3.01 (1H, dd, *J* = 11.5, 1.1 Hz, SCH_aH_b), 2.31–2.19 (1H, m, $CH(CH_3)_2$), 1.23 (9H, s, $C(CH_3)_3$), 1.06 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(CH_3)_b$), 0.94 (3H, d, *J* = 6.9 Hz, $CH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.4 (C), 177.8 (C), 168.8 (C), 136.1 (C), 135.3 (CH), 128.6 (CH), 128.1 (CH), 126.7 (CH), 124.6 (CH), 81.6 (CH), 73.5 (CH), 71.6 (CH), 56.8 (CH_3), 38.7 (C), 30.5 (CH), 30.5 (CH_2), 27.0 (CH_3), 18.9 (CH_3), 17.5 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OCH_3]^+$ $C_{22}H_{28}NO_3S_2$: 418.1505, found: 418.1518.



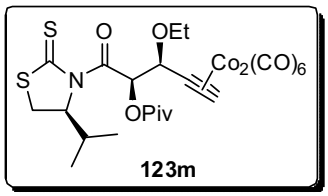
(*S*)-4-Isopropyl-*N*-[(*2R*, *3S*)-3-methoxy-5-phenyl-2-pivaloyloxypent-4-enoyl]-1,3-thiazolidine-2-thione (**122m**). Yellow oil; $\mathbf{R_f}$ = 0.45 (CH_2Cl_2); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.59–7.25 (5H, m, ArH), 6.98 (1H, d, *J* = 3.8 Hz, COCH), 6.73 (1H, dd, *J* = 16.0, 7.9 Hz, CH=CHPh), 6.69 (1H, d, *J* = 16.0 Hz, CH=CHPh), 5.38 (1H, ddd, *J* = 8.8, 5.2, 1.1 Hz, NCH), 4.74 (1H, dd, *J* = 7.9, 3.8 Hz, $CHOCH_3$), 3.59 (1H, dd, *J* = 11.6, 8.8 Hz, SCH_aH_b), 3.32 (3H, s, OCH_3), 3.02 (1H, dd, *J* = 11.6, 1.1 Hz, SCH_aH_b), 2.31–2.17 (1H, m, $CH(CH_3)_2$), 1.27 (9H, s, $C(CH_3)_3$), 0.97 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(CH_3)_b$), 0.93 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_a(CH_3)_b$).

4.7.17. (*S*)-*N*-[(*2R,3R*)-Hexacarbonyl[μ-η^4-(3-ethoxy-2-pivaloyloxypent-4-ynoyl)dicobalt (*Co-Co*)]-4-isopropyl-1,3-thiazolidine-2-thione (123)

The thioimide **123** was prepared according to the General Procedure in section 4.2. from thioimide **4m** (152 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (7.0 mg, 25 μmol), cobalted acetal **88** (311 mg, 0.75 mmol), TESOTf (250 μL, 1.1 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. A 85:15 diastereomeric ratio of the *anti/syn* diastereomers was established by HPLC of the crude product. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc 9:1) afforded 264 mg of *anti* diastereomer **123** (0.39 mmol, 79%) and 41 mg of the *syn* diastereomer **123m** (0.06 mmol, 12%).



(*S*)-*N*-[(*2R,3R*)-Hexacarbonyl[μ-η^4-(3-ethoxy-2-pivaloyloxypent-4-ynoyl)dicobalt (*Co-Co*)]-4-isopropyl-1,3-thiazolidine-2-thione (**123**). Deep maroon solid; **mp** = 115–116 ºC; $\mathbf{R_f}$ = 0.35 (hexanes/EtOAc 9:1); **HPLC** (Tracer Spherisorb S3W (N4184) column, 5% of EtOAc in hexanes, 0.9 mL/min, 254 nm), t_R = 12.0 min; $\mathbf{[\alpha]_D}$ = +337.0 (*c* 0.01, $CHCl_3$), $\mathbf{[\alpha]_D}$ = +375.7 (*c* 0.10, $CHCl_3$); **IR** (ATR) 2962, 2870, 2091, 2046, 2017, 1998, 1720, 1683, 1357, 1283, 1179, 1134, 1090 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 6.84 (1H, d, *J* = 7.8 Hz, COCH), 6.02 (1H, d, *J* = 0.8 Hz, $C[Co_2(CO)_6]H$), 5.20 (1H, ddd, *J* = 8.1, 5.9, 0.9 Hz, NCH), 4.98 (1H, dd, *J* = 7.8, 0.8 Hz, COCHCH), 3.81 (1H, dq, *J* = 8.6, 7.0 Hz, OCH_aH_b), 3.63 (1H, dd, *J* = 11.4, 8.1 Hz, SCH_aH_b), 3.60 (1H, dq, *J* = 8.6, 7.0, OCH_aH_b), 3.03 (1H, dd, *J* = 11.4, 0.9 Hz, SCH_aH_b), 2.42–2.34 (1H, m, $CH(CH_3)_2$), 1.24 (9H, s, $C(CH_3)_3$), 1.17 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 1.10 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(CH_3)_b$), 1.04 (3H, d, *J* = 6.9 Hz, $CH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.8 (C), 199.4 (C), 177.7 (C), 169.7 (C), 91.0 (C), 79.5 (CH), 73.3 (CH), 72.5 (CH), 71.7 (CH), 66.6 (CH_2), 38.5 (C), 30.8 (CH), 30.5 (CH_2), 27.0 (CH_3), 19.1 (CH_3), 17.5 (CH_3), 14.7 (CH_3); **HRMS** (+ESI): *m/z* calculated for $[M–OC_2H_5]^+$ $C_{22}H_{22}Co_2NO_9S_2$: 625.9394, found: 625.9394; *m/z* calculated for $[M+Na]^+$ $C_{24}H_{27}Co_2NNaO_{10}S_2$: 693.9633, found: 693.9640.



(*S*)-*N*-[(*2R,3S*)-Hexacarbonyl[μ-η^4-(3-ethoxy-2-pivaloyloxypent-4-ynoyl)dicobalt (*Co-Co*)]-4-isopropyl-1,3-thiazolidine-2-thione (**123m**). Deep maroon solid; $\mathbf{R_f}$ = 0.30 (hexanes/EtOAc 9:1); **HPLC** (Tracer Spherisorb S3W (N4184) column, 5% of EtOAc in hexanes, 0.9 mL/min, 254 nm), t_R = 16.3 min; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 6.65 (1H, d, *J* = 2.4 Hz, COC<u>H</u>), 6.13 (1H, s, C[$Co_2(CO)_6$]<u>H</u>), 5.28 (1H, ddd, *J* = 7.1, 5.9, 1.7 Hz, NC<u>H</u>).

<u>4.7.18. (*S*)-*N*-[(*2R,3R*)-Hexacarbonyl[μ-η^4-(3-ethoxy-5-phenyl-2-pivaloyloxypent-4-ynoyl)dicobalt (*Co-Co*)]-4-isopropyl-1,3-thiazolidine-2-thione (113) from 1.5 equivalents of acetal 138</u>

The thioimide **113** was prepared according to the General Procedure in section 4.2. from thioimide **4m** (152 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (7.0 mg, 25 μmol), cobalted acetal **138** (368 mg, 0.75 mmol), TESOTf (250 μL, 1.1 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. A 94:6 diastereomeric ratio of the *anti/syn* diastereomers was established by HPLC of the crude product. Purification of the crude product by flash column chromatography on silica gel (from hexanes/CH_2Cl_2 1:1 to 3:7) to afford a first fraction of 152 mg of pure *anti* diastereomer **113** (0.20 mmol), a second fraction of 137 mg of a 1:0.19 mixture of *anti* and *syn* diastereomers **113** (0.16 mmol) and **113m** (0.03 mmol), and a third fraction of 35 mg of a 1:6.96 mixture of *anti* diastereomer **113** (0.01 mmol) and starting material **4m** (0.08 mmol). The overall calculated yield was 74% (0.37 mmol) for the *anti* diastereomer **113** and 6% (0.03 mmol) for the *syn* diastereomer **113m**.

<u>4.7.19. (*S*)-*N*-[(*2R,3R*)-Hexacarbonyl[μ-η^4-(3-ethoxy-5-phenyl-2-pivaloyloxypent-4-ynoyl)dicobalt (*Co-Co*)]-4-isopropyl-1,3-thiazolidine-2-thione (113) from 2.2 equivalents of acetal 138</u>

The thioimide **113** was prepared according to the General Procedure in section 4.2. from thioimide **4m** (152 mg, 0.50 mmol), $(Me_3P)_2NiCl_2$ (7.0 mg, 25 μmol), cobalted acetal **138** (539 mg, 1.1 mmol), TESOTf (250 μL, 1.1 mmol), 2,6-lutidine (88 μL, 0.75 mmol) and CH_2Cl_2 (1.0 mL) at –20 ºC for 15 h. A 94:6 diastereomeric ratio of the *anti/syn* diastereomers was established by HPLC of the crude product. Purification of the crude product by flash column chromatography on silica gel (from hexanes/CH_2Cl_2 1:1 to 3:7) to afford a first fraction of 226 mg of pure *anti* diastereomer **113** (0.30 mmol) and a second fraction of 113 mg of a 1:0.28 mixture of *anti* and *syn* diastereomers **113** (0.12 mmol) and **113m** (0.03 mmol). The overall calculated yield was 84% (0.42 mmol) for the *anti* diastereomer **113** and 6% (0.03 mmol) for the *syn* diastereomer **113m**.

ABBREVIATIONS

$[\alpha]_D$	Specific rotation
δ	Chemical shift
Ac	Acetyl
anh	Anhydrous
d.r.	Diastereomeric ratio
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
BOM	Benzyloxymethyl
Box	Bis(oxazoline)
bp	Boiling point
Bz	Benzoyl
calc.	Calculated
cat.	Catalytic
Chx	Cyclohexyl
Conv	Conversion
CSA	Camphorsulfonic acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-*p*-benzoquinone
DIBALH	Di(isobutyl)aluminium hydryde
DIPEA	Di(isopropyl) ethyl amine
DMAP	4-(Dimethylamino)pyridine
dppe	1,2-Bis(diphenylphosphino)ethane
dppp	1,3-Bis(diphenylphosphino)propane
DTBMP	2,6-Di(*tert*-butyl)-4-methylpyridine
d.r.	Diastereomeric ratio.
EDC	*N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide
ee	Enantiomeric excess
EI	Electron ionization
ent	Enantiomer
eq	Equivalents
e.r.	Enantiomeric ratio
ESI	Electrospray ionization
FAB	Fast atom bombardment
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectrometry
IR	Infrared spectroscopy
KHMDS	Potassium hexamethyldisilylazide
L.A.	Lewis acid

LiHMDS	Lithium hexamethyldisilylazide
lit.	Literature
L	Ligand
LG	Leaving group
MOM	Methoxymethyl
MS	Mass spectrometry
mp	Melting point
NBS	*N*-Bromosuccinimide
NIS	*N*-Iodosuccinimide
NMO	*N*-Methylmorpholine *N*-oxide
NMM	*N*-Methyl morpholine
NMR	Nuclear magnetic resonance spectroscopy
Nu	Nucleophile
OTf	Triflate or trifluoromethansulfonate
PG	Protecting group
Phth	Phthalamidyl
Piv	Pivaloyl or dimethylpropanoyl
PMB	*p*-Methoxybenzyl
PPTS	Pyridinium *p*-toluenesulfonate
r.s.m.	Recovered Starting Material
r.t.	Room temperature
sat	Saturated
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TES	Triethylsilyl
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin-layer chromatography
TMEDA	*N, N, N', N'*-Tetramethylethylenediamine
TMP	2,2,6,6-Tetramethylpiperidine
TMS	Trimethylsilyl

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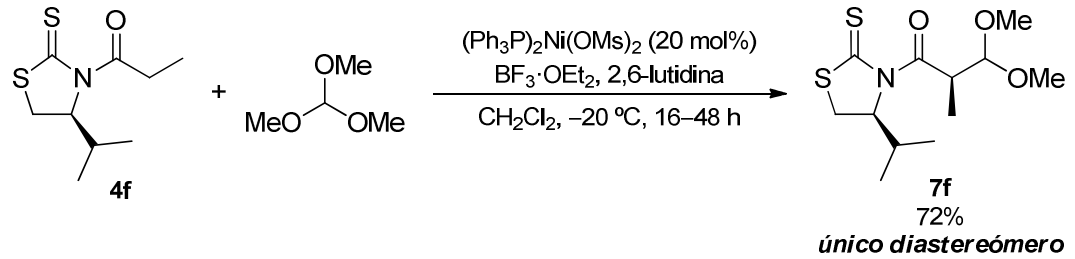
RESUMEN Y CONCLUSIONES

En la presente tesis doctoral se ha desarrollado un nuevo sistema catalítico estereoselectivo basado en complejos de níquel(II) para la adición tipo S_N1 de *N*-acil tiazolidintionas quirales a electrófilos capaces de generar especies carbocatiónicas en condiciones ácidas. Los complejos de níquel(II) usados a lo largo de los respectivos estudios son estructuralmente simples, comercialmente disponibles y baratos, y fáciles de manipular y almacenar.

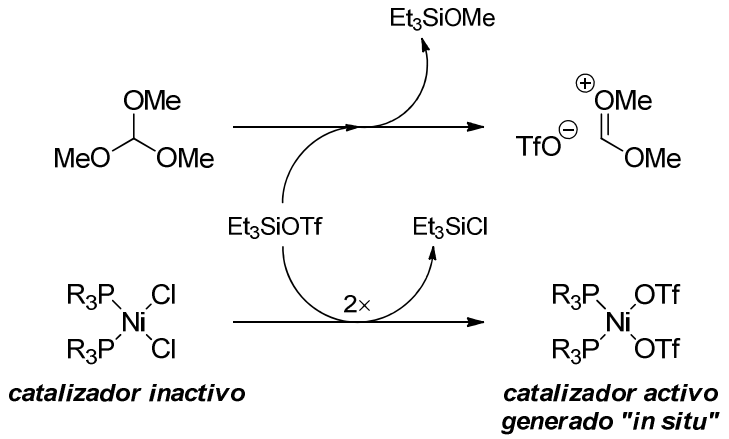
Capítulo 1: Reacciones estereoselectivas de *N*-acil tiazolidintionas con ortoformiato de trimetilo catalizadas por Ni(II)

En el Capítulo 1 se ha optimizado y desarrollado una adición catalítica totalmente estereoselectiva de *N*-acil tiazolidintionas a ortoformiato de trimetilo activado por un ácido de Lewis, lo que permite la introducción de un grupo formilo en la posición β. Una primera aproximación que usa $(Ph_3P)_2Ni(OMs)_2$ como catalizador, BF3·OEt como ácido de Lewis y 2,6-lutidina como base fue propuesta por Érik Gálvez en nuestros laboratorios. Esta reacción permitía obtener el aducto **7f** con un rendimiento elevado, y demuestra que el auxiliar quiral es capaz de controlar completamente la estereoquímica resultante del proceso. A pesar del éxito del proceso, este catalizador debe ser preparado y utilizado con delicadez, y por tanto no cumplía nuestras expectativas.



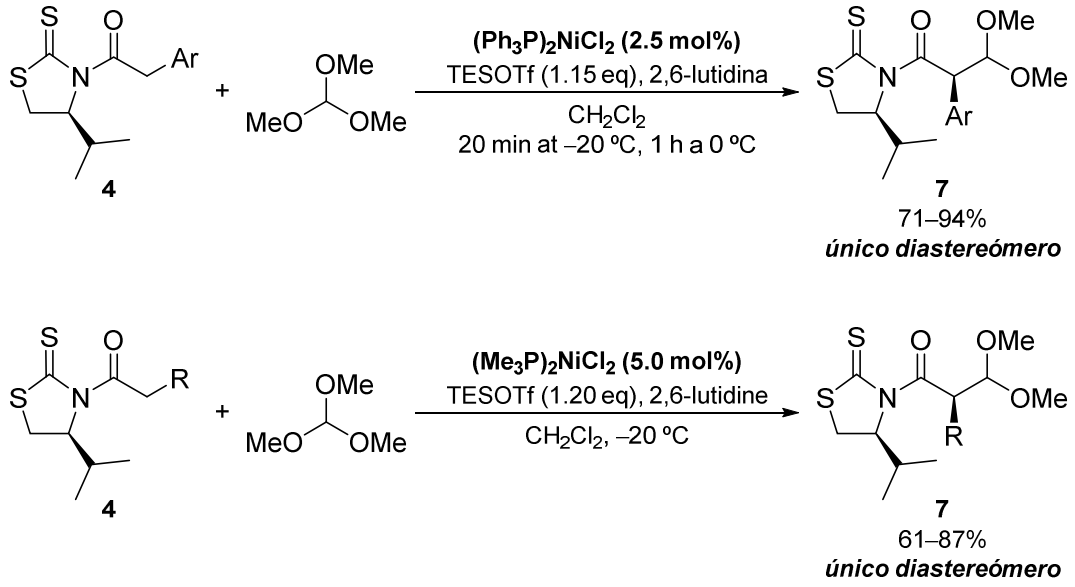
Esquema 189

Este Capítulo 1 se ha centrado, pues, en el desarrollo de una alternativa más sencilla a nivel experimental que permitiera el uso de catalizadores comerciales. Así, la introducción de TESOTf como ácido de Lewis permitió el uso de $(Ph_3P)_2NiCl_2$ como catalizador. La utilización de este ácido de Lewis es crucial para el uso de complejos de níquel(II) con ligandos cloruro, ya que el TESOTf no sólo actúa como ácido de Lewis, sino también como activador del catalizador por intercambio de ligandos cloruro por grupos triflato.



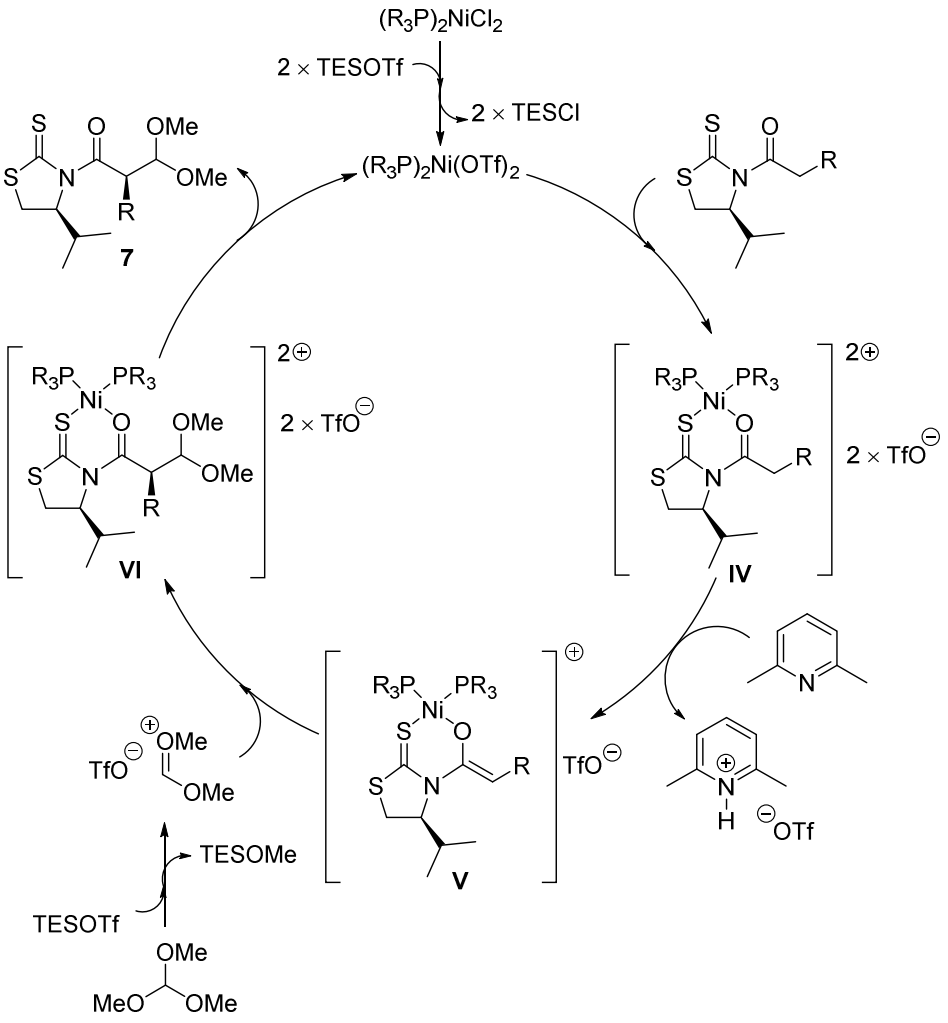
Esquema 190

Estas condiciones de reacción acabaron convirtiéndose en el proceso experimental de elección. Mientras que *N*-arilacetiltiazolidintionas sólo requieren de 2.5 mol% de $(Ph_3P)_2NiCl_2$, otras *N*-aciltiazolidintionas necesitan un mínimo de 20 mol% de $(Ph_3P)_2NiCl_2$ para proporcionar rendimientos aceptables. Alternativamente, la búsqueda de un catalizador más activo nos ha llevado a proponer unas condiciones de reacción ligeramente diferentes en las cuales se permiten usar tan sólo un 2.5–5 mol% de $(Me_3P)_2NiCl_2$ y obtener los aductos correspondientes con elevados rendimientos y para un extenso abanico de substratos. Los productos formilados pueden ser fácilmente convertidos en diferentes compuestos de forma enantioméricamente pura y en una gran variedad de grupos funcionales.



Esquema 191

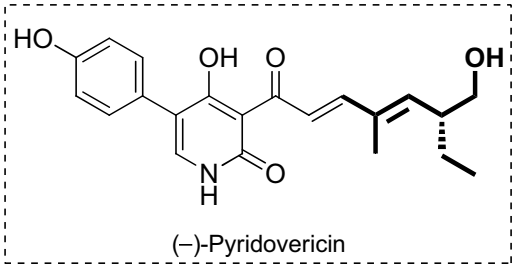
El ciclo catalítico que proponemos pasa por la generación catalítica de un enolato de níquel(II) quiral, el cual reacciona con el catión oxonio del trimetil ortoformiato formado en el seno de la reacción. Hay que remarcar que este sistema catalítico no es trivial, ya que el ácido de Lewis debe evitar reaccionar con la 2,6-lutidina en una reacción ácido-base. Por otro lado, el catión oxonio debe formarse con efectividad en el sí de la reacción en presencia del enolato y su material de partida, y sin verse afectado por un posible ataque nucleofílico de la base. Finalmente, el catalizador ha tenido que ser capaz de descoordinarse del producto final para coordinarse a una nueva molécula de material de partida y así empezar un nuevo ciclo.



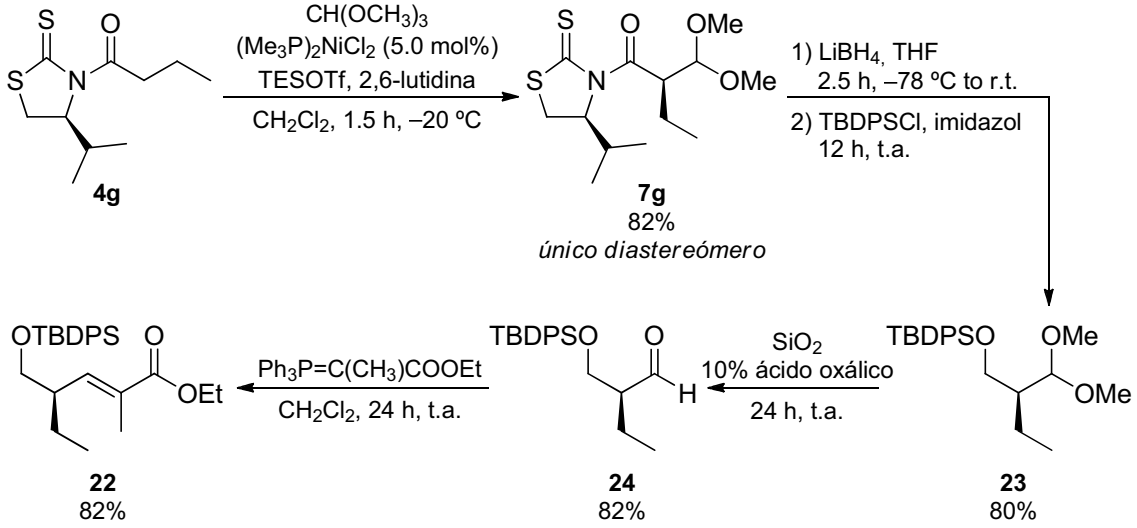
Esquema 192

La mayoría de estos resultados han sido publicados en la siguiente comunicación: *"Diastereoselective Methyl Orthoformate Alkylations of Chiral N-Acylthiazolidinethiones Catalyzed by Nickel(II) Complexes"*, Romo, J. M.; Gálvez, E.; Nubiola, I.; Romea, P.; Urpí, F.; Kindred, M. *Adv. Synth. Catal.* **2013**, *355*, 2781.

Este método ha sido aplicado con gran éxito a la síntesis estereoselectiva de la cadena lateral de la (–)-piridovericina con rendimiento global del 44%.

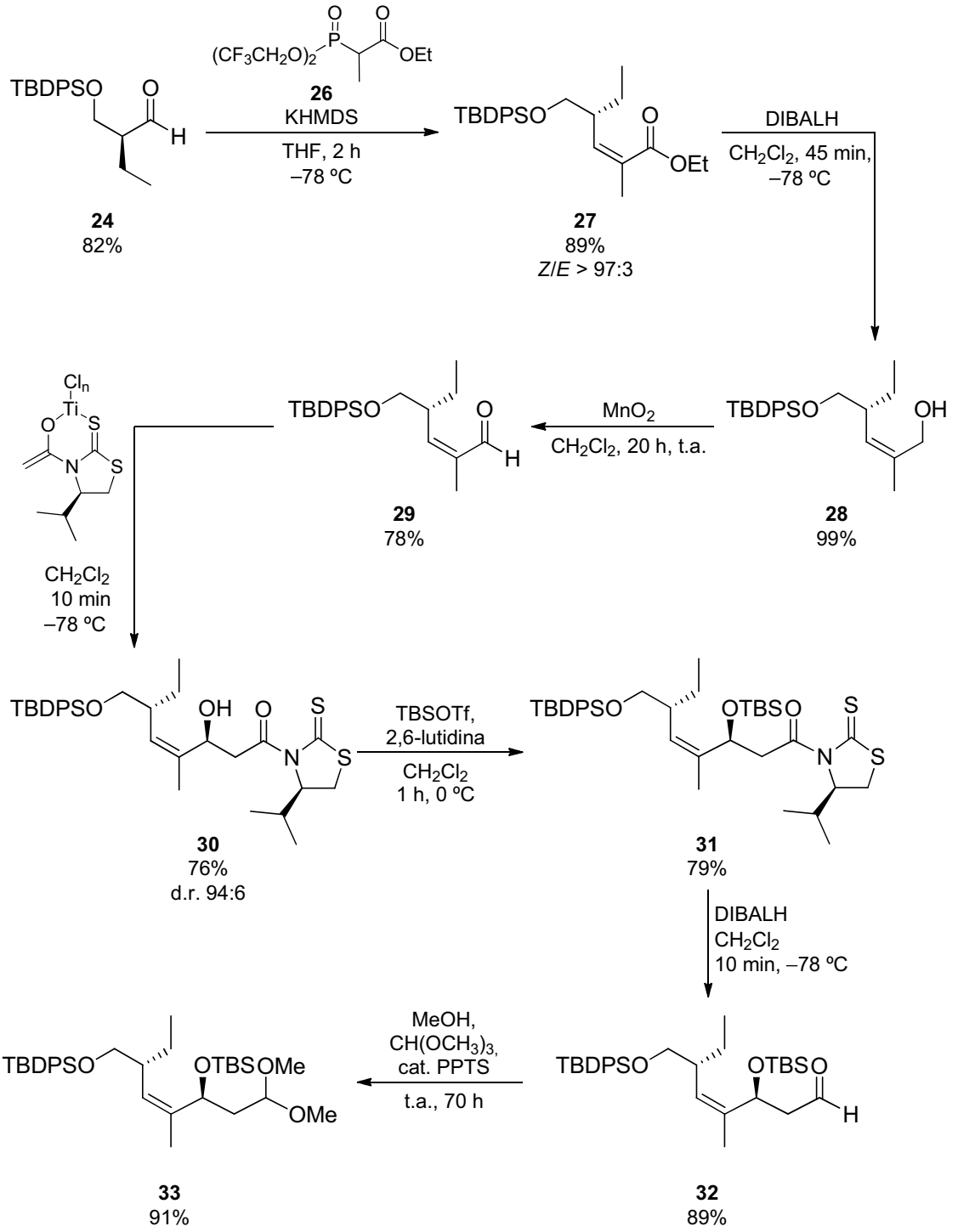


(–)-Pyridovericin



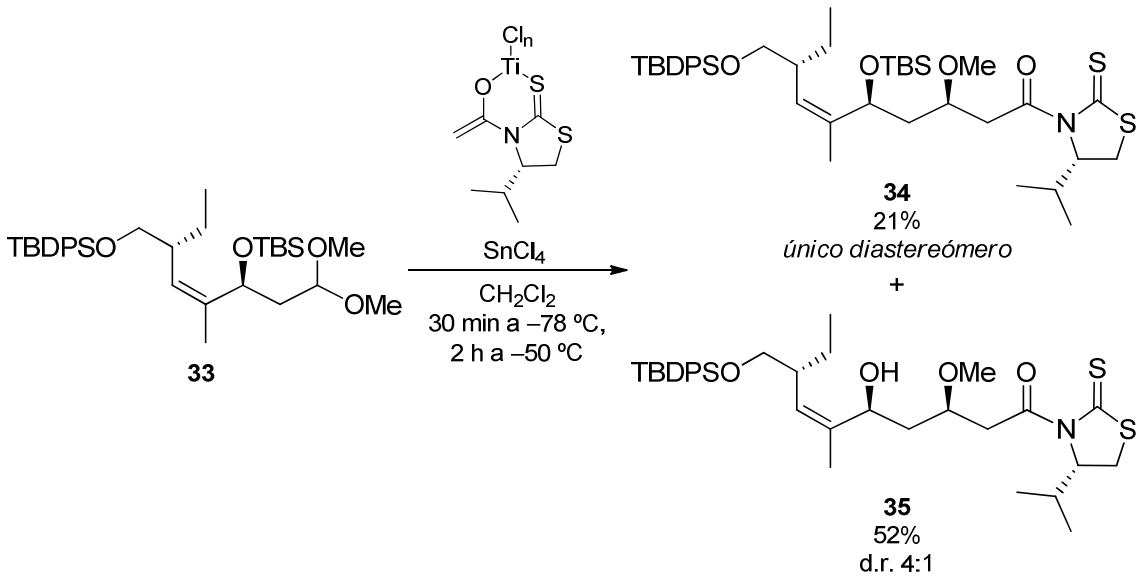
Esquema 193

Aprovechando el aldehído **24**, se ha procedido a la preparación del fragmento C11–C19 de la (+)-pelorusida A, con un rendimiento global del 4%.



Esquema 194

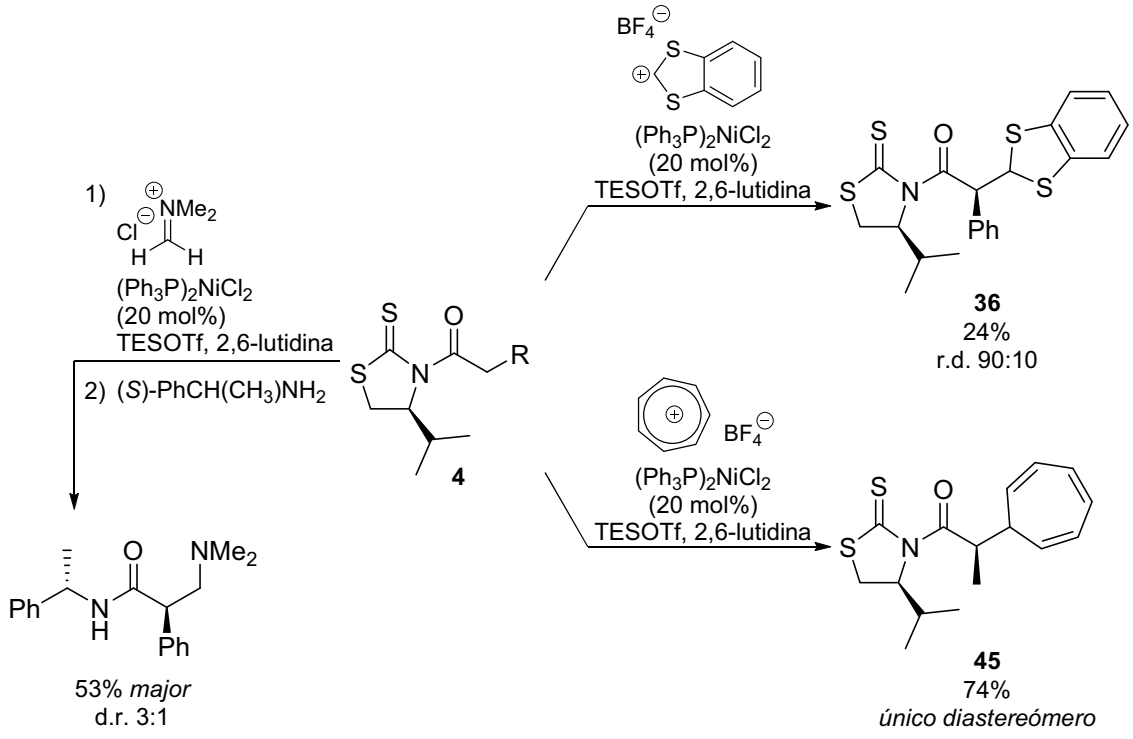
Hay que reconocer que la última reacción de esta síntesis, ilustrada en el Esquema 195, no ha sido totalmente satisfactorio y se está trabajando actualmente para adquirir el máximo rendimiento del producto final deseado (**34**).


TBDPSO
OTBS OMe
OMe
33
Cln
Ti
O
S
N
S
SnCl4
CH2Cl2
30 min a –78 ºC,
2 h a –50 ºC
TBDPSO
OTBS OMe
O
S
N
S
34
21%
único diastereómero
+
TBDPSO
OH
OMe
O
S
N
S
35
52%
d.r. 4:1

Esquema 195

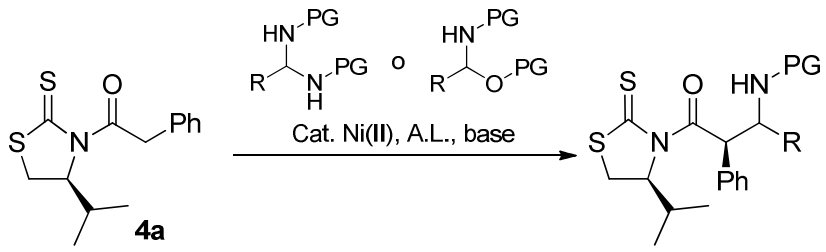
Capítulo 2: Reacciones de alquilación estereoselectivas de *N*-acil tiazolidintionas catalizadas por Ni(II)

En el Capítulo 2, el sistema catalítico basado en complejos de níquel(II) previamente desarrollado fue aplicado a diferentes sales carbocatiónicas comercialmente disponibles, como tetrafluoroborato de 1,3-benzoditiolilio, tetrafluoroborato de tropilio y la sal de Eschenmoser. Las reacciones con este último electrófilo requieren de una derivatización *in situ* del auxiliar quiral por tan de obtener productos aislables. Aunque los resultados no son extraordinariamente buenos, las reacciones con estos carbocationes demuestran la viabilidad del sistema hacia otros tipos de electrófilos mediante una reacción del tipo S_N1.



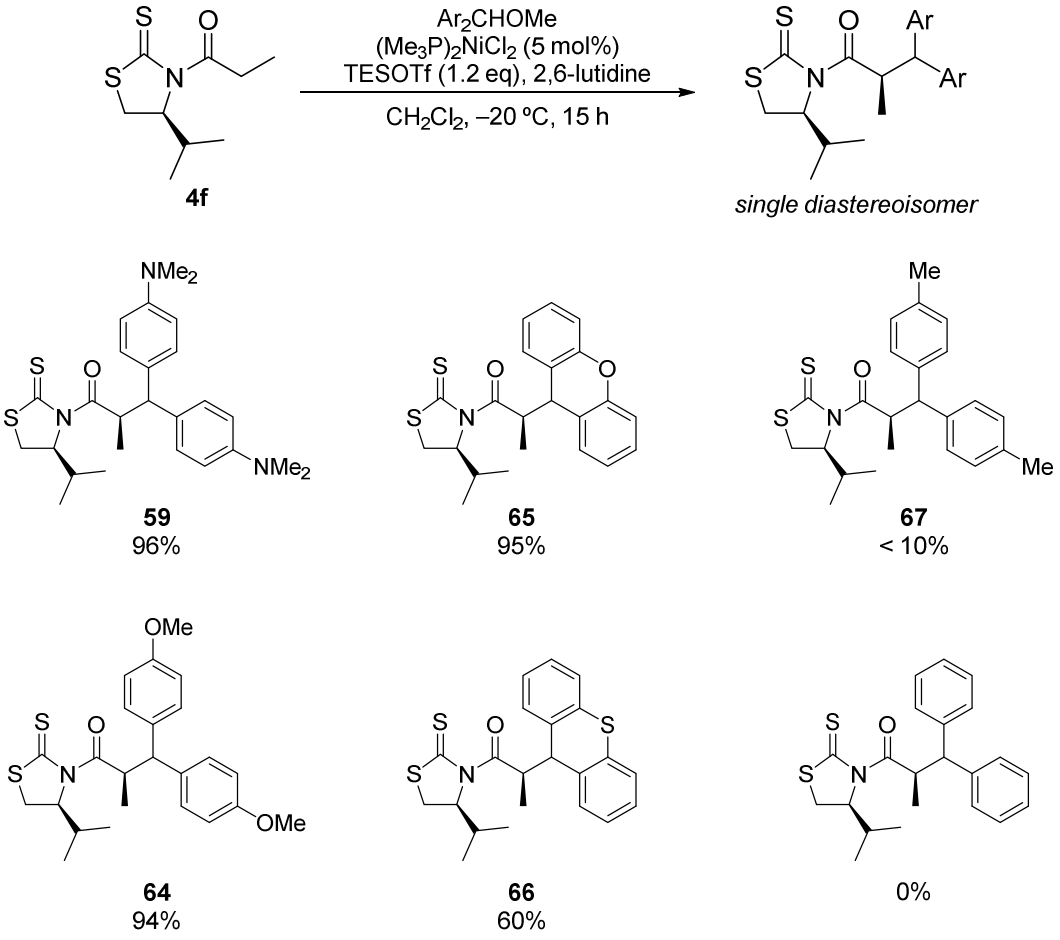
Esquema 196

Hay que destacar que la reacción con la sal de Eschenmoser nos abre un nuevo camino hacia un posible método futuro para la preparación de sistemas β-aminocarboxílicos a partir de aminales y/o hemiaminales.



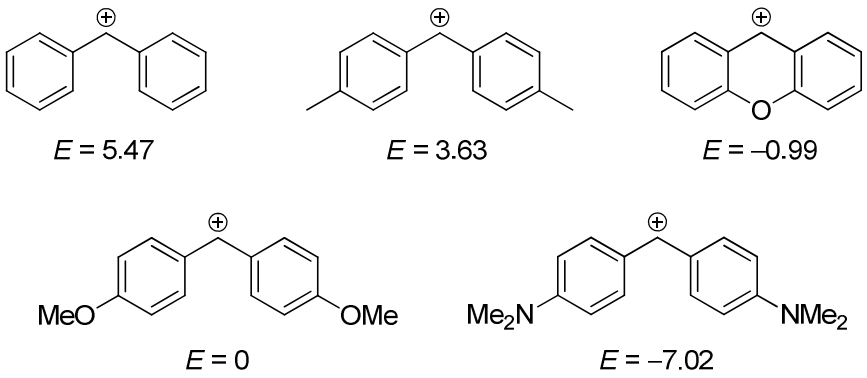
Esquema 197

Además, aprovechando la potencialidad de este sistema catalítico, se ha desarrollado una nueva reacción de alquilación estereoselectiva con diarilmetil metil éteres. La reacción funciona increíblemente bien siempre y cuando los intermedios carbocatiónicos sean lo suficientemente estables.



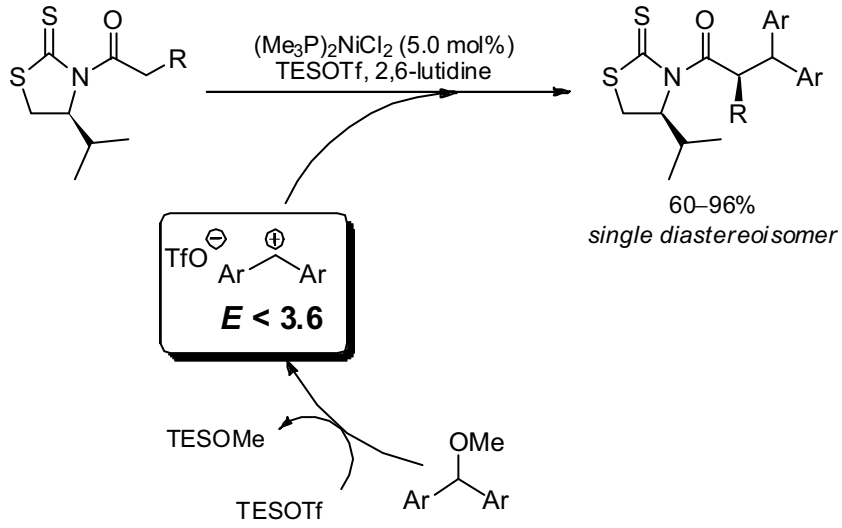
Equema 198

La estabilidad de los intermedios carbocatiónicos va estrechamente relacionada con la electrofilia de éstos, la cual está cuantificada y tabulada en forma de un parámetro de electrofilia (*E*) en lo que se conoce como "la escala de electrofilia" de Mayr.



Equema 199

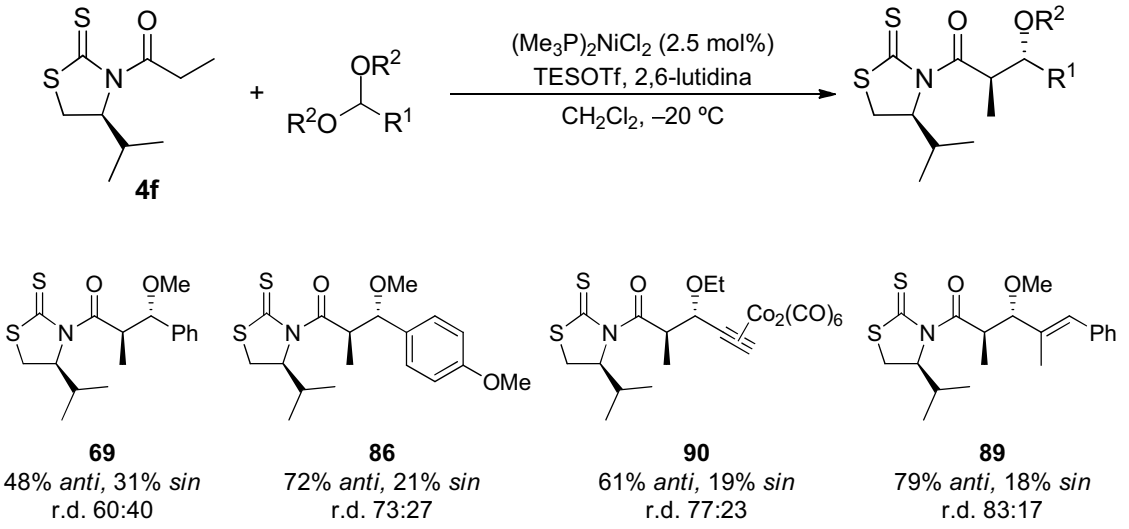
En este contexto, y con nuestros resultados en mano, podemos concluir que los sustratos electrófilos que tengan una $E < 0$ reaccionan con nuestros enolatos de níquel(II), mientras que sustratos con una $E > 3.6$ no dan lugar al aducto deseado. Posibles sustratos que contengan un parámetro de electrofilia en el intervalo entre $0 < E < 3.6$ deben de ser estudiados cuidadosamente.



Equema 200

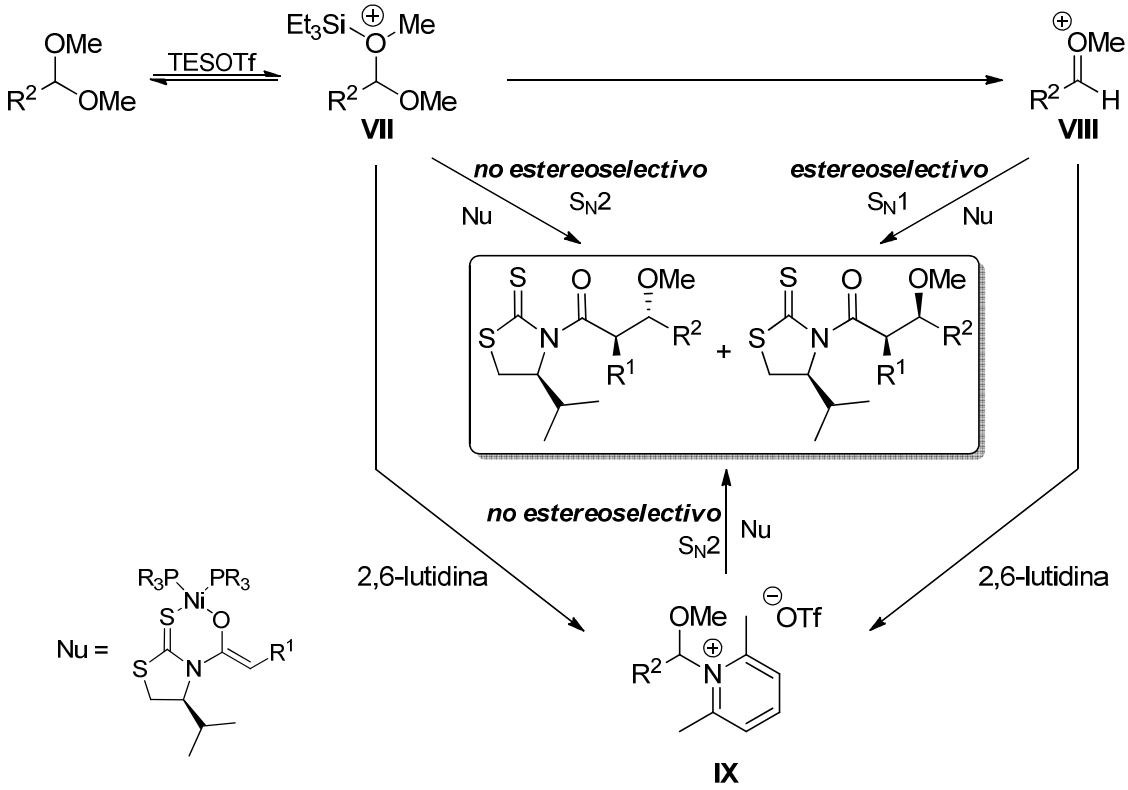
Capítulo 3: Reacciones estereoselectivas de *N*-acil tiazolidintionas con acetales catalizadas por Ni(II)

En el Capítulo 3 nos embarcamos en la aplicación del sistema catalítico a acetales, lo que supuso un aumento de la complejidad en la reacción a estudiar, ya que los correspondientes aductos incorporan, en este caso, dos nuevos estereocentros en una sola reacción. Los resultados confirman el hecho que el estereocentro en la posición α es completamente controlado, mientras que el esterocentro en la posición β debe de ser sujeta a estudio. Las reacciones proporcionan aductos *anti* como productos mayoritarios y funcionan con acetales aromáticos, α,β–insaturados y propargílicos cobaltados con relaciones diastereoméricas y rendimientos del aducto *anti* que van de bajos a moderados. Un análisis exhaustivo de las condiciones de reacción y el tipo de reactivos usados no permitieron mejorar la mediocre diastereoselectividad del proceso. Sorprendentemente, la estereoselectividad de tales adiciones ha resultado depender fuertemente de la estructura del acetal. Más concretamente, acetales que producen cationes oxocarbenio estables proporcionan los mejores estereocontroles que llegan hasta una relación diastereomérica de 83:17.



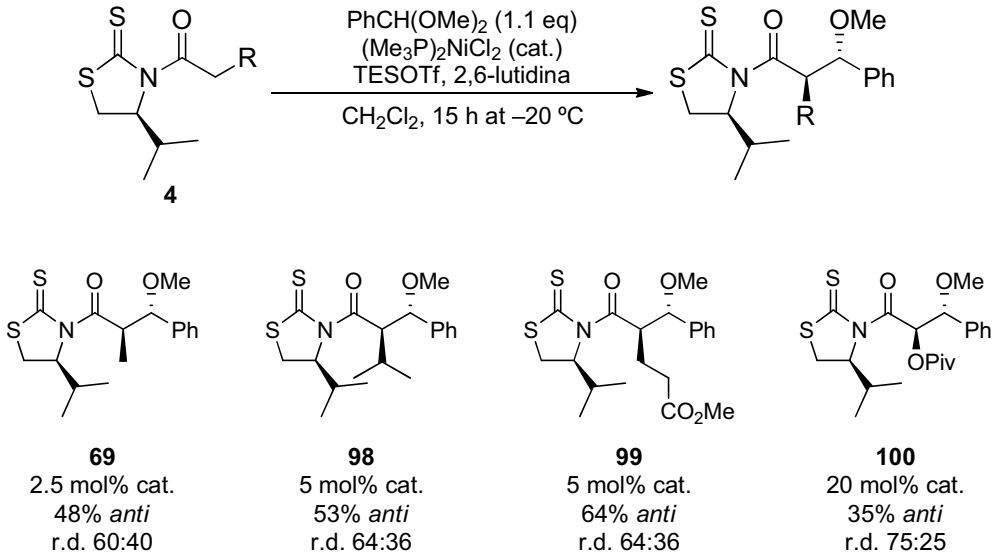
Esquema 201

Las moderadas relaciones diastereoméricas y su directa relación con la facilidad en la activación del acetal puede ser racionalizada a través de una propuesta mecanística en la que la formación de otros tipos de intermedios que incitan a procesos del tipo S_N2 pueden jugar un papel importante si el acetal no acaba de formar el catión oxonio con efectividad. Si ese es el caso, podría justificarse las bajas estereoselectividades de las reacciones de adición.



Esquema 202

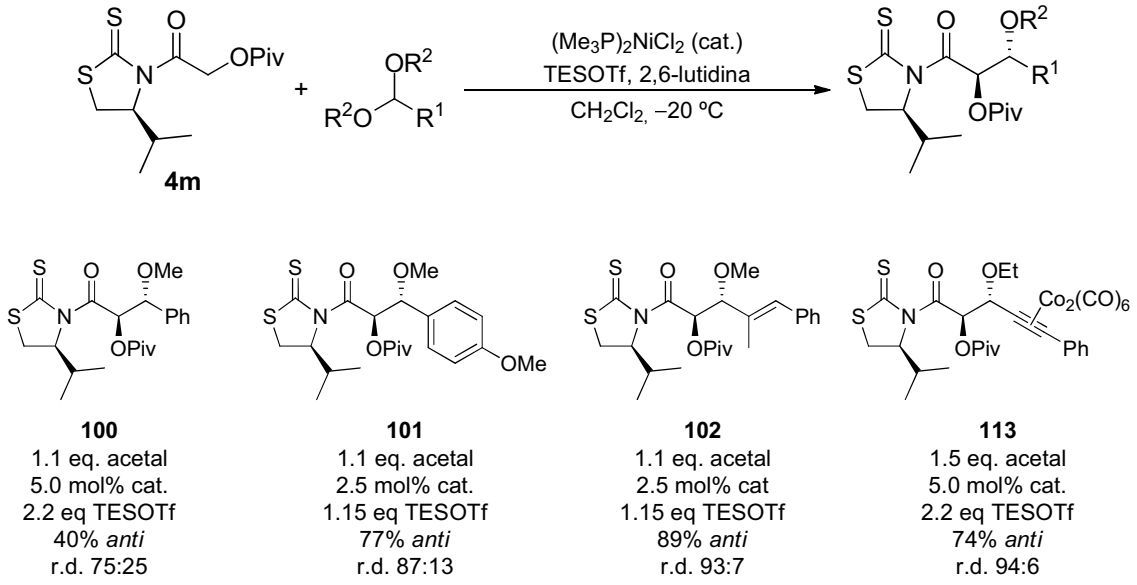
A continuación, la reacción con acetales se expandió a otras *N*-acil tioimidas usando el acetal dimetílico del benzaldehído. Se observaron rendimientos similares y diastereoselectividades del orden de 64:36. Como excepción, la tioimida derivada del ácido glicólico proporcionó una diastereoselectividad notablemente más alta (75:25), aunque un 20 mol% de $(Me_3P)_2NiCl_2$ hizo falta para obtener un rendimiento moderado (35%).


PhCH(OMe)2 (1.1 eq)
(Me3P)2NiCl2 (cat.)
TESOTf, 2,6-lutidina
CH2Cl2, 15 h at –20 ºC
4
69
2.5 mol% cat.
48% anti
r.d. 60:40
98
5 mol% cat.
53% anti
r.d. 64:36
99
5 mol% cat.
64% anti
r.d. 64:36
100
20 mol% cat.
35% anti
r.d. 75:25

Esquema 203

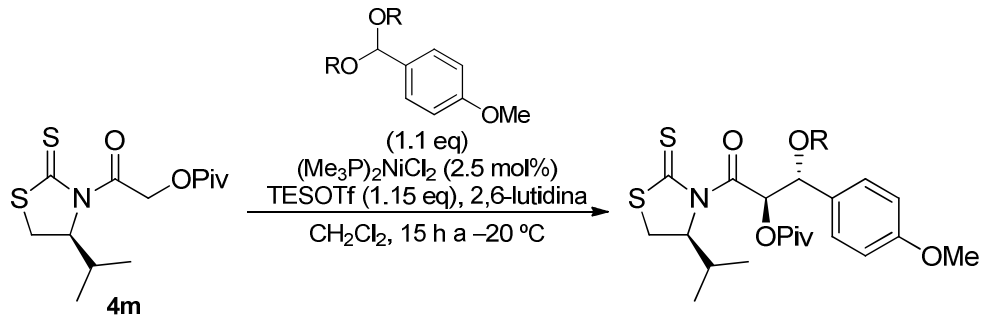
Capítulo 4: Reacciones estereoselectivas de *N*-glicolil tiazolidintionas con acetales catalizadas por Ni(II)

Entusiasmados por la mejora en el estereocontrol de esta última reacción, en el Capítulo 4 nos centramos en el desarrollo de un nuevo método de obtención de sistemas *anti*-α,β-dihidroxicarboxílicos a partir de *N*-hidroxiacetil tioimidas debidamente protegidos y diferentes acetales. En este contexto, una optimización exhaustiva del grupo protector del hidroxilo de la *N*-hidroxiacetil tioimida reveló que aquél que continene un grupo pivaloílo (**4m**) era el más indicado para estas reacciones. La reacción funciona increíblemente bien con acetales aromáticos, α,β-insaturados y propargílicos cobaltados, con rendimientos de moderados a muy buenos y relaciones diastereoméricas que oscilan entre buenos (75:25) a excelentes (94:6). Un análisis exhaustivo de las condiciones de reacción mostró que aquellos acetales que son difíciles de activar requieren de un exceso de ácido de Lewis y/o de acetal.



Esquema 204

Esta metodología también es extrapolable a otros tipos de acetales, como los acetales dibencílicos y dialílicos, permitiendo así un acceso a aldoles *anti* protegidos.



Entry	R	Aducto	r.d..[a]	Rendimiento (%)[b]
1	Me	**101**	87:13	77
2	$-CH_2CH=CH_2$	**114**	84:16	73
3	Bn	**115**	83:17	69

[a] Establecido por análisis de HPLC analysis del crudo de reacción.

[b] Rendimiento del producto *anti* aislado después de purificación por columna cromatográfica.

Tabla 52

Resumen

En conclusion, todos estos resultados prueban que la adición de *N*-acil tiazolidintionas a una gran variedad de electrófilos catalizados por complejos de níquel(II) estructuralmente sencillos, comercialmente disponibles y muy fáciles de manipular y almacenar es un método increíblemente eficiente para la construcción estereoselectiva de enlaces carbono–carbono. Parece ser que una transformación como ésta tiene lugar mediante un mecanismo de tipo S_N1 en el que un supuesto enolato de níquel(II) se adiciona a un intermedio carbocatiónico generado en el seno de la reacción. Los precursores de tales carbocationes pueden ser ortoésteres, acetales o éteres que den lugar a carbocationes estabilizados. Además, el auxiliar quiral puede ser eliminado muy fácilmente en condiciones suaves para dar lugar a un gran abanico de compuestos enantioméricamente puros. El potencial sintético del método ha sido demostrado mediante la preparación de la cadena lateral de la piridovericina y el fragmento C11–C19 de la pelorusida A.