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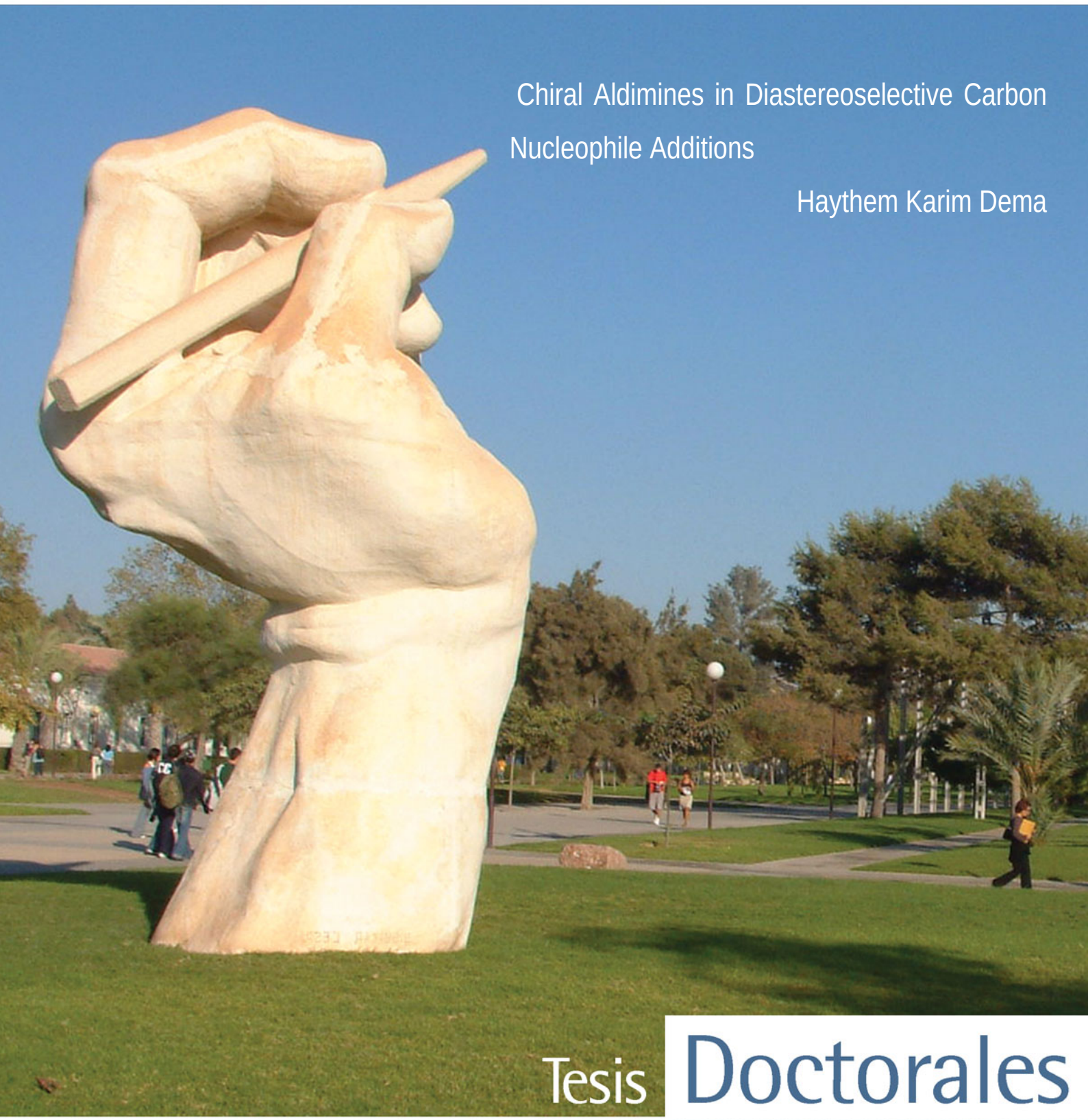
Chiral Aldimines in Diastereoselective Carbon Nucleophile Additions

Haythem Karim Dema



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Institute of Organic Synthesis

Department of Organic Chemistry

Faculty of Sciences

Chiral Aldimines in Diastereoselective Carbon Nucleophile Additions

A Memory that the Chemical Engineer Haythem Karim Dema presents to opt for the Ph.D. in Chemical Sciences:

Haythem K. Dema

On July 27th, 2012

Supervisors

Miguel Yus Astiz *Francisco Foubelo García*

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Miguel Yus Astiz, Professor of Organic Chemistry and Director of the Institute of Organic Synthesis at the University of Alicante,

CERTIFIES THAT:

"Chiral Aldimines in Diastereoselective Carbon Nucleophile Additions", presented by Chemical Eng. Haythem K. Dema to opt for the Ph.D. grade in Chemical Sciences, was conducted at the Instituto de Síntesis Orgánica under my Supervision and also Doctor Francisco Foubelo García.

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Alicante, July 2012

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To My Father, for his Inspiration

To my Mother, for her Support

To my Wife, for her Love

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Preface

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Part of the described results in the present memory was subject of the following publications:

"Stereoselective Synthesis of α-Methylene-γ-butyrolactams from Ethyl 2-(Bromomethyl)acrylate and Chiral Sulfinyl Aldimines Mediated by Indium"
Haythem K. Dema, Francisco Foubelo, and Miguel Yus, *Heterocycles*, **2010**, *80*, 125-131

"Enantioselective Synthesis of α-Methylene-γ-butyrolactams Using N-tert-Butanesulfinamides"
Haythem K. Dema, Francisco Foubelo, and Miguel Yus, *Heterocycles*, **2011**, *82*, 1411-1421

"Indium-Mediated Allylation of N-tert-Butylsulfinylaldimines with Dimethyl 2-[2-(Chloromethyl)allyl]malonate"
Haythem K. Dema, Francisco Foubelo, and Miguel Yus, *Jordan Journal of Chemistry*, **2011**, *6*, 247-255

"Diastereoselective Coupling of N-tert-Butanesulfinyl Imines and Dimethyl Malonate. Synthesis of Enantioenriched β-Aminoesters and β-Lactams"
Haythem K. Dema, Francisco Foubelo, and Miguel Yus, *Helvetica Chimica Acta*, **2012**, sent for publication

"Diastereoselective Aza-Henry Reaction of N-tert-Butanesulfinyl Imines. Easy Access to Vicinal Diamines and α–Amino Acids"
Haythem K. Dema, Francisco Foubelo, and Miguel Yus, manuscript under preparation

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This work was possible thanks to the financial support from the Ministry of Science and Innovation with reference to the research projects "Chiral Homoallylsulfinylimines: New Methodologies based on Catalysis by Transition Metals (CTQ2007-65218/BQU)", "Preparation and Application to the Bioactive Natural Compounds (GRE09-18), and "Consolider Ingenio 2010-CSD2007-00006", and from the Generalitat Valenciana [Grant No. PROMETEO/2009/039, FEDER and New Methodologies based on Catalysis by Transition Metals (Grisolía08/50)].

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Summary/Resumen

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The reactivity of chiral *N*-*tert*-butanesulfinyl imines **3** with different carbonucloephiles is reported in this present work, which has been divided in two main blocks: reactions with allylic indium species and reactions with stabilized carbanions derived from organic compounds with acidic hydrogens.

- The reaction of ethyl 2-(bromomethyl)acrylate (**4**) with chiral *N*-*tert*-butanesulfinyl aldimines **3** and indium powder in THF at 100 °C for 48 hours affords, after hydrolysis, a mixture of *N*-*tert*-butanesulfinyl aminoesters **5** and α-methylene-γ-butyrolactams **6**. From the reaction mixture, compounds **5** were quantitatively converted to the expected butyrolactams **6** after removal of the *tert*-butanelsulfinyl group under acidic conditions and final basic workup. The whole process takes place in high overall yields and with fairly good stereoselectivities. However, when the indium-mediated coupling of ethyl 2-(bromomethyl)acrylate (**4**) and chiral *N*-*tert*-butanelsulfinyl imines **3** is carried out in a saturated sodium bromide aqueous solution, *N*-*tert*-butanesulfinyl aminoesters **5** are formed exclusively in high yields and diastereoselectivities. After column chromatography purification, enantiomerically pure aminoesters **5** were converted into the expected α-methylene-γ-butyrolactams **6** in a one-pot process.
- The reaction of *N*-*tert*-butanesulfinyl imines **3** with dimethyl 2-[2-(chloromethyl)allyl]malonate (**10**), in the presence of indium metal and sodium iodide, at room temperature for 72 hours, led to the corresponding amino ester derivative **11**. The reaction proceeds in high yields and in a total stereoselective fashion, a single diastereoisomer being always isolated.
- The reaction of dimethyl malonate (**7**) with *N*-*tert*-butanesulfinyl imines **3** in the presence of sodium iodide or sodium bicarbonate at room temperature for 72 hours, led to 2-(1-aminoalkyl)malonates **24** in high yields and total diastereoselectivity. These compounds were easily converted into β-lactams **28** through a two step process.
- The coupling of nitromethane (**29**) and *N*-*tert*-butanesulfinyl imines **3** was carried out in good yields and high diastereomeric ratios in the presence of sodium bicarbonate at 60 °C for 72 hours. The resulting β-nitroamine derivatives **30** are precursors of *N*-*tert*-butanesulfinyl α-amino acids **31** and selectively protected 1,2-diamines **33**.

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En la presente Memoria se describe la reactividad de *N*-*terc*-butanosulfinil iminas quirales **3** con diferentes carbonucleófilos, estructurándose la *Discusión de Resultados* en dos partes: las reacciones con especies de alilindio y las reacciones con carbaniones estabilizados derivados de compuestos orgánicos con hidrógenos ácidos.

- La reacción de 2-(bromometil)acrilato de etilo (**4**) con *N*-*terc*-butanosulfinil iminas quirales **3** e indio metal en THF a 100 °C durante 48 horas da lugar, después de hidrólisis, a una mezcla de *N*-*terc*-butanosulfinil aminoésteres **5** y α-metilen-γ-butirolactamas **6**. A partir de esta mezcla, los compuestos **5** fueron transformados cuantitativamente en las correspondientes butirolactamas **6**, previa eliminación del grupo *terc*-butanosulfinilo en medio ácido seguido de hidrólisis básica. Todo el proceso tiene lugar con altos rendimientos y relativamente buenas estereoselectividades. Sin embargo, la formación de *N*-*terc*-butanosulfinil aminoésteres **5** con altos rendimientos y diastereoselectividades tiene lugar de manera exclusiva cuando el acoplamiento mediado por indio de 2-(bromometil)acrilato de etilo (**4**) y *N*-*tert*-butanosulfinil iminas quirales **3** se lleva a cabo en una disolución acuosa saturada de bromuro de sodio. Después de purificación por columna cromatográfica, los aminoésteres **5** enantioméricamente puros fueron transformados en α-metilen-γ-butirolactamas **6** en un proceso "one-pot".
- La reacción de *N*-*terc*-butanosulfinil iminas **3** con 2-[2-(clorometil)alil]malonato de dimetilo (**10**) en presencia de indio metal y yoduro de sodio, a temperatura ambiente durante 72 horas, lleva a la formación del correspodiente derivado de aminoéster **11** como un único diastereoisómero y con altos rendimientos.
- La reacción de malonato de dimetilo (**7**) con *N*-*terc*-butanosulfinil imines **3** en presencia de yoduro o bicarbonate de sodio, a temperatura ambiente durante 72 horas, conduce de manera estereoselectiva a 2-(1-aminoalquil)malonatos **24**, precursores de β-lactamas **28**, con buenos rendimientos.
- El acoplamiento de nitrometano (**29**) y *N*-*terc*-butanosulfinil iminas **3** mediado por bicarbonate de sodio a 60 °C durante 72 horas tiene lugar con buenos rendimientos y altas relaciones diastereoméricas. Los β-nitroamino derivados resultants **30** son precursors de *N*-*terc*-butanosulfinil α-aminoácidos **31** y 1,2-diaminas selectivamente protegidas **33**.

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Introduction

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Imines are easily accessible through the condensation of a primary amine and a cabonyl compound. They are reactive species to both nucleophiles and electrophiles: the nucleophilic attack takes place on the carbon atom and the electrophilic attack on the nitrogen. These processes were widely studied because they are used to happen in biological systems, being involved in many metabolic routes that lead to the formation of natural products that bear nitrogenated heterocycles in their structures. In turn, imines are frequently used as reaction intermediates in many organic syntheses.

Since 1988, our research group in the Department of Organic Chemistry of the Faculty of Science and at the Institute of Organic Synthesis of the Universidad de Alicante has been interested in the preparation of different organometallic compounds and their application in organic synthesis.* In the present work, the stereoselective addition of different carbon nucleophiles to *N-tert*-butanesulfinyl imines is studied. Allylic bromides as well as dimethyl malonate and nitromethane have been used as precursors of the nucleophilic species.

The previously mentioned justifies the following exposition order:

I. Bibliographic Background
II. Results and Discussion
III. Experimental Part
IV. Conclusions
V. Abbreviations
VI. Publications

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**Ph.D. thesis of: D. J. Ramón (1993); J. F. Gil (1994); D. Guijarro (1994); A. Guijarro (1995); J. Almena (1996); A. Bachki (1997); F. F. Huerta (1998); E. Alonso (1998); A. Gutiérrez (1999); E. Lorenzo (2000); J. J. Ortiz (2000); I. M. Pastor (2000); T. Soler (2001); P. Martínez (2002); I. Gómez (2002); J. V. Ferrández (2003), J. Gomis (2003), P. Candela (2003), R. P. Herrera (2003), R. Ortiz (2004), B. Moreno (2005), C. Behlou (2005), B. Maciá (2005), J. Meléndez (2006), A. Abou (2007), R. Torregrosa (2007), V. Lillo (2009), D. García (2010), H. Pérez (2010), and M. Medjahdi (2011).*

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I. Bibliographic Background

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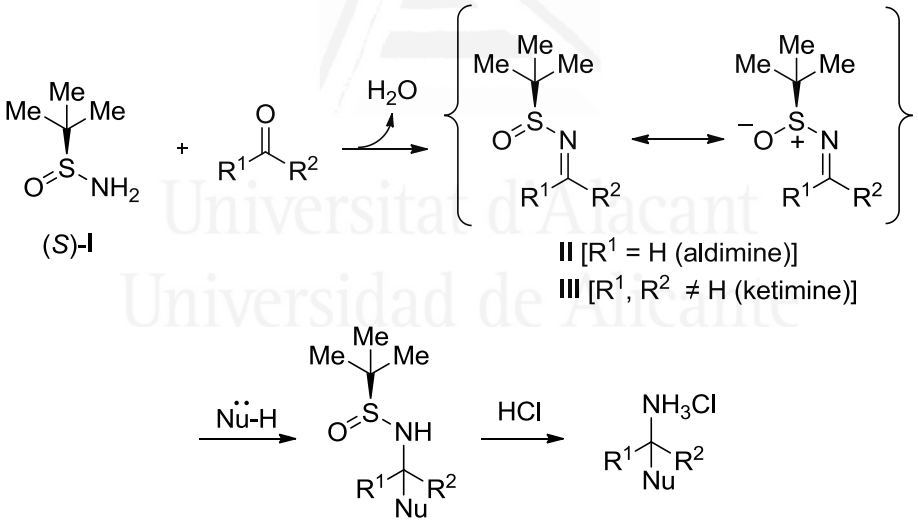
I.1. *N-tert*-Butanesulfinyl imines and their synthetic utility

Amines are present in a large majority of drugs and drug candidates. Over the past decade, an ever increasing collection of methods based upon the chiral amine reagent *tert*-butanesulfinamide (**I**) have become some of the most extensively used synthetic approaches for both the discovery and production of drug candidates. Moreover, *tert*-butanesulfinamide (**I**) is increasingly being applied across many additional research areas, including the development of agrochemicals, natural product synthesis, and the preparation of chemical tools for a wide range of biological investigations.

A number of factors have led to the popularity of *tert*-butanesulfinamide (**I**). From a practical standpoint, either enantiomer of **I** is inexpensive to prepare on a large scale in enantiomerically pure form. Indeed, greater than 75 chemical suppliers currently market **I** in many cases at reasonable prices (<$1/g for bulk quantities). More importantly, the synthesis steps used to prepare amines from **I** are typically robust, straightforward, and broad in scope (Scheme 1).



Scheme 1.

Numerous researchers in both academia and industry have contributed innovative and useful new methods based on **I** and have applied these methods to efficient syntheses of drug candidates and natural products, often in the context of densely functionalized structures. While many of these contributions rely on nucleophilic additions to *N-tert*-butanesulfinyl imines **II** and **III**, a number of alternative approaches to convergently assemble complex molecules

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with multiple stereocenters have also been developed. Particularly notable are methods to reductively couple *N*-*tert*-butanesulfinyl imines **II** and **III** with carbonyl compounds, imines, and electron deficient alkenes in high yield and with excellent diastereoselectivity.

Another general strategy for the convergent assembly of amines with two or more stereocenters proceeds via the diastereoselective addition of *N*-*tert*-butanesulfinyl metalloenamines to electrophiles such as aldehydes, imines, Michael acceptors, and alkylating agents to produce *N*-*tert*-butanesulfinyl imine products to which nucleophiles can then readily be added.[1]

I.1.1. Key characteristics of *N*-*tert*-butanesulfinyl imines

There are several distinguishing characteristics of this chemistry:

1) The direct condensation of **I** with a wide range of aldehydes and ketones proceeds in high yields under mild conditions to give stable *N*-*tert*-butanesulfinyl aldimines **II** and ketimines **III**, respectively, that are much less hydrolytically labile or prone to tautomerization than most *N*-alkyl, aryl, acyl, or carbamoyl imines.
2) *N*-*tert*-Butanesulfinyl imines **II** and **III**, despite their stability, are significantly more electrophilic than typical *N*-alkyl or aryl imines, which can be explained by the significant positive charge on sulfur. This enhanced electrophilicity enables clean and high yield additions of a very wide range of diverse nucleophiles, including organo-magnesium, lithium, zinc, silicon, indium, cerium, and boron reagents, stabilized carbanions exemplified by enolates, and noncarbon nucleophiles such as phosphorus, boron, tin, and silicon species as well as numerous hydride reagents. Moreover, additions to R-heteroatom substituted imines **II** and **III** typically proceed in high yield, and when an R-stereocenter is present, without epimerization.
3) The *tert*-butanesulfinyl group is not only chiral but also capable of metal coordination, resulting in high diastereoselectivities for the addition of many different nucleophiles to imines **II** and **III**.
4) The *tert*-butanesulfinyl group in addition products serves as an extremely versatile protecting group that parallels the reactivity of carbamoyl protecting groups in attenuating the nucleophilicity of the protected amine. The *N*-*tert*-butanesulfinyl group is also stable to a wide range of reaction conditions, including strong bases, nucleophiles,

[1] Robak, M. A. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600.

and a variety of transition metal catalyzed processes such as olefin metathesis and Pd-mediated cross-coupling.

5) Convenient and high yielding cleavage of the *N*-*tert*-butanesulfinyl group can be accomplished by simple treatment with methanolic HCl to provide the amine hydrochloride products after precipitation with ethereal solvents, often in nearly quantitative yields and in analytically pure form.

I.1.2. Synthesis of *N*-*tert*-butanesulfinyl imines via condensation with *tert*-butanesulfinamide

The synthesis of *N*-*tert*-butanesulfinyl imines **II** or **III** is usually carried out via a straightforward condensation reaction between *tert*-butanesulfinamide (**I**) and a precursor aldehyde or ketone. A wide variety of imines have been prepared to date, ranging from very simple to densely functionalized. Other *N*-*tert*-butanesulfinyl C=N containing derivatives, such as amidines and imidate esters, have also been prepared.

The combination of the ease of synthesis (including functional group compatibility), hydrolytic stability (most *N*-*tert*-butanesulfinyl imines are stable enough to be purified by silica gel chromatography and handled on the benchtop with exposure to air), electrophilicity (the *N*-*tert*-butanesulfinyl group activates the imine toward nucleophilic attack), and stereocontrol (the *N*-*tert*-butanesulfinyl group is a powerful chiral directing group for diastereoselective reactions) makes *N*-*tert*-butanesulfinyl imines attractive intermediates for the synthesis of amine-containing compounds.

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The first synthesis of *tert*-butanesulfinyl aldimines **II** in enantiomerically pure form was reported by García Ruano and co-workers in 1996, in the context of their work on the preparation of chiral aziridines.[2] But the synthesis of *tert*-butanesulfinyl aldimines via the direct condensation of *tert*-butanesulfinamide (**I**) with carbonyl compounds was first reported by Ellman and co-workers in 1997.[3] The condensation of enantiomerically pure **I** with 2-3 equivalents of aldehyde was carried out in the presence of the acidic catalyst pyridinium *p*-toluenesulfonate (PPTS) and an excess amount of $MgSO_4$ in CH_2Cl_2 to provide high yields of both aromatic and aliphatic aldimines **II**. No racemization of the sulfinyl stereocenter was observed. Further studies revealed that the more Lewis acidic $CuSO_4$ was a more effective agent for this

[2] García Ruano, J. L.; Fernández, I.; del Prado Catalina, M.; Alcudia Cruz, A. *Tetrahedron: Asymmetry* **1996**, *7*, 3407.
[3] Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913.

transformation, allowing the use of a smaller excess (1.1 equivalents) of aldehyde.[4,5] A few substrates were found to be unreactive under the $CuSO_4$ conditions. In these cases, it was found that $Ti(OEt)_4$ was an effective water scavenger and Lewis acid catalyst.

I.2. Stereoselective synthesis of homoallylic amines

The addition of an organometallic reagent to a carbonyl compound or an imine represents an important process in synthetic organic chemistry because in this reaction, together with a new carbon-carbon bond, a new functionality (an alcohol or an amine, respectively) is formed.[6] A special case for the nucleophilic reagents appears by using an allylic system: in this case, the allylic moiety allows further possible transformations due to the presence of a double bond that can be manipulated synthetically.[7] Remarkably, the asymmetric version of this technology, above all in the catalytic fashion, would produce chiral homoallylic alcohols and amines, which constitute valuable building blocks in organic synthesis for the above-mentioned reasons.[8-13]

The reaction of allylic organometallic compounds with imines gives nitrogenated homoallylic derivatives of a great organic synthesis utility.[14] These compounds can be converted into aminoalcohols, aminoacids and nitrogenated heterocycles like pyrrolidines and piperidines, as well as others.[15,16] The allylation of imines would also be considered, having in mind its synthetic potential and the economy of atoms, an alternative to the Mannich reaction, given that the resultant homoallylimines can be transformed into the correspondent β-aminocarbonylic compound without losing any carbon atom (Scheme 2).

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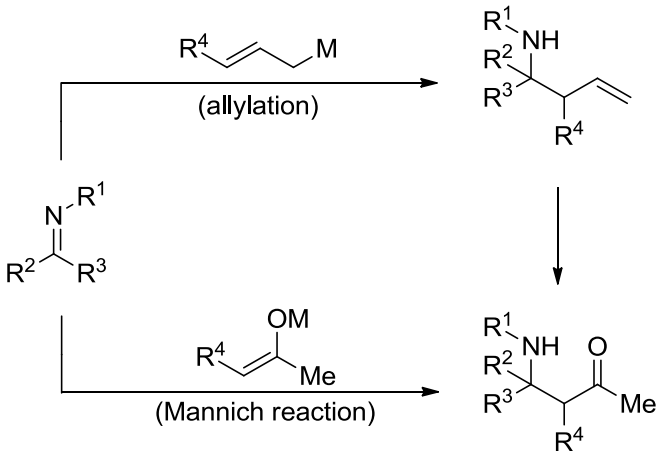
[4] Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 268.
[5] Liu, G.; Coga, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278.
[6] Smith, M. B.; March, J. *March's Advanced Organic Chemistry Reactions, Mechanisms and Structure.* 6th. Hoboken, NJ : Wiley-Interscience, 2007. pp. 1251-1476.
[7] Carreira, E. M.; Kvaerno, L. *Classics in Stereoselective Synthesis.* Weinheim, Germany : Whiley-VCH, 2009. pp. 153-185.
[8] Tietze, L, F.; Kinzel, T.; Brazel, C. C. *Acc. Chem. Res.* **2009**, *42*, 367.
[9] Merino, P.; Tejero, T.; Delso, J. I.; Mannucci, V. *Curr. Org. Synth.* **2005**, *2*, 479.
[10] Kargbo, R. B.; Cook, G. R. *Curr. Org. Chem.* **2007**, *11*, 1287.
[11] Ding, H.; Friestad, G. K. *Synthesis* **2005**, 2815.
[12] Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541.
[13] Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2011**, *111*, 7774.
[14] Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.
[15] Bloch, R. *Chem. Rev.* **1998**, *98*, 1407.
[16] Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895.



Scheme 2.

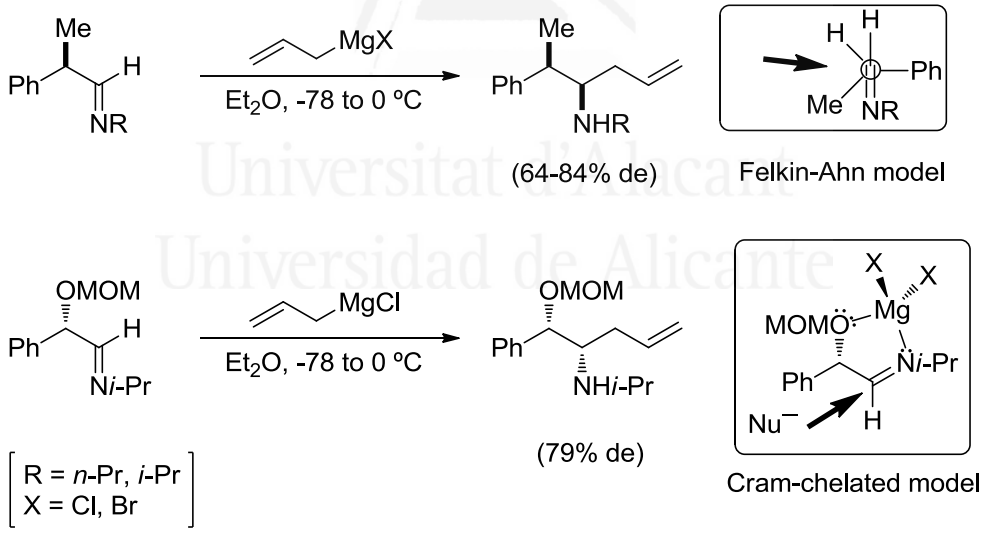
In 1985, Yamamoto published the first article about enantioselective imine allylation.[17] The importance of the field was shown through the big quantities of publications that appeared on the mentioned field since that date. Therefore it's well known and studied, taking place in a more efficient way in prescence of Lewis acids, when the allylic organometallic compounds are not sufficiently reactive. Then, the use of allyl stannanes and allyltrimethyl silanes as allylation agents requires the prescence of Lewis acids to activate the C=N double bond. Among other, $NbCl_5$,[18] $SnCl_2$,[19,20] $LiClO_4$,[21] Me_3SiCl,[22] Bu_4NF[23] and CuCl[24] were used as Lewis acids. The imine allylations are also important in the synthesis of natural products when these are obtained with high enantiomeric purity. The induction to the asymmetry could proceed from the substrates (utilization of imines or non-racemic chiral arylic derivatives) or from an external source (chiral catalysts). Some examples of stereoselective allylation reactions will be shown in the following paragraphs, in which pure enantiometic compounds are prepared, being classified according to the

[17] Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Org. Chem.* **1985**, *50*, 3115.
[18] Andrade, C. K.; Oliveira, G. R. *Tetrahedron Lett.* **2002**, *43*, 1935.
[19] Masuyama, Y.; Tosa, J.; Kurusu, Y. *Chem. Commun.* **1999**, 1075.
[20] Akiyama, T.; Onuma, Y. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1157.
[21] Yadav, J. S.; Reddy, B. V. S.; Reddy, P. S. R.; Rao, M. S. *Tetrahedron Lett.* **2002**, *43*, 6245.
[22] Wang, D.-K.; Dai, L.-X.; Hou, X.-L. *Tetrahedron Lett.* **1995**, *36*, 8649.
[23] Wang, D.-K., Zhou, Y.-G.; Tang, Y.; Hou, X.-L.; Dai, L. X. *J. Org. Chem.* **1999**, *64*, 4233.
[24] Yamasaki, S.; Fujii, K.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 6536.

organometallic compound used as allylation agent. [25-27] We will pay special attention to those allylation reactions where *N*-*tert*-butanesulfinyl imines are involved.

I.2.1. Magnesium

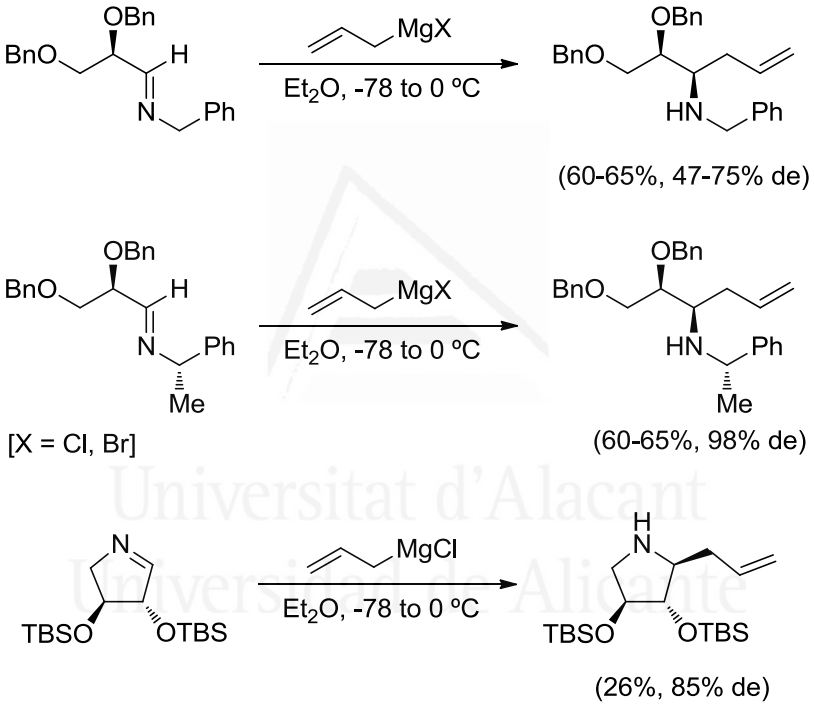
The use of allylmagnesium halides presents some advantages over other metallic derivatives because itsn't necessary the preparation, isolation and manipulation of toxic or unstable reagents. Also, the allylmagnesium derivatives are less basic than the corresponding ones of lithium, avoiding undesired deprotonation reactions. An example of this type of stereoselective allylation is the allylation of racemic *N*-propylaldimines obtained from 2-phenylpropanal. When the rection takes place with bromo or chloro allylmagnesium as an allylation agent, the homoallylamine which predicts the Felkin-Ahn model is predominantly obtained (Scheme 3).[28] The prescence of a chiral group in α position could invert the induction direction. In this context, an α-alcoxyimine under the same reaction conditions gives preferably the compound resulting from the nucleophilic addition to the proposed intermediate by the Cram-chelated model (Scheme 3).[29]



Scheme 3.

[25] Nakamura, H.; Iwama, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6641.
[26] Nakamura, H.; Iwama, H.; Yamamoto, Y. *Chem. Commun.* **1996**, 1459.
[27] Nakamura, H.; Shim, J.-G.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 8113.
[28] Yamamoto, Y.; Maruyama, K.; Komatsu, T.; Ito, W. *J. Am. Chem. Soc.* **1986**, *108*, 7778.
[29] Yamamoto, Y.; Ito, W.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1985**, 1131.

The addition of allylmagnesium halides to the α-alcoxyimines derived from D-glyceraldehyde also produces *sin* adducts (Scheme 4).[30] The preference in the formation of *sin* adducts could be explained through a chiral controlled model. The diastereoselectivity is high when in addition, a stereogenic center in present at the substituent bonded to the nitrogen (typical example of a double asymmetric induction). It was demonstrated also that the diasterioselectivity in these processes depends much on the nature of the substituents attached to the oxygen and the nitrogen, and also to the temperature.[31] The allylation of cyclic imines took place with high diastereoselectivity but, unfortunately, low chemical yield (Scheme 4).[32]



Scheme 4.

The first example of an addition of allylmagnesium bromide to an *N-tert*-butanesulfinyl imine was reported by Ellman and co-workers in their seminal report on additions of Grignard and organolithium reagents to *N-tert*-butanesulfinyl aldimines and ketimines.[33] Excellent yields and with high

[30] Badorrey, R.; Cativiela, C.; Díaz de Villegas, M. D.; Díez, R.; Gávez, J. A. *Eur. J. Org. Chem.* **2002**, 3763.
[31] Cainelli, G.; Giacomini, D.; Galletti, P.; Quintavalla, A. *Eur. J. Org. Chem.* **2002**, 3153.
[32] Chapman, T. M.; Courtney, S.; Hay, P.; Davis, B. G. *Chem. Eur. J.* **2003**, *9*, 3397.
[33] Cogan, D. A.; Liu, G.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883.

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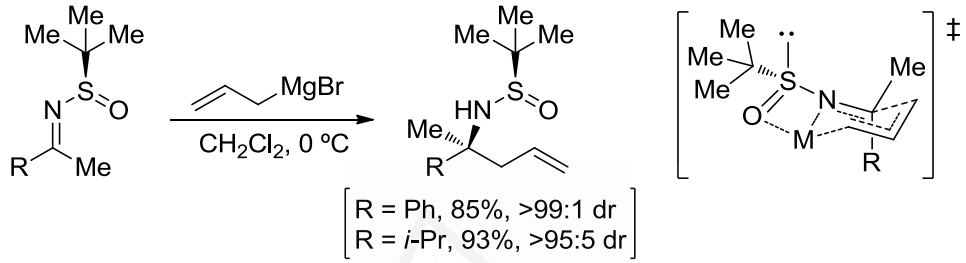
diastereoselectivities were obtained in all cases using the noncoordinating solvent CH_2Cl_2 (Scheme 5). The high level of diastereocontrol exhibited in this reaction was consistent with a chelated transition state, previously proposed by Hua and co-workers for the allylations of *N*-*p*-toluenesulfinyl imines,[34] where addition to the imine occurs from the *Si*-face and both the sulfinyl oxygen and imine nitrogen are coordinated to the metal. The coordination of the nitrogen to the metal could serve to activate the imine, which may explain the higher yields and diastereoselectivities observed for allylations relative to the additions of other Grignard reagents.



Scheme 5.

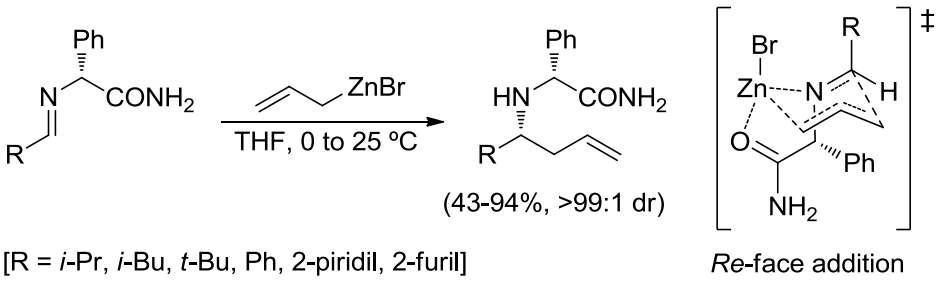
The addition of allylic magnesium bromides to *N*-*tert*-butanesulfinyl aldimines have been used as a key step in the synthesis of different natural products and biologically active compounds, such as some ureapeptoid macrocycles,[35] (+)-preussin (with antifungal, antiviral, and anticancer activity),[36] (-)-aphanorphine (natural alkaloid),[37] (-)-cernuine and (+)-cermizine D (*Lycopodium* alkaloids).[38]

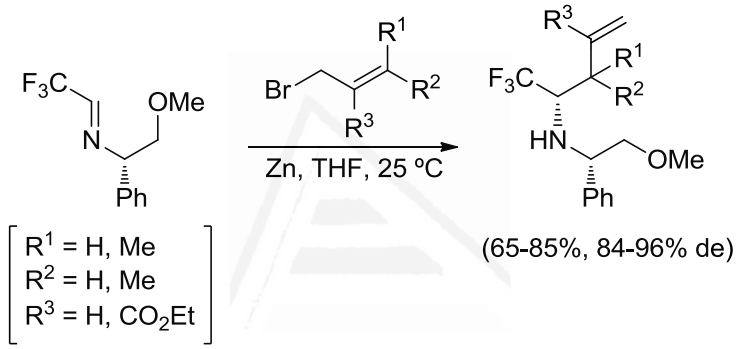
I.2.2. Zinc

The allylzinc halides are sufficiently reactive to be added to imines at low temperatures, without the need of a Lewis acid that acts as an activator of the imine. Thus, the addition of allylzinc bromide to the aldimines derived from amino acids (for instance: valine, phenylglycine) takes place in high yields and stereoselectivities to give the corresponding homoallylic amines. The high stereoselectivity obtained could be explained considering a chelated model, where the coordination of a heteroatom contributes to the stabilization of a six

[34] (a) Hua, D. H.; Lagneau, N.; Wang, H.; Chen, J. *Tetrahedron: Asymmetry* **1995**, *6*, 349. (b) Hua, D. H.; Miao, S. W.; Chen, J. S.; Iguchi, S. *J. Org. Chem.* **1991**, *56*, 4.
[35] Wang, X.-Z.; Burke, T. R., Jr. *Synlett* **2004**, 469.
[36] Bertrand, M. B.; Wolfe, J. P. *Org. Lett.* **2006**, *8*, 2353.
[37] Grainger, R. S.; Welsh, E. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 5377.
[38] Nishikawa, Y.; Kitajima, M.; Kogure, N.; Takayama, H. *Tetrahedron* **2009**, *65*, 1608.

membered transition state (Scheme 6).[39] Allylation could be also performed with allylzinc bromides formed *in situ* under Barbier type reaction conditions (formation of the organometallic compound in prescence of the electrophile, Scheme 6).[40]





Scheme 6.

The synthesis of both stereoisomers of chiral homoallylic amines from a common *N*-*tert*-butanesulfinyl imine precursor was achieved by Lin, Xu, and Sun (Scheme 7).[41,42] Allylzinc bromide, which was prepared *in situ*, was chosen as the allylation reagent. Optimization of the reaction conditions revealed that the addition of the Lewis acid $In(OTf)_3$ resulted in an increase in diastereoselectivity in THF, and the configuration of the reaction products was consistent with a chelated transition state. Notably, the opposite diastereomer was obtained upon use of wet HMPA as solvent in the absence of additives, presumably due to the disruption of the chelation between zinc and the *N*-*tert*-butanesulfinyl imine through an open transition state.

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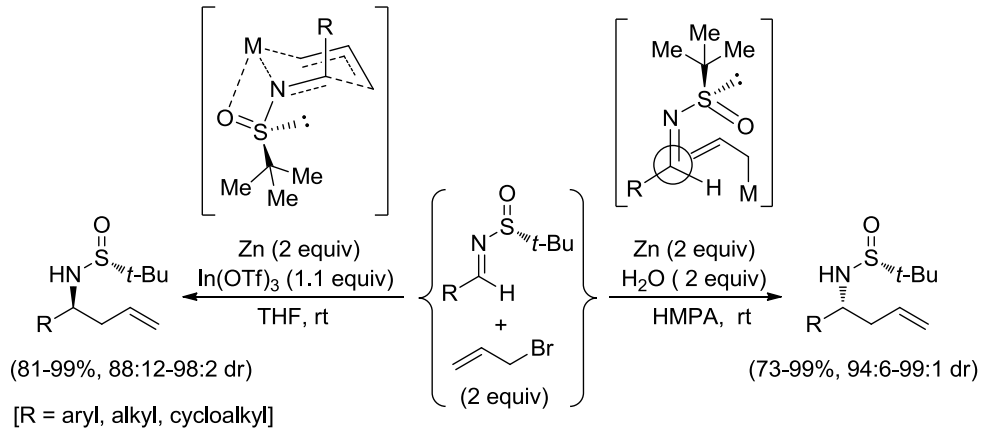
[39] van der Sluis, M.; Dalmolen, J.; de Lange, B.; Kaptein, B.; Kellogg, R. M.; Broxterman, Q. B. *Org. Lett.* **2001**, *3*, 3943

[40] Legros, J.; Meyer, F.; Coliboeuf, M.; Crousse, B.; Bonnet-Delpon, D.; Bégué, J. P. *J. Org. Chem.* **2003**, *68*, 6444.

[41] Sun, X.-W.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2006**, *8*, 4979.

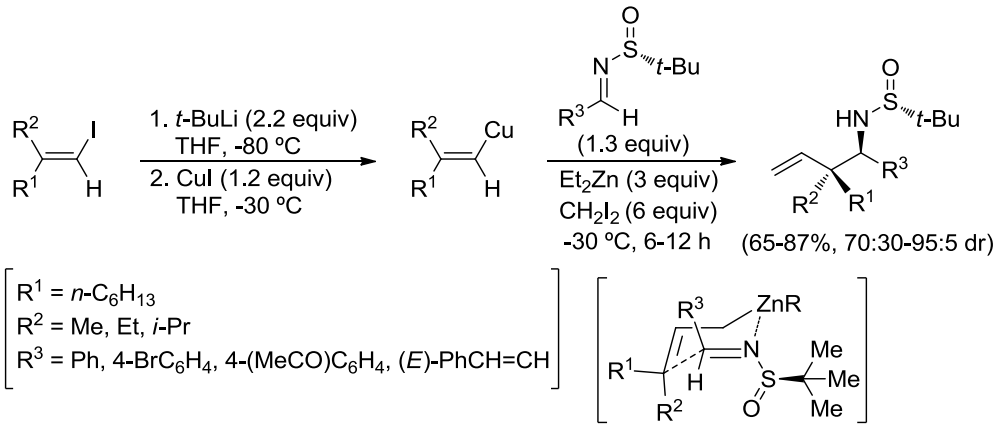
[42] Liu, M.; Sun, X.-W.; Xu, M.-H.; Lin, G.-Q. *Chem. Eur. J.* **2009**, *15*, 10217.



Scheme 7.

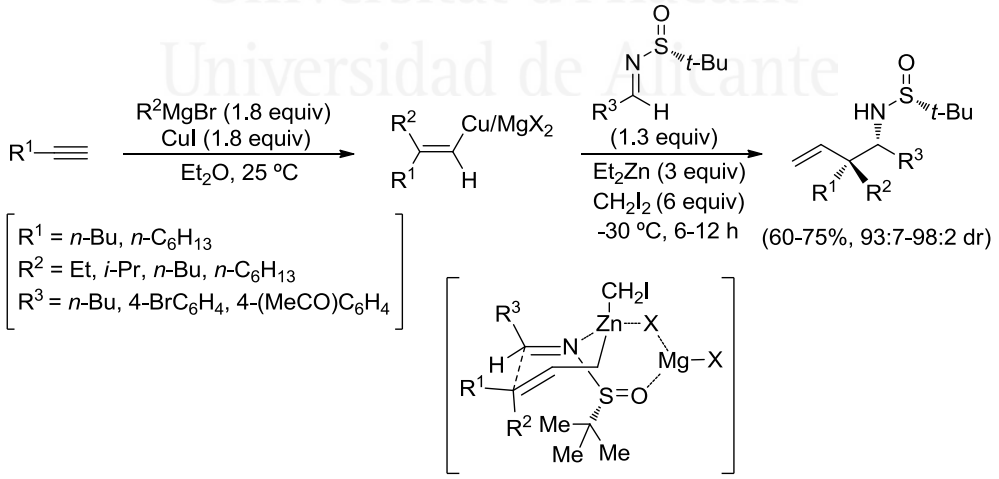
Marek, Knochel, and co-workers devised a novel synthesis of *N-tert*-butanesulfinyl protected homoallylic amines bearing a quaternary carbon stereocenter (Scheme 8).[43] Treatment of disubstituted vinyl iodides with *t*-BuLi at low temperature followed by addition of CuI provided vinyl copper intermediates, which underwent homologation reactions with a zinc carbenoid, prepared *in situ* from diethylzinc and diiodomethane, before addition to *N-tert*-butanesulfinyl imines. This sequence provided also homoallylic amines in good yields (65-87%) and diastereoselectivities (95:5). Primary and secondary alkyl substituents on the vinyl iodide and aromatic or alkenyl *N-tert*-butanesulfinyl imines were all tolerated. However, the authors noted that additions to aliphatic *N-tert*-butanesulfinyl imines gave poor diastereomeric ratios (70:30). The stereochemical outcome of this one-pot sequence was confirmed by X-ray structural analysis of one of the reaction products and was rationalized by a chelated transition state (Scheme 8).

[43] Kolodney, G.; Sklute, G.; Perrone, S.; Knochel, P.; Marek, I. *Angew. Chem. Int. Ed.* **2007**, *46*, 9291.



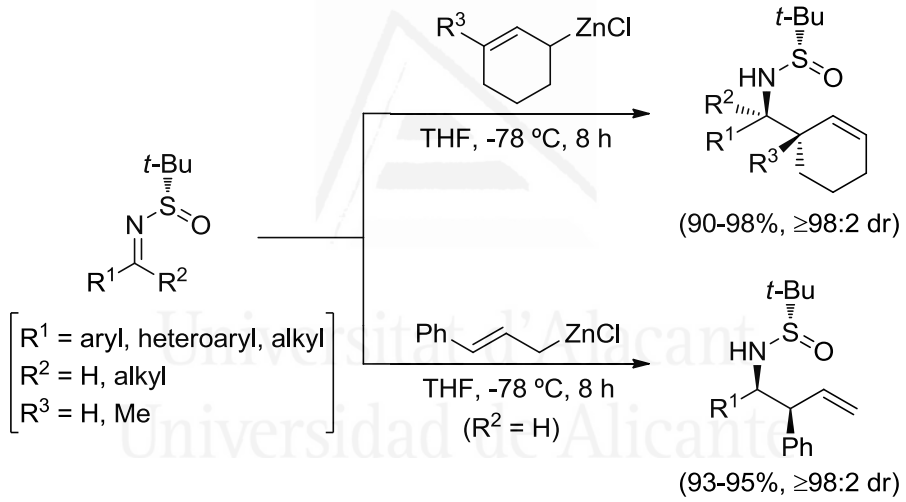
Scheme 8.

Interestingly, a switch in diastereoselectivity was observed upon the addition of the metal salt $MgBr_2$ (Scheme 9). For this transformation, vinyl copper species were prepared by direct carbocupration of alkynes with $R_2Cu/MgBr_2$ and were subjected to the same homologation with a zinc carbenoid, as described in Scheme 8. Nucleophilic addition to *N-tert*-butanesulfinyl imines **2** provided homoallylic amines in good yields (60-75%) and with excellent diastereoselectivities. The switch in facial selectivity was rationalized by invoking a cyclic transition state, where the sulfinyl oxygen is coordinated to the magnesium salt.



Scheme 9.

The addition of substituted racemic allylic zinc reagents to *N-tert*-butanesulfinyl aldimines was developed by Reddy and co-workers, allowing the synthesis of a variety of homoallylic amines bearing adjacent stereogenic centers (Scheme 10).[44] Treatment of a variety of *N-tert*butanesulfinyl aromatic imines with racemic cyclohexenylzinc chloride at low temperature (-78 °C) afforded the corresponding homoallylic amine derivatives in high yields and diastereoselectivities. Linear and branched aliphatic aldimines were also effective substrates. Likewise, the addition of the cinnamylzinc chloride to aromatic, heteroaromatic, and alkyl imines proceeded smoothly, providing the corresponding homoallylic amines in excellent yields (93-95%) and with excellent diastereoselectivities (>98:2). However, the authors noted that the method was not suitable for crotylation, as it resulted in a mixture of diastereomers. The absolute configurations of these homoallylic amines were determined by X-ray structural analysis.



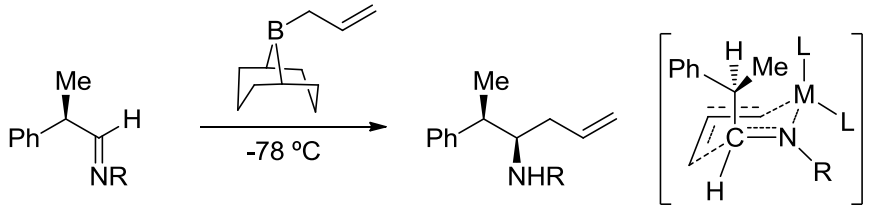
Scheme 10.

I.2.3. Boron

The imine allylation that takes place in a sterogenic center at position α with allylboranes is generally a complementary process to the allylation with allylmagnesium reagents. In the case of imines derived from 2-phenylpropanal, the selectivity obtained based on the Felkin-Ahn model that conducts to the *sin* adducts (the Cram model gives the formation of the same reaction products) is considerably higher when allyl-9-borobicyclononane is used as an allylation

[44] Reddy, L. R.; Hu, B.; Prashad, M.; Prasad, K. *Org. Lett.* **2008**, *10*, 3109.

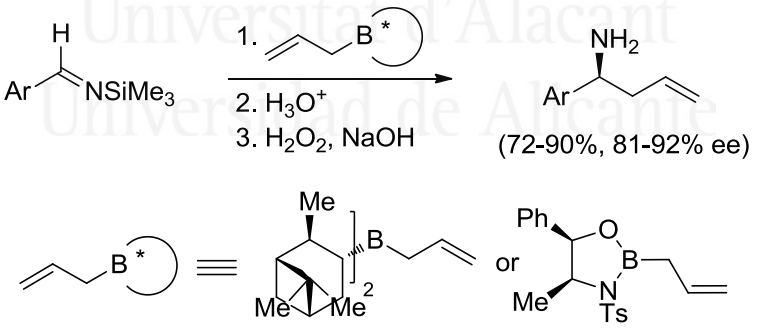
agent instead of the magnesium derivative (Scheme 11).[45] The obtained high selectivity could be explained bearing in mind a six-membered chair type model. When the metal (M) is boron, the chair is more compact (small bonds) than when the metal is magnesium, therefore, more sensible to the 1,3-diaxial interactions responsible of the facial stereoselectivity in these cases.



[R = *n*-Pr, *i*-Pr] (88-98%, 96-100% de)

Scheme 11.

The asymmetric allylation of imines using allylboranes could be carried out using a different strategy: a prochiral imine that reacts with an enantimetrically enriched chiral allylborane. The best results through this approximation were obtained by reaction of aromatic *N*-trimethylsilyl aldimines with chiral allylboranes derived from the α-pinene and norefedrine. In this way, benzylic homoallylimines were obtained with high enantioselectivities after removal of the chiral auxiliary (Scheme 12).[46,47]

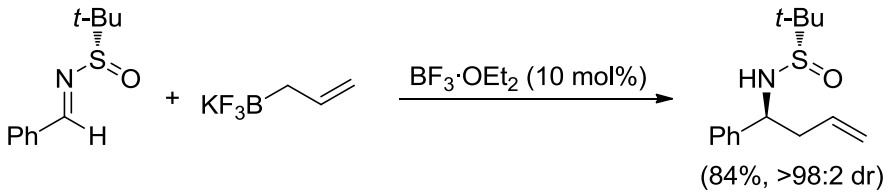


[Ar = Ph, 2-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-furyl, 2-thienyl]

Scheme 12.

[45] Yamamoto, Y.; Komatsu, K.; Maruyama, K. *J. Am. Chem. Soc*. **1984**, *106*, 5031.
[46] Watanabe, K.;, Ito, K.; Itsuno, S. *Tetrahedron: Asymmetry* **1995**, *6*, 1531.
[47] Itsuno, S.; Watanabe, K.; Ito, K.; El-Shehawy, A. A.; Sarhan, A. A. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 109.

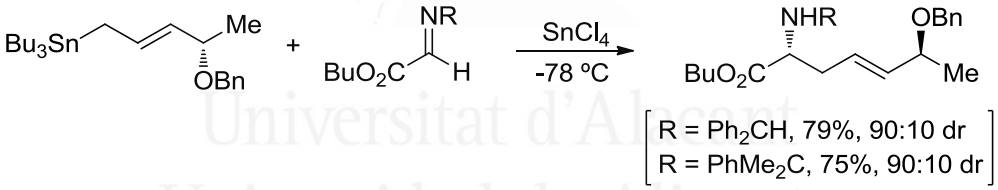
Batey and Li provided the only example of addition of an allyl borane, in this case an allyltrifluoroborate, to a *N*-*tert*-butanesulfinyl imine using a catalytic amount of $BF_3{\cdot}OEt_2$ (Scheme 13).[48] Under these reaction conditions, the desired product was obtained in 84% yield as a single diastereomer.



Scheme 13.

I.2.4. Tin

Generally, aryl and alkylimines don't react with allylstannanes and, the presence of strong Lewis acids, like $SnCl_4$, is necessary to carry out the reaction. The role of $SnCl_4$ is to generate *in situ* the trichloro allylstannane, a sufficiently reactive species to be added to the imines.[49] Under these reaction conditions, a non-racemic allylstannane reacted with imines derived from glyosylic acid *tert*-butyl ester at -78 ºC to give predominantly the *anti* amino ester (Scheme 14).[50]



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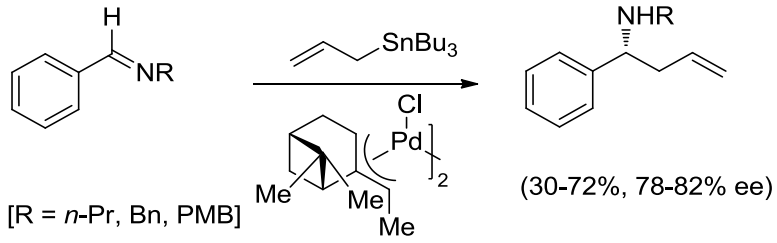
Scheme 14.

Not only the strong Lewis acids can promote the imine allylation with allylstannanes, but also, this allylation can occur in the presence of catalytic quantities (about 10 mol%) of $PtCl_2(PPh_3)_2$, $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$. The use of chiral ligands in the case of the palladium complexes could favor the transfer of the chirality in these processes. Therefore, the allylation of the benzaldimines with allyltributyltin in presence of a palladium π-allylic chiral complex gave the correspondent amines with good enantiomeric excess

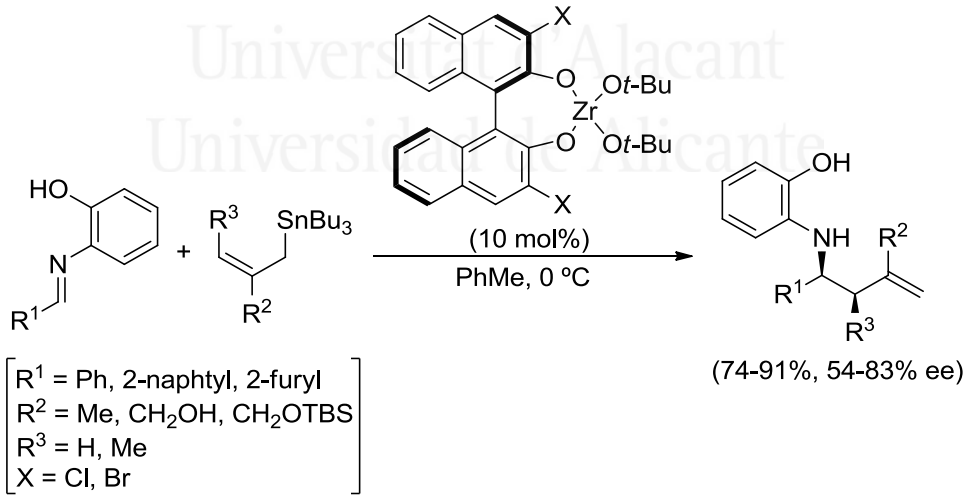
[48] Li, S.-W.; Batey, R. A. *Chem. Commun.* **2004**, 1382.
[49] Thomas, E. J. *Chem. Commun.* **1997**, 411.
[50] Hallett, D. J.; Thomas, E. J. *Tetrahedron: Asymmetry* **1995**, *6*, 2575.

(Scheme 15).[51] The use of chiral π-allylic palladium complexes supported on polymers permitted the extension of this methodology to the solid phase synthesis.[52]



Scheme 15.

The enantioselective allylation of *N*-aryl aldimines was carried out with substituted allylstannanes in presence of a zirconium catalyst derived from (*R*)-BINOL. To obtain high estereoselectivities in such processes, it´s necessary that a 2-hidroxy substituted aromatic ring is attached to the nitrogen of the imine. The catalyst is formed *in situ* combining equimolar quantities of Zr(O*t*-Bu)$_4$ and the corresponding BINOL. In addition to the high enantioselectivities found in the formation of homoallylamine derivatives, the rate of reaction is also increased considerably compared with other processes catalyzed by other species (Scheme 16).[53]



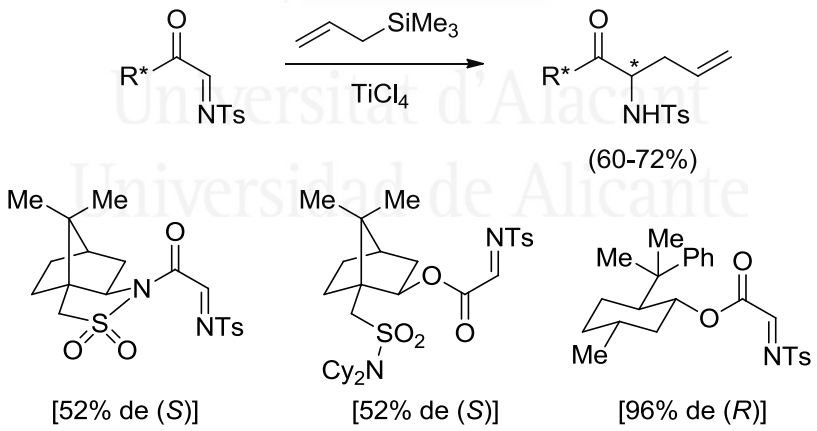
Scheme 16.

[51] Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4242.
[52] Bao, M.; Nakamura, H.; Yamamoto, Y. *Tetrahedron Lett.* **2000**, *41*, 131.
[53] Gastner, T.; Ishitani, H.; Akiyama, R.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2001**, *40*, 1896.

Allylstannanes have not been used in the allylation of *N-tert*-butanesulfinyl imines. Since the *N-tert*-butanesulfinyl group is sensitive to acidic conditions it seems to be no compatible with the use of a strong Lewis acid, like $SnCl_4$, as a promoter of the addition.

I.2.5. Silicon

Silicon compounds show a reactivity patron similar to the tin compounds. In this case, the presence of Lewis acids is necessary to carry out the addition of allylsilanes to imines. The diasterioselective allylation of the non-racemic chiral derivatives of iminoglyoxylic acids in presence of different Lewis acids was studied.[54] Different esters derived from the phenylmenthol, from sultam and sulfonamide of Oppolzer were isolated to understand the influence of the chiral auxiliary attached to the carboxyl.[55] The influence of different Lewis acids on the reaction was also studied, determining that the best results were found in the cases of $ZnBr_2$ and $TiCl_4$. Curiously, while imines derived from the sultam and the sulfonamide of Oppolzer conduct to products with an *S* configuration at the resultant stereogenic center, the one derived from phenylmenthol gives a compound with *R* configuration. The diasteriomeric excesses are moderate but only in the case of the phenylmenthol derivative a good de was obtained (Scheme 17).

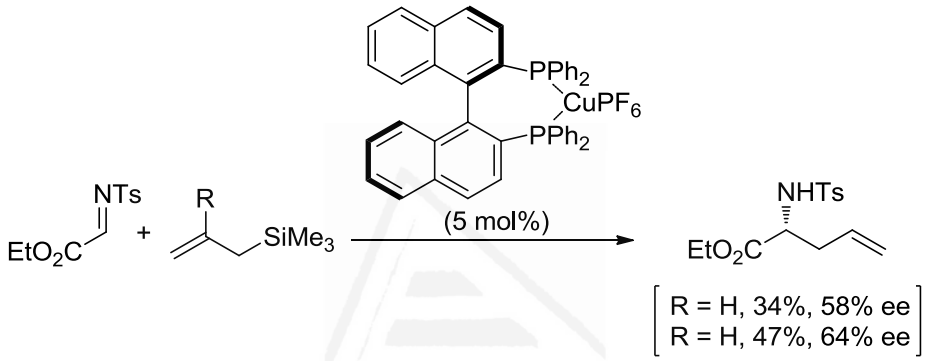


Scheme 17.

Allylsilanes could be used as an alternative to the more toxic allylstannanes. Therefore, under the same reaction conditions mentioned in Scheme 15, where the chirality derives from a palladium π-allylic chiral

[54] Kulesza, A.; Jurczak, J. *Chirality* **2001**, *13*, 634.
[55] Kulesza, A.; Mieczkowski, A.; Jurczak, J., *Tetrahedron: Asymmetry* **2002**, *13*, 2061.

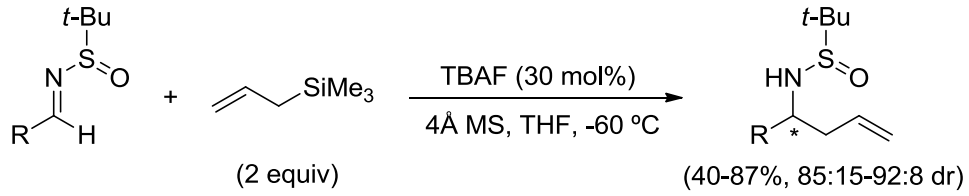
complex, it´s possible to carry out the stereoselective allylation of imines using allyltrimethylsilane. However, the presence of 0.5 equivalents of tetrabutylamonium floride is necessary for the reaction to advance. Other allylsilanes, like the allyltrimethoxysilane or the allyltrichlorosilane are not so effective in these reactions.[56] The *N*-tosyl ethyl iminoester of glyoxylic acid react with allyltrimethylsilanes in presence of the (*S*)-Tol-BINAP-$CuPF_6$ complex. The reaction occurs in moderate yields and enantioselectivities. Generally, the silanes are less reactive to the imines than the corresponding stannanes and the reactions should be performed at higher temperatures (Scheme 18).[57]



Scheme 18.

The addition of allyltrimethylsilane to *N-tert*-butanesulfinyl aldimines was studied by Zhang and co-workers. A screen of reaction conditions revealed that the optimal results were obtained when 30 mol % of tetrabutylammonium fluoride (TBAF) was used and the reaction was conducted at -60 °C in THF. Molecular sieves were a necessary additive to remove any adventitious water. Both linear and α-branched aliphatic imines were examined. However, yields were higher when *N-tert*butanesulfinyl aromatic aldimines were used as substrates and, the relative stereochemistry of the major isomer was unfortunately not determined (Scheme 19).[58]

[56] Nakamura, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 2614.
[57] Fang, X.; Johannsen, M.; Yao, S.; Gathergood, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1999**, *64*, 4844.
[58] Zhang, W. X.; Hou, X. L. *Chin. Chem. Lett.* **2006**, *17*, 1037.

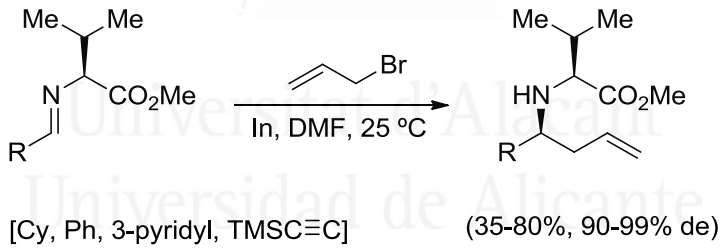


[R = *n*-Pr, i-Pr, *s*-Bu, $Ph(CH_2)_2$, Ph, $4\text{-}FC_6H_4$, $Me\text{-}FC_6H_4$, $4\text{-}MeOC_6H_4$]

Scheme 19.

I.2.6. Indium

Chiral homoallylamines were also prepared by the indium mediated allylation of chiral imines derived from the methylester of the L-valine. The allylindium reagent is prepared *in situ* from the allylbromide and indium metal. Aliphatic and aromatic imines conduct to the reaction products with excellent stereoselectivities, being *S* the confituration of the new stereocenter obtained starting from the L-aminoacid as a chiral auxiliary. It has to be mentioned also that the reaction can be carried out in presence of Lewis acids like $La(OTf)_3$ or $InCl_3$, even though, the best stereoselectivities were found when the reaction goes in absence of this type of additives (Scheme 20).[59]

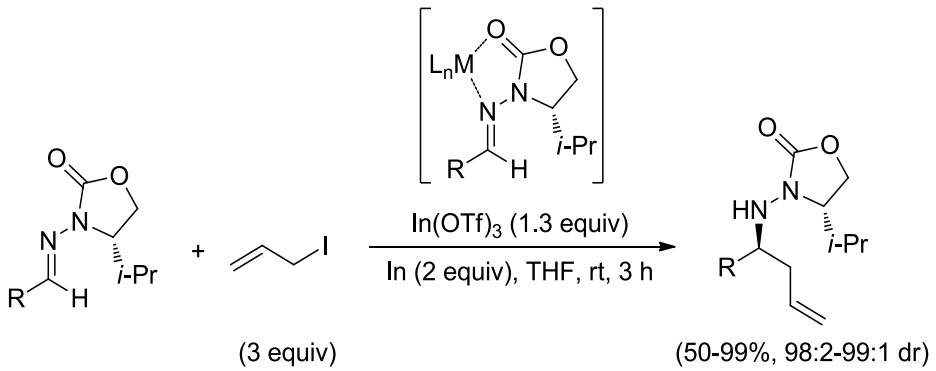


Scheme 20.

Indium-mediated allylation of chiral hydrazones have been also accomplished in a highly diastereoselective manner. Reactions were operationally simple and reaction times were short. With the employment of $In(OTf)_3$ Lewis acid increased both the selectivity and the rate of the reaction. In all cases, the reaction was complete within 1 h. Presumably, the Lewis acid coordinates the hydrazone in a chelating fashion to both activate the substrate

[59] Loh, T.-P.; Ho, D. S.-C.; Xu, K.-C.; Sim, K.-Y. 1997, *Tetrahedron Lett.* **1997**, *38*, 865.

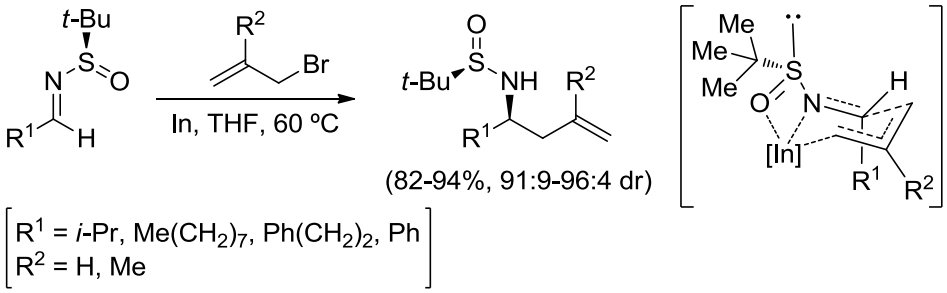
as well as restrict the conformational mobility allowing for greater reactivity and selectivity (Scheme 21).[60]



Scheme 21.

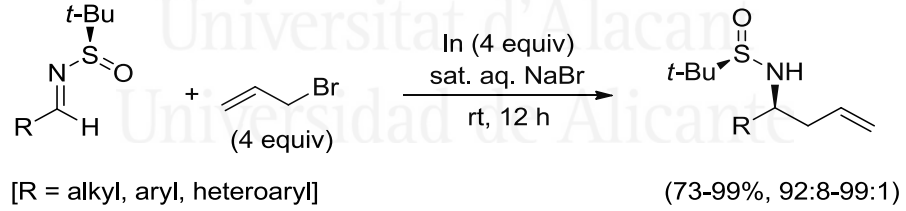
An asymmetric synthesis of homoallylic amines by the indium-mediated addition of allyl bromides to *N*-*tert*-butanesulfinyl aldimines has been developed in our research group. The optimal reaction conditions were achieved with 1.3 equivalents of indium in THF at elevated temperature (60 °C). The reaction was found to be general, allowing addition of allyl bromides to a variety of *N*-*tert*-butanesulfinyl alkyl or aryl imines with high yields and diastereoselectivities. The absolute configuration of the major reaction product was determined by chemical correlation and the stereochemical outcome was consistent with a chelated transition state (Scheme 22).[61] This methodology was applied to the synthesis of four naturally occurring 2,6-*cis*-disubstituted piperidines.[62] The same homoallylic amine derivatives could be prepared in a one-pot process, with high chemo- and stereoselectivities, starting from commercially available aldehydes, allyl bromides, indium, and chiral *tert*-butanesulfinamide. The reaction should be performed in the presence of 2 equivalents of titanium tetraethoxide in order to facilitate the *in situ* formation first of the *N*-*tert*-butanesulfinyl imine.[63]

[60] Cook, G. R.; Maity, B. C.; Kargbo, R. *Org. Lett.* **2004**, *6*, 1741.
[61] Foubelo, F.; Yus, M**.** *Tetrahedron: Asymmetry* **2004**, *15*, 3823.
[62] González-Gómez, J. C.; Foubelo, F.; Yus, M. *Synlett* **2008**, 2777.
[63] González-Gómez, J. C.; Medjahdi, M.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2010**, *75*, 6308.



Scheme 22.

The indium mediated allylation of *N*-*tert*-butanesulfinyl imines could be also performed in aqueous media. When the reaction was conducted with water as the solvent, a low yield of the desired homoallylic amine product was observed. Yields were dramatically improved when the solvent was changed to an aqueous saturated salt solution, with saturated aqueous NaBr being optimal. Notably, the use of 4 equivalents of indium was found to be necessary to achieve the highest yield. The scope of the reaction was explored employing these optimized reaction conditions, and additions to a wide variety of diverse aryl, heteroaryl, alkenyl, and alkyl substituted *N*-*tert*-butanesulfinyl aldimines were investigated to produce in all cases *N*-*tert*butanesulfinyl homoallylic amines in high yields (73-99%) and with diastereomeric ratios ranging from 92:8 to >99:1 (Scheme 23).[64]



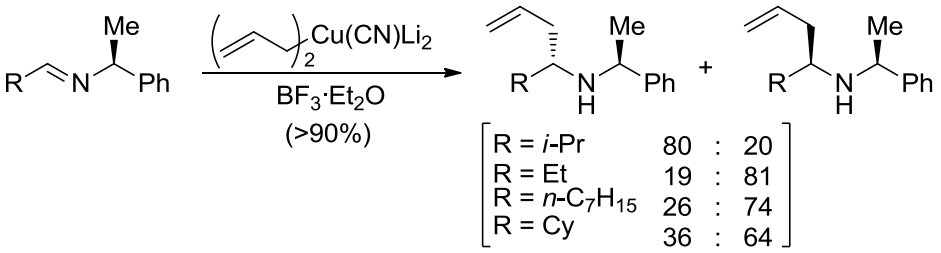
Scheme 23.

I.2.7. Copper

The cuprates of high order also react with chiral imines to give the corresponding homoallylimines. To carry out these processes, it is necessary the presence of a Lewis acid. In the case of *N*-(1-phenylethyl)aldimines, it was found that the best yields were attained when $BF_3.Et_2O$ was used. The obtained yields were always higher than 90%, with the *sin*-1,3 isomer as the major

[64] Sun, X.-W.; Liu, M.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2008**, *10*, 1259.

product in all cases, except for the imine derived from the isobutyraldehyde, where the *anti*-1,3 isomer was the major product (Scheme 24).[65]



Scheme 24.

As in the case of allylstannanes, there are not reports in the literature about the allylation of *N*-*tert*-butanesulfinyl imines with allyl copper reagents.

I.3. Asymmetric additions of malonate-derived enolates to chiral imines

β-Aminomalonates and β-amino acids belong to important building blocks for the study of natural products, pharmaceuticals, peptides, and copolymers.[66-70] They serve as direct precursors to chiral amino alcohols that are also chemically and biologically important.[71,72] In recent years, there has been a continuing interest in asymmetric synthesis of β-amino acids and their derivatives in organic and medicinal chemistry, among them the asymmetric Mannich reaction has become a powerful and practical protocol for this purpose.[73,74]

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However a practical Mannich reaction of dialkyl malonate derived enolates with simple imines remains less explored. Deng and co-workers have developed an efficient enantioselective direct Mannich reaction of *N*-Boc-

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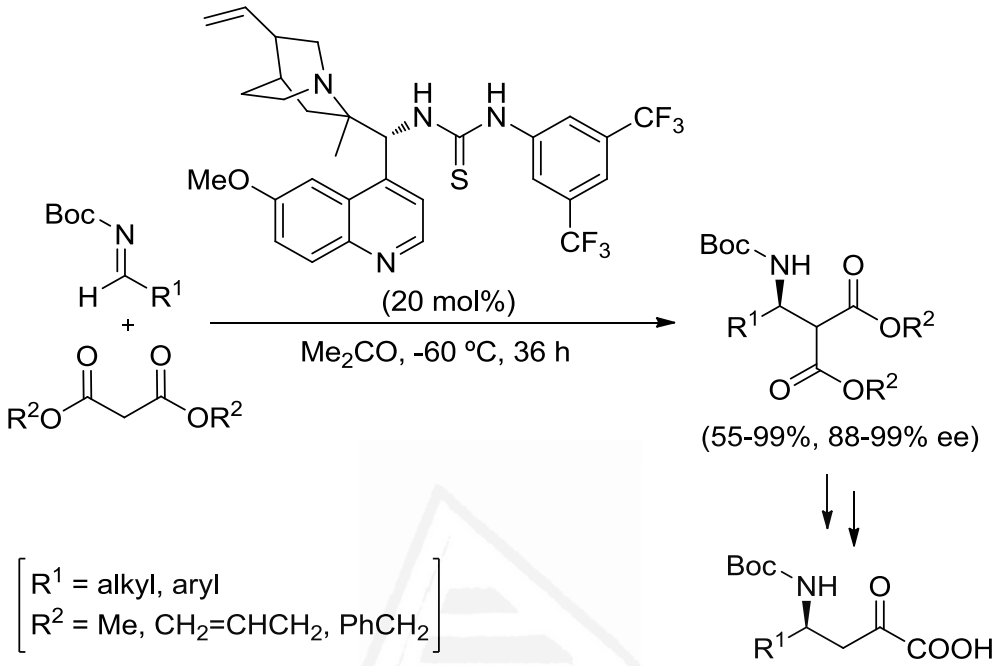
[65] Bandini, M.; Cozzi, P. G.; Umani-Ronchi, A.; Villa, M. *Tetrahedron* **1999**, *55*, 8103.
[66] Lee, M.; Raguse, T. L.; Schinnerl, M.; Pomerantz, W. C.; Wang, X.; Wipf, P.; Gellman, S. H. *Org. Lett.* **2007**, *9*, 1801.
[67] Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991.
[68] Iijima, K.; Katada, J.; Hayashi, Y. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 413.
[69] Shapiro, R. *J. Org. Chem.* **1993**, *58*, 5759.
[70] Studer, P.; Larras, V.; Riess, G. *Eur. Polym.* **2008**, *44*, 1714.
[71] Enders, D.; Moser, M.; Geibel, G.; Laufer, M. C. *Synthesis* **2004**, 2040.
[72] Kochi, T.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 11276.
[73] Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102.
[74] Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.

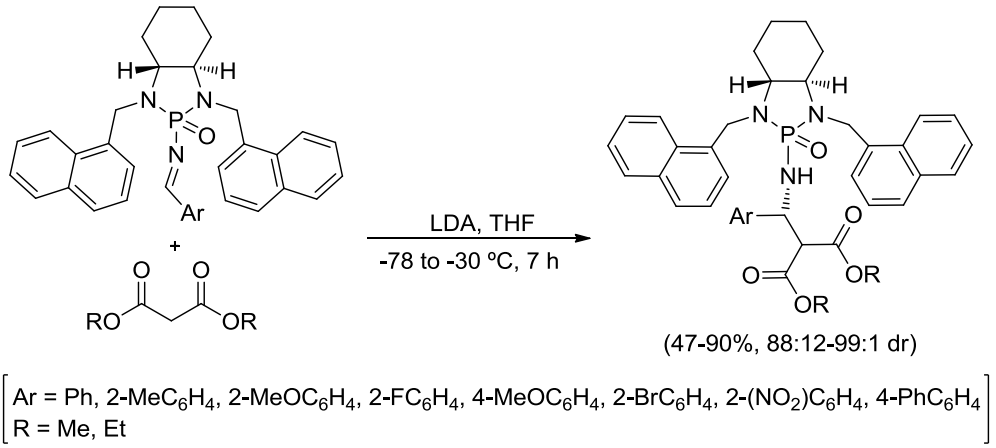
protected imines with malonates under mild conditions by using a bifunctional cinchona alkaloid as catalyst (Scheme 25).[75]



Scheme 25.

More recently, Z.-X. Chen reported that chiral *N*-phosphonyl imines bearing a 1-naphthylmethyl group bonded to the nitrogen atom were found to react with lithium malonate enolates smoothly to give chiral β-aminomalonates in high yields and excellent diastereoselectivity. The chiral auxiliary can be readily removed by treating with trifluoroacetic acid (TFA) to give free amino malonates (Scheme 26).[76]

[75] Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048.
[76] Chen, Z.-X.; Ai, T.; Kaur, P.; Li, G. *Tetrahedron Lett.* **2009**, *50*, 1079.



Scheme 26.

I.4. Stereoselective aza-Henry reactions

The nucleophilic addition of nitroalkanes to imines and related compounds (aza-Henry or nitro-Mannich reaction) is a powerful synthetic transformation that allows creation of a carbon–carbon bond with concomitant generation of two vicinal stereogenic centers bearing nitro and amino functional groups (Scheme 27).[77] The resulting β-nitroamines represent rather useful synthetic building blocks because the two nitrogenated functions are present in different oxidation states, thus giving access to further transformations with complete chemoselectivity. In addition, the β-nitroamines can easily be converted into α-amino acids and vicinal diamines through Nef reactions[78,79] and by reduction[80-82] of the nitro group.

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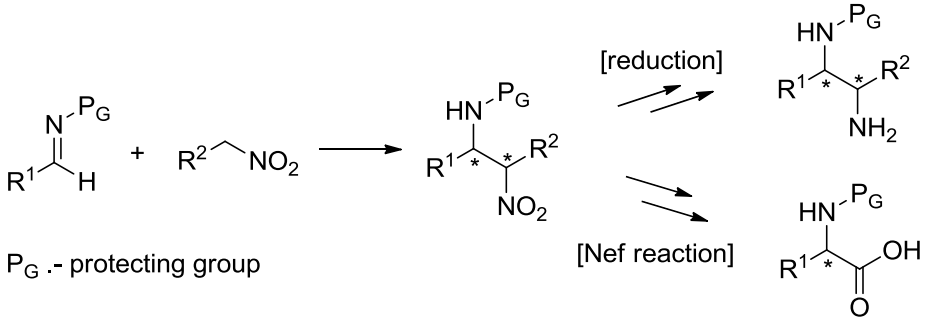
[77] Westermann, B. *Angew. Chem. Int. Ed.* **2003**, *42*, 151.
[78] Kende, A. S.; Mendoza, J. S. *Tetrahedron Lett.* **1991**, *32*, 1699.
[79] Sturgess, M. A.; Yarberry, D. J. *Tetrahedron Lett.* **1993**, *34*, 4743.
[80] Kotti, S. R. S.; Timmons, C.; Li, G. *Chem. Biol. Drug Des.* **2006**, *67*, 101.
[81] Viso, A.; Fernández de la Pradilla, R.; García, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167.
[82] Merino, P.; Lanaspa, A.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1998**, *9*, 629.



Scheme 27.

Many natural products possessing valuable biological properties contain 1,2-diamino moieties. In recent years several synthetic diamine derivatives have also been employed as medicinal agents, in particular in chemotherapy as antiarrhythmics,[83] antidepressant agents,[84] antihypertensives,[85] analgesics,[86] anticancer and antiviral drugs[87] and as antiparasitic agents.[88] In addition to their applications in medicinal chemistry, the use of vicinal diamines in organic synthesis in the field of catalytic asymmetric synthesis has also increased considerably during the last years, due to their use both as ligands[89-92] and as organocatalysts.[93,94]

Although nucleophilic additions of nitroalkanes to imines were studied by several groups in the past,[95] all the associated work was devoted to racemic derivatives. The first stereoselective aza-Henry reaction was reported by

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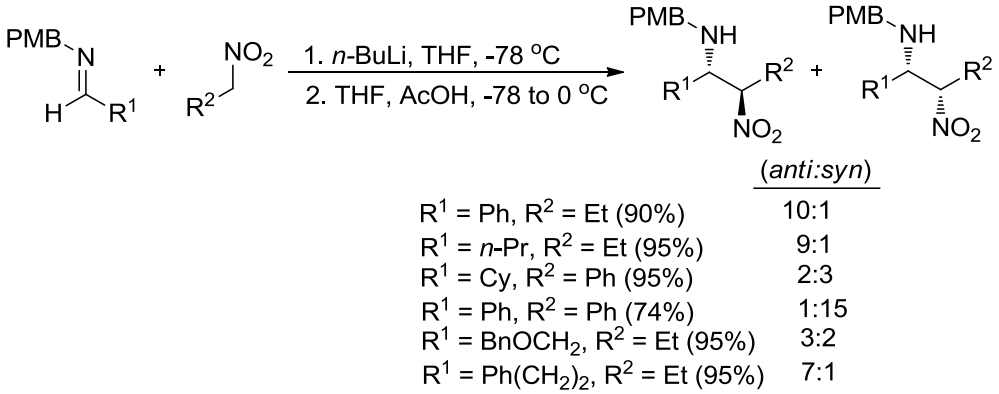
[83] Zubovics, Z.; Toldy, L.; Varró, A.; Rablocky, G.; Kürthy, M.; Dvorták, P.; Jerkovich, G.; Tomory, É. *Eur. J. Med. Chem.* **1986**, *21*, 370.
[84] Szmuszkovicz, J.; VonVoigtlander, P. F.; Kane, M. P. *J. Med. Chem.* **1981**, *24*, 1230.
[85] Szilagyi, G.; Kasztreiner, E.; Matyus, P.; Kosary, J.; Czako, K.; Cseh, G.; Huszti, Z.; Tardos, L.; Kosa, E.; Kaszlits, L. *Eur. J. Med. Chem.* **1984**, *19*, 111.
[86] González-Sabín, J.; Gotor, V.; Rebolledo, F. *Chem. Eur. J.* **2004**, *10*, 5788.
[87] Mibu, N.; Yokomizo, K.; Miyata, T.; Sumoto, K. *Chem. Pharm. Bull.* **2007**, *55*, 1406.
[88] Rebollo, O.; del Olmo, E.; Ruiz, G.; López-Pérez, J. L.; Giménez, A.; San Feliciano, A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 184.
[89] Blaser, H. U. *Chem. Rev.* **1992**, *92*, 935.
[90] Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833.
[91] Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
[92] Mitchell, J. M.; Finney, N. S. *Tetrahedron Lett.* **2000**, *41*, 8431.
[93] Sohtome, Y.; Takemura, N.; Takagi, R.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron* **2008**, *64*, 9423.
[94] Pignataro, L.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Celentano, G. *Chirality* **2005**, *17*, 396.
[95] Baer, H. H.; Urbas, L. *The Chemistry of the Nitro and Nitroso Groups, Part 2.* [ed.] S. Patai. New York : Interscience, 1970. p. 117.

Anderson and co-workers,[96] who described the addition of the lithium salts of various nitroalkanes to *N*-(*p*-methoxybenzyl) imines (Scheme 28).



	(*anti*:*syn*)
R^1 = Ph, R^2 = Et (90%)	10:1
R^1 = *n*-Pr, R^2 = Et (95%)	9:1
R^1 = Cy, R^2 = Ph (95%)	2:3
R^1 = Ph, R^2 = Ph (74%)	1:15
R^1 = $BnOCH_2$, R^2 = Et (95%)	3:2
R^1 = $Ph(CH_2)_2$, R^2 = Et (95%)	7:1

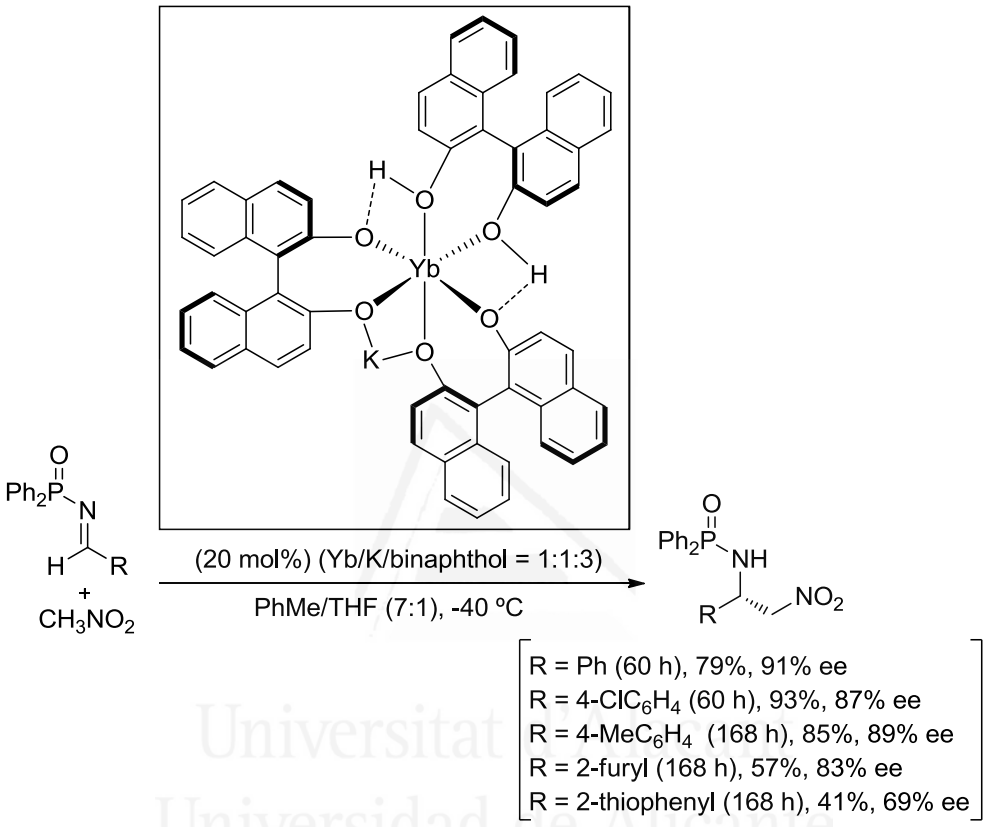
Scheme 28.

The additions of nitroalkanes to *N*-(*p*-methoxybenzyl) imines in the presence of acetic acid in most cases gave β-nitroamines with good yields and diastereoselectivities. Both aryl and alkyl imines proved to be compatible with the procedure, affording mixtures of *syn* and *anti* isomers in all cases.[97] Notably, imines derived from enolizable aliphatic aldehydes could be used in this process, in contrast with the strongly basic conditions required for the addition of other α-amino anions to imines.[98,99]

The first examples of catalytic enantioselective aza-Henry reactions, between highly coordinating *N*-phosphinoylimines and nitromethane were reported by Shibasaki and co-workers in 1999. These authors investigated several catalysts prepared from $Yb(OiPr)_3$, KO*t*Bu and (*R*)-binaphthol in different ratios. Interestingly, whereas the complex prepared in a 1:1:2 ratio did not promote the reaction, the same components mixed in 1:1:3 ratio afforded the best results, furnishing nitroamines with good yields and enantioselectivities. No base was needed because the formed complex contained both Brønsted basic and Lewis acid functionalities, capable of activating both the electrophile and the nucleophile (Scheme 29).[100] An important drawback of the catalyst is that it is not able to promote the aza-

[96] Adams, H.; Anderson, J. C.; Peace, S.; Pennell, A. M. K. *J. Org. Chem.* **1998**, *63*, 9932.
[97] Masamune, S.; Ali, S. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 557.
[98] Kise, N.; Kashiwagi, K.; Watanabe, M.; Yoshida, J. *J. Org. Chem.* **1996**, *61*, 428.
[99] Park, Y. S.; Boys, M. L.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 3757.
[100] Yamada, K.; Harwood, S. J.; Gröger, H.; Shibasaki, M. *Angew. Chem. Int. Ed.* **1999**, *38*, 3504.

Henry reaction with bulkier substituted nitroalkanes at low temperatures. This lack of activity was attributed to the reduced size of the binding pocket of the catalyst, which could have insufficient space to accommodate both the imine and the nitroalkane.

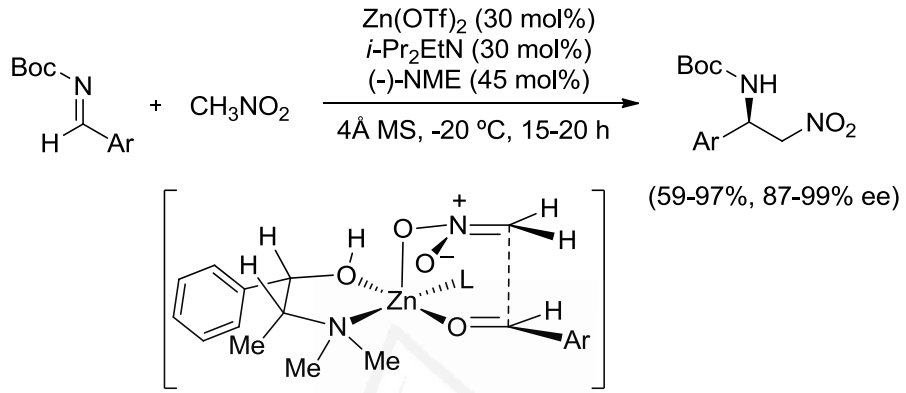


Scheme 29.

Palomo and co-workers have reported enantioselective aza-Henry reactions between nitromethane and *N*-Boc arylimines in the presence of the combination of $Zn(OTf)_2$, (–)-*N*-methylephedrine (NME) and Hünig's base, all commercially available, as an activating system for the reactions (Scheme 30).[101,102] It was observed that the presence of traces of moisture or protic contaminants in the reaction mixture were detrimental to the enantioselectivity. In this regard, the addition of molecular sieves was beneficial and gave the highest enantioselectivity in these aza-Henry reactions.

[101] Palomo, C.; Oiarbide, M.; Laso, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 3881.
[102] Palomo, C.; Oiarbide, M.; Halder, R.; Laso, A.; López, R. *Angew. Chem. Int. Ed.* **2006**, *45*, 117.

A practical aspect of the method, although restricted to aromatic imines, is that a single recrystallization of the crude nitroamine from hexane and/or mixtures of ethyl acetate and hexane could provide products of increased enantiomeric purity. The sense of the asymmetric induction imparted may be correctly predicted by a boat transition model which is in accord with reported steric and electronic considerations in similar systems.[103]



Scheme 30.

In terms of organocatalysis, the first organocatalytic aza-Henry reaction was reported by Takemoto and co-workers, who used a thiourea derivative as a bifunctional catalyst in the reactions of *N*-diphenylphosphinoyl imines with an excess of nitromethane (Scheme 31).[104] The reactions were restricted to aromatic *N*-phosphinoyl imines; good yields and moderate enantioselectivities were obtained. It has been proposed that the corresponding nitronate could be produced from nitroalkane with the bifunctional thiourea via the hydrogen-bonding activation with the thiourea moiety and subsequent deprotonation by the neighboring tertiary amino group, thus taking place an asymmetric aza-Henry reaction.

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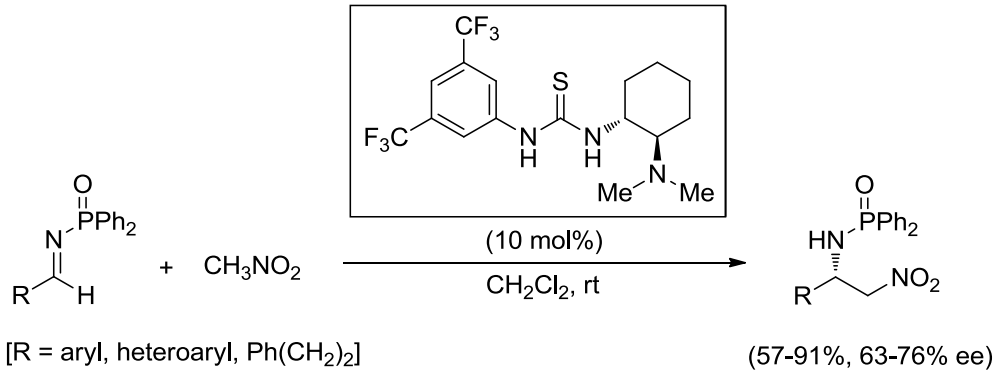
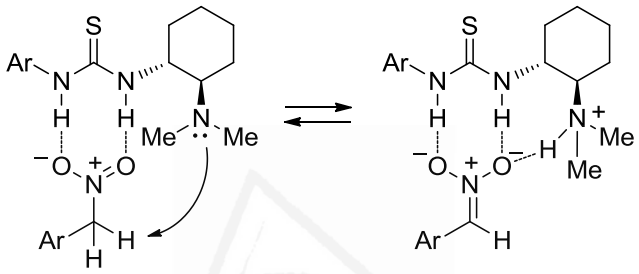
[103] Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692.
[104] Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625.

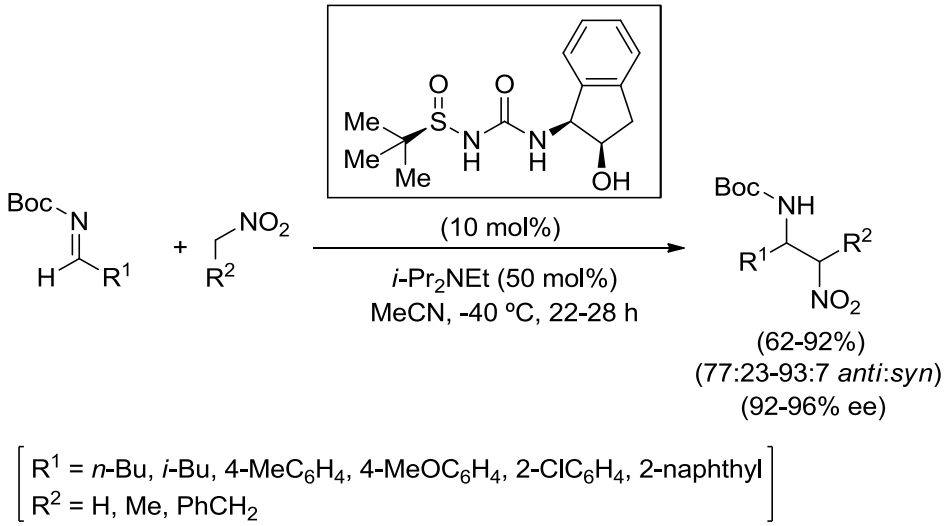




Scheme 31.

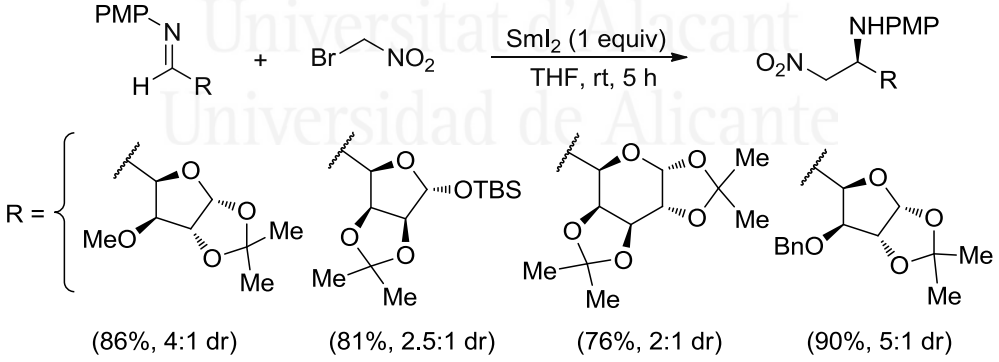
Ellman and co-workers have reported the use of a *N*-sulfinyl urea as a new class of organocatalyst, the effectiveness of which was demonstrated by performing aza-Henry reactions with high selectivities, including the first example of enantioselective H-bonding-catalyzed additions to aliphatic *N*-Boc imines (Scheme 32).[105] Excellent enantioselectivities were observed with imines bearing both electron-rich and electron-poor aromatic substituents. More significantly, aliphatic *N*-Boc imines were found to be effective substrates yielding hitherto unreported compounds. High diastereoselectivities and enantioselectivities were also achieved in the additions to unbranched and β-branched imine substrates.

[105] Robak, M. A. T.; Trincado, M.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 15110.



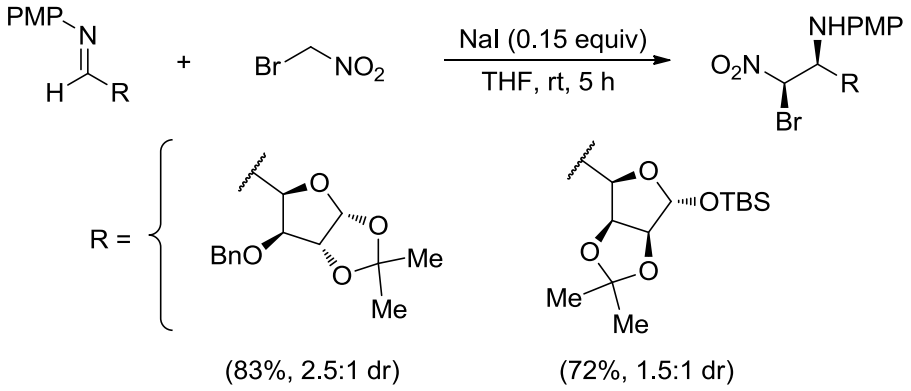
Scheme 32.

Recently, Rodríguez-Solla and co-workers reported a novel reaction of bromonitromethane with a variety of imines under very mild conditions, promoted by SmI_2 and NaI, to afford nitroamines or bromonitroamines. When these reactions were performed on sugar-based imines, the corresponding nitroamines or bromonitroamines were obtained in high yields and from moderate to good stereoselectivities (Schemes 33 and 34).[106]



Scheme 33.

[106] Rodríguez-Solla, H.; Concellón, C.; Alvarado, N.; Soengas, R. G. *Tetrahedron* **2012**, *68*, 1736.



Scheme 34.

Taking into account these antecedents and based on the experience of our research group, we considered of interest to extend the study of the indium mediated addition of different allylic bromides to *N*-*tert*-butanesulfinyl imines to other allylic halides with the ester functionality in order to elaborate more complex molecular structures. At the same time, we would like to explore the reactivity of chiral *N*-*tert*-butanesulfinyl imines with easily accessible carbon nucleophiles in a stereoselectivity manner, avoiding sophisticated ligands or highly demanding reaction conditions (solvent, temperature, moisture sensitive…).

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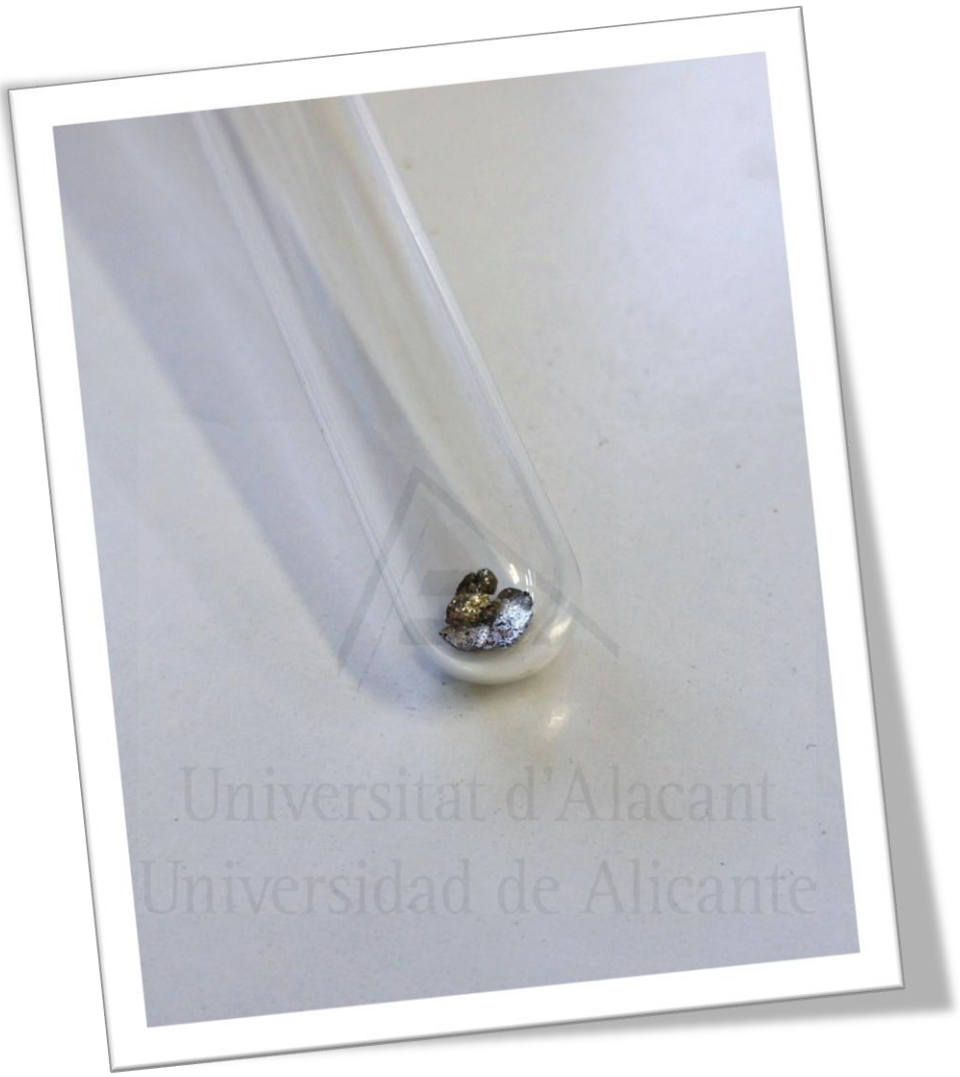
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Agglomeration of unreacted indium after the allylation reaction in saturated solution of NaBr (photo taken on the 15th of April, 2010)

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II. Results and Discussion

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II.1. Indium mediated addition of allylic halides to *N-tert*-butanesulfinyl imines

II.1.1. Introduction

Very recently, the X-ray structure of an allylindium reagent was elucidated for the first time.[107] The reaction of allyl bromides with indium(0) gives a mixture of allylindium species which have been generally referred as *sesqui*allylindium bromides regarding the overall stoichiometry of the reaction. In the case of cinnamyl bromide, the reaction affords two species, cinnamylindium(III) dibromide and dicinnamylindium(III) bromide, which could be detected as separate ones in solution by ^{1}H-NMR. Both species were isolated after complexation with pyridine-type Lewis bases and analyzed by X-ray crystallography (Scheme 35). Later, the nature of these organoindium(III) species could be identified with those involved in organoindium allylations in aqueous media.[108] The allylindium complexes reveal interesting structural features. The monohapto coordinative behavior of the allylic ligand and the bipiramidal trigonal geometrical coordination around the In(III) centre. It is also noticeable that the allyl groups occupy only the equatorial positions in the complex, sharing them with the bromide (a low field ligand), while the pyridine ligands occupy the apical positions. On the other hand, this does not seem to be the only coordination operating with allylindium reagents. In the presence of alkoxydes (e.g. as reaction products) an oxygen-bridged binuclear complex of In(III) (μ-oxide) seems to be the preferred nuclear configuration. In this case, the indium(III) centre has a tetrahedral coordination, maintaining the monohapto coordination of the allyl group in the periphery of the complex. This μ-oxide complex has been shown to be moderately reactive with different electrophiles. This opens the possibility to different coordination spheres around the metal center, and therefore to a richer variety of reaction pathways to be explored.

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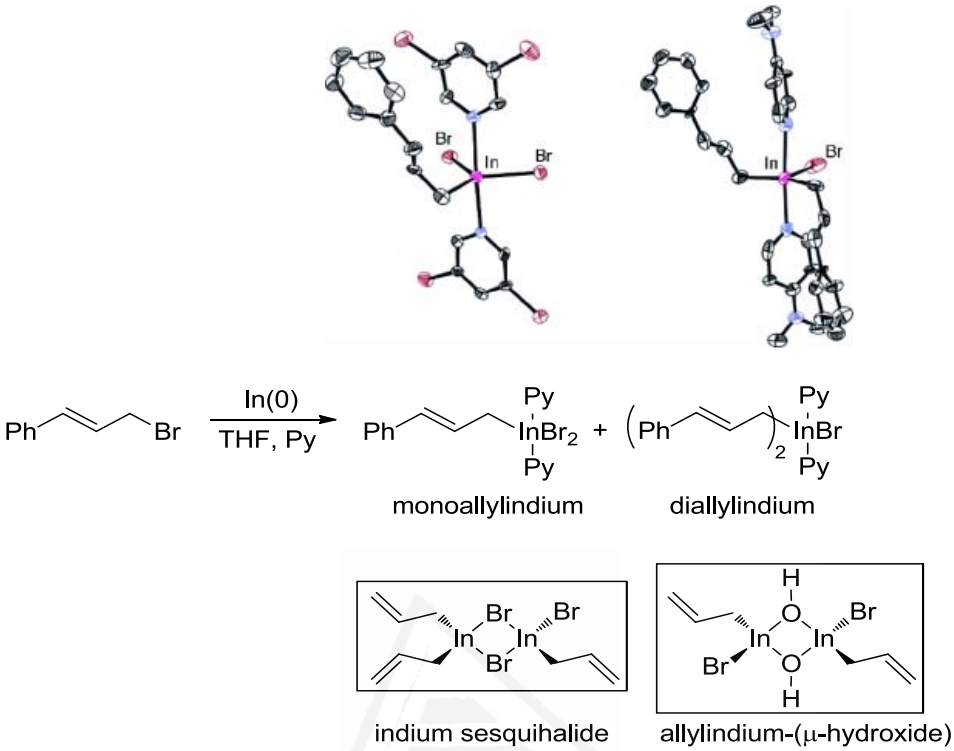
[107] Yasuda, M.; Haga, M.; Baba, A. *Eur. J. Org. Chem.* **2009**, 5513.
[108] Yasuda, M.; Haga, M.; Nagaoka, Y.; Baba, A. *Eur. J. Org. Chem.* **2010**, 5359.



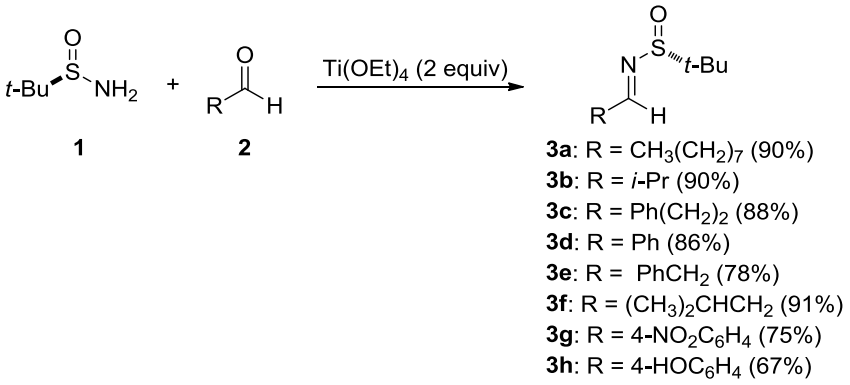
Scheme 35.

II.1.2. Objetives

We would like to study the indium mediated addition of different ester functionalized allylic halides to *N-tert*-butanesulfinyl imines, paying attention mainly to the stereochemical pathway of the processes and to synthetic application of the resulting reaction products.

II.1.3. Synthesis of *N-tert*-butanesulfinyl aldimines 3

The reaction of the (*R*)- or (*S*)-*tert*-butanosulfinamide (**1**), both enantiomerically pure and commercially available, with an aldehide **2** in the presence of an excess of $Ti(OEt)_4$ in THF at room temperature, led to the formation of the correspondent *N-tert*-Butanesulfinyl imines **3** with good yields (Scheme 36). No racemization occurred during the condensation process and the aldimines **3** were isolated exclusively as the (*E*)-isomer.



Scheme 36.

II.1.4. Reaction with ethyl 2-(bromomethyl)acrylate (4)

II.1.4.1. Optimization of the reaction conditions

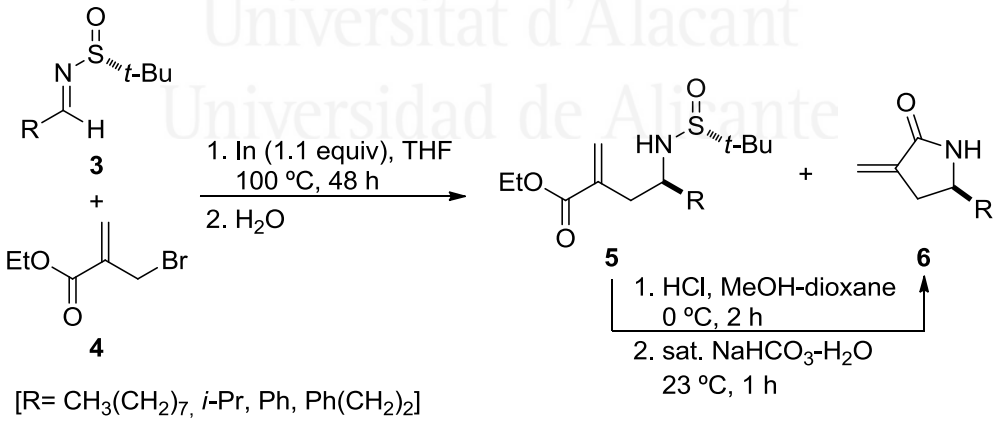
We first investigated the reaction conditions for the allylation of *N*-*tert*-butanesulfinyl imine (*R*)-**3d** by treatment with ethyl 2-(bromomethyl)acrylate (**4**) in the presence of indium metal. Based on our previous experience with indium-mediated allylation of these type of aldimines, we used 1.1 equivalents of indium metal and 1.2 equivalents of the allylic bromide, THF being the solvent of choice at 60 ^{0}C.[61,109,110,111] However, under these reaction conditions, the allylation did not take place, even after 3 days (Table 1, entry 1). It was supposed that in these processes the formation of an allylindium intermediate was facilitated in aqueous media,[112] although in the case of using a 1:1 water/THF mixture, hydrolysis of the starting aldimine **3d** occurred, yielding benzaldehyde and other reaction products derived from it (Table 1, entry 2). Regarding the temperature, although the reaction does not progress at 60 °C in THF, while at 80 °C it takes 7 days to drive it to an only 15% conversion (Table 1, entry 3), complete conversion was achieved at 100 °C after 48 hours to give a 3:1 mixture of the expected aminoester derivative **5d** and the butyrolactam **6d** (Table 1, entry 4).[113] Under these reaction conditions, compound **3d** could partially cyclize to give α-methylene-γ-butyrolactam **4d**. Overall yields and selectivities were not improved when the allylation was performed at 100 °C in acetonitrile, *N*,*N*-dimethylformamide and toluene (Table 1, entries 5, 6 and 7,

[61] Foubelo, F.; Yus, M**.** *Tetrahedron: Asymmetry* **2004**, *15*, 3823.
[109] Medjahdi, M.; González-Gómez, J. C.; Foubelo, F.; Yus, M. *Heterocycles* **2008**, *76*, 569.
[110] González-Gómez, J. C.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2009**, *74*, 2547.
[111] Medjahdi, M.; González-Gómez, J. C.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2009**, *74*, 7859.
[112] Chen, T. H.; Yang, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3228
[113] Dema, H. K.; Foubelo, F.; Yus, M. *Heterocycles* **2010**, *80*, 125.

respectively), meanwhile in ethanol decomposition of aldimine **3d** occurred without formation of the expected aminoester derivative **5d** (Table 1, entry 8). Further optimization in search of milder conditions led, surprisingly, to the total conversion when the reaction was carried out in a saturated aqueous sodium bromide solution in the presence of 4 equivalents of indium at room temperature for 48 hours,[64] and compound **5d** was the only isolated reaction product in 79% yield (Table 1, entry 9). On the other hand, a 46% yield was obtained when zinc was used instead of indium under the same reaction conditions (Table 1, entry 10).

II.1.4.2. Stereoselective synthesis of α-methylene-γ-butyrolactams 6[114]

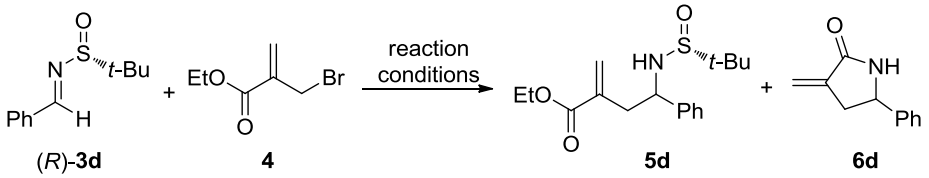
It was possible to synthesize α-methylene-γ-butyrolactams **6** in a stereoselective manner by applying to different aliphatic and aromatic chiral imines **3** the reaction conditions depicted on Table 1, entry 4. That is, heating for 48 h equimolecular amounts of ethyl 2-(bromomethyl)acrylate (**4**), indium powder and the corresponding chiral *N*-*tert*-butanesulfinyl imine **3**, in THF at 100 °C, in a pressure flask. After hydrolysis with water, extraction with ethyl acetate and evaporation, a mixture of the corresponding *N*-*tert*-butanesulfinyl aminoester **5** and α-methylene-γ-butyrolactam **6** was always obtained (Scheme 37 and Table 2). The aminoester **5** could be converted into butyrolactam **6** from the reaction mixture upon removal of the *tert*-butanesulfinyl group under acidic conditions and final basic workup (Scheme 37).



Scheme 37.

[64] Sun, X.-W.; Liu, M.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2008**, *10*, 1259.
[114] Dema, H. K.; Foubelo, F.; Yus, M. *Heterocycles* **2011**, *82*, 1411.

Table 1. *Optimization of the reaction conditions*



(*R*)-**3d** **4** **5d** **6d**

Entry	Reaction conditions[a]	Conversion (%)[b]	Products (%)[c] **5d**	**6d**
1	In (1.1 equiv), THF (2 mL), 60 °C, 72 h	0	--	--
2[c]	In (1.1 equiv), THF:H_2O (2 mL, 1:1), 60 °C, 72 h	100	--	--
3	In (1.1 equiv), THF (2 mL), 80 °C, 168 h	15	15	--
4	In (1.1 equiv), THF (2 mL), 100 °C, 48 h	100	51	17
5	In (1.1 equiv), MeCN (1.5 mL), 100 °C, 48 h	100	35	43
6	In (1.1 equiv), DMF (1.5 mL), 100 °C, 48 h	88	32	12
7	In (1.1 equiv), PhMe (1.5 mL), 100 °C, 48 h	100	29	35
8[d]	In (1.1 equiv), EtOH (1.5 mL), 100 °C, 48 h	100	--	--
9	In (4 equiv), sat. NaBr-H_2O (2 mL), 23 °C, 48 h	100	79	--
10	Zn (4 equiv), sat. NaBr-H_2O (2 mL), 23 °C, 48 h	100	46	--

[a] All the reactions were carried out using 0.2 mmol of aldimine (*R*)-**3d** and 0.25 mmol of bromoester **4**. [b] Conversion is given based on the disappearance of the starting (*R*)-**3d**. [c] Isolated yield after column chromatography (silica gel, hexane/EtOAc) based on the starting aldimine (*R*)-**3d**. [d] Decomposition of the starting aldimine (*R*)-**3d** occurred.

In general, relatively high overall yields of the isolated products **6**, after column chromatography, were obtained (Table 2). Regarding the diastereoselectivity of the nucleophilic addition to the chiral imines, the enantiomeric ratios were determined by chiral HPLC analysis, ranging from 92:8 in the case of the aldimine (*S*)-**3d** derived from benzaldehyde (Table 2,

entry 8) to 68:32 in the case of aldimine (*S*)-**2a** derived from nonanal (Table 2, entry 5). Importantly, it was found that the diastereomeric ratio in amino ester derivatives **5** was the same as the enantiomeric ratio in the corresponding α-methylene-γ-butyrolactams **6** after the first step in the reaction mixtures **5**:**6**. That means that resolution does not take place at any extension during the cyclization process.

In order to determine the configuration of the newly created stereogenic centre in the major diastereoisomer, we found that specific rotation of **6d** {$[\alpha]_D^{22}$ -10 (*c* 0.54, $CHCl_3$)}, which derived from aldimine (*R*)-**3d** matched with that provided in the literature for (*R*)-3-methylene-5-phenylpyrrolidin-2-one {$[\alpha]_D^{26}$ -17 (*c* 1.35, $CHCl_3$)}.[115] After this result, we assume that the nucleophilic attack occurs predominantly to the *Re*-face of the imine unit for R_S-isomers (Table 2, entries 1-4) and to the *Si*-face in the case of S_S-derivatives (Table 2, entries 5-8).

II.1.4.3. Synthesis of enantiopure α-methylene-γ-butyrolactams 6

Considering the reaction conditions depicted on Table 1, entries 9 and 10, not only the yield but the stereoselectivity was considerable much higher in the case of using indium metal instead of zinc, when the allylation was performed in a saturated aqueous sodium bromide solution. A diastereomeric mixture of amino ester derivatives **5d** and **5'd** was obtained in an almost 1:1 ratio with zinc; menawhile diastereoselectivity was 91:9 with indium (Scheme 38). The diastereomeric ratio was easily determined by ^{1}H-NMR analysis of the crude reaction mixture paying attention to the integrals of the *tert*-butyl group and the N-H of the diastereoisomers (the largest chemical shift difference has been always observed for the N-H signal).

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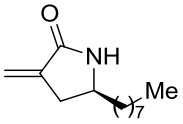
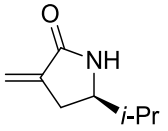
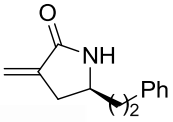
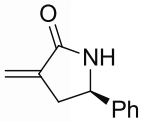
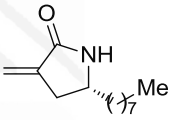
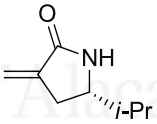
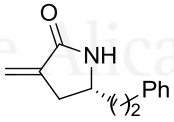
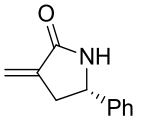
[115] Dembele, Y. A.; Belaud, C.; Villiéras, J. *Tetrahedron: Asymmetry* **1992**, *3*, 511.

Table 2**. Preparation of α-methylene-γ-butyrolactams **6** from aldimines **3

	Aldimines **3**			Butyrolactams **6**[b]				
Entry	No.	R	**5**:**6**[a] ratio	No.	Structure	yield (%)[c]	er[d]	t_{ret} (min)[e]
1	(*R*)-**3a**	$CH_3(CH_2)_7$	1:1	**6a**		74	75:25	16.89
2	(*R*)-**3b**	*i*-Pr	1:5	**6b**		84	81:19	20.26
3	(*R*)-**3c**	$Ph(CH_2)_2$	1:3	**6c**		75	70:30	43.84
4	(*R*)-**3d**	Ph	3:1	**6d**		69	91:9	36.92
5	(*S*)-**3a**	$CH_3(CH_2)_7$	1:1	*ent*-**6a**		72	68:32	11.25
6	(*S*)-**3b**	*i*-Pr	1:5	*ent*-**6b**		79	71:29	14.20
7	(*S*)-**3c**	$Ph(CH_2)_2$	1:3	*ent*-**6c**		73	80:20	12.01
8	(*S*)-**3d**	Ph	3:1	*ent*-**6d**		68	92:8	33.20

[a] Determined by ^{1}H-NMR analysis of the crude reaction mixture. [b] All products were >95% pure (GLC and/or 300 MHz ^{1}H NMR). [c] Isolated yield after column chromatography (silica gel, hexane/EtOAc) based on the starting aldimine **2**. [d] Enantiomeric ratio determined by HPLC using a Chiralcel OD-H column (conditions: hexane/isopropanol, 9:1; 0.5 mL/min). [e] Retention time of the major enantiomer.

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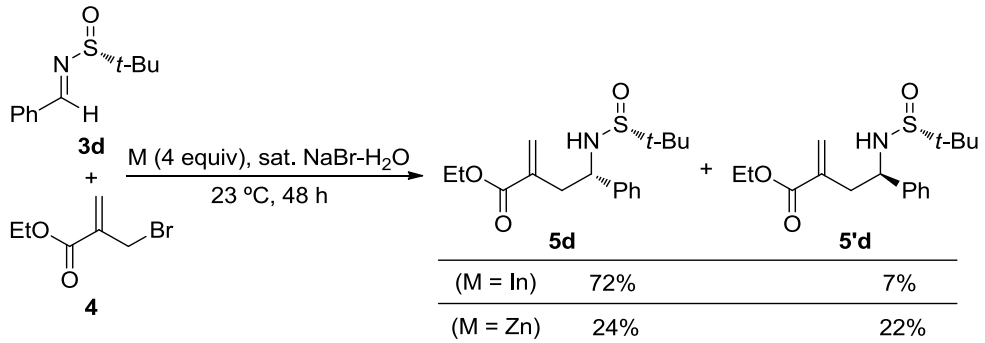
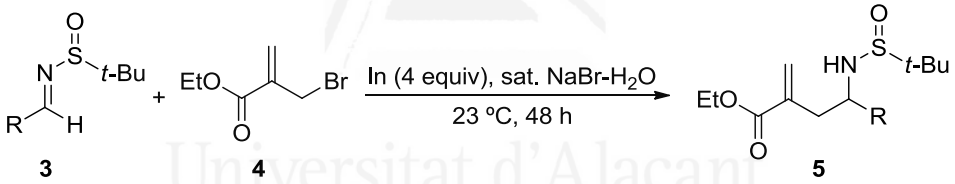


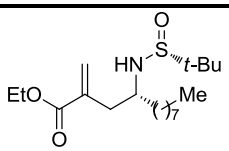
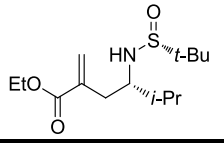
(M = In)	72%	7%
(M = Zn)	24%	22%

Scheme 38.

The reaction of ethyl 2-(bromomethyl)acrylate (**4**) with different chiral *N*-sulfinyl aldimines **3** under the mentioned conditions led to compounds **5** in good yields (Table 3) and diastereomeric ratios ranging between 86:14 and 95:5 (Table 3, entries 2 and 1, respectively). The major diastereomer was easily isolated after column chromatography and fully characterized in all cases.

Table 3**. Preparation of amino ester derivatives **5



	Aldimine **3**		Amino ester **5**[a]			
Entry	No.	R	No.	Structure	Yield(%)[b]	dr[c]
1	(*R*)-**3a**	$CH_3(CH_2)_7$	**5a**		80	95:5
2	(*R*)-**3b**	*i*-Pr	**5b**		73	86:14

[a] All products were >95% pure (GLC and/or 300 MHz ^{1}H-NMR). [b] Isolated yield after column chromatography (silica gel, hexane/EtOAc) based on the starting aldimine **3**. [c] Ratio determined by ^{1}H-NMR analysis of the crude reaction mixture.

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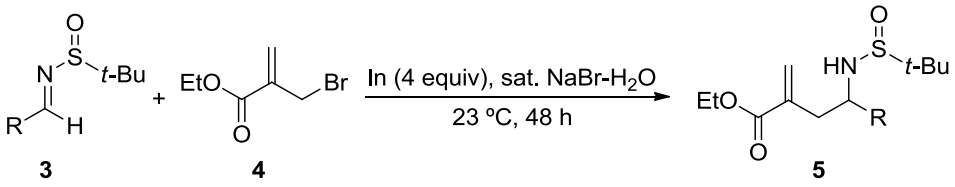
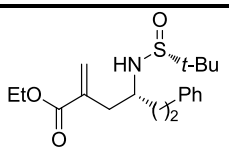
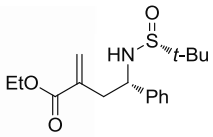
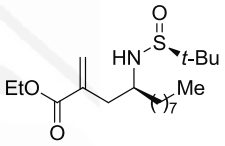
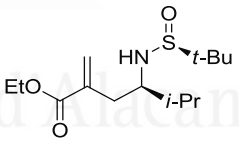
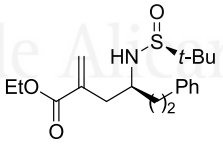
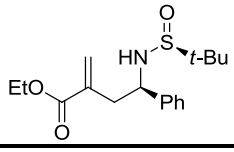
***Table 3**. Preparation of amino ester derivatives **5** (cont.)*



3 **4** **5**

	Aldimine **3**		Amino ester **5**[a]			
Entry	No.	R	No.	Structure	Yield(%)[b]	dr[c]
3	(*R*)-**3c**	$Ph(CH_2)_2$	**5c**		82	93:7
4	(*R*)-**3d**	Ph	**5d**		72	91:9
5	(*S*)-**3a**	$CH_3(CH_2)_7$	*ent*-**5a**		79	89:11
6	(*S*)-**3b**	*i*-Pr	*ent*-**5b**		77	91:9
7	(*S*)-**3c**	$Ph(CH_2)_2$	*ent*-**5c**		77	88:12
8	(*S*)-**3d**	Ph	*ent*-**5d**		75	93:7

[a] All products were >95% pure (GLC and/or 300 MHz ^{1}H-NMR). [b] Isolated yield after column chromatography (silica gel, hexane/EtOAc) based on the starting aldimine **3**. [c] Ratio determined by ^{1}H-NMR analysis of the crude reaction mixture.

Finally, optical pure amino ester derivatives **5** were converted into butyrolactams **6** upon removal of the *tert*-butanesulfinyl group by treatment first with a 4M HCl dioxane solution in methanol and then with sodium

methoxide in methanol until basic pH. Yields were in all cases over 90% and ee≥95% (Table 4).

Regarding the configuration of the newly created stereogenic centre in the major diasteroisomer **5d** (Scheme 38), it was assigned to by *S*, after comparing the specific rotation of *ent*-**6d** {$[\alpha]_D^{23}$ +14 (*c* 0.50, $CHCl_3$)}, which derived from **5d**, with that provided in the literature for (*R*)-3-methylene-5-phenylpyrrolidin-2-one {$[\alpha]_D^{26}$ -17 (*c* 1.35, $CHCl_3$)}.[115] In this case, we assume that the nucleophilic attack occurs predominantly to the *Si*-face of the imine unit for R_S-isomers (Table 3, entries 1-4) and to the *Re*-face in the case of S_S-derivatives (Table 3, entries 5-8).

II.1.4.4. Stereochemical pathway of the nucleophilic addition

Importantly, the nucleophilic addition of the allyl indium intermediates to chiral *N*-*tert*-butanesulfinyl imines **3** occurs, depending on the reaction conditions, through different stereochemical pathways. As previously commented, when the indium promoted allylation of imines **3** was carried out in THF at 100 °C (Scheme 37), the nucleophilic attack occurs predominantly to the *Re*-face of the imine unit for R_S-isomers and to the *Si*-face in the case of S_S-derivatives. This result is consistent with an approach of the nucleophile through an open transition state **TSI** (Figure 1)[116] or a monochelate chair-like model **TSII** (Figure 1).[43,117] To the contrary, if the indium promoted allylation is performed at room temperature in a saturated sodium bromide aqueous solution (Table 3), R_S-isomers underwent attack of the nucleophile to the *Si*-face, and consequently to the *Re*-face for R_S imines **3**. In this case, a six-membered ring model **TSIII** (Figure 1), with a four-membered metallacycle, in which the metal is chelated both by the oxygen and the nitrogen atoms of the imine moiety, could operate. The last one has also been proposed for the indium-promoted allylation of these chiral aldimines with allyl bromide[61] and it led to the opposite configuration as if models **TSI** and **TSII** operate.

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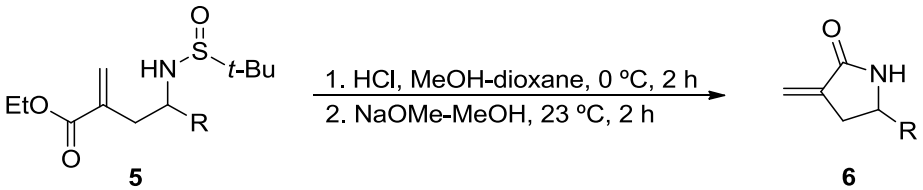
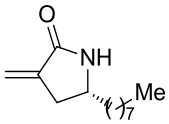
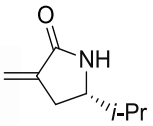
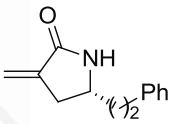
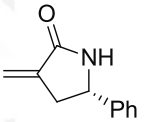
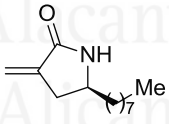
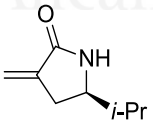
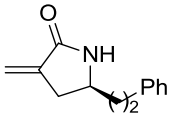
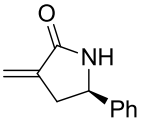
[43] Kolodney, G.; Sklute, G.; Perrone, S.; Knochel, P.; Marek, I. *Angew. Chem. Int. Ed.* **2007**, *46*, 9291.
[61] Foubelo, F.; Yus, M**.** *Tetrahedron: Asymmetry* **2004**, *15*, 3823.
[115] Dembele, Y. A.; Belaud, C.; Villiéras, J. *Tetrahedron: Asymmetry* **1992**, *3*, 511.
[116] Ferreira, F.; Botuha, C.; Chemla, F.; Pérez-Luna, A. *Chem. Soc. Rev.* **2009**, *38*, 1162.
[117] Marek, I. *Chem. Eur. J.* **2008**, *14*, 7460.

Table 4**. Preparation of α-methylene-γ-butyrolactams **6** from amino esters **5



5 **6**

	Amino ester **5**		Butyrolactam **6**[a,b]		
Entry	No.	R	No.	Structure	Yield (%)[c]
1	**5a**	$CH_3(CH_2)_7$	*ent*-**6a**		92
2	**5b**	*i*-Pr	*ent*-**6b**		91
3	**5c**	$Ph(CH_2)_2$	*ent*-**6c**		94
4	**5d**	Ph	*ent*-**6d**		93
5	*ent*-**5a**	$CH_3(CH_2)_7$	**6a**		93
6	*ent*-**5b**	*i*-Pr	**6b**		90
7	*ent*-**5c**	$Ph(CH_2)_2$	**6c**		95
8	*ent*-**5d**	Ph	**6d**		92

[a] All products were >95% pure (GLC and/or 300 MHz ^{1}H-NMR). [b] ee≥95%, as determined by HPLC using a Chiralcel OD-H column (condidtions: hexane/isopropanol, 9:1; 0.5 mL/min). [c] Isolated yield after column chromatography (silica gel, hexane/EtOAc) based on the starting amino ester **5**.

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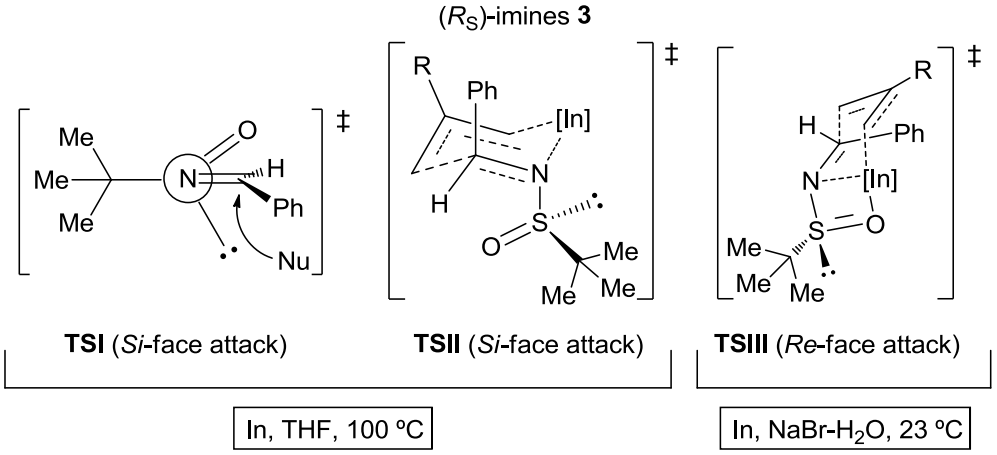


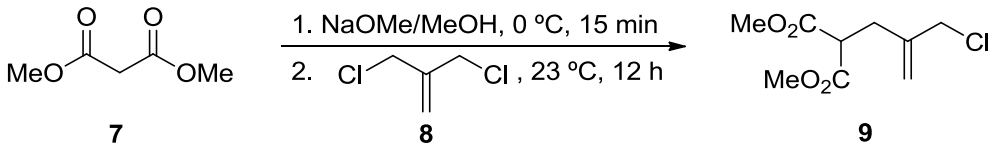
Figure 1.

Compairing, the two previous described methodologies for the synthesis of α-methylene-γ-butyrolactams **6**, the indium mediated allylation in a saturated sodium bromide aqueous solution seems to be superior to the process in THF at high temperature, in terms of optical purity of the final reaction products. However, the need of a large excess of indium metal (4 *vs.* 1.1 equivalents) represents a major drawback for this strategy.

II.1.5. Reaction with dimethyl 2-[2-(chloromethyl)allyl]malonate (9)

II.1.5.1. Synthesis of dimethyl 2-[2-(chloromethyl)allyl]malonate (9)

Starting allylic halide dimethyl 2-[2-(chloromethyl)allyl]malonate **9** was easily prepared by alkylation of the enolate of dimethyl malonate (**7**) with commercially available 3-chloro-2-(chloromethyl)prop-1-ene (**8**). The enolate was generated by deprotonation of dimethyl malonate (**7**) with sodium methoxide in methanol. The monoalkylated reaction product **9** was isolated in 37% yield after column chromatography (Scheme 39), the product of double alkylation being also obtained in a large extension (27%).



Scheme 39.

II.1.5.2. Optimization of the reaction conditions

In order to know the best reaction conditions for the indium-promoted allylation of *N*-*tert*-butylsulfinyl aldimines **3** with dimethyl 2-[2-(chloromethyl)allyl]malonate (**9**), we took also aldimine (*R*)-**3d**, derived from benzaldehyde and (*R*)-*tert*-butanesulfinamide [(*R*)-**1**], as the imine model. The reaction did not take place using 1.3 equivalents of indium and 1.5 equivalents of the allylic chloride **9** in THF at 60 °C for 72 hours (Table 5, entry 1), which are the standard reaction conditions for the allylation of this type of imines with allyl bromide. The allylation did not also take place at 100 °C in a high pressure flask (Table 5, entry 2).

A promising result was obtained when the reaction was performed in the absence of any solvent but using 3 equivalents of allylic chloride **9** at 23 °C, allylated product **10d** being isolated in 12% yield after column chromatography (Table 5, entry 3).

Under similar reaction conditions, we tried to improve the yield by adding 2 equivalents of potassium iodide, in order to facilitate the formation of the allylindium intermediate (chlorine-iodine exchange would lead to a more reactive allylic iodide), however, we obtained the expected product **10d** in just 8% yield (Table 5, entry 4).

Fortunately, compound **10d** was isolated in 75% yield by simply switching from potassium to sodium iodide under almost identical reactions conditions (Table 5, entry 5).

Finally, yield was not improved when the reaction was carried out in a saturated aqueous sodium bromide solution in the presence of 4 equivalents of indium and 2 equivalents of allylic chloride **9** at room temperature for 72 hours, compound **10d** being now isolated in 22% yield (Table 5, entry 6). Regarding the stereoselectivity of the process, surprisingly, a single diastereoisomer was observed by ^{1}H-NMR analysis of the crude reaction mixture in all cases.

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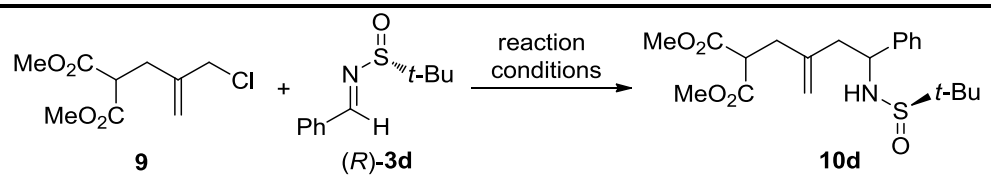
***Table 5**. Optimization of the reaction conditions*



Entry	Reaction conditions[a]	**10d** (%)[b]
1	**9** (1.5 equiv), In (1.3 equiv), THF (3 mL), 60 °C, 72 h	0
2	**9** (1.5 equiv), In (1.3 equiv), THF (3 mL), 100 °C, 72 h	0
3	**9** (3 equiv), In (1.3 equiv), 23 °C, 72 h	12
4	**9** (3 equiv), In (1.3 equiv), KI (2 equiv), 23 °C, 12 h	8
5	**9** (3 equiv), In (1.3 equiv), NaI (2 equiv), 23 °C, 72 h	75
6	**9** (3 equiv), In (4 equiv), saturated NaBr-H_2O (5 mL), 23 °C, 72 h	22[c]

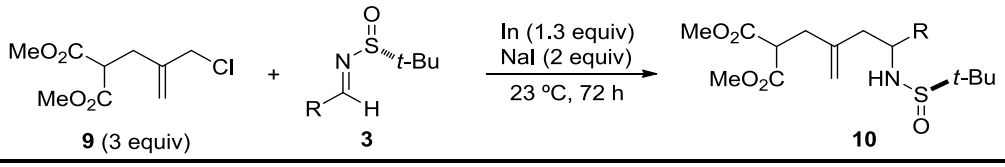
[a] All the reactions were carried out using 0.2 mmol of aldimine (*R*)-**3d**. [b] Isolated yield after column chromatography (silica gel, hexane/EtOAc) based on the starting aldimine (*R*)-**3d**. [c] Partial decomposition of the starting aldimine (*R*)-**3d** occurred.

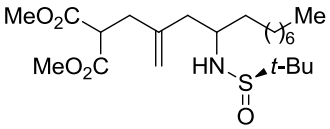
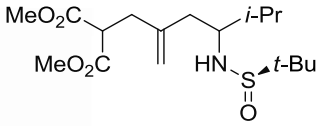
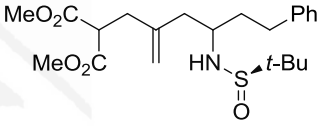
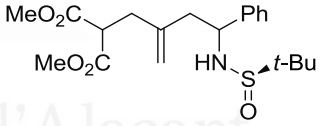
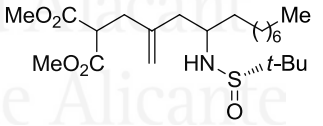
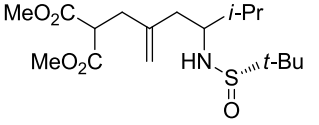
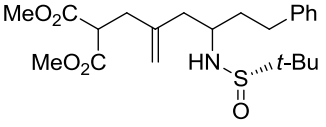
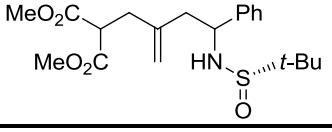
II.1.5.3. Synthesis of ε-amino ester derivatives 10

The reaction of dimethyl 2-[2-(chloromethyl)allyl]malonate (**9**) with different chiral *N*-sulfinyl aldimines **3** under the optimized conditions (Table 5, entry 5) led to compounds **10** in good yields (Table 6) and excellent diastereoselectivities (a single stereoisomer was always isolated).

The highest yield was obtained with aldimine (*R*)-**3c** derived from 3-phenylpropanal (Table 6, entries 3 and 7). As it was expected, [α] values regarding the optical rotation of amino ester derivatives **10** showed opposite sign for each enantiomer.

Table 6**. Preparation of amino ester derivatives **10



	Aldimine **3**		Amino ester **10**[a]		
Entry	No.	R	No.	Structure	Yield (%)[b]
1	(*R*)-**3a**	$CH_3(CH_2)_7$	**10a**		87
2	(*R*)-**3b**	*i*-Pr	**10b**		87
3	(*R*)-**3c**	$Ph(CH_2)_2$	**10c**		90
4	(*R*)-**3d**	Ph	**10d**		71
5	(*S*)-**3a**	$CH_3(CH_2)_7$	*ent*-**10a**		77
6	(*S*)-**3b**	*i*-Pr	*ent*-**10b**		75
7	(*S*)-**3c**	$Ph(CH_2)_2$	*ent*-**10c**		82
8	(*S*)-**3d**	Ph	*ent*-**10d**		72

[a] All products were >95% pure (GLC and/or 300 MHz ^{1}H-NMR). [b] Isolated yield after column chromatography (silica gel, hexane/EtOAc) based on the starting aldimine **3**.

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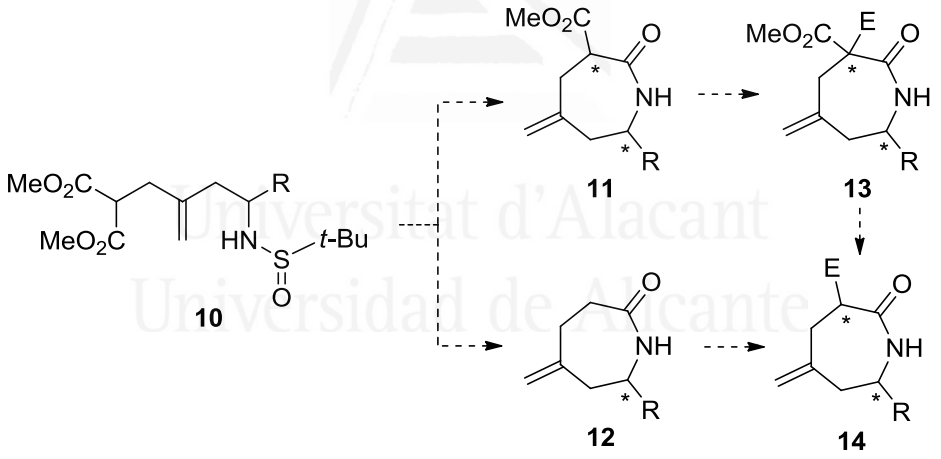
The configuration of the newly created stereogenic centre was not yet assigned. In general, two different models have been proposed in order to explain the stereochemical outcome of the addition of allylic nucleophiles, in our case, an allylindium sesquihalide intermediate (Scheme 35), to *N*-*tert*-butanesulfinyl aldimines **3**: an open transition state **TSI** (Figure 1) and a six-membered ring chelation control model **TSII** (Figure 1). Opposite configurations are obtained depending on the operating mechanism. Based on our experience, we think that allylation of the imines would take place through a cyclic transition state of type **TSII** and the nucleophilic attack would occur to the *Si*-face of the imine unit for R_S-isomers (Table 6, entries 1-4) and to the *Re*-face in the case of S_S-derivatives (Table 6, entries 5-8).

II.1.5.4. Synthetic applications of ε-amino ester derivatives 10

Enantiomerically pure amino ester derivatives **10** are of interest because they could be easily transformed into substituted-5-methyleneazepan-2-ones **11**-**14** (Scheme 40). Work in this area is under progress and will be reported in the future in due course.



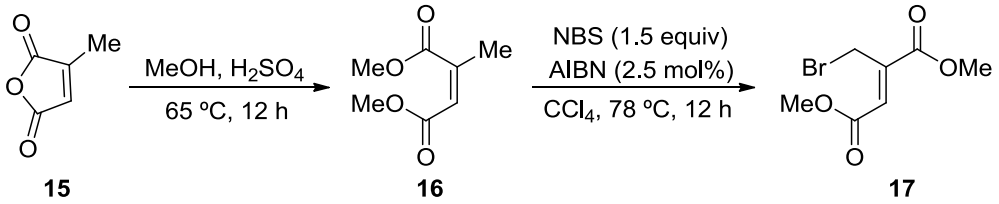
Scheme 40.

II.1.6. Reaction with dimethyl 2-bromomethylfumarate (17) and (*E*)-methyl 4-bromocrotonate (18)

II.1.6.1. Synthesis of Dimethyl 2-Bromomethylfumarate (17)

We also studied the reaction of *N*-*tert*-butanesulfinyl imines **3** with easily accessible dimethyl 2-bromomethylfumarate (**17**) and commercially available (*E*)-methyl 4-bromocrotonate (**18**). Allylic bromide **17** was prepared from citraconic anhydride (**15**) through a two-step procedure in a 71% overall

yield: first treatment with sulphuric acid in methanol under reflux to give dimethyl methylmaleate **16**, followed by smooth allylic bromination of **16** with simultaneous isomerization of the double bond upon reaction with *N*-bromosuccinimide (NBS) in the presence of a catalytic amount of azo-bis-isobutyronitrile (AIBN, Scheme 41).[118]

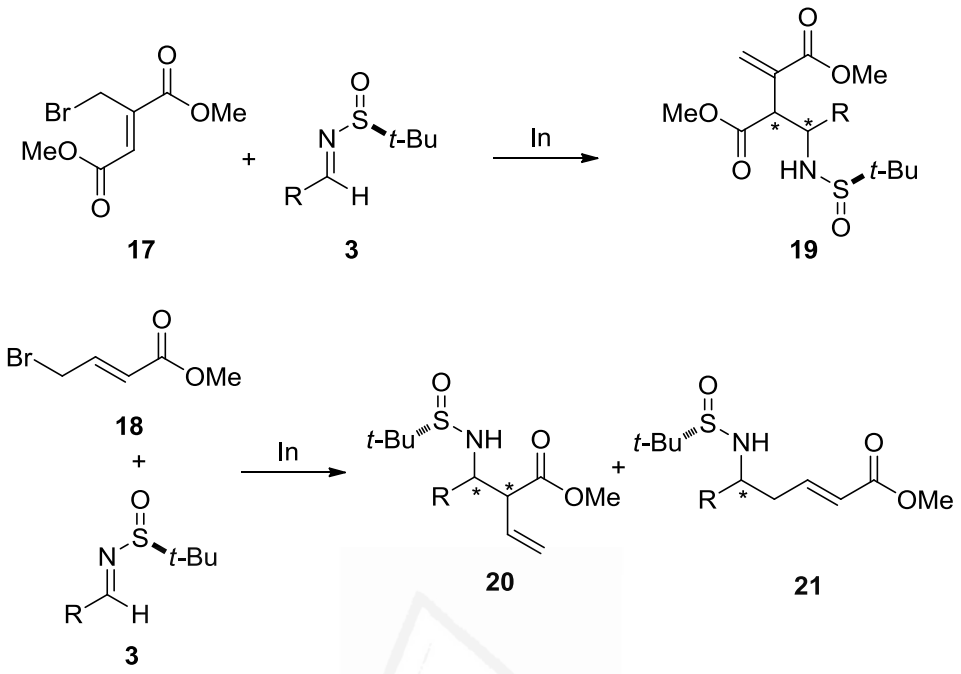


Scheme 41.

II.1.6.2. Optimization of the reaction conditions

Unfortunatelly, indium mediated addition of allylic bromides **17** and **18** to *N*-*tert*-butanesulfinyl imines **3** led always to a mixture of reaction products, independently on the applied reaction conditions (solvent, stoichiometry, temperature, reaction time, etc.). In spite of the structurally interesting potential reaction products, we could not find reaction conditions that allow us to produce selectively a major isomer. For instance, the reaction of dimethyl 2-bromomethylfumarate (**17**) with chiral imines **3** took place in a regioselective fashion, leading to a mixture of diastereoisomers **19** which could not be purified (Scheme 42). On the other hand, in the case of (*E*)-methyl 4-bromocrotonate (**18**), regioisomers **20** and **21** were always isolated. Branched regioisomers **20** were obtained as a complex mixture of stereoisomers, due to *syn*:*anti* relative configuration and poor face selectivity. In general, regioisomers **20** were predominant in the reaction mixture, but in the case of chiral imine derived from isobutyraldehyde **3b**, due probably to the bulkyness of the R group (Scheme 42).

[118] Kar, A.; Argade, N. P. *J. Org. Chem.* **2002**, *67*, 7131.

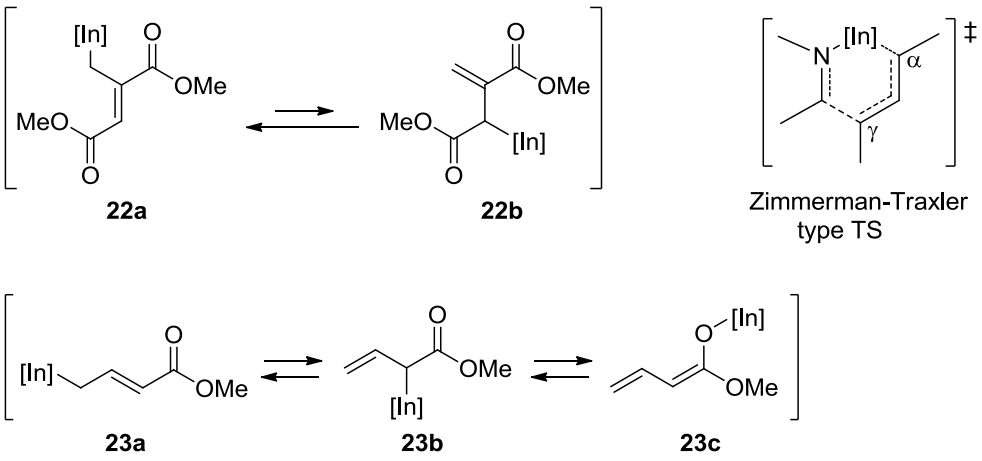


Scheme 42.

II.1.6.3. Regiochemistry in the reaction of dimethyl 2-bromomethylfumarate (17) and (*E*)-methyl 4-bromocrotonate (18)

The structure of the allyl indium intermediate determines the regiochemistry of the allylation.[119] It has been proposed that a Zimmerman–Traxler type transition state (Scheme 43) operates in the Barbier-type allylation involving a γ-substituted allyl indium intermediate,[120] taking always place a γ-addition instead of an α-addition. Thus, allyl indium species **22a** seems to be formed in the reaction of dimethyl 2-bromomethylfumarate (**17**), since regioisomers **19** are the reaction products, meanwhile for (*E*)-methyl 4-bromocrotonate (**18**), intermediates **23** could be involved (Scheme 43).

[119] Yasuda, M.; Haga, M.; Nagaoka, Y.; Baba, A. *Eur. J. Org. Chem.* **2010**, 5359.
[120] Capps, S. M.; Lloyd-Jones, G. C.; Murray, M.; Peakman, T. M. *Tetrahedron Lett.* **1998**, *39*, 2853.



Scheme 43.

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II.2. Base-induced reaction of *N*-*tert*-butanesulfinyl imines 3 with compounds with acidic hydrogens

II.2.1. Objetives

At this point, we decide to study the addition to *N*-*tert*-butanesuldinyl imines **3** of other carbon nucleophiles different than allyl indium species. Dimethyl malonate and nitromethane were chosen as precursors of such as nucleophiles, due to their easy deprotonation under mild reaction conditions. We specially will pay attention to the stereochemical pathway of the processes and to further synthetic application of the resulting reaction products, as in the previous chapter.

II.2.2. Diastereoselective coupling of *N*-*tert*-butanesulfinyl imines (3) and dimethyl malonate (7)

II.2.2.1. Introduction

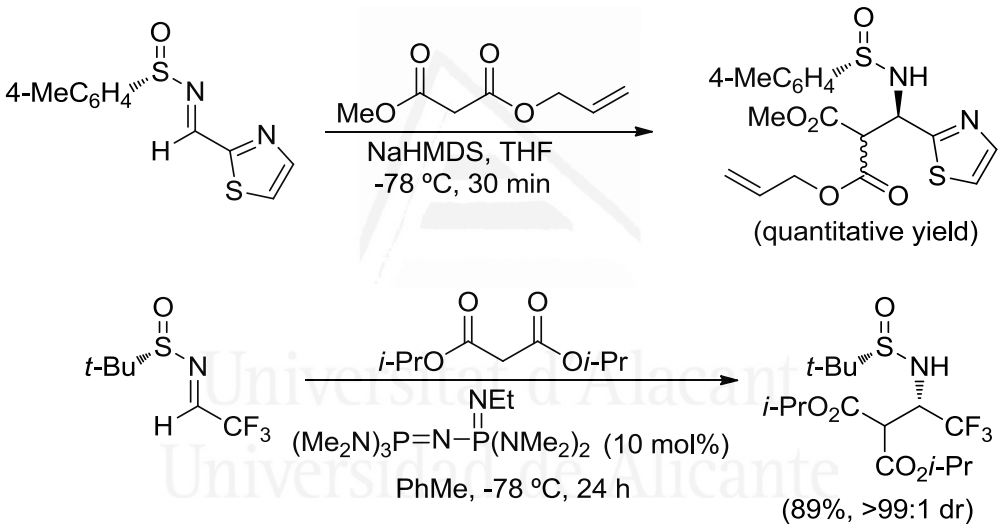
One of the most direct and reliable methods for the synthesis of enantioenriched amine derivatives is the stereoselective addition of an organometallic reagent to the C=N bond of an imine.[12,121] Significant achievements have been reached in the condensation of enolyzable carbonyl compounds and imines catalyzed by chiral organic and organometallic reagents.[122] The resulting β-aminocarbonyl compounds, the so called Mannich adducts, are versatile intermediates that could be easily transformed into a wide range of interesting multifunctionalized molecules, as for instance, β-aminoesters which are direct precursors of β-lactams.[123]

A different strategy, leading to the Mannich adducts in a stereoselective fashion, consists in the use of chiral imines as electrophiles, and among them, *N*-*tert*-butanesulfinyl imines **3**. Nucleophilic additions of organometallic reagents used to take place in high diastereoselectivities because the *tert*-butanesulfinyl group is capable of metal coordination. Thus, the reaction of ester enolates with *N*-*tert*-butanesulfinyl imines **3** produced β-aminoesters.

---

[12] Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541.
[121] For reviews, see: (a) Vilaivan, T.; Bhanthumnavin, W.; Sritana-Anant, Y. *Curr. Org. Chem.* **2005**, *9*, 1315. (b) Petrini, M.; Torregiani, E. *Synthesis* **2007**, 159.
[122] For reviews, see: (a) Greco, S. J.; Lacerda, V.; dos Santos, R. B. *Aldrichimica Acta* **2011**, *44*, 15. (b) Bernardi, L.; Ricci, A.; Franchini, M. C. *Curr. Org. Chem.* **2011**, *15*, 2210. (c) Han, B.; Li, J. L.; Xiao, Y. C.; Zhou, S. L.; Chen, Y. C. *Curr. Org. Chem.* **2011**, *15*, 4128. (d) Merino, P.; Tejero, T. *Synthesis* **2011**, 1965.
[123] For a review, see: Myrboh, B.; Laloo, B. M.; Mizar, P. *Curr. Org. Chem.* **2011**, *15*, 647.

The highest yields and diastereoselectivities were achieved by using ester titanium enolates at -78 °C in THF.[124] The Reformatsky addition of unsubstituted acetate enolates allowed also access to these compounds under milder reaction conditions (0 °C or room temperature).[125] Considering enolates derived from malonates, as far as we know, there are only two examples of nucleophilic addition to chiral *N*-sulfinyl imines: the reaction of allyl methyl malonate with *p*-toluenesulfinyl imine derived from 2-formylthiazole which Sunazuka and Omura used in one step of the synthesis of antibiotic bottromycin A_2,[126] and the organic base-catalyzed reaction of (*S*)-*N*-*tert*-butanesulfinyl (3,3,3)-trifluoroacetaldimine with dialkyl malonates (Scheme 44).[127] Because of our interest in enolate addition to chiral *N*-*tert*-butanesulfinyl imines **3**,[110,128] we report here the base mediated condensation of these imines with dimethyl malonate (**7**).



Scheme 44.

[110] González-Gómez, J. C.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2009**, *74*, 2547.
[124] (a) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12. (b) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **2002**, *67*, 7819.
[125] (a) Staas, D. D.; Savage, K. L.; Homnick, C. F.; Tsou, N. N.; Ball, R. G. *J. Org. Chem.* **2002**, *67*, 8276. (b) Brinner, K.; Doughan, B.; Poon, D. J. *Synlett* **2009**, 991. (c) Concellon, J. M.; Rodriguez-Solla, H.; Simal, C. *Adv. Synth. Catal.* **2009**, *351*, 1238. (d) Girgis, M. J.; Liang, J. K.; Du, Z.; Slade, J.; Prasad, K. *Org. Process Res. Dev.* **2009**, *13*, 1094.
[126] Shimamura, H.; Gouda, H.; Nagai, K.; Hirose, T.; Ichioka, M.; Furuya, Y.; Kobayashi, Y.; Hirono, S.; Sunazuka, T.; Omura, S. *Angew. Chem. Int. Ed.* **2009**, *48*, 914.
[127] Shibata, N.; Nishimine, T.; Shibata, N.; Tokunaga, E.; Kawada, K.; Kagawa, T.; Sorochinsky, A. E.; Soloshonok, V. A. *Chem. Commun.* **2012**, *48*, 4124.
[128] (a) González-Gómez, J. C.; Foubelo, F.; Yus, M. *Tetrahedron Lett.* **2008**, *49*, 2343. (b) González-Gómez, J. C.; Foubelo, F.; Yus, M. *Synthesis* **2009**, 2083.

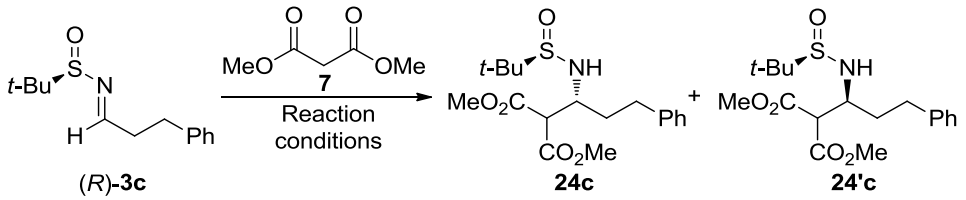
II.2.2.2. Optimization of the reaction conditions

Compound (*R*)-**3c**, derived from 3-phenylpropanal and (*R*)-*tert*-butanesulfinamide [(*R*)-**1**], was taken as the imine model for the optimization of the reaction conditions in the base promoted coupling reaction of dimethyl malonate (**7**) and *tert*-butanesulfinyl imines **3**. Many assays were undertaken and the most significant ones are reported on Table 7.

A good conversion (68%) but a relativety poor diastereoselectivity (32:68) were obtained in the reaction of imine (*R*)-**3c** (1 M) with 2 equivalents of dimethyl malonate (**7**) in the presence of 1.5 equivalents of sodium methoxide in methanol (1 M) in THF as solvent at 0 °C for 12 hours (Table 7, entry 1). A similar result was obtained using 1.5 equivalents of sodium hydroxide as a base, but in this case, performing the reaction at room temperature for 72 hours (Table 7, entry 2). Fortunately, conversion and diastereselectivity were slightly improved when a stronger base, such as potassium *tert*-butoxide, was used under the same reaction conditions (Table 7, entry 3). The reaction with 2 equivalents of sodium bicarbonate in THF at room temperature led to a lesser conversion (39%) but, surprisingly, to a significantly higher and opposite diastereselectivity (91:9, Table 7, entry 4). It seems that the nucleophilic addition of dimethyl malonate (**7**) to chiral *tert*-butanesulfinyl imines **3** follows different stereochemical pathways, depending on the base. A better result (90% conversion) was obtained when the reaction was performed in the absence of any solvent but using 4 equivalents of dimethyl malonate (**7**). Importantly, a single diastereoisomer **24c** was isolated as reaction product (Table 7, entry 5). Switching from sodium to potassium bicarbonate as a base did not lead to a better result (slightly higher conversion, but poorer diastereoselectivity, Table 7, entry 6), as in the case of using triethylamine (Table 7, entry 7). Sodium iodide has recently been used successfully as a base in the condensation of compounds with acidic hydrogens, such as bromonitromethane, with imines,[106,129] and identical results were obtained when 1 equivalent of sodium iodide was used instead of sodium bicarbonate (Table 7, compare entries 5 and 8). In these heterogeneous reactions, conversion was not improved using 3 equivalents of sodium iodide (Table 7, entry 9). Finally, potassium iodide was not as effective as a base as the sodium salt to perform this coupling reaction (Table 7, entry 10).

[106] Rodríguez-Solla, H.; Concellón, C.; Alvarado, N.; Soengas, R. G. *Tetrahedron* **2012**, *68*, 1736.
[129] Concellón, J. M.; Rodríguez-Solla, H.; Concellón, C.; García-Granda, S.; Díaz, M. R. *Org. Lett.* **2006**, *8*, 5979.

***Table 7**. Optimization of the reaction conditions*



Entry	Reaction conditions[a]	Conversion (%)[b]	**24c**:**24'c** ratio[c]
1	**7** (2 equiv), 1 M NaOMe/MeOH (1.5 equiv), THF (2 mL), 0 °C, 12 h	68	32:68
2	**7** (2 equiv), NaOH (1.5 equiv), THF (2 mL), 23 °C, 72 h	69	28:72
3	**7** (2 equiv), KO*t*-Bu (1.5 equiv), THF (2 mL), 23 °C, 72 h	77	17:83
4	**7** (2 equiv), $NaHCO_3$ (2 equiv), THF (2 mL), 23 °C, 72 h	39	91:9
5	**7** (4 equiv), $NaHCO_3$ (2 equiv), 23 °C, 72 h	90	99:1
6	**7** (4 equiv), $KHCO_3$ (2 equiv), 23 °C, 72 h	93	75:25
7	**7** (2 equiv), Et_3N (2 equiv), 23 °C, 72 h	15	--
8	**7** (2 equiv), NaI (1 equiv), 23 °C, 72 h	90	99:1
9	**7** (2 equiv), NaI (3 equiv), 23 °C, 72 h	88	99:1
10	**7** (2 equiv), KI (1 equiv), 23 °C, 72 h	5	--

[a] All the reactions were carried out using 0.2 mmol of aldimine (*R*)-**3c**. [b] Conversion is given based on the disappearance of the starting (*R*)-**3c** by ^{1}H-NMR. [c] Diastereomeric ratio was determined by ^{1}H-NMR.

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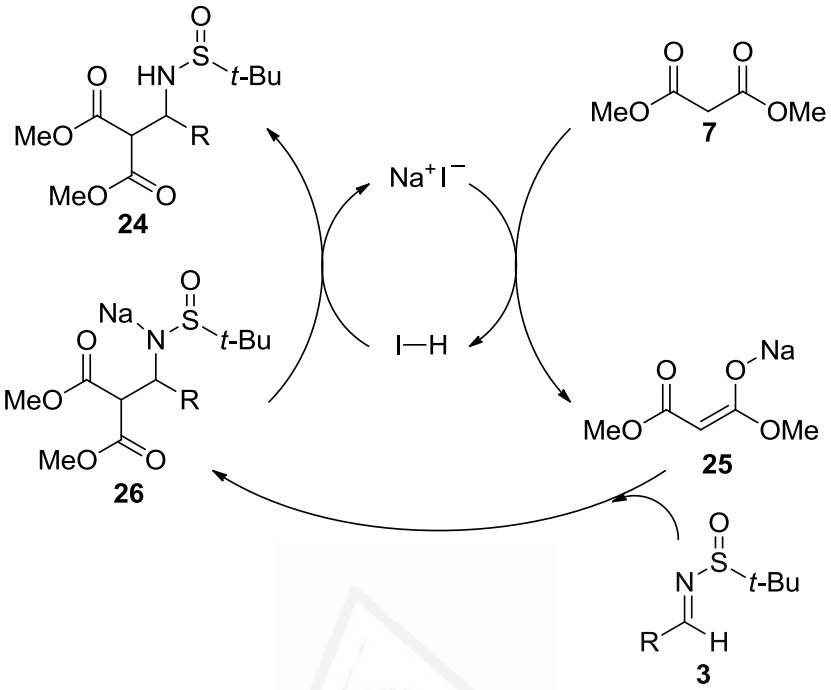
The reaction under the influence of sodium iodide took place due to the high acidity of dimethyl malonate (**7**) and, on the other hand, taking into account that although the iodide is a very weak base in an aqueous medium, in THF could be sufficiently strong to abstract an acidic hydrogen from dimethyl malonate (**7**). Thus, an acid-base reaction of dimethyl malonate (**7**) with the iodide anion could generate sodium malonate enolate (**25**) that could react with aldimines **3** to afford the amides **26**, which after protonolysis with the in situ generated hydrogen iodide would generate the obtained reaction product **24**, releasing the iodide anion that would continue the catalytic system (Scheme 45).



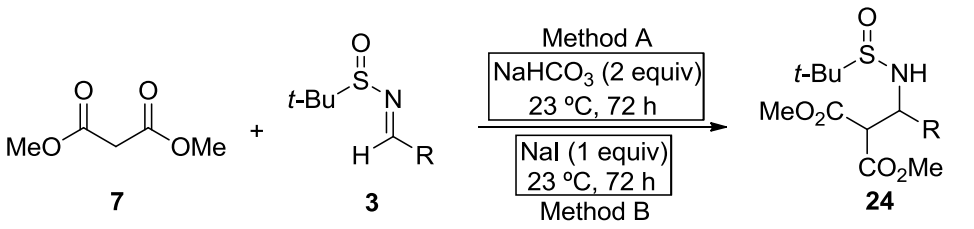
Scheme 45.

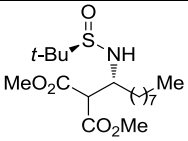
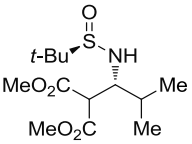
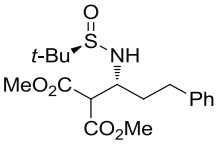
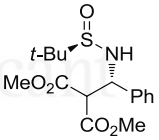
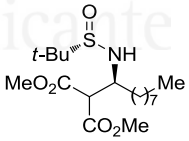
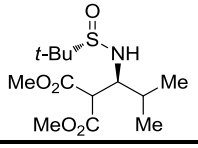
II.2.2.3. Synthesis of enantioenriched β-amino esters derivatives 24

We studied next the coupling reaction of different *N*-*tert*-butanesulfinyl imines **3** with dimethyl malonate (**7**) by applying the optimized conditions depicted in Table 7, entries 5 (Method A) and 8 (Method B). The expected 2-(1-aminoalkyl)malonates **24** were obtained in moderate to good yields as a single diastereoisomer in all cases (Table 8) but for aldimine **3d** derived from benzaldehyde. Compound **24d** was isolated in only 7% yield using sodium bicarbonate as a base (Table 8, entry 7) and was not detected nor isolated performing the reaction in the presence of sodium iodide (Table 2, entry 8). In these two cases, the starting aldimine (*R*)-**3d** was the major component of the reaction mixture. Mannich-coupling reaction did not also occur with aromatic aldimines **3g** and **3h**, derived from *p*-nitro- and *p*-hydroxybenzaldehyde, respectively. It has been previously reported that *N*-sulfonyl imines derived from benzaldehyde react with dialkyl malonates al low temperature, but easily undergo a retro-Mannich processes when standing at room temperature under basic conditions[130] as in Methods A and B. In general, Method B led to slightly higher yields than Method A (Table 8, entries 1-8).

[130] Wang, H. F.; Yang, T.; Xu, P. F.; Dixon, D. J. *Chem. Commun.* **2009**, 3916.

Table 8**. Preparation of 2-(1-aminoalkyl)malonates **24



	Aldimine **3**			2-(1-Aminoalkyl)malonates **24**[b]		
Entry	No.	R	Method[a]	No.	Structure	Yield (%)[c]
1	(*R*)-**3a**	$CH_3(CH_2)_7$	A	**24a**		74
2	(*R*)-**3a**	$CH_3(CH_2)_7$	B	**24a**		86
3	(*R*)-**3b**	*i*-Pr	A	**24b**		43
4	(*R*)-**3b**	*i*-Pr	B	**24b**		60
5	(*R*)-**3c**	$Ph(CH_2)_2$	A	**24c**		77
6	(*R*)-**3c**	$Ph(CH_2)_2$	B	**24c**		86
7	(*R*)-**3d**	Ph	A	**24d**		7
8	(*R*)-**3d**	Ph	B	**24d**		--
9	(*S*)-**3a**	$CH_3(CH_2)_7$	A	*ent*-**24a**		78
10	(*S*)-**3b**	*i*-Pr	A	*ent*-**24b**		47

[a] Method A: 4 equivalents of **7** were used; Method B: 2 equivalents of **7** were used. [b] All products were >95% pure (GLC and/or 300 MHz ^{1}H-NMR). [c] Isolated yield after column chromatography (silica gel, hexane/EtOAc) based on the starting aldimine **3**.

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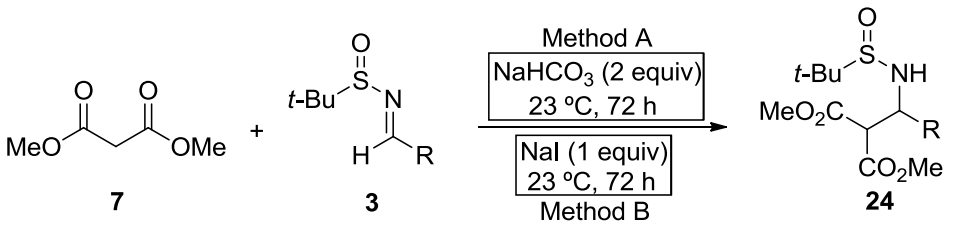
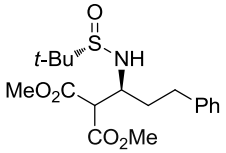
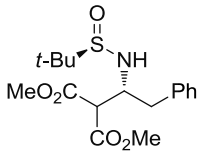
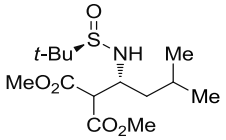
***Table 8**. Preparation of 2-(1-aminoalkyl)malonates **24** (cont.)*



	Aldimine **3**			2-(1-Aminoalkyl)malonates **24**[b]		
Entry	No.	R	Method[a]	No.	Structure	Yield (%)[c]
11	(*S*)-**3c**	$Ph(CH_2)_2$	A	*ent*-**24c**		82
12	(*R*)-**3e**	$PhCH_2$	B	**24e**		78
13	(*R*)-**3f**	*i*-Bu	B	**24f**		77

[a] Method A: 4 equivalents of **7** were used; Method B: 2 equivalents of **7** were used. [b] All products were >95% pure (GLC and/or 300 MHz ^{1}H-NMR). [c] Isolated yield after column chromatography (silica gel, hexane/EtOAc) based on the starting aldimine **3**.

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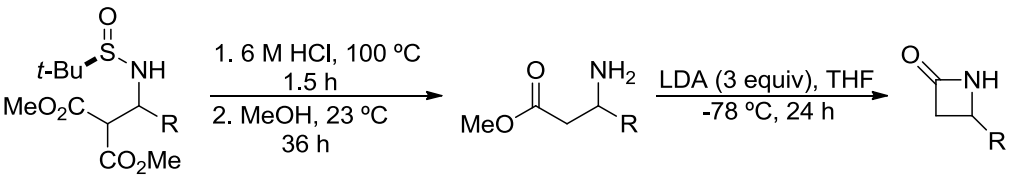
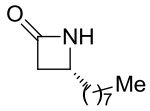
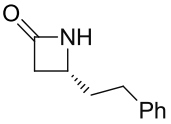
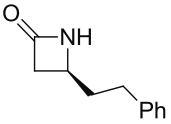
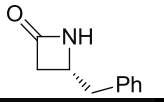
II.2.2.4. Synthesis of β-lactams 28

In order to prove the utility of the obtained 2-(1-aminoalkyl)malonates **24**, some of them were transformed first into the corresponding β-aminoester **27** and them to the β-lactam **28** in high optical purity, the same than the starting Mannich products **24**. Acid hydrolysis was performed with 6 M hydrochloric acid under reflux. The expected β-amino esters **27** were obtained in high yields (Table 9) that no further purification for the next step was needed. Intramolecular cyclization of β-aminoesters **27** was achieved upon treatment with an excess of LDA at -78 °C, leading to the expected β-lactam **28** in moderate yields in all cases (Table 9).

Table 9**. Preparation of β–amino esters **27** and β–lactams **28



24 **27** **28**

	Compound	β-Amino ester **27**		β-Lactam **28**		
Entry	**24**	No.	Yield (%)[a]	No.	Structure	Yield (%)[b]
1	**24a**	**27a**	91	**28a**		45
2	**24c**	**27c**	82	**28c**		58
3	*ent*-**24c**	*ent*-**27c**	83	*ent*-**28c**		53
4	**24e**	**27e**	81	**28e**		43

[a] Isolated yield based on the starting 2-(1-aminoalkyl)malonates **24**. [b] Isolated yield after column chromatography (silica gel, hexane/EtOAc) based on the starting amino ester **27**.

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II.2.2.5. Stereochemical pathway of the nucleophilic addition

The configuration of the newly created stereogenic centre in 2-(1-aminoalkyl)malonates **24** was determined by comparing the specific rotation of **28c** {$[\alpha]_D^{23}$ +11 (*c* 1.35, $CHCl_3$)}, which derived from **24c**, with that provided in the literature for (*R*)-4-(2-phenylethyl)azetidin-2-one {$[\alpha]_D^{25}$ +19 (*c* 0.21, $CHCl_3$)}.[131] This experimental result could be explained considering that a six-membered ring model **TSIV** (Figure 2), with a four-membered metallacycle, in which the metal is chelated both by the oxygen and the nitrogen atoms of the imine moiety, would be involved. Thus, we assume that the nucleophilic attack occurs to the *Si*-face of the imine unit for R_S-isomers (Table 8, entries 1-8, 12 and 13) and to the *Re*-face in the case of S_S-derivatives (Table 8, entries 9-11). As previously commented, the stereochemical pathway under the solvent free

[131] Tasnádi, G.; Forró, E.; Fülöp, F. *Tetrahedron: Asymmetry* **2007**, *18*, 2841.

reaction conditions in Methods A and B is the opposite to that obtained when the reaction is performed in THF (Table 7, entries 1-3). This result is consistent with an approach of the malonate to the less hindered face of C=N in a s-*cis* like conformation through a non-chelated transition state model **TSV** (Figure 2). In this case, the less hindered face for R_S-isomers is the *Re*-face.

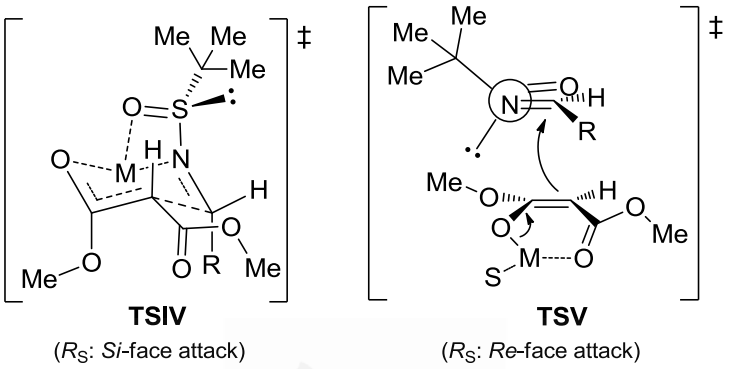


Figure 2.

II.2.3. Diastereoselective coupling of *N-tert*-butanesulfinyl imines (3) and nitromethane (29)

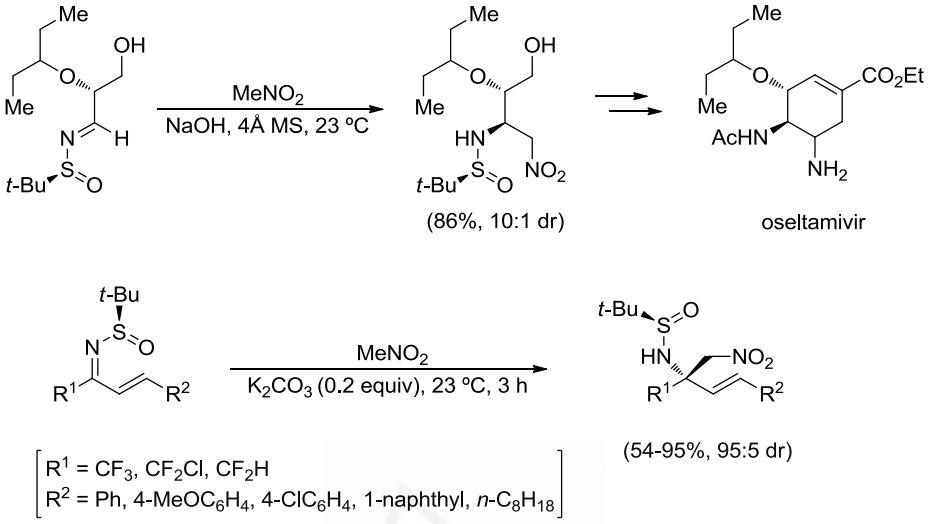
II.2.3.1. Introduction

The reaction of nitroalkanes with imines under basic conditions leads to the formation of β-nitroamines which are useful synthetic building blocks. For that reason, the development of new chiral non-racemic catalysts to promote the production of enantiomerically pure β-nitroamines has been a challenging task. In 2005, García Ruano reported the asymmetric aza-Henry reaction of *N-p*-toluenesulfinyl imines, in which excellent yield and selectivity were achieved.[132] However, to our best knowledge, there is only one report involving the aza-Henry reaction of *N-tert*butanesulfinyl aldimine in one step of the synthesis of antiviral oseltamivir by the group of G. Lu (Scheme 46).[133] More recently, Liu reported on the aza-Henry reaction of chiral fluoroalkyl α,β-

[132] (a) García Ruano, J. L.; Topp, M.; López-Cantarero, J.; Alemán, J.; Remuiñán, M. J.; Cid, M. B. *Org. Lett.* **2005**, *7*, 4407. (b) García Ruano, J. L.; López-Cantarero, J.; De Haro, T.; Alemán, J.; Cid, M. B. *Tetrahedron* **2006**, *62*, 12197.

[133] Weng, J.; Li, Y.-B.; Wang, R.-B.; Li, F.-Q.; Liu, C.; Chan, A. S. C.; Lu, G. *J. Org. Chem.* **2010**, *75*, 3125.

unsaturated *N*-*tert*-butanesulfinyl ketoimines and nitromethane in the presence of 0.2 equivalents of anhydrous potassium carbonate (Scheme 46).[134]



Scheme 46.

II.2.3.2. Optimization of the reaction conditions

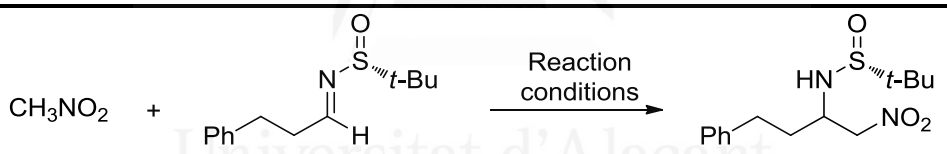
In order to find the best reaction conditions to carry out the coupling of nitromethane (**29**) and chiral *N*-*tert*-butanesulfinyl imines **3**, we took imine (*R*)-**3c** (derived from 3-phenylpropanal) as the model compound. Sodium iodide has recently been used successfully as a base in the condensation of bromonitromethane with imines,[106] and also in the reaction of dimethyl malonate (**7**) with chiral imines **3** (see section II.2.2.). Unfortunately, no reaction occurred when 2 equivalents of nitromethane (**29**) and imine (*R*)-**3c** where treated with 1 equivalent of sodium iodide in THF at room temperature for 72 hours (Table 10, entry 1). The same result was obtained under solvent free reaction conditions but using 3 equivalents of nitromethane (**29**) and 1 equivalent of sodium iodide for 3 days at both, room temperature and 60 °C (Table 10, entries 2 and 3). Switching from sodium iodide to sodium bicarbonate as a base under solvent free conditions led to a low conversion (28%) and relativety high diastereoselectivity (90:10, Table 10, entry 4) of the expected β-nitroamine derivative **30c**. Surprisingly, conversion was dramatically improved when the sodium bicarbonate mediated coupling was performed at 60 °C instead of at room temperature (from 28 to 95%), and in

[106] Rodríguez-Solla, H.; Concellón, C.; Alvarado, N.; Soengas, R. G. *Tetrahedron* **2012**, *68*, 1736.
[134] Zhang, F.; Liu, Z.-J.; Liu, J.-T. *Org. Biomol. Chem.* **2011**, *9*, 3625.

addition, a slightly higher diastereomeric ratio was also achieved (Table 10, entry 5). By contrary, lower conversion and diastereoselectivity were obtained when the reaction was performed in THF solution at 60 °C (Table 10, entry 6).

The reaction did not take place in THF at room temperature when a stronger base, such as a 2 M aqueous solution of sodium hydroxide, was used (Table 10, entry 7). At this point, we applied to chiral *N*-*tert*-butanesulfinyl imine (*R*)-**3c**, the same reaction conditions that García Ruano reported in the highly effective asymmetric aza-Henry reaction of nitromethane (**29**) with *N*-*p*-toluenesulfinyl imines.[132] Thus, the reaction of (*R*)-**3c** in a large excess of nitromethane (**29**, reagent and solvent) with 5 equivalents of sodium hydroxide in the presence of 4Å molecular sieves at 40 °C for 24 hours led to 72% conversion and 90:10 diastereomeric ratio (Table 10, entry 8). On the other hand, complete conversion and significant lower and reverse diastereoselectivity were obtained when a 1 M THF solution of tetrabutylammonium fluoride (TBAF) was used at room temperature for 1 hour, instead of the combination of sodium hydroxide in the presence of 4Å molecular sieves (Table 10, entry 9).

***Table 10**. Optimization of the reaction conditions*



29 (*R*)-**3c** **30c**

Entry	Reaction conditions[a]	Conversion (%)[b]	dr[c]
1	CH_3NO_2 (2 equiv), NaI (1.1 equiv), THF (1 mL), 23 °C, 72 h	0	--
2	CH_3NO_2 (3 equiv), NaI (1.1 equiv), 23 °C, 72 h	0	--
3	CH_3NO_2 (3 equiv), NaI (1.1 equiv), 60 °C, 72 h	0	--
4	CH_3NO_2 (3 equiv), $NaHCO_3$ (2 equiv), 23 °C, 72 h	28	90:10

[a] All reactions were carried out using 0.2 mmol of aldimine (*R*)-**3c**. [b] Conversion is given based on the disappearance of the starting (*R*)-**3c** by ^{1}H-NMR. [c] Diastereomeric ratio was determined by ^{1}H-NMR.

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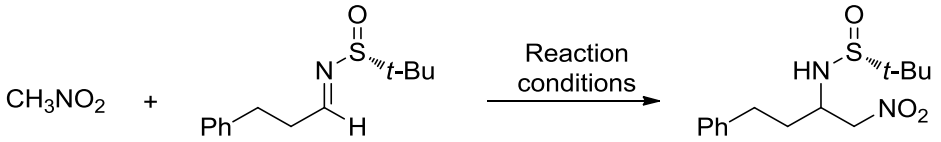
Table 10. *Optimization of the reaction conditions (cont.)*



29 (*R*)-**3c** **30c**

Entry	Reaction conditions[a]	Conversion (%)[b]	dr[c]
5	CH_3NO_2 (3 equiv), $NaHCO_3$ (2 equiv), 60 °C, 72 h	95	92:8
6	CH_3NO_2 (2 equiv), $NaHCO_3$ (2 equiv), THF (1 mL), 60 °C, 72 h	70	73:27
7	CH_3NO_2 (2 equiv), 2 M $NaOH/H_2O$ (1.1 equiv), THF (1 mL), 23 °C, 72 h	0	--
8	CH_3NO_2 (280 equiv, 3 mL), NaOH (5 equiv), 4Å MS (40 mg), 40 °C, 24 h	84	93:7
9	CH_3NO_2 (145 equiv, 1 mL), 1 M TBAF/THF (0.2 equiv), 23 °C, 1 h	100	30:70

[a] All reactions were carried out using 0.2 mmol of aldimine (*R*)-**3c**. [b] Conversion is given based on the disappearance of the starting (*R*)-**3c** by ^{1}H-NMR. [c] Diastereomeric ratio was determined by ^{1}H-NMR.

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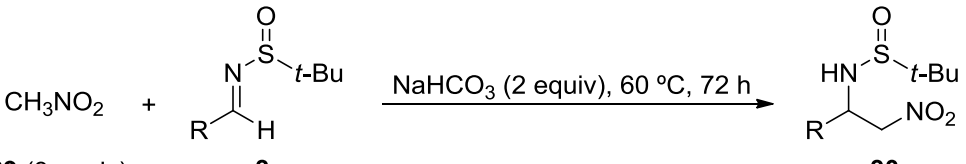
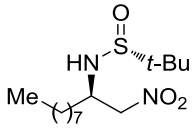
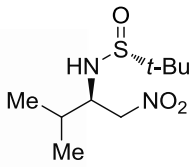
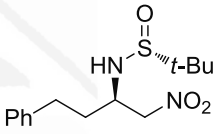
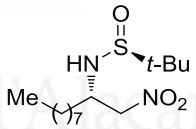
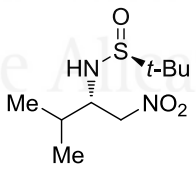
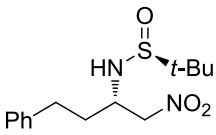
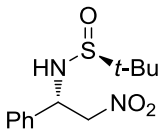
II.2.3.3. Synthesis of enantioenriched β-nitroamine derivatives 30

In order to broaden the scope of the sodium bicarbonate promoted aza-Henry reaction we applied the optimized conditions depicted in Table 10, entry 5, to different *N*-*tert*-butanesulfinyl imines **3**. When chiral alkyl aldimines **3** where used, β-nitroamine derivatives **30** were obtained in moderate to good yields and high diastereomeric ratios (Table 11, entries 1-6). However, in the case of aromatic aldimine (*S*)-**3d** derived from benzaldehyde, the expected reaction product *ent*-**30d** was isolated in 7% yield and lower diastereoselectivity when compared with the rest of the imines (Table 11, entry 7). A possible explanation for the low yield could be that retro aza-Henry reaction could occur in a significant extension for aromatic aldimines.

Table 11**. Preparation of β–nitroamine derivatives **30



29 (3 equiv) **3** **30**

	Aldimine **3**		β-Nitroamine derivative **30**			
Entry	No.	R	No.	Structure	Yield (%)[b]	dr[b]
1	(*R*)-**3a**	$CH_3(CH_2)_7$	**30a**		63	93:7
2	(*R*)-**3b**	*i*-Pr	**30b**		75	90:10
3	(*R*)-**3c**	$Ph(CH_2)_2$	**30c**		78	92:8
4	(*S*)-**3a**	$CH_3(CH_2)_7$	*ent*-**30a**		67	92:8
5	(*S*)-**3b**	*i*-Pr	*ent*-**30b**		72	90:10
6	(*S*)-**3c**	$Ph(CH_2)_2$	*ent*-**30c**		82	91:9
7	(*S*)-**3d**	Ph	*ent*-**30d**		28	74:26

[a] All products were >95% pure (GLC and/or 300 MHz ^{1}H-NMR). [b] Isolated yield after column chromatography (silica gel, hexane/EtOAc) based on the starting aldimine **3**. [c] Diastereomeric ratio was determined by ^{1}H-NMR.

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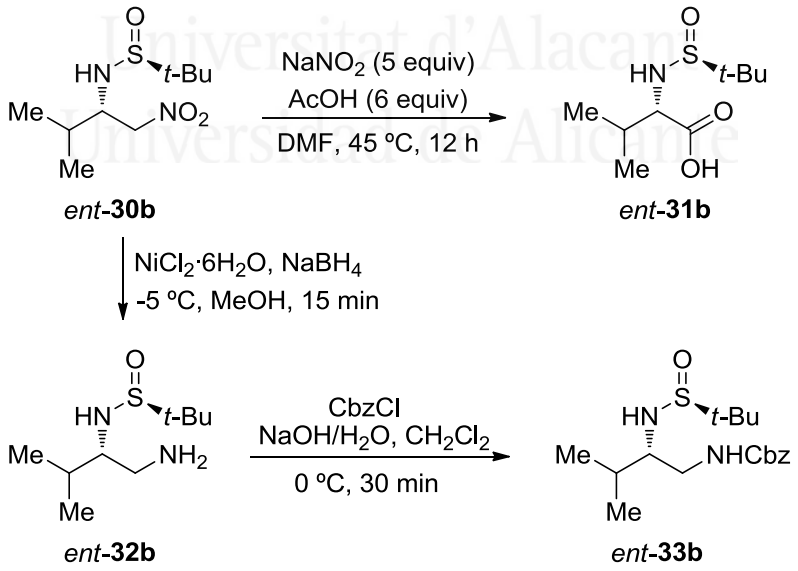
II.2.3.4. Synthesis of α-amino acid *ent*-31b and 1,2-diamino derivative *ent*-33b

To show the potential synthetic usefulness of these β-nitroamine derivatives **30**, compound *ent*-**30b** was transformed into α-amino acid *ent*-**31b** upon treatment with sodium nitrite and acetic acid in dimethylformamide (DMF) at 45 °C for 12 h (Scheme 47).[135] After base-acid extraction, pure compound *ent*-**31b** was obtained in 68% yield as a white solid (no column chromatography purification was needed). Importantly, this variant of Nef oxidation of primary nitroalkanes proceeds under mild acidic conditions that render it compatible with the *N*-*tert*-butanesulfinamide acid sensitive functionality. In addition, the nitro group was reduced to the amino group by means of sodium borohydride in the presence of nickel dichloride hexahydrate. The resulting compound *ent*-**32b**, underwent subsequent protection of the free amino group with benzyloxycarbonyl chloride (CbzCl) under basic conditions to give 1,2-diamino derivative *ent*-**33b** in 52% yield, based on the starting nitro compound *ent*-**30b** (Scheme 47). Vicinal diamine derivative *ent*-**33b** could be transformed with complete chemoselectivity involving the amino functionalities because the protecting groups could be removed under rather different reaction conditions: acid medium for the *tert*-butanesulfinyl unit and catalytic hydrogenation for the benzyloxylcarbonyl group.

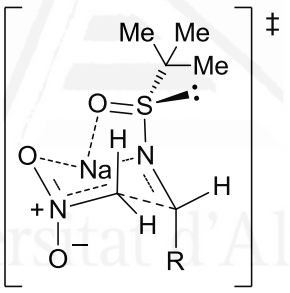


Scheme 47.

[135] Matt, C.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* **1997**, *62*, 234.

II.2.3.5. Stereochemical pathway of the nucleophilic addition

In this case, the configuration of the newly created stereogenic centre in compounds **30** was assigned after comparing the physical and spectroscopic data of *ent*-**31b** {configuration (S_S,*S*), mp 125-128 °C, $[\alpha]_D^{23}$ +84.2 (*c* 1.07, $CHCl_3$)} with that provided in the literature for its enantiomer (R_S,*R*)-*N*-*tert*-butanesulfinyl-2-amino-3-methylbutanoic acid (**31b**, D-*N*-*tert*-butanesulfinyl-valine) {configuration (R_S,*R*), mp 124-126 °C, $[\alpha]_D^{23}$ -98.2 (*c* 1.12, $CHCl_3$)}.[136] They exhibited identical ^{1}H and ^{13}C-NMR spectra, and optical rotations with opposite sign. In order to explain the stereochemical pathway of the nucleophilic addition of the proposed sodium nitronate intermediate to chiral *N*-*tert*-butanesulfinyl imines **3**, a six-membered ring model **TSVI**, similar to other previously presented, with a four-membered metallacycle, in which sodium is chelated both by the oxygen and the nitrogen atoms of the imine moiety, is proposed (Figure 3). Here, we assume that the nucleophilic attack occurs to the *Si*-face of the imine unit for R_S-isomers (Table 11, entries 1-3) and to the *Re*-face in the case of S_S-derivatives (Table 11, entries 4-7).



TSVI
(R_S: *Si*-face attack)

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Figure 3.

[136] Reddy, L. R.; Gupta, A. P.; Liu, Y. *J. Org. Chem.* **2011**, *76*, 3409.

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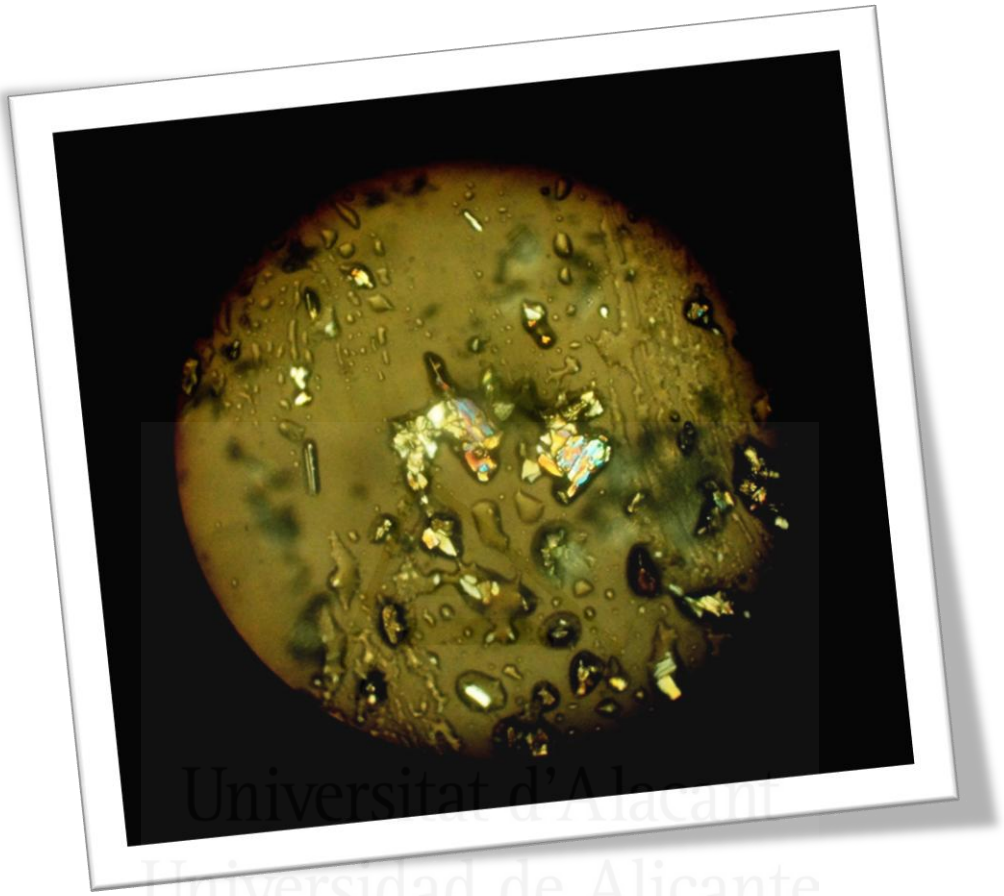

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*Fusion of the (R)-4-Octylazetidin-2-one (**28a**) crystals during a melting point experiment (photo taken on the 17th of January, 2012)*

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III. Experimental Part

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III.1. General

III.1.1. Solvents and reagents

Dry tetrahydrofuran (THF) was purchased from (Aldrich), and it was kept under Argon, covering the head of the bottle with a septum, as well as the dry dichloromethane and dry DMF. The rest of the employed solvents were of the best commercially available grade. *N*-*tert*-Butanesulfinylamides **1** (*S* and *R*) were provided by Medalchemy S.L. (>99% ee by HPLC with a Chiracel AS column, 90:10 *n*-hexanol/*i*-PrOH, 1.2 mL/min, λ = 222 nm)

III.1.2. Equipment

The infrared spectra (IR) were registered in a Fourier Transform (FT) Jasco FT-IR 4100 spectrophotometer. Characteristic frequencies were given in cm^{-1}.

The low resolution mass spectrometry analysis (MS) was carried out in an Agilent 6890N spectrometer, using an electronic impact (EI) of 70 eV as ionization source. The samples (2 μL volume) were introduced by injection through a gas chromatograph (equipped with an HP-1 column, 12 m long, 0.22 mm internal diameter, 0.25 μm crossed-chain methylsilicon polymer film thinckness and helium as a moving phase). The ions derived from the ruptures are given as percentage relative intensity versus the base peak. The analyses of high resolution mass spectrometry (HRMS) were obtained with a Finningan MAT95S spectrometer.

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The optical rotation measurements were measured with a Perkin-Elmer 341 polarimeter with a 5 cm cell thermostated to 20 °C, concentrations (c) were given approximately in g/100 mL.

The nuclear magnetic resonace spectra (NMR) were registered at the NMR service of the Servicios Tecnicos de Investigación of the University of Alicante, with a Bruker AC-300 spectrophotometer (300 MHz), using deuterated chloroform ($CDCl_3$) as a solvent and trimethylsilane (TMS) as an internal reference, unless otherwise indicated. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were carried out on a 300 MHz frequency, and the carbon (^{13}C-NMR) on a 75 MHz frequency, unless otherwise indicated. The chemical shifts (δ) were given in part per million (ppm) with respect to the TMS, and the coupling constants (*J*) were given in hertz (Hz). The signals were assigned based on the following abbreviations: s (singlet), br s (broad singlet),

d (doublet), t (triplet), q (quartet), h (heptet), m (multiplet), and any possible combination between each other.

The melting points (mp) were determined with a Reichert-Thermovar apparatus using a glass support, and they were described without corrections.

III.1.3. Chromatography

The thin layer chromatography (TLC) was carried out in a prefab Merck cromatoplates silica gel 60 F_{254}, (20 cm × 20 cm) area and 0.2 mm silica gel 60 thickness, on an aluminum support, with a fluorescent indicator (phosphomolibdic acid) sensitive to a wave length of λ = 254 nm. The R_f values were given under these conditions.

The column chromatography was carried out in plastic columns, using Merck 60 silica gel as a stationary phase, with a particle size of 0.06–0.2 nm. The mentioned stationary phase was introduced in the column using a Büchi Cartridger C-670. The mobile phase (hexane and ethyl acetate mixtures of increasing polarity) was introduced through a Büchi C-610 pump.

The gas chromatograms were carried out in an Agilent 6890N spectrometer with a gas chromatograph. The chromatographic conditions were: FID detector, Helium as carrier gas (2 mL/min), 12 psi injector pressure, a temperature of 270 °C in the injection and detection blocks, 2.0 μL sample volume and a registering rate of 5 mm/min. The selected temperature program was: initial temperature (60 °C), initial time (3 min), heating rate (15 °C/min) and a final temperature of 270 °C. The employed column was of a HP-1 type, 12 m long, 0.22 mm internal diameter, 0.25 μm cross-chain methylsilicon polymer film thickness, being the stationary phase OV-101, with a thickness of 0.2 μm. the given retention times (t_r) were obtained under these conditions and they are shown in minutes.

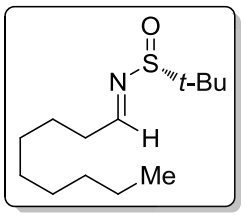
The HPLC analysis were carried out under 25 °C in a Jasco apparatus equipped with a quaternary pump PU-2089 Plus, a diode array MD-2010 Plus detector and an automatic As-2059 injector. As a solvent, *n*-hexane, isopropanol or mixtures of different proportions of them were used. Chiralcel OD-H chiral column was used, unless otherwise indicated.

III.2. Experimental part of chapter II.1.

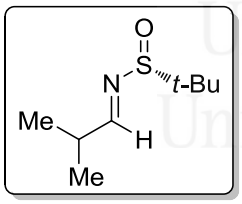
III.2.1. Synthesis of *N-tert*-butanesulfinyl aldimines 3

General procedure.- To a solution of *tert*-butanesulfinamide **1** (0.605 g, 5 mmol) and the corresponding aldehyde (5.5 mmol) in dry THF (20 mL) under argon at 23 °C was slowly added titanium tetraetoxide (2.2281 g, 2.095 mL, 10 mmol). The reaction mixture was stirred for 12 h at the same temperature. The resulting mixture was hydrolyzed with brine (30 mL), extracted with ethyl acetate (3 × 15 mL), dried with anhydrous $MgSO_4$ and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to yield pure compounds **3**. Yields are given in Scheme 36. Physical and spectroscopic data follow.

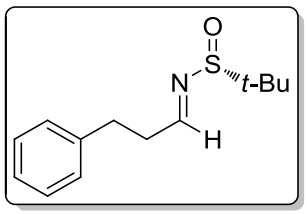
*(*R*)*-N-*(*tert-*Butanesulfinyl)*-N-*nonylidenamine* [(*R*)-**3a**]: Colourless oil; $[\alpha]_D^{23}$ -189 (*c* 1.70, CH_2Cl_2); R_f 0.72 (hexane/EtOAc: 2/1); IR *ν* (film) 2955, 2925, 2855, 1621, 1457, 1362, 1088 cm^{-1}; δ_H 0.88 (3H, t, *J* = 6.9, C*H*$_3$CH$_2$), 1.20 [9H, s, (CH$_3$)$_3$C], 1.26-1.37 (10H, m, 5×CH$_2$), 1.57-1.67 (2H, m, CH$_2$), 2.48-2.54 (2H, m, CH$_2$), 8.06 (1H, t, *J* = 4.8, CHN); δ_C 14.0, 22.3 (CH$_3$), 22.6, 25.4, 29.1, 29.2, 29.3, 31.7, 36.0 (CH$_2$), 56.4 (C), 169.8 (CH); LRMS (EI) *m/z* 139 (M^+-*t*-BuSOH, 1%), 124 (12), 110 (46), 97 (39), 96 (100), 83 (61), 84 (95), 69 (58), 57 (26), 55 (34), 54 (43).



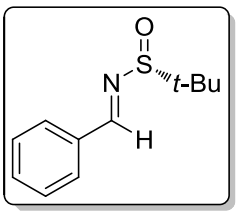
*(*R*)*-N-*(*tert-*Butanesulfinyl)*-N-*(2-methylpropyliden)amine* [(*R*)-**3b**]: Colourless liquid; $[\alpha]_D^{23}$ -232 (*c* 0.49, CH_2Cl_2); R_f 0.70 (hexane/EtOAc: 3/1); IR *ν* (film) 2966, 2930, 2872, 1621, 1460, 1364, 1086 cm^{-1}; δ_H 1.13 (3H, d, *J* = 7.0, C*H*$_3$CHCH$_3$), 1.14 (3H, d, *J* = 7.0, CH$_3$CHC*H*$_3$), 1.16 [9H, s, (CH$_3$)$_3$C], 2.68 [1H, m, (CH$_3$)$_2$C*H*], 7.95 (1H, d, *J* = 4.3, CHN); δ_C 18.8, 22.2 (CH$_3$), 34.8 (CH), 56.4 (C), 173.5 (CH); LRMS (EI) *m/z* 175 (M^+, 2%), 119 (20), 57 (100), 56 (52), 55 (10).



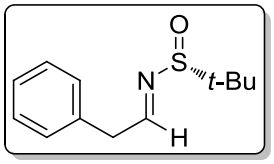
*(*R*)*-N-*(*tert-*Butanesulfinyl)-N-(3-phenylpropyliden)amine* [(*R*)-**3c**]: Colourless oil; $[\alpha]_D^{23}$ -138 (*c* 1.53, CH_2Cl_2); R_f 0.57 (hexane/EtOAc: 3/1); IR *ν* (film) 3061, 3026, 2959, 2925, 2850, 1622, 1454, 1363, 1080 cm^{-1}; δ_H 1.12 [9H, s, (CH$_3$)$_3$C], 2.82-2.89 (2H, m, CH$_2$), 2.95-3.00 (2H, m, CH$_2$), 2.63-2.73 (2H, m, CH$_2$), 7.19-7.22 (3H, m, ArH), 7.26-7.31 (2H, m, ArH), 8.11 (1H, t, *J* = 4.1, CHN); δ_C 22.2 (CH$_3$), 31.3, 37.4 (CH$_2$), 56.5 (C), 126.2, 128.3, 128.5, 140.2, (ArC), 168.5 (CH); LRMS (EI) *m/z* 131 (M^+-*t*-BuSOH, 34%), 92 (11), 91 (100), 65 (19), 51 (10).



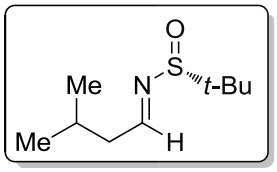
*(*R*)*-N-*Benzyliden*-N-*(*tert-*butanesulfinyl)amine* [(*R*)-**3d**]: Colourless oil; $[\alpha]_D^{23}$ -98 (*c* 0.93, CH_2Cl_2); R_f 0.65 (hexane/EtOAc: 3/1); IR *ν* (film) 3062, 3024, 2978, 2926, 1606, 1450, 1363, 1086 cm^{-1}; δ_H 1.27 [9H, s, $(CH_3)_3C$], 7.45-7.53 (3H, m, ArH), 7.85-7.88 (2H, m, ArH), 8.59 (1H, s, CHN); δ_C 22.6 (CH_3), 57.7 (C), 128.9, 129.4, 132.4, 134.0 (ArC), 162.7 (CH); LRMS (EI) *m/z* 103 (M^+-*t*-BuSOH), 100%), 76 (31), 50 (19).



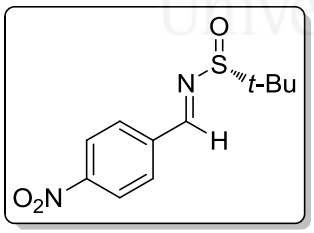
*(*R*)*-N-*(*tert-*Butanesulfinyl)*-N-*(2-phenylethyliden)amine* [(*R*)-**3e**]: Colourless oil; $[\alpha]_D^{23}$ -151 (*c* 1.55, CH_2Cl_2); R_f 0.47 (hexane/EtOAc: 3/1); IR *ν* (film) 3070, 3028, 2977, 2959, 2901, 1619, 1454, 1363, 1181, 1080 cm^{-1}; δ_H 1.19 [9H, s, $(CH_3)_3C$], 3.72-3.88 (2H, m, CH_2), 7.22-7.36 (5H, m, ArH), 8.13 (1H, t, *J* = 5.2, CHN); δ_C 22.4 (CH_3), 42.6 (CH_2), 56.8 (C), 127.1, 128.8, 129.2, 134.7 (ArC), 167.4 (CH); LRMS (EI) *m/z* 117 (M^+-*t*-BuSOH, 100%), 116 (38), 90 (41), 89 (28), 63 (12), 51 (15).



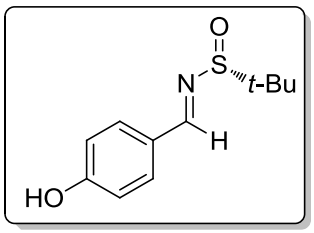
*(*R*)*-N-*(*tert-*Butanesulfinyl)*-N-*(3-methylbutyliden)amine* [(*R*)-**3f**]: Colourless liquid; $[\alpha]_D^{23}$ -307 (*c* 1.40, CH_2Cl_2); R_f 0.44 (hexane/EtOAc: 3/1); IR *ν* (film) 2957, 2929, 2870, 1620, 1462, 1363, 1083 cm^{-1}; δ_H 0.99 (3H, d, *J* = 6.7, CH_3CHCH_3), 1.00 (3H, d, *J* = 6.7, CH_3CHCH_3), 1.21 [9H, s, $(CH_3)_3C$], 2.04-2.10 [1H, m, $(CH_3)_2CH$], 2.40-2.43 (2H, m, CH_2), 8.06 (1H, t, *J* = 5.2, CH=N); δ_C 22.4, 22.5, 22.6 (CH_3), 26.2 (CH), 44.9 (CH_2), 56.5 (C), 169.4 (CH); LRMS (EI) *m/z* 189 (M^+, 1%), 133 (28), 91 (22), 77 (17), 57 (100).



*(*R*)*-N-*(*tert-*Butanesulfinyl)*-N-*(*para-*nitrobenzyliden)amine* [(*R*)-**3g**]: White solid; mp 112-113 °C (hexane/CH_2Cl_2); $[\alpha]_D^{23}$ -47 (*c* 1.0, CH_2Cl_2); R_f 0.34 (hexane/EtOAc: 3/1); IR *ν* (KBr) 3113, 3025, 2948, 2914, 2360, 2341, 1584, 1529, 1343, 1087 cm^{-1}; δ_H 1.32 [9H, s, $(CH_3)_3C$], 8.08 (2H, dt, *J* = 8.8, 2.1, ArH), 8.35 (2H, *J* = 8.8, 2.1, ArH), 8.71 (1H, s, CHN); δ_C 22.3 (CH_3), 58.1 (C), 123.8, 129.7, 138.5, 149.4 (ArC), 160.4 (CH); LRMS (EI) *m/z* 148 (M^+-*t*-BuSOH, 100%), 118 (16), 102 (100), 90 (27), 76 (22), 75 (40), 51 (25).



*(*R*)*-N-*(*tert-*Butanesulfinyl)*-N-*(para-hydroxybenzyliden)amine* [(*R*)-**3h**]: White solid; decomposition >208 °C; $[\alpha]_D^{23}$ +15 (*c* 1.36, CH_3OH); R_f 0.14 (hexane/EtOAc: 3/1); IR *ν* (KBr) 3230-3126, 2981, 2360, 2341, 1589, 1576, 1514, 1437, 1280, 1160, 1035 cm^{-1}; δ_H 1.27 [9H, s, $(CH_3)_3C$], 6.14 (1H, br s, OH), 6.94 (2H, dt, *J* = 8.7, 2.4, ArH), 7.77 (2H, *J* = 8.7, 2.4, ArH), 8.49 (1H, s,

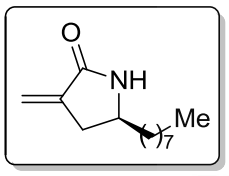


CHN); δ_C 22.5 (CH_3), 57.7 (C), 115.9, 126.8, 131.6, 159.7 (ArC), 161.8 (CH); LRMS (EI) *m/z* 119 (M^+-*t*-BuSOH, 100%), 91 (17), 64 (22).

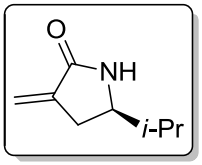
III.2.2. Stereoselective synthesis of α-methylene-γ-butyrolactams 6

General procedure.- A mixture of aldimine **3** (0.5 mmol), ethyl 2-(bromomethyl)acrylate (**4**, 0.106 g, 0.55 mmol) and indium powder (0.075 g, 0.65 mmol) in THF (3 mL) was stirred for 48 h at 100 °C in a pressure flask. Then, the resulting mixture was hydrolyzed with water (10 mL), extrated with EtOAc (3 × 10 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The residue was dissolved in MeOH (1 mL) and a HCl 4M dioxane solution (0.5 mL) was added at 0 °C. After 2 h stirring at the same temperature, a $NaHCO_3$ saturated aqueous solution (3 mL) was added, and after 1 h stirring at room temperature, the reaction mixture was extrated with EtOAc (3 × 15 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The resulting residue was purified by column chromatography to give compounds **6**. Yields and er are given in Table 2. Physical and spectroscopic data follow.

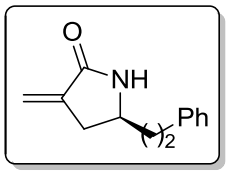
(S)-3-Methylene-5-octylpyrrolidin-2-one (**6a**): White solid; mp 47-48 °C (pentane/CH_2Cl_2); R_f 0.45 (hexane/EtOAc: 1/1); IR ν (KBr) 3176, 3090, 2916, 2849, 1697, 1659, 1466, 1396, 1307, 917 cm^{-1}; δ_H 0.88 (3H, t, *J* = 7.1 Hz, C*H*$_3$CH$_2$), 1.19-1.34 (12H, m, 6×CH_2), 1.41-1.48 (1H, m, C*H*H), 1.52-1.56 (1H, m, CH*H*), 2.39-2.45 (1H, m, C*H*HC=CH_2), 2.91-2.99 (1H, m, CH*H*C=CH_2), 3.60-3.66 (1H, m, C*H*NH), 5.32 (1H, s, C=C*H*H), 5.95 (1H, t, *J* = 2.5 Hz, C=CH*H*), 7.58 (1H, br s, NH); δ_C 14.0 (CH_3), 22.6, 25.4, 29.1, 29.4, 31.8, 33.0, 37.3 (CH_2), 51.4 (CH), 115.5 (CH_2), 139.7 (C), 170.7 (CO); LRMS (EI) *m/z* 209 (M^+, 8%), 97 (14), 96 (100), 68 (11), 53 (25); HRMS (EI) calcd for $C_{13}H_{23}NO$ 209.1780, found 209.1753; HPLC t_{ret} (min) 16.89.



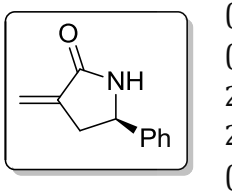
(R)-5-Isopropyl-3-methylenepyrrolidin-2-one (**6b**): White solid; mp decomposed >300 °C (pentane/CH_2Cl_2); R_f 0.27 (hexane/EtOAc: 1/1); IR ν (KBr) 3211, 2960, 2926, 2874, 1696, 1658, 1391, 1284, 1042, 807 cm^{-1}; δ_H 0.90 (3H, d, *J* = 7.0 Hz, C*H*$_3$CH), 0.93 (3H, d, *J* = 7.0 Hz, C*H*$_3$CH), 1.65 (1H, h, *J* = 6.7 Hz, CHCH$_3$), 2.48-2.57 (1H, m, C*H*HC=CH_2), 2.85-2.95 (1H, m, CH*H*C=CH_2), 3.38-3.44 (1H, m, C*H*NH), 5.34 (1H, br s, C=C*H*H), 5.97 (1H, t, *J* = 2.7 Hz, C=CH*H*), 6.18 (1H, br s, NH); δ_C 17.8, 18.1 (CH_3), 30.6 (CH_2), 33.6, 56.9 (CH), 115.6 (CH_2), 139.5 (C), 170.6 (CO); LRMS (EI) *m/z* 96 [(M^+-*i*-Pr), 100%], 95 (17), 68 (11), 67 (14), 53 (36); HRMS (EI) calcd for $C_8H_{13}NO$ 139.0997, found 139.0982; HPLC t_{ret} (min) 20.26.



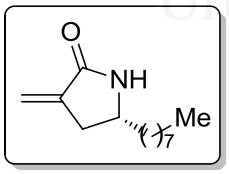
(S)-3-Methylene-5-(2-phenylethyl)pyrrolidin-2-one (**6c**): White solid; mp 69-70 °C (pentane/CH_2Cl_2); R_f 0.36 (hexane/EtOAc: 1/1); IR ν (film) 3229, 3061, 3026, 2926, 1692, 1650, 1494, 1442, 1331, 1299, 1030, 936, 697 cm^{-1}; δ_H 1.74-1.95 (2H, m, C*H*$_2$CHN), 2.42-2.50 (1H, m, C*H*HC=CH_2), 2.61-2.76 (2H, m, PhCH_2), 2.92-3.02 (1H, m, CH*H*C=CH_2), 3.62-3.70 (1H, m, C*H*NH), 5.32 (1H, br s, C=C*H*H), 5.97 (1H, t, *J* = 2.4 Hz, C=CH*H*), 7.75 (1H, br s, NH); δ_C 31.8, 33.0, 38.9 (CH_2), 50.8 (CH), 115.8 (CH_2), 126.0, 128.3, 128.5 (CH), 139.4, 140.9 (C), 170.7 (CO); LRMS (EI) *m/z* 201 (M^+, 21%), 132 (11), 123 (15), 117 (10), 110 (29), 103 (18), 97 (30), 96 (100), 91 (34), 77 (17), 65 (15), 53 (36); HRMS (EI) calcd for $C_{13}H_{15}NO$ 201.1154, found 201.1142; HPLC t_{ret} (min) 43.84.



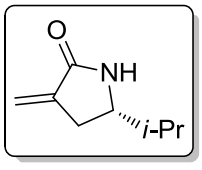
(R)-3-Methylene-5-phenylpyrrolidin-2-one (**6d**): White solid; mp 172-174 °C (pentane/CH_2Cl_2) [mp 191-192 °C (hexano/EtOAc)];[6b] R_f 0.34 (hexane/EtOAc: 1/1); IR ν (film) 3184, 3094, 3028, 2923, 2852, 1696, 1657, 1452, 1337, 1282, 935, 763 cm^{-1}; δ_H 2.64-2.80 (1H, m, C*H*HC=CH_2), 3.26-3.36 (1H, m, CH*H*C=CH_2), 4.75 (1H, dd, *J* = 8.1, 4.7 Hz, C*H*NH), 5.38 (1H, br s, C=C*H*H), 6.06 (1H, t, *J* = 2.7 Hz, C=CH*H*), 6.55 (1H, br s, NH), 7.27-7.40 (5H, m, ArH); δ_C 36.8 (CH_2), 54.8 (CH), 116.6 (CH_2), 125.7, 128.1, 129.0 (CH), 138.6, 142.6 (C), 170.6 (CO); LRMS (EI) *m/z* 173 (M^+, 100%), 172 (59), 144 (33), 128 (12), 104 (61), 96 (22), 78 (23), 77 (40), 68 (28), 51 (37); HRMS (EI) calcf for $C_{11}H_{11}NO$ 173.0841, found 173.0848; HPLC t_{ret} (min) 36.92.



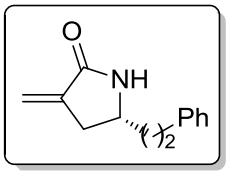
(R)-3-Methylene-5-octylpyrrolidin-2-one (*ent*-**6a**): Physical and spectroscopic data were found to be the same than for **6a**; HPLC t_{ret} (min) 12.25.



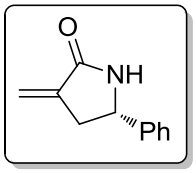
(S)-5-Isopropyl-3-methylenepyrrolidin-2-one (*ent*-***6b***): Physical and spectroscopic data were found to be the same than for **6b**; HPLC t_{ret} (min) 14.20.



*(*R*)-3-Methylene-5-(2-Phenylethyl)pyrrolidin-2-one* (*ent*-**6c**): Physical and spectroscopic data were found to be the same than for **6c**; HPLC t_{ret} (min) 12.01.



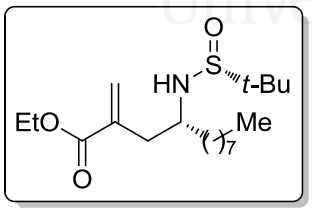
*(*S*)-3-Methylene-5-phenylpyrrolidin-2-one* (*ent*-**6d**): Physical and spectroscopic data were found to be the same than for **6d**; HPLC t_{ret} (min) 33.20.



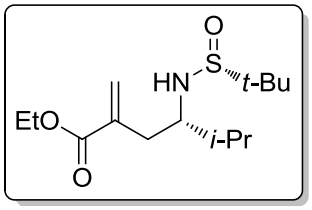
III.2.3. Synthesis of amino ester derivatives 5

General procedure.- A mixture of the corresponding aldimine **3** (0.5 mmol), ethyl 2-(bromomethyl)acrylate (**4**, 0.128 g, 0.65 mmol) and indium powder (0.226 g, 2.0 mmol) in a saturated aqueous NaBr solution (5 mL) was stirred for 48 h at 23 °C. Then, the resulting mixture was hydrolyzed with water (10 mL), extrated with EtOAc (3 × 10 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield pure products **5**. Yields are given in Table 3. Physical and spectroscopic data follow.

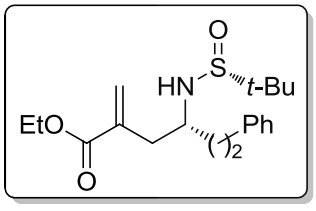
*(4*R,R*S)-Ethyl 4-amino*-N-*(*tert-*butanesulfinyl)-2-methylenedodecanoate* (**5a**): Colourless oil; $[\alpha]_D^{20}$ -41 (*c* 1.43, CH_2Cl_2); R_f 0.46 (hexane/EtOAc: 1/1); IR *ν* (film) 3223, 2924, 2855, 1715, 1627, 1464, 1364, 1303, 1150, 1053, 942 cm^{-1}; δ_H 0.88 (3H, t, *J* = 7.1 Hz, C*H*$_3$CH$_2$), 1.19 [9H, s, (CH$_3$)$_3$C], 1.31 (3H, t, *J* = 7.1 Hz, C*H*$_3$CH$_2$O), 1.25-1.50 (14H, m, 7×CH$_2$), 2.59 (2H, d, *J* = 6.2 Hz, C*H*$_2$CHNH), 3.40-3.44 (1H, m, C*H*NH), 3.52 (1H, d, *J* = 6.0 Hz, NH), 4.21 (2H, c, *J* = 7.1 Hz, CH$_3$C*H*$_2$O), 5.68 (1H, s, C=C*H*H), 6.30 (1H, s, C=CH*H*); δ_C 14.0, 14.1, (CH$_3$), 22.6 (CH$_2$), 22.65 (CH$_3$), 25.4, 29.1, 29.3, 29.4, 31.7, 35.4, 38.3 (CH$_2$), 55.2 (CH), 55.6 (C), 60.9 (CH$_2$), 128.0 (CH$_2$), 137.3 (C), 167.4 (CO); LRMS (EI) *m/z* 303 [M$^+$-(CH$_3$)$_2$C=CH$_2$, 6%], 285 (19), 258 (11), 212 (100), 300 (17), 189 (72), 187 (76), 140 (14), 133 (22), 114 (28), 100 (33), 84 (23), 70 (30), 55 (18).



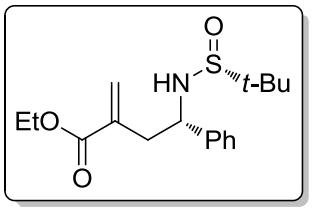
*(4*S,R*S)-Ethyl 4-amino*-N-*(*tert-*butanesulfinyl)-5-methyl-2-methylenehexanoate* (**5b**): Colourless liquid; $[\alpha]_D^{20}$ -97 (*c* 0.70, CH_2Cl_2); R_f 0.40 (hexane/EtOAc: 1/1); IR *ν* (film) 3274, 2959, 1713, 1628, 1465, 1366, 1315, 1153, 1057, 904 cm^{-1}; δ_H 0.91 (3H, d, *J* = 6.8 Hz, C*H*$_3$CH), 0.92 (3H, d, *J* = 6.9 Hz, C*H*$_3$CH), 1.21 [9H, s, $(CH_3)_3C$], 1.31 (3H, t, *J* = 7.1 Hz, C*H*$_3$CH$_2$O), 1.83-1.90 (1H, m, C*H*CH$_3$), 2.48-2.51 (2H, m, C*H*$_2$C=CH$_2$), 3.26-3.33 (1H, m, C*H*NH), 3.56 (1H, d, *J* = 5.5 Hz, NH), 4.21 (2H, c, *J* = 7.0 Hz, CH$_3$C*H*$_2$O), 5.70 (1H, s, C=C*H*H), 6.31 (1H, s, C=CH*H*); δ_C 14.1, 17.3, 18.1, 22.7 (CH_3), 31.8 (CH), 34.7 (CH_2), 55.8 (C), 60.6 (CH), 61.0 (CH_2), 127.9 (CH_2), 137.7 (C), 167.6 (CO); LRMS (EI) *m/z* 233 [M^+-$(CH_3)_2C=CH_2$, 23%], 215 (21), 186 (36), 172 (29), 142 (76), 123 (54), 100 (100), 94 (38), 72 (45), 57 (61).



*(4*R,R*S)-Ethyl 4-amino*-N-*(*tert-*butanesulfinyl)-2-methylene-6-phenylhexanoate* (**5c**): Colourless oil; $[\alpha]_D^{20}$ -33 (*c* 0.98, CH_2Cl_2); R_f 0.34 (hexane/EtOAc: 1/1); IR *ν* (film) 3222, 3061, 3026, 2951, 1712, 1454, 1176, 1052, 699 cm^{-1}; δ_H 1.23 [9H, s, $(CH_3)_3C$], 1.28 (3H, t, *J* = 7.2 Hz, C*H*$_3$CH$_2$O), 1.74-1.85 (2H, m, C*H*$_2$CHN), 2.59-2.80 (4H, m, PhC*H*$_2$, C*H*$_2$C=CH$_2$), 3.46-3.52 (1H, m, C*H*NH), 3.67 (1H, d, *J* = 5.5 Hz, NH), 4.20 (2H, c, *J* = 7.2 Hz, CH$_3$C*H*$_2$O), 5.68 (1H, s, C=C*H*H), 6.30 (1H, s, C=CH*H*), 7.15-7.30 (5H, m, ArH); δ_C 14.1, 22.7 (CH_3), 31.8, 37.3, 38.3 (CH_2), 55.0 (CH), 55.8 (C), 61.0 (CH_2), 125.8, 128.2 (CH), 128.3 (CH_2), 128.4 (CH), 137.0, 141.6 (C), 167.4 (CO); LRMS (EI) *m/z* 295 [M^+-$(CH_3)_2C=CH_2$, 4%], 277 (27), 204 (100), 181 (18), 117 (62), 91 (87), 65 (14).



*(4*S,R*S)-Ethyl 4-amino*-N-*(*tert-*butanesulfinyl)-2-methylene-4-phenylbutanoate* (**5d**): Colourless oil; $[\alpha]_D^{20}$ -101 (*c* 0.96, CH_2Cl_2); R_f 0.29 (hexane/EtOAc: 1/1); IR *ν* (film) 3301, 3094, 3028, 2983, 1720, 1629, 1454, 1363, 1315, 1193, 1172, 1052, 916, 868, 698 cm^{-1}; δ_H 1.19 [9H, s, $(CH_3)_3C$], 1.30 (3H, t, *J* = 7.2 Hz, C*H*$_3$CH$_2$O), 2.71 (1H, dd, *J* = 14.1, 7.9 Hz, C*H*HC=CH$_2$), 2.80 (1H, dd, *J* = 14.1, 6.2 Hz, CH*H*C=CH$_2$), 4.08 (1H, br s, NH), 4.19 (2H, c, *J* = 7.2 Hz, CH$_3$C*H*$_2$O), 4.59-4.64 (1H, m, C*H*NH), 5.52 (1H, s, C=C*H*H), 6.25 (1H, s, C=CH*H*), 7.26-7.33 (5H, m, ArH); δ_C 14.1, 22.6 (CH_3), 41.1 (CH_2), 55.5 (C), 57.7 (CH), 61.1 (CH_2), 127.5, 127.6, 128.3 (CH), 128.6 (CH_2), 136.6, 141.5 (C), 167.2 (CO); LRMS (EI) *m/z* 267 [M^+-$(CH_3)_2C=CH_2$, 2%], 249 (21), 176 (100), 153 (69), 136 (16), 115 (12), 104 (35), 77 (28), 69 (21), 51 (16).



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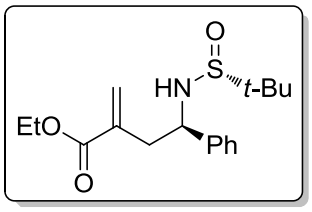
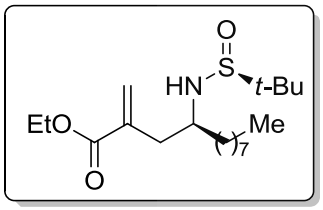
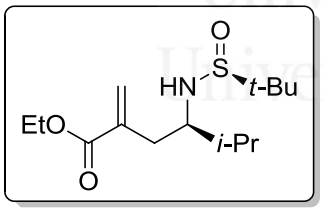
*(4*R,R*S)-Ethyl 4-amino*-N-*(*tert-*butanesulfinyl)-2-methylene-4-phenylbutanoate* (**5'd**): Colourless oil; $[\alpha]_D^{20}$ +17 (*c* 0.35, CH_2Cl_2); R_f 0.32 (hexane/EtOAc: 1/1); IR ν (film) 3305, 3095, 3029, 2984, 1721, 1631, 1455, 1362, 1312, 1190, 1173, 1052, 915, 870, 697 cm^{-1}; δ_H 1.19 [9H, s, $(CH_3)_3C$], 1.26 (3H, t, *J* = 7.2 Hz, CH_3CH_2O), 2.73 (1H, dd, *J* = 13.8, 7.3 Hz, $CHHC=CH_2$), 2.98 (1H, dd, *J* = 13.8, 7.3 Hz, $CHHC=CH_2$), 3.60 (1H, d, *J* = 5.0 Hz, NH), 4.12 (2H, c, *J* = 7.2 Hz, CH_3CH_2O), 4.54-4.59 (1H, m, CHNH), 5.45 (1H, s, C=CHH), 6.17 (1H, s, C=CHH), 7.28-7.33 (5H, m, ArH); δ_C 14.2, 22.6 (CH_3), 39.8 (CH_2), 56.1 (C), 58.9 (CH), 60.8 (CH_2), 127.5, 127.6, 128.3 (CH), 128.1 (CH_2), 136.9, 141.7 (C), 171.2 (CO); LRMS (EI) *m/z* 267 [M^+-$(CH_3)_2C=CH_2$, 6%], 207 (14), 176 (12), 163 (15), 153 (100), 136 (22), 131 (19), 129 (16), 115 (15), 104 (35), 91 (13), 77 (16).



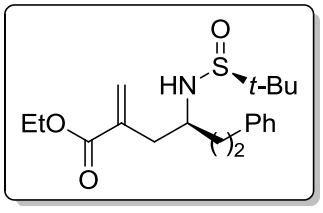
*(4*S,S*S)-Ethyl 4-amino*-N-*(*tert-*butanesulfinyl)-2-methylenedodecanoate* (*ent*-**5a**): Physical and spectroscopic data were found to be the same than for **5a**; $[\alpha]_D^{20}$ +38 (*c* 0.78, CH_2Cl_2).



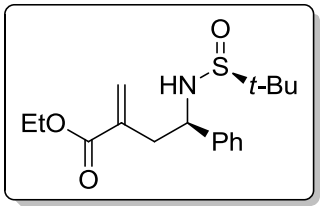
*(4*R,S*S)-Ethyl 4-amino*-N-*(*tert-*butanesulfinyl)-5-methyl-2-methylenehexanoate* (*ent*-**5b**): Physical and spectroscopic data were found to be the same than for **5b**; $[\alpha]_D^{20}$ +84 (*c* 1.30, CH_2Cl_2).



*(4*S,S*S)-Ethyl 4-amino*-N-*(*tert-*butanesulfinyl)-2-methylene-6-phenylhexanoate* (*ent*-**5c**): Physical and spectroscopic data were found to be the same than for **3c**; $[\alpha]_D^{20}$ +33 (*c* 0.34, CH_2Cl_2).



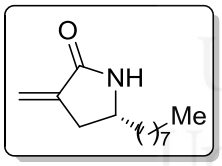
*(4*R,S*S)-Ethyl* N-*(*tert-*butanesulfinyl)-4-amino-2-methylene-4-phenylbutanoate* (*ent*-**5d**): Physical and spectroscopic data were found to be the same than for **5d**; $[\alpha]_D^{20}$ +102 (*c* 0.89, CH_2Cl_2).



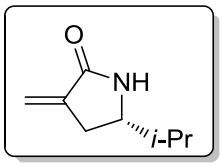
III.2.4.Synthesis of enantiopure α-methylene-γ-butyrolactams 6 from ester derivatives 5

General procedure.- To a solution of the corresponding aminoester **3** (0.2 mmol) in MeOH (1 mL) was added a 4M HCl dioxane solution (0.5 mL) at 0 °C. After 2 h stirring at the same temperature, a 2M solution of NaOMe in MeOH (2 mL) was added and the resulting mixture was stirred for 1 h at 0 °C. After that, it was hydrolyzed with water (10 mL), extrated with EtOAc (3 × 10 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield pure products **6**. Yields are given in Table 4 and physical and spectroscopic data are given above. Specific optical rotation follow.

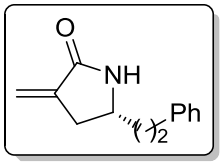
*(*R*)-3-Methylene-5-octylpyrrolidin-2-one* (*ent*-**6a**): $[\alpha]_D^{20}$ +21 (*c* 0.55, CH_2Cl_2).



*(*S*)-5-Isopropyl-3-methylenepyrrolidin-2-one* (*ent*-**6b**): $[\alpha]_D^{20}$ +3 (*c* 0.46, CH_2Cl_2).



*(*R*)-3-Methylene-5-(2-Phenylethyl)pyrrolidin-2-one* (*ent*-**6c**): $[\alpha]_D^{20}$ +25 (*c* 0.53, CH_2Cl_2).



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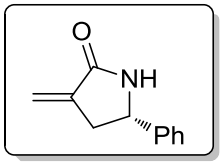
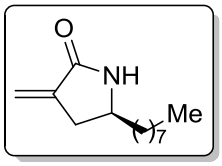
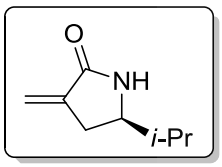
(S)-3-Methylene-5-phenylpyrrolidin-2-one (*ent*-**6d**): $[\alpha]_D^{20}$ +14 (c 0.50, CH_2Cl_2).



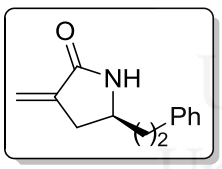
(S)-3-Methylene-5-octylpyrrolidin-2-one (**6a**): $[\alpha]_D^{20}$ -21 (*c* 0.51, CH_2Cl_2).



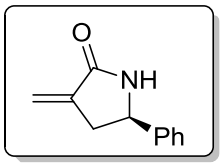
(R)-5-Isopropyl-3-methylenepyrrolidin-2-one (**6b**): $[\alpha]_D^{20}$ -2 (*c* 1.00, CH_2Cl_2).



(S)-3-Methylene-5-(2-Phenylethyl)pyrrolidin-2-one (**6c**): $[\alpha]_D^{20}$ -29 (*c* 0.56, CH_2Cl_2).



(R)-3-Methylene-5-phenylpyrrolidin-2-one (**6d**): $[\alpha]_D^{20}$ -13 (*c* 0.40, CH_2Cl_2).



III.2.5. Synthesis of dimethyl 2-[2-(chloromethyl)allyl]malonate (9)

To a 1 M solution of NaOMe in MeOH (20 mmol, 20 mL) was slowly added dimethyl malonate (**7**, 2.694 g, 2.330 mL, 20.0 mmol) at 0 °C. After stirring the reaction mixture for 15 min at the same temperature, 3-chloro-2-(chloromethyl)prop-1-ene (**8**, 2.551 g, 2.362 mL, 20 mmol) was added dropwise and stirring was continued for 12 h at room temperature. The

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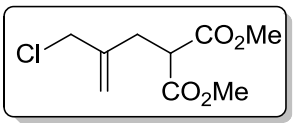
resulting mixture was hydrolyzed with water (10 mL), extracted with EtOAc (3 × 20 mL), dried with anhydrous $MgSO_4$ and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to give 1.619 g (7.37 mmol, 37% yield) of pure compound **9**

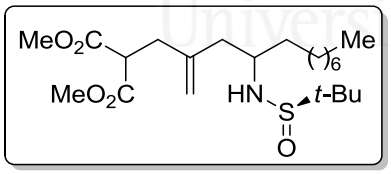
Dimethyl 2-[2-(chloromethyl)allyl]malonate (**9**): Colourless liquid; R_f 0.54 (hexane/EtOAc: 3/1); IR ν (film) 3040, 3002, 2956, 2847, 1739, 1437, 1341, 1232, 1154, 1028 cm^{-1}; δ_H 2.81 (2H, d, J = 7.9, CH_2CH), 3.67 (1H, t, J = 7.8, CHCH_2), 3.75 (6H, s, 2×CH_3), 4.06 (2H, s, CH_2), 5.01 (1H, s, C=CHH), 5.20 (1H, s, C=CHH); δ_C 32.0 (CH), 47.7 (CH_3), 50.1, 52.7 (CH_2), 116.7 (CH_2), 141.3 (C), 169.0 (C); LRMS (EI) *m/z* 185 (M^+-Cl, 100%), 157 (31), 153 (18), 129 (26), 125 (93), 101 (10), 67 (14), 65 (19), 59 (23).



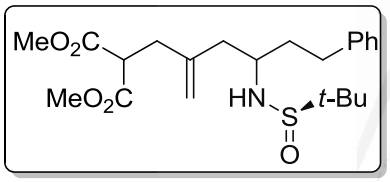
III.2.6. Synthesis of α-amino ester derivatives 10

General procedure.- A mixture of the corresponding aldimine **3** (0.5 mmol), dimethyl 2-[2-(chloromethyl)allyl]malonate (**9**, 0.337 g, 1.5 mmol), NaI (0.153 g, 1 mmol) and indium powder (0.075 g, 0.65 mmol) was stirred for 72 h at 23 °C. Then, the resulting mixture was hydrolyzed with 1M hydrochloric acid (10 mL), extrated with EtOAc (3 × 10 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield pure products **10**. Yields are given on Table 6. Physical and spectroscopic data follow.

(6S,R_S*)-Methyl 6-amino*-N-*(*tert-*butanesulfinyl)-2-methoxycarbonyl-4-methylenetetradecanoate* (**10a**): Colourless oil; $[\alpha]_D^{20}$ = -46 (*c* 1.29, CH_2Cl_2); R_f 0.38 (hexane/EtOAc: 1/1); IR ν (film) 3281, 2954, 2926, 2855, 1739, 1436, 1240, 1153, 1069 cm^{-1}; δ_H 0.88 (3H, t, J = 5.4 Hz, CH_3CH_2), 1.19 [9H, s, $(CH_3)_3$C], 1.20-1.40 (12H, m, 6×CH_2), 1.48-1.53 (1H, m, CH_2), 2.22-2.38 (2H, m, CH_2CHNH), 2.63-2.67 (2H, m, CH_2CHCO), 3.23 (1H, d, J = 4.7 Hz, NH), 3.37-3.42 (1H, m, CHNH), 3.64 (1H, t, J = 8.0 Hz, CH_2CHCO), 3.73 (6H, s, 2×CH_3O), 4.92 (2H, br s, C=CH_2); δ_C 13.9, 22.45 (CH_3), 25.05, 29.0, 29.3, 29.4, 31.6, 34.2, 35.0, 42.5 (CH_2), 50.1, 52.3 (CH), 53.05, 52.4 (CH_3), 55.5 (C), 114.6 (CH_2), 142.1 (C), 169.05, 169.1 (CO); LRMS (EI) *m/z* 266 [M^+-$(CH_3)_3SO$-HCO_2CH_3, 28%], 252 (18), 251 (100), 221 (11), 193 (10), 178 (14), 165 (12), 90 (16), 57 (13).



*(6*R,R*S)-Methyl 6-amino*-N-*(*tert-*butanesulfinyl)-2-methoxycarbonyl-7-methyl-4-methyleneoctanoate* (**10b**): Colourless oil; $[\alpha]_D^{20}$ = -54 (*c* 1.09, CH_2Cl_2); R_f 0.32 (hexane/EtOAc: 1/1); IR *ν* (film) 3286, 2957, 1738, 1645, 1436, 1240, 1153, 1069, 900 cm^{-1}; δ_H 0.89 (3H, d, *J* = 7.1 Hz, C*H*$_3$CH), 0.90 (3H, d, *J* = 8.1 Hz, C*H*$_3$CH), 1.21 [9H, s, $(CH_3)_3C$], 1.95-1.99 (1H, m, C*H*CH_3), 2.17 (1H, dd, *J* = 9.1, 14.1 Hz, C*H*HCHNH), 2.31 (1H, dd, *J* = 5.3, 14.1 Hz, CH*H*CHNH), 2.62-2.71 (2H, m, C*H*$_2$CHCO), 3.11 (1H, d, *J* = 4.1 Hz, NH), 3.29-3.33 (1H, m, C*H*NH), 3.64 (1H, t, *J* = 7.9 Hz, CH_2C*H*CO), 3.73 (6H, s, 2×CH_3O), 4.93 (1H, s, C=C*H*H), 4.94 (1H, s, C=CH*H*); δ_C 17.4, 17.6, 22.7 (CH_3), 30.5 (CH), 34.1, 38.4 (CH_2), 50.3 (CH), 52.6, 52.65 (CH_3), 55.8 (CH), 56.5 (C), 61.0 (CH_2), 114.8 (CH_2), 142.4 (C), 169.2, 169.3 (CO); LRMS (EI) *m/z* 287 [M^+-(CH_3)-(CO_2CH_3), 12%], 272 (31), 187 (16), 142 (100), 119 (28), 100 (37), 59 (22).

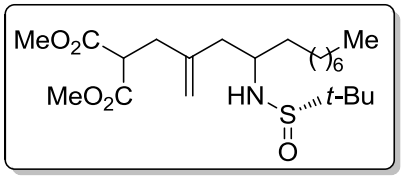


*(6*S,R*S)-Methyl 6-amino*-N-*(*tert-*butanesulfinyl)-2-methoxycarbonyl-4-methylene-8-phenyloctanoate* (**10c**): Colourless oil; $[\alpha]_D^{20}$ = -36 (*c* 1.27, CH_2Cl_2); R_f 0.29 (hexane/EtOAc: 1/1); IR *ν* (film) 3281, 3060, 3025, 2952, 2865, 1738, 1436, 1362, 1242, 1153, 1050, 901 cm^{-1}; δ_H 1.23 [9H, s, $(CH_3)_3C$], 1.80-1.89 (2H, m, CH_2C*H*$_2$CHN), 2.36-2.39 (2H, m, C*H*$_2$CHNH), 2.60-2.77 (4H, m, PhC*H*$_2$, C*H*$_2$C=CH_2), 3.31 (1H, d, *J* = 5.2 Hz, NH), 3.44-3.50 (1H, m, C*H*NH), 3.64 (1H, t, *J* = 7.8 Hz, CH_2C*H*CO), 3.72 (3H, s, CH_3O), 3.73 (3H, s, CH_3O), 4.92 (2H, br s, C=CH_2), 7.16-7.21 (3H, m, ArH), 7.26-7.31 (2H, m, ArH); δ_C 22.55 (CH_3), 31.5, 34.2, 36.8, 42.6 (CH_2), 55.0, 52.2 (CH), 52.5 (CH_3), 55.7 (C), 114.8 (CH_2), 125.8, 128.2 128.3 (CH), 141.5, 141.9 (C), 169.1 (CO); LRMS (EI) *m/z* 316 [M^+-Ph(CH_2)$_2$, 6%], 302 (16), 261 (10), 233 (41), 213 (19), 185 (84), 165 (15), 153 (22), 132 (14), 117 (17), 105 (16), 91 (100), 77 (22), 65 (18).

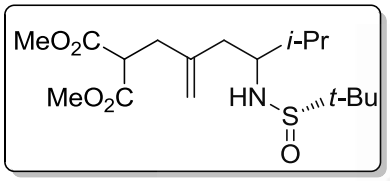
*(6*R,R*S)-Methyl 6-amino*-N-*(tert-butanesulfinyl)-2-methoxycarbonyl-4-methylene-6-phenylhexanoate* (**10d**): Colourless oil; $[\alpha]_D^{20}$ = -76 (*c* 1.08, CH_2Cl_2); R_f 0.28 (hexane/EtOAc: 1/1); IR *ν* (film) 3278, 3090, 3025, 2954, 1739, 1645, 1436, 1372, 1242, 1153, 1048, 903 cm^{-1}; δ_H 1.19 [9H, s, $(CH_3)_3C$], 2.40-2.50 (2H, m, C*H*$_2$CHNH), 2.63-2.68 (2H, m, C*H*$_2$C=CH_2), 3.62 (1H, t, *J* = 7.8 Hz, CH_2C*H*CO), 3.71 (1H, br s, NH), 3.72 (6H, s, 2×CH_3O), 4.53-4.58 (1H, m, C*H*NH), 4.97 (1H, s, C=C*H*H), 5.00 (1H, s, C=CH*H*), 7.26-7.31 (5H, m, ArH); δ_C

22.4 (CH_3), 34.1, 45.6 (CH_2), 50.1 (CH), 52.55 (CH_3), 55.0 (CH), 55.5 (C), 115.42 (CH_2), 127.4, 127.65, 128.4 (CH), 141.55, 141.7 (C), 168.95, 169.0 (CO); LRMS (EI) *m/z* 217 [M^+-$(CH_3)_3SONH$-HCO_2CH_3, 100%], 189 (81), 161 (43), 133 (22), 105 (15), 103 (13), 80 (10), 66 (15).

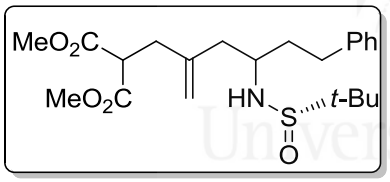
*(6*R,S*S)-Methyl 6-amino*-N-*(tert-butanesulfinyl)-2-methoxycarbonyl-4-methylene-tetradecanoate* (*ent*-**10a**): Physical and spectroscopic data were found to be the same than for **10a**; $[\alpha]_D^{20}$ = +49 (*c* 0.92, CH_2Cl_2).



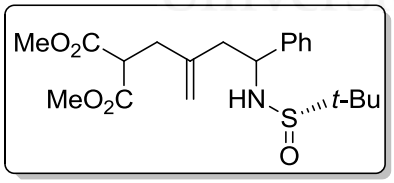
*(6*S,S*S)-Methyl 6-amino*-N-*(tert-butanesulfinyl)-2-methoxycarbonyl-7-methyl-4-methyl-eneoctanoate* (*ent*-**10b**): Physical and spectroscopic data were found to be the same than for **10b**; $[\alpha]_D^{20}$ = +67 (*c* 1.19, CH_2Cl_2).



*(6*R,S*S)-Methyl 6-amino*-N-*(tert-butanesulfinyl)-2-methoxycarbonyl-4-methylene-8-phenyloctanoate* (*ent*-**10c**): Physical and spectroscopic data were found to be the same than for **10c**; $[\alpha]_D^{20}$ = +36 (*c* 1.03, CH_2Cl_2).



*(6*S,S*S)-Methyl 6-amino*-N-*(tert-butanesulfinyl)-2-methoxycarbonyl-4-methylene-6-phenylhexanoate* (*ent*-**10d**): Physical and spectroscopic data were found to be the same than for **10d**; $[\alpha]_D^{20}$ = +62 (*c* 1.09, CH_2Cl_2).



III.2.7. Synthesis of dimethyl 2-bromomethylfumarate (17)

A solution of citraconic anhydride (**15**, 4.48 g, 40 mmol) in MeOH (40 mL) and concentrated H_2SO_4 (0.5 mL) was refluxed for 12 h under nitrogen. The reaction mixture was concentrated in vacuo (15 Torr). The residue was diluted with water and extracted with EtOAc (20 mL × 3). The combined organic layer was washed with water (20 mL) and brine and dried over $MgSO_4$. Concentration of organic layer in vacuo (15 Torr) gave 4.74 g (85% yield) of dimethyl methylmaleate (**16**) that was pure enough for the next reaction step.

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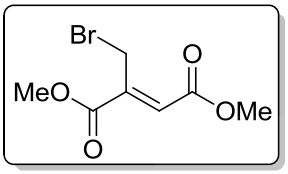
Dimethyl methylmaleate (**16**, 4.74 g, 30 mmol), NBS (8.00 g, 45 mmol), and catalytic amount of AIBN (200 mg, 1.22 mmol) in CCl_4 (150 mL) was gently refluxed for 12 h in a 250 mL round-bottom flask. The mixture was left overnight at room temperature and then filtered. The residue was washed with CCl_4 (25 mL × 2), and the combined organic layer was washed with water (50 mL × 2) and brine (50 mL) and then dried over $MgSO_4$ and concentrated in vacuo (15 Torr) to furnish a thick yellow oil, which was purified by column chromatography (silica gel, hexane/EtOAc, 10:1) to give 6.05 g (25.52 mmol, 85% yield) of dimethyl 2-bromomethylfumarate (**17**)

Dimethyl 2-bromomethylfumarate (**17**): Thick oil; R_f 0.56 (hexane/EtOAc: 3/1);



IR ν (film) 3052, 3005, 2954, 1720, 1434, 1274, 1212, 1152, 1010 cm^{-1}; δ_H 3.83 (3H, s, CH_3), 3.88 (3H, s, CH_3), 4.72 (2H, s, CH_2), 6.83 (1H, s, C=CH); δ_C 22.4 (CH_2), 52.2, 53.0 (CH_3), 128.3 (CH), 142.7 (C), 165.0, 165.1 (CO); LRMS (EI) *m/z* 206 (M^+, 86%), 204 (89), 179 (10), 177 (11), 125 (100), 98 (18), 68 (16), 59 (31).

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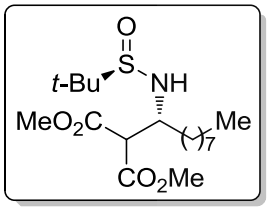
III.3. Experimental part of chapter II.2.

III.3.1. Synthesis of enantioenriched β-amino esters derivatives 24

III.3.1.1. Method A

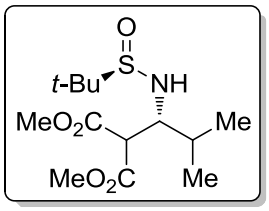
General procedure.- A heterogeneous mixture of dimethyl malonate (**7**, 1.056 g, 0.94 mL, 8.0 mmol), $NaHCO_3$ (236 mg, 4.0 mmol) and the corresponding *N-tert*-butanesulfinyl imine **3** (2.0 mmol) was stirred at room temperature for 72 h. The resulting mixture was hydrolyzed with water (10 mL), acidified with 2 M hydrochloric acid (3 mL), extracted with EtOAc (3×15 mL), dried with anhydrous $MgSO_4$ and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield pure compounds **24**. Yields are given on Table 8. Physical and spectroscopic data follow.

*(*R,R$_S$*)-Dimethyl 2-(1-aminononyl)*-N-*(*tert-*butanesulfinyl)malonate* (**24a**):



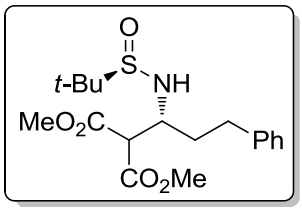
Colourless oil; $[\alpha]_D^{23}$ -38 (*c* 1.23, CH_2Cl_2); R_f 0.37 (hexane/EtOAc: 1/1); IR ν (film) 2953, 2925, 2856, 1735, 1434, 1240, 1159, 1075 cm^{-1}; δ_H 0.88 (3H, t, *J* = 6.8, C*H*$_3$CH$_2$), 1.22 [9H, s, (CH$_3$)$_3$C], 1.24-1.46 (12H, m, 6×CH$_2$), 1.54-1.59 (2H, m, CH$_2$), 3.77 (3H, s, CH$_3$), 3.80 (3H, s, CH$_3$), 3.78-3.84 (2H, m, CHCHN), 4.53 (1H, d, *J* = 9.3, NH); δ_C 14.1 (CH$_3$), 22.6 (CH$_2$), 22.7 (CH$_3$), 26.2, 29.0, 29.2, 29.4, 31.8, 34.1 (CH$_2$), 52.5, 52.8 (CH$_3$), 56.0 (CH), 56.2 (C), 56.9 (CH), 168.3, 168.8 (CO); LRMS (EI) *m/z* 270 (M$^+$-*t*-BuSOH$_2$, 7%), 255 (11), 225 (23), 200 (24), 187 (100), 175 (68), 143 (30), 133 (81), 101 (21), 69 (38), 55 (43).

*(*R,R$_S$*)-Dimethyl 2-(1-amino-2-methylpropyl)*-N-*(*tert-*butanesulfinyl)malonate* (**24b**):



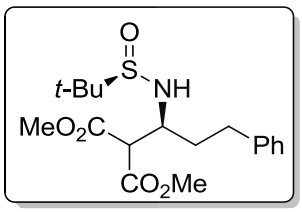
Colourless oil; $[\alpha]_D^{23}$ -38 (*c* 1.23, CH_2Cl_2); R_f 0.28 (hexane/EtOAc: 1/1); IR ν (film) 2957, 2930, 1731, 1434, 1262, 1194, 1159, 1076 cm^{-1}; δ_H 0.92 (6H, d, *J* = 6.8, 2×CH$_3$), 1.25 [9H, s, (CH$_3$)$_3$C], 1.75 [1H, h, *J* = 6.8, (CH$_3$)$_2$C*H*], 3.61-3.68 (1H, m, CHN), 3.73-3.76 (1H, m, C*H*CHN), 3.79 (3H, s, CH$_3$), 3.82 (3H, s, CH$_3$), 4.89 (1H, d, *J* = 8.4, NH); δ_C 18.8, 20.2, 23.0 (CH$_3$), 33.3 (CH), 52.6, 53.1 (CH$_3$), 53.9 (CH), 56.5 (C), 62.6 (CH), 168.0, 169.4 (CO); LRMS (EI) *m/z* 251[M$^+$-(CH$_3$)$_2$C=CH$_2$, 6%], 231 (15), 207 (18), 163 (19), 140 (37), 55 (100).

*(*R,R$_S$*)-Dimethyl 2-(1-amino-3-phenylpropyl)*-N-*(*tert-*butanesulfinyl)malonate*



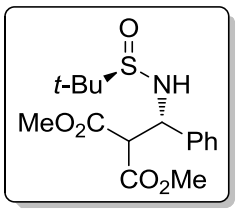
(**24c**): Colourless oil; $[\alpha]_D^{23}$ -32 (*c* 1.43, CH_2Cl_2); R_f 0.29 (hexane/EtOAc: 1/1); IR *ν* (film) 3060, 3024, 2953, 2924, 2855, 1734, 1434, 1240, 1071, 1045 cm^{-1}; δ_H 1.26 [9H, s, $(CH_3)_3C$], 1.89-1.95 (2H, m, CH_2), 2.59-2.66 (1H, m, C*H*H), 2.80-2.87 (1H, m, CH*H*), 3.72 (3H, s, CH_3), 3.78 (3H, s, CH_3), 3.80-3.86 (1H, m, CHN), 3.88 (1H, d, *J* = 4.1, C*H*CHN), 4.64 (1H, d, *J* = 9.6, NH), 7.15-7.21 (3H, m, ArH), 7.26-7.30 (2H, m, ArH); δ_C 22.7 (CH_3), 32.4, 35.8 (CH_2), 52.4, 52.8 (CH_3), 56.0 (CH), 56.2 (C), 56.3 (CH), 126.0, 128.2, 128.3, 140.8 (ArC), 168.0, 168.6 (CO); LRMS (EI) *m/z* 263 (M$^+$-*t*-BuSOH, 4%), 247 (11), 207 (36), 175 (100), 143 (44), 132 (23), 115 (30), 91 (82), 77 (19), 65 (16).

*(*S,R$_S$*)-Dimethyl 2-(1-amino-3-phenylpropyl)*-N-*(*tert-*butanesulfinyl)malonate*



(**24'c**): Colourless oil; $[\alpha]_D^{23}$ -96 (*c* 1.15, CH_2Cl_2); R_f 0.35 (hexane/EtOAc: 1/1); IR *ν* (film) 3183, 3062, 3028, 2955, 2931, 2860, 1727, 1258, 1239, 1152, 1039, 1021 cm^{-1}; δ_H 1.19 [9H, s, $(CH_3)_3C$], 1.86-1.95 (2H, m, C*H*H), 2.14-2.23 (1H, m, CH*H*), 2.67-2.75 (1H, m, C*H*H), 2.82-2.90 (1H, m, CH*H*), 3.68 (1H, d, *J* = 5.7, C*H*CHN), 3.70 (3H, s, CH_3), 3.75 (3H, s, CH_3), 3.83-3.92 (1H, m, CHN), 4.30 (1H, d, *J* = 9.3, NH), 7.15-7.21 (3H, m, ArH), 7.26-7.30 (2H, m, ArH); δ_C 22.6 (CH_3), 32.1, 36.1 (CH_2), 52.5, 52.6 (CH_3), 56.1 (CH), 56.2 (C), 57.0 (CH), 126.0, 128.4, 128.5, 140.7, (ArC), 168.0, 168.5 (C); LRMS (EI) *m/z* 263 (M$^+$-*t*-BuSOH, 1%), 248 (10), 216 (21), 183 (40), 156 (17), 128 (23), 117 (12), 91 (100), 65 (18).

*(*S,R$_S$*)-Dimethyl 2-(aminophenylmethyl)*-N-*(*tert-*butanesulfinyl)malonate* (**24d**):



Colourless oil; $[\alpha]_D^{23}$ -21 (*c* 0.98, CH_2Cl_2); R_f 0.26 (hexane/EtOAc: 1/1); IR *ν* (film) 3281, 3060, 2985, 2955, 1755, 1715, 1312, 1263, 1067, 1057 cm^{-1}; δ_H 1.19 [9H, s, $(CH_3)_3C$], 3.67 (3H, s, CH_3), 3.69 (3H, s, CH_3), 4.01 (1H, d, *J* = 6.7, C*H*CHN), 4.81 (1H, d, *J* = 9.4, NH), 5.09 (1H, dd, *J* = 9.3, 6.7, CHN), 7.30-7.41 (5H, m, ArH); δ_C 22.5 (CH_3), 52.6, 52.7 (CH_3), 56.4 (C), 58.1, 60.1 (CH), 127.0, 128.1, 128.6, 138.8 (ArC), 167.2, 168.2 (C); LRMS (EI) *m/z* 235 (M$^+$-*t*-BuSOH, 14%), 219 (77), 164 (12), 152 (100), 132 (29), 103 (51), 77 (48), 69 (17), 59 (21), 51 (20).

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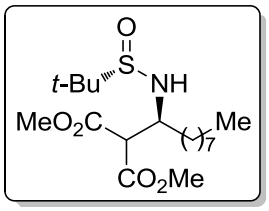
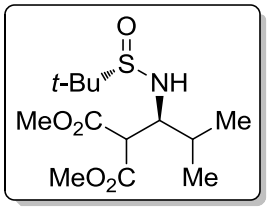
*(*S,S$_S$*)-Dimethyl 2-(1-aminononyl)*-N-*(*tert-*butanesulfinyl)malonate* (*ent*-**24a**).

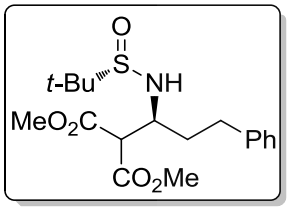


Physical and spectroscopic data were found to be same than for **24a**. $[\alpha]_D^{23}$ = +36 (*c* 1.46, CH_2Cl_2).

*(*S,S$_S$*)-Dimethyl 2-(1-amino-2-methylpropyl)*-N-*(*tert-*butanesulfinyl)malonate* (*ent*-**24b**). Physical and spectroscopic data were found to be same than for **24b**. $[\alpha]_D^{23}$ = +42 (*c* 1.40, CH_2Cl_2).



*(*S,S$_S$*)-Dimethyl 2-(1-amino-2-phenylpropyl)*-N-*(*tert-*butanesulfinyl)malonate* (*ent*-**24c**). Physical and spectroscopic data were found to be same than for **24c**. $[\alpha]_D^{23}$ = +29 (*c* 0.94, CH_2Cl_2).



III.3.1.2. Method B

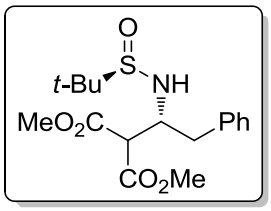
General procedure.- A heterogeneous mixture of dimethyl malonate (**7**, 0.528 g, 0.47 mL, 4.0 mmol), NaI (0.300 g, 2.0 mmol) and the corresponding *N-tert*-butanesulfinyl imine **3** (2.0 mmol) was stirred at room temperature for 72 h. The resulting mixture was hydrolyzed with water (10 mL), acidified with 2 M hydrochloric acid, extracted with EtOAc (3×15 mL), dried with anhydrous $MgSO_4$ and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield pure compounds **24**. Yields are given on Table 8. Physical and spectroscopic data follow.

*(*R,R$_S$*)-Dimethyl 2-(1-aminononyl)*-N-*(*tert-*butanesulfinyl)malonate* (**24a**). Physical and spectroscopic data are given above.

*(*R,R$_S$*)-Dimethyl 2-(1-Amino-2-methylpropyl)*-N-*(*tert-*butanesulfinyl)malonate* (**24b**). Physical and spectroscopic data are given above.

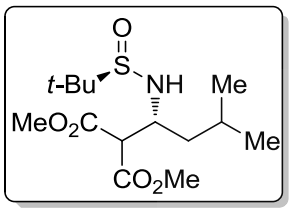
*(*R,R$_S$*)-Dimethyl 2-(1-amino-3-phenylpropyl)*-N-*(*tert-*butanesulfinyl)malonate* (**24c**). Physical and spectroscopic data are given above.

*(*R,R$_S$*)-Dimethyl 2-(1-amino-2-phenylethyl)*-N-*(*tert-*butanesulfinyl)malonate*



(**24e**): Colourless oil; $[\alpha]_D^{23}$ -35 (*c* 1.62, CH_2Cl_2); R_f 0.39 (hexane/EtOAc: 1/1); IR ν (film) 3050, 3023, 2978, 2954, 2924, 2854, 1734, 1240, 1073, 1046 cm^{-1}; δ_H 1.07 [9H, s, $(CH_3)_3C$], 2.92 (2H, d, *J* = 7.0, CH_2), 3.76-3.78 (1H, m, C*H*CHN), 3.80 (3H, s, CH_3), 3.81 (3H, s, CH_3), 4.11-4.14 (1H, m, CHN), 4.62 (1H, d, *J* = 9.3, NH), 7.17-7.31 (5H, m, ArH); δ_C 22.4 (CH_3), 40.6 (CH_2), 52.6, 53.0 (CH_3), 55.0 (CH), 56.1 (C), 58.5 (CH), 126.7, 128.5, 129.4, 137.5 (ArC), 168.2, 168.8 (C); LRMS (EI) *m/z* 249 (M^+-*t*-BuSOH, 15%), 234 (29), 132 (12), 117 (22), 91 (100), 65 (13).

*(*R,R$_S$*)-Dimethyl 2-(1-amino-3-methylbutyl)*-N-*(*tert-*butanesulfinyl)malonate*

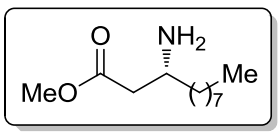


(**24f**): Colourless oil; $[\alpha]_D^{23}$ -38 (*c* 1.59, CH_2Cl_2); R_f 0.51 (hexane/EtOAc: 1/1); IR ν (film) 3330, 2953, 2925, 2870, 1745, 1721, 1254, 1160, 1064 cm^{-1}; δ_H 0.90 (3H, d, *J* = 6.5, CH_3), 0.92 (3H, d, *J* = 6.6, CH_3), 1.22 [9H, s, $(CH_3)_3C$], 1.24-1.28 (1H, m, C*H*H), 1.55-1.65 (1H, m, CH*H*), 1.72-1.79 [1H, m, $(CH_3)_2CH$], 3.77 (3H, s, CH_3), 3.80 (3H, s, CH_3), 3.84-3.92 (2H, m, CHCHN), 4.51 (1H, d, *J* = 9.7, NH); δ_C 20.9, 22.6 (CH_3), 23.1 (CH), 42.9 (CH_2), 52.3, 52.7 (CH_3), 55.1 (CH), 56.1 (C), 56.2 (CH), 168.1, 168.7 (C); LRMS (EI) *m/z* 169 [M^+-$(CH_3)_2CHCH_2$- *t*-BuSOH, 17%], 145 (10), 136 (71) 126 (100), 113 (34), 98 (53), 68 (34), 59 (21).

III.3.2. Synthesis of β-amino esters 27

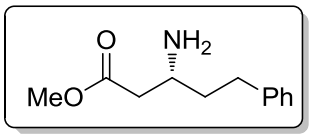
General procedure.- A mixture of dimethyl *2-(1-aminoalkyl)malonates* **3** (1.0 mmol) and 6 M hydrochloric acid (4 mL) was heated under reflux for 1.5 h. The mixture was cooled down to room temperature, and MeOH (16 mL) was added. The reaction mixture was stirred for 36 h at the same temperature and quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL). The resulting mixture was extracted with EtOAc (3×15 mL), dried with anhydrous $MgSO_4$ and evaporated (15 Torr). The residue **27** was pure enough for the next reaction. Yields are given on Table 9. Physical and spectroscopic data follow.

*(*R*)-Methyl 3-aminoundecanoate* (**27a**): Colourless oil; $[\alpha]_D^{23}$ -9 (*c* 1.48, CH_2Cl_2); R_f 0.45 (EtOAc); IR ν (film) 2953, 2923, 2854, 1735, 1436, 1165, 1017 cm^{-1}; δ_H 0.88 (3H, t, *J* = 7.0, CH_3CH_2), 1.27-1.43 (14H, m, 7×CH_2), 2.34 (1H, dd, *J* = 15.9, 8.8, C*H*H), 2.52 (1H, dd, *J* = 15.9, 4.1, CH*H*), 2.76 (2H, br s,

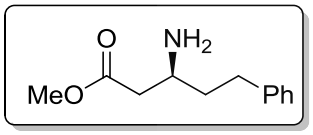


NH_2), 3.20-3.26 (1H, m, CHN), 3.70 (3H, s, CH_3); δ_C 14.1 (CH_3), 22.6, 26.0, 29.2, 29.5, 31.8, 36.9, 41.5 (CH_2), 48.4 (CH), 51.6 (CH_3), 172.8 (C); LRMS (EI) *m/z* 200 (M^+-NH_3, 8%), 142 (79), 102 (100), 70 (31), 60 (24), 56 (15).

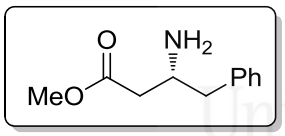
*(*R*)-Methyl 3-amino-5-phenylpentanoate* (**27c**): Colourless oil; $[\alpha]_D^{23}$ +5 (*c* 0.61, CH_2Cl_2); R_f 0.37 (EtOAc); IR ν (film) 3025, 2950, 2923, 2857, 1731, 1435, 1158, 838 cm^{-1}; δ_H 1.62-1.82 (4H, m, CH_2, NH_2), 2.33 (1H, dd, *J* = 15.7, 6.9, C*H*H), 2.52 (1H, dd, *J* = 15.7, 4.0, CH*H*), 2.62-2.81 (2H, m, CH_2), 3.15-3.26 (1H, m, CHN), 3.69 (3H, s, CH_3), 7.16-7.21 (3H, m, ArH), 7.24-7.31 (2H, m, ArH); δ_C 32.4, 39.2, 42.4 (CH_2), 48.0 (CH), 51.5 (CH_3), 125.9, 128.3, 128.4, 141.6 (ArC), 172.8 (C); LRMS (EI) *m/z* 207 (M^+, 15%), 190 (22), 134 (42), 130 (29), 117 (27), 102 (100), 91 (83), 70 (30), 60 (21).



(S)-Methyl 3-amino-5-phenylpentanoate (*ent*-**27c**). Physical and spectroscopic data were found to be same than for **27c**. $[\alpha]_D^{23}$ = -5 (*c* 1.32, CH_2Cl_2).



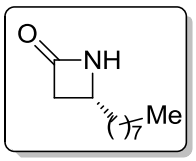
*(*R*)-Methyl 3-amino-4-phenylbutanoate* (**27e**): Colourless oil; $[\alpha]_D^{23}$ +7 (*c* 1.54, CH_2Cl_2); R_f 0.55 (MeOH/CH_2Cl_2: 1/1); IR ν (film) 3060, 3026, 2950, 2922, 2853, 1731, 1454, 1436, 1258, 1195, 1160 cm^{-1}; δ_H 1.69 (2H, br s, NH_2), 2.34 (1H, dd, *J* = 15.9, 8.8, C*H*H), 2.52 (1H, dd, *J* = 15.9, 4.1, CH*H*), 2.63 (1H, dd, *J* = 13.4, 5.7, C*H*H), 3.43-3.51 (1H, m, CHN), 3.68 (3H, s, CH_3), 7.19-7.33 (5H, m, ArH); δ_C 41.5, 43.9 (CH_2), 49.6 (CH), 51.6 (CH_3), 126.5, 128.5, 129.3, 138.4 (ArC), 172.8 (C); LRMS (EI) *m/z* 120 [M^+-$CH_2CO_2CH_3$, 24%), 102 (100), 91 (17), 70 (22), 60 (18).



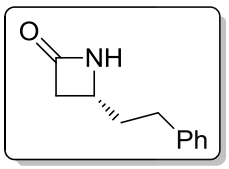
III.3.3. Synthesis of β-lactams 28

General procedure.- To a THF solution (8 mL) of diisopropylamine (0.272 mg, 0.377 mL, 2.7 mmol) was added *n*-BuLi (2.5 M in *n*-hexane, 1.0 mL, 2.5 mmol) at 0 °C. After stirring for 30 min, the mixture was cooled down to –78 °C. To the mixture was added a solution of the corresponding β-amino ester **27** (0.7 mmol) in THF (3 mL). After stirring at the same temperature for 24 h, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL). The resulting mixture was extracted with EtOAc (3×15 mL), dried with anhydrous $MgSO_4$ and evaporated (15 Torr). The residue was purified by

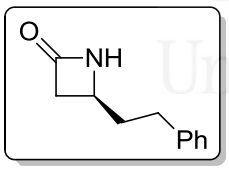
column chromatography (silica gel, hexane/EtOAc) to yield pure compounds **28**. Yields are given on Table 9. Physical and spectroscopic data follow.



*(*R*)-4-Octylazetidin-2-one* (**28a**): White solid; mp 47-48 ºC (CH_2Cl_2/hexane); $[\alpha]_D^{23}$ -8 (*c* 1.06, CH_2Cl_2); R_f 0.57 (hexane/EtOAc: 1/1); IR *ν* (KBr) 3190-3130, 2955, 2918, 2849, 1779, 1701, 1467, 1199 cm^{-1}; δ_H 0.88 (3H, t, *J* = 7.0, C*H*$_3$CH$_2$), 1.27-1.44 (12H, m, 6×CH_2), 1.54-1.67 (2H, m, CH_2), 2.52 (1H, ddd, *J* = 16.9, 4.6, 3.4, C*H*HCO), 3.04 (1H, ddd, *J* = 14.8, 5.0, 2.1, CH*H*CO), 3.56-3.63 (1H, m, CHN), 6.61 (1H, br s, NH); δ_C 13.9 (CH_3), 22.5, 26.1, 29.1, 29.2, 29.3, 31.7, 35.3, 43.3 (CH_2), 48.1 (CH), 168.5 (C); LRMS (EI) *m/z* 140 (M^+-HN=C=O, 31%), 111 (15), 97 (32), 83 (38), 70 (100), 69 (67), 56 (96).



*(*R*)-4-(2-Phenylethyl)azetidin-2-one* (**28c**): Colourless oil; $[\alpha]_D^{23}$ +11 (*c* 1.35, CH_2Cl_2); R_f 0.40 (hexane/EtOAc: 1/1); IR *ν* (film) 3290-3220, 3060, 3025, 2925, 1736, 1495, 1454, 1373, 1182 cm^{-1}; δ_H 1.97 (2H, t, *J* = 7.6, CH_2), 2.57 (1H, ddd, *J* = 14.9, 2.4, 1.3, C*H*HCO), 2.63-2.76 (2H, m, CH_2Ph), 3.06 (1H, ddd, *J* = 14.9, 5.0, 2.2, CH*H*CO), 3.60-3.67 (1H, m, CHN), 5.79 (1H, br s, NH), 7.16-7.33 (5H, m, ArH); δ_C 32.9, 36.9, 43.5 (CH_2), 47.8 (CH), 126.3, 128.3, 128.6, 140.5 (ArC), 167.8 (C); LRMS (EI) *m/z* 175 (M^+, 23%), 158 (19), 133 (44), 132 (35), 91 (100), 65 (12).



*(*S*)-4-(2-Phenylethyl)azetidin-2-one* (*ent*-**28c**). Physical and spectroscopic data were found to be same than for **28c**. $[\alpha]_D^{23}$ = -10 (*c* 1.31, CH_2Cl_2).

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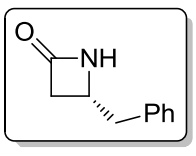
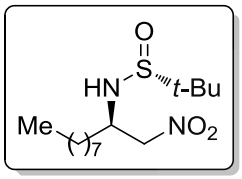


*(*R*)-4-Benzylazetidin-2-one* (**28e**): Colourless oil; $[\alpha]_D^{23}$ +18 (*c* 1.44, CH_2Cl_2); R_f 0.36 (hexane/EtOAc: 1/1); IR *ν* (film) 3305-3210, 2951, 2923, 2852, 1738, 1454, 1364, 1179 cm^{-1}; δ_H 2.69 (1H, ddd, *J* = 14.8, 2.3, 1.2, C*H*HCO), 2.85 (1H, dd, *J* = 13.7, 7.8, C*H*H), 2.97 (1H, dd, *J* = 13.7, 5.9, CH*H*), 3.06 (1H, ddd, *J* = 14.8, 4.9, 2.2, CH*H*CO), 3.80-3.87 (1H, m, CHN), 6.10 (1H, br s, NH), 7.16-7.37 (5H, m, ArH); δ_C 41.8, 43.2 (CH_2), 48.9 (CH), 126.8, 128.7, 128.8, 137.5 (ArC), 167.6 (C); LRMS (EI) *m/z* 161 (M^+, 9%), 133 (11), 118 (100), 117 (42), 91 (64), 70 (39), 65 (16).

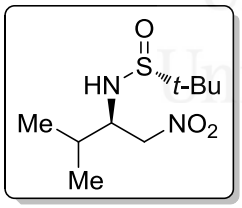
III.3.4. Synthesis of enantioenriched β-nitroamine derivatives 30

General procedure.- A heterogeneous mixture of nitromethane (**29**, 186 mg, 0.165 mL, 3.0 mmol), $NaHCO_3$ (118 mg, 2.0 mmol) and the corresponding *N-tert*-butanesulfinyl imine **3** (1.0 mmol) was stirred at room temperature for 72 h. The resulting mixture was hydrolyzed with water (10 mL), acidified with 2 M hydrochloric acid (3 mL), extracted with EtOAc (3×15 mL), dried with anhydrous $MgSO_4$ and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to yield pure compounds **30**. Yields are given on Table 11. Physical and spectroscopic data follow.

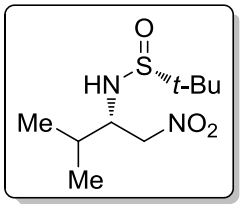
*(*R,R*S)*-N-*(*tert-*Butanesulfinyl)-1-nitrodecan-2-amine* (**30a**): White solid; mp 56-57 °C (hexane/CH_2Cl_2); $[\alpha]_D^{23}$ -33 (*c* 1.21, CH_2Cl_2); R_f 0.62 (hexane/EtOAc: 1/1); IR *ν* (KBr) 3136, 2949, 2922, 2854, 1554, 1378, 1364, 1042 cm^{-1}; δ_H 0. 0.88 (3H, t, *J* = 6.7, C*H*$_3$CH$_2$), 1.23 [9H, s, $(CH_3)_3C$], 1.24-1.49 (12H, m, 6×CH_2), 1.54-1.69 (2H, m, CH_2), 3.76-3.82 (1H, m, C*H*CHN), 4.12 (1H, d, *J* = 9.3, NH), 4.64-4.72 (2H, m, CH_2NO_2); δ_C 13.8 (CH_3), 22.2 (CH_2), 22.4 (CH_3), 25.5, 28.2, 28.9, 29.1, 31.5, 32.8 (CH_2), 54.9 (CH), 56.1 (C), 79.6 (CH_2); LRMS (EI) *m/z* 187 (M^+-*t*-BuSON, 40%), 170 (17), 143 (28), 140 (25), 129 (77), 95 (35), 90 (33), 81 (46), 69 (58), 57 (69), 55 (100).



*(*R,R*S)*-N-*(*tert-*Butanesulfinyl)-3-methyl-1-nitrobutan-2-amine* (**30b**): White solid; mp 39-40 °C (hexane/CH_2Cl_2); $[\alpha]_D^{23}$ -61 (*c* 1.23, CH_2Cl_2); R_f 0.49 (hexane/EtOAc: 1/1); IR *ν* (KBr) 3157, 2962, 2925, 2871, 1555, 1469, 1379, 1042 cm^{-1}; δ_H 0.99 (3H, d, *J* = 6.8, CH_3), 1.00 (3H, d, *J* = 6.7, CH_3), 1.25 [9H, s, $(CH_3)_3C$], 1.91 [1H, h, *J* = 6.7, C*H*$(CH_3)_2$], 3.53-3.60 (1H, m, CHN), 4.12 (1H, d, *J* = 8.5, NH), 4.75 (2H, d, *J* = 5.1, CH_2NO_2); δ_C 18.2, 19.1, 22.4 (CH_3), 30.7 (CH), 56.3 (C), 60.6 (CH), 77.7 (CH_2); LRMS (EI) *m/z* 220 (M^+, 1%), 132 (12), 119 (25), 90 (10), 69 (21), 57 (100).

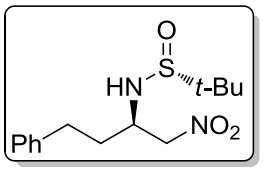


*(*S,R*S)*-N-tert-*Butanesulfinyl-3-methyl-1-nitrobutan-2-amine* (**30'b**): Colourless oil; $[\alpha]_D^{23}$ -28 (*c* 1.05, CH_2Cl_2); R_f 0.43 (hexane/EtOAc: 1/1); IR *ν* (film) 3158, 2960, 2927, 2869, 1556, 1472, 1380, 1043 cm^{-1}; δ_H 1.04 (3H, d, *J* = 6.8, CH_3), 1.05 (3H, d, *J* = 6.8, CH_3), 1.18 [9H, s, $(CH_3)_3C$], 2.07 [1H, h, *J* = 6.8, C*H*$(CH_3)_2$], 3.39 (1H, d, *J* = 8.7, NH), 3.85-3.92 (1H, m, CHN), 4.39 (1H, dd, *J* = 12.5, 9.7, C*H*HNO_2), 4.48 (1H, dd, *J* = 12.5, 3.2, CH*H*NO_2); δ_C 18.2, 18.8, 22.4 (CH_3), 31.4 (CH), 56.5 (C), 60.9 (CH),



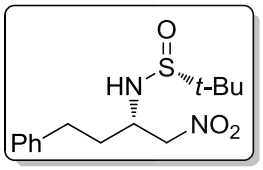
77.9 (CH_2); LRMS (EI) *m/z* 220 (M^+, 1%), 132 (11), 119 (20), 90 (15), 69 (23), 57 (100).

*(*R,R*S)*-N-*(*tert-*Butanesulfinyl)-1-nitro-4-phenylbutan-2-amine* (**30c**): Colourless



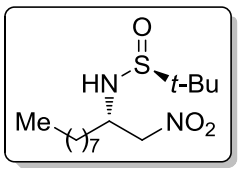
oil; $[\alpha]_D^{23}$ -24 (*c* 1.14, CH_2Cl_2); R_f 0.55 (hexane/EtOAc: 1/1); IR *ν* (film) 3298, 3026, 2955, 2923, 2854, 1550, 1375, 1240, 1045 cm^{-1}; δ_H 1.25 [9H, s, $(CH_3)_3C$], 1.86-1.97 (2H, m, CH_2), 2.65-2.72 (1H, m, C*H*H), 2.79-2.86 (1H, m, CH*H*), 3.74-3.80 (1H, m, CHN), 4.21 (1H, d, *J* = 9.4, NH), 4.61 (1H, dd, *J* = 13.0, 5.3, C*H*HNO_2), 4.71 (1H, dd, *J* = 13.0, 4.8, CH*H*NO_2), 7.14-7.22 (3H, m, ArH), 7.26-7.31 (2H, m, ArH); δ_C 22.4 (CH_3), 31.6, 34.6 (CH_2), 54.2 (CH), 56.3 (C), 79.6 (CH_2), 126.0, 128.2, 128.5, 140.1 (ArC); LRMS (EI) *m/z* 179 (M^+-*t*-BuSON, 12%), 136 (15), 131 (21), 104 (73), 91 (100), 90 (62), 77 (18), 65 (17).

*(*S,R*S)*-N-*(*tert-*Butanesulfinyl)-1-nitro-4-phenylbutan-2-amine* (**30'c**): Colourless



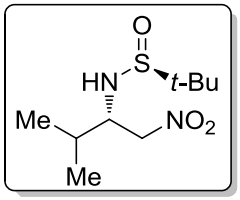
oil; $[\alpha]_D^{23}$ -28 (*c* 0.80, CH_2Cl_2); R_f 0.58 (hexane/EtOAc: 1/1); IR *ν* (film) 3296, 3027, 2955, 2922, 2856, 1551, 1374, 1240, 1045 cm^{-1}; δ_H 1.27 [9H, s, $(CH_3)_3C$], 1.86-1.98 (2H, m, CH_2), 2.60-2.74 (1H, m, C*H*H), 2.80-2.88 (1H, m, CH*H*), 3.73-3.79 (1H, m, CHN), 4.15 (1H, d, *J* = 9.4, NH), 4.63 (1H, dd, *J* = 13.0, 5.2, C*H*HNO_2), 4.75 (1H, dd, *J* = 13.0, 4.5, CH*H*NO_2), 7.14-7.22 (3H, m, ArH), 7.26-7.31 (2H, m, ArH); δ_C 22.6 (CH_3), 31.8, 34.8 (CH_2), 54.3 (CH), 56.5 (C), 79.8 (CH_2), 126.0, 128.4, 128.7, 140.2 (ArC); LRMS (EI) *m/z* 179 (M^+-*t*-BuSON, 14%), 136 (16), 131 (18), 104 (74), 91 (100), 90 (65), 77 (19), 65 (19).

*(*S,S*S)*-N-*(*tert-*Butanesulfinyl)-1-nitrodecan-2-amine* (*ent*-**30a**). Physical and



spectroscopic data were found to be same than for **30a**. $[\alpha]_D^{23}$ = +31 (*c* 1.08, CH_2Cl_2).

*(*S,S*S)-(*N-tert-*Butanesulfinyl)-3-methyl-1-nitrobutan-2-amine* (*ent*-**30b**).



Physical and spectroscopic data were found to be same than for **30b**. $[\alpha]_D^{23}$ = +59 (*c* 1.25, CH_2Cl_2).

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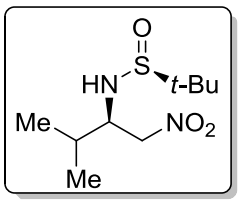
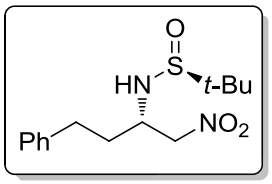
*(*R,S*S)*-N-*(*tert-*Butanesulfinyl)-3-methyl-1-nitrobutan-2-amine* (*ent*-**30'b**).



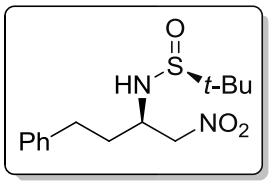
Physical and spectroscopic data were found to be same than for **30'b**. $[\alpha]_D^{23}$ = +26 (*c* 1.25, CH_2Cl_2).

*(*S,S*S)*-N-*(*tert-*Butanesulfinyl)-1-nitro-4-phenylbutan-2-amine* (*ent*-**30c**).



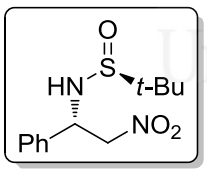
Physical and spectroscopic data were found to be same than for **30c**. $[\alpha]_D^{23}$ = +25 (*c* 1.70, CH_2Cl_2).

*(*R,S*S)*-N-*(*tert-*Butanesulfinyl)-1-nitro-4-phenylbutan-2-amine* (*ent*-**30'c**):

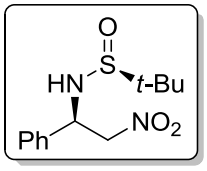


Physical and spectroscopic data were found to be same than for **30'c**. $[\alpha]_D^{23}$ = +30 (*c* 0.77, CH_2Cl_2).

*(*S,S*S)*-N-*(*tert-*Butanesulfinyl)-2-nitro-1-phenylethanamine* (*ent*-**30d**): White solid; mp 59-60 °C (hexane/CH_2Cl_2); $[\alpha]_D^{23}$ +63 (*c* 1.12, CH_2Cl_2); R_f 0.61 (hexane/EtOAc: 1/1); IR ν (KBr) 3259, 3060, 3025, 2981, 2962, 1551, 1377, 1050 cm^{-1}; δ_H 1.19 [9H, s, $(CH_3)_3C$], 3.90 (1H, d, *J* = 7.0, NH), 4.67 (1H, dd, *J* = 12.7, 5.2, C*H*HNO_2), 4.78 (1H, dd, *J* = 12.7, 9.0, CH*H*NO_2), 5.14-5.20 (1H, m, CHN), 7.33-7.42 (5H, m, ArH); δ_C 22.4 (CH_3), 56.6 (C), 57.8 (CH), 79.7 (CH_2), 126.7, 129.0, 129.3, 137.0 (ArC); LRMS (EI) *m/z* 165 (M^+-*t*-BuSO, 41%), 150 (10), 117 (41), 106 (49), 104 (90), 91 (29), 77 (61), 57 (100), 51 (32).



*(*R,S*S)*-N-*(*tert-*Butanesulfinyl)-2-nitro-1-phenylethanamine* (*ent*-**30'd**): Colourless oil; $[\alpha]_D^{23}$ +94 (*c* 0.44, CH_2Cl_2); R_f 0.56 (hexane/EtOAc: 1/1); IR ν (KBr) 3230-3180, 3061, 3025, 2978, 2960, 1551, 1375, 1046 cm^{-1}; δ_H 1.25 [9H, s, $(CH_3)_3C$], 4.45 (1H, d, *J* = 5.0, NH), 4.79 (1H, dd, *J* = 13.3, 4.7, C*H*HNO_2), 4.85 (1H, dd, *J* = 13.3, 7.4, CH*H*NO_2), 5.06-5.10 (1H, m, CHN), 7.33-7.42 (5H, m, ArH); δ_C 22.5 (CH_3), 56.2 (C), 56.8 (CH), 80.0 (CH_2), 127.3,

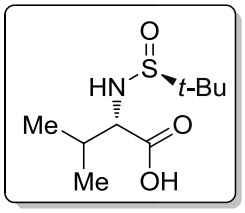


129.0, 129.1, 136.1 (ArC); LRMS (EI) *m/z* 165 (M^+-*t*-BuSO, 36%), 150 (13), 117 (40), 106 (53), 104 (81), 91 (34), 77 (57), 57 (100), 51 (36).

III.3.5. Synthesis of β-amino acid derivative *ent*-31b

Solid $NaNO_2$ (207 mg, 3.0 mmol) was added to a stirred solution of compound *ent*-**30b** (118 mg, 0.50 mmol) and AcOH (150 mg, 0.143 mL, 2.50 mmol) in a 7:1 mixture of DMF and water (1.25 mL) at 23 °C. The reaction was heated at 45 °C for 12 hours. After that, it was quenched with a 2 M NaOH water solution (10 mL) and extracted with CH_2Cl_2 (2×15 mL). The aqueous layer was acidified with 2 M hydrochloric acid (12 mL) and extrated with EtOAc (3×15 mL), dried with anhydrous $MgSO_4$ and evaporated (15 Torr) to give 76 mg (0.34 mmol, 68% yield) of title compound (*S*,S_S)-*N*-*tert*-butanesulfinyl-2-amino-3-methylbutanoic acid

(S,S_S)-N-tert-butanesulfinyl-2-amino-3-methylbutanoic acid (*ent*-**31b**): White solid; decomposed >120 °C; $[\alpha]_D^{23}$ +75 (*c* 1.07, $CHCl_3$); R_f 0.69 (MeOH/CH_2Cl_2: 1/1); IR *ν* (KBr) 3269, 2958, 2929, 2872, 1721, 1384, 1257, 1024, 1014 cm^{-1}; δ_H 0.90 (3H, d, *J* = 6.8, CH_3), 0.98 (3H, d, *J* = 6.8, CH_3), 1.31 [9H, s, $(CH_3)_3C$], 2.05-2.16 [1H, m, C*H*$(CH_3)_2$], 3.72 (1H, dd, *J* = 7.8, 5.0, CHN), 4.45 (1H, d, *J* = 7.9, NH); δ_C 17.2, 19.3, 22.85 (CH_3), 32.1 (CH), 56.9 (C), 64.0 (CH), 173.9 (C); LRMS (EI) *m/z* 165 [M^+-$(CH_3)_2C{=}CH_2$, 17%], 119 (42), 105 (10), 72 (33), 57 (100), 56 (27).



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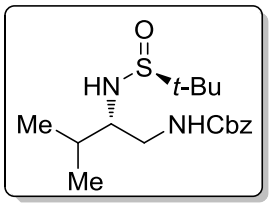
III.3.6. Synthesis of 1,2-diamino derivative *ent*-33b

To a solution of compound *ent*-**30b** (160 mg, 0.68 mmol) and $NiCl_2{\cdot}6H_2O$ (161.4 mg, 0.68 mmol) in dry MeOH (5 mL) under argon at -5 °C was slowly added $NaBH_4$ (128.8 mg, 2.31 mmol). The mixture was stirred at the same temperature for 25 min, quenched with a saturated $NaHCO_3$ aqueous solution (5 mL) and filtered through a Celite path. The filtrated was concentrated under vacumn (15 Torr), and extrated with EtOAc (3×15 mL), dried with anhydrous $MgSO_4$ and evaporated (15 Torr) to give crude diamine derivative *ent*-**32b** as a brown oil: 103.5 mg (0.5 mmol, 74% yiedl). Then a solution of *ent*-**30b** (103 mg, 0.50 mmol) in CH_2Cl_2 (2 mL) was added to a 2 M NaOH aqueous solution (1.25 mL) at 0 °C. After that, CbzCl (0.128 mg, 0.106 mL, 0.75 mmol) was slowly added to the reaction mixture at the system was allowed to reach 23 °C after 1 h. The reaction was quenched with brine (10 mL), extrated with EtOAc (3×15 mL), dried with anhydrous $MgSO_4$ and evaporated (15 Torr) to give 88 mg (0.26 mmol, 52% yield) of title compound (*S*,S_S)-N^1-benzyloxycarbonyl-N^2-(*tert*-butanesulfinyl)butane-1,2-diamine

(S,S_S)-N^1-benzyloxycarbonyl-N^2-(tert-butanesulfinyl)butane-1,2-diamine (*ent*-**33b**): 

Colourless oil; $[\alpha]_D^{23}$ +56 (*c* 1.04, CH_2Cl_2); R_f 0.41 (hexane/EtOAc: 1/1); IR ν (KBr) 3290-3245, 3057, 3035, 2960, 2928, 2872, 1705, 1535, 1264, 1042, 1027 cm^{-1}; δ_H 0.91 (3H, d, *J* = 6.8, CH_3), 0.94 (3H, d, *J* = 6.8, CH_3), 1.24 [9H, s, $(CH_3)_3C$], 1.73-1.81 [1H, m, C*H*$(CH_3)_2$], 3.06-3.13 (2H, m, CH_2N), 3.40 (1H, d, *J* = 7.7, NH), 3.48-3.55 (1H, m, CHN), 5.06-5.15 (2H, m, CH_2O), 6.32 (1H, br s, NH), 7.25-7.38 (5H, m, ArH); δ_C 17.6, 19.5, 22.8 (CH_3), 31.8 (CH), 44.35 (CH_2), 56.25 (C), 63.7 (CH), 66.5 (CH_2), 127.7, 127.8, 128.3, 136.7 (ArC), 157.2 (C); LRMS (EI) *m/z* 205 (M^+-BnOCO, 7%), 176 (11), 91 (100), 72 (44), 65 (13), 55 (10).

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IV. Conclusions

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1) Enantioenriched amino ester derivatives **5** could be prepared in high yields through an indium-mediated coupling of ethyl 2-(bromomethyl)acrylate (**4**) with chiral *N*-*tert*-butanesulfinyl imines **3**.

2) Enantiomerically pure butyrolactams **6** are accessible from amino ester derivatives **5** in a one-pot process upon removal of the *tert*-butanesulfinyl group under acidic conditions followed by basic workup.

3) Indium-mediated coupling of dimethyl 2-[2-(chloromethyl)allyl]malonate (**9**) with chiral *N*-*tert*-butanesulfinyl imines **3** in the presence of sodium iodide under solvent free conditions occurs in a total stereoselective fashion.

4) The reaction of dimethyl 2-bromomethylfumarate (**17**) and commercially available (*E*)-methyl 4-bromocrotonate (**18**) with chiral *N*-*tert*-butanesulfinyl imines **3** in the presence of indium metal proceeds with poor regio- and stereoselectivity under different reaction conditions.

5) Sodium bicarbonate is an effective base to promote the stereoselective coupling of dimethyl malonate (**7**) and nitromethane (**27**) with chiral *N*-*tert*-butanesulfinyl imines **3** to render dimethyl 2-(1-aminoalkyl)malonates **24** and primary 2-aminonitroalkanes **30**, respectively.

6) Enantioenriched β-lactams **27** are accessible from dimethyl 2-(1-aminoalkyl)malonates **24**.

7) Primary 2-aminonitroalkanes **30** are appropriate precursors of α-amino acids and vicinal diamines upon selective oxidation and reduction of the nitro group, respectively.

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V. Abbreviations

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^{13}C-NMR	carbon 13 nuclear magnetic resonance
^{1}H-NMR	proton nuclear magnetic resonance
Ac	acetyl
AcOEt	ethyl acetate
AcOH	acetic acid
AIBN	azo-bis-isobutyronitrile
aq	aqueous
Ar	aryl
BINAP	2,2 '-bis(diphenylphosphine) -1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br s	broad singlet
c	concentration
Cbz	benzyloxycarbonyl
Cy	cyclohexyl
d	doublet
de	diasteriomeric excess
DMF	*N,N*-dimethylformamide
dr	diasteriomeric ratio
ee	enantiomeric excess
EI	electronic impact
equiv	equivalent
er	enantiomeric ratio
Et	ethyl
g	gram
GLC	gas-liquid chromatography
h	heptet
h	hour
HMPA	Hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
IR	infrared
J	coupling constant
LDA	lithium diisopropylamide
LRMS	low resolution mass spectroscopy
M	metal
m	multiplet
Me	methyl
MeOH	methanol
min	minute
MOM	methoxy methyl
mp	melting point
MS	molecular sieves
NaHMDS	sodium hexamethyldisilazane
NaOMe	sodium methoxide

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NBS	*N*-bromosuccinimide
NME	(–)-*N*-methylephedrine
No.	number
Nu^-	nucleophile
P_G	protecting group
Ph	phenyl
PhMe	toluene
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
Py	pyridine
q	quartet
rt	room temperatura
s	singlet
sat.	saturated
sol.	solution
t	triplet
TBAF	tetra-*n*-butylamonium fluoride
TBS	*tert*-butyldimethylsilyl
t-Bu	tert-butyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofurane
TLC	thin layer chromatography
TMS-	trimethylsilyl
t_{ret}	retention time
Ts	*p*-toluenosulfonyl (tosyl)
TSI	transition state I
TSII	transition state II
TSIII	transition state III
TSIV	transition state IV
TSV	transition state V
TSVI	transition state VI
X	halogen
δ	chemical shift

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VI. Publications

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VI.1. Stereoselective Synthesis of α-Methylene-γ-butyrolactams from Ethyl 2-(Bromomethyl)acrylate and Chiral Sulfinyl Aldimines Mediated by Indium

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STEREOSELECTIVE SYNTHESIS OF α-METHYLENE-γ-BUTYRO-LACTAMS FROM ETHYL 2-(BROMOMETHYL)ACRYLATE AND CHIRAL SULFINYL ALDIMINES MEDIATED BY INDIUM

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Abstract – The reaction of ethyl 2-(bromomethyl)acrylate (**1**) with chiral *N-tert*-butylsulfinyl aldimines **2** and indium powder in THF at 100 °C for 48 h affords, after hydrolysis, a mixture of *N-tert*-butylsulfinyl aminoesters **3** and α-methylene-γ-butyrolactams **4**. From the reaction mixture, compounds **3** were quantitatively converted to the expected butyrolactams **4** after removal of the *tert*-butylsulfinyl group under acidic conditions and final basic workup. The whole process takes place in high overall yields and with fairly good stereoselectivities.

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Homoallylic amines,[1] which are compounds of interest themselves because they can be intermediates in the synthesis of other nitrogenated materials, are easily accessible in enantioenriched form by asymmetric allylation of imines using chiral auxiliaries[2] or under asymmetric catalysis,[3] as well. Allyl indium species[4] are ideal allylating reagents in these processes. They can be generated in the presence of the imine from allyl halides and indium metal under mild reaction conditions and exhibit high tolerance to a wide range of functional groups in many solvents.[5] Among chiral auxiliaries, sulfinimines[6] have been widely studied, specially the *N-tert*-butylsulfinyl derivatives, due to the possibility of preparing both enantiomers in large scale processes,[7] and also because the chiral auxiliary can be easily removed under acidic conditions.[8] In addition, a practical process for recycling the *tert*-butylsulfinyl group upon deprotection of the *N-tert*-butylsulfinylamines has been recently reported.[9] On the other hand, the α-methylene-γ-butyrolactone and γ-butyrolactam rings are present in many bioactive natural products

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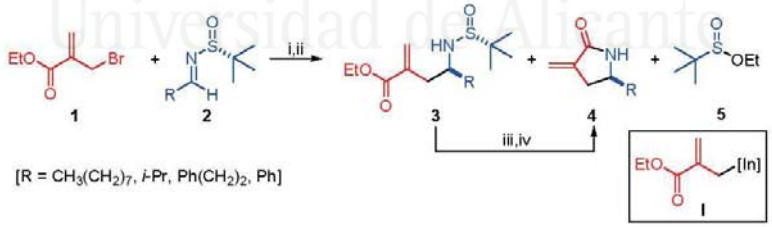
This paper is dedicated to Professor Dr. Akira Suzuki on occasion of his 80th birthday.

with interesting cytotoxic, allergenic, antiinflammatory, phytotoxic, and antimicrobial properties.[10] These compounds interact with nucleophiles in the active site of enzymes, due to the electrophilic character of the α,β-unsaturated carbonyl unit, acting as inhibitors. Lactone derivatives are more abundant in Nature, however they exhibit higher cytotoxic activity than lactams, the last ones being more promising candidates for drugs in the pharmaceutical industry. Synthetic methodologies to access efficiently to α-methylene-γ-butyrolactams[11] include nucleophilic addition of 2-alkoxycarbonyl allyl metal intermediates to imines.[12] More recently, an expeditious synthesis of these compounds through a three component assembling of an aldehyde, ammonia and a 2-alkoxycarbonylallylboronate in a single synthetic operation has been reported.[13] Because of our interest in indium-promoted reactions,[14] we report here the use of this metal for the stereoselective preparation of α-methylene-γ-butyrolactams[15] from ethyl 2-(bromomethyl)acrylate and chiral *N-tert*-butylsulfinyl aldimines.

Equimolecular amounts of ethyl 2-(bromomethyl)acrylate (**1**), indium powder and the corresponding chiral *N-tert*-butylsulfinyl aldimines **2** in THF were heated at 100 °C in a pressure flask for 48 h and then hydrolyzed with water. After extraction and evaporation, a mixture of the corresponding *N-tert*-butylsulfinyl aminoester **3** and α-methylene-γ-butyrolactam **4** was obtained (Scheme 1 and Table 1). This reaction did not take place when the process was performed at 66 °C (THF reflux), and very low conversion was observed at 80 °C after one week. Fortunately, nucleophilic addition of the proposed initially formed allylindium sesquihalide intermediate of type **I** (Scheme 1) to the imine **2** took place at 100 °C, in spite of the thermal liability of the *N-tert*-butylsulfinyl group, leading first to *N-tert*-butylsulfinyl aminoester **3**. Under these reaction conditions, compound **3** could partially cyclize to give α-methylene-γ-butyrolactam **4** and ethyl *tert*-butanesulfinate (**5**, Scheme 1), which was not detected. Finally, the aminoester **3** was converted into butyrolactam **4** from the reaction mixture upon removal of the *tert*-butylsulfinyl group under acidic conditions and final basic workup (Scheme 1).



Scheme 1. Reagents and conditions: (i) In, THF, 100 °C, 48 h; (ii) H_2O; (iii) HCl-dioxane, MeOH, 0 °C, 2 h; (iv) $NaHCO_3$-H_2O, 20 °C, 1 h.

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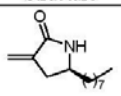
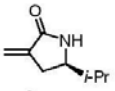
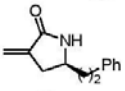
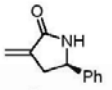
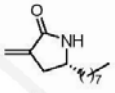
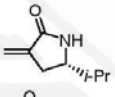
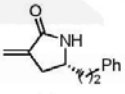
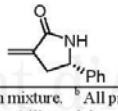
Table 1. Preparation of α-methylene-γ-butyrolactams **4**

	Aldimine **2**			Butyrolactam **4**[b]				
Entry	No.	R	**3**:**4** Ratio[a]	No.	Structure	Yield (%)[c]	er[d]	t_{ret} (min)[e]
1	(*R*)-**2a**	$CH_3(CH_2)_7$	1:1	**4a**		74	75:25	16.89
2	(*R*)-**2b**	*i*-Pr	1:5	**4b**		84	81:19	20.26
3	(*R*)-**2c**	$Ph(CH_2)_2$	1:3	**4c**		75	70:30	43.84
4	(*R*)-**2d**	Ph	3:1	**4d**		69	91:9	36.92
5	(*S*)-**2a**	$CH_3(CH_2)_7$	1:1	**4e**		72	68:32	11.25
6	(*S*)-**2b**	*i*-Pr	1:5	**4f**		79	71:29	14.20
7	(*S*)-**2c**	$Ph(CH_2)_2$	1:3	**4g**		73	80:20	12.01
8	(*S*)-**2d**	Ph	3:1	**4h**		68	92:8	33.20

[a]Ratio determined by ^{1}H-NMR analysis of the crude reaction mixture. [b] All products were >95% pure (GLC and/or 300 MHz ^{1}H RMN). [c] Isolated yield after column chromatography (silica gel, hexane/EtOAc) based on the starting aldimine **2**. [d] Enantiomeric ratio determined by HPLC using a Chiralcel OD-H column (condidtions: hexane/isopropanol, 9:1; 0.5 mL/min). [e] Retention time of the major enantiomer.

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In general, overall yields of the isolated products **4**,[16] after column chromatography, are good (Table 1). Regarding the diastereoselectivity of the nucleophilic addition to the chiral imines, the er values were determined by chiral HPLC analysis, ranging from 92:8 in the case of the aldimine (*S*)-**2d** derived from benzaldehyde (Table 1, entry 8) to 68:32 in the case of aldimine (*S*)-**2a** derived from nonanal (Table 1, entry 5). In order to determine the configuration of the newly created stereogenic centre in the major diasteroisomer, we found that specific rotation of **4d** {$[\alpha]_D^{22}$ -10 (*c* 0.54, $CHCl_3$)}, which derived from aldimine (*R*)-**2d** matched with that provided in the literature for (*R*)-3-methylene-5-phenylpyrrolidin-2-one {$[\alpha]_D^{26}$ -17 (*c* 1.35, $CHCl_3$)}.[12b] This result is consistent with an approach of the nucleophile from the

Re-face of C=N through an open transition state **TSI** (Chart 1)[6g] or a monochelate chair-like model **TSII** (Chart 1)[17] instead of a six-membered ring model **TSIII** (Chart 1), with a four-membered metallacycle, in which the metal is chelated both by the oxygen and the nitrogen atoms of the imine moiety. The last one has been proposed for the indium-promoted allylation of these chiral aldimines with allyl bromide[14b] and it would lead to the opposite configuration. The imine adopts in all these cases a kind of *s-cis* conformation which is the less energetic conformation in the *N-tert*-butylsulfinyl aldimines. After this result, we assume that the nucleophilic attack occurs predominantly to the *Re*-face of the imine unit for R_S-isomers (Table 1, entries 1-4) and to the *Si*-face in the case of S_S-derivatives (Table 1, entries 5-8) according to the proposed transition states **TSI** and **TSII** (Chart 1).

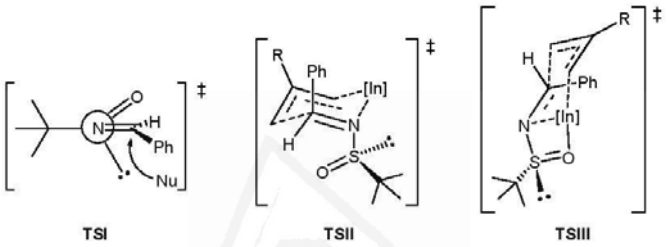

Chart 1

In conclusion, we have reported herein a stereoselective synthesis of α-methylene-γ-butyrolactam from ethyl 2-(bromomethyl)acrylate (**1**) and chiral *N-tert*-butylsulfinyl aldimines **3**. The key step of the process is an indium promoted nucleophilic addition to the chiral imine. Studies are currently in progress trying to find milder reaction conditions and to improve the stereoselectivity.

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16. *Typical procedure for the synthesis of* ***4d***.- A mixture of aldimine (*R*)-**2a** (0.104 g, 0.5 mmol), ethyl 2-(bromomethyl)acrylate (**1**, 0.106 g, 0.55 mmol) and indium powder (0.075 g, 0.65 mmol) in THF (3 mL) was stirred for 48 h at 100 °C in a pressure flask. Then, the resulting mixture was hydrolyzed with water (10 mL), extrated with EtOAc (3 × 10 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The residue was dissolved in MeOH (1 mL) and a HCl 4M dioxane solution (0.5 mL) was added at 0 °C. After 2 h stirring at the same temperature, a $NaHCO_3$ saturated aqueous solution (3 mL) was added, and after 1 h stirring at room temperature, the reaction mixture was extrated with EtOAc (3 × 15 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc) to give 0.062 g (71%) of (*R*)-3-methylene-5-phenylpyrrolidin-2-one (**4d**): White solid; mp 172-174 °C (pentane/CH_2Cl_2) [mp 191-192 °C (hexane/EtOAc)];[12b] $[\alpha]_D^{22}$ -10 (*c* 0.54, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64-2.78 (1H, m, C*H*H), 3.26-3.36 (1H, m, CH*H*), 4.75 (1H, dd, *J* = 4.7, 8.2 Hz, PhC*H*), 5.38 (1H, br s, C=C*H*H), 6.06 (1H, t, *J* = 2.7 Hz, C=CH*H*), 6.55 (1H, br s, NH), 7.26-7.40 (5H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.8 (CH_2), 54.8 (CH), 116.6 (CH_2), 125.7, 128.1, 129.0 (CH), 138.6, 142.6 (C), 170.6 (CO); LRMS (EI) *m/z* 173 [(M^+), 100%], 172 (56), 144 (31), 104 (57), 96 (18), 78 (19), 77 (40), 68 (21), 51 (33); HRMS (EI) calcd for $C_{11}H_{11}NO$ 173.0841, found 173.0848.

17. (a) G. Kolodney, G. Sklute, S. Perrone, P. Knochel, and I. Marek, *Angew. Chem. Int. Ed.*, 2007, **46**, 9291; (b) I. Marek, *Chem. Eur. J.*, 2008, **14**, 7460.

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VI.2. Enantioselective Synthesis of α-Methylene-γ-butyrolactams Using *N-tert*-Butanesulfinamides

Haythem K. Dema, Francisco Foubelo, and Miguel Yus

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ENANTIOSELECTIVE SYNTHESIS OF α-METHYLENE-γ-BUTYROLACTAMS USING *N-TERT*-BUTANESULFINAMIDES

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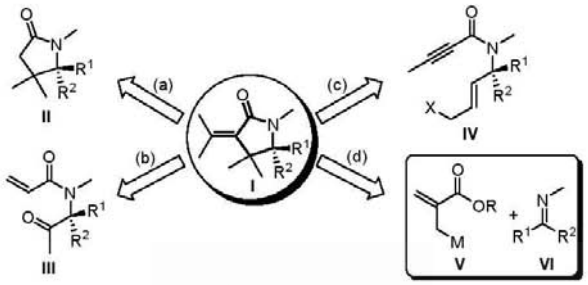
Abstract – Indium-mediated coupling of ethyl 2-(bromomethyl)acrylate (**1**) and chiral *N-tert*-butanelsulfinylimines **2** in a saturated sodium bromide aqueous solution leads to *N-tert*-butanesulfinyl aminoesters **3** in high yields and diastereoselectivities. After column chromatography purification, enantiomerically pure aminoesters **3** were converted into the expected α-methylene-γ-butyrolactams **4** in a one-pot process.

INTRODUCTION

The development of synthetic methodologies which allow an easy access in a stereoselective fashion to α-methylene-γ-butyrolactams is of interest because many of them exhibit promising biological activities, and lower citotoxicity when comparing with the corresponding, and more abundant in Nature, lactones.[1] Four main different strategies have been employed for the stereoselective synthesis of α-methylene-γ-butyrolactams of type **I** (Scheme 1): (a) α-methylenation of chiral γ-butyrolactams **II** under Horner–Wadsworth–Emmons conditions[2] or using the Bredereck reagent, followed, in this case by reduction with $LiAlH_4$;[3] (b) intramolecular Baylis-Hillman coupling of chiral acrylamides **III**;[4] (c) intramolecular cyclisation of amides of type **IV** promoted by transition metals, mostly Pd, in the presence of a chiral ligand;[5] and (d) nucleophilic addition of allylic organometallic compounds of type **V**, derived from metacrylic acid (metacrylates and metacrylamides), to imine derivatives **VI**. Among organometallic compounds of type **V**, allylzinc intermediates[6] are the most commonly used, along with allylboranes.[7] Due to our interest in indium-promoted reactions,[8] we report here the use of this metal for the stereoselective preparation of α-methylene-γ-butyrolactams[9] from ethyl 2-(bromomethyl)acrylate (**1**) and chiral *N-tert*-butanelsulfinamides (**2**). These chiral electrophilic reagents have found high applicability in

This paper is dedicated to Professor Dr. Albert Eschenmoser on occasion of his 85th birthday.

synthesis[10] due to the possibility of preparing their both enantiomers[11] and also because the chiral auxiliary can be easily removed under acidic conditions.[12] In addition, practical processes for recycling the *tert*-butanesulfinyl group upon deprotection of *N-tert*-butanelsulfinylamines have been reported recently, making this chiral auxiliary of interest for large scale industrial processes.[13]



Scheme 1. General strategies for the stereoselective synthesis of α-methylene-γ-butyrolactams

RESULTS AND DISCUSSION

We first investigated the reaction conditions for the allylation of *N-tert*-butanesulfinamide (*R*)-**2d** by treatment with ethyl 2-(bromomethyl)acrylate (**1**) in the presence of indium metal. Based on our previous experience with indium-mediated allylation of these type of aldimines, we used 1.1 equiv of indium metal and 1.2 equiv of the allylic bromide, THF being the solvent of choice at 60 °C.[8c-g] However, under these reaction conditions the allylation did not take place, even after 3 days (Table 1, entry 1). It was supposed that in these processes the formation of an allylindium intermediate[14] was facilitated in aqueous media, although in the case of using a 1:1 water/THF mixture, hydrolysis of the starting aldimine **2d** occurred, yielding benzaldehyde and other reaction products derived from it (Table 1, entry 2). Regarding the temperature, although the reaction does not progress at 60 °C in THF while at 80 °C it takes 7 days to drive it to an only 15% conversion (Table 1, entry 3), complete conversion was achieved at 100 °C after 48 hours to give a mixture of the expected aminoester derivative **3d** and the butyrolactam **4d** in and 3:1 ratio (Table 1, entry 4).[15] Under these reaction conditions, compound **3d** could partially cyclise to give α-methylene-γ-butyrolactam **4d**. Overall yields and selectivities were not improved when the allylation was performed at 100 °C in acetonitrile, *N,N*-dimethylformamide and toluene (Table 1, entries 5, 6 and 7, respectively), meanwhile in ethanol decomposition of aldimine **2d** occurred without formation of the expected aminoester derivative **3d** (Table 1, entry 8). Surprisingly, total conversion occurred when the reaction was carried out in a saturated aqueous sodium bromide solution in the presence of 4 equivalents

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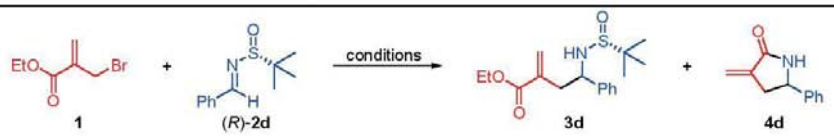
of indium at room temperature for 48 hours,[16] and compound **3d** was the only isolated reaction product in 79% yield (Table 1, entry 9). On the other hand, a 46% yield was obtained when zinc was used instead of indium under the same reaction conditions (Table 1, entry 10).

Table 1. Optimization of the reaction conditions



1 (*R*)-**2d** **3d** **4d**

Entry	Conditions[a]	Conversion[b]	Reaction products (%)[c] **3d**	**4d**
1	In (1.1 equiv), THF (2 mL), 60 °C, 72 h	0	--	--
2[d]	In (1.1 equiv), THF:H_2O (2 mL, 1:1), 60 °C, 72 h	100	--	--
3	In (1.1 equiv), THF (2 mL), 80 °C, 168 h	15	15	--
4	In (1.1 equiv), THF (2 mL), 100 °C, 48 h	100	51	17
5	In (1.1 equiv), MeCN (1.5 mL), 100 °C, 48 h	100	35	43
6	In (1.1 equiv), DMF (1.5 mL), 100 °C, 48 h	88	32	12
7	In (1.1 equiv), PhMe (1.5 mL), 100 °C, 48 h	100	29	35
8[d]	In (1.1 equiv), EtOH (1.5 mL), 100 °C, 48 h	100	--	--
9	In (4 equiv), saturated NaBr-H_2O (2 mL), 23 °C, 48 h	100	79	--
10	Zn (4 equiv), saturated NaBr-H_2O (2 mL), 23 °C, 48 h	86	46	--

[a] All the reactions were carried out using 0.2 mmol of aldimine (*R*)-**2d** and 0.25 mmol of bromoester **1**. [b] Conversion is given based on the disappearance of the starting (*R*)-**2d**. [c] Isolated yield after column chromatography (silica gel, hexane/EtOAc) based on the starting aldimine (*R*)-**2d**. [d] Decomposition of the starting aldimine (*R*)-**2d** occurred.

Not only the yield but the stereoselectivity was considerable much higher in the case of using indium metal instead of zinc when the allylation was performed in a saturated aqueous sodium bromide solution. A diastereomeric mixture of aminoester derivatives **3d** and **3d'** was obtained in an almost 1:1 ratio with zinc, menawhile diastereoselectivity was 91:1 with indium (Scheme 2). The diastereomeric ratio was easily determined by ^{1}H-NMR analysis of the crude reaction mixture paying attention to the integrals of the *t*-Bu group and the N-H of the diastereoisomers (the largest chemical shift difference has been always observed for the N-H).

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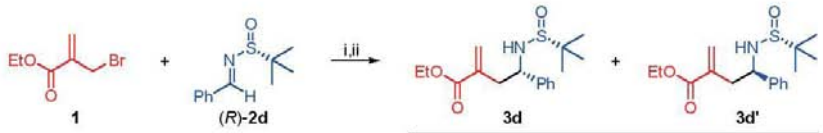
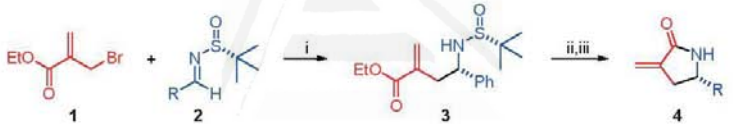


(M = In)	72%	7%
(M = Zn)	24%	22%

Scheme 2. Reagents and conditions: (i) M (4 equiv), saturated NaBr-H_2O (2 mL), 23 °C, 48 h

The reaction of ethyl 2-(bromomethyl)acrylate (**1**) with different chiral *N*-sulfinyl aldimines **2** under the optimized conditions (Table 1, entry 9) led to compounds **3** in good yields (Scheme 3, Table 2) and diastereomeric ratios ranging between 86:14 and 95:5 (Table 2, entries 2 and 1, respectively). The major diastereomer was easily isolated after column chromatography and fully characterized in all cases. Finally, aminoester derivatives **3** were converted into butyrolactams **4** upon removal of the *tert*-butylsulfinyl by treatment first with a 4M HCl dioxane solution in methanol and then with sodium methoxide in methanol until basic pH. Yields were in all cases over 90% and ee≥95% (Scheme 3 and Table 2).



Scheme 3. Reagents and conditions: (i) In (4 equiv), saturated NaBr-H_2O (2 mL), 23 °C, 48 h; (ii) HCl-dioxane, MeOH, 0 °C, 2 h; (iii) NaOMe/MeOH, 0 °C, 1 h

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Regarding the configuration of the newly created stereogenic centre in the major diasteroisomer **3d** (Scheme 2) it was determined by comparing the specific rotation of **4d** {$[\alpha]_D^{23}$ +14 (*c* 0.50, $CHCl_3$)}, which derived from **3d**, with that provided in the literature for (*R*)-3-methylene-5-phenylpyrrolidin-2-one {$[\alpha]_D^{26}$ -17 (*c* 1.35, $CHCl_3$)}.[6b] This result is consistent with an approach of the nucleophile, an allylindium sesquihalide of type **VII** (Figure 1), through a six-membered ring model **TSI** or **TSII** (Figure 1), with a four-membered metallacycle, in which the metal is chelated both by the oxygen and the nitrogen atoms of the imine moiety. We assume that the nucleophilic attack occurs predominantly to the *Si*-face of the imine unit for R_S-isomers (Table 1, entries 1-4) and to the *Re*-face in the case of S_S-derivatives (Table 1, entries 5-8). The stereochemical pathway under the reaction conditions described in Scheme 3 is the opposite to that obtained when the reaction is performed in THF at 100 °C as we have previously reported.[15]

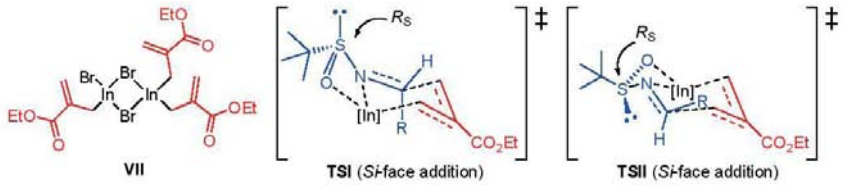
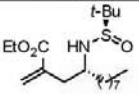
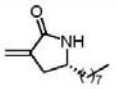
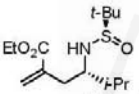
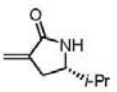
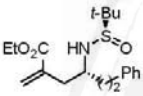
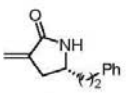
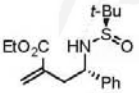
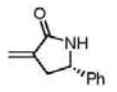
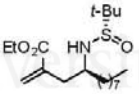
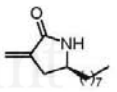
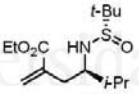
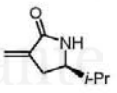
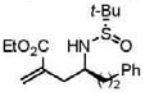
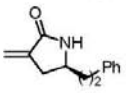
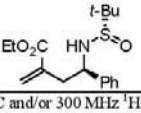
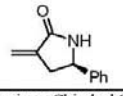


Figure 1. Proposed allylindium sesquihalide intermediate **VII** and possible transition state **PSI**

Table 2. Preparation of amino ester derivatives **3** and α-methylene-γ-butyrolactams **4**

		Aminoester **3**[a]				Butyrolactam **4**[a,b]		
Entry	Aldimne **2**	No.	Structure	Yield (%)[c]	dr[d]	No.	Structure	Yield (%)[e]
1	(*R*)-**2a**	**3a**		80	95:5	**4a**		92
2	(*R*)-**2b**	**3b**		73	86:14	**4b**		91
3	(*R*)-**2c**	**3c**		82	93:7	**4c**		94
4	(*R*)-**2d**	**3d**		72	91:9	**4d**		93
5	(*S*)-**2a**	**3e**		79	89:11	**4e**		93
6	(*S*)-**2b**	**3f**		77	91:9	**4f**		90
7	(*S*)-**2c**	**3g**		77	88:12	**4g**		95
8	(*S*)-**2d**	**3h**		75	93:7	**4h**		92

[a] All products were >95% pure (GLC and/or 300 MHz ^{1}H RMN). [b] ee≥95%, as determined by HPLC using a Chiralcel OD-H column (condidtions: hexane/isopropanol, 9:1; 0.5 mL/min). [c] Isolated yield after column chromatography (silica gel, hexane/EtOAc) based on the starting aldimine **2**. [d] Ratio determined by ^{1}H-NMR analysis of the crude reaction mixture. [e] Isolated yield after column chromatography (silica gel, hexane/EtOAc) based on the aminoester **3**.

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In conclusion, we have reported herein an enantioselective synthesis of α-methylene-γ-butyrolactams **4** from ethyl 2-(bromomethyl)acrylate (**1**) and chiral *N*-*tert*-butanesulfinyl aldimines **2**. The key step of the process is an indium promoted nucleophilic addition to the chiral imine. The resulting aminoesters **3** were purified by column chromatography and the major diastereoisomers converted in high yields in a one-pot process to the corresponding butyrolactam **4**.

EXPERIMENTAL

All chemicals were commercially available (Acros, Aldrich). TLC was performed on Merck silica gel 60 F_{254}, using aluminum plates and visualized with phosphomolybdic acid (PMA) stain. Chromatographic purification was performed by flash chromatography using Merck silica gel 60 (0.040-0.063 mm) and hexane/EtOAc as eluent. IR spectra were measured (film) with a Nicolet Impact 510 P-FT Spectrometer. Melting points were recorded on an OptiMelt (Stanford Research Systems) apparatus and reported without corrections. HPLC analyses were performed on a JASCO 200-series equipped with a Chiralcel OD-H column (condidtions: hexane/isopropanol, 9:1; 0.5 mL/min). NMR spectra were recorded with a Bruker AC-300 or a Bruker ADVANCE DRX-500 using $CDCl_3$ as the solvent and TMS as internal standard. HRMS (EI) were recorded on a Finnigan MAT 95S.

Preparation of aminoesters 3. General procedure.

A mixture of the corresponding aldimine **2** (0.5 mmol), ethyl 2-(bromomethyl)acrylate (**1**, 0.128 g, 0.65 mmol) and indium powder (0.226 g, 2.0 mmol) in a saturated aqueous NaBr solution (5 mL) was stirred for 48 h at 23 °C. Then, the resulting mixture was hydrolyzed with water (10 mL), extrated with EtOAc (3 × 10 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield pure products **3**. Yields, physical and spectroscopic data follow.

(4*R*,*R*$_S$)-Ethyl *N*-(*tert*-butylsulfinyl)-4-amino-2-methylenedodecanoate (3a): Colourless oil; R_f 0.46 (hexane/EtOAc: 1/1); IR ν (film) 3223, 2924, 2855, 1715, 1627, 1464, 1364, 1303, 1150, 1053, 942 cm^{-1}; δ_H 0.88 (3H, t, J = 7.1 Hz, C*H*$_3$CH$_2$), 1.19 [9H, s, (CH$_3$)$_3$C], 1.31 (3H, t, J = 7.1 Hz, C*H*$_3$CH$_2$O), 1.25-1.50 (14H, m, 7×CH$_2$), 2.59 (2H, d, J = 6.2 Hz, C*H*$_2$CHNH), 3.40-3.44 (1H, m, C*H*NH), 3.52 (1H, d, J = 6.0 Hz, NH), 4.21 (2H, c, J = 7.1 Hz, CH$_3$C*H*$_2$O), 5.68 (1H, s, C=C*H*H), 6.30 (1H, s, C=CH*H*); δ_C 14.0, 14.1, (CH$_3$), 22.6 (CH$_2$), 22.65 (CH$_3$), 25.4, 29.1, 29.3, 29.4, 31.7, 35.4, 38.3 (CH$_2$), 55.2 (CH), 55.6 (C), 60.9 (CH$_2$), 128.0 (CH$_2$), 137.3 (C), 167.4 (CO); LRMS (EI) *m/z* 303 [M$^+$-(CH$_3$)$_2$C=CH$_2$, 6%], 285 (19), 258 (11), 212 (100), 300 (17), 189 (72), 187 (76), 140 (14), 133 (22), 114 (28), 100 (33), 84 (23), 70 (30), 55 (18); $[\alpha]_D^{20}$ -41 (c 1.43, CH_2Cl_2).

(4*S*,*R*S)-Ethyl *N*-(*tert*-butylsulfinyl)-4-amino-5-methyl-2-methylenehexanoate (3b): Colourless liquid; R_f 0.40 (hexane/EtOAc: 1/1); IR ν (film) 3274, 2959, 1713, 1628, 1465, 1366, 1315, 1153, 1057, 904 cm^{-1}; δ_H 0.91 (3H, d, J = 6.8 Hz, CH_3CH), 0.92 (3H, d, J = 6.9 Hz, CH_3CH), 1.21 [9H, s, $(CH_3)_3$C], 1.31 (3H, t, J = 7.1 Hz, CH_3CH$_2$O), 1.83-1.90 (1H, m, C*H*CH$_3$), 2.48-2.51 (2H, m, CH_2C=CH$_2$), 3.26-3.33 (1H, m, C*H*NH), 3.56 (1H, d, J = 5.5 Hz, NH), 4.21 (2H, c, J = 7.0 Hz, CH$_3$CH_2O), 5.70 (1H, s, C=C*H*H), 6.31 (1H, s, C=CH*H*); δ_C 14.1, 17.3, 18.1, 22.7 (CH_3), 31.8 (CH), 34.7 (CH_2), 55.8 (C), 60.6 (CH), 61.0 (CH_2), 127.9 (CH_2), 137.7 (C), 167.6 (CO); LRMS (EI) *m/z* 233 [M^+-$(CH_3)_2C=CH_2$, 23%], 215 (21), 186 (36), 172 (29), 142 (76), 123 (54), 100 (100), 94 (38), 72 (45), 57 (61); $[\alpha]_D^{20}$ -97 (c 0.70, CH_2Cl_2).

(4*R*,*R*S)-Ethyl *N*-(*tert*-butylsulfinyl)-4-amino-2-methylene-6-phenylhexanoate (3c): Colourless oil; R_f 0.34 (hexane/EtOAc: 1/1); IR ν (film) 3222, 3061, 3026, 2951, 1712, 1454, 1176, 1052, 699 cm^{-1}; δ_H 1.23 [9H, s, $(CH_3)_3$C], 1.28 (3H, t, J = 7.2 Hz, CH_3CH$_2$O), 1.74-1.85 (2H, m, CH_2CHN), 2.59-2.80 (4H, m, PhCH_2, CH_2C=CH$_2$), 3.46-3.52 (1H, m, C*H*NH), 3.67 (1H, d, J = 5.5 Hz, NH), 4.20 (2H, c, J = 7.2 Hz, CH$_3$CH_2O), 5.68 (1H, s, C=C*H*H), 6.30 (1H, s, C=CH*H*), 7.15-7.30 (5H, m, ArH); δ_C 14.1, 22.7 (CH_3), 31.8, 37.3, 38.3 (CH_2), 55.0 (CH), 55.8 (C), 61.0 (CH_2), 125.8, 128.2 (CH), 128.3 (CH_2), 128.4 (CH), 137.0, 141.6 (C), 167.4 (CO); LRMS (EI) *m/z* 295 [M^+-$(CH_3)_2C=CH_2$, 4%], 277 (27), 204 (100), 181 (18), 117 (62), 91 (87), 65 (14); $[\alpha]_D^{20}$ -33 (c 0.98, CH_2Cl_2).

(4*S*,*R*S)-Ethyl *N*-(*tert*-butylsulfinyl)-4-amino-2-methylene-4-phenylbutanoate (3d): Colourless oil; R_f 0.29 (hexane/EtOAc: 1/1); IR ν (film) 3301, 3094, 3028, 2983, 1720, 1629, 1454, 1363, 1315, 1193, 1172, 1052, 916, 868, 698 cm^{-1}; δ_H 1.19 [9H, s, $(CH_3)_3$C], 1.30 (3H, t, J = 7.2 Hz, CH_3CH$_2$O), 2.71 (1H, dd, J = 14.1, 7.9 Hz, C*H*HC=CH$_2$), 2.80 (1H, dd, J = 14.1, 6.2 Hz, CH*H*C=CH$_2$), 4.08 (1H, br s, NH), 4.19 (2H, c, J = 7.2 Hz, CH$_3$CH_2O), 4.59-4.64 (1H, m, C*H*NH), 5.52 (1H, s, C=C*H*H), 6.25 (1H, s, C=CH*H*), 7.26-7.33 (5H, m, ArH); δ_C 14.1, 22.6 (CH_3), 41.1 (CH_2), 55.5 (C), 57.7 (CH), 61.1 (CH_2), 127.5, 127.6, 128.3 (CH), 128.6 (CH_2), 136.6, 141.5 (C), 167.2 (CO); LRMS (EI) *m/z* 267 [M^+-$(CH_3)_2C=CH_2$, 2%], 249 (21), 176 (100), 153 (69), 136 (16), 115 (12), 104 (35), 77 (28), 69 (21), 51 (16); $[\alpha]_D^{20}$ -101 (c 0.96, CH_2Cl_2).

(4*R*,*R*S)-Ethyl *N*-(*tert*-butylsulfinyl)-4-amino-2-methylene-4-phenylbutanoate (3d'): Colourless oil; R_f 0.32 (hexane/EtOAc: 1/1); IR ν (film) 3305, 3095, 3029, 2984, 1721, 1631, 1455, 1362, 1312, 1190, 1173, 1052, 915, 870, 697 cm^{-1}; δ_H 1.19 [9H, s, $(CH_3)_3$C], 1.26 (3H, t, J = 7.2 Hz, CH_3CH$_2$O), 2.73 (1H, dd, J = 13.8, 7.3 Hz, C*H*HC=CH$_2$), 2.98 (1H, dd, J = 13.8, 7.3 Hz, CH*H*C=CH$_2$), 3.60 (1H, d, J = 5.0 Hz, NH), 4.12 (2H, c, J = 7.2 Hz, CH$_3$CH_2O), 4.54-4.59 (1H, m, C*H*NH), 5.45 (1H, s, C=C*H*H), 6.17 (1H, s, C=CH*H*), 7.28-7.33 (5H, m, ArH); δ_C 14.2, 22.6 (CH_3), 39.8 (CH_2), 56.1 (C), 58.9 (CH), 60.8 (CH_2), 127.5, 127.6, 128.3 (CH), 128.1 (CH_2), 136.9, 141.7 (C), 171.2 (CO); LRMS (EI) *m/z* 267 [M^+-$(CH_3)_2C=CH_2$, 6%], 207 (14), 176 (12), 163 (15), 153 (100), 136 (22), 131 (19), 129 (16), 115 (15),

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104 (35), 91 (13), 77 (16); $[\alpha]_D^{20}$ +17 (c 0.35, CH_2Cl_2).

(4*S*,*S*$_S$)-Ethyl *N*-(*tert*-butylsulfinyl)-4-amino-2-methylenedodecanoate (3e): Physical and spectroscopic data were found to be the same than for **3a**; $[\alpha]_D^{20}$ +38 (c 0.78, CH_2Cl_2).

(4*R*,*S*$_S$)-Ethyl *N*-(*tert*-butylsulfinyl)-4-amino-5-methyl-2-methylenehexanoate (3f): Physical and spectroscopic data were found to be the same than for **3b**; $[\alpha]_D^{20}$ +84 (c 1.30, CH_2Cl_2).

(4*S*,*S*$_S$)-Ethyl *N*-(*tert*-butylsulfinyl)-4-amino-2-methylene-6-phenylhexanoate (3g): Physical and spectroscopic data were found to be the same than for **3c**; $[\alpha]_D^{20}$ +33 (c 0.34, CH_2Cl_2).

(4*R*,*S*$_S$)-Ethyl *N*-(*tert*-butylsulfinyl)-4-amino-2-methylene-4-phenylbutanoate (3h): Physical and spectroscopic data were found to be the same than for **3d**; $[\alpha]_D^{20}$ +102 (c 0.89, CH_2Cl_2).

Preparation of butyrolactams 4 from aminoesters 3. General procedure.

To a solution of the corresponding aminoester **3** (0.2 mmol) in MeOH (1 mL) was added a 4M HCl dioxane solution (0.5 mL) at 0 °C. After 2 h stirring at the same temperature, a 2M NaOMe MeOH solution (2 mL) was added and the resulting mixture was stirred for 1 h at 0 °C. After that, it was hydrolyzed with water (10 mL), extrated with EtOAc (3 × 10 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield pure products **4**. Yields, physical and spectroscopic data follow. (min)

(*R*)-3-Methylene-5-octylpyrrolidin-2-one (4a): White solid; mp 47-48 °C (pentane/CH_2Cl_2); R_f 0.45 (hexane/EtOAc: 1/1); IR ν (film) 3176, 3090, 2916, 2849, 1697, 1659, 1466, 1396, 1307, 917 cm^{-1}; δ_H 0.88 (3H, t, J = 7.1 Hz, CH_3CH_2), 1.19-1.34 (12H, m, 6×CH_2), 1.41-1.48 (1H, m, C*H*H), 1.52-1.56 (1H, m, CH*H*), 2.39-2.45 (1H, m, C*H*HC=CH_2), 2.91-2.99 (1H, m, CH*H*C=CH_2), 3.60-3.66 (1H, m, C*H*NH), 5.32 (1H, s, C=C*H*H), 5.95 (1H, t, J = 2.5 Hz, C=CH*H*), 7.58 (1H, br s, NH); δ_C 14.0 (CH_3), 22.6, 25.4, 29.1, 29.4, 31.8, 33.0, 37.3 (CH_2), 51.4 (CH), 115.5 (CH_2), 139.7 (C), 170.7 (CO); LRMS (EI) *m/z* 209 (M^+, 8%), 97 (14), 96 (100), 68 (11), 53 (25); HRMS (EI) calcd for $C_{13}H_{23}NO$ 209.1780, found 209.1753; $[\alpha]_D^{20}$ +21 (c 0.55, CH_2Cl_2); HPLC t_{ret} (min) 16.89.

(*S*)-5-Isopropyl-3-methylenepyrrolidin-2-one (4b): White solid; mp decomposed >300 °C (pentane/CH_2Cl_2); R_f 0.27 (hexane/EtOAc: 1/1); IR ν (film) 3211, 2960, 2926, 2874, 1696, 1658, 1391, 1284, 1042, 807 cm^{-1}; δ_H 0.90 (3H, d, J = 7.0 Hz, CH_3CH), 0.93 (3H, d, J = 7.0 Hz, CH_3CH), 1.65 (1H, heptet, J = 6.7 Hz, $CHCH_3$), 2.48-2.57 (1H, m, C*H*HC=CH_2), 2.85-2.95 (1H, m, CH*H*C=CH_2), 3.38-3.44 (1H, m, C*H*NH), 5.34 (1H, br s, C=C*H*H), 5.97 (1H, t, J = 2.7 Hz, C=CH*H*), 6.18 (1H, br s, NH); δ_C 17.8, 18.1 (CH_3), 30.6 (CH_2), 33.6, 56.9 (CH), 115.6 (CH_2), 139.5 (C), 170.6 (CO); LRMS (EI) *m/z* 96 [(M^+-*i*-Pr), 100%], 95 (17), 68 (11), 67 (14), 53 (36); HRMS (EI) calcd for $C_8H_{13}NO$ 139.0997, found 139.0982; $[\alpha]_D^{20}$+3 (c 0.46, CH_2Cl_2); HPLC t_{ret} (min) 20.26.

(*R*)-3-Methylene-5-(2-Phenylethyl)pyrrolidin-2-one (4c): White solid; mp 69-70 °C (pentane/CH_2Cl_2); R_f 0.36 (hexane/EtOAc: 1/1); IR ν (film) 3229, 3061, 3026, 2926, 1692, 1650, 1494, 1442, 1331, 1299, 1030, 936, 697 cm^{-1}; δ_H 1.74-1.95 (2H, m, C*H*$_2$CHN), 2.42-2.50 (1H, m, C*H*HC=CH$_2$), 2.61-2.76 (2H, m, PhCH$_2$), 2.92-3.02 (1H, m, CH*H*C=CH$_2$), 3.62-3.70 (1H, m, C*H*NH), 5.32 (1H, br s, C=C*H*H), 5.97 (1H, t, J = 2.4 Hz, C=CH*H*), 7.75 (1H, br s, NH); δ_C 31.8, 33.0, 38.9 (CH$_2$), 50.8 (CH), 115.8 (CH$_2$), 126.0, 128.3, 128.5 (CH), 139.4, 140.9 (C), 170.7 (CO); LRMS (EI) *m/z* 201 (M^+, 21%), 132 (11), 123 (15), 117 (10), 110 (29), 103 (18), 97 (30), 96 (100), 91 (34), 77 (17), 65 (15), 53 (36); HRMS (EI) calcd for $C_{13}H_{15}NO$ 201.1154, found 201.1142; $[\alpha]_D^{20}$ +25 (c 0.53, CH_2Cl_2); HPLC t_{ret} (min) 43.84.

(*S*)-3-Methylene-5-phenylpyrrolidin-2-one (4d): White solid; mp 172-174 °C (pentane/CH_2Cl_2) [mp 191-192 °C (hexano/EtOAc)];[6b] R_f 0.34 (hexane/EtOAc: 1/1); IR ν (film) 3184, 3094, 3028, 2923, 2852, 1696, 1657, 1452, 1337, 1282, 935, 763 cm^{-1}; δ_H 2.64-2.80 (1H, m, C*H*HC=CH$_2$), 3.26-3.36 (1H, m, CH*H*C=CH$_2$), 4.75 (1H, dd, J = 8.1, 4.7 Hz, C*H*NH), 5.38 (1H, br s, C=C*H*H), 6.06 (1H, t, J = 2.7 Hz, C=CH*H*), 6.55 (1H, br s, NH), 7.27-7.40 (5H, m, ArH); δ_C 36.8 (CH$_2$), 54.8 (CH), 116.6 (CH$_2$), 125.7, 128.1, 129.0 (CH), 138.6, 142.6 (C), 170.6 (CO); LRMS (EI) *m/z* 173 (M^+, 100%), 172 (59), 144 (33), 128 (12), 104 (61), 96 (22), 78 (23), 77 (40), 68 (28), 51 (37); HRMS (EI) calcf for $C_{11}H_{11}NO$ 173.0841, found 173.0848; $[\alpha]_D^{20}$ +14 (c 0.50, CH_2Cl_2); HPLC t_{ret} (min) 36.92.

(*S*)-3-Methylene-5-octylpyrrolidin-2-one (4e): Physical and spectroscopic data were found to be the same than for **4a**; $[\alpha]_D^{20}$ -21 (c 0.51, CH_2Cl_2); HPLC t_{ret} (min) 12.25.

(*R*)-5-Isopropyl-3-methylenepyrrolidin-2-one (4f): Physical and spectroscopic data were found to be the same than for **4b**; $[\alpha]_D^{20}$ -2 (c 1.00, CH_2Cl_2); HPLC t_{ret} (min) 14.20.

(*S*)-3-Methylene-5-(2-Phenylethyl)pyrrolidin-2-one (4g): Physical and spectroscopic data were found to be the same than for **4c**; $[\alpha]_D^{20}$ -29 (c 0.56, CH_2Cl_2); HPLC t_{ret} (min) 12.01.

(*R*)-3-Methylene-5-phenylpyrrolidin-2-one (4h): Physical and spectroscopic data were found to be the same than for **4d**; $[\alpha]_D^{20}$ -13 (c 0.40, CH_2Cl_2); HPLC t_{ret} (min) 33.20.

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VI.3. Indium-Mediated Allylation of *N-tert*-Butylsulfinylaldimines with Dimethyl 2-[2-(Chloromethyl)allyl]malonate

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Indium-Mediated Allylation of *N-tert*-Butylsulfinylaldimines with Dimethyl 2-[2-(Chloromethyl)allyl]malonate

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Abstract

The reaction of *N-tert*-butylsulfinylaldimines **5** with dimethyl 2-[2-(chloromethyl)allyl]-malonate (**10**), in the presence of indium metal and sodium iodide, at room temperature for 72 hours, led to the corresponding amino ester derivative **11**. The reaction preceeded in high yields and in a total stereoselective fashion, a single diastereoisomer being always isolated.

Keywords: *N-tert*-Butylsulfinylaldimines; Diastereoselective allylation; Indium; Amino esters.

Introduction

The addition of an allylic organometallic reagent to an imine represents an important process in synthetic organic chemistry because it is possible to perform the addition in a highly enantio- or diastereoselective manner. One, two or even more stereogenic centres can be generated in a single synthetic operation depending on the structure of the reactants, mainly of the allylic system.[1-5] In addition, the allylic moiety allows further possible transformations due to the presence of a double bond that can be manipulated synthetically. For the previously commented reasons, chiral homoallylic amines are valuable building blocks in organic synthesis. Nucleophilic addition to the less hindered face of the prostereogenic substrate takes always place in the allylation of chiral imines. This methodology is especially interesting when chiral imines with stereogenic centres located at the substituent bonded to the nitrogen are used (it could be a chiral auxiliary). These substrates are easily prepared from a carbonyl compound and an enantiopure chiral amine (access to both enantiomers would be highly desirable). Diastereoselective allylations of achiral imines are also possible by means of chiral allylating reagents. Through this strategy, chiral information could be located either on the allylic moiety or on the ligands bonded to the metal. In the last case, the ligands are not incorporated into the hydrocarbon back-bone of the resulting allylated product (Scheme 1).

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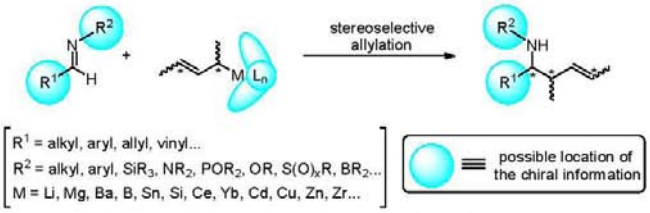

Scheme 1: Diastereoselective allylation of imines and imine derivatives

Typical examples of chiral imines **1**,[6] **2**,[7,8] **3**,[9] **4**[10] and **5**. Chiral allylating reagents **6**,[11] **7**,[12] **8**[13] and **9**[14] which have been efficiently used in diastereoselective allylation reactions are shown on Figure 1. It is worthy to be mentioned that *N-tert*-butanesulfinimines **5** have found high applicability in synthesis[15-20] due to the possibility of preparing their both enantiomers[21,22] and also because the chiral auxiliary can be easily removed under acidic conditions.[23] In addition, practical processes for recycling the *tert*-butylsulfinyl group upon deprotection of the resulting *N-tert*-butylsulfinylamines have been reported recently, making this chiral auxiliary of interest for large scale industrial processes.[24,25]

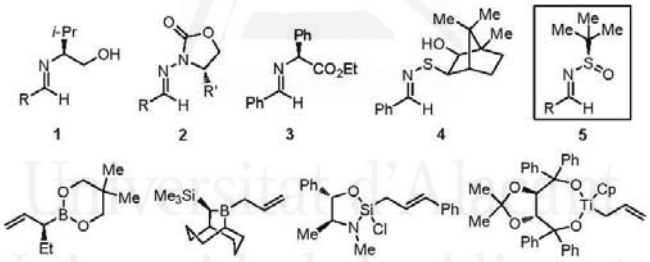

Figure 1

Continuing with our interest in indium mediated allylation of carbonyl compounds and *N-tert*-butylsulfinylaldimines **5** with allylic halides,[26-31] we report here the use of this metal for the stereoselective allylation of different *N-tert*-butylsulfinylaldimines **5** with dimethyl 2-[2-(chloromethyl)allyl]malonate (**10**).

Experimental

Materials and instruments

All chemicals were commercially available (Acros, Aldrich). TLC was performed on Merck silica gel 60 F_{254}, using aluminum plates and visualized with phosphomolybdic acid (PMA) stain. Chromatographic purification was performed by

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flash chromatography using Merck silica gel 60 (0.040-0.063 mm) and hexane/EtOAc as eluent. IR spectra were measured (film) with a Nicolet Impact 510 P-FT Spectrometer. Melting points were recorded on an OptiMelt (Stanford Research Systems) apparatus and reported without corrections. NMR spectra were recorded with a Bruker AC-300 or a Bruker ADVANCE DRX-500 using $CDCl_3$ as the solvent and TMS as internal standard. LRMS (EI) were recorded on a Agilent 6890N.

(i) Preparation of dimethyl 2-[2-(chloromethyl)allyl]malonate (**10**).

To a solution of NaOMe (1.136 g, 20 mmol) in MeOH (50 mL) was added dropwise dimethyl malonate (2.693 g, 2.33 mL, 20 mmol) at 0 ºC. After stirring at the same temperature for 15 min, 3-chloro-2-(chloromethyl)prop-1-ene (2.551 g, 2.36 mL, 20 mmol) was also added. The resulting reaction mixture was stirred for 12 hours at 23 ºC. Then, MeOH was removed under vacuum and the resulting mixture was hydrolyzed with water (20 mL), extrated with EtOAc (3 × 20 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield pure compound **10** (1.215 g, 5.52 mmol, 28%). Physical and spectroscopic data for this compound follow: Colourless liquid; R_f 0.38 (hexane/EtOAc: 5/1); IR ν (film) 3002, 2956, 2847, 1739, 1437, 1341, 1232, 1154, 1028 cm^{-1}; ^{1}H-NMR: δ_H 2.81 (2H, d, J = 7.9 Hz, CH_2CH), 3.67 (1H, t, J = 7.9 Hz, C*H*CH_2), 3.75 (6H, s, 2×CH_3), 4.06 (2H, s, CH_2Cl), 5.01 (1H, s, C=C*H*H), 5.20 (1H, s, C=CH*H*); ^{13}C-NMR: δ_C 32.0, 47.7 (CH_2), 50.1 (CH), 52.7 (CH_3), 116.7 (CH_2), 141.4 (C), 169.1 (CO); LRMS (EI) *m/z* 185 (M^+-Cl, 100%), 157 (30), 153 (19), 129 (27), 125 (92), 67 (13), 65 (20), 59 (23).

(ii) Preparation of amino ester derivatives (**11**). *General procedure*.

A mixture of the corresponding aldimine **5** (0.5 mmol), dimethyl 2-[2-(chloromethyl)allyl]malonate (**10**, 0.337 g, 1.5 mmol), sodium iodide (0.153 g, 1 mmol) and indium powder (0.075 g, 0.65 mmol) was stirred for 72 h at 23 °C. Then, the resulting mixture was hydrolyzed with 1M HCl solution (10 mL), extrated with EtOAc (3 × 10 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield pure products **11**. Yields are given on Table 2. Physical and spectroscopic data follow.

(6S,R_S)-Methyl N-(tert-butylsulfinyl)-6-amino-2-methoxycarbonyl-4-methylenetetradecanoate (**11a**): Colourless oil; R_f 0.38 (hexane/EtOAc: 1/1); IR ν (film) 3281, 2954, 2926, 2855, 1739, 1436, 1240, 1153, 1069 cm^{-1}; ^{1}H-NMR: δ_H 0.88 (3H, t, J = 5.4 Hz, C$H_3$$CH_2$), 1.19 [9H, s, $(CH_3)_3$C], 1.20-1.40 (12H, m, 6×CH_2), 1.48-1.53 (1H, m, CH_2), 2.22-2.38 (2H, m, CH_2CHNH), 2.63-2.67 (2H, m, CH_2CHCO), 3.23 (1H, d, J = 4.7 Hz, NH), 3.37-3.42 (1H, m, C*H*NH), 3.64 (1H, t, J = 8.0 Hz, CH_2*CH*CO), 3.73 (6H, s, 2×CH_3O), 4.92 (2H, br s, C=CH_2); ^{13}C-NMR: δ_C 13.9, 22.45 (CH_3), 25.05, 29.0, 29.3, 29.4, 31.6, 34.2, 35.0, 42.5 (CH_2), 50.1, 52.3 (CH), 53.05, 52.4 (CH_3), 55.5 (C), 114.6 (CH_2), 142.1 (C), 169.05, 169.1 (CO); LRMS (EI) *m/z* 266 [M^+-$(CH_3)_3$SO-HCO_2CH_3,

28%], 252 (18), 251 (100), 221 (11), 193 (10), 178 (14), 165 (12), 90 (16), 57 (13); $[\alpha]_D^{20}$ = -46 (c 1.29, CH_2Cl_2).

(6R,R$_S$)-Methyl N-*(tert-butylsulfinyl)-6-amino-2-methoxycarbonyl-7-methyl-4-methyl-eneoctanoate* (**11b**): Colourless oil; R_f 0.32 (hexane/EtOAc: 1/1); IR ν (film) 3286, 2957, 1738, 1645, 1436, 1240, 1153, 1069, 900 cm^{-1};^{1}H-NMR: δ_H 0.89 (3H, d, *J* = 7.1 Hz, C*H*$_3$CH), 0.90 (3H, d, *J* = 8.1 Hz, C*H*$_3$CH), 1.21 [9H, s, (CH$_3$)$_3$C], 1.95-1.99 (1H, m, C*H*CH$_3$), 2.17 (1H, dd, *J* = 9.1, 14.1 Hz, C*H*HCHNH), 2.31 (1H, dd, *J* = 5.3, 14.1 Hz, CH*H*CHNH), 2.62-2.71 (2H, m, C*H*$_2$CHCO), 3.11 (1H, d, *J* = 4.1 Hz, NH), 3.29-3.33 (1H, m, C*H*NH), 3.64 (1H, t, *J* = 7.9 Hz, CH$_2$C*H*CO), 3.73 (6H, s, 2×CH$_3$O), 4.93 (1H, s, C=C*H*H), 4.94 (1H, s, C=CH*H*); ^{13}C-NMR: δ_C 17.4, 17.6, 22.7 (CH$_3$), 30.5 (CH), 34.1, 38.4 (CH$_2$), 50.3 (CH), 52.6, 52.65 (CH$_3$), 55.8 (CH), 56.5 (C), 61.0 (CH$_2$), 114.8 (CH$_2$), 142.4 (C), 169.2, 169.3 (CO); LRMS (EI) *m/z* 287 [M$^+$-(CH$_3$)-(CO$_2$CH$_3$), 12%], 272 (31), 187 (16), 142 (100), 119 (28), 100 (37), 59 (22); $[\alpha]_D^{20}$ = -54 (c 1.09, CH_2Cl_2).

(6S,R$_S$)-Methyl N-*(tert-butylsulfinyl)-6-amino-2-methoxycarbonyl-4-methylene-8-phe-nyloctanoate* (**11c**): Colourless oil; R_f 0.29 (hexane/EtOAc: 1/1); IR ν (film) 3281, 3060, 3025, 2952, 2865, 1738, 1436, 1362, 1242, 1153, 1050, 901 cm^{-1}; ^{1}H-NMR:δ_H 1.23 [9H, s, (CH$_3$)$_3$C], 1.80-1.89 (2H, m, CH$_2$C*H*$_2$CHN), 2.36-2.39 (2H, m, C*H*$_2$CHNH), 2.60-2.77 (4H, m, PhC*H*$_2$, C*H*$_2$C=CH$_2$), 3.31 (1H, d, *J* = 5.2 Hz, NH), 3.44-3.50 (1H, m, C*H*NH), 3.64 (1H, t, *J* = 7.8 Hz, CH$_2$C*H*CO), 3.72 (3H, s, CH$_3$O), 3.73 (3H, s, CH$_3$O), 4.92 (2H, br s, C=CH$_2$), 7.16-7.21 (3H, m, ArH), 7.26-7.31 (2H, m, ArH); ^{13}C-NMR: δ_C 22.55 (CH$_3$), 31.5, 34.2, 36.8, 42.6 (CH$_2$), 55.0, 52.2 (CH), 52.5 (CH$_3$), 55.7 (C), 114.8 (CH$_2$), 125.8, 128.2 128.3 (CH), 141.5, 141.9 (C), 169.1 (CO); LRMS (EI) *m/z* 316 [M$^+$-Ph(CH$_2$)$_2$, 6%], 302 (16), 261 (10), 233 (41), 213 (19), 185 (84), 165 (15), 153 (22), 132 (14), 117 (17), 105 (16), 91 (100), 77 (22), 65 (18); $[\alpha]_D^{20}$ = -36 (c 1.27, CH_2Cl_2).

(6R,R$_S$)-Methyl N-*(tert-butylsulfinyl)-6-amino-2-methoxycarbonyl-4-methylene-6-phe-nylhexanoate* (**11d**): Colourless oil; R_f 0.28 (hexane/EtOAc: 1/1); IR ν (film) 3278, 3090, 3025, 2954, 1739, 1645, 1436, 1372, 1242, 1153, 1048, 903 cm^{-1}; ^{1}H-NMR: δ_H 1.19 [9H, s, (CH$_3$)$_3$C], 2.40-2.50 (2H, m, C*H*$_2$CHNH), 2.63-2.68 (2H, m, C*H*$_2$C=CH$_2$), 3.62 (1H, t, *J* = 7.8 Hz, CH$_2$C*H*CO), 3.71 (1H, br s, NH), 3.72 (6H, s, 2×CH$_3$O), 4.53-4.58 (1H, m, C*H*NH), 4.97 (1H, s, C=C*H*H), 5.00 (1H, s, C=CH*H*), 7.26-7.31 (5H, m, ArH); ^{13}C-NMR: δ_C 22.4 (CH$_3$), 34.1, 45.6 (CH$_2$), 50.1 (CH), 52.55 (CH$_3$), 55.0 (CH), 55.5 (C), 115.42 (CH$_2$), 127.4, 127.65, 128.4 (CH), 141.55, 141.7 (C), 168.95, 169.0 (CO); LRMS (EI) *m/z* 217 [M$^+$-(CH$_3$)$_3$SONH-HCO$_2$CH$_3$, 100%], 189 (81), 161 (43), 133 (22), 105 (15), 103 (13), 80 (10), 66 (15); $[\alpha]_D^{20}$ = -76 (c 1.08, CH_2Cl_2).

(6R,S$_S$)-Methyl N-*(tert-butylsulfinyl)-6-amino-2-methoxycarbonyl-4-methylenetetra-decanoate* (**11e**): Physical and spectroscopic data were found to be the same as that for **11a**; $[\alpha]_D^{20}$ = +49 (c 0.92, CH_2Cl_2).

(6S,S_S)-Methyl N-*(tert-butylsulfinyl)-6-amino-2-methoxycarbonyl-7-methyl-4-methyl-eneoctanoate* (**11f**): Physical and spectroscopic data were found to be the same as that for **11b**; $[\alpha]_D^{20}$ = +67 (c 1.19, CH_2Cl_2).

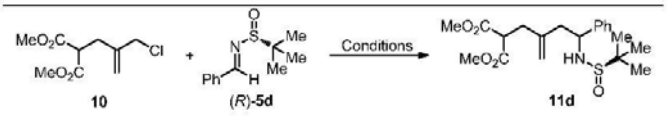
(6R,S_S)-Methyl N-*(tert-butylsulfinyl)-6-amino-2-methoxycarbonyl-4-methylene-8-phenyloctanoate* (**11g**): Physical and spectroscopic data were found to be the same as that for **11c**; $[\alpha]_D^{20}$ = +36 (c 1.03, CH_2Cl_2).

(6S,S_S)-Methyl N-*(tert-butylsulfinyl)-6-amino-2-methoxycarbonyl-4-methylene-6-phenylhexanoate* (**11h**): Physical and spectroscopic data were found to be the same as that for **11d**; $[\alpha]_D^{20}$ = +62 (c 1.09, CH_2Cl_2).

Results and discussion

In order to know the best reaction conditions for the indium-promoted allylation of *N-tert*-butylsulfinyl aldimines **5** with dimethyl 2-[2-(chloromethyl)allyl]malonate [**10**, easily accessible from commercially available dimethyl malonate and 3-chloro-2-(chloromethyl)prop-1-ene], we took aldimine (*R*)-**5d**, derived from benzaldehyde and (*R*)-2-methyl-2-propanesulfinamide,[27] as the imine model. The reaction did not take place using 1.3 equivalents of indium and 1.5 equivalents of the allylic chloride **10** in THF at 60 ºC for 72 hours (Table 1, entry 1), which are the standard reaction conditions for the allylation of this type of imines with allyl bromide.[26] The allylation did not also took place at 100 ºC in a high pressure flask (Table 1, entry 2). A promising result was obtained when the reaction was performed in the absence of any solvent but using 3 equivalents of allylic chloride **10** at 23 ºC, allylated product **11d** being isolated in 12% yield after column chromatography (Table 1, entry 3). Under similar reaction conditions, we tried to improve the yield by adding 2 equivalents of potassium iodide, in order to facilitate the formation of the allylindium intermediate (chlorine-iodine exchange would lead to a more reactive allylic iodide), however, we obtained the expected product **11d** in just 8% yield (Table 1, entry 4). Fortunately, compound **11d** was isolated in 75% yield by simply switching from potassium to sodium iodide under almost identical reactions conditions (Table 1, entry 5). Finally, yield was not improved when the reaction was carried out in a saturated aqueous sodium bromide solution in the presence of 4 equivalents of indium and 2 equivalents of allylic chloride **10** at room temperature for 72 hours, compound **11d** being now isolated in 22% yield (Table 1, entry 6). Regarding the stereoselectivity of the process, surprisingly, a single diastereoisomer was observed by ^{1}H-NMR analysis of the crude reaction mixture in all cases.

Table 1. Optimization of the reaction conditions.

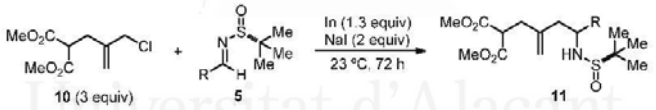


10 (*R*)-**5d** **11d**

Entry	Conditions[a]	**11d** (%)[b]
1	**10** (1.5 equiv), In (1.3 equiv), THF (3 mL), 60 ºC, 72 h	0
2	**10** (1.5 equiv), In (1.3 equiv), THF (3 mL), 100 ºC, 72 h	0
3	**10** (3 equiv), In (1.3 equiv), 23 ºC, 72 h	12
4	**10** (3 equiv), In (1.3 equiv), KI (2 equiv), 23 ºC, 12 h	8
5	**10** (3 equiv), In (1.3 equiv), NaI (2 equiv), 23 ºC, 72 h	75
6	**10** (3 equiv), In (4 equiv), saturated NaBr-H_2O (5 mL), 23 ºC, 72 h	22[c]

[a] All the reactions were carried out using 0.2 mmol of aldimine (*R*)-**5d**. [b] Isolated yield after column chromatography (silica gel, hexane/EtOAc) based on the starting aldimine (*R*)-**5d**. [c] Partial decomposition of the starting aldimine (*R*)-**5d** occurred.

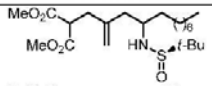
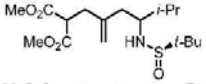
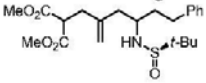
The reaction of dimethyl 2-[2-(chloromethyl)allyl]malonate (**10**) with different chiral *N*-sulfinyl aldimines **5** under the optimized conditions (Table 1, entry 5) led to compounds **11** in good yields (Scheme 2 and Table 2) and excellent diastereoselectivities (a single stereoisomer was always isolated). The highest yield was obtained with aldimine (*R*)-**5c** derived from 3-phenylpropanal (Table 2, entries 3 and 7). As it was expected, [α] values regarding the optical rotation of amino ester derivatives **11** showed opposite sign for each enantiomer (see Experimental part above).

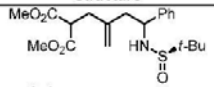
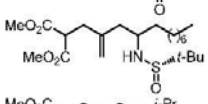
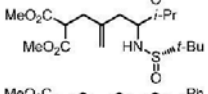
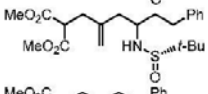
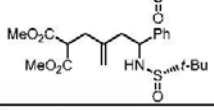


10 (3 equiv) **5** **11**

Scheme 2

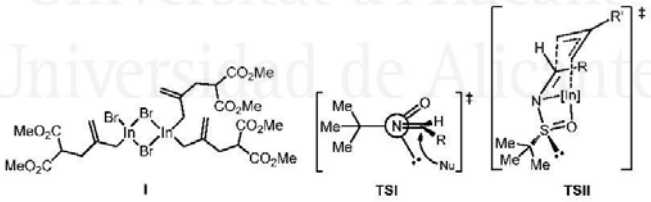
Table 2. Preparation of amino ester derivatives **11**.

	Aldimine **5**		Amino ester **11**[a]		
Entry	No.	R	No.	Structure	Yield (%)[b]
1	(*R*)-**5a**	$CH_3(CH_2)_7$	**11a**		87
2	(*R*)-**5b**	*i*-Pr	**11b**		87
3	(*R*)-**5c**	$Ph(CH_2)_2$	**11c**		90

	Aldimine **5**		Amino ester **11**[a]		
Entry	No.	R	No.	Structure	Yield (%)[b]
4	(*R*)-**5d**	Ph	**11d**		71
5	(*S*)-**5a**	$CH_3(CH_2)_7$	**11e**		77
6	(*S*)-**5b**	*i*-Pr	**11f**		75
7	(*S*)-**5c**	$Ph(CH_2)_2$	**11g**		82
8	(*S*)-**5d**	Ph	**11h**		72

[a] All products were >95% pure (GLC and/or 300 MHz ^{1}H RMN). [b] Isolated yield after column chromatography (silica gel, hexane/EtOAc) based on the starting aldimine **5**.

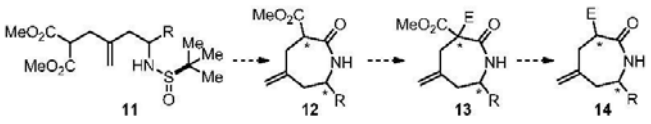
The configuration of the newly created stereogenic centre was not yet assigned. Two different models have been proposed in order to explain the stereochemical outcome of the addition of allylic nucleophiles, in our case, an allylindium sesquihalide intermediate of type **I** (Figure 2), to *N*-*tert*-butylsulfinyl aldimines: an open transition state **TSI**[19] (Figure 2) and a six-membered ring chelation control model **TSII**[26] (Figure 2). Opposite configurations are obtained depending on the operating mechanism. Based on our experience, we think that allylation of the imines takes place through a cyclic transition state of type **TSII** and the nucleophilic attack occurs to the *Si*-face of the imine unit for R_S-isomers (Table 2, entries 1-4) and to the *Re*-face in the case of S_S-derivatives (Table 2, entries 5-8).



I **TSI** **TSII**

Figure 2

Enantiomerically pure amino ester derivatives **11** are of interest because they could be easily transformed into 3,7-disubstituted-5-methyleneazepan-2-ones **12-14** (Scheme 3). Work in this area is under progress and will be reported in the future in due course.



Scheme 3

Conclusions

We have reported herein that the indium-mediated allylation of *N-tert*-butylsulfinyl aldimines with dimethyl 2-[2-(chloromethyl)allyl]malonate in the presence of sodium iodide proceeded in high yields with an excellent diastereoselectivity. The resulting amino ester derivatives being potential precursors of interesting nitrogen-containing seven-membered heterocycles.

Acknowledgements

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Biography

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I was born in Baghdad - Iraq, on the 25th of August, 1980.

In 1987, I started the studies of the primary school at Al-Warka'a Primary School in the city of Al-Mahmoodiyah, then moved to Spain in 1989 and continued the studies at the Iraqui School in Madrid.

I also carried out the studies of secondary school at the Iraqui School in Madrid and after leaving Spain, I continued the studies at Abd-Alwahab Al-Greiry Secondary School, also in the city of Al-Mahmoodiyah.

I should mention that during my stay in Spain, I was also studying the E.G.B. at the C.P. Fernando de los Rios in the city of Burjassot, from which I was graduated in 1994.

Since 1998, I started my carreer at the Department of Chemical Engineering, at the University of Technology in Baghdad - Iraq, from which I was graduated as a Chemical Engineer in 2003, and then continued my studies to obtain the Master degree in Chemical Engineering (Unit Operation) at the same department in may 2005.

In September 2007, I started my Ph.D. studies at the Department of Chemistry of the Polytechnic University of Valencia, where I carried out part of the required courses to opt for the Ph.D. degree, and then moved to the Institute of Organic Synthesis (Organic Chemistry Department) at the University of Alicante to complete the rest of the courses and the investigation period of the Ph.D. Studies.

Since then, and till now, I was preparing the Doctoral Thesis, whose results are gathered in the present memory.

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