VNIVERSITAT DE VALÈNCIA Facultat de Química

Departament de Química Orgànica

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DIASTEREO- AND ENANTIOSELECTIVE CONJUGATE ADDITION REACTIONS WITH α,β-UNSATURATED IMINES

Doctoral Thesis

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CERTIFICAN:

Que la presente Tesis Doctoral, titulada **"Diastereo- and Enantioselective Conjugate Addition Reactions with α,β-Unsaturated Imines"** ha sido realizada bajo su dirección en el Departamento de Química Orgánica de la Universitat de València por el licenciado en Química **D. Miguel Espinosa López** y autorizan su presentación para que sea calificada como Tesis Doctoral.

Burjassot, Mayo 2017

Fdo. Gonzalo Blay Llinares

Fdo. M. Luz Cardona Prósper

“Talking nonsense is the sole privilege mankind possesses over the other organisms. It’s by talking nonsense that one gets to the truth! I talk nonsense, therefore I’m human”

Fyodor Dostoievsky: *Notes from Underground, White Nights, The Dream of a Ridiculous Man, and Selections from The House of the Dead.*

“The darker the night, the brighter the stars,
The deeper the grief, the closer is God!”

Fyodor Dostoievsky: *Crime and Punishment.*

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INDEX

ABBREVIATIONS

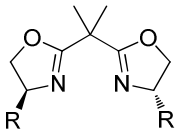
Å	angstrom
Ac	acetyl
acac	acetylacetone
AcOH	acetic acid
al.	*alii* (others)
Ar	aryl
BA	Brønsted acid
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Bs	benzenesulfonyl
Bz	benzoyl
Boc	*tert*-butoxycarbonyl
BOPA	bis(oxazolinylphenyl)amide
BOX	bisoxazoline
br	broad
briphos	bicyclic bridgehead phosphoramidites
Bu	butyl
c	concentration (g/100 mL)
ca.	*circa* (aproximately)
cat	catalyst
COD	1,5-cyclooctadiene
coe	cis-(cycloocctene)
col.	collaborator/s
Cp	cyclopentadiene
Cy	cyclohexyl
d	doublet/days
DBFOX	4,4'-disubstituted(dibenzofuran-4,6-diyl)-2,2'-bioxazolines
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DCE	dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	distorsionless enhancement by polarization transfer
DFT	density functional theory
DIBAL	diisobutylaluminum hydride
DIEA/DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMSO	dimethylsulfoxide
DOPA	3,4-dihydroxyphenylalanine
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereoisomeric ratio

ee	enantiomeric excess
equiv.	equivalent
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
EWG	electron withdrawing group
g	gram
h	hour
Hex	hexyl
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IBX	2-iodobenzoic acid
i.e.	*id est* (it is)
J	coupling constant (NMR)
Kbar	kilobar
kV	kilovolts
L	liter
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
Lit.	literature
M	molar
M^+	molecular ion
m	multiplet
Me	methyl
mg	milligram
MHz	megahertz
min	minutes
mL	milliliter
mm	millimeter
mmol	millimol
mp	melting point
MS	mass spectrometry/molecular sieves
Mes/Ms	mesyl
n.d.	not determined
NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
OFBA	*ortho*-fluorobenzoic acid
PCC	Pyridinium chlorochromate

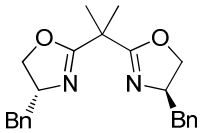
PG	protecting group
Ph	phenyl
pin	pinacolate
piv	pivaloyl
PMP	*p*-methoxyphenyl
POP	4-phenoxylphenyl
ppm	parts per million
Pr	propyl
PS	polystyrene
pyBOX	2,6-pyridin bisoxazoline
q	quadruplet
Q-ToF	quadrupole time-of-flight
rt/RT	room temperature
s	singlet
S_N	nucleophilic substitution
t	triplet
t	time
T	temperature
TADDOL	α,α,α,α-tetraaryl-1,3-dioxolane-4,5- dimethanol
TBAB	tetrabutylammonium fluoride
TBDMS/TBS	*tert*-butyldimethylsilyl
TC	thiophene-2-carboxylate
Tcpp	tetra(*p*-chlorophenyl)porphyrin
TDMPP	5,10,15,20-tetrakis(2,6-dimethylphenyl)porphyrinato
Tf	triflate (trifluoromethanesulfonate)
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TIBPS	triisobutylphosphine sulfide
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
Tol	toluene
t_r	retention time
TS	transition state
Ts	tosyl
UV	ultraviolet
[α]	specific rotation
δ	chemical shift
µL	microliter

LIGAND STRUCTURES

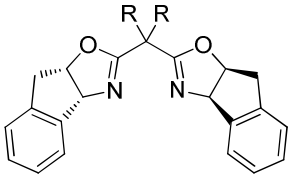
BOX LIGANDS



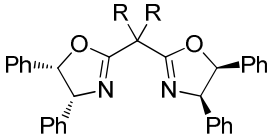
BOX1, R = Ph
BOX2, R = *i*Pr
BOX3, R = *t*Bu
BOX4, R = 1-naphthyl-CH_2



BOX5

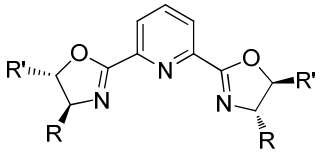


BOX6, R = H
BOX7, R = Me

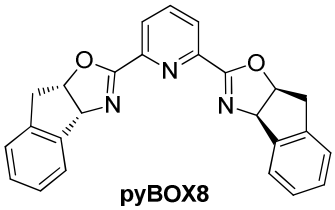


BOX8, R = H
BOX9, R = Me
BOX10, R,R = CH_2-CH_2

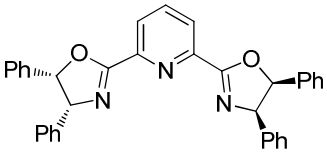
pyBOX LIGANDS



pyBOX1, R = Ph, R'= H
pyBOX2, R = *i*Pr, R'= H
pyBOX3, R = *t*Bu, R' = H
pyBOX4, R = *i*PrCH_2, R' = H
pyBOX5, R = BnCH_2, R'= H
pyBOX6, R = 1-naphthyl-CH_2, R'= H
pyBOX7, R = Me, R'= Ph



pyBOX8



pyBOX9

1. INTRODUCTION

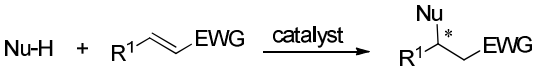
1. INTRODUCTION

Chirality has profound implications in the biological activity of organic molecules. Agrochemicals and drugs interact with biological matrices or drug targets such as proteins, nucleic acids or biomembranes that display complex three-dimensional structures capables of recognizing specifically a molecule in only one of the many possible arrangements in the three dimensional space, determining the binding mode and affinity of a drug molecule.[1] As the drug target is made of small fragments with chirality, biological systems in most cases, recognize a pair of enantiomers as different substances, and the two enantiomers will elicit different responses. Thus, one enantiomer may act as a very effective therapeutic drug whereas the other enantiomer is totally inactive or even highly toxic. Thalidomide is a classical example with this regards. This drug was synthesized as a racemate and widely prescribed for morning sickness from 1957 to 1962 in the European countries and Canada. This led to an estimated over 10.000 babies born with defects due to the teratogenic properties of the *S* enantiomer. Although further studies demonstrated that the stereogenic center of thalidomide is easily racemized *in vivo* and that the teratogenic effects would not have been avoided by using enatiomerically pure *R*-thalidomide, the chirality story about this drug had a great impact on modern chiral drug discovery and development. Drug agencies are imposing more regulation constrains for the approval of new racemic drugs. Similarly, chirality may determine the mechanical, optical or electromagnetic properties of materials by imposing determined molecular arrangements.[2]

Although the majority of natural products are in single enantiomeric form, for example, amino acids and carbohydrates, there are still great demands for chiral artificial products in high enantiomeric purity to be used in different ways, especially in the pharmaceutical industry. Accordingly, chemists have developed different methods to obtain enantiomerically enriched compounds which involve the conversion or derivatization of readily available natural chiral compounds (chiral pool), the resolution of racemates or asymmetric synthesis.[3]

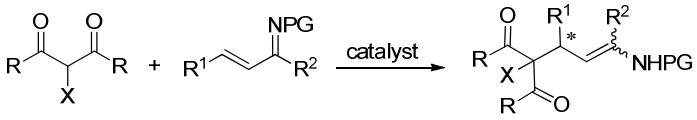
Asymmetric synthesis refers to the conversion of an achiral starting material to a single enantiomeric form of a chiral product by using a properly dessigned reaction. It is currently the most powerful and most commonly used method for chiral molecule preparation. In asymmetric synthesis a certain amount of a chiral substance is required to induce enantioselectivity to the reaction. Among the types of asymmetric reactions, the most desirable and the most challenging is catalytic asymmetric synthesis, in which a molecule of a chiral catalyst can create millions of chiral product molecules, just as enzymes do in biological systems. Catalytic asymmetric synthesis often has significant economic advantages over stoichiometric asymmetric synthesis of enantiomerically pure compounds, since it requires less chiral material and minimizes the production of chemical waste. [4]

On the other hand, C-C bond formation is a proccess of most importance in organic synthesis for the construction of the carbon skeleton in organic molecules. Among them, the conjugate addition of carbon nucleophiles to electrophilic double bonds, usually referred as Michael addition, is one of the most attractive and frequently used methods for this purpose (Scheme 1). The research on this transformation has been boosted by the wide diversity of compounds that can serve as nucleophiles and electrophiles to generate a varied array of products.[5] Such reactions often result in the generation of a new stereocenter, and consequently a considerable effort has been devoted to the development of asymmetric catalytic versions of 1,4-addition reactions.[6] Unsaturated carbonyl compounds, nitroalkenes and less frequently unsaturated sulfones have been used as electrophilic partners in asymmetric conjugate additions of easily enolizable nucleophiles such as 1,3-dicarbonyl and related compounds.



Scheme 1. Nucleophilic conjugate addition to electrophilic alkenes

In this context, α,β-unsaturated imines (1-azabutenes), readily prepared *via* condensation of *N*-substituted amines with the parent unsaturated ketones, have emerged as an interesting family of compounds with important applications in the synthesis of nitrogen-containing molecules. However, in contrast to carbonyl substrates and nitroalkenes, the asymmetric conjugate addition to α,β-unsaturated imines has been scarcely explored probably due to the lower electrophilicity of these substrates. [7] This thesis is aimed to developing new catalytic asymmetric reactions using α,β-unsaturated imines as electrophiles. In particular the addition of malonate ester derivatives will be explored (Scheme 2).



Scheme 2. Conjugate addition of malonate ester derivatives to α,β-unsaturated imines

2. LITERATURE REVIEW

2. LITERATURE REVIEW

In this chapter the most relevant literature involving conjugate imines as reaction substrates will be reviewed. Only reactions involving the participation of the whole moiety will be considered, therefore simple 1,2-nucleophilic additions to the imine group will not be reviewed. Because of length reasons, reactions involving conjugate oximes or hydrazones will be only exceptionally mentioned. Similarly, examples in which the double C=N bond is a part of an aromatic heterocycle, such as 2-vinylpyridines, or where the electrophilicity of the C=C double bond arises primarily from conjugation with a carbonyl group as in vinyl pyrrolidinones will neither be considered.

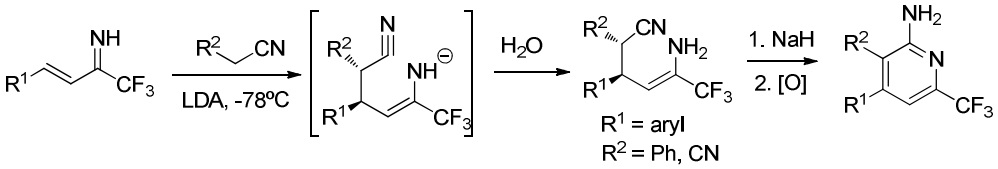
2.1. 1-Aza-1,3-butadienes as simple Michael acceptors

2.1.1. Reactions involving carbon nucleophiles

2.1.1.1. Conjugate addition of carbonyl and related compounds

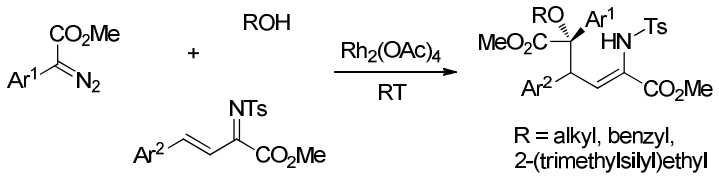
Owing to their ambident electrophilic character, α,β-unsaturated imines can undergo either 1,2- or 1,4- (conjugate) nucleophilic addition processes. However control of the regioselectivity is generally difficult, and very often double nucleophilic addition products are obtained. One of the first conjugate additions of carbon nucleophiles to unsaturated C=N double bonds was described by Mahgoub who reported in 1990 the addition of 1,3-pentanedione and methyl acetoacetate to 2-styryl-2(1H)quinoxalinones in the presence of triethylamine.[8]

In 2013, as a part of their research addressed to the synthesis of pyridines, the group of Palacios reported the related addition of malononitrile and phenylacetonitrile to fluorinated imines to give the corresponding enamines, which can be further transformed into amino pyridines after treatment with NaH and dehydrogenation (Scheme 3).[9]



Scheme 3. Conjugate addition of nitriles to fluorinated α,β-unsaturated imines

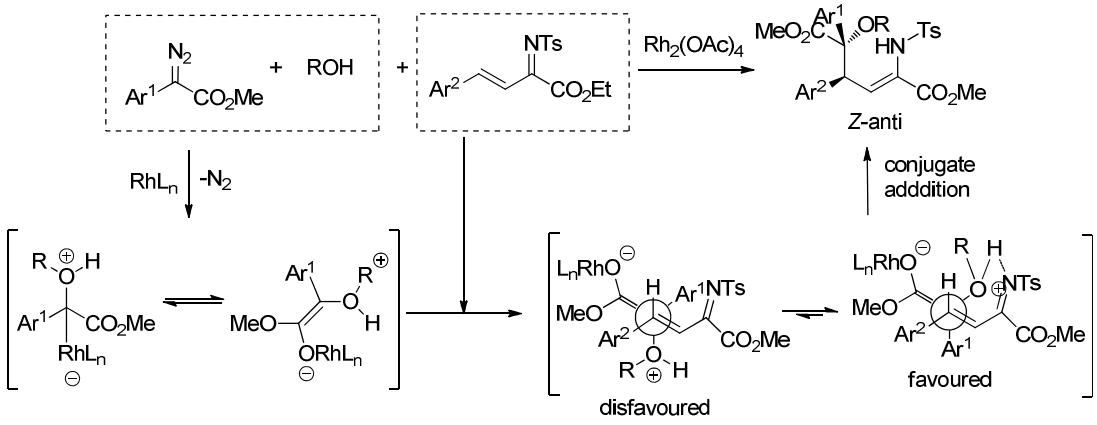
In 2014, the group of Hu developed a formal 1,4-conjugate addition of α-alcoxy esters to *β,γ*-unsaturated *N*-sulfonylimino esters (Scheme 4).



Scheme 4. Formal 1,4-conjugate addition of α-alcoxy esters to *β,γ*-unsaturated *N*-sulfonylimino esters

This three-component process catalyzed by Rh(II) allowed the synthesis of a wide variety of conjugate addition products from imines and diazo esters having aromatic groups and alkyl or benzyl alcohols, with yields ranging from 5% to 95% and diastereomeric ratios higher than 95:5 in all cases.

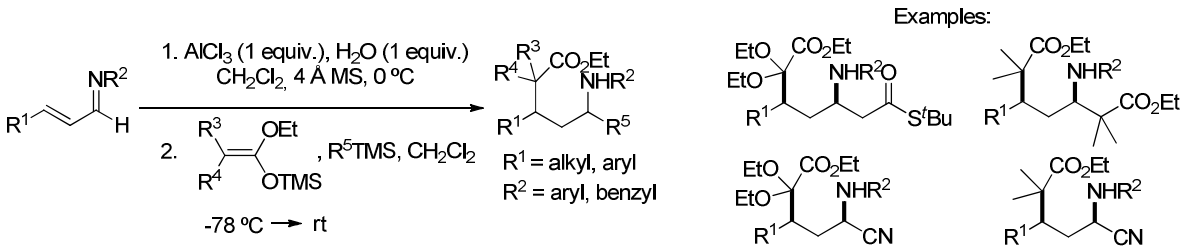
The authors propose a mechanism where the alcohol and the diazo ester react in the presence of Rh to give an oxonium ylide in equilibrium with an enolate, which is trapped by the unsaturated imine in a transition state where an intramolecular hydrogen bond interaction is the key factor for the control of the diastereoselectivity of the reaction (Scheme 5).



Scheme 5. Proposed mechanism for the diastereoselective three component reaction

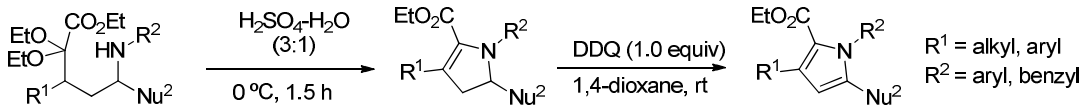
The resulting products could be subjected to different transformations. For instance, the enamine could be hydrogenated on Pd/C to give the corresponding amine with only a slight loss of diastereisomeric ratio. Depending on the R group, the hydroxyl group can be deprotected under different conditions. Finally, the products with the free hydroxyl group, can lead to the corresponding 2,3-dihydrofurans *via* cyclization with *p*-toluenesulfonic acid under reflux in toluene.[10]

Silyl enol ethers as nucleophiles in the Mukaiyama-Michael addition with unsaturated aldimines have been extensively used by Shimizu. This group has carried out several examples of double nucleophilic addition in which a silyl enol ether first attacks the β-carbon followed by the 1,2-addition of a second silyl enol ether or another carbon nucleophile. The reaction is performed in the presence of a Lewis acid such as a Ti(IV) halides or $AlCl_3$ in the presence of a controlled amount of water, and permitted a variety of nucleophiles (Scheme 6).



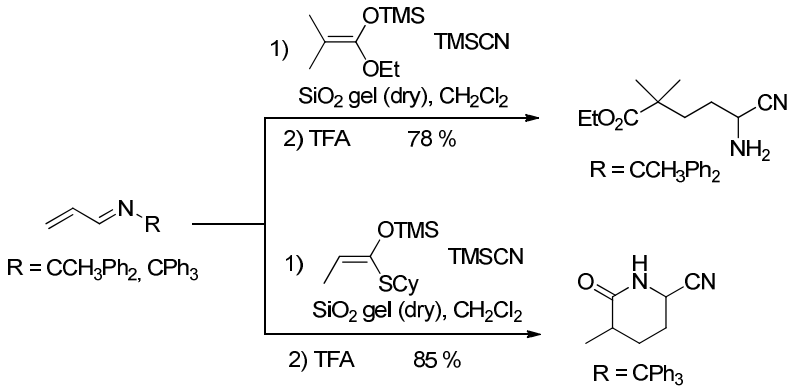
Scheme 6. Double nucleophilic addition of silyl enol ether and other nucleophiles

The double addition products can be transformed into dihydropyrroles and pyrroles with good to excellent yields (Scheme 7).[11-14]



Scheme 7. Synthesis of dihydropyrroles and pyrroles by Shimizu

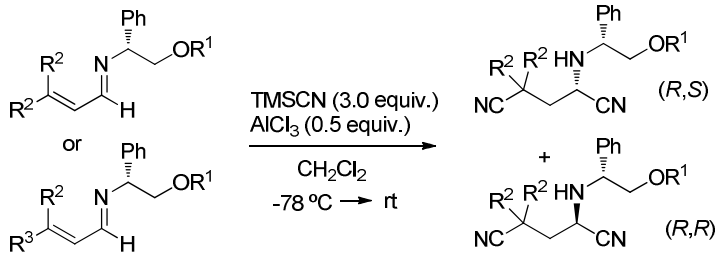
The same group has also reported the double addition reaction of different silyl enol ethers and trimethylsilyl cyanide to *N*-allylidene amines prepared from acrolein and diphenylethyl- or tritylamine. Work-up with TFA allowed obtaining homoglutamic acid derivatives or, in the case of the product obtained from the ketene silyl thiocetal derived from *S*-cyclohexyl propanothioate, a valerolactam derivative (Scheme 8).[15]



Scheme 8. Synthesis of homoglutamic acid derivatives and valerolactams from acrolein imines

2.1.1.2. Conjugate addition of cyanide

Shimizu has also applied the double nucleophilic addition methodology in the enantioselective synthesis of chiral 2-aminopentadinitriles. The bis-cyanation of unsaturated aldimines derived from (*R*)-phenylglycinol with TMSCN catalyzed by $AlCl_3$ provided the expected products with high diastereoselectivities in almost all the cases (Scheme 9, Table 1).[16]



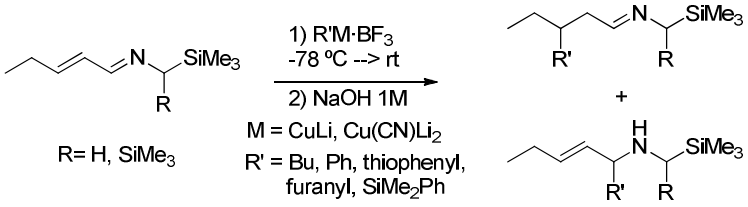
Scheme 9. Diastereoselective bis-cyanation of (*R*)-phenylglycinol-derived imines

Table 1. Asymmetric bis-cyanation of chiral α,β-unsaturated aldimines.

Entry	R^1	R^2	R^3	Yield (%)	(*R*,*S*):(*R*,*R*)
1	Me	Me	-	76	93:3
2	$CH_2CH=CH_2$	Me	-	71	96:4
3	(*E*)-$CH_2CH=CHMe$	Me	-	68	86:14
4	(*E*)-$CH_2CH=CHPh$	Me	-	50	90:10
5	$CH_2(Me)C=CH_2$	Me	-	73	92:8
6	$CH_2CH=CH_2$	H	TMS	54	91:9
7	(*E*)-$CH_2CH=CHMe$	H	TMS	64	81:19
8	$CH_2C\equiv CH$	H	TMS	47	79:21

2.1.1.3. Conjugate addition of organometallic reagents.

The first example involving the conjugate addition of an organometallic reagent to α,β-unsaturated aldimines was reported in 1997 by the group of Ricci. These researchers studied the nucleophilic addition of different organocuprates to 1-aza-1,3-butadienes derived from bis- and mono(trimethylsilyl)methylamine in the presence of a stoichiometric amount of $BF_3.Et_2O$ (Scheme 10).

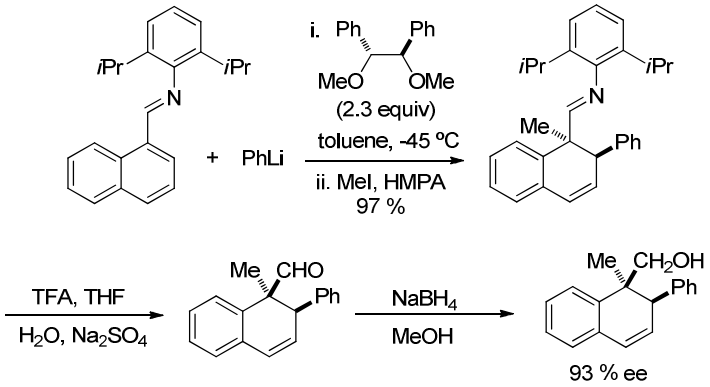


Scheme 10. Nonenantioselective addition of organocuprates to unsaturated silylmethyl aldimines

The reaction performed in a 1,4- regioselective manner in the majority of the examples studied, except with cuprates having heteroaromatic ligands (thiophene or furan) that favored the 1,2-addition product.[17]

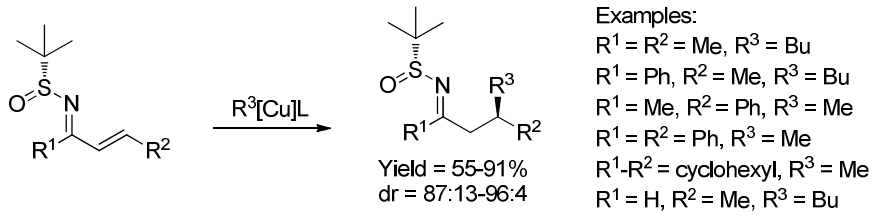
In 2001, Tomioka et *al.* reported the regioselective addition of organolithium reagents to α,β-unsaturated aldimines. The regioselectivity of the reaction was determined by the electronic and steric properties of the N protecting group. Imines having electron-withdrawing aryl groups on the nitrogen favor the 1,2-addition product

while alkyl or bulky aryl groups (2,6-diisopropylphenyl) favored the 1,4-addition process. The reaction allowed the preparation of alcohols after hydrolysis of the imine and reduction. The enantioselective 1,4-addition of phenyllithium was achieved in 93% ee by performing the reaction in the presence of an excess of a C2 symmetric ether as chiral inducer (Scheme 11). This example constitutes the first enantioselective conjugate addition of an organometallic reagent to an α,β-unsaturated imine.[18]



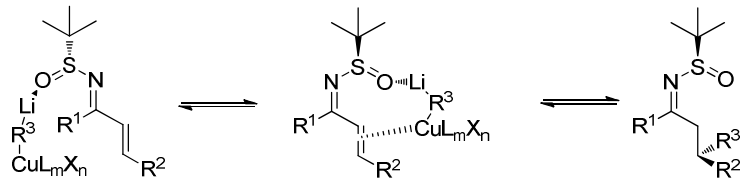
Scheme 11. Regio- and enantioselective 1,4-addition of PhLi to α,β-unsaturated aldimines and subsequent derivatization to the corresponding alcohol

The asymmetric conjugate addition of organocopper reagents to chiral *N-tert*-butanesulfinyl α,β-unsaturated imines was described by Ellman in 2005. Two different reaction conditions involving the use of $Bu_2CuCN \cdot BF_3 \cdot Et_2O$ or Me_2CuLi were tested with a few ketimines and one aldimine, the reaction products being obtained with moderate yields and diastereoselectivities (Scheme 12).



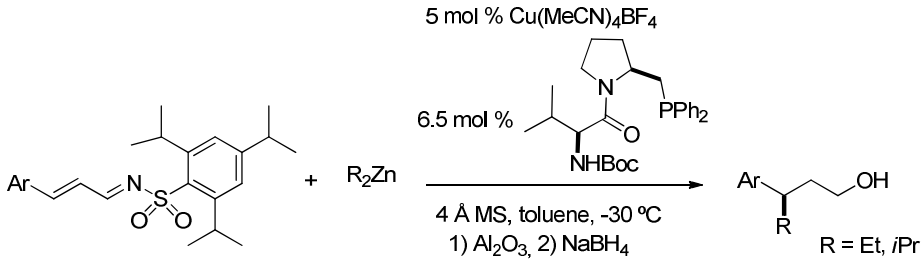
Scheme 12. Diastereoselective conjugate addition of organocuprates to chiral *N*-sulfinyl α,β-unsaturated imines

The authors rationalized the facial selectivity of the reaction following a model in which, the cuprate coordinates to the sulfinyl oxygen on the opposite face from the *tert*-butyl group. Coordination activates the molecule for the conjugate addition and at the same time aligns the cuprate for the addition reaction. Delivery of the cuprate is only possible through one of the imine isomers accessible *via* equilibration of the imine isomers (Scheme 13).[19]



Scheme 13. Proposed model of diastereofacial selectivity for the conjugate addition to chiral *N*-sulfinyl imines

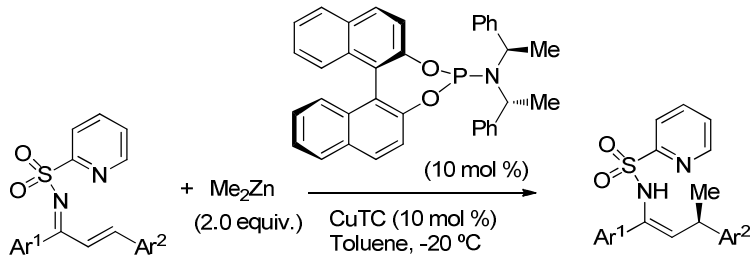
The first asymmetric catalytic conjugate addition of an organometallic reagent to a unsaturated imine was developed by Tomioka in 2005. This group reported the conjugate addition of dialkylzinc reagents to *N*-2,4,6-triisopropylphenylsulfonyl aldimines using a complex of $Cu(MeCN)_4BF_4$ with a chiral amidophosphine ligand as catalyst. The resulting enamines were hydrolyzed and reduced to give the corresponding β-alkylated alkanols with moderate to high enantiomeric excesses. The use of the bulky 2,4,6-triisopropylphenyl group attached to the imine nitrogen was essential to favor the conjugate addition by hampering the approach of the reagent to the azomethinic carbon due to steric hindrance (Scheme 14).[20]



Scheme 14. Conjugate addition of dialkylzinc reagents to *N*-arylsulfonyl aldimines

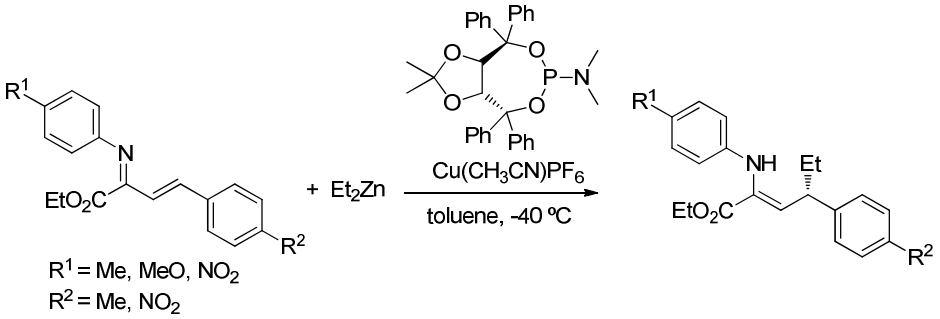
One of the authors of this work (Soeta) and others reported in 2016 the 1,2-addition of dialkylzinc reagents to related *N*-tosyl aldimines using a Cu-NHC catalyst. Although the regioselectivity could be shifted to the 1,4- pathway by changing the copper source and the NHC catalyst, the enantioselectivities obtained were low in all the cases.[21]

Also in 2005, the group of Carretero described the first catalytic enantioselective 1,4-addition of dialkylzinc reagent to α,β-unsaturated ketimines. A copper(I)-phosphorimidite complex catalyzed the conjugate addition of dimethylzinc to a variety of substituted *N*-(2-pyridylsulfonyl) α,β-unsaturated imines derived from chalcones to give the corresponding enamines with excellent yields and diastereisomeric ratios, and moderate enantiomeric excess for the majority of products (Scheme 15). The enamines could be hydrolyzed or subjected to ozonolysis without loss of the optical purity. Addition of bulkier dialkylzinc reagents such as diethyl- or dibutylzinc, at low temperatures, took place with similar yields but with lower enantiomeric excesses than in the case of Me_2Zn. The presence of the coordinating 2-pyridylsulfonyl group proved to be essential for the reaction to proceed.[22]



Scheme 15. Copper-phosphorimidite-catalyzed enantioselective conjugate addition of dimethylzinc to *N*-(2-pyridyl)sulfonyl imines derived from chalcones

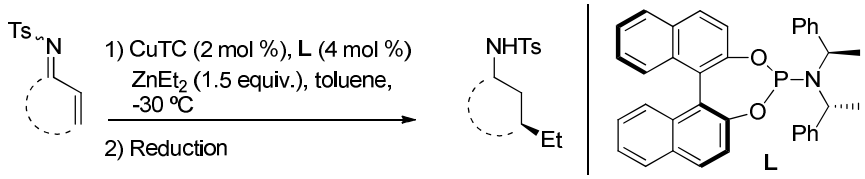
Palacios and Vicario have developed a copper(I)-catalyzed enantioselective conjugate addition of diethylzinc to *N*-aryl α,β-unsaturated imines derived from α-keto esters. The best results in this case were obtained with a phosphoramidite ligand derived from TADDOL, which lead regioselectively to the 1,4-adduct, obtaining exclusively the *Z*-α-dehydroaminoesters bearing a stereogenic center in the γ-position, with high yields and fair to good enantiomeric excesses (Scheme 16).



Scheme 16. Enantioselective synthesis of α-dehydroaminoesters

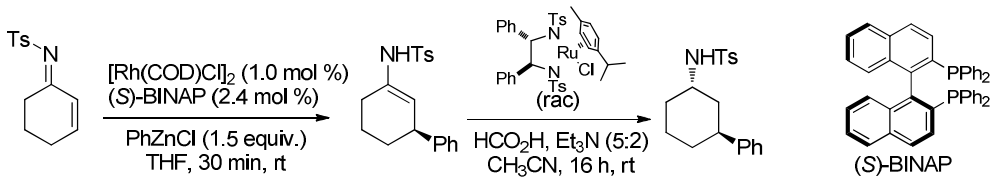
The reaction worked with substrates having electron poor or electron rich aromatic rings attached at either the double bond or the nitrogen atom. The authors demonstrated the possibility of transforming the resulting α-dehydroaminoesters into chiral carboxylic acids by ozonolysis, or into α-aminoesters *via* hydrogenation.[23,24]

The alkylation of imines derived from cyclic enones has been studied by the group of Zezschwitz and Westmeier. In 2014, they described the first enantioselective conjugate addition of dialkylzinc reagents to cyclic *N*-tosyl imines employing the same copper(I)-phosphorimidite catalyst previously used by Carretero. In this way, different five or six member cyclic enamines were prepared with moderate to good yields, diastereoselectivities and with excellent enantiomeric excesses. The enamines could be transformed into chiral cyclopentyl- and cyclohexylamines using different reductive methods (Scheme 17). The reaction was also tested with the *N*-tosyl imine derived from chalcone although with a moderate yield and ee. The tosyl amines can be detosylated by treatment with Boc_2O and Mg.[25]



Scheme 17. Enantioselective synthesis chiral cyclic enanimes

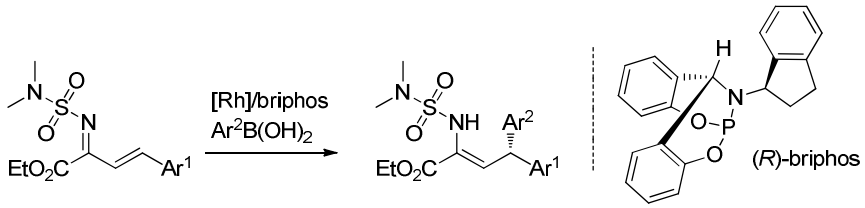
The same group developed a procedure for the enantioselective 1,4-conjugate addition of aryl groups to cyclic α,β-unsaturated *N*-tosyl imines using in this case arylzinc halides as reagents and a Rh-BINAP complex as catalyst. After stereodivergent reduction of the intermediate enamines with a Ru complex and formic acid, the corresponding 3-arylcycloakylamines were obtained with high yields, high diastereoselectivity (dr > 97:3) and excellent enantioselectivities (Scheme 18).[26]



Scheme 18. Enantioselective synthesis of 3-arylcycloalkylamines by rhodium-catalyzed 1,4-addition and subsequent stereodivergent reduction

The same Rh-BINAP catalyst has been applied in the enantioselective 1,2-addition of Me_3Al to cyclic *N*-tosyl imines. The authors noticed that a change of solvent to toluene inverted the regioselectivity favoring the 1,4-addition product (6:1) with the tosyl imine derived from 2-cyclohexenone. The 1,4-addition pathway was also favored with imines derived from substituted cyclohexanones having a stereogenic center (mismatched catalyst) or with the imine derived from 4,4-dimethyl-2-cyclopentenone.[27]

Recently, Ansoo and Hyunwoo reported the conjugate addition of arylboronic acids to imines from β,γ-unsaturated α-keto esters using a rhodium(I) complex with the chiral bicyclic bridgehead phosporamidite ligand (*R*)-briphos (Scheme 19).



Scheme 19. Rh-catalyzed asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated *N*,*N*-dimethylsulfamoyl imino esters

The reaction has a wide scope, permitting variation at both the γ-aryl substituent on the substrate and the aryl group on the boronic acid. The resulting enamines were obtained with good yields, good diastereoselectivities favoring the *Z*-isomer, and excellent enantioselectivities regardless of the substitution on the aromatic groups. The

authors showed the synthetic utility of the resulting products with several transformations.

Based on DFT calculations and X-ray analysis of the Rh-briphos complex, the authors proposed a transition state to explain the observed stereochemistry (Figure 1).[28]

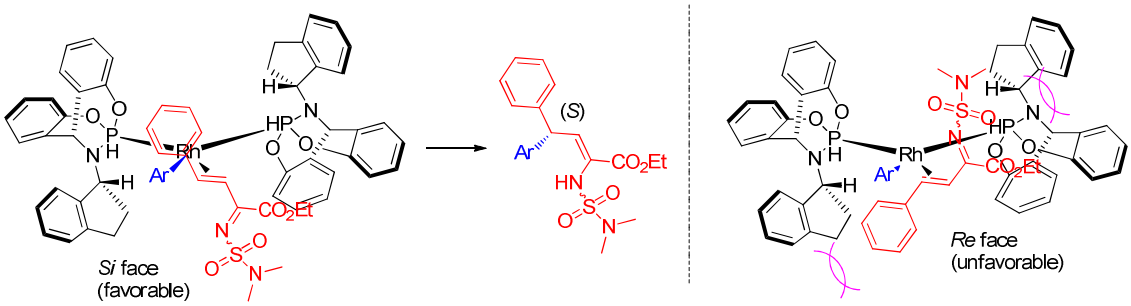
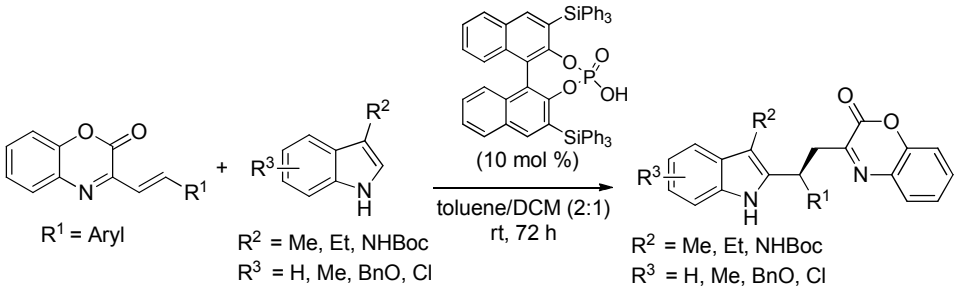


Figure 1. Stereochemical model for the Rh-briphos catalyzed reaction

The same catalyst proved to be useful for the conjugate addition of arylboronic acids to enones and α,β-unsaturated imines derived from chalcones, as well as in the 1,2-addition to imines.[29]

2.1.1.4. Friedel-Crafts alkylation

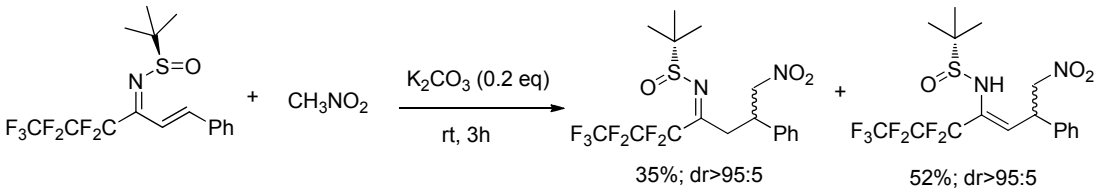
The only example of Friedel-Crafts alkylation involving 1,4-addition to unsaturated imines reported to date was described by Hu and Zhao in 2015. These authors carried out the alkylation at the C2 position of C3-substituted indoles using β,γ-unsaturated α-ketimino esters catalyzed by a chiral phosphoric acid. Substitution on the C3 position of the indole, which is the most reactive position, shifted the reaction to the C2 position. Both the indole and the imine were amenable to substitution, providing products with good enantiomeric excesses in most of the examples. The reaction could be scaled up to one gram without erosion of optical purity (Scheme 20).[30]



Scheme 20. Enantioselective Friedel-Crafts alkylation of indoles and β,γ-unsaturated α-ketimino esters

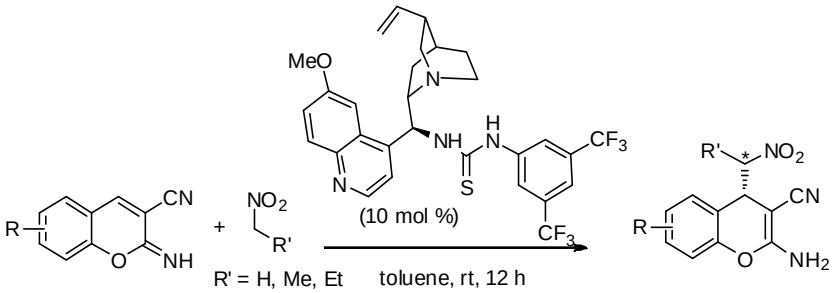
2.1.1.5. Nitro-Michael reaction

In 2011, the group of Liu reported the aza-Henry reaction of nitromethane with chiral *N-tert*-butanesulfinylimines derived from 1,1,1-trifluoromethyl enones. The authors discovered that conjugated imines having a perfluoropropyl group attached to the azomethinic carbon reacted in a 1,4-regioselective manner to give two 1,4-adducts with excellent diastereoselectivities (Scheme 21).[31]



Scheme 21. Diastereoselective conjugate addition of nitromethane to perfluoro-α,β-unsaturated *N-tert*-butanesulfinyl ketimines

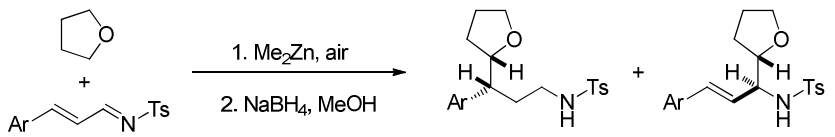
On the other hand, Jiang and Wang have reported the organocatalytic conjugate addition of nitroalkanes to 2-iminochromenes yielding 2-amino-4H-chromenes which have a wide application in medicinal chemistry. The desired products were obtained with excellent yields and enantioselectivities when nitromethane was used as nucleophile. Bulkier nitroalkenes provided the expected products with good yields and high enantioselectivities but with poor diastereoselectivities (Scheme 22).[32]



Scheme 22. Enantioselective synthesis of 2-amino-4H-chromenes

2.1.1.6. Radicalary conjugate addition reactions

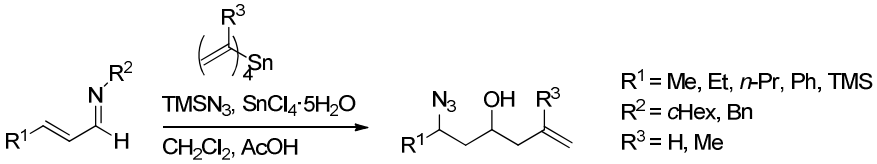
The group of Tomioka reported in 2008 the reaction of the tetrahydrofuran-2-yl radical, generated directly by addition of dimethylzinc to THF in air, with α,β-unsaturated *N*-tosyl aldimines to give the 1,4-adducts as major products. The slow addition of the imine and the use of dimethylzinc instead of diethylzinc were proved essential to favor the 1,4-addition (Scheme 23).[33]



Scheme 23. Addition of the tetrahydrofuran-2-yl radical to α,β-unsaturated *N*-tosyl aldimines

2.1.2. Reactions involving nitrogen and phosphorous nucleophiles

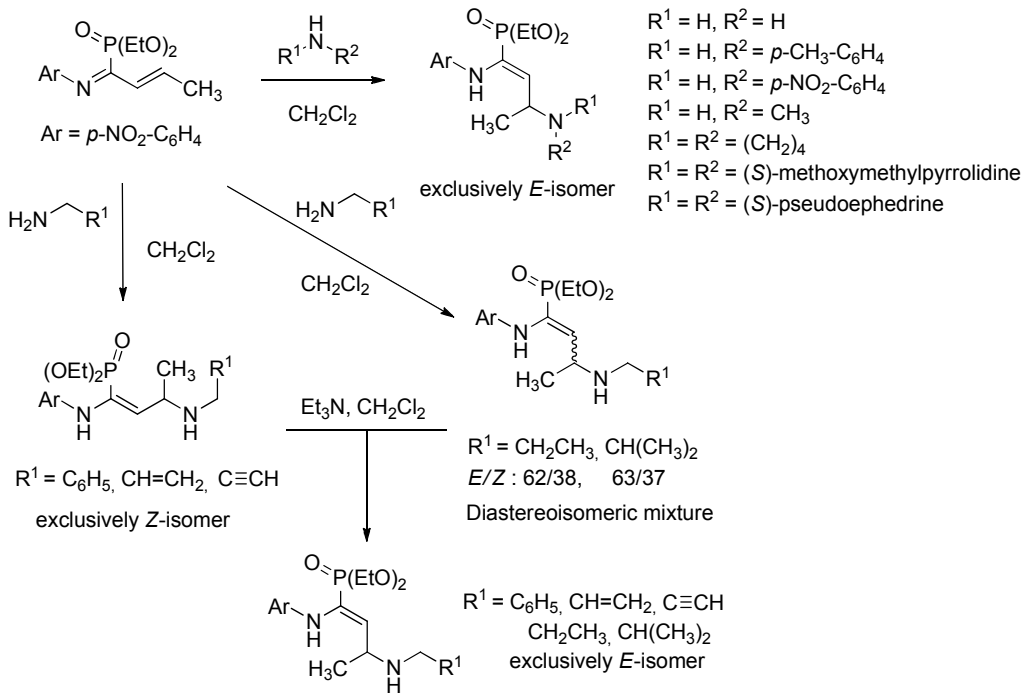
In 2004 the group of Shimizu described the double nucleophilic addition of azides and tetraallyl tin reagents to α,β-unsaturated aldimines promoted by $SnCl_4 \cdot 5H_2O$ to obtain good yields of 1,3-hydroxy azides in a reaction where the unsaturated aldimine played as a latent unsaturated aldehyde (Scheme 24).[34]



Scheme 24. Double nucleophilic addition of azide and tetraallyl tin reagents to unsaturated aldimines

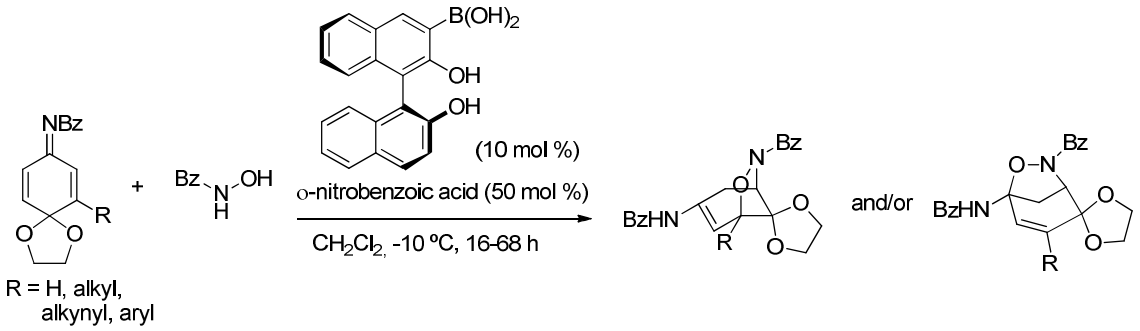
The reaction most probably proceeds *via* reaction of $TMSN_3$ with acetic acid to give HN_3 which adds to the unsaturated imine in a 1,4-fashion, followed by hydrolysis of the imine effected by the liberated HCl from $SnCl_4 \cdot 5H_2O$, and addition of the tin reagent to the resulting aldehyde.

In 2009, the group of Palacios reported the conjugate addition of amines to an α,β-unsaturated imine derived from an α-aminophosphonate to afford α-dehydroaminophosphonates with a γ-stereogenic center bearing an amino group with excellent yields. Depending on the amine, different double bond isomers were obtained, which could be isomerized to the *E* isomer by treatment with triethylamine in dichloromethane. The reaction could also be performed in a multicomponent fashion generating the imine *in situ* and subsequently adding the amine (Scheme 25).[35]



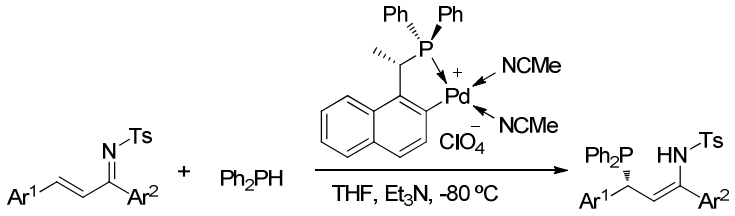
Scheme 25. Synthesis of γ-amino-α-dehydroaminophosphonates

Later, in 2015, Maruoka developed a highly enantioselective aza-Michael reaction of hydroxamic acid to quinone imine ketals catalyzed by chiral boronic acids, allowing the synthesis of densely functionalized cyclohexenes (Scheme 26).[36]



Scheme 26. Enantioselective aza-Michael addition of hydroxamic acid to quinone imine ketals

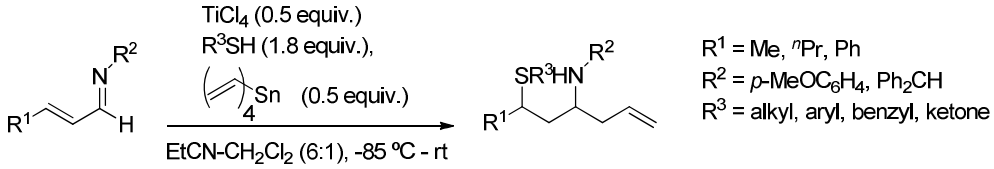
Even though different conjugate additions of phosphites to α,β-unsaturated imines have been reported during the last twenty years,[37-39] the first enantioselective example involving a phosphorous nucleophile was not described until 2012. That year, the group of Leung reported the enantioselective hydrophosphination of α,β-unsaturated ketimines with diphenylphosphine catalyzed by a chiral palladacycle yielding the desired enamino phosphines with high yields and high enantiomeric excesses (Scheme 27).[40]



Scheme 27. Enantioselective conjugate addition of diphenylphosphine to unsaturated imines

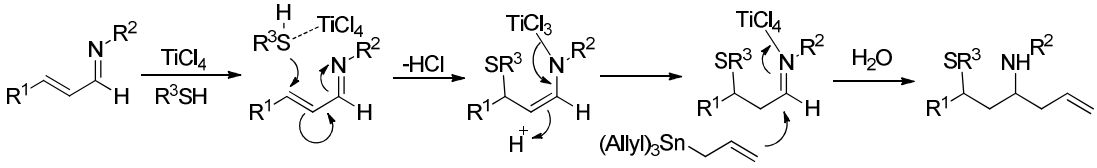
2.1.3. Reactions involving sulfur nucleophiles

The first example found in the literature regarding the conjugate addition of sulfur nucleophiles to α,β-unsaturated imines was reported by Shimizu in 2002. This group performed the double addition of thiols and tetraallyl tin to α,β-unsaturated aldimines to give 1,3-amino sulfurs with variable yields and poor diastereoselectivity (Scheme 28).[41]



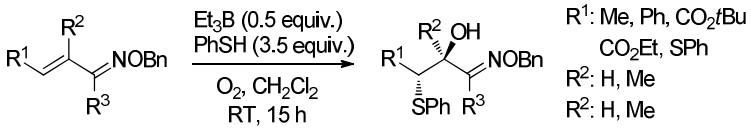
Scheme 28. Double addition of thiols and tetraallyl tin to α,β-unsaturated aldimines

The reaction most probably proceeds *via* a mechanism involving the initial conjugate addition of the thiol promoted by $TiCl_4$. Subsequent protonation is carried out by the HCl liberated from $TiCl_4$ and the thiol to generate an imino species, which in turn is attacked by the allyltin to give the double nucleophilic addition product (Scheme 29).



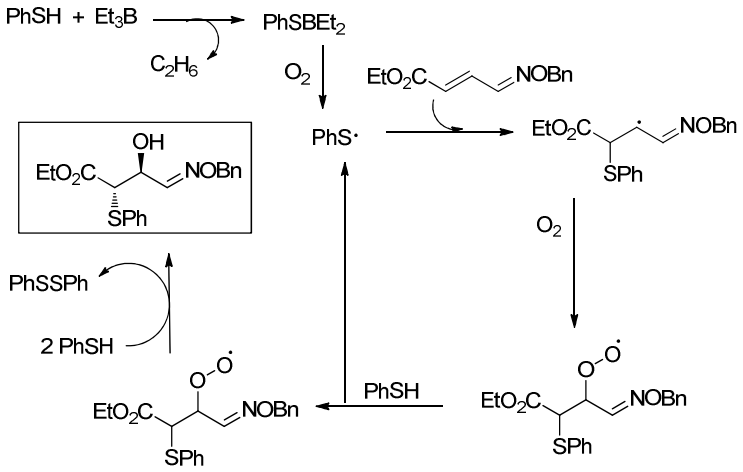
Scheme 29. Mechanism for the double nucleophilic addition

In 2008, Naito reported the regioselective hydroxysulfenylation of α,β-unsaturated oxime ethers *via* a radical mechanism using triethylborane, thiophenol and oxygen (Scheme 30).



Scheme 30. Hydroxysulfenylation of α,β-unsaturated oxime ethers

The authors proposed a radical mechanism in which $PhSBEt_2$ acts as an initiator for the reaction with triplet oxygen leading to the formation of the final products (Scheme 31).[42]

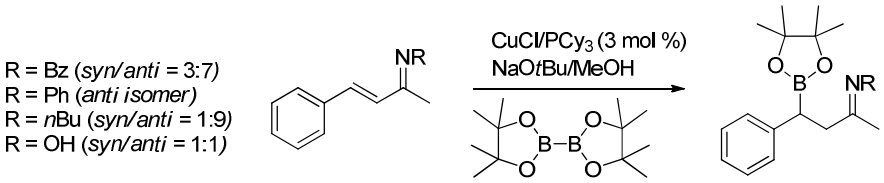


Scheme 31. Proposed mechanism for the hydroxysulfenylation reaction

2.1.4. Reactions involving boron nucleophiles

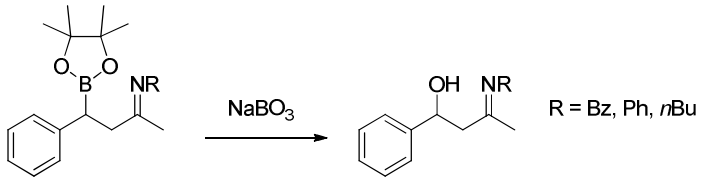
In 2009, the group of Fernandez published the conjugate addition of bis(pinacolato)diboron to different α,β-unsaturated imines. The reaction was carried out in the presence of MeOH as additive, an alcoxide or hydroxide as base, and a combination of copper chloride and a phosphine ligand as catalyst, to obtain the

corresponding β-boryl imines with good conversions except in the case of unsaturated oximes (Scheme 32).



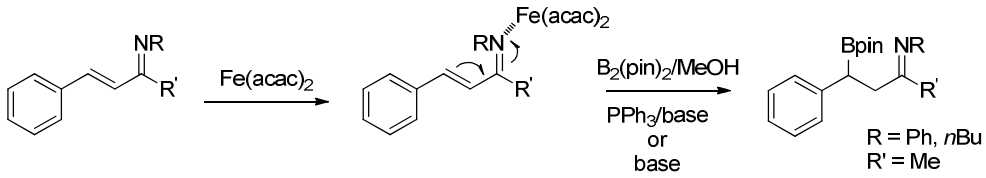
Scheme 32. Cu-mediated conjugate addition of B_2pin_2 to α,β-unsaturated imines

The corresponding imino boronates (except when R = OH) could be oxidized with sodium borate affording different β-imino alcohols with excellent yields (Scheme 33).[43,44]



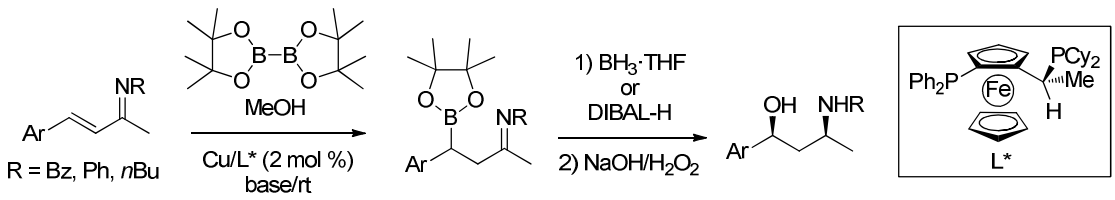
Scheme 33. Oxidation of imino boronates with sodium perborate

In a later research, the same group studied the effect of iron salts in the reaction. They showed that the iron salt coordinates with the nitrogen of the imine, increasing the electrophilicity on the β-position. In this reaction, the boron nucleophile is generated upon interaction of bis(pinacolate)diboron and a PPh_3/Cs_2CO_3 organocatalyst. Both, the iron salt and the organocatalyst play in a synergetic way and none of them alone can activate the substrates (Scheme 34).[45]



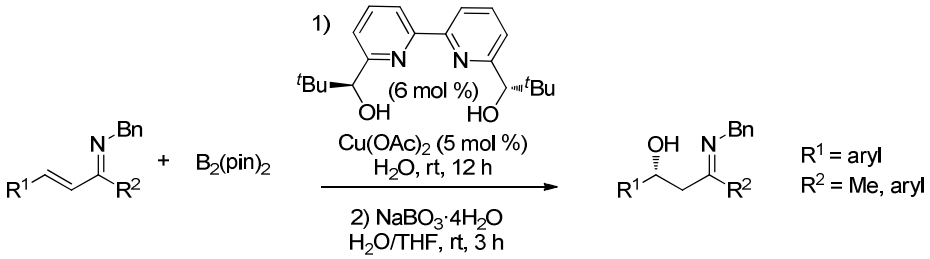
Scheme 34. Iron-activated conjugate addition of boron nucleophiles

In 2011, the group of Fernandez developed a highly enantio- and diastereoselective synthesis of γ-amino alcohols from α,β-unsaturated imines. The reaction was carried out in a one-pot fashion involving a copper-catalyzed enantioselective conjugate addition of $B_2(pin)_2$ to the imine, followed by reduction of the imine moiety with BH_3 or DIBAL-H and oxidation of the borane with H_2O_2 in basic medium. The chiral γ-amino alcohols were obtained with excellent yields, good *syn* (reduction with BH_3) or *anti* (reduction with DIBAL-H) diastereoselectivity and high enantiomeric excesses (Scheme 35).[46,47]



Scheme 35. Enantioselective one pot synthesis of chiral γ-amino alcohols

Finally, in 2014, Kobayashi et *al.* reported another example of enantioselective conjugate addition of bis(pinacolato)diboron to α,β-unsaturated *N*-benzyl imines catalyzed by a chiral copper-bipyridine complex in water. After oxidation of the resulting imino boronates with sodium perborate, β-imino alcohols were obtained with excellent enantiomeric excesses (Scheme 36).[48]



Scheme 36. Copper-bipyridine-catalyzed enantioselective synthesis of chiral β-imino alcohols in water

2.2. 1-Aza-1,3-butadienes as substrates in cycloaddition reactions

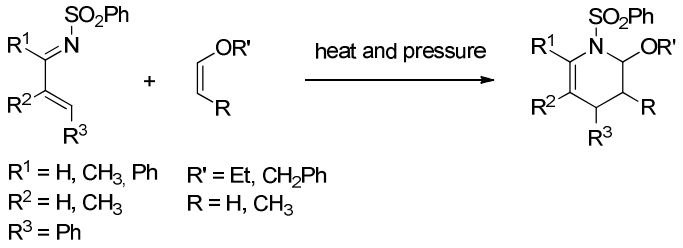
2.2.1. Diels-Alder and formal [4+2] cycloaddition reactions

2.2.1.1. Diels-Alder reaction

With minor exceptions, in this section we will only consider reactions involving conjugate imines and alkenes as substrates to give 6-membered aza-cycles.

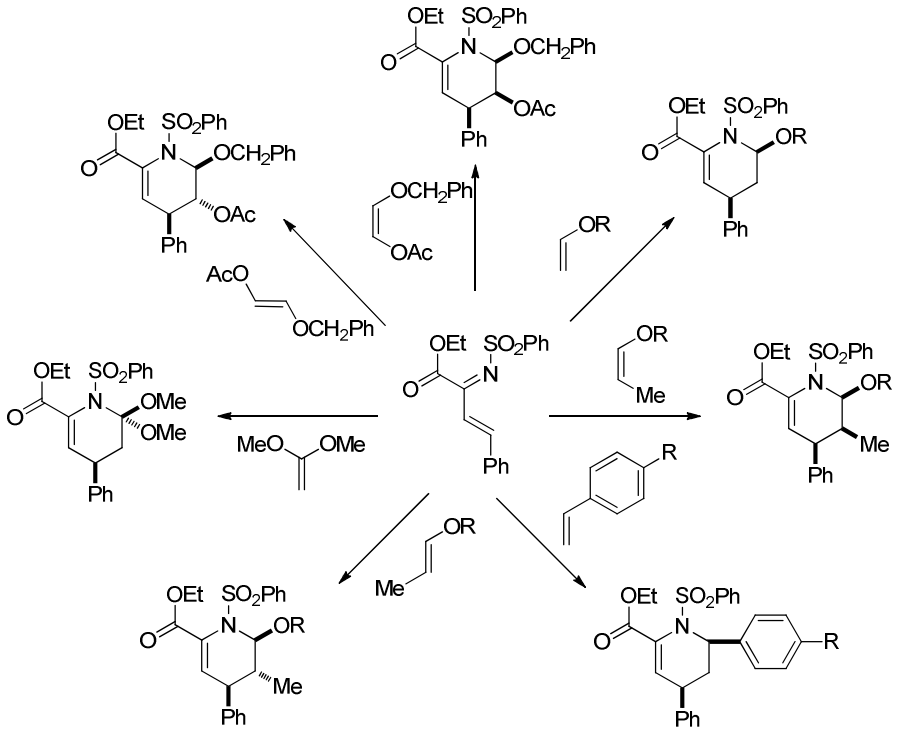
a) Nonenantioselective reactions

The participation of simple α,β-unsaturated imines as heterodienes in Diels-Alder reactions typically suffers from low conversions, competitive imine additions or imine tautomerization hampering or precluding [4+2] cycloadditions.[49-56] In 1989, the group of Boger introduced the use of α,β-unsaturated *N*-benzenesulfonyl imines with the expectation that the presence of an electron-withdrawing substituent would accentuate the electron-deficient nature of the 1-aza-1,3-butadiene and accelerate the [4+2] reaction with electron-rich dienophiles. This group reported the reaction of these substrates with different alkenes to give the corresponding *N*-benzenesulfonyl-1,2,3,4-tetrahydropyridines with moderate yields and excellent diastereoselectivities (Scheme 37).[57]



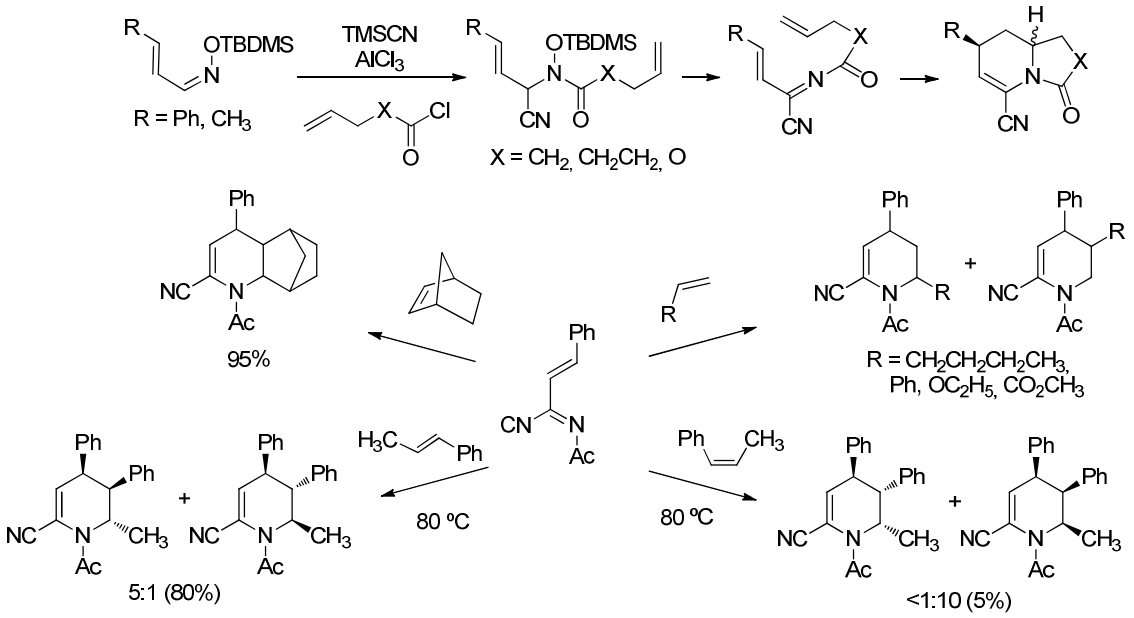
Scheme 37. Diels-Alder reaction of α,β-unsaturated *N*-benzenesulfonyl imines with vinyl ethers

The scope of the Diels-Alder reaction with α,β-unsaturated *N*-benzenesulfonyl imines has been expanded with different dienophiles obtaining a wide range of tetrahydropyridines with a high control of diastereoselectivity (Scheme 38),[58-61] and the reaction has been applied in the synthesis of many biologically active natural products.[62-65]



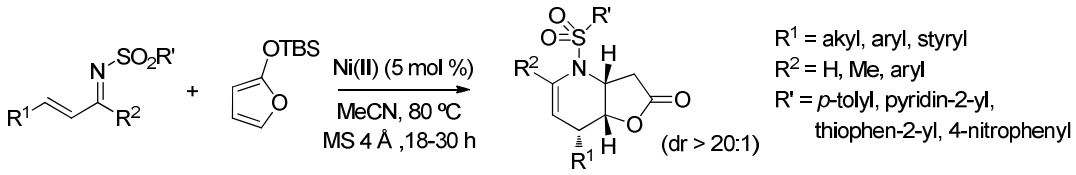
Scheme 38. Synthesis of tetrahydropyridines from α,β-unsaturated *N*-benzenesulfonyl imines

On the other hand, Fowler introduced in 1990 the use of *N*-acyl-α-cyano-1-azadienes, which have been applied as dienophiles in aza-Diels-Alder reactions with different kinds of dienes obtaining the cyclic adducts with variable yields (Scheme 39).[66]



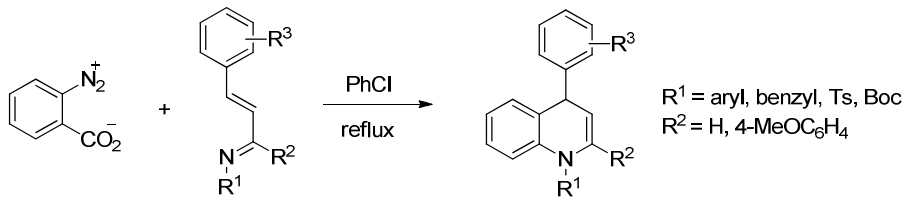
Scheme 39. Examples of aza-Diels-Alder reactions with *N*-acyl-α-cyano-1-azadienes

Recently, the reaction between α,β-unsaturated *N*-sulfonyl imines and 2-trimethylsilyloxyfuran catalyzed by nickel(II) has been described by the group of Wang. For this reaction, the authors propose a cascade mechanism involving a vinylogous Mukaiyama 1,6-Michael/Michael addition sequence, in which 2-silyloxyfuran performs as nucleophile and electrophile sequentially. This methodology combined with subsequent reduction provides a facile access to biologically important fused piperidine/butyrolactone skeletons in good yield with exclusive diastereoselectivity under mild reaction conditions (Scheme 40).[67]



Scheme 40. Diastereoselective synthesis of fused piperidine/butyrolactone compounds

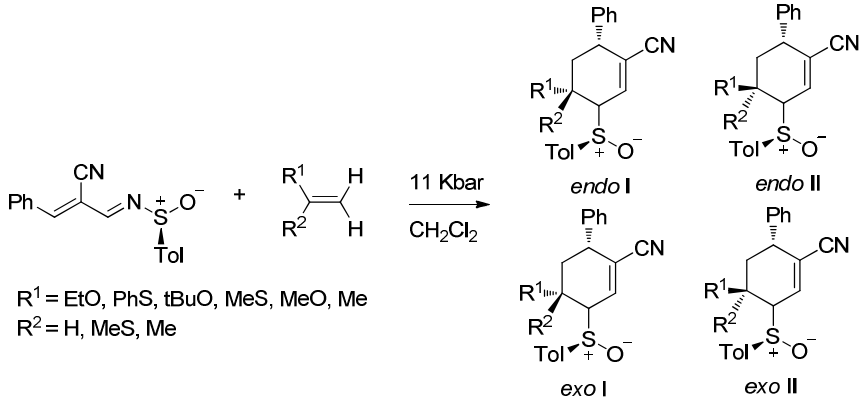
Highly reactive benzines have also been used as dienophiles in the [4+2] cycloaddition of benzyne and different 1-azadienes to obtain 1,4-dihydroquinolines with moderate to good yields (Scheme 41).[68] The resulting dihydroquinolines were converted into 2,4-diarylquinolones.[69]



Scheme 41. Synthesis of 1,4-dihydroquinolines

b) Asymmetric diastereoselective reactions

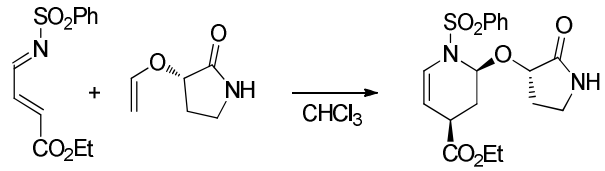
In 1998, Tietze reported the synthesis of tetrahydro- and dihydropyridines by the hetero Diels-Alder reaction of enantiopure α,β-unsaturated *N*-sulfinyl imines and enol ethers (Scheme 42). The reaction was performed at 11 Kbar of pressure and led to tetrahydropyridines in high yield, good *endo/exo* selectivities, but with low induced diastereoselectivities (up to 2.1:1). The reaction did not work with tetrasubstituted alkenes. The sulfinyl group could be removed with MeLi followed by treatment with acetyl chloride or dimethyl sulfate. An example of intramolecular reaction was also reported.[70]



Scheme 42. Diastereoselective Diels-Alder reaction with α,β-unsaturated *N*-sulfinyl imines

In 2005, Barluenga described a single example of diastereoselective Diels-Alder reaction between an unsaturated aldimine and an alkynyl(carboxy)carbene complex derived from (-)-8-phenylmenthol. The resulting dihydropyridine was obtained with 98:2 diastereomeric ratio and the chiral auxiliary could be removed by treatment with $[Cu(MeCN)_4]BF_4$ in wet CH_2Cl_2 to give an aldehyde group with 99.5% ee.[71]

Boger has developed a procedure for the diastereoselective Diels-Alder reaction of *N*-sulfonyl-1-aza-1,3-butadienes with optically active enol ethers derived from chiral benzyl alcohols or α-hydroxy lactams as dienophiles (Scheme 43). The reaction was highly *endo* selective and the highest facial selectivity was obtained with the enol ether derived from 3-hydroxypyrrolidin-2-one (48:1). The protecting group on the nitrogen can also be amenable to variation although the best results were obtained with arylsulfonyl groups. The high diastereoselectivity was attributed to a highly organized [4+2] cycloaddition transition state.[72]



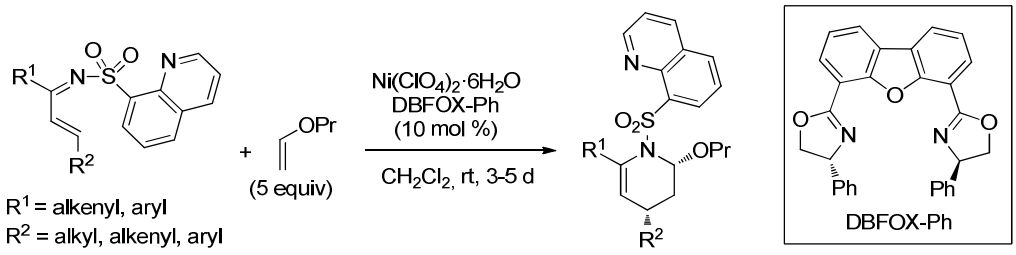
Scheme 43. Diastereoselective Diels-Alder reaction with chiral enol ethers

A similar strategy has been reported by Palacios but using enamines derived from α-amino acids as dienophiles obtaining modest diastereoselectivities.[73]

c) Asymmetric catalytic reactions

A first attempt of enantioselective Lewis acid-catalyzed Diels-Alder reaction with 1-azadienes was carried out by Motorina in 1999. The intramolecular reaction of a 1-cyano-1-aza-1,3-butadiene was achieved in the presence of Cu(II)-BOX complexes. Although the reaction proceeded under smoother conditions than the thermal process, very low enantiomeric induction was observed (ee = 8%).[74,75]

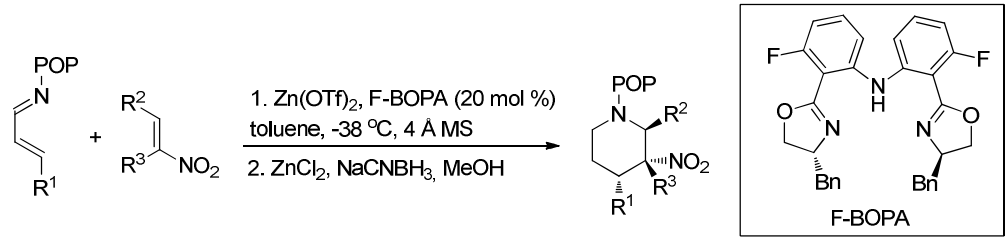
In 2007, Carretero et *al.* developed the first highly enantioselective aza-Diels-Alder reaction of vinyl ethers with *N*-sulfonyl α,β-unsaturated imines derived from chalcone using a DBFOX-Ni complex as catalyst. The choice of the *N*-(8-quinolinesulfonyl) group attached to the imine nitrogen was crucial to obtain the cycloadduct with high stereocontrol (Scheme 44).



Scheme 44. Enantioselective synthesis of chiral lactams

In most cases, the products were obtained with moderate yields (61-73%) and good to excellent enantiomeric excesses (77-92%). Different vinyl ethers including dihydrofuran were good substrates for the reaction. Aryl substituents of different electronic and steric nature at the β-position (R^2) were tolerated. In contrast, substitution compatibility at the imine carbon was more limited with a dramatic drop of yield and enantioselectivity being observed with bulky groups (R^1 = naphthyl).[76,77]

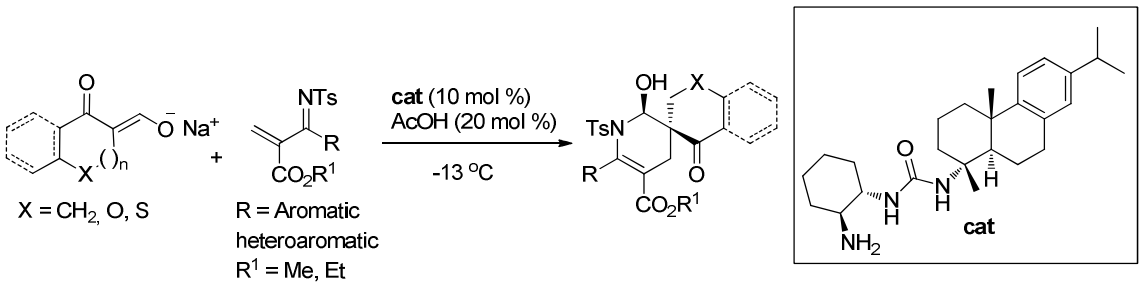
Recently, Rovis has developed an enantio- and diastereoselective formal [4+2] cycloaddition involving nitroalkenes and 1-azadienes as two electron-deficient partners (Scheme 45).



Scheme 45. Formal [4+2] addition of 1-azadienes and nitroalkenes

The resulting nitropiperidines were obtained with good yields, diastereoselectivity and variable enantioselectivity (46-92% ee). The electronic properties of the aryl rings at the 4-position of the azadiene have no apparent effect on the yield and enantiomeric excesses remained high in all the cases. However, *ortho* substitution, although tolerated, produced lower yields and enantioselectivities. Aliphatic enal-derived azadienes were not competent substrates and chalcone derived imines required higher catalyst load and gave the cycloadducts with lower yield and enantioselectivity. Only nitroalkenes bearing aliphatic substituents at the β-position of the double bond were reactive, and sterically more-demanding nitroalkenes required longer reaction times. The reaction uses zinc as catalyst and a novel BOPA ligand. The presence of two fluorine atoms in the ligand was essential, by limiting the undesired coordination of the azadiene to the Lewis acid, thus allowing the reaction to be carried out at lower temperature. The reaction seems to proceed in a stepwise mechanism involving initial conjugate addition of the imine nitrogen to the nitroalkene followed by conjugate addition of the resulting nitronate to the unsaturated iminium.[78]

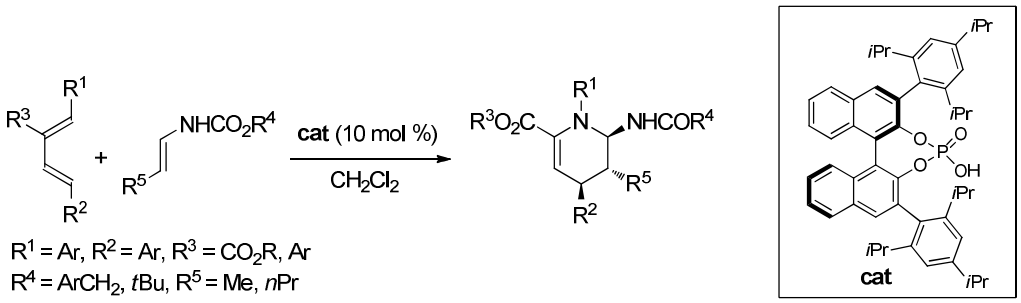
A bifunctional organocatalytic strategy for the enantioselective construction of aza-spirocyclic skeletons has been developed by Wang through the Diels-Alder reaction between cyclic keto/enolate salts and 1-aza-1,3-butadienes. The desired products were obtained with good yields, diastereo- and enantioselectivities (Scheme 46). The use of a bifunctional organocatalyst bearing a primary amine and a thiourea moiety was essential for the success of the reaction, which is believed to take place through a double activation mechanism in which the primary amine activates the enolate via iminium formation while the thiourea moiety activates de *N*-sulfonyl azadiene through hydrogen bond formation.[79]



Scheme 46. Organocatalytic Diels-Alder reaction between cyclic keto/enolate salts and 1-aza-1,3-butadienes

On the other hand, Masson has reported the enantioselective Diels-Alder reaction of 1-aza-dienes with enecarbamates catalyzed by chiral phosphoric acids to give 4,5,6-trisubstituted 1,4,5,6-tetrahydropyridines. The resulting products were obtained with high diastereoselectivity favoring the all-*trans* isomer and with excellent enantioselectivities in most of the examples (Scheme 47). The authors proposed a highly asynchronous concerted mechanism with the chiral phosphoric acid serving as a

bifunctional catalyst with the OH group activating the 1-azadiene as Brønsted acid and the phosphoryl oxygen atom activating the enecarbamate as a Lewis base.[80]

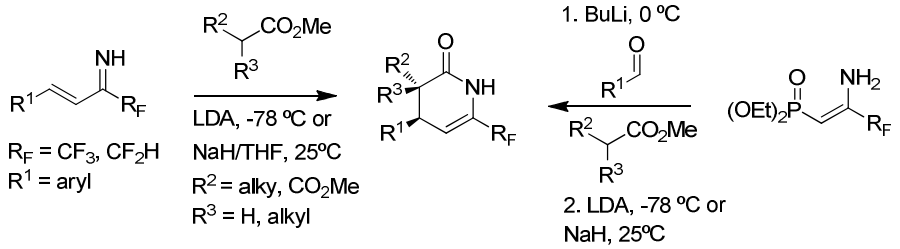


Scheme 47. Enantioselective Diels-Alder reaction of 1-aza-dienes with enecarbamates catalyzed by chiral phosphoric acids

2.2.1.2. Base-promoted formal [4+2] cycloadditions with carbonyl compounds

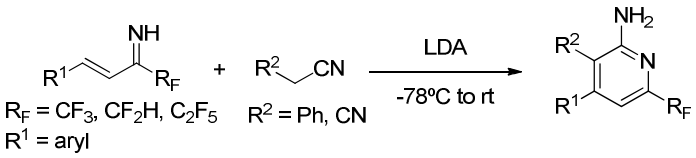
The sequential Michael addition of carbonyl enolates to 1-aza-1,3-butadienes followed by a intramolecular nitrogen nucleophilic attack to the carbonyl group allows the synthesis of 6-membered aza-cyclic compounds. A first example reported by Jones in 1988 involved the Michael addition of diethyl malonate to 2-(1-alkenyl)-2-imidazolines to give the 1,4-adduct which cyclized during chromatography on silica gel to a hexahydroimidazol[1,2-a]pyridine.[81]

This strategy has been employed by Palacios in the synthesis of fluorinated 3,4-dihydropyridin-2-ones from azadienes and esters *via* a Michael addition/lactamization reaction. The reaction with dimethyl malonate had to be carried out at rt to avoid 1,2-addition to the imine. The required fluorinated unsaturated imines were prepared *via* a Wittig-Horner reaction. Both, the Wittig-Horner and the cyclization reactions could be achieved in a one pot manner (Scheme 48).[82]



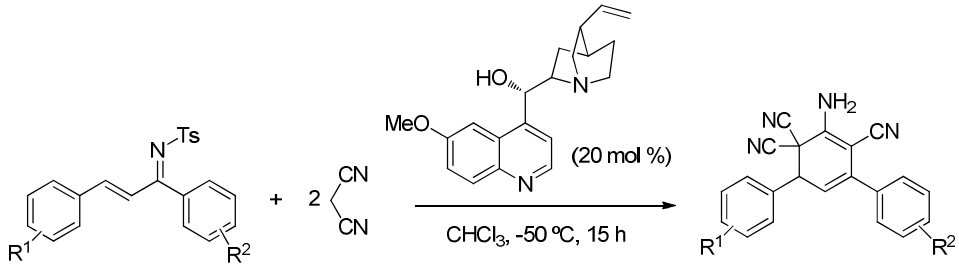
Scheme 48. Synthesis of dihydropyridin-2-ones and pyridines *via* Michael/cyclization strategy

The same authors extended this methodology to the synthesis of pyridines by using nitriles instead of esters and performing the reaction at rt (Scheme 49).[83]



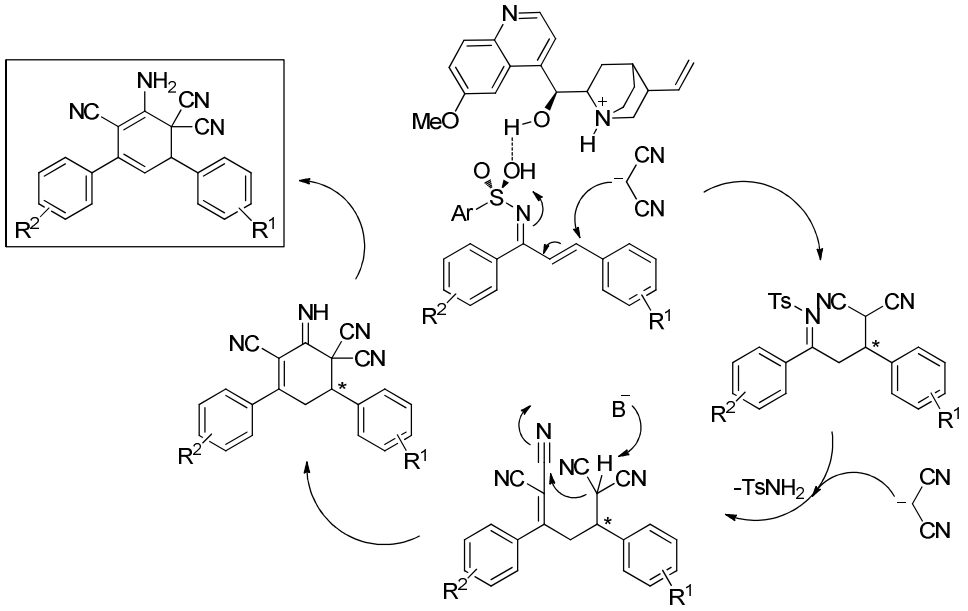
Scheme 49. Synthesis of fluorinated pyridines

However, when malononitrile was reacted with α,β-unsaturated *N*-tosyl imines derived from chalcone under dual hydrogen-bonding/basic catalysis, Lu and Xie obtained chiral cyclohexa-1,3-dienes instead of the expected dihydropyridines. By using cinchonine as catalyst moderate yields (31-53%) and good enantioselectivities (81-91%) were obtained (Scheme 50).



Scheme 50. Reaction between *N*-tosyl β,γ-unsaturated imines and malononitrile to obtain the corresponding cyclohexa-1,3-dienes

The authors propose a stepwise mechanism involving a Michael addition of malononitrile to give an intermediate that undergoes a Knoevenagel condensation, followed by an intramolecular cyclization and a proton transfer resulting in the corresponding cyclohexa-1,3-dienes (Scheme 51).[84]

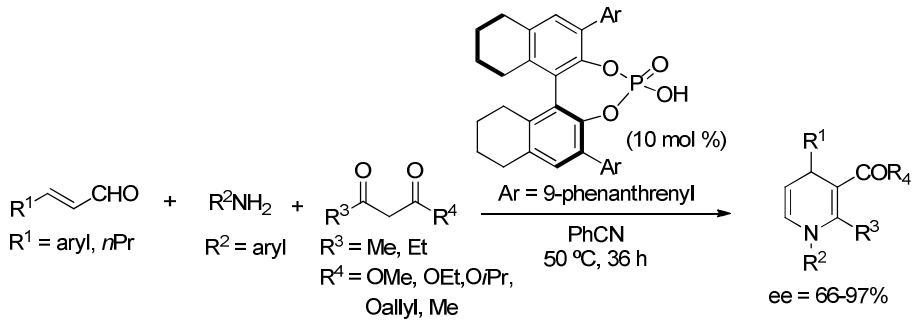


Scheme 51. Proposed mechanism for the formation of cyclohexa-1,3-dienes

2.2.1.3. Acid-promoted formal [4+2] cycloadditions with carbonyl compounds

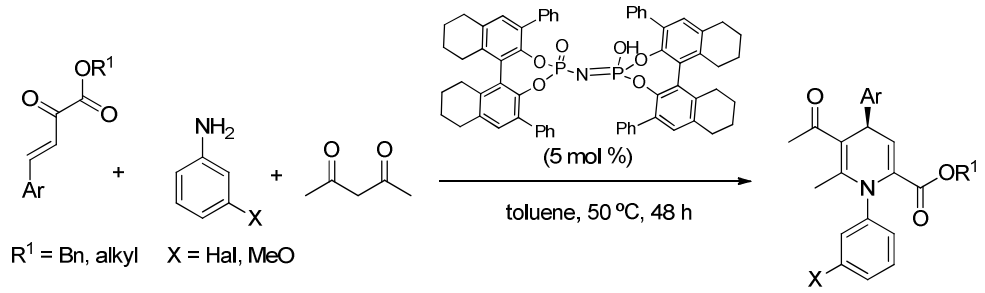
Under acidic conditions 1-aza-1,3-butadienes have been shown to undergo cyclocondensation with β-keto esters and 1,3-diketones to give acyl substituted dihydropyridines.[85-86]

The first enantioselective version of this reaction was reported by Gong in 2008 in a three-component manner using α,β-unsaturated aldehydes, primary amines and 1,3-dicarbonyl compounds (Scheme 52). The proposed mechanism for this reaction involves the *in situ* formation of the unsaturated imine by condensation between a primary amine and the unsaturated aldehyde, which undergo a 1,4- conjugate addition with a 1,3-dicarbonyl compound followed by condensation and dehydration. The use of a chiral phosphoric acid that activates the imine led to the formation of enantioenriched products. The reaction allowed variation in all the reactants and the dihydropyridines were obtained with excellent enantiomeric excesses. The procedure is also applicable to 2,4-pentanedione as nucleophile, although in this case lower enantioselectivities were obtained.[87]



Scheme 52. Three component asymmetric synthesis of dihydropyridines

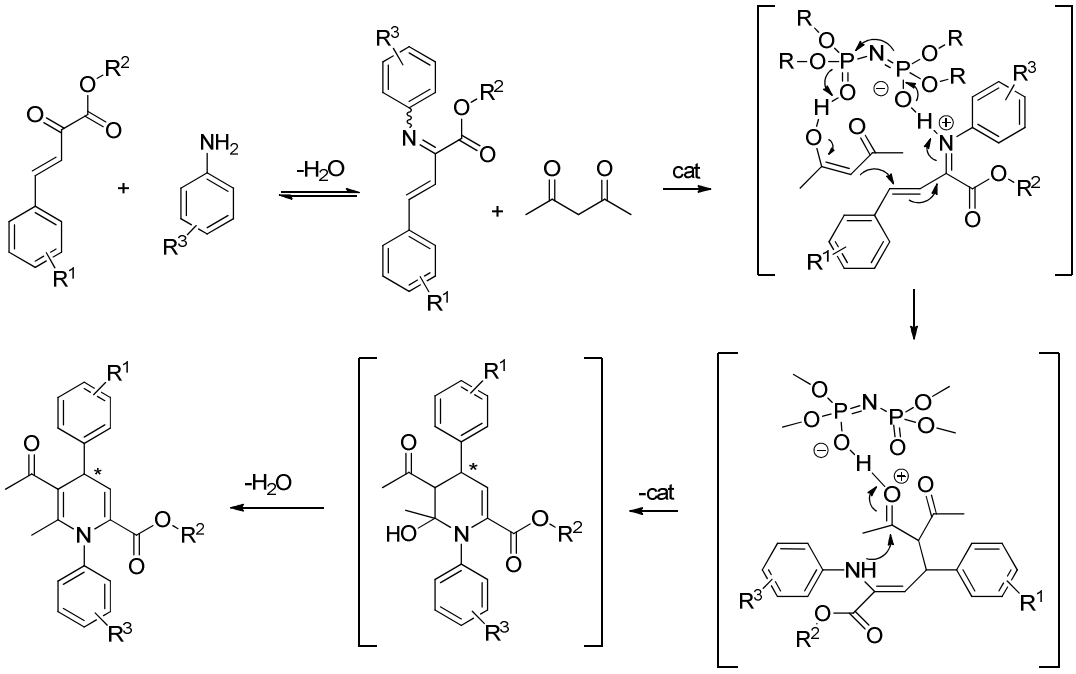
Later, Zheng and Zhang reported a similar reaction with β,γ-unsaturated α-keto esters instead of enals and pentanedione instead of keto esters, using in this case a chiral imidodiphosphoric acid as catalyst (Scheme 53). The reaction performed with high enantioselectivities but low yields in most of the cases.



Scheme 53. Reaction between β,γ-unsaturated α-keto esters, aryl amines and pentanedione

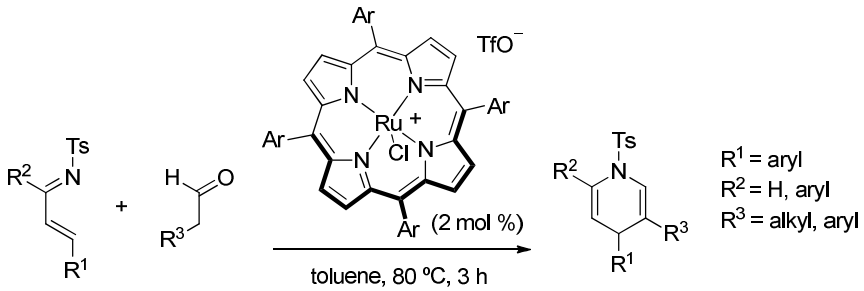
A mechanistic proposal by the authors involved the condensation between the β,γ-unsaturated α-keto ester and the aryl amine to give a β,γ-unsaturated α-imino ester

which is activated by hydrogen bonding with the imidophosphoric acid at the same time as the pentanedione. Michael addition followed by attack of the amino group to the carbonyl group and dehydration would deliver the chiral 1,4-dihydropyridines (Scheme 54).[88]



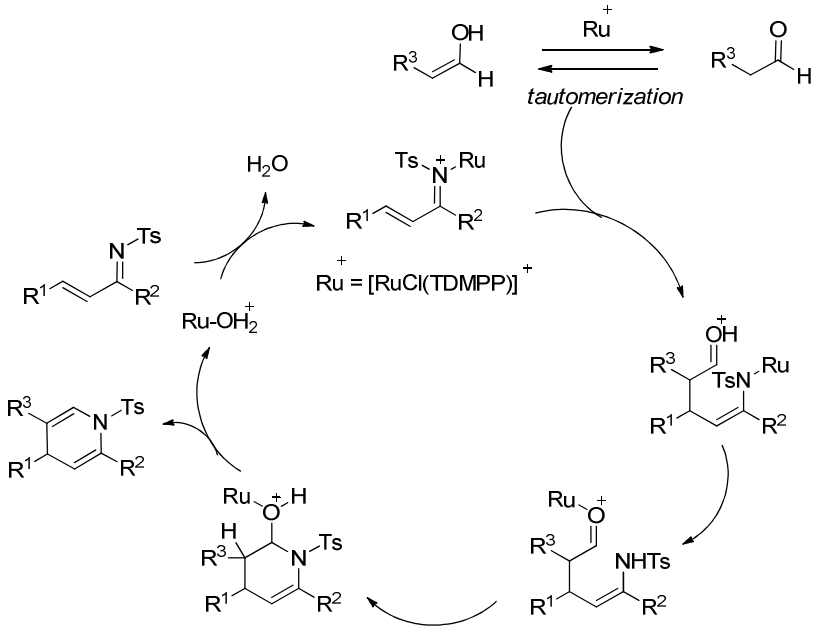
Scheme 54. Mechanistic proposal for the cyclization reaction

A formal [4+2] cycloaddition reaction between α,β-unsaturated *N*-tosyl imines and aldehydes to give dihydropyridines catalyzed by a ruthenium porphyrin complex as Lewis acid has been developed by the group of Matsubara. The reaction provided the cycloaddition products with unprecedented substitution patterns. Reduction with SmI_2 yielded the detosylated dihydropyridines (Scheme 55).



Scheme 55. Ruthenium catalyzed synthesis of unsymmetrical dihydropyridines

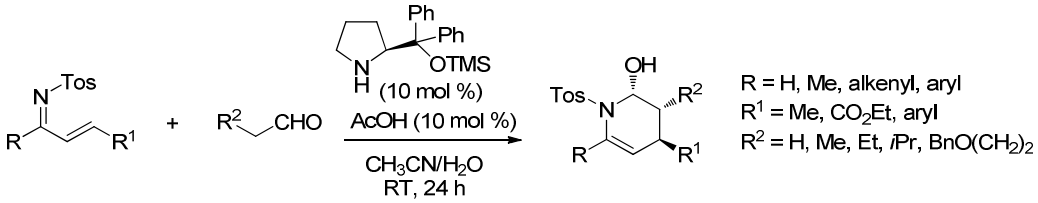
The authors proposed a mechanism in which the catalyst both activates the imine and forms the enolate. After the 1,4-addition step, the corresponding dihydropyridines would be obtained upon attack of the nitrogen atom to the carbonyl group and water elimination (Scheme 56).[89]



Scheme 56. Reaction mechanism for the ruthenium catalyzed synthesis of dihydropyridines

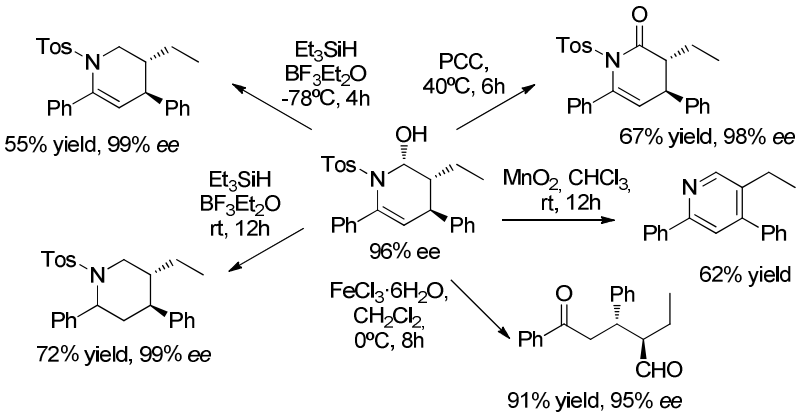
2.2.1.4. Formal [4+2] cycloadditions with carbonyl compounds via enamine activation

Nucleophilic activation of carbonyl compounds can be achieved by conversion into enamines upon treatment with catalytic secondary or primary amines. The group of Chen reported in 2008 the aza-Diels-Alder reaction between α,β-unsaturated *N*-tosyl imines and aliphatic aldehydes in the presence of the Hayashi-Jørgensen catalyst, a prolinol derivative (Scheme 57).[90]



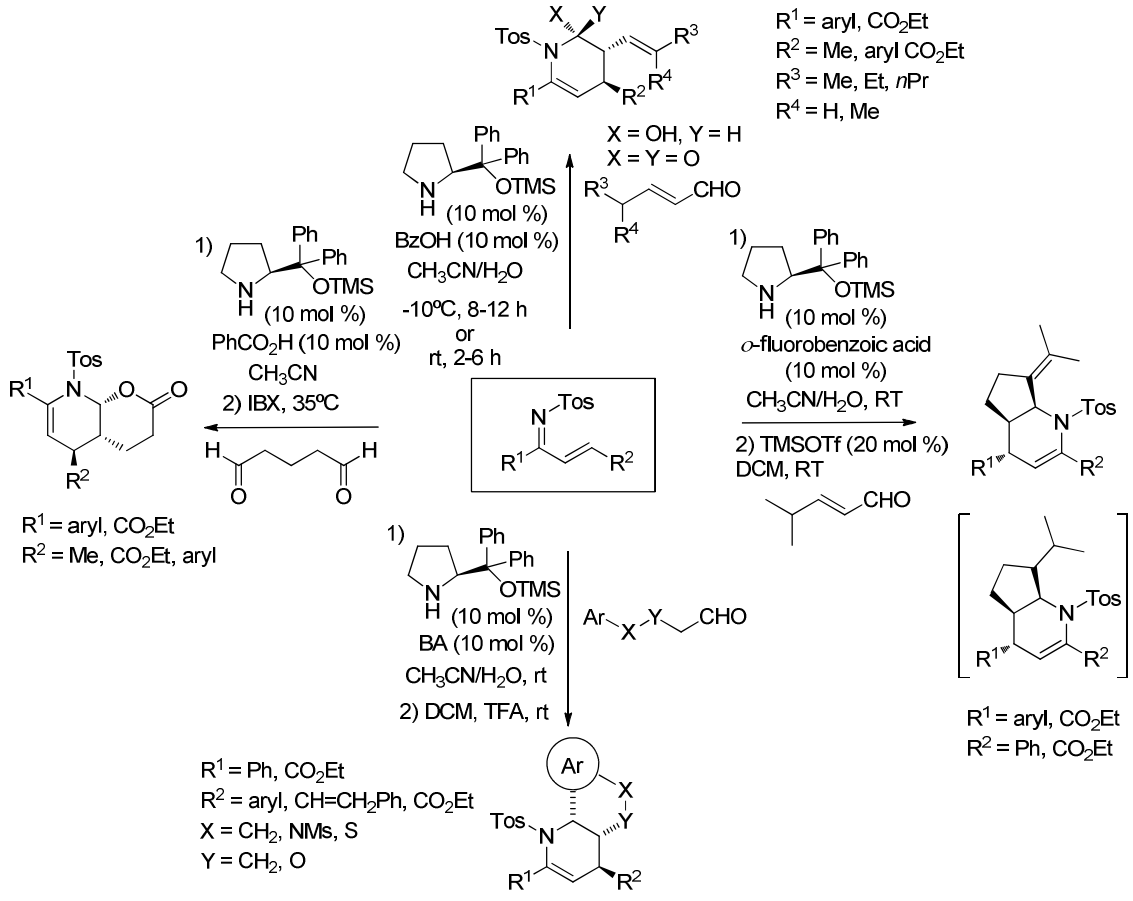
Scheme 57. Enantioselective Diels-Alder reaction between *N*-tosyl α,β-unsaturated imines and aliphatic aldehydes

The obtained hemiaminals were subjected to different transformations such as oxidation of the hydroxyl group to give pyrimidones, dehydrogenation to pyridines, hydrogenation to dihydro- or tetrahydropyridines, or hydrolysis to dicarbonyl compounds keeping intact the integrity of the chiral center (Scheme 58).



Scheme 58. Synthetic transformations of a chiral hemiaminal

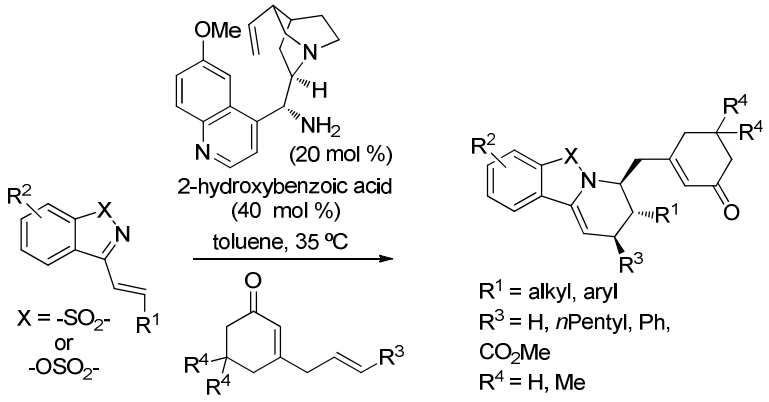
Over the following years, these authors have expanded the applicability of this methodology with different aldehydes, obtaining a wide range of chiral aza-cyclic compounds with high enantiomeric excesses (Scheme 59).[91-94]



Scheme 59. Organocatalytic enantioselective Diels-Alder reactions with aldehydes

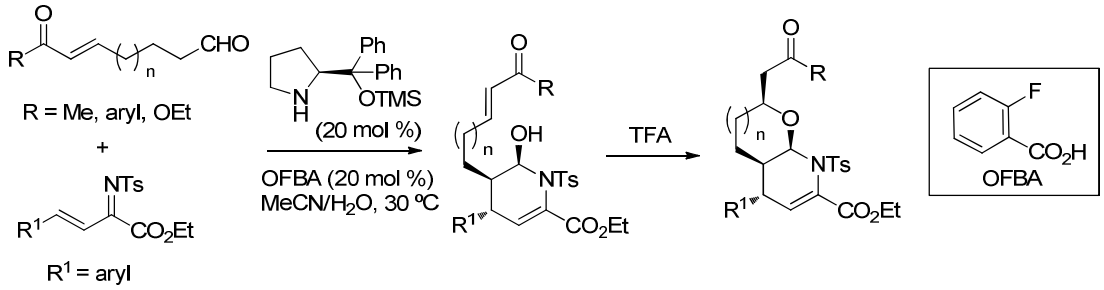
The same authors have also studied the enamine activation strategy in the reaction of 1-azadienes derived from saccharin and interrupted cyclic 2,5-dienones. The reaction catalyzed by 9-amino-9-deoxyepiquinidine and benzoic acid yields the cycloadducts with exclusive δ,ε-regioselectivity, and excellent diastereo- and enantioselectivity.

Remarkably, the reaction does not work with fully conjugate 2,4-dienones. The substrate scope is wide and besides saccharin derivatives, 1-azadienes with the 1,2,3-benzoxathiazine-2,2-dioxide motif and acyclic unsaturated *N*-tosyl imines are appropriate substrates in this reaction (Scheme 60).[95]



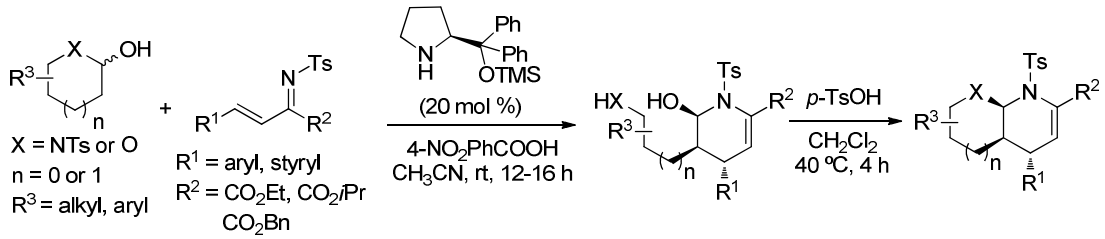
Scheme 60. Cycloaddition of 1-azadienes and interrupted cyclic 2,5-dienones

Moreover, the group of Chen reported the enantioselective synthesis of hydropyrano[2,3]pyridines *via* a sequential aza-Diels-Alder/oxa-Michael reaction between enone enals and unsaturated *N*-tosyl imines with variable yields but excellent enantiomeric excesses (Scheme 61). The reaction also allowed the synthesis of hexahydrofuro[2,3-b]pyridines enantioselectively. However, attempts to construct a fused oxepane ring were not successful.[96]



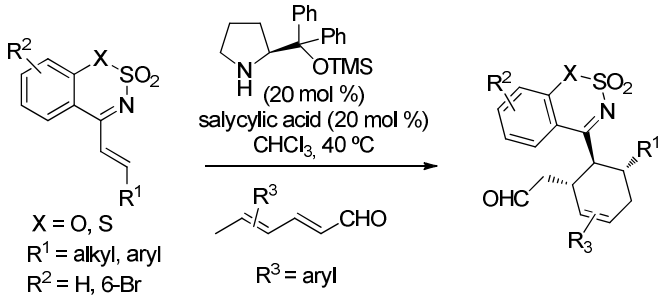
Scheme 61. Asymmetric sequential aza-Diels-Alder/oxa-Michael reaction

Very recently, Liu et *al.* accomplished the asymmetric synthesis of ring-fused piperidines in a one-pot operation from cyclic hemiaminals and α,β-unsaturated *N*-tosyl imines using the Hayashi-Jørgensen catalyst (Scheme 62). The piperidine fused products containing *N,O*- or *N,N*- acetal moieties were obtained with variable yields, but with full diastereoselectivity and enantiomeric excesses above 99%.[97]



Scheme 62. Synthesis of piperidine fused products

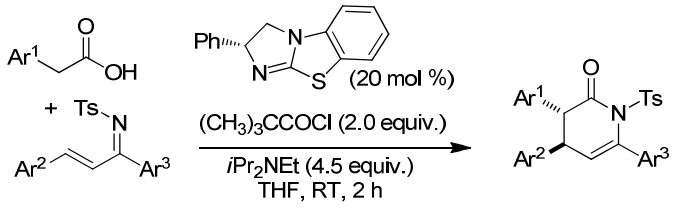
Finally, the group of Chen has reported the cycloaddition between 1-aza-1,3-butadienes containing a 1,2-benzoisothiazole-1,1-dioxide or 1,2,3-benzoxathiazine-2,2-dioxide motif and conjugate linear dienals in the presence of the Hayashi-Jørgensen catalyst to give chiral cyclohexene derivatives. Remarkably, in this case the 1-azadienes react as regio- and chemoselective dienophiles in normal-electron-demand Diels-Alder reactions with HOMO-raised trienamines (Scheme 63).[98]



Scheme 63. 1-Azadienes as dienophiles in Diels-Alder reactions

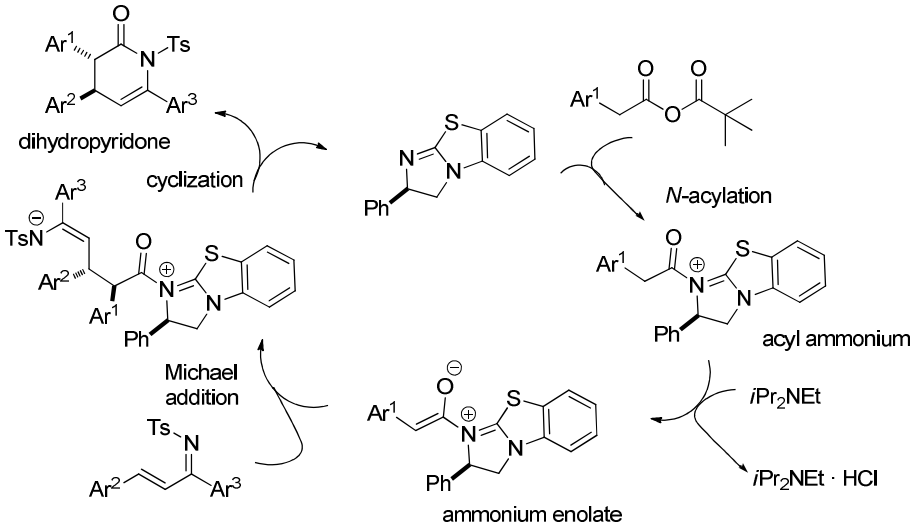
2.2.1.5. Formal [4+2] cycloadditions with carbonyl compounds via acyl activation

Nucleophilic addition of tertiary nitrogen atoms to acid derivatives yields *N*-acyl ammonium derivatives, increasing the acidity of the α-hydrogens and therefore activating the nucleophilicity of the carbonyl compound. Chiral guanidines and isothioureas have been frequently used as acyl activation catalysts in asymmetric synthesis. In 2012, the Smith group reported the enantioselective conjugate addition of carboxylic acids to *N*-tosyl α,β-unsaturated imines catalyzed by a chiral isothiourea to yield dihydropyridones (Scheme 64).[99] In a later work, the same authors extended this methodology to imines derived from γ-oxo-α,β-unsaturated esters with excellent results using (-)-tetramisole hydrochloride as the catalyst.[100]



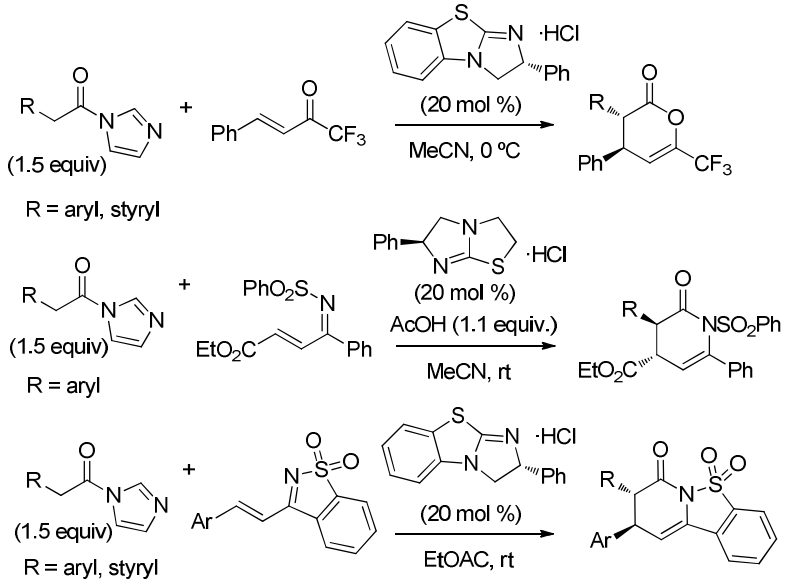
Scheme 64. [4+2] Cycloaddition of carboxylic acids and unsaturated imines catalyzed by isothioureas

The authors postulate a mechanism in which nucleophilic addition of the catalyst to a mixed anhydride formed *in situ* is followed by deprotonation by a base to give an ammonium enolate which undergoes a Michael addition with the unsaturated imine, to give an acyl ammonium cation which is intramolecularly attacked by the imine nitrogen to give the final dihydropyridone (Scheme 65).[99]



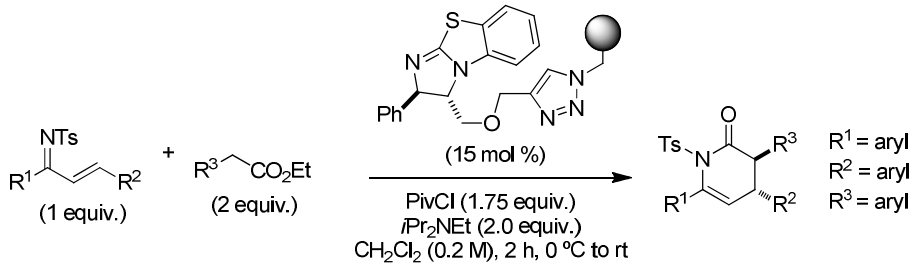
Scheme 65. Mechanism of dihydropyridone formation

The group of Smith has also described the enantioselective formal cycloaddition of bench-stable *N*-acyl imidazoles with β-trifluoromethyl α,β-unsaturated ketimines and α,β-unsaturated saccharin derivatives catalyzed by isothiourea hydrochloride salts in the absence of base with moderate to excellent enantioselectivities (Scheme 66). Detailed mechanistic studies revealed the importance of the "imidazolium effect" in promoting reactivity and highlighted key differences with traditional base-promoted processes.[101]



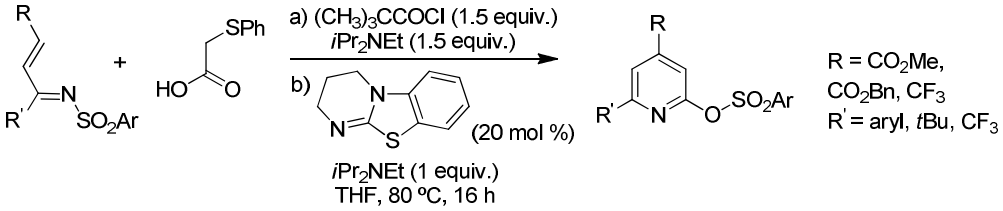
Scheme 66. Enantioselective cycloaddition between acyl imidazoles and different Michael acceptors

Pericàs and Izquierdo have developed a PS-supported isothiourea catalyst that has been used in batch and flow processes for the cycloaddition of carboxylic acid esters and α,β-unsaturated *N*-tosyl imines derived from chalcones or conjugate imines derived from saccharin with excellent enantiomeric excesses (Scheme 67).[102]



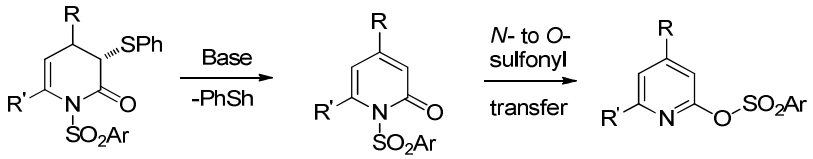
Scheme 67. Enantioselective synthesis of chiral lactams with a PS-supported isothiourea catalyst

N-acyl activation has also been employed for the synthesis of pyridines when the acid derivative bears a leaving group on the α-carbon. According to this strategy, the group of Smith reported the synthesis of functionalized pyridines by reacting (phenylthio)acetic acid and *N*-tosyl α,β-unsaturated ketimines or β-trifluoromethyl α,β-unsaturated *N*-tosyl imines in the presence of an achiral isothiourea catalyst (Scheme 68).[103]



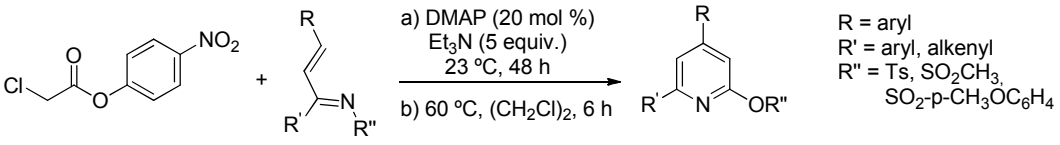
Scheme 68. Synthesis of pyridines from α,β-unsaturated *N*-tosyl imines and (phenylthio)acetic acid

The reaction takes place through acyl activation as in the synthesis of dihydropyridones, but after the cyclization step, the resulting lactam undergoes elimination of thiophenol followed by a thermal *N*- to *O*- sulfonyl migration affording the corresponding pyridines (Scheme 69).



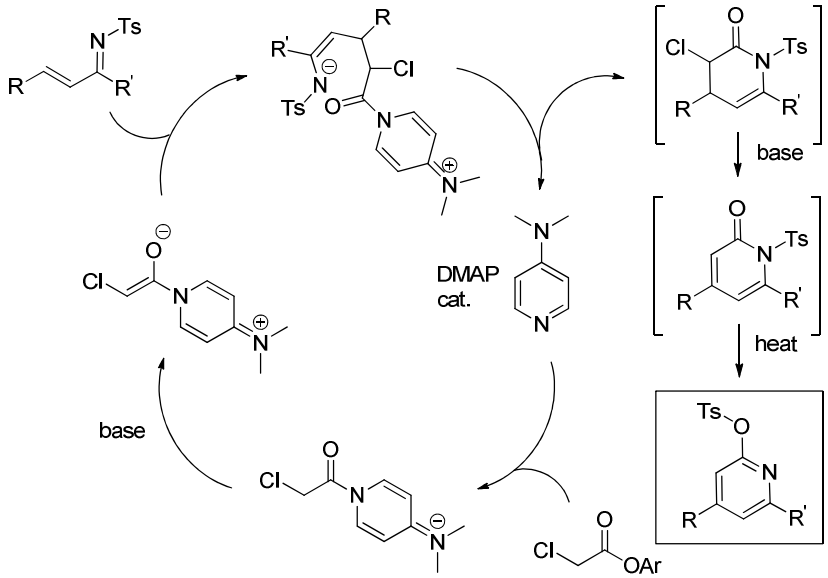
Scheme 69. Elimination and sulfonyl migration affording pyridines

A similar strategy for the synthesis of trisubstituted pyridines starting from *p*-chlorophenyl chloroacetate and α,β-unsaturated *N*-tosyl imines has been employed by Chi using 4-dimethylaminopyridine (DMAP) instead of an isothiourea as the catalyst (Scheme 70).[104]



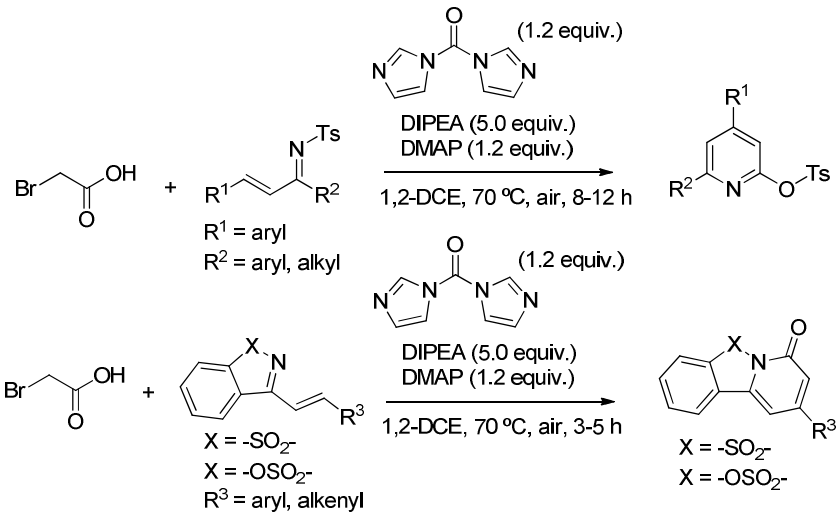
Scheme 70. DMAP catalyzed synthesis of trisubstituted pyridines

The mechanism of this reaction is similar to that of the reaction catalyzed by isothiurea, with the DMAP activating the acid through the formation of an *N*-acyl pyridinium cation (Scheme 71).



Scheme 71. Mechanism for the formation of pyridines catalyzed by DMAP

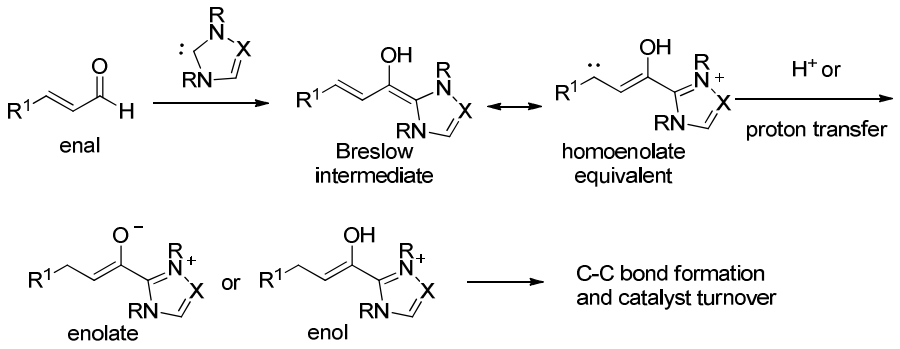
Recently, Du and Lu reported a similar reaction catalyzed by DMAP using α-bromo acetic acid instead of the α-chloro acetic ester justified by the lower price of the nucleophile. This new methodology was also extended to the synthesis of fused pyridin-2-ones using cyclic 1-azadienes derived from saccharin as electrophiles (Scheme 72).[105]



Scheme 72. Synthesis of pyridines and pyridin-2-ones from α-bromoacetic acid

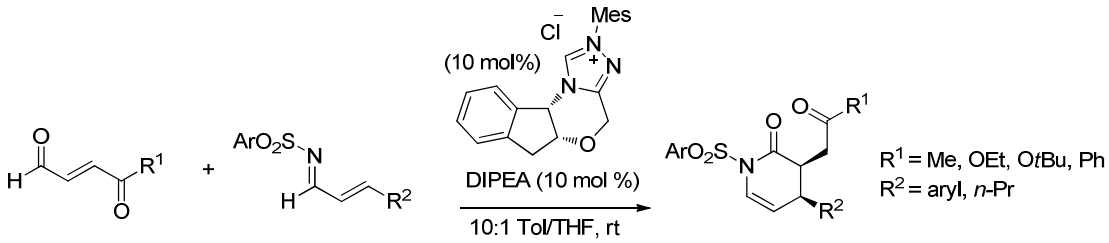
2.2.1.6. NHC-catalyzed formal [4+2] cycloadditions with carbonyl compounds

In 2006, in the context of N-heterocyclic carbene (NHC) catalysis studies, the group of Bode recognized that protonation or trapping of Breslow-type intermediates should lead to catalyst-bound enols or enolates poised for C-C bond formation (Scheme 73).



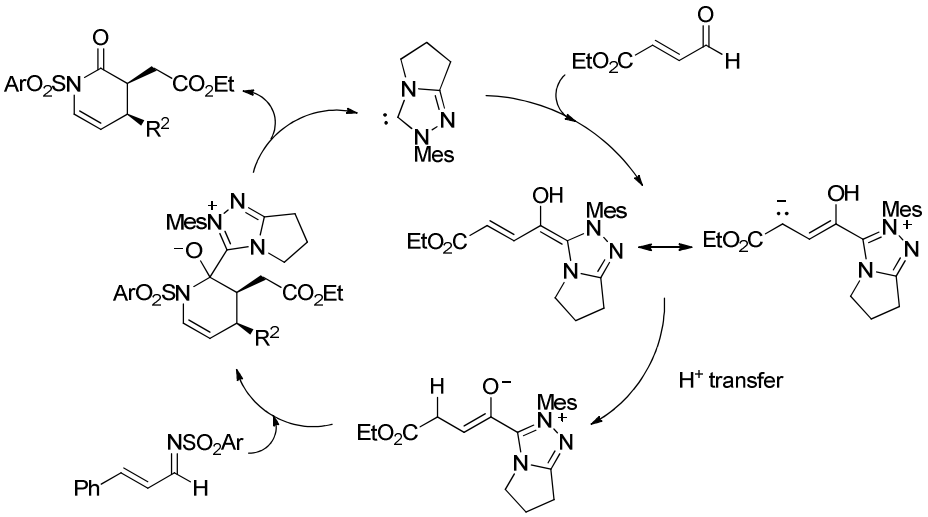
Scheme 73. NHC activation of enals

By implementing this strategy, this group used the generated enolates as dienophiles and developed the first NHC catalyzed Diels-Alder reaction with α,β-unsaturated *N*-sulfonyl aldimines. To increase the electrophilicity of the enal, *trans*-4-oxo-2-butenoates were used as substrates. Hindered triazolium catalysts were required to avoid formation of γ-lactams resulting from 1,2-addition to the imine. Under the optimized conditions, dihydropyridones were obtained with fair yields and excellent enantioselectivities (Scheme 74).



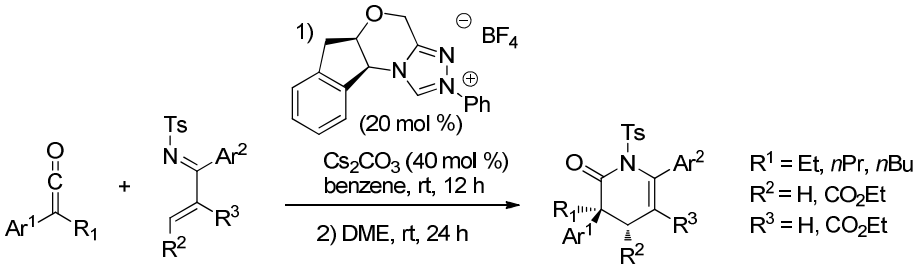
Scheme 74. NHC catalyzed Diels-Alder reaction of enals and unsaturated imines

The authors postulated a mechanism in which the formed *Z*-enolate reacts as the dienophile with the α,β-unsaturated imine through an *endo* transition state (Scheme 75).[106]



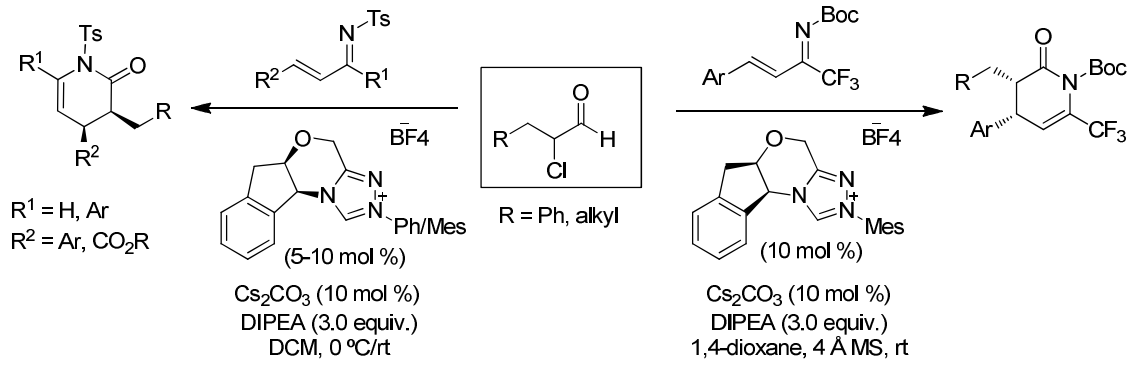
Scheme 75. Mechanism for the NHC catalyzed cycloaddition of enals and unsaturated imines

In 2011, the group of Ye described the Diels-Alder addition of ketenes to 1-aza-1,3-butadienes *via* NHC catalysis obtaining chiral dihydropyridones. This procedure represents the first example of enantioselective cycloaddition reaction with α,β-unsaturated *N*-tosyl imines in which a quaternary chiral center is generated (Scheme 76).[107]



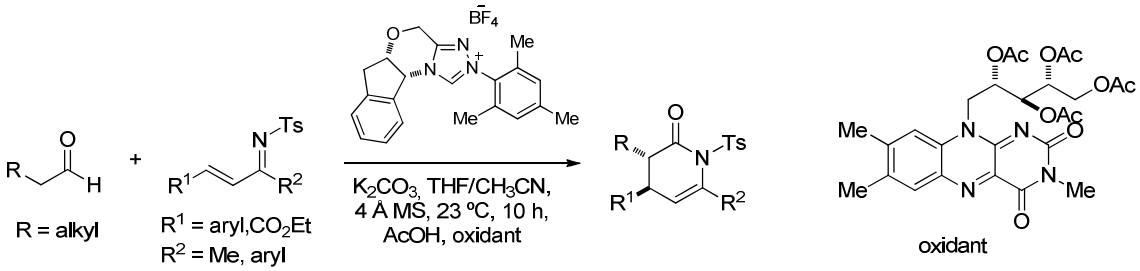
Scheme 76. NHC catalyzed synthesis of chiral dihydropiridones from ketenes and unsaturated imines

Later, they applied this methodology for the asymmetric conjugate addition of α-chloro aldehydes to β-trifluoromethyl β,γ-unsaturated imines *via* NHC catalysis obtaining the corresponding *N*-tosyl or *N*-boc protected lactames with excellent diastereomeric ratios (dr > 20:1) and enantiomeric excesses (96-99%). According to the exclusive *cis*-stereoselectivity observed in the obtained lactams, the authors suggested that the reaction takes place through a concerted [4+2] cycloaddition reaction pathway instead of a stepwise mechanism involving a Michael type reaction followed by intramolecular cyclization (Scheme 77).[108,109]



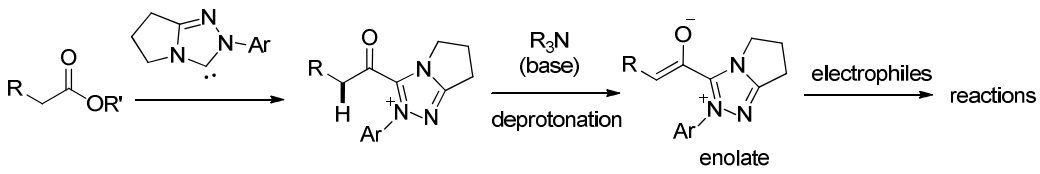
Scheme 77. Enantioselective synthesis of trisubstituted chiral lactams from α-chloroaldehydes *via* NHC-catalysis

In 2012, the group of Rovis developed a procedure for the NHC asymmetric cycloaddition of simple aliphatic aldehydes with α,β-unsaturated *N*-tosyl imines derived from chalcones, obtaining dihydropyridones with excellent yields, diastereo- and enantioselectivity (Scheme 78).[110] The use of an oxidant allowed the generation of the enolate intermediates from simple aldehydes instead of enals or α-chloroaldehydes.



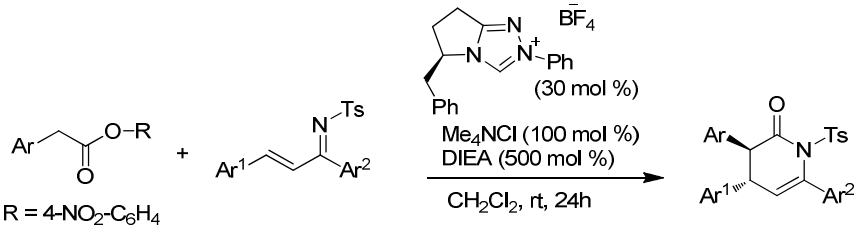
Scheme 78. NHC catalyzed asymmetric oxidative cycloaddition of aliphatic aldehydes with *N*-tosyl α,β-unsaturated imines

Almost simultaneously, the group of Chi developed NHC catalyzed cycloadditions of unsaturated imines with esters instead of aldehydes. In these cases the NHC catalyst activates the ester favoring formation of the enolate by a base in a similar manner as in the acyl activation catalysis with isothioureas or DMAP (Scheme 79).



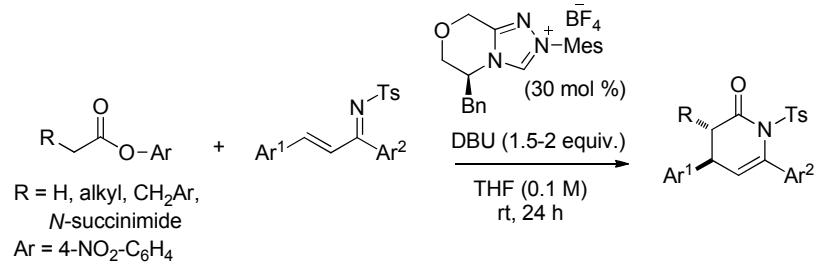
Scheme 79. NHC activation of esters

This group first reported the cycloaddition of *p*-nitrophenyl arylacetic esters with *N*-tosyl imines derived from chalcones (Scheme 80). Both, the arylacetic ester and the imine were amenable to different substitution, and the resulting chiral dihydropyridones were obtained with fair to good yields, good diastereoselectivity and moderate to good enantiomeric excesses (60-98%).[111]



Scheme 80. NHC catalyzed reaction of arylacetic esters and α,β-unsaturated imines

Later, the group extended the scope of the reaction with alkylacetic or acetic esters and chalcones or α,β-unsaturated *N*-tosyl imines derived from chalcones, obtaining in all the cases the corresponding lactones or lactams with excellent enantiomeric excesses (Scheme 81).[112,113]

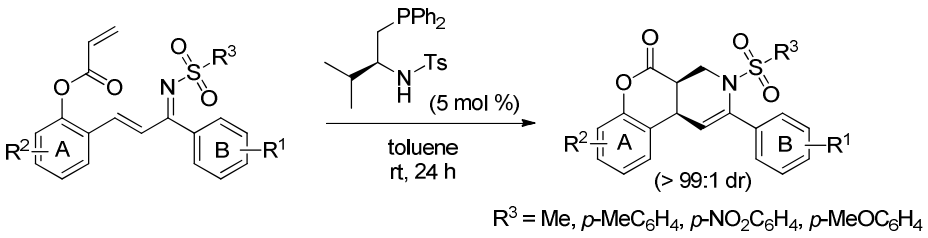


Scheme 81. NHC catalyzed reaction of alkylylacetic and acetic acid esters with α,β-unsaturated imines

A variation of this reaction was reported in 2016 by the group of She. These authors proposed the use of 1,3-dioxoisoindolin-2-yl acetic esters as nucleophiles because the required catalyst loading is lower than the required with 4-nitrophenol esters and because the *N*-hydroxy-phthalimide from the ester can catalyze a subsequent *N*- to *C*-sulfonyl migration reaction.[114]

2.2.1.7. Formal [4+2] cycloadditions via Rauhut-Currier reaction catalyzed by phosphines or amines

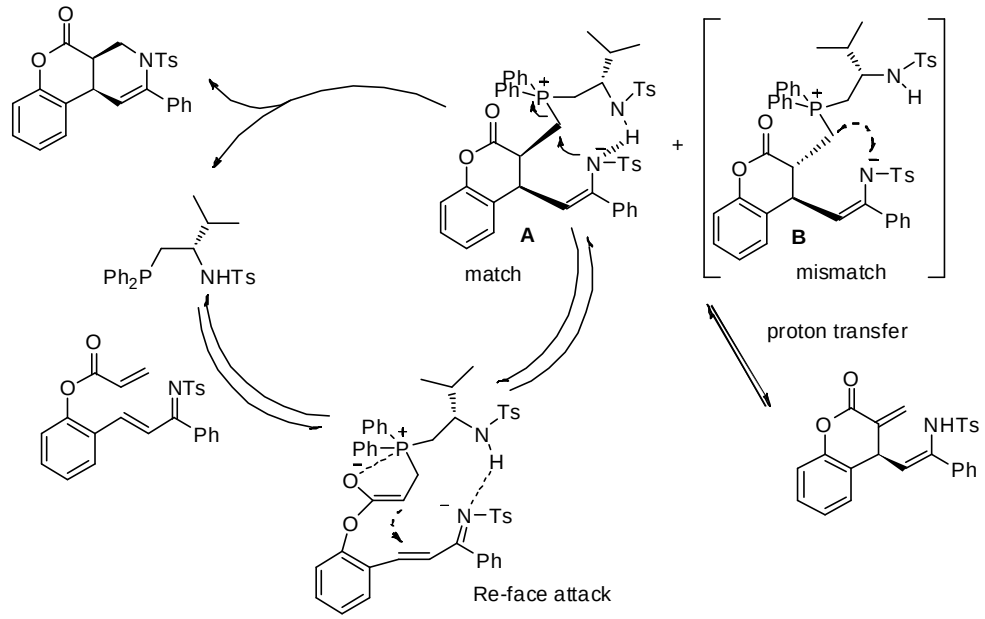
In 2012, the group of Chi employed a chiral aminophosphine catalyst to achieve the first enantioselective intramolecular [4+2] annulation of electron-deficient alkenes and *N*-sulfonyl α,β-unsaturated imines (Scheme 82).[115]



Scheme 82. Intramolecular phosphine catalyzed enantioselective [4+2] annulation of acrylates and *N*-sulfonyl α,β-unsaturated imines

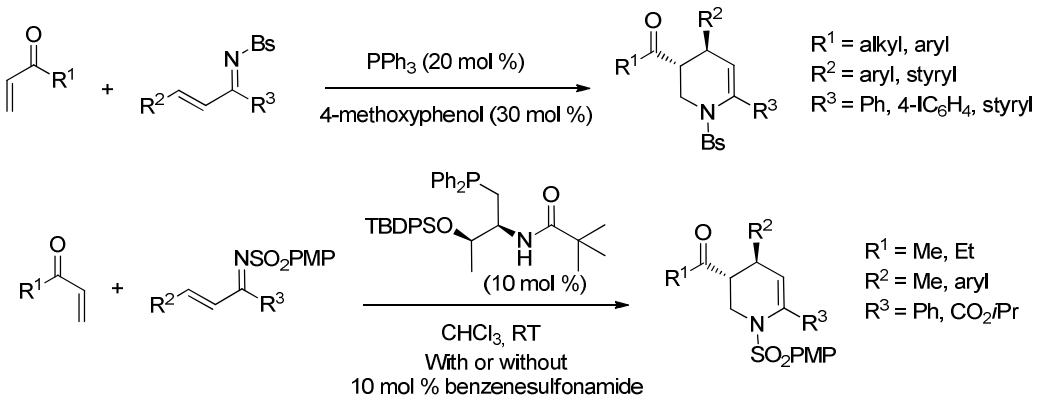
Furthermore, the reaction can be carried out with azatrienes having a second vinyl substituent instead of the B aromatic ring. These substrates can undergo a second [4+2] to provide polycyclic chiral sulfonyl enamines.

The authors postulated the reaction mechanism as a tandem Rauhut-Currier/S_N2-substitution sequence in which the high diastereoselectivity likely results from a favorable S_N2 reaction of intermediate **A** and reversible interconversion between intermediates **A** and **B** (Scheme 83)**.**



Scheme 83. Tandem Rauhut-Currier/S_N2 mechanism

The same year, the group of Zhong reported an intermolecular version for this reaction with vinyl ketones in both nonenantioselective and enantioselective fashion affording a wide range of substituted tetrahydropyridines (Scheme 84).[116,117]



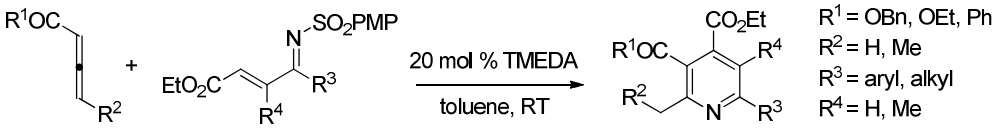
Scheme 84. Intermolecular phosphine catalyzed [4+2] annulation of vinyl ketones and α,β-unsaturated imines

Later, Wei and Shi applied a thiourea-phosphine catalyst derived from a natural amino acid in the reaction between vinyl ketone and oxindole derived α,β-unsaturated imines in the enantioselective synthesis of 2',3'-dihydro-1'H-spiro[indoline-3,4'-pyridin]2-ones.[118]

Other chiral aminophospine catalysts have been reported by Wu to perform the enantioselective cycloaddition of methyl vinyl ketone to α,β-unsaturated *N*-tosyl imines with variable yields, moderate to good diastereoselectivities and moderated enantiomeric excesses.[119]

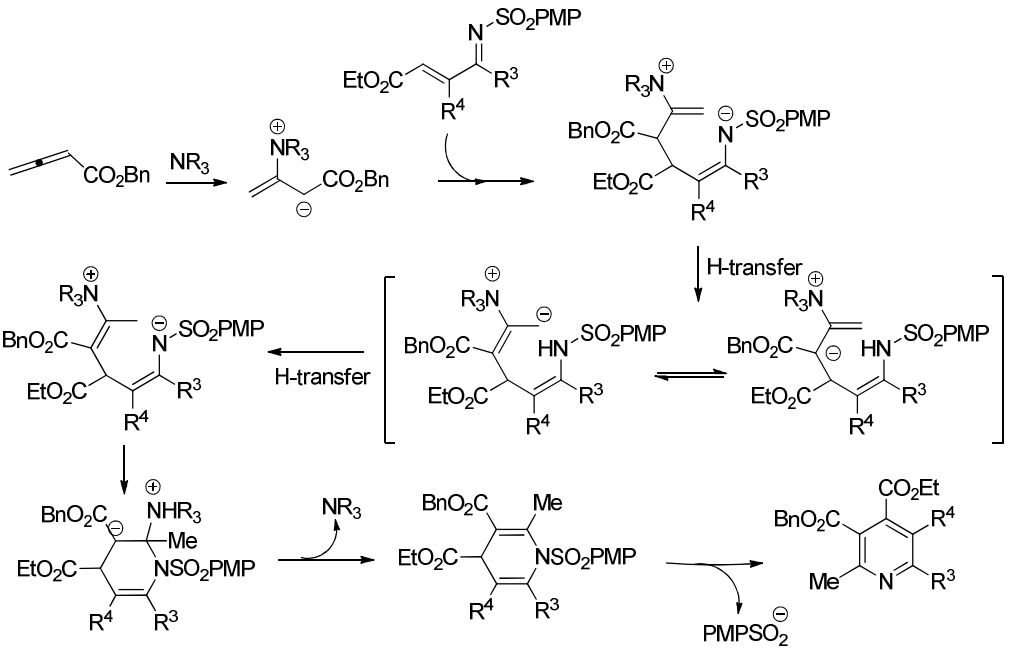
Finally, the triphenylphosphine catalyzed reaction of enones and α,β-unsaturated imines has been applied by Fan and Bakulev in the synthesis of tetrahydropyridines containing a thiazole moiety. These compounds were studied for their fungicidal and insecticidal properties.[120]

On the other hand, the group of Loh reported in 2013 the synthesis of highly functionalized pyridines from allenoate esters and unsaturated imines *via* an aza-Rauhut-Currier/cyclization/desulfonylation sequence using a tertiary amine (TMEDA) instead of a phosphine as catalyst (Scheme 85).[121]



Scheme 85. Synthesis of pentasubstituted pyridines catalyzed by TMEDA

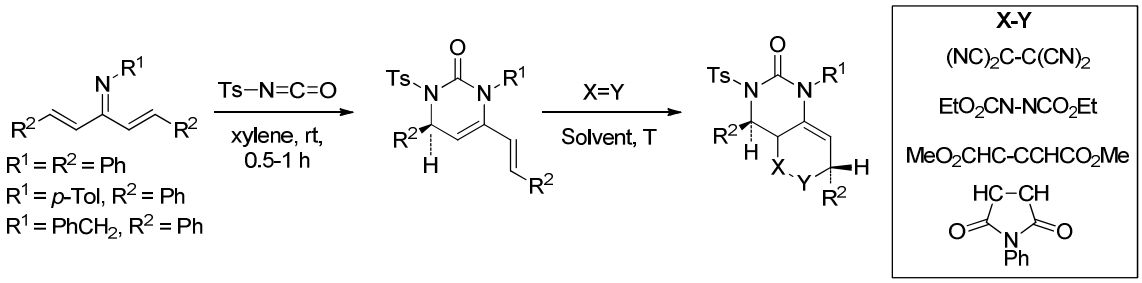
In the proposed mechanism, TMEDA reacts with the allenoate ester to give an ammonium ylide which undergoes 1,4-addition to the unsaturated imine. After intramolecular proton transfer, intramolecular aza-1,4-addition yields the cyclized product which expulses the TMEDA catalyst and suffers desulfonylation to afford the pyridine (Scheme 86).



Scheme 86. Proposed mechanism for the synthesis of pyridines catalyzed by TMEDA

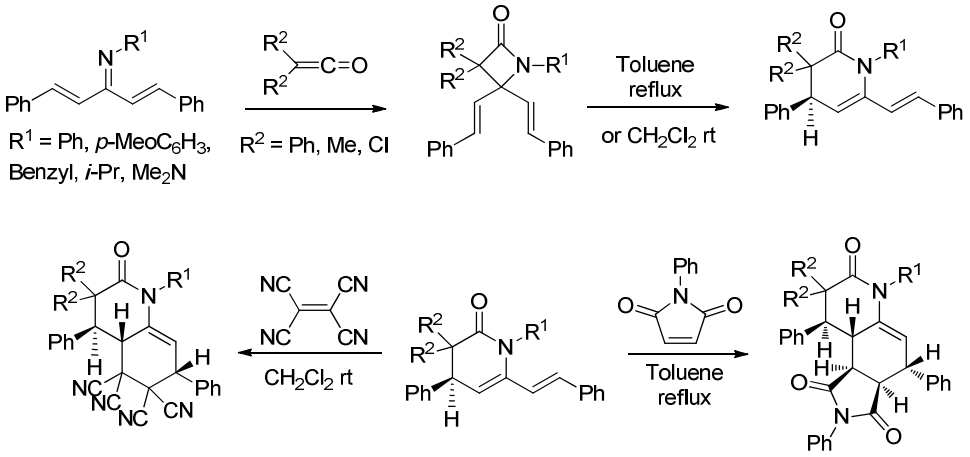
2.2.1.8. Other formal [4+2] cycloadditions

Saito and coworkers developed cross-conjugated azatrienes as substrates in diene-transmissive Diels-Alder reactions, *i.e.*, two sequential (tandem) cycloadditions that involve and initial Diels-Alder reaction of a cross-conjugated triene (or equivalent) with a dienophile, followed by a second Diels-Alder reaction of the mono-adduct on the newly formed diene unit to give a bis-adduct. In their first example, these authors performed the hetero Diels-Alder cycloaddition reaction using tosyl isocyanate and the cross-conjugated azatrienes, obtaining the corresponding dihydropyrimidones with a diene system that allowed a second cycloaddition with different dienophiles to give bicyclic products (Scheme 87).[122]



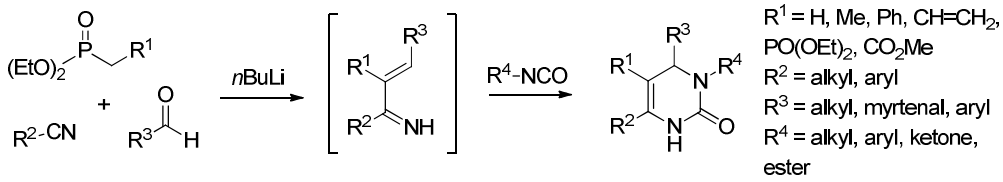
Scheme 87. Diene-transmissive Diels-Alder reactions using tosyl isocyanate and cross-conjugated azatrienes

Over the next years, this group enlarged the scope of this reaction using ketenes and alkenes as dienophiles to obtain lactams and tetrahydropyridines which can undergo a second cyclization reaction with a wide range of dienophiles. In the first case, the first [4+2] cycloaddition is believed to take place through a [2+2] cycloaddition followed by [1,3]-sigmatropic rearrangement of the resulting lactam (Scheme 88).[123-125]



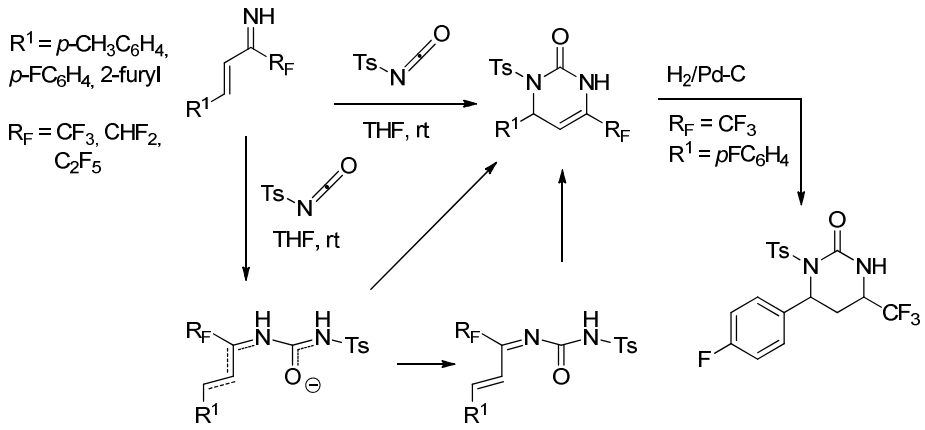
Scheme 88. Examples of diene-transmissive hetero Diels-Alder reactions of cross-conjugated azatrienes with ketenes or alkenes

In 2006 the group of Orru reported a multicomponent approach for the synthesis of dihydropyrimidones. The reaction involves the *in situ* generation of 1-azadienes *via* a Horner-Wadsworth-Emmons reaction from phosphonates, aldehydes and isocyanides, and their ulterior cycloaddition with isocyanates (Scheme 89).[126]



Scheme 89. Horner-Wadsworth-Emmons/aza-Diels-Alder synthesis of dihydropyrimidones

On the other hand, the group of Palacios has reported a related cycloaddition between *N*-tosyl isocyanate and fluoroalkylated α,β-unsaturated imines yielding 3,4-dihydropyridin-2(1*H*)-ones with good yields under mild conditions (Scheme 90). The use of *N*-tosyl isocyanate was essential in this reaction, since phenylisocyanate promoted 1,2-addition to give triazinane-2,4-diones.



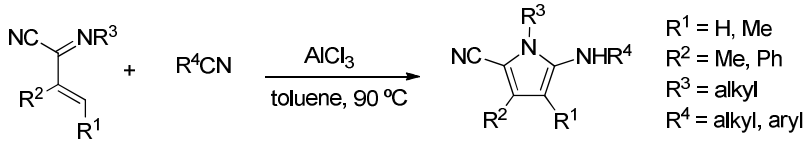
Scheme 90. Synthesis of fluorinated 3,4-dihydropyridin-2(1*H*)-ones

Supported by computational studies, the authors propose a mechanism involving a first nucleophilic attack of the unsaturated imine nitrogen to the electron-deficient carbon of the isocyanate followed by an intramolecular aza-Michael addition leading to the formation of the 3,4-dihydropyridin-2(1*H*)-one.[127]

2.2.2. Formal [4+1] cycloaddition reactions

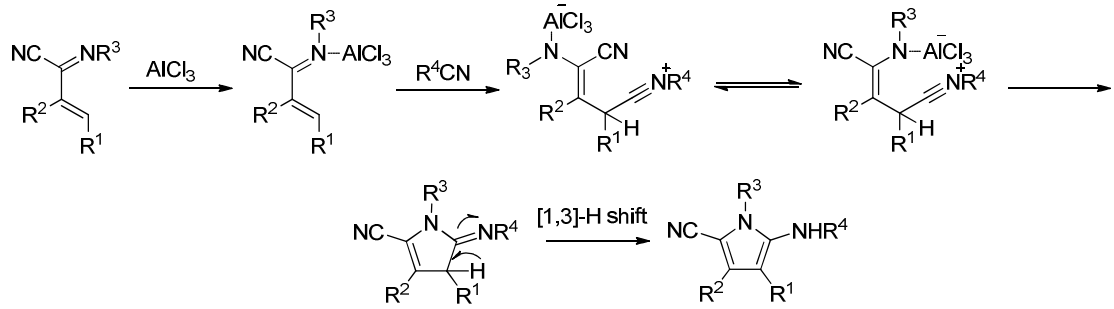
The use of azadienes in [4+1] annulation reactions to give pyrrole derivatives has been barely explored compared with the [3+2] approach. The first [4+1] annulation using unsaturated imines was reported in 1999 by Murai and coworkers. The reaction of α,β-unsaturated imines with carbon monoxide catalyzed with $Ru_3(CO)_{12}$ provided β,γ- or α,β-unsaturated γ-lactams.[128]

In 2009, Masson and Zhu reported the synthesis of 2-amino-5-cyanopyrroles *via* a [4+1] cycloaddition between 2-cyano-1-azadienes and isocyanides in the presence of a catalytic amount of $AlCl_3$ with good to excellent yields. The required azadienes were prepared in a multicomponent fashion from enals, amines and TMSCN involving an IBX/TBAB-mediated oxidative Strecker reaction (Scheme 91).



Scheme 91. [4+1] Cycloaddition of isocyanides and 2-cyano-1-azadienes

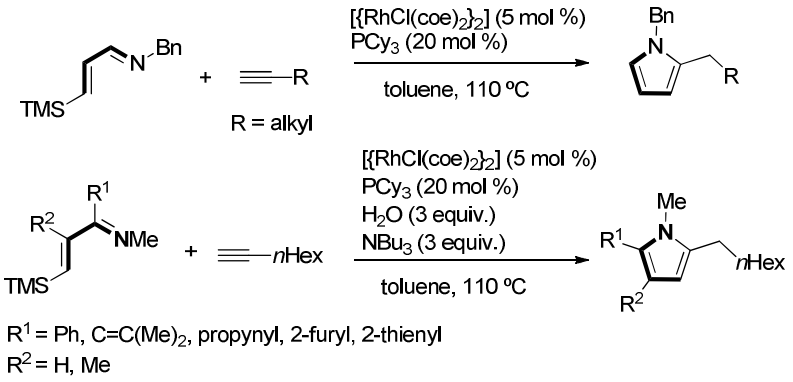
The authors proposed a mechanism for this reaction involving 1,4-addition of the isocyanide to the imine coordinated to $AlCl_3$, followed by attack of the nitrogen atom to the nitrilium and a subsequent [1,3]-H shift in the resulting cycloadduct to produce the pyrrole (Scheme 92).[129]



Scheme 92. Proposed mechanism for the [4+1] cycloaddition reaction

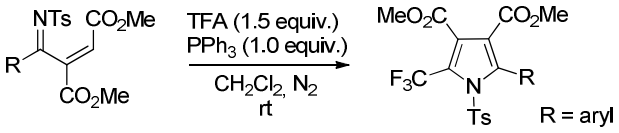
A similar strategy for the synthesis of pyrroles from alkyl or acyl isocyanides and unsaturated imines has been reported by Liu using Cp_2ZrCl_2. The reaction is thought to proceed through the formation of circonocene 1-aza-1,3-butadiene complexes.[130,131]

Simultaneously, Iwasawa et al. developed a [4+1] cycloaddition of terminal alkynes with *N*-benzyl or *N*-methyl α,β-unsaturated imines catalyzed by rhodium(I) giving rise to pyrroles with moderate to good yields (Scheme 93).[132]



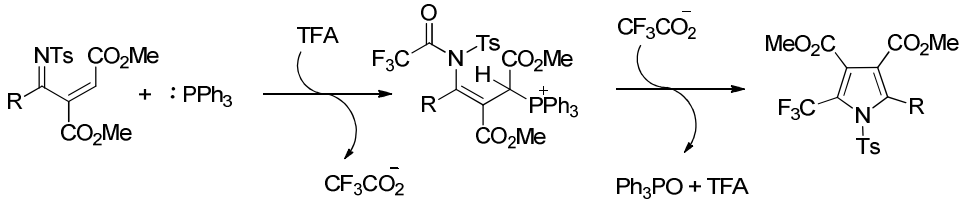
Scheme 93. Synthesis of pyrroles from alkynes and α,β-unsaturated imines catalyzed by Rh(I)

In 2014, Wang and Xu reported a novel methodology for the synthesis of trifluoromethylated pyrroles from unsaturated imines and trifluoroacetic anhydride. Excellent yields were obtained for a number of 2-trifluoromethyl pyrroles having differently substituted aromatic rings at the 5 position (Scheme 94).



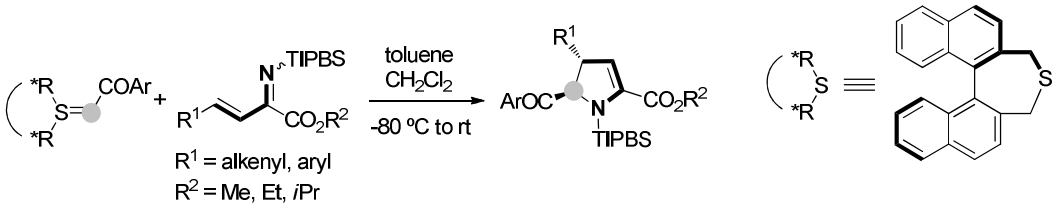
Scheme 94. Synthesis of trifluoromethylated pyrroles

The authors proposed a reaction mechanism involving the initial 1,4-addition of triphenylphosphine to the imine, subsequent attack of the negatively charged nitrogen to a TFA molecule to form an amide and intramolecular substitution to give the pyrrole (Scheme 95).[133]



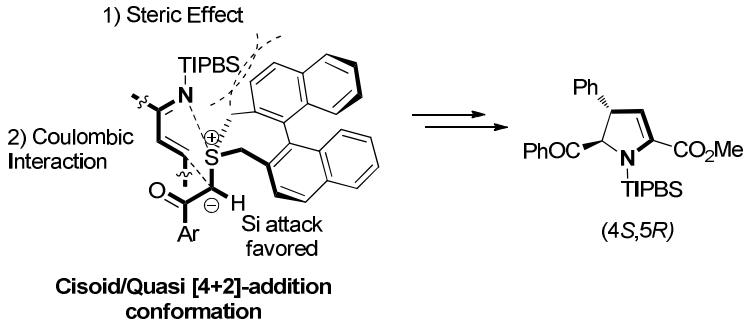
Scheme 95. Proposed mechanism for the synthesis of trifluoromethylated pyrroles

In 2010, Xiao and Chen reported the diastereoselective [4+1] annulation of sulfur ylides with α,β-unsaturated *N*-sulfonyl imines derived from keto esters. The use of chiral sulfur ylides prepared from an atropoisomeric binapthyl-derived sulfide allowed the preparation of chiral pyrrolines with high to excellent yields, diastereoselectivities and enantiomeric excesses (Scheme 96). The use of *N*-sulfonyl imines was crucial as PMP-protected imines did not react with the sulfur ylide.[134]



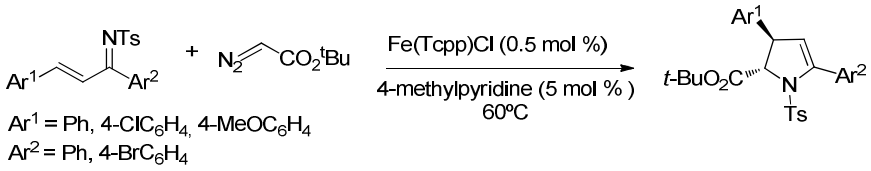
Scheme 96. Synthesis of chiral pyrrolines from chiral sulfur ylides

A study rationalized the stereoinduction of the reaction on the basis of two effects: a) the preferential approach of the imine from the *Si* face of the ylide to avoid the steric repulsion between the TIPBS group of the imine and the naphthalenyl ring of the atropoisomeric sulfide, and b) the favorable Coulombic interactions between the negative charged N of the imine and the positive charged S of the ylide, leading to a cisoid/quasi [4+2]-addition conformation (Scheme 97).



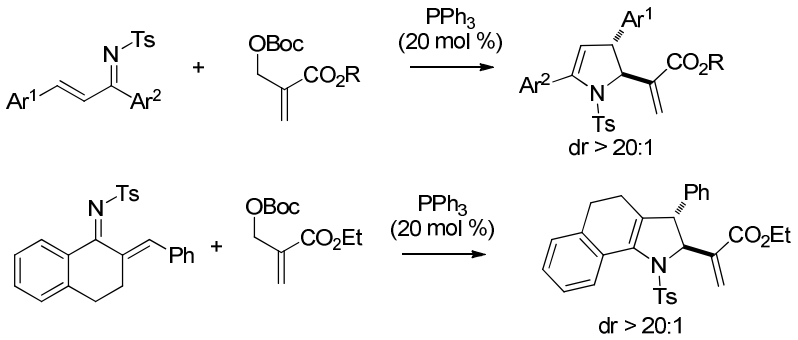
Scheme 97. Rationalization of the origin of stereoselectivity

Another diastereoselective synthesis of dihydropyrroles *via* a [4+1] annulation reaction was described by Tang in 2011. *N*-Tosyl imines derived from chalcone reacted with *tert*-butyl diazoacetate in the presence of catalytic amounts of Fe(Tcpp)Cl and 4-methylpyridine to produce 2-alcoxycarbonyl dihydropyrroles with good yields and excellent diastereoselectivities (>50:1). Aliphatic imines were not suitable substrates for this reaction (Scheme 98). The reaction with unsaturated diesters also allowed the synthesis of dihydrofurans.[135]



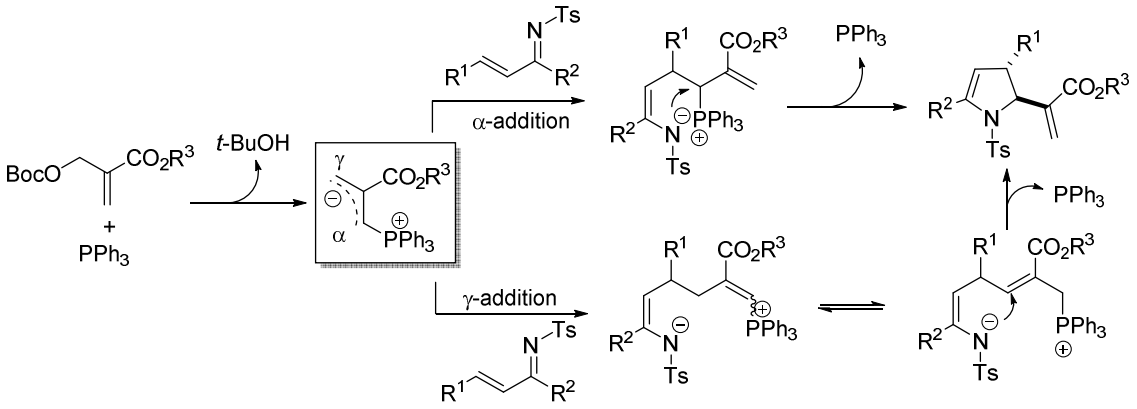
Scheme 98. [4+1] cycloaddition of unsaturated imines and *tert*-butyl diazoacetate

Simultaneously, the group of He reported the diastereoselective [4+1] annulation of allylic carbonates and α,β-unsaturated *N*-tosyl imines derived from chalcone catalyzed by triphenylphosphine. The reaction with cyclic α,β-unsaturated imines gave the corresponding cyclic fused pyrrolines (Scheme 99).[136]



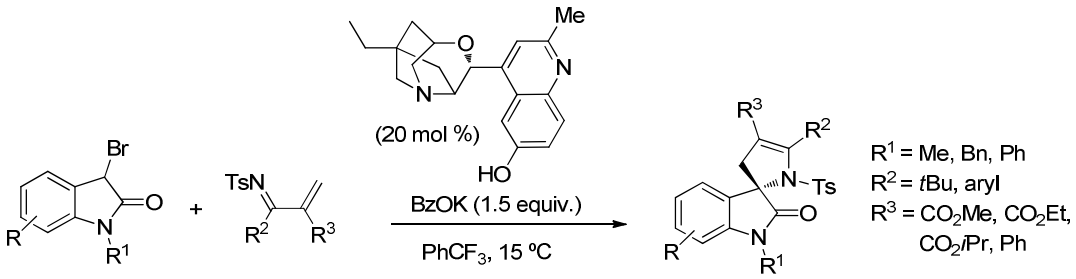
Scheme 99. Cycloaddition of allylic carbonates and *N*-tosyl α,β-unsaturated imines

The authors proposed two plausible mechanisms for the formation of the pyrrolines involving α- or γ-addition of the initially formed allylic phosphorous ylide to the imine (Scheme 100).



Scheme 100. Possible mechanisms for the Ph_3P catalyzed cycloaddition

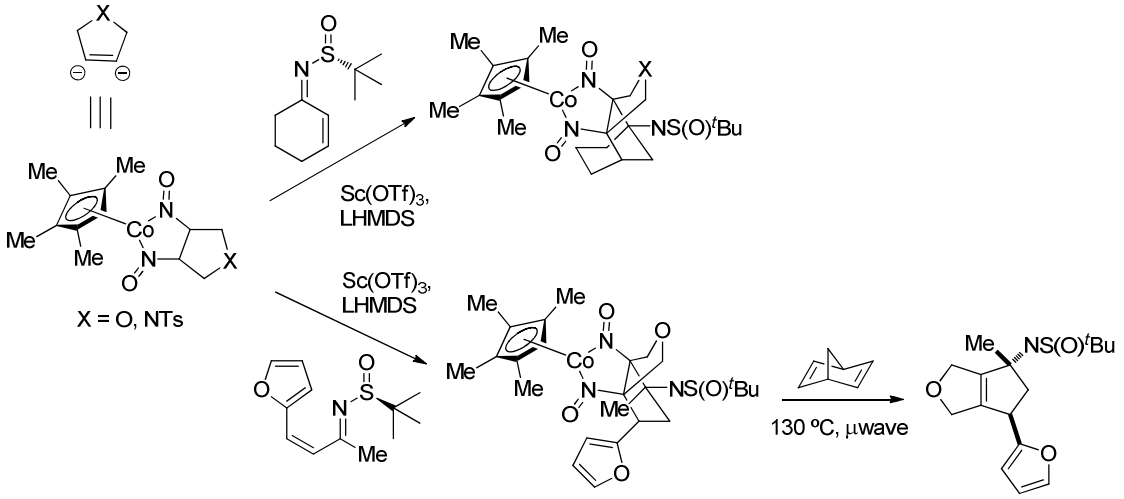
Finally in 2015, the group of Chen developed the first catalytic enantioselective [4+1] annulation reaction between ammonium ylides derived from 3-bromooxindoles and α,β-unsaturated imines catalyzed by cinchona alkaloid derivatives. Moreover, the reaction could be extended to acyclic α-bromo esters with slight modification of the reaction conditions (Scheme 101).[137]



Scheme 101. Catalytic enantioselective [4+1] annulation of 3-bromooxindoles and α,β-unsaturated imines

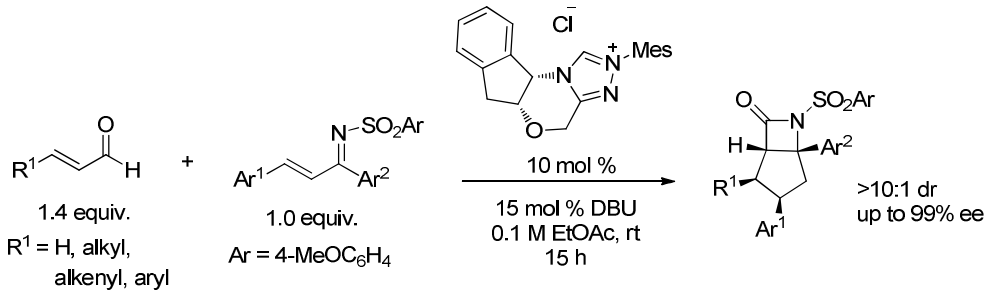
2.2.3. Formal [3+2] and [2+3] cycloaddition reactions

One of the first examples of [3+2] cycloaddition reactions involving α,β-unsaturated imines was reported by the group of Bergman. This group utilized cobalt dinitrosyl/alkene adducts as the two atom components that underwent [3+2] annulation reaction with either α,β-unsaturated aldehydes or imines catalyzed by $Sc(OTf)_3$ to give tri- or tetracycles, which after retrocycloaddition with bicyclo[2.2.1]hepta-2,5-diene led to the formation of bicyclic olefins (Scheme 102).[138]



Scheme 102. [3+2] Cycloaddition involving cobalt dinitrosyl/alkene adduct and α,β-unsaturated imines

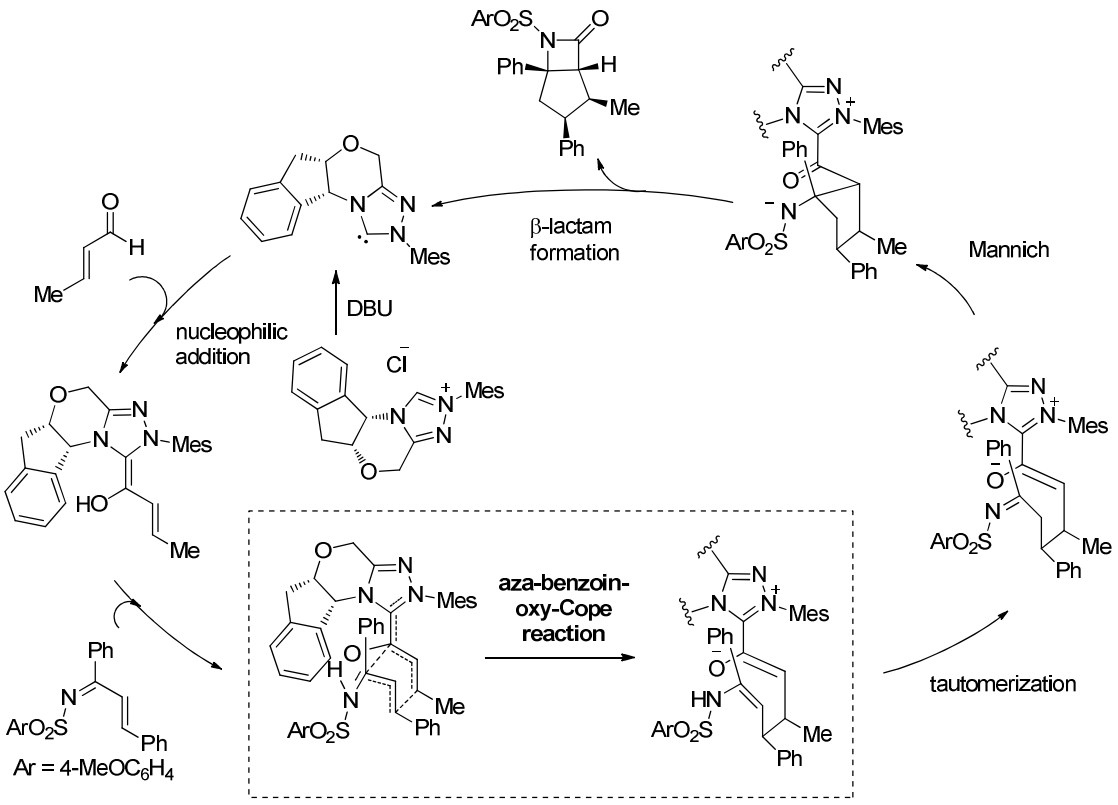
In 2008, the group of Bode reported the enantioselective synthesis of cyclopentane fused β-lactams using NHC catalysis. By changing from β-acyl substituted enals to β-alkyl or β-aryl substituted enals, from unsaturated aldimines to unsaturated ketimines, and the base, a shift of reactivity from the previously described [4+2] reaction[106] to a formal [3+2] reaction was observed (Scheme 103).[139] The resulting products were obtained with moderate to excellent yields, good diastereomeric ratios and excellent enantiomeric excesses.



Scheme 103. NHC catalyzed enantioselective synthesis of bicyclo[3.2.0]lactams

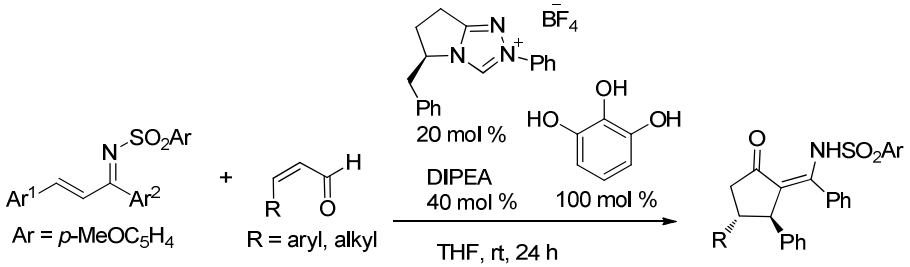
Supported by the all *cis* substitution observed in the bicyclo-β-lactams, the authors proposed a mechanism involving a crossed-benzoin/oxy-Cope rearrangement as the key bond-forming step. The preference for this reaction mechanism instead of a Diels-Alder

reaction is probably due to the use of nonactivated enals in which the protonation on the β-carbon is too slow (Scheme 104).[140]



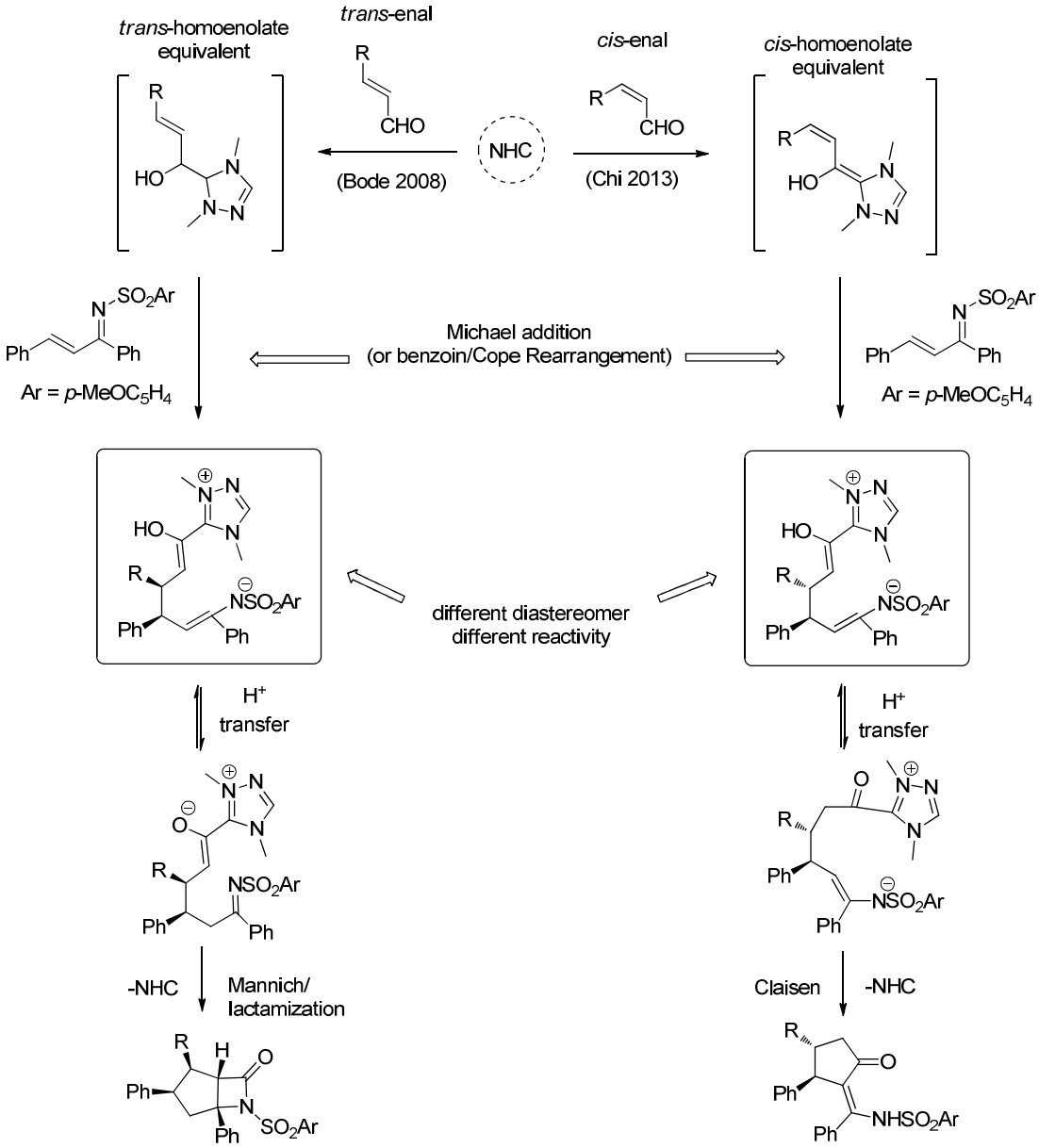
Scheme 104. Proposed mechanism for the formation of bicyclo[3.2.0]lactams

Later in 2013, Chi discovered that by using *cis*-enals and phenol-derived additives, the NHC catalyzed reaction with α,β-unsaturated *N*-sulfonyl imines delivered cyclopentanones instead of lactams as reported by Bode, with excellent diastereo- and enantioselectivity (Scheme 105).[141] The use of additives was essential to avoid isomerization of the *cis*- to the *trans*-enal that led to the fused lactam products observed by Bode.[139]



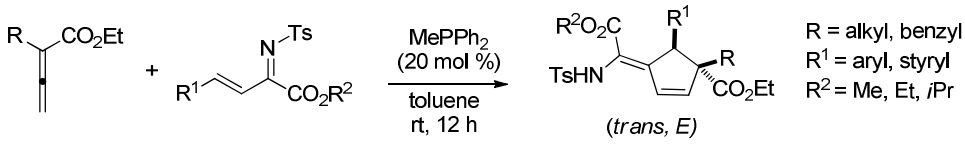
Scheme 105. Enantioselective synthesis of chiral cyclopentanones *via* NHC catalysis

The authors attributed the change of reactivity to the formation of different diastereomeric intermediates, which would prefer to undergo a final Mannich-type reaction in the case of *trans* enals or a Claisen-type reaction in the case of *cis* enals (Scheme 106).



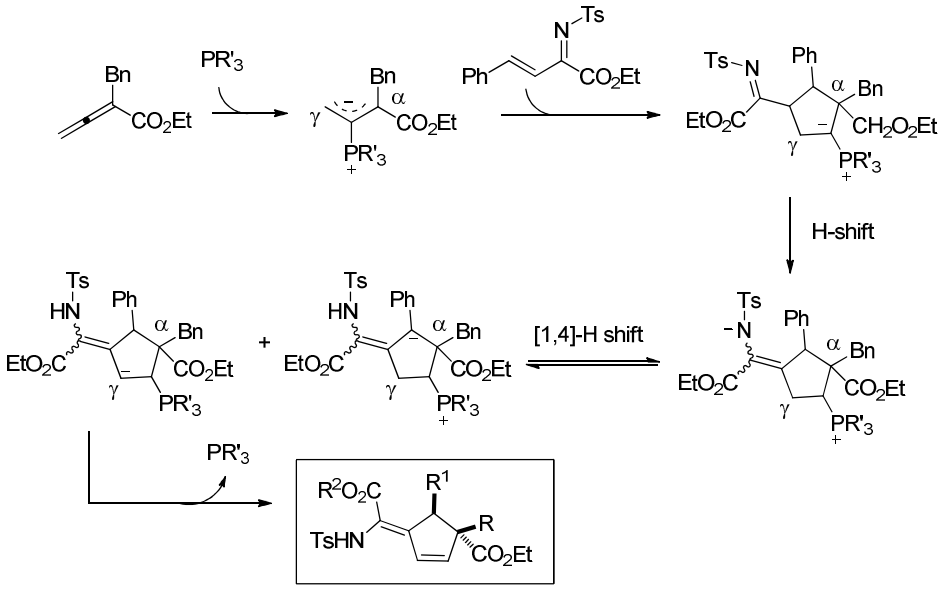
Scheme 106. Compared mechanistic pathways for the reaction of *cis*- and *trans*-enals

Previous to the work of Chi, He and Tian described the [3+2] annulation reaction of α-benzyl allenoates with α,β-unsaturated *N*-tosyl imino esters catalyzed by phosphines to yield cyclopentenes with a *trans* exocyclic enamine moiety with moderate to high diastereoselectivities and moderate yields (Scheme 107).



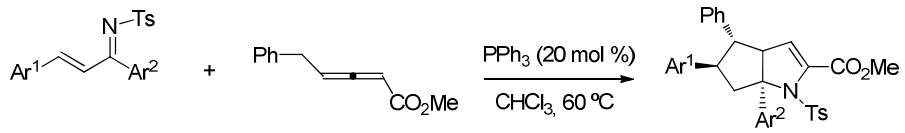
Scheme 107. Phosphine catalyzed [3+2] annulation between allenoates and α,β-unsaturated *N*-tosyl imino esters

Based on a deuterium-labelled experiment the authors proposed the mechanism outlined in Scheme 108 for the formation of the cyclopentenes.[142]



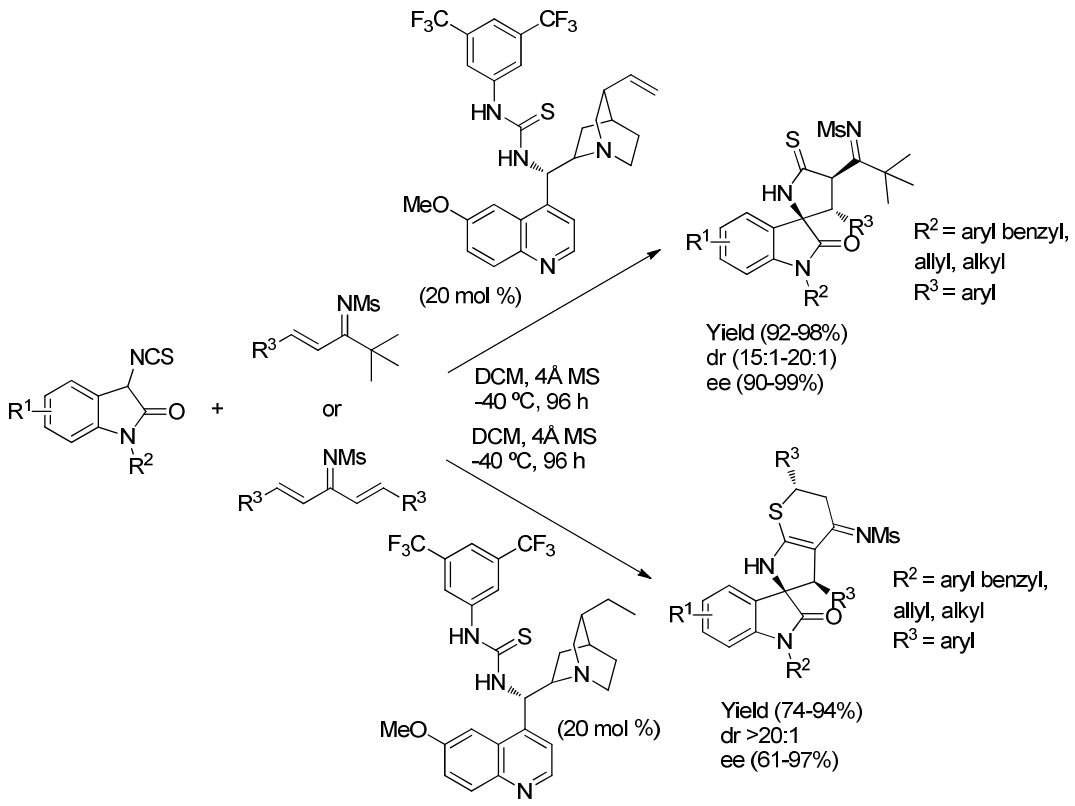
Scheme 108. Mechanism for the synthesis of cyclopentenes

Later, the group of Huang reported the sequential [2+3] and [3+2] annulation domino reaction of allenoates and α,β-unsaturated *N*-tosyl imines derived from chalcones, using triphenylphosphine as a catalyst to give cyclopentane fused dihydropyrroles with moderate to high yields and excellent diastereoselectivities. The presence of the phenyl group attached to the γ-carbon of the allenoate was required for the reaction to proceed, probably due to activation of the methylene by π-conjugative effect (Scheme 109).[143]



Scheme 109. Sequential [2+3] and [3+2] annulation domino reaction between methyl 6-phenylhexa-2,3-dienoate and α,β-unsaturated *N*-tosyl imines

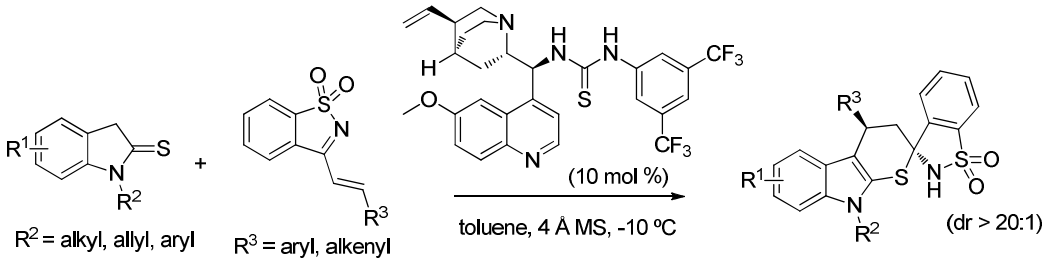
Finally, Shi reported recently the enantioselective [3+2] or [3+2]/ [4+2] cascade reaction between α,β-unsaturated imines and 3-isothiocyanato oxindoles to give spirocyclic oxindoles using a bifunctional thiourea derived from cinchona alkaloid as the catalyst. Furthermore, when *N*-((1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-ylidene)methane-sulfonamide was used as electrophile, the first [3+2] cycloaddition reaction was followed by a subsequent [4+2] cycloaddition reaction to give tricyclic compounds (Scheme 110).[144]



Scheme 110. Enantioselective synthesis of spirocyclic oxindoles

2.2.4. Formal [3+3] cycloaddition reactions

In 2015, the group of Zhou and Wang reported the spiroannulation [3+3] between 1-azadienes derived from saccharin and indoline-2-thiones using a thiourea bifunctional catalyst. A wide range of different products could be obtained with this methodology in 82-99% yield and 76-99% ee (Scheme 111).

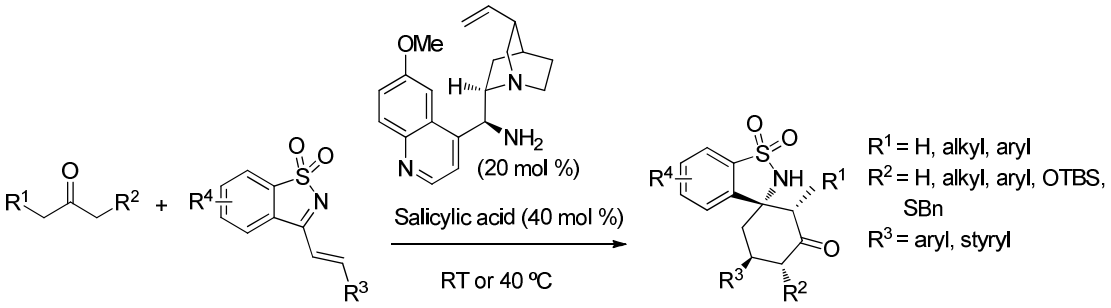


Scheme 111. Synthesis of chiral spiro[thiopyranoindole-benzoisothiazole] heterocycles

Furthermore, α,β-unsaturated *N*-tosyl imines derived from chalcone could also be used as substrate to give the corresponding product with 90% yield, >20:1 dr and 94% ee.[145]

Simultaneously, the group of Chen developed a [3+3] cycloaddition using the same kind of imines derived from saccharin with different ketones *via* enamine-enamine catalysis. After optimization of reaction conditions they obtained the desired

cycloadducts with excellent yields and enantiomeric excesses in most of the cases, using 9-amino-9-deoxyepiquinine as the catalyst and salicylic acid as an additive (Scheme 112).

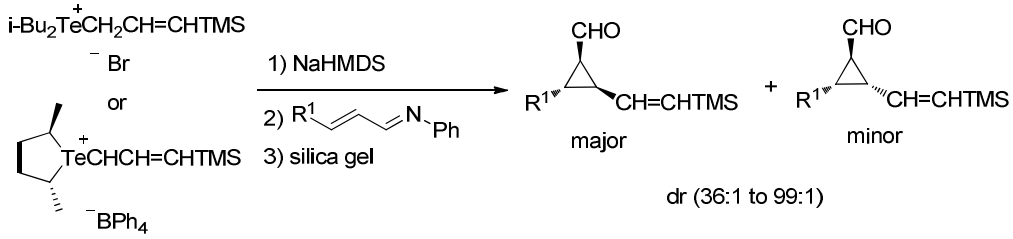


Scheme 112. Enamine-enamine catalysis in the [3+3] cycloaddition of ketones to unsaturated imines

The analogous cyclic (*E*)-4-styryl-benzo[e][1,2,3]oxathiazine-2,2-dioxide also gave the [3+3] adduct with good yield and ee. However, when an acyclic *β,γ*-unsaturated *N*-tosyl imino ester was used, hydrolysis to the corresponding keto ester was observed.[146]

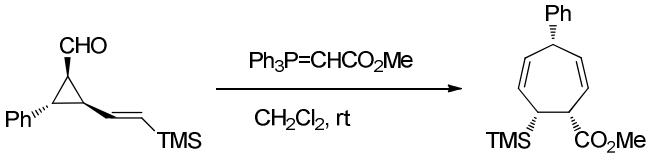
2.2.5. Cyclopropanation and other cyclization reactions

In 2005, the group of Tang, described the cyclopropanation of α,β-unsaturated imines *via* a Michael addition-elimination reaction of tellurium ylides to give vinyl cyclopropanecarbaldehydes with high diastereoselectivities and good yields in the majority of examples. Enantiomerically enriched products (95-99% ee) could be obtained by using enantiomerically enriched chiral tellurium ylides (Scheme 113).



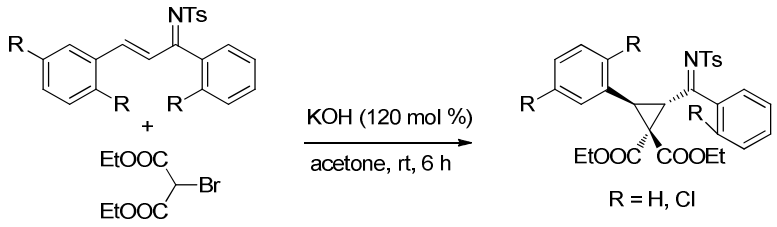
Scheme 113. Diastero- and enantioselective cyclopropanation of α,β-unsaturated *N*-phenyl imines with tellurium ylides

Furthermore, the major vinyl cyclopropanecarbaldehyde could be transformed into a cycloheptadiene *via* a Wittig reaction followed by a [3,3] sigmatropic rearrangement (Scheme 114).[147]



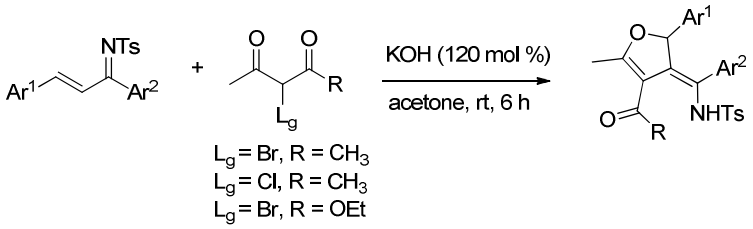
Scheme 114. Synthesis of a cycloheptadiene

As a part of a study addressed to the synthesis of dihydrofurans, Zhue and Xie described two examples of cyclopropanation of unsaturated imines with diethyl bromomalonate in basic medium (Scheme 115). The reaction proceeded through a Michael addition/intramolecular substitution domino process.[148]



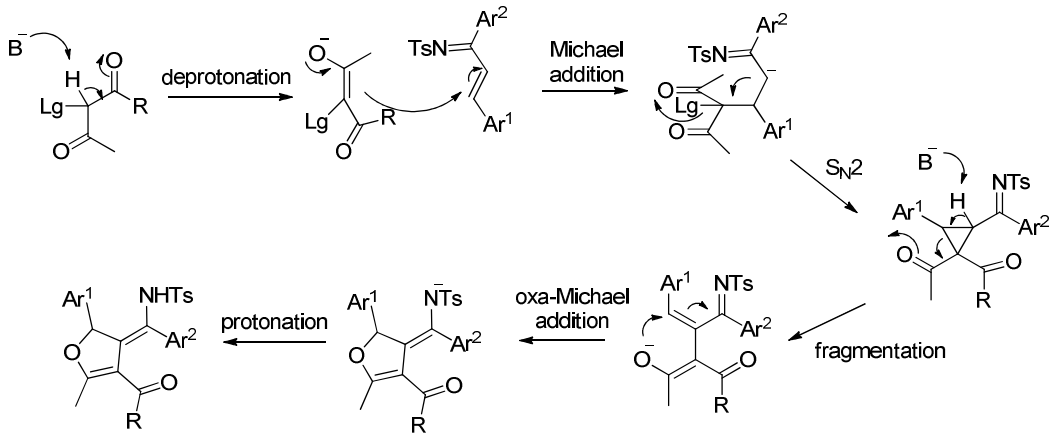
Scheme 115. Cyclopropanation of *N*-tosyl imines with diethyl 2-bromomalonate

When 2-halo-1,3-diketones were used as substrates under the same reaction conditions functionalized 2,3-dihydrofurans instead of cyclopropanes were obtained. (Scheme 116).[148]



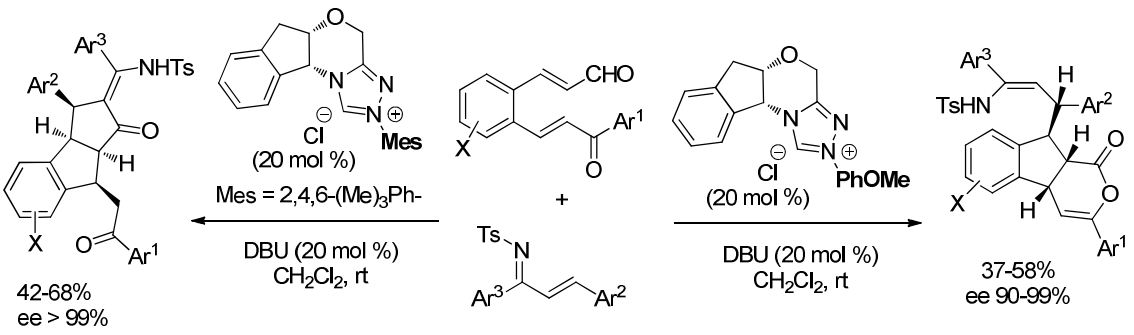
Scheme 116. Base-promoted synthesis of dihydrofurans from 2-halo-1,3-diketones and *N*-tosyl imines

The authors proposed a domino sequence involving deprotonation of the dione followed by a Michael addition to the unsaturated imine and intramolecular alkylation to give a cyclopropane. Base-promoted fragmentation of the cyclopropane ring and oxa-Michael addition to the resulting unsaturated imine to gave corresponding 2,3-dihydrofurans (Scheme 117).



Scheme 117. Proposed domino mechanism for the formation of 2,3-dihydrofurans

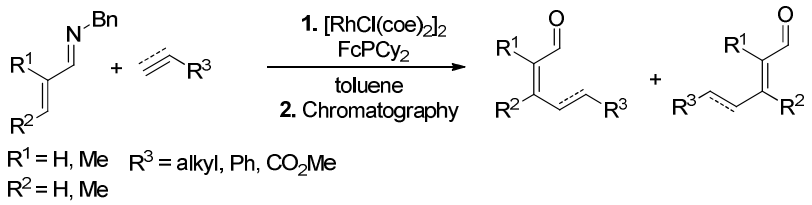
The group of Cheng has developed several cascade reactions *via* NHC catalysis involving α,β-unsaturated *N*-sulfonyl ketimines and 2-acylvinyl cinnamaldehydes for the stereoselective synthesis of highly functionalized indane derivatives. Depending on the structure of the catalyst, indeno[2,1-c]pyran-1-one derivatives or indenocyclopenta-1-ones were obtained selectively and with excellent enantioselectivity (Scheme 118).[149,150]



Scheme 118. Diastereo- and enantioselective synthesis of indane derivatives

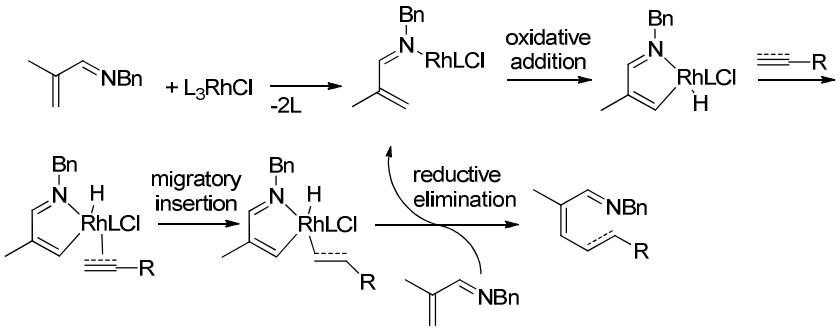
2.3. Reactions involving C-H activation or metalation of 1,3-butadienes

Bergman and Ellman have described the alkylation and alkenylation at the β position of conjugated imines by using alkenes or alkynes, respectively, catalyzed by rhodium salts. After alkylation, the resulting products were hydrolyzed to unsaturated aldehydes. Hydrolysis with aqueous acid favored the formation of the *E* isomer, while the *Z* isomer could be obtained by hydrolysis under milder conditions with AcOH in THF. The procedure allows the synthesis of β,β-substituted enals, which are difficult to obtain by other methods (Scheme 119).[151]



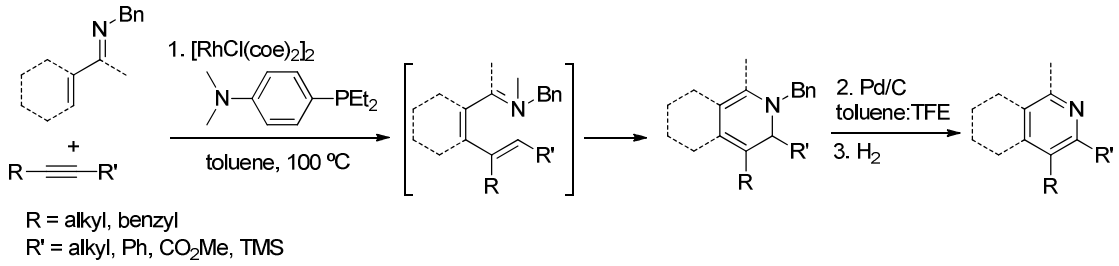
Scheme 119. Formation of unsaturated aldehydes from unsaturated imines and alkenes

The reaction is believed to proceed *via* coordination of the imine to the Rh catalyst followed by oxidative addition to the C-H bond. Association of the alkene followed by migratory insertion of the Rh-H bond and subsequent reductive elimination gives the alkylated aza-diene or the aza-triene in the reaction with alkynes (Scheme 120).



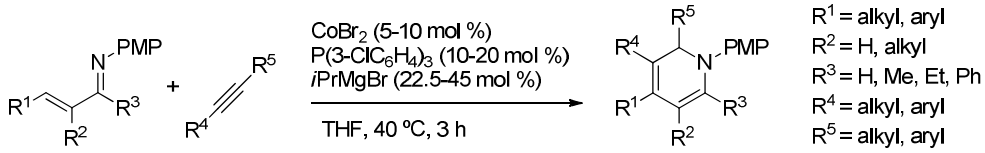
Scheme 120. Rh-catalyzed alkylation of unsaturated imines

On the other hand, when terminal alkynes were used, instead of the expected azatrienes the reaction delivered dihydropyridines, which could be converted into pyridines by oxidation and deprotection of the nitrogen.[152] Formation of the dihydropyridine most likely happens through the *in situ* electrocyclization of the aza-triene (Scheme 121).



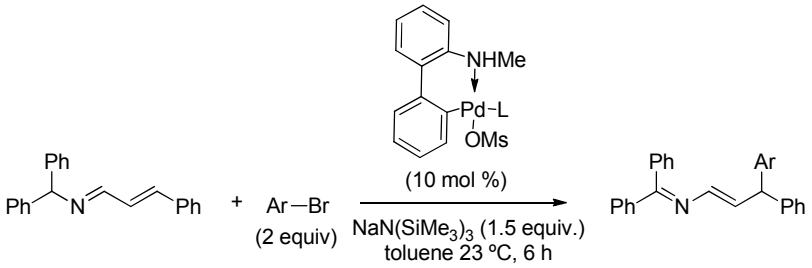
Scheme 121. One-pot synthesis of dihydropyridines and pyridines

A similar cycloaddition of alkynes and α,β-unsaturated imines *via* C-H activation catalyzed by cobalt has been reported by Yoshiaki (Scheme 122).[153]



Scheme 122. Synthesis of unsymmetrical dihydropyridines catalyzed by cobalt

Recently, the group of Walsh also reported the cross-coupling reaction of arylbromides and unsaturated *N*-(biphenylmethyl) imines catalyzed by palladium complexes, obtaining the corresponding 1,2- or 1,4-addition products with excellent regioselectivities and high yields by properly choosing the reaction conditions (Scheme 123).[38] The use of acidic (biphenylmethyl)amines was a requirement to generate the π-allyl intermediate.



Scheme 123. Pd-catalyzed cross coupling of aryl bromides and unsaturated aldimines

3. OBJETIVES

3. OBJETIVES

α,β-Unsaturated imines (1-azabutenes) have been used as starting materials in the synthesis of nitrogen-containing molecules since long time ago. The conjugate addition of carbon nucleophiles to this kind of compounds is an efficient way to form a new C-C bond giving rise to enamines with the concomitant formation of a new stereogenic center. However, in contrast to unsaturated carbonyl compounds and nitroalkenes, the asymmetric conjugate addition of carbon nucleophiles to α,β-unsaturated imines has been more scarcely explored and, in particular, no asymmetric examples with 1,3-dicarbonyl compounds as nucleophiles appeared in the literature prior to the start of our research.

The development of asymmetric conjugate additions to α,β-unsaturated imines poses several challenges:

a. Low electrophilicity of the substrate due to the low electronegativity of the N atom.

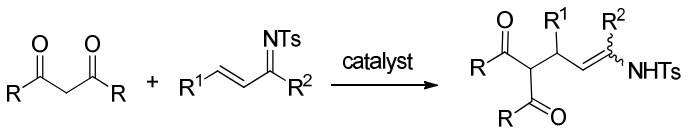
b. Control of regioselectivity: 1-azabutenes often prefer to undergo 1,2-addition or give double nucleophilic addition.

c. Control of diastereoselectivity: the enamine double bond can be obtained with either *E* or *Z* geometry.

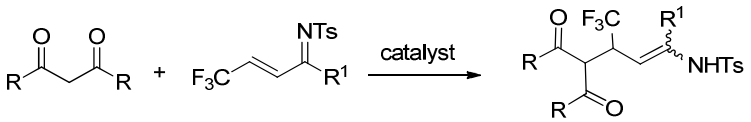
d. Control of enantioselectivity: the newly formed stereogenic center should be formed in only one configuration.

Considering these challenges, this thesis has been focused in the development of new diastereo- and enantioselective conjugate addition reactions of carbon nucleophiles to α,β-unsaturated imines employing metal catalysis for this purpose. The following reactions have been studied:

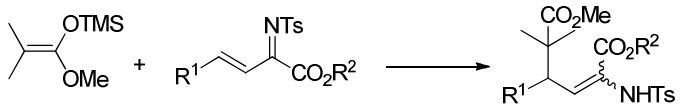
1. Asymmetric conjugate addition of malonate esters to α,β-unsaturated *N*-tosyl imines catalyzed by La(III) complexes.



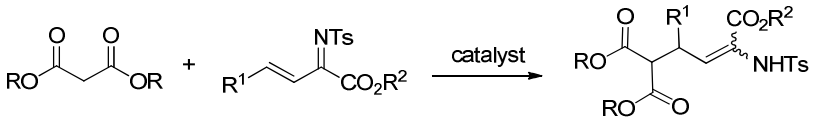
2. Asymmetric conjugate addition of malonate esters to β-trifluoromethyl α,β-unsaturated *N*-tosyl imines catalyzed by Cu(II) and Mg(II) complexes.



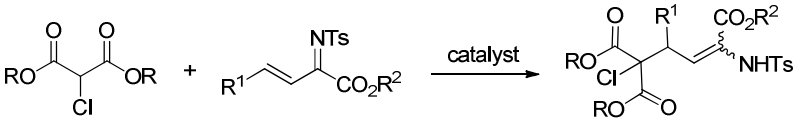
3. Diastereoselective Mukaiyama-Michael reaction of silylketene acetals with *N*-tosyl imines derived from β,γ-unsaturated α-keto esters.



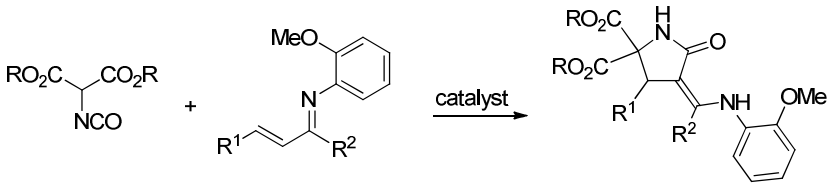
4. Asymmetric conjugate addition of malonate esters to *N*-tosyl imines derived from β,γ-unsaturated α-keto esters catalyzed by La(III) complexes.



5. Diastereodivergent enantioselective conjugate addition of 2-chloromalonate esters to *N*-tosyl imines derived from β,γ-unsaturated α-keto esters catalyzed by La(III) or Ca(II) complexes.



6. Catalytic asymmetric [3+2] cycloaddition of 2-isocyanatomalonate esters and α,β-unsaturated imines through a tandem Michael addition/intramolecular addition to isocyanate process.

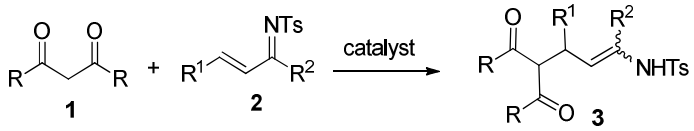


4. RESULTS AND DISCUSSION

4. RESULTS AND DISCUSSION

4.1. Asymmetric conjugate addition of malonate esters to α,β-unsaturated *N*-tosyl ketimines catalyzed by pyBOX-La(OTf)$_3$

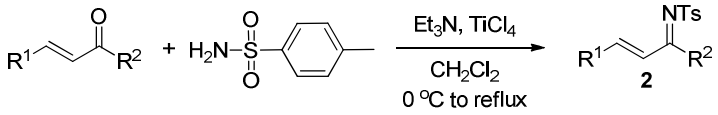
At the onset of our research there where only a limited number of methods for the enantioselective conjugate addition of carbon nucleophiles to α,β-unsaturated imines reported in the literature, most of them involving the reaction of organometallic reagents. These include the asymmetric conjugate addition of organocuprates to chiral *N*-*tert*-butylsulfinyl imines reported by Ellman[19] and the copper(I)-catalyzed additions of dialkylzinc reagents to different unsaturated imines reported by Tomioka,[20] Carretero[22] and Palacios,[23,24] respectively. Besides these examples, a conjugate addition of malonate esters or related 1,3-dicarbonyl compounds to unsaturated imines in an enantioselective fashion had not been reported, to the best of our knowledge, although Palacios had described the nonenantioselective conjugate addition of malonate esters to fluorinated unsaturated imines followed by lactamization to give pyridones.[82] In this chapter, we will describe our efforts to develop the first example of asymmetric conjugate addition of malonate esters to unsaturated imines as an efficient procedure to access chiral δ-amino acid derivatives (Scheme 124).



Scheme 124. Conjugate addition of malonate esters to α,β-unsaturated *N*-tosyl imines

4.1.1. Synthesis of α,β-unsaturated *N*-tosyl imines 2

In this investigation we have used *N*-tosyl imines **2** as electrophiles since the reactivity of imines toward nucleophilic attack is significatively increased by the presence of strong electron-withdrawing groups on the azomethinic nitrogen. Compounds **2** were prepared from the corresponding enones and $TsNH_2$ upon treatment with $TiCl_4$ and Et_3N following the procedure described by Carretero (Scheme 125).[22] A number of tosyl imines **2** derived from chalcones (R^1 and R^2 = Ar) or β-alkyl substituted aryl imines (R^1 = Ar, R^2 = alkyl) were prepared following this procedure in 75-85% yield. However, the synthesis of the unsaturated imine where R^2 is aliphatic (Me) was not possible because of enolization of the *N*-sulfonyl imine during the preparation of the starting material.



2a, R^1 = Ph, R^2 = Ph
2b, R^1 = 4-FC_6H_4, R^2 = Ph
2c, R^1 = 4-ClC_6H_4, R^2 = Ph
2d, R^1 = 4-BrC_6H_4, R^2 = Ph
2e, R^1 = 4-$NO_2C_6H_4$, R^2 = Ph
2f, R^1 = 4-$MeOC_6H_4$, R^2 = Ph
2g, R^1 = 2-furanyl, R^2 = Ph
2h, R^1 = 3-furanyl, R^2 = Ph
2i, R^1 = Me, R^2 = Ph
2j, R^1 = *t*Bu, R^2 = Ph
2k, R^1 = Ph, R^2 = 4-FC_6H_4,
2l, R^1 = Ph, R^2 = 4-ClC_6H_4
2m, R^1 = Ph, R^2 = 4-$NO_2C_6H_4$
2n, R^1 = Ph, R^2 = 4-$MeOC_6H_4$,
2o, R^1 = Ph, R^2 = 2-FC_6H_4,
2p, R^1 = Ph, R^2 = 3-$NO_2C_6H_4$

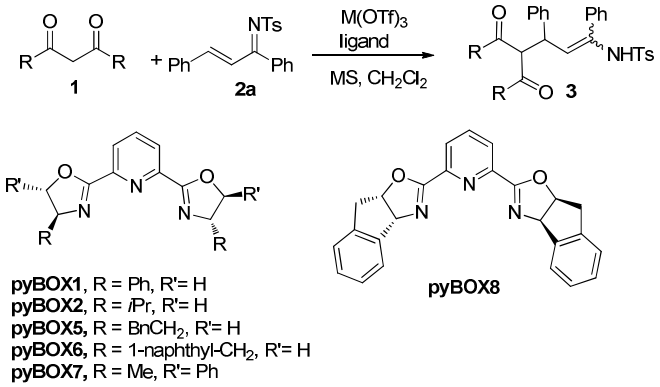
Scheme 125. Synthesis of α,β-unsaturated *N*-tosyl imines **2**

4.1.2 Optimization of the reaction conditions

For the optimization of the reaction conditions, we studied the addition of dimethyl malonate (**1a**, R = OMe) to *N*-tosyl imine **2a** (R^1 = R^2 = Ph). Following previous experience of the group on the conjugate addition of nitromethane[155] to unsaturated imines we decided to test complexes of trivalent metals and pyBOX ligands as potential catalysts in our reaction (Table 2).

When the reaction was carried out in the presence of the **pyBOX1**-$La(OTf)_3$ in dichloromethane we did not observe any advance of the reaction after 24 h (Table 2, entry 1). However, after addition of 4Å molecular sieves (MS) the reaction proceeded smoothly to give compound **3aa** (R = MeO, R^1 = R^2 = Ph) in 81% yield (Table 2, entry 2). The combined use of Lewis acid and MS has been documented in a number of reactions involving metal enolates as intermediates. 4Å MS most likely works as an effective proton scavenger favoring the generation of metal enolates in high concentration.[156] Compound **3aa** was obtained as a *ca.* 9:1 mixture of diastereomers with 86% enantiomeric excess for the major diastereomer (Table 2, entry 2). The geometry of the double bond was assigned as *E* for the major diastereomer and *Z* for the minor one by NOESY experiments (Figure 2). Particularly relevant for the assignment of this stereochemistry was the interaction between the NH of the sulfonamide group at δ 7.81 ppm and the triplet benzylic proton at δ 3.89 ppm observed in the minor *Z*-diastereomer. These results contrast with those reported for the Cu(I)-catalyzed addition of diethylzinc to related unsaturated imines, which give the *Z*-isomers as the major products.[22] On the other hand, no cyclization to the corresponding lactam was observed under the reaction conditions. Yb(III), Sc(III) and In(III) triflates in combination with **pyBOX1** were also tested (Table 2, entries 3-5) although we did not observe any advance of the reaction.

Table 2. Enantioselective addition of 1,3-dicarbonyl compounds **1** to unsaturated imine **2a** ($R^1 = R^2 = Ph$).[a]



entry	M	ligand	1	R	*T* (°C)	*t* (h)	3	yield (%)[b]	ee (%)[c]
1[d]	La	**pyBOX1**	**1a**	MeO	rt	48	**3aa**	-[e]	-
2	La	**pyBOX1**	**1a**	MeO	rt	24	**3aa**	81	86
3	Yb	**pyBOX1**	**1a**	MeO	rt	48	**3aa**	-[e]	-
4	Sc	**pyBOX1**	**1a**	MeO	rt	48	**3aa**	-[e]	-
5	In	**pyBOX1**	**1a**	MeO	rt	48	**3aa**	-[e]	-
6	La	**pyBOX2**	**1a**	MeO	rt	24	**3aa**	65	-8
7	La	**pyBOX5**	**1a**	MeO	rt	16	**3aa**	60	-6
8	La	**pyBOX6**	**1a**	MeO	rt	42	**3aa**	59	12
9	La	**pyBOX7**	**1a**	MeO	rt	24	**3aa**	86	56
10	La	**pyBOX8**	**1a**	MeO	rt	106	**3aa**	25	12
11	La	**pyBOX1**	**1a**	MeO	0	64	**3aa**	63	92
12	La	**pyBOX1**	**1b**	EtO	rt	48	**3ba**	73	83
13	La	**pyBOX1**	**1c**	*i*PrO	rt	120	**3ca**	16	-
14	La	**pyBOX1**	**1d**	Me	rt	170	**3da**	69	36
15	La	**pyBOX1**		-[f]	rt	48		-[e]	-

[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.125 mmol), ligand (0.0125 mmol), $M(OTf)_3$ (0.0125 mmol), 4Å MS (20 mg), CH_2Cl_2 (0.8 mL). [b] Yield of isolated product. [c] Only for the major (*E*)-diastereomer. Determined by HPLC with chiral stationary phases; opposite sign indicates different enantiomers. [d] Reaction carried out without MS. [e] No reaction observed after 48 h. [f] Malononitrile was used as nucleophile.

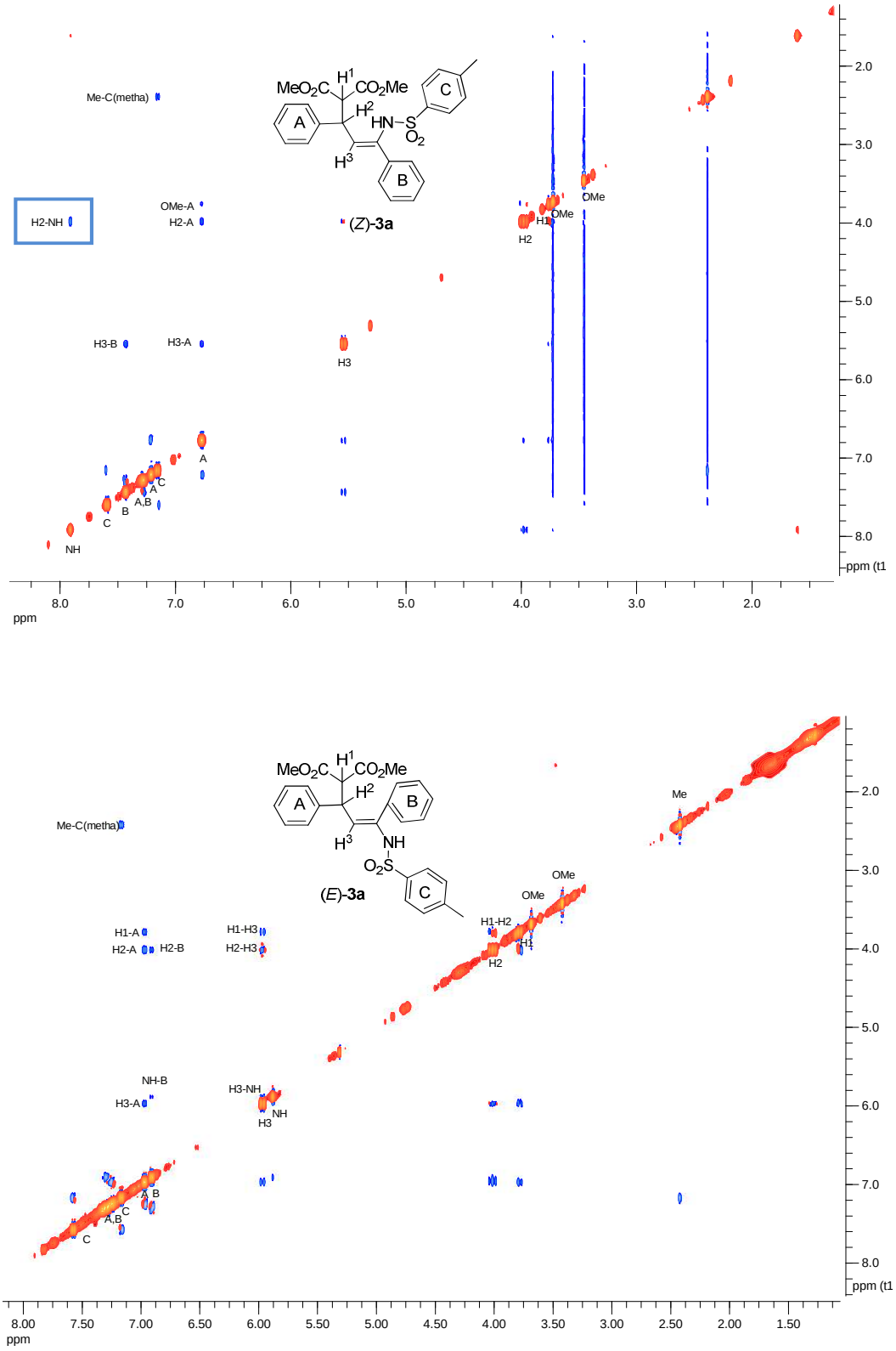


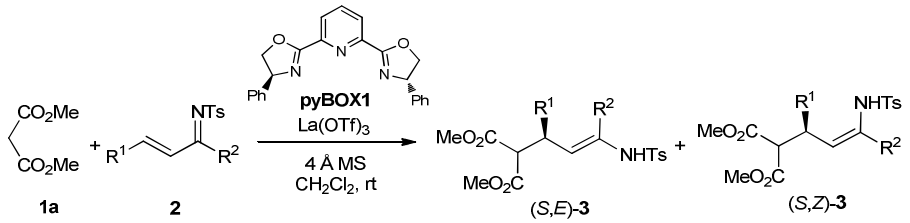
Figure 2. NOESY experiments carried out with the minor (above) and major (below) diastereomers of compound **3aa**

We also tested different pyBOX ligands with $La(OTf)_3$ (Table 2, entries 6-10), although none of them provided better results than **pyBOX1**. The use of toluene, hexane or THF was prevented due to the low solubility of the imine in these solvents. Finally, the enantioselectivity of the reaction could be increased up to 92% ee by carrying out the reaction at 0 °C, although with a loss of yield (Table 2, entry 11). The effect of the substituent R attached to the carbonyl group of the nucleophile was also tested. First, we tested the use of other malonate esters. Diethyl malonate (**1b**, R = EtO) performed similarly to dimethyl malonate providing the expected addition product (**3ba**, R = EtO, $R^1 = R^2$ = Ph) with 73% yield and 83% ee (Table 2, entry 12). However, increasing the bulk of the alkoxy group as in diisopropyl malonate (**1c**, R = *i*PrO) produced a serious decrease on the reaction rate and the conjugate addition product was obtained in only 16% yield after 120 h (Table 2, entry 13). Moreover, 2,4-pentanedione (**1d**, R = Me) reacted slowly with imine **2a** to give the corresponding product (**3da**, R = Me, $R^1 = R^2$ = Ph) with 59% yield but with low diastereo- and enantioselectivity (Table 2, entry 14). Finally, malononitrile did not react under the optimized conditions.

4.1.3 Scope of the reaction

Next, we studied the scope of the addition of dimethyl malonate (**1a**, R = MeO) to different imines **2a-p** under the optimized conditions. The results are gathered in Table 3. The reaction could be carried out with imines bearing an aromatic ring attached to the β carbon, substituted with either electron-donating or electron-withdrawing substituents (Table 3, entries 1-8) to give the expected products with good diastereoselectivities (from 71:29 to 97:3) favoring the *E*-diastereomer and high enantiomeric excesses (70-92%). The group R^1 can be also a heterocyclic furanyl ring (Table 3, entries 9 and 10). When R^1 was a phenyl group substituted with electron-withdrawing groups, good yields of the addition products could be obtained after 24 h. However, when R^1 was an aromatic ring substituted with an electron-donating group, or an electron-rich heterocycle (Table 3, entries 8-10), the reaction required longer times and the corresponding products were obtained with slightly lower yields. Finally, the reaction allowed imines with R^1 being an aliphatic group. Imine **2i** (R^1 = Me) reacted with dimethyl malonate to give the expected product **3ai** in almost quantitative yield, with good diastereoselectivity and 75% ee for the major diastereomer (Table 3, entry 11). However, imine **2j** bearing a bulky *tert*-butyl group did not react under similar conditions (Table 3, entry 12). The R^2 group attached to the imine was also amenable to variation (Table 3, entries 13-18). Aromatic rings bearing either electron-donating or electron-withdrawing groups were permitted without much influence on the enantioselectivity of the reaction.

Table 3. Enantioselective addition of dimethyl malonate to unsaturated imines catalyzed by **pyBOX1**-La(OTf)$_3$.[a]

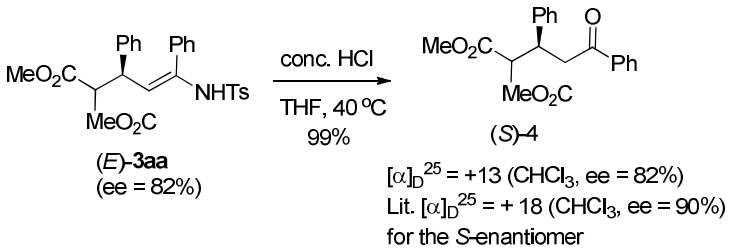


entry	2	R^1	R^2	*t* (h)	3	yield(%)[b]	dr (*E*/*Z*)	ee (*E*/*Z*)[c]
1	**2a**	Ph	Ph	24	**3aa**	81	89:11	86/-
2[d]	**2a**	Ph	Ph	64	**3aa**	63	95:5	92/-
3	**2b**	4-FC_6H_4	Ph	24	**3ab**	88	90:10	86/-
4[d]	**2b**	4-FC_6H_4	Ph	64	**3ab**	66	97:3	90/-
5	**2c**	4-ClC_6H_4	Ph	24	**3ac**	93	88:12	86/-
6	**2d**	4-BrC_6H_4	Ph	24	**3ad**	99	77:23	85/-
7	**2e**	4-$NO_2C_6H_4$	Ph	24	**3ae**	97	87:13	90/-
8	**2f**	4-$MeOC_6H_4$	Ph	72	**3af**	80	71:29	69/-
9	**2g**	2-furanyl	Ph	45	**3ag**	78	79:21	94/52
10	**2h**	3-furanyl	Ph	45	**3ah**	66	84:16	85/60
11	**2i**	Me	Ph	24	**3ai**	98	88:12	75/54
12	**2j**	*t*-Bu	Ph	64	**3aj**	-[e]	-	-
13	**2k**	Ph	4-FC_6H_4	24	**3ak**	67	88:12	86/55
14	**2l**	Ph	4-ClC_6H_4	24	**3al**	80	84:16	80/46
15	**2m**	Ph	4-$NO_2C_6H_4$	24	**3am**	84	80:20	82/49
16	**2n**	Ph	4-$MeOC_6H_4$	24	**3an**	86	71:29	80/42
17	**2o**	Ph	2-FC_6H_4	24	**3ao**	84	76:24	82/28
18	**2p**	Ph	3-$NO_2C_6H_4$	24	**3ap**	99	82:18	84/48

[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.125 mmol), **pyBOX1** (0.0125 mmol), La(OTf)$_3$ (0.0125 mmol), 4Å MS (20 mg), CH_2Cl_2 (0.8 mL), rt. [b] Yield of isolated product. [c] Determined by HPLC with chiral stationary phases. [d] Reaction carried out at 0 °C. [e] No reaction was observed after 64 h.

4.1.4 Determination of the absolute stereochemistry of compound 3aa

The absolute stereochemistry of compound **3aa** was established by chemical correlation with compound **4** of known stereochemistry. A sample of compound (*E*)-**3a** (ee = 82% ee) was hydrolyzed upon treatment with HCl in THF at 40 °C to give ketone **4** in quantitative yield without loss of optical purity (Scheme 126). By comparison of the optical rotation sign and chiral HPLC retention times of compound **4** obtained in this way with those described in the literature for (*S*)-**4**,[157] we established the configuration of the stereogenic center of (*E*)-**3aa** (Table 3, entry 1) to be *S*. Hydrolysis of the minor (*Z*)-**3aa** diastereomer provided again (*S*)-**4** but with only 20% ee. For the other compounds **3ab-ap**, the stereochemistry was assigned upon the assumption of a common stereochemical mechanism.



Scheme 126. Hydrolysis and determination of the absolute stereochemistry of compound (*E*)-**3aa**

These results indicate the preference of methyl malonate to attack from the *Re* face of the double bond of the unsaturated imine **2**. Taking into account previous studies on La(III)-pyBOX catalyzed reactions,[155,158] we propose a plausible catalytic cycle with the participation of an octa-coordinated La(III) species **III** with both the 1,3-dicarbonyl compound and the imine coordinated to the metal center (Figure 3).[159] In this complex, the unsaturated imine **2**, in its s-*trans* conformation would be oriented to avoid the steric interaction with the phenyl group of the ligand, thus leading to the conjugate addition product **3** having the *S*-configuration at the stereogenic center and the *E*-geometry at the double bond.

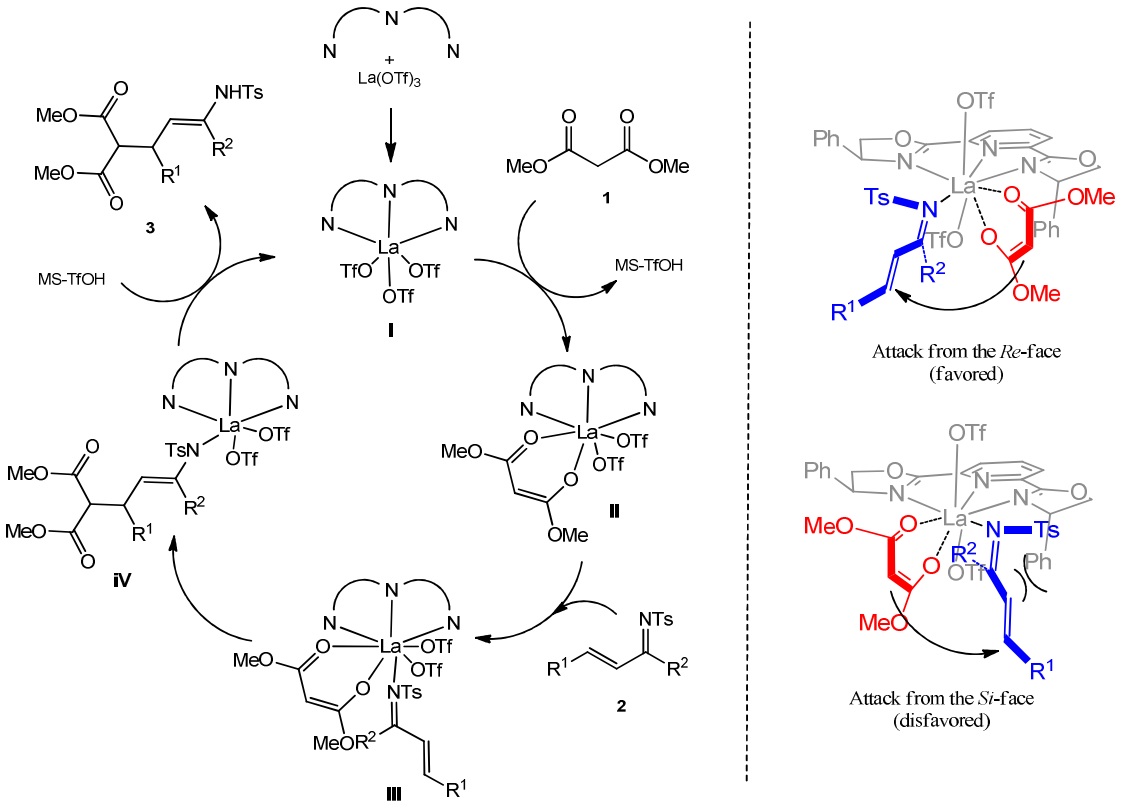
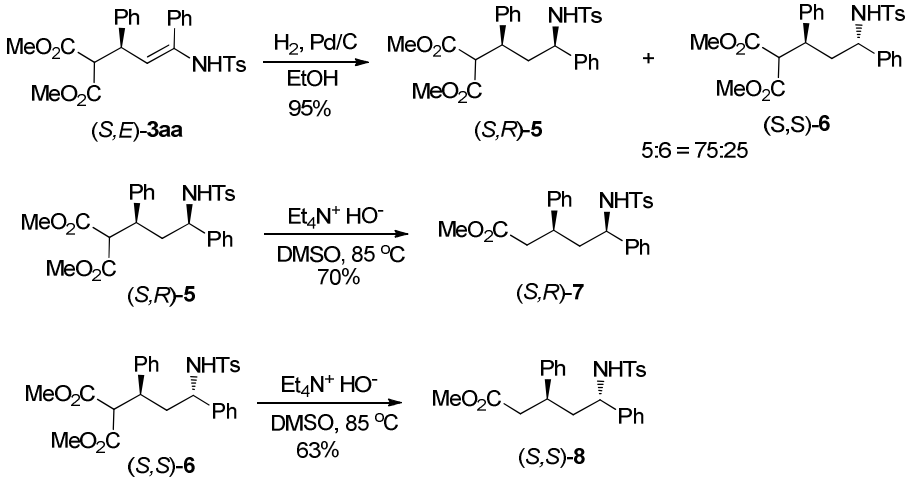


Figure 3. Plausible mechanism and stereochemical model

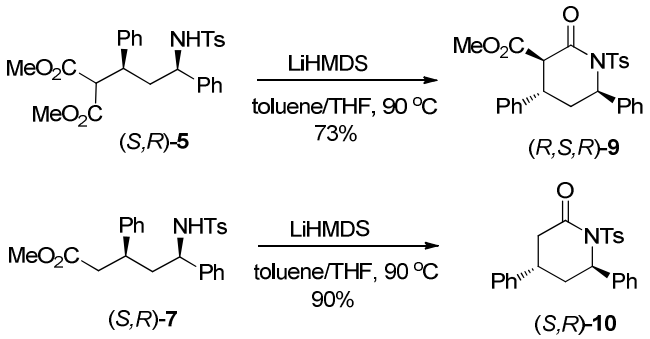
4.1.5 Synthetic transformations

Enamines **3** can be used as starting materials for the synthesis of optically active nitrogenated compounds such as δ-amino esters and piperidones. Thus, hydrogenation of (*S*,*E*)-**3aa** over Pd/C gave a 75:25 mixture of two diastereomeric δ-amino diesters **5** and **6** in 95% yield, favoring the (*S*,*R*)-diastereomer **5**. Both diastereomers **5** and **6** could be separated after column chromatography and subjected to chemical transformations separately. Decarboxylation of either **5** or **6** upon treatment with tetraethylammonium hydroxide[160] in DMSO gave the monoesters **7** and **8** in 70% and 60% yield, respectively (Scheme 127).



Scheme 127. Hydrogenation and decarboxylation of compound **3aa**

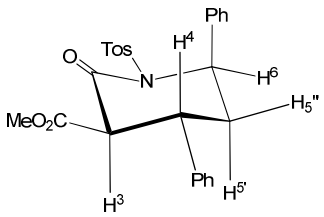
On the other hand, lactamization of compounds **5** and **7** by basic treatment with LiHMDS in toluene[161] gave the chiral piperidones **9** and **10**, respectively (Scheme 128).



Scheme 128. Synthesis of chiral piperidones **9** and **10**

The relative stereochemistry of compound **9**, was established considering the coupling constants of the ring-attached protons (Figure 4). The signal corresponding to H3 appeared at 3.72 ppm as a doublet with a J = 12.0 Hz (ax-ax), indicating its axial disposition as well as that of H4. Moreover H6 appeared as a dd at 5.90 ppm showing coupling constant values of 5.1 Hz (ax-ax) and 2.4 Hz (eq-eq) which indicated the equatorial disposition of this proton. Accordingly, the stereochemistry of compound **9**

was assigned to be 3*R*,4*S*,6*R*. Hence, the stereochemistry of compounds **5**-**10** was assigned as indicated in Schemes 126 and 127.



H^3	δ = 3.72 (d)	J_{3-4} = 12.0 Hz (ax-ax)
H^4	δ = 3.50 (td)	J_{3-4} = 12.0 Hz (ax-ax), $J_{4-5'}$=12.0 Hz (ax-ax), $J_{4-5''}$=3.0 Hz (ax-eq)
$H^{5'}$	δ = 2.59 (td)	$J_{5'-5''}$ = 13.5 Hz (gem), $J_{4-5'}$=12.0 Hz (ax-ax), $J_{5'-6}$=5.4 Hz (ax-eq)
$H^{5''}$	δ = 2.21 (dt)	$J_{5'-5''}$ = 13.5 Hz (gem), $J_{4-5''}$=3.0 Hz (ax-eq), $J_{5''-6}$=2.5 Hz (eq-eq)
H^6	δ = 5.90 (dd)	$J_{5',6}$ = 5.1 Hz (ax-ax), $J_{5''-6}$=2.4 Hz (eq-eq)

Figure 4. NMR coupling constants in compound **9**

In summary, in this chapter we have developed the first enantioselective conjugate addition of dimethyl malonate to α,β-unsaturated *N*-tosyl imines, catalyzed by La(III)-pyBOX complexes, to give the corresponding γ-dehydro-δ-amino diesters bearing a stereogenic center at the allylic position. The reaction provided the (*E*)-enamine as the major diastereomer with good yields and enantioselectivities. The enamino esters were shown to be effective synthons for the preparation of optically active δ-amino esters bearing two stereogenic centers at the β and δ positions, and for the preparation of optically active lactams.

4.2. Enantioselective Michael addition of malonate esters to β-trifluoromethyl-α,β-unsaturated imines

The interest in the chemistry of chiral organofluorine compounds has experienced a tremendous growth in the last years due to their wide range of applications in medicinal and agricultural chemistry, as well as in material science.[162] Among organofluorinated compounds, those having a trifluoromethyl group attached to a stereogenic center deserve special attention due to the occurrence of this structural motif in bioactive compounds[163] and chiral reagents (Figure 5).[164]

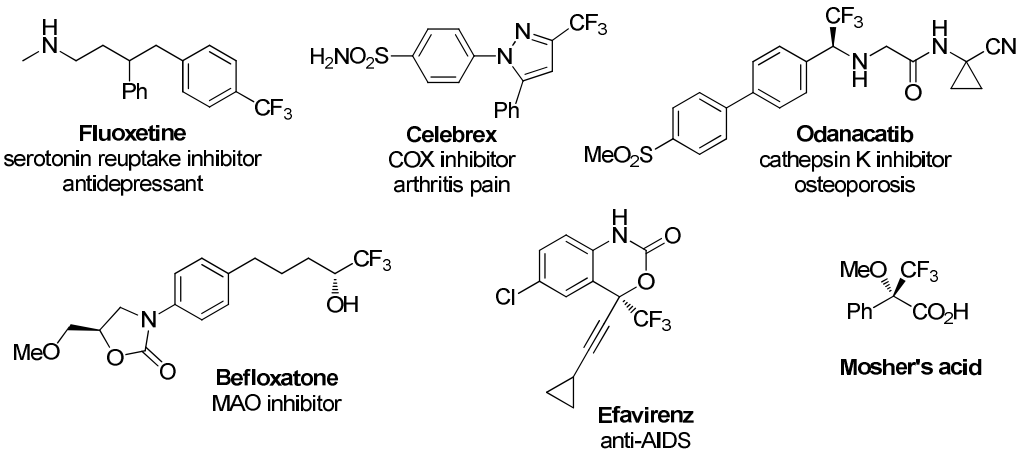
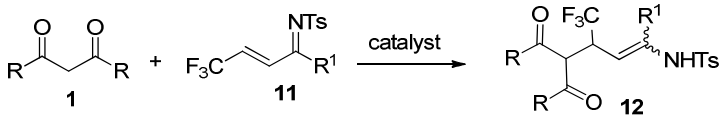


Figure 5. Examples of drugs and chiral auxiliaries bearing a trifluoromethyl group

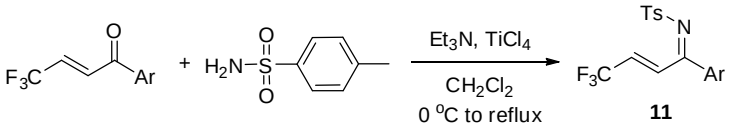
These stereocenters are most frequently prepared by nucleophilic addition reactions to trifluoromethylated prostereogenic groups such as trifluoromethyl ketones and trifluoromethyl imines.[165] In this context, several carbon nucleophiles have been also reported to undergo enantioselective Michael-type reactions with β-trifluoromethyl α,β-unsaturated carbonyl compounds[166] or with nitroalkenes[167] to obtain compounds with a trifluoromethylated sterogenic center not connected to a heteroatom. However, no examples of enantioselective conjugate addition of carbon nucleophiles to β-trifluoromethyl α,β-unsaturated imines have been reported previously, to the best of our knowledge. Considering this, and keeping in mind the importance of fluorine-containing amino acids in medicinal chemistry,[168] we decided to study the enantioselective conjugate addition of malonate esters to β-trifluoromethyl α,β-unsaturated *N*-tosyl imines as an efficient procedure to access to chiral β-trifluoromethyl-δ-amino acid derivatives, a reaction that has no precedents in the literature (Scheme 129).



Scheme 129. Conjugate addition of malonate esters to β-trifluoromethyl α,β-unsaturated *N*-tosyl imines

4.2.1. Synthesis of β-trifluoromethyl α,β-unsaturated *N*-tosyl imines 11

The imines to be used in this study **11a-l** were synthesized by condensation of the corresponding (*Z*)-β-trifluoromethyl enones and *p*-toluenesulfonamide in the presence of $TiCl_4$ and Et_3N, following the procedure described by A. D. Smith.[103] Imines **11**, specially those containing nitro groups, were sensitive to hydrolysis by silica gel and their purification was difficult. In most of the cases, after a fast column chromatography, further purification by crystallization from hexane-EtOAc or Et_2O-EtOAc was required giving rise to moderate or low yields. Following this procedure we were able to prepare a set of twelve imines having an aromatic ring with different substitution and electronic character attached to the azomethinic carbon, with yields ranging from 24-74% (Scheme 130). Again, the preparation of unsaturated imines **11** having an aliphatic (Me) group attached to the imine carbon was not possible due to enolization of the *N*-sulfonyl imine.



11a, Ar = Ph
11b, Ar = 4-MeC_6H_4
11c, Ar = 4-ClC_6H_4
11d, Ar = 4-BrC6H4
11e, Ar = 4-$NO_2C_6H_4$
11f, Ar = 4-$MeOC_6H_4$
11g, Ar = 3-MeC_6H_4
11h, Ar = 3-ClC6H4
11i, Ar = 3-$NO_2C_6H_4$
11j, Ar = 3-$MeOC_6H_4$
11k, Ar = 2-$MeOC_6H_4$
11l, Ar = 2-naphthyl

Scheme 130. Synthesis and structure of β-trifluoromethyl α,β-unsaturated *N*-sulfonyl imines **11**

Imines **11** were obtained as only one C=N geometric isomer. It was possible to obtain a monocrystal of imine **11a** suitable for X-ray analysis (CCDC 1535016) that showed the *E,E* geometry for the C-C and C-N double bonds in this compound (Figure 6).

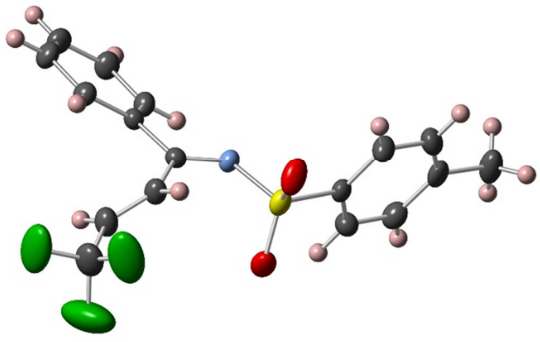
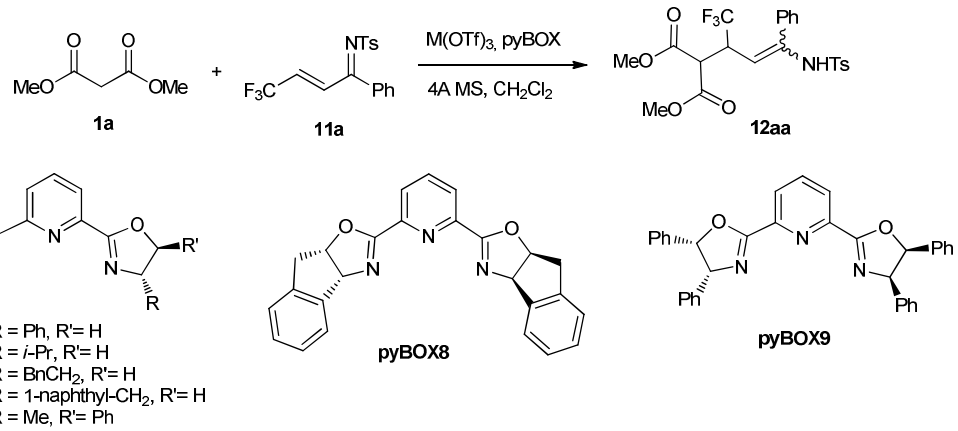


Figure 6. Ortep plot for the X-ray structure of compound **11a**. The thermal ellipsoids are drawn at the 50% probability level

4.2.2. Optimization of the reaction conditions with copper(II) triflate

The reaction between dimethyl malonate **1a** and the imine **11a** was firstly attempted by using pyBOX-La(OTf)$_3$ complexes as in our previous reaction with tosyl imines derived from chalcone (Section 4.1). However, when this catalytic system was applied, the expected Michael addition product **12aa** was obtained with good yields but low enantioselectivities (Table 4). Other pyBOX complexes with trivalent metal triflates such as Yb(OTf)$_3$, Sc(OTf)$_3$ or In(OTf)$_3$ performed similarly or even worse than La(OTf)$_3$.

Table 4. Enantioselective conjugate addition of dimethyl malonate **1a** to imine **11a** catalyzed by pyBOX-M(III) complexes.[a]

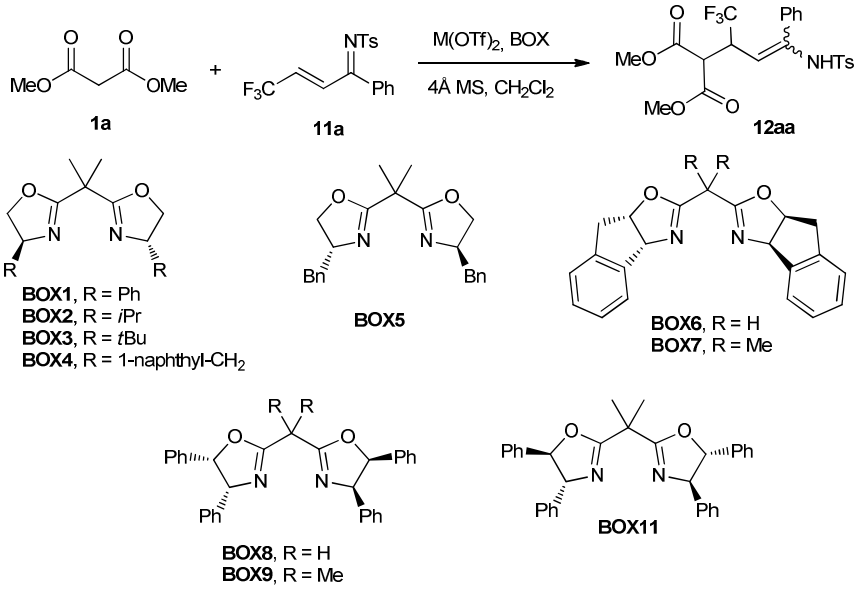


entry	M(OTf)$_3$	pyBOX	*t* (h)	yield (%)[b]	dr (*E*/*Z*)	ee (%) (*E*/*Z*)[c]
1	La(OTf)$_3$	**pyBOX1**	16	99	72:28	75/34
2	La(OTf)$_3$	**pyBOX2**	43	99	78:23	-15/-2
4	La(OTf)$_3$	**pyBOX4**	40	99	82;18	-18/-9
5	La(OTf)$_3$	**pyBOX5**	40	99	82:18	-28/-11
6	La(OTf)$_3$	**pyBOX6**	37	79	89:11	-16/5
7	La(OTf)$_3$	**pyBOX7**	44	86	73:27	-76/-39
3	La(OTf)$_3$	**pyBOX8**	48	99	77:23	45/-3
8	Sc(OTf)$_3$	**pyBOX1**	96	-[d]	--	--
9	Yb(OTf)$_3$	**pyBOX1**	96	19	43:57	69/42
10	In(OTf)$_3$	**pyBOX1**	96	-[d]	--	--

[a] Reaction conditions: **1a** (0.3 mmol), **11a** (0.125 mmol), ligand (0.0125 mmol), M(OTf)$_3$ (0.0125 mmol), 4Å MS (110 mg), CH_2Cl_2 (1.1 mL), rt. [b] Yield of isolated product. [c] Determined by HPLC with chiral stationary phases. [d] Little advance of the reaction was observed after the indicated time.

The low stereocontrol obtained with pyBOX-trivalent metal complexes led us to test the reaction in the presence of other potential catalysts. First, we tested the reaction in the presence of BOX-Cu(OTf)$_2$ complexes, which are very commonly used chiral Lewis acids (Table 5).[169]

Table 5. Enantioselective conjugate addition of dimethyl malonate **1a** to imine **11a** catalyzed by BOX-M(II) complexes.[a]



entry	M	BOX	*t* (h)	yield (%)[b]	dr (*E*/*Z*)[c]	ee (%) (*E*/*Z*)[d]
1[e]	Cu	**BOX1**	24	-[f]	-	-
2	Cu	**BOX1**	96	60	80:20	-33/35
3	Cu	**BOX2**	96	85	66:34	-85/71
4	Cu	**BOX3**	96	-[f]	-	-
5	Cu	**BOX4**	96	31	70:30	-55/54
6	Cu	**BOX5**	72	77	80:20	67/-41
7	Cu	**BOX6**	96	-[f]	-	-
8	Cu	**BOX7**	72	93	90:10	95/-75
9	Cu	**BOX8**	96	58	36:64	30/-70
10	Cu	**BOX9**	96	92	72:28	-2/-7
11	Cu	**BOX10**	96	47	80:20	-32/25
12[e,g]	Cu	**BOX7**	96	-[h]	-	-
13[g]	Cu	**BOX7**	72	36	47:53	76/-65
14[i]	Cu	**BOX7**	24	23	38:62	4/7
15	Zn	**BOX7**	96	36	92:8	57/-43
16[e]	Mg	**BOX7**	20	99	92:8	86/-52
17	Ca	**BOX7**	96	81	84:16	69/-49

[a] Reaction conditions: **1a** (0.3 mmol), **11a** (0.125 mmol), **BOX** (0.0125 mmol), $M(OTf)_2$ (0.0125 mmol), 4Å MS (110 mg), CH_2Cl_2 (1.1 mL). [b] Yield of isolated product. [c] Determined by ^1H NMR. [d] Determined by HPLC with chiral stationary phases; opposite sign within a same diastereomer indicates opposite enantiomers. [e] MS was not used. [f] Little advance of the reaction was observed after the indicated time. [g] Et_3N (0.016 mmol). [h] Hydrolysis of the imine was observed. [i] Et_3N (0.3 mmol).

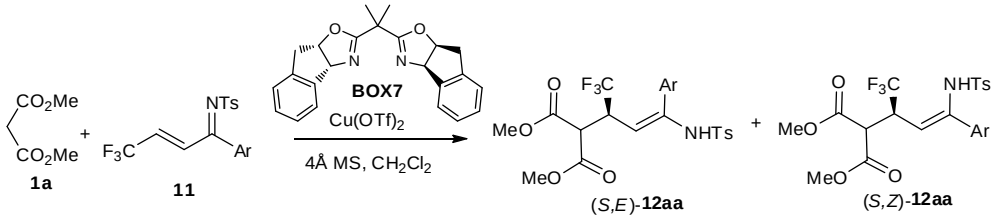
All the BOX ligands with the exception of **BOX8** favored the formation of the *E*-enamine. Indene-derived bis-oxazoline (**BOX7**) lead to the best results in terms of yield and stereoselectivity providing enamine **12aa** in 93% yield, as a *ca.* 90:10 mixture of *E/Z*-diastereomers and 95% ee for the major *E*-diastereomer, after 96 hours (Table 5, entry 8). Addition of a catalytic amount of triethylamine in an attempt to speed up the reaction brought about a decrease in the yield due to hydrolysis of the imine, as well as an erosion in the stereoselectivity, which could not be avoided even in the presence of MS (Table 5, entries 12 and 13). Addition of one equivalent of triethylamine produced an inversion in diastereoselectivity, the *Z*-isomer being obtained as the major one in almost racemic form (Table 5, entry 14).

We also tested the reaction in the presence of the **BOX7** complexes with Zn(II), Mg(II) and Ca(II) triflates. The reaction with the Zn(II) complex proceeded sluggishly and gave compound **12aa** in only 36% yield after 96 hour (Table 5, entry 15). On the other hand, in the presence of the Ca(II) complex compound **12aa** was obtained with good yield (81%), fair diastereo- and poor enantioselectivity after 96 h (Table 5, entry 17). Remarkably, the reaction in the presence of **BOX7**-$Mg(OTf)_2$ proceeded fast in absence of MS and was completed after only 20 hours producing compound **12aa** in quantitative yield with good diastereoselectivity (*E:Z* = 92:8) although with a slighly lower enantiomeric excess (Table 5, entry 16) than the obtained with the **BOX7**-Cu(II) catalyst.

4.2.3. Scope of the reaction catalyzed by the BOX7-$Cu(OTf)_2$ catalyst

The conditions established in Table 5, entry 8, were applied to the β-trifluoromethyl-α,β-unsaturated *N*-tosyl imines **11a-l** previously synthesized, all of them having an aromatic ring attached to the imine carbon. The results are gathered in Table 6. The reaction could be carried out with imines bearing an aromatic ring attached to the imine carbon substituted with either electron-donating or electron-withdrawing groups. Good to excellent yields of compounds **12** were obtained in almost all the cases except when the phenyl group is substituted with a strong electron donating group (MeO) at the *ortho* or *para* positions (Table 6, entries 6 and 11). However, this drawback is not found when this group is in *meta* position (Table 6, entry 10). A bulky 2-naphthyl group attached to the azomethinic carbon was also tolerated (Table 6, entry 12). Compounds **12a-l** were obtained with fair to good diastereoselectivities (from 60:40 to 90:10) favoring the *E*-diastereomer and with high enantiomeric excesses (from 83% to 97% ee for the major *E*-diastereomer) regardless of the electronic character of the substituent on the aromatic ring, although *para*-substituted rings gave slightly higher enantioselectivities (Table 6, entries 2-6).

Table 6. Enantioselective conjugate addition of dimethyl malonate (**1a**) to β-trifluoromethyl-α,β-unsaturated *N*-tosyl imines **11** catalyzed by **BOX7**-Cu(OTf)$_2$.[a]



entry	11	Ar	*t* (h)	12	yield (%)[b]	dr (*E*/*Z*)[c]	ee (%) (*E*/*Z*)[d]
1	**11a**	Ph	68	**12aa**	93	90:10	95/75
2	**11b**	4-MeC_6H_4	89	**12ab**	86	89:11	94/40
3	**11c**	4-ClC_6H_4	112	**12ac**	82	87:13	97/32
4	**11d**	4-BrC_6H_4	89	**12ad**	75	89:11	95/43
5	**11e**	4-$NO_2C_6H_4$	89	**12ae**	86	74:26	90/54
6	**11f**	4-MeOC_6H_4	112	**12af**	34	84:16	94/56
7	**11g**	3-MeC_6H_4	136	**12ag**	97	87:13	94/41
8	**11h**	3-ClC_6H_4	89	**12ah**	86	82:18	91/49
9	**11i**	3-$NO_2C_6H_4$	64	**12ai**	94	60:40	83/58
10	**11j**	3-MeOC_6H_4	89	**12aj**	87	83:17	87/82
11	**11k**	2-MeOC_6H_4	112	**12ak**	23	72:28	89/17
12	**11l**	2-naphthyl	112	**12al**	60	87:13	93/27

[a] **1a** (0.3 mmol), **11** (0.125 mmol), **BOX7** (0.0125 mmol), Cu(OTf)$_2$ (0.0125 mmol), 4Å MS (110 mg), CH_2Cl_2 (1.1 mL), rt. [b] Yield of isolated product. [c] Determined by ^{1}H NMR. [d] Determined by HPLC with chiral stationary phases.

4.2.4. Determination of the absolute stereochemistry of compound 12aa

Compound **12aa** obtained in the presence of the **BOX7**-Cu(OTf)$_2$ ligand could be crystallized (CCDC 1535017) and subjected to X-ray analysis (Figure 7).

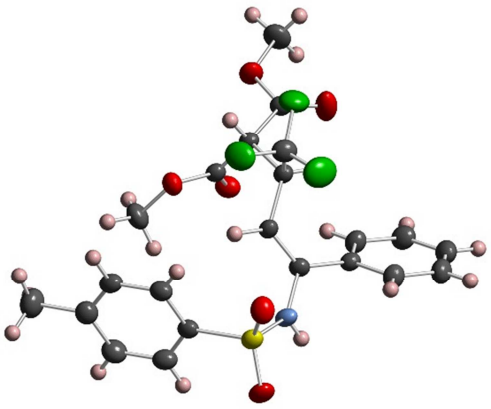


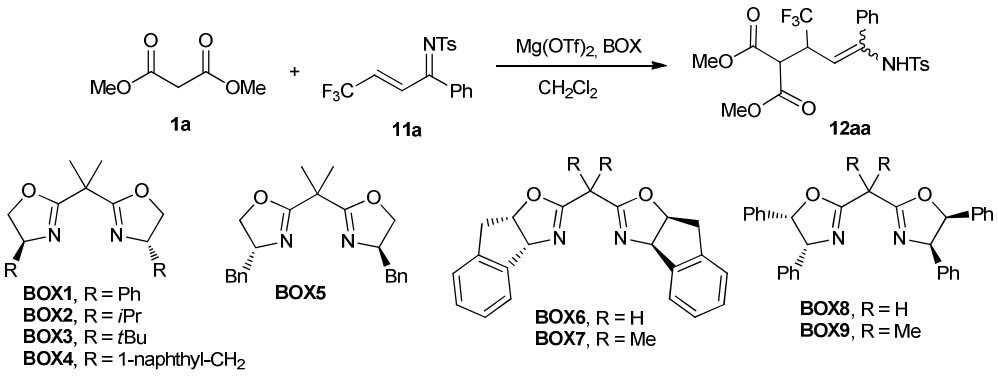
Figure 7. Ortep plot for the X-ray structure of compound **12aa**. The thermal ellipsoids are drawn at the 50% probability level. Flack parameter-0.01(3)

From this analysis it could be established the configuration of the stereogenic center as *S*, and also confirmed the *E*-geometry of the enamine double bond in the major diastereomer, similarly as in the major product obtained in the addition of malonate esters to imines derived from chalcone under La(III) catalysis. The stereochemistry of all compounds **12** was assigned by analogy.

4.2.5. Optimization of the reaction conditions with magnesium(II) triflate

As indicated previously in section 4.2.2., the **BOX7**-$Mg(OTf)_2$ complex showed high catalytic activity in the reaction between dimethyl malonate (**1a**) and imine **11aa** (Table 5, entry16). Accordingly, we decided to study the application of magnesium(II)-BOX complexes in the conjugate addition of dialkyl malonates to β-trifluoromethyl α,β-unsaturated *N*-tosyl imines. Further optimization of the reaction conditions was achieved by testing $Mg(OTf)_2$ in combination with several BOX complexes (Table 7).

Table 7. Enantioselective conjugate addition of dimethyl malonate **1a** to imine **11a** catalyzed by BOX-$Mg(OTf)_2$ complexes.[a]



entry	BOX	*T* (°C)	*t* (h)	yield (%)[b]	dr (*E*/*Z*)[c]	ee (%) (*E*/*Z*)[d]
1	**BOX1**	rt	20	82	92:8	51/44
2	**BOX2**	rt	15	99	88:12	-74/66
3	**BOX3**	rt	46	40	65:35	0/0
4	**BOX4**	rt	20	99	92:8	-29/18
5	**BOX5**	rt	15	92	90:10	55/-39
6	**BOX6**	rt	16	96	95:5	85/-44
7	**BOX7**	rt	20	99	92:8	86/-52
8	**BOX8**	rt	5	99	91:9	68/-57
9	**BOX9**	rt	50	63	91:9	59/-38
10[e]	**BOX7**	0	40	99	96:4	89/-75
11[f]	**BOX7**	0	16	98	96:4	89/-55
12[g]	**BOX7**	0	4d	56	89:11	91/-83
13[e]	**BOX7**	-10	41	93	96:4	91/-49

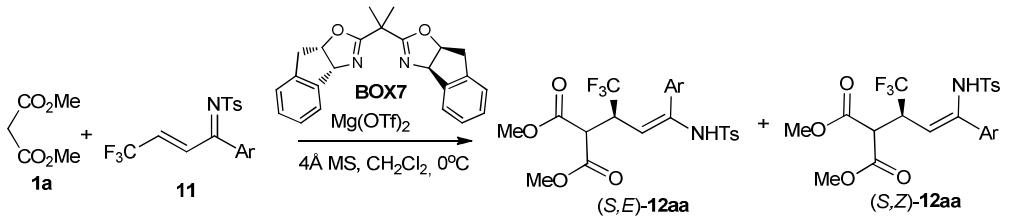
[a] Reaction conditions: **1a** (0.3 mmol), **11a** (0.125 mmol), **BOX** (0.0125 mmol), $Mg(OTf)_2$ (0.0125 mmol), CH_2Cl_2 (1.1 mL). [b] Yield of isolated product. [c] Determined by ^1H NMR. [d] Determined by HPLC with chiral stationary phases; opposite sign within a same diastereomer indicates opposite enantiomers. [e] 4 Å MS was used. [f] 3 Å MS was used . [g] 5 Å MS was used.

Unfortunately, none of the BOX ligands tested improved the enantioselectivity of the reaction (Table 7, entries 1-9). Only ligand **BOX6** provided compound **12aa** with similar diastereo- and enantioselectivity as **BOX7**. A decrease of temperature to 0 °C almost completely stopped the reaction, which required the addition of 4 Å MS to proceed. In this way (Table 7, entry 10), compound **12aa** was obtained with slightly improved enantiomeric excess (89%) and diastereomeric ratio (96:4). 3 Å MS led to similar results (Table 7, entry11). On the other hand, the reaction in the presence of 5 Å MS was notably slower and, although a slight increase of ee (91%), was observed, product **12aa** was obtained with low yield and poorer dr (Table 7, entry 12). We tried further optimization in the presence of 4 Å MS. Thus, performing the reaction at -10 °C gave compound **12aa** in 96:4 dr and 91% ee for the major diastereomer (Table 7, entry 13). Other solvents ($CHCl_3$, DCE, THF, acetonitrile, toluene or *i*PrOH) were tested but none of them improved the results obtained in dichloromethane.

4.2.6. Scope of the reaction catalyzed by the BOX7-Mg(OTf)$_2$ catalyst

Although performing the reaction at -10 °C allowed to increase the ee in the case of compound **12aa**, reactions carried out with other imines proved this was not a general trend, no improvement being observed in many cases after decreasing the temperature from 0 °C to -10 °C. Therefore, Table 8 shows the results obtained at 0 °C.

Table 8. Enantioselective conjugate addition of dimethyl malonate (**1a**) to β-trifluoromethyl-α,β-unsaturated *N*-tosyl imines **11** catalyzed by **BOX7**-Mg(OTf)$_2$.[a]



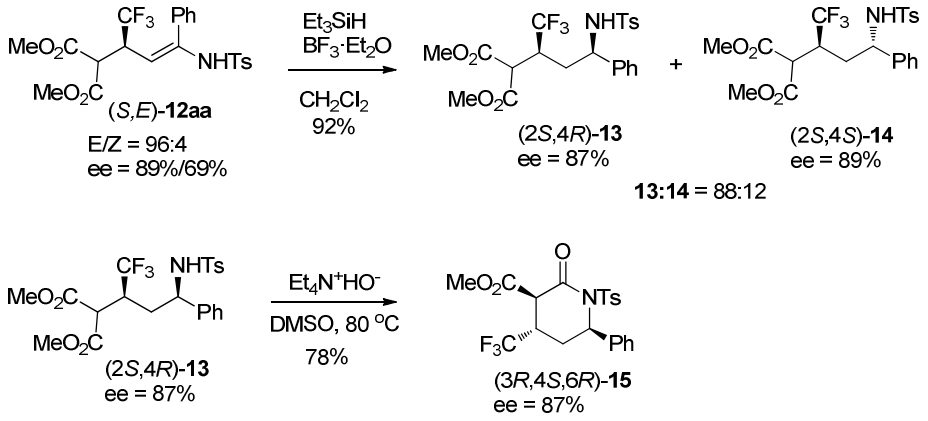
entry	11	Ar	*t* (h)	12	yield (%)[b]	dr (*E*/*Z*)[c]	ee (%) (*E*/*Z*)[d]
1	**11a**	Ph	68	**12aa**	99	96:4	89/75
2	**11b**	4-MeC_6H_4	16	**12ab**	99	95:5	89/61
3	**11c**	4-ClC_6H_4	18	**12ac**	93	95:5	97/63
4	**11d**	4-BrC_6H_4	72	**12ad**	85	95:5	91/43
5	**11e**	4-$NO_2C_6H_4$	17	**12ae**	97	84:16	89/78
6	**11f**	4-MeOC_6H_4	40	**12af**	92	93:7	93/69
7	**11g**	3-MeC_6H_4	16	**12ag**	91	95:5	86/58
8	**11h**	3-ClC_6H_4	19	**12ah**	99	93:7	83/96
9	**11i**	3-$NO_2C_6H_4$	16	**12ai**	97	78:22	79/62
10	**11j**	3-MeOC_6H_4	16	**12aj**	99	93:7	86/62
11	**11k**	2-MeOC_6H_4	72	**12ak**	91	94:6	92/11
12	**11l**	2-naphthyl	20	**12al**	99	94:6	88/49
13[e]	**11a**	Ph	100	**12ba**	94	88:12	85/35

[a] **1a** (0.3 mmol), **11** (0.125 mmol), **BOX7** (0.0125 mmol), Mg(OTf)$_2$ (0.0125 mmol), 4Å MS (110 mg), CH_2Cl_2 (1.1 mL), 0 ºC. [b] Yield of isolated product. [c] Determined by ^{1}H NMR. [d] Determined by HPLC with chiral stationary phases. [e] reaction carried out with diethyl malonate (**1b**).

In general, the reaction with **BOX7**-$Mg(OTf)_2$ gave compounds **12** with better diastereomeric ratios but slightly lower enantiomeric excesses than the reaction with **BOX7**-$Cu(OTf)_2$. The best enantioselectivities were observed with imines having *para* substitution in the aromatic ring attached to the imine (Table 8, entries 2-6), especially in the cases of a 4-Cl or a 4-MeO substituent. Good diastereomeric *E/Z* ratios above 90:10 were obtained in all the cases except with imines having nitrophenyl substituents (Table 8, entries 5 and 9). The reaction of diethyl malonate and imine **11a** was also carried out to give compound **12ba** with good dr and ee (Table 8, entry 13), although these results were inferior to those obtained with dimethyl malonate. Finally, diisopropyl malonate did not react with **11a** under the optimized conditions.

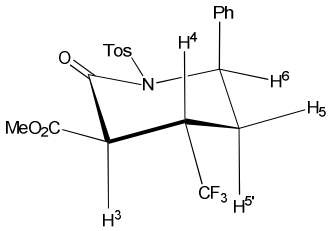
4.2.7. Synthetic transformations

Some transformations on compound **12aa** that show the potential application of enamines **12** in the synthesis of optically active trifluoromethyl-containing nitrogenated compounds are displayed in Scheme 131. For instance, reduction of compound **12aa** could be efficiently achieved by treatment with triethylsilane in the presence of boron trifluoride to give δ-amino esters **13** and **14** in 92% yield with good diastereoselectivity (dr 88:12) and without noticeable erosion in the ee. On the other hand, treatment of compound **13** with triethylammonium hydroxide in DMSO brought about cyclization instead of decarboxylation giving the trifluoromethylated piperidone **5a** with good yield.



Scheme 131. Synthetic transformations of compound **12aa**

As in the case of compound **9** (section 4.1.5), the relative stereochemistry of compound **15**, and hence, of its precursor **13**, was established considering the coupling constants of the ring-attached protons (Figure 8). In particular the proton in α to the carbonyl group appeared as a doublet with J = 11.4 Hz (ax-ax) indicating its axial disposition, while the proton in α to the phenyl group appeared as a triplet with J = 3.8 Hz characteristic of a proton in equatorial disposition.



H6 5.93 ppm (t) $J_{6,5}$ = 3.8 Hz (eq-eq), $J_{6,5'}$ = 3.8 Hz (eq-ax)
H3 3.65 ppm (d) $J_{3,4}$ =11.4 Hz (ax-ax),

Figure 8. Significative coupling constants in compound **15**

In summary, in this chapter we have developed the first enantioselective conjugate addition of malonates to β-trifluoromethyl α,β-unsaturated *N*-tosyl imines to give the corresponding γ-dehydro-δ-amino esters bearing a trifluoromethylated stereogenic center at the allylic position. The reaction can be catalyzed either by BOX-Cu(II) and BOX-Mg(II) complexes. Both catalysts provided the *E*-enamine as the major diastereomer with good yields, fair to good diastereoselectivities and good to excellent enantioselectivities. In general, best enantioselectivities were obtained with the copper catalyst while the magnesium complex favored higher diastereoselectivities. The enamino esters have been proved to be effective synthons for the preparation of optically active β-trifluoromethyl δ-amino esters and optically active trifluoromethyl piperidones.

4.3. Mukaiyama-Michael addition to *N*-tosyl imines derived from β,γ-unsaturated α-keto esters: *E,Z*-stereodivergent synthesis of α,β-dehydroamino esters

α,β-Dehydroamino acid derivatives are non-proteinogenic amino acids that are often found as structural subunits in natural products produced by bacteria, fungi, marine organisms and plants, and play an important role in the biosynthesis of other non-proteinogenic amino acids and $_D$-amino acids (Figure 9).[170]

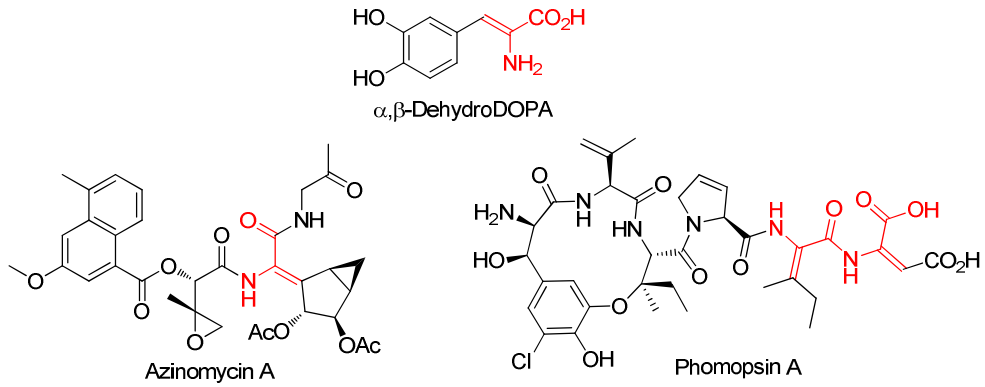
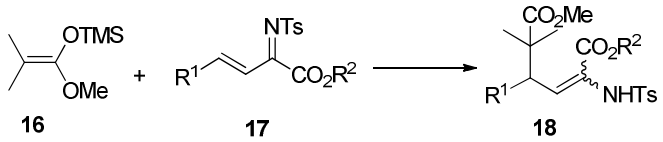


Figure 9. Examples of natural and bioactive α,β-dehydroamino acid derivatives

Some of these compounds have shown antibiotic and other intriguing biological activities.[171] The presence of the double bond in the dehydroamino acid residue reduces the conformational flexibility of peptides, a property that is useful for structure-activity studies and for the design of secondary structure in peptides,[172] and it also confers resistance to enzymatic degradation and alters their bioactivity.[173] These properties are affected by the *E*/*Z* configuration of the double bond of the dehydroamino acid moiety.[174] Furthermore, α,β-dehydroamino acid derivatives are widely used as starting materials in the synthesis of natural and unnatural α-amino acids as well as in the synthesis of heterocyclic compounds.[175] According to these pharmacological and synthetic potential, much synthetic effort has been devoted to the preparation of dehydroamino acids and their derivatives.[170] In most of the reported procedures the thermodynamically stable *Z*-isomer is predominantly formed while the synthesis of the *E*-isomer normally takes place with lower selectivity or requires the use of stereoisomerically pure starting materials that are usually prepared in multistep sequences or involves difficult isomer separation.

On the other hand, the conjugate addition of different nucleophiles to β,γ-unsaturated α-keto esters has been applied as a new strategy in the synthesis of α,β-dehydroamino esters by the groups of Palacios,[23,24] Liu[10] and Kim.[28] In all these cases the reaction takes place stereoselectively to give the corresponding dehydroamino esters with the *Z*-configuration at the double bond. Therefore, the development of synthetic procedures based on this approach that could lead stereoselectively to the either *E* or *Z* dehydroamino esters starting from a same set of reactants would represent an important advance in the synthesis of this kind of compounds.

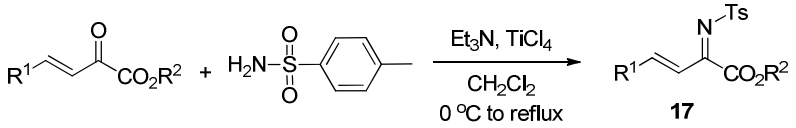
In this chapter we report the development of new procedures for the *E*/*Z* stereodivergent synthesis of α,β-dehydroamino esters *via* a Mukaiyama-Michael addition of silylketene acetals to *N*-tosyl imines of β,γ-unsaturated α-keto esters (Scheme 132).



Scheme 132. Mukaiyama-Michael reaction with *N*-tosyl imines of β,γ-unsaturated α-keto esters

4.3.1. Synthesis of *N*-tosyl imines 17 derived from β,γ-unsaturated α-keto esters

The imines to be used in this section and in sections 4.4 and 4.5 were synthesized by condensation of the corresponding (*E*)-β,γ-unsaturated α-keto esters and *p*-toluenesulfonamide in the presence of $TiCl_4$ and Et_3N, following the same procedure used in the synthesis of imines **2** as described by Carretero.[22] Following this procedure a number of differently substituted imines **17a-o** were prepared in 36-76% yield from the corresponding unsaturated keto esters (Scheme 133).



17a, R^1= Ph, R^2 = Et
17b, R^1= 4-MeC_6H_4, R^2 = Et
17c, R^1= 4-ClC_6H_4, R^2 = Et
17d, R^1= 4-$NO_2C_6H_4$, R^2 = Et
17e, R^1= 4-$MeOC_6H_4$, R^2 = Et
17f, R^1= 3-ClC_6H_4, R^2 = Et
17g, R^1= 3-$NO_2C_6H_4$, R^2 = Et
17h, R^1= 3-$MeOC_6H_4$, R^2 = Et
17i, R^1= 2-ClC_6H_4, R^2 = Et
17j, R^1= 2-$NO_2C_6H_4$, R^2 = Et
17k, R^1= 2-$MeOC_6H_4$, R^2 = Et
17l, R^1= 2-furanyl, R^2 = Et
17m, R^1= 2-thiophenyl, R^2 = Et
17n, R^1= Ph, R^2 = Me
17o, R^1= Ph, R^2 = *i*Pr

Scheme 133. Synthesis and structure of *N*-tosyl imines **17** derived from β,γ-unsaturated α-keto esters

Imines **17** were obtained as only one diastereomer. X-ray analysis of imine 1**7b** (CCDC 1442206) indicated the *Z*-geometry of the C=N in these imines, unlike in imines **11** where the C=N bond geometry was *E*. The X-ray analysis also showed the preference for the s-*trans* conformation in the crystal structure (Figure 10).

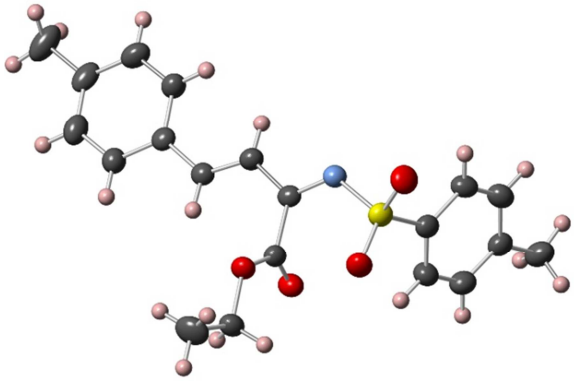


Figure 10. Ortep plot for the X-ray structure of compound **17b**. The thermal ellipsoids are drawn at the 50% probability level

4.3.2. *E/Z*-stereodivergent Mukaiyama-Michael reaction with imines 17

Our initial goal was to develop an enantioselective Mukaiyama-Michael reaction of silylketene acetals with *N*-tosyl imines derived from β,γ-unsaturated α-keto esters. We expected that the 1,2-imino carbonyl moiety would act as a chelating scaffold or as a double hydrogen-bond acceptor, improving the binding of the substrate to the catalyst and expediting the catalytic action by Lewis acid or hydrogen-bonding catalysts.

Accordingly, we tested the reaction between trimethylsilyl ketene acetal **16** and unsaturated imine **17a** (R^1 = Ph, R^2 = Et, Scheme 132) catalyzed by different chiral BOX-Cu$(OTf)_2$ and pyBOX-La$(OTf)_3$ complexes. In all the cases the reaction was completed in 2 h to give compound **18a** with good diastereoselectivity although with low enantiomeric excess (best 31% ee obtained with the **BOX1**-Cu$(OTf)_2$ catalyst). This low enantioselectivity was attributed to a fast nonenantioselective background reaction. In fact, Cu$(OTf)_2$ alone was able to catalyze the reaction to give compound **18a** in 95% yield as a 97:3 *E/Z* mixture of diastereomers after 45 minutes.

In the view of these results we attempted the reaction in the presence of several hydrogen-bonding catalysts (Figure 11).

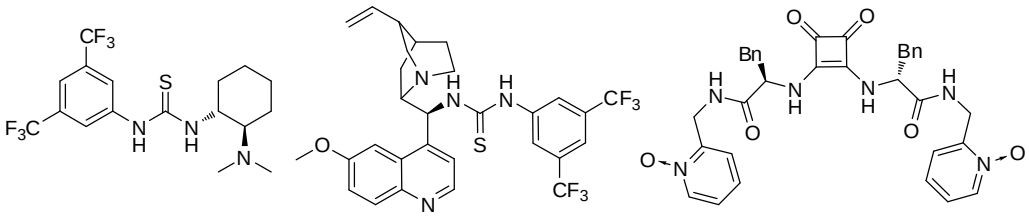


Figure 11. Hydrogen-bonding catalysts tested in the reaction of compounds **16** and **17a**

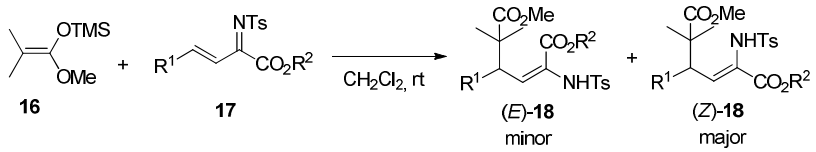
In these cases, the reaction required longer times to be completed and, remarkably, delivered compound **18a** favoring the formation of the *Z*-isomer, although in racemic form. In fact, similar results were obtained when the reaction was carried out in the absence of any catalyst, compound **18a** being obtained as a 9:91 *E/Z* mixture of diastereomers in 84% yield after 20 hours.

Thus, although we were not able to develop an enantioselective method for this Mukaiyama-Michael reaction, the fact that both *E/Z* diastereomers of compound **18** could be selectively prepared from the same set of reagents encouraged us to study the scope of this diastereodivergent reaction.

a) Non-catalyzed Z-selective Mukaiyama-Michael reaction

The reaction between 2-methyl-1-methoxy-1-trimethylsilyoxyprop-1-ene (**16**) and imines **17** was carried out at room temperature in dichloromethane as the solvent (Table 9).

Table 9. Non-catalyzed Mukaiyama Michael addition of trimethylsilyl ketene acetal **16** to *N*-tosyl imines of α-keto esters **17**.[a]



entry	17	Ar	R	18	yield (%)[b]	dr (*E*/*Z*)[c]
1	**17a**	Ph	Et	**18a**	84	9:91
2	**17b**	4-MeC_6H_4	Et	**18b**	77	9:91
6	**17c**	4-ClC_6H_4	Et	**18c**	80	9:91
9	**17d**	4-$NO_2C_6H_4$	Et	**18d**	98	8:92
3	**17e**	4-MeOC_6H_4	Et	**18e**	56	14:86
7	**17f**	3-ClC_6H_4	Et	**18f**	87	11:89
10	**17g**	3-$NO_2C_6H_4$	Et	**18g**	99	10:90
4	**17h**	3-MeOC_6H_4	Et	**18h**	82	11:89
8	**17i**	2-ClC_6H_4	Et	**18i**	95	13:87
11	**17j**	2-$NO_2C_6H_4$	Et	**18j**	58	1:99
5	**17k**	2-MeOC_6H_4	Et	**18k**	72	15:85
12	**17l**	2-furyl	Et	**18l**	69	14:86
13	**17n**	Ph	Me	**18n**	82	11:89
14	**17o**	Ph	*i*Pr	**18o**	75	11:89

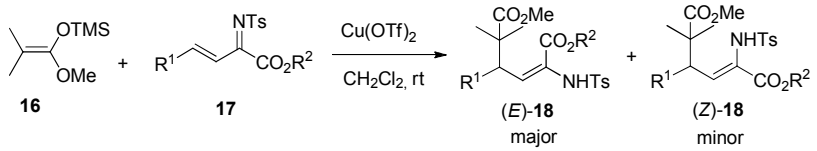
[a] **16** (0.6 mmol), **17** (0.25 mmol), CH_2Cl_2 (1.2 mL), rt, 20-24 h. [b] Yield of the diastereomer mixture after chromatography. [c] Determined by ^{1}H NMR.

The reaction conditions were applied to a number of *N*-tosyl imines derived from ethyl γ-aryl-β,γ-unsaturated α-keto esters **17a-k**, bearing either electron-donating or electron-withdrawing groups at the *ortho*, *metha* or *para* positions of the phenyl ring, and to an heteroaryl-substituted ester **17l**. The reaction provided the expected α,β-dehydroamino esters favoring the formation of the *Z*-isomers (*Z*)-**18a-l** in all the examples studied, with diastereomeric ratios ranging from 85:15 to 99:1 (Table 9, entries 1-12). The methyl and isopropyl esters **17n** and **17o** gave similar results to ethyl ester **17a** (Table 9, entries 12-13).

b) Copper(II)-catalyzed E-selective Mukaiyama-Michael reaction

The *E*-selective reaction was carried out using a 10 mol % load of copper(II) triflate as catalyst in dichloromethane at room temperature. The results are summarized in Table 10.

Table 10. Mukaiyama Michael addition of trimethylsilyl ketene acetal **16** to *N*-tosyl imines of α-keto esters **17** catalyzed by $Cu(OTf)_2$.[a]



entry	17	Ar	R	18	yield (%)[b]	dr (*E*/*Z*)[c]
1	**17a**	Ph	Et	**18a**	95	97:3
2	**17b**	4-MeC_6H_4	Et	**18b**	99	93:7
6	**17c**	4-ClC_6H_4	Et	**18c**	99	94:6
9	**17d**	4-$NO_2C_6H_4$	Et	**18d**	99	92:8
3	**17e**	4-$MeOC_6H_4$	Et	**18e**	95	88:12
7	**17f**	3-ClC_6H_4	Et	**18f**	99	97:3
10	**17g**	3-$NO_2C_6H_4$	Et	**18g**	99	94:6
4	**17h**	3-$MeOC_6H_4$	Et	**18h**	99	96:4
8	**17i**	2-ClC_6H_4	Et	**18i**	99	99:1
11	**17j**	2-$NO_2C_6H_4$	Et	**18j**	99	86:14
5	**17k**	2-$MeOC_6H_4$	Et	**18k**	91	97:3
12	**17l**	2-furyl	Et	**18l**	80	91:9
13	**17n**	Ph	Me	**18n**	99	97:3
14	**17o**	Ph	*i*Pr	**18o**	87	96:4

[a] **16** (0.6 mmol), **17** (0.25 mmol), $Cu(OTf)_2$ (0.025 mmol), CH_2Cl_2 (1.9 mL), rt, 20-90 min. [b] Yield of the diastereomer mixture after chromatography. [c] Determined by ^1H NMR.

When the reaction between silyl ketene acetal **16** and imines **17a-o** was carried out in the presence of 10 mol % copper(II) triflate in dichloromethane at room temperature, a faster reaction took place to give the expected α,β-dehydroamino esters in high yield, favoring in these cases the formation of the *E*-isomers (*E*)-**18a-o** in all the examples studied (Table 10). In general, better yields and diastereoselectivities were observed for the copper-catalyzed reaction compared with the non-catalyzed reaction, with diastereomeric ratios *E/Z* above 90:10 in most of the cases.

4.3.3. Assignment of the stereochemistry of compounds 18

Initial attempts to assign the *E/Z* configuration of the double bond in compounds **18** by ^{1}H NMR following four different spectroscopic criteria established by Mazurkiewicz et al.[176] for related *N*-acyl-α,β-dehydro-α-amino acid esters led to contradictory results (Table 11).

Table 11. Application of ^{1}H NMR spectroscopic *criteria* by Mazurkiewicz et al. to determine the geometry of the double bond in compounds **18**.[176]

	criterion	**δ for *Z*-18a**	**δ for *E*-18a**	**concordance**
1	$\delta_{CH=}{}^{Z}<\delta_{CH=}{}^{E}$	7.31	6.91	-
2	$\delta_{NH}{}^{Z}<\delta_{NH}{}^{E}$	6.16	6.65	+
		$\delta_{CH=}$ ($CDCl_3$) for *Z*-18a	**$\delta_{CH=}$ (TFA) for *Z*-18a**	
3	$\delta_{CH=}{}^{Z}(CDCl_3)<\delta_{CH=}{}^{Z}$ (TFA)	7.31	7.64	+
		$\delta_{CH=}$ ($CDCl_3$) for *E*-18a	**$\delta_{CH=}$ (TFA) for *E*-18a**	
4	$\delta_{CH=}{}^{E}$ ($CDCl_3$)>$\delta_{CH=}{}^{E}$ (TFA)	6.91	7.04	-

Thus, we performed NOESY experiments with samples of products **18** obtained under non-catalytic conditions and under copper catalysis. 4-Nitrophenyl derivatives **18d** were used in these experiments in order to avoid overlapping of ^{1}H NMR signals in the aromatic region. NOESY experiments with compound **18d** (major compound in non-catalytic conditions) showed a small interaction between the NH proton (δ 6.16 ppm) and the benzylic proton (δ 4.69 ppm), which indicated the possible *Z*-geometry for the double bond in this compound. No significative interactions were found however in NOESY experiments with the Cu-catalyzed reaction product (Figure 12).

Furthermore, suitable crystals for X-ray analysis (CCDC 1442362) of compound **18n** (copper-catalyzed reaction) could be obtained which allowed us to unambiguously establish the (*E*)-configuration for the double bond in this compound (Figure 13).

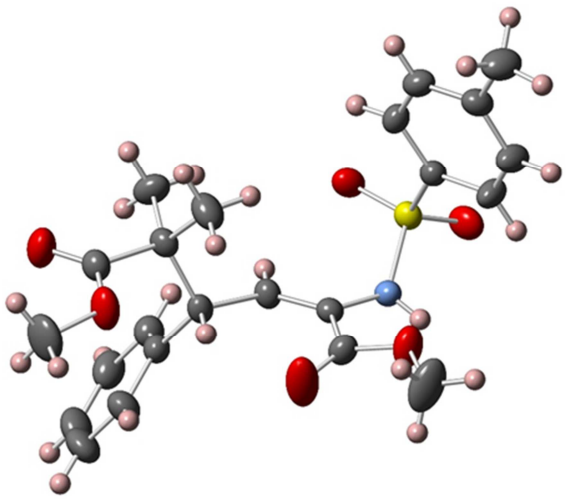


Figure 13. Ortep plot for the X-ray structure of compound **18n** (copper catalyzed reaction). The thermal ellipsoids are drawn at the 50% probability level

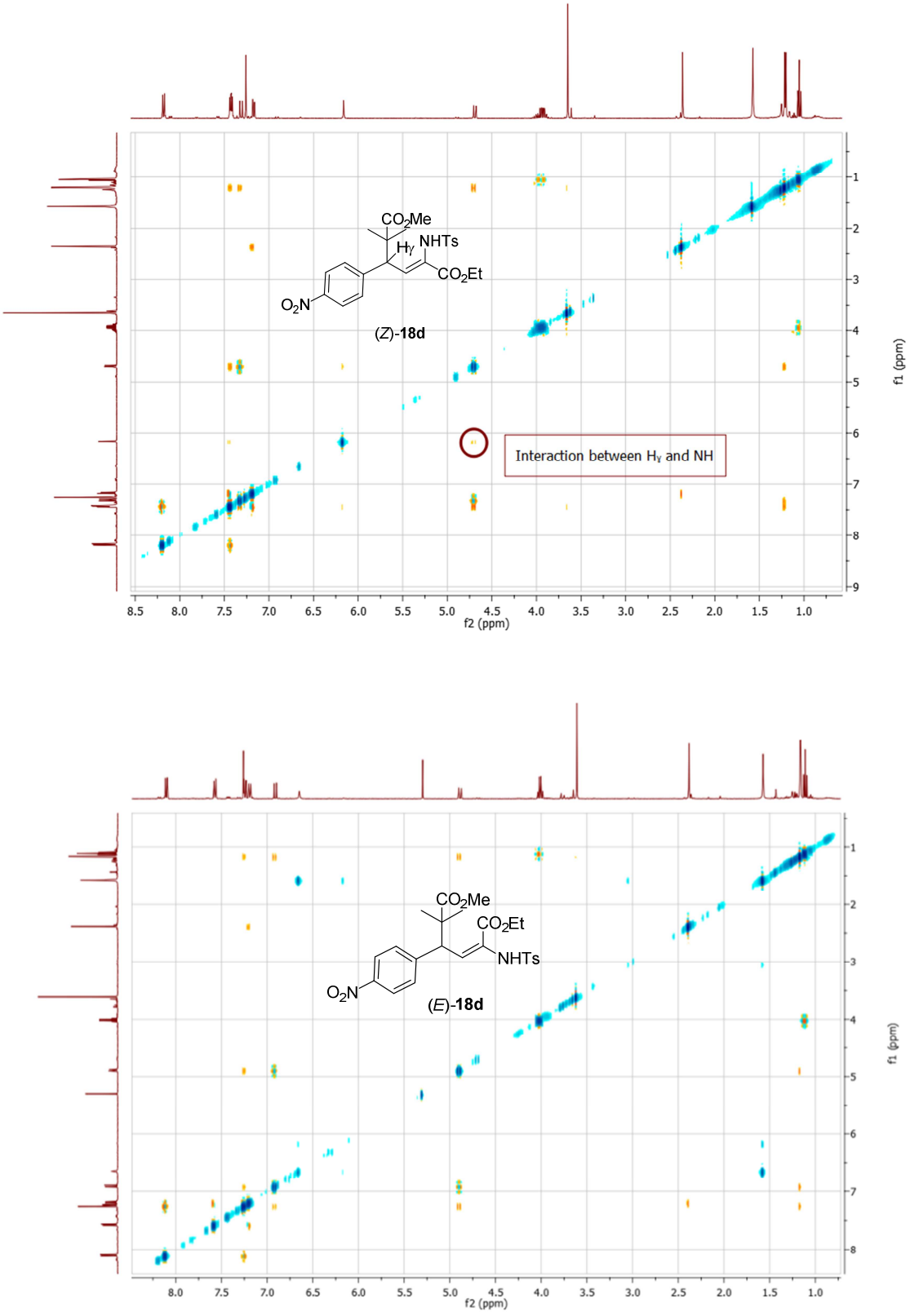


Figure 12. NOESY experiments carried out with compound **18d** obtained under non-catalytic conditions (above) and under $Cu(OTf)_2$ catalysis (below)

On the basis of these results and ^{1}H NMR characteristic chemical shifts (Table 12) we established that all compounds **18** resulting from the non-catalyzed reaction have the *Z*-configuration at the double bond while those obtained through the copper-catalyzed reaction have the *E*-configuration. Thus, in all the cases the olefinic hydrogens appear at higher field for the *E*-isomer ($\delta_{CH=}^{Z} > \delta_{CH=}^{E}$) while the N-H proton appears at higher field for the *Z*-isomer ($\delta_{NH}^{E} > \delta_{NH}^{Z}$). Similarly, the benzylic proton in the β-substituent also appears at higher field for the *Z*-isomer ($\delta_{ArCH}^{E} > \delta_{ArCH}^{Z}$).

Table 12. Comparation of significative ^{1}H NMR chemical shifts for compounds (*Z*)-**18** and (*E*)-**18**.[a]

entry	**18**	Ar	R	δ_{NH} (*Z*)-**18**	δ_{NH} (*E*)-**18**	$\delta_{CH=C}$ (*Z*)-**18**	$\delta_{CH=C}$ (*E*)-**18**	δ_{ArCH} (*Z*)-**18**	δ_{ArCH} (*E*)-**18**
1	**a**	Ph	Et	6.20	6.61	7.31	7.01	4.41	4.81
2	**b**	4-MeC_6H_4	Et	6.14	6.58	7.29	6.97	4.35	4.77
3	**c**	4-MeOC_6H_4	Et	6.18	6.58	7.27	6.96	4.35	4.76
4	**d**	3-MeOC_6H_4	Et	6.18	6.59	7.27	6.97	4.37	4.79
5	**e**	2-MeOC_6H_4	Et	6.19	6.57	7.34	7.06	4.69	5.18
6	**f**	4-ClC_6H_4	Et	6.28	6.62	7.26	6.91	4.46	4.77
7	**g**	3-Cl-C_6H_4	Et	6.30	6.67	7.23	6.89	4.41	4.75
8	**h**	2-Cl -C_6H_4	Et	6.11	6.65	7.35	6.93	5.03	5.35
9	**i**	4-$NO_2C_6H_4$	Et	6.16	6.71	7.31	6.90	4.69	4.88
10	**j**	3-$NO_2C_6H_4$	Et	6.21	6.74	7.29	6.89	4.65	4.88
11	**k**	2-$NO_2C_6H_4$	Et	6.65	6.69	7.03	6.88	4.93	5.42
12	**l**	2-furyl	Et	6.40	6.71	7.04	6.69	4.56	5.04
13	**m**	Ph	Me	6.23	6.57	7.30	7.00	4.35	4.72
14	**n**	Ph	*i*Pr	6.24	6.60	7.29	6.98	4.45	4.86

[a] ^{1}H NMR carried out in $CDCl_3$ at 300 MHz. δ values referenced to residual $CHCl_3$ (δ = 7.26 ppm).

The results indicate that the unsaturated imine **17** adopts the s-*cis* conformation in the non-catalytic reaction while it prefers the s-*trans* conformation during the copper-catalyzed reaction. Although a full explanation for this preference is not possible at this moment, our hypothesis is that the non-catalyzed reaction takes place through a cyclic Diels-Alder-like transition state (Figure 14, TS-1) with the incipient negative charge on the nitrogen atom stabilizing the incipient positive charge at the acetal carbon, which is only possible in the s-*cis* conformation.[59,73] On the other hand, in the presence of copper triflate, coordination of the copper ion to the imine renders the substrate more electrophilic and the reaction takes place through an acyclic transition state (Figure 14, TS-2) with the unsaturated imine having the s-*trans* conformation.

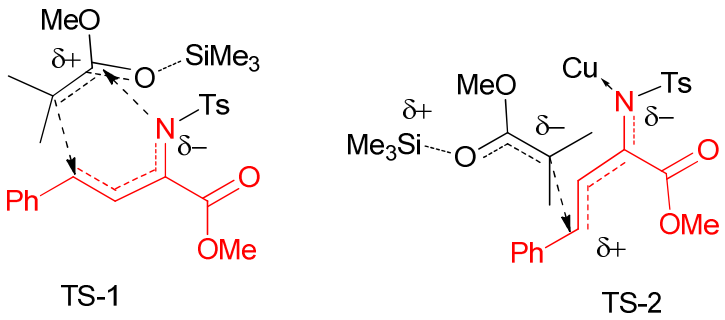


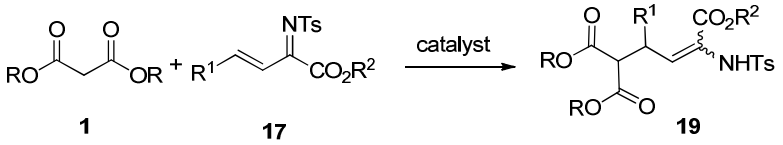
Figure 14. Proposed transition states for the Mukaiyama-Michael reaction. Non-catalyzed (TS-1) and copper-catalyzed (TS-2)

In summary, we have developed new protocols for the stereodivergent synthesis of *N*-tosyl α,β-dehydroamino esters *via* a Mukaiyama-Michael addition. The reaction of silylketene acetals with *N*-tosyl imines derived from β,γ-unsaturated α-keto esters provided the corresponding (*Z*)-α,β-dehydroamino esters. Morover, the *E*-isomers were obtained when the reaction was performed in the presence of a catalytic amount of copper triflate. This strategy allowed the stereoselective synthesis of (*E*)- or (*Z*)-α,β-dehydroamino esters from a same set of reactants, which has no precedents in the literature. We have also established a correlation between the ^{1}H NMR chemical shifts and the stereochemistry of the double bond in these compounds.

4.4. Enantioselective conjugate addition of malonate esters to *N*-tosyl imines derived from β,γ-unsaturated α-keto esters

In the previous chapter we disclosed the synthesis of α,β-dehydroamino acid derivatives *via* nucleophilic conjugate addition to imines derived from β,γ-unsaturated α-keto esters. By a judicious election of the reaction conditions we were able to carry out the Mukaiyama-Michael reaction of silylketene acetals and *N*-tosyl imines derived from β,γ-unsaturated α-keto esters to selectively give *E*- or Z- α,β-dehydroamino esters from the same set of reactants. Unfortunately, high levels of enantiocontrol in these reactions could not be obtained under the action of any of the chiral catalysts that were tested.

On the other hand, we have shown in sections 4.1 and 4.2 that 1,3-dicarbonyl compounds are prone to catalysis by chiral Lewis acid such as pyBOX-M(III) and BOX-M(II) complexes, which efficiently promoted the enantioselective conjugate addition of malonate esters to unsaturated ketimines to give chiral enamines. By considering both strategies together, we envisioned that chiral α,β-dehydroamino esters may be obtained in an enantioselective fashion by achieving the conjugate addition of malonate esters **1** to imines **17** derived from β,γ-unsaturated α-keto esters under the proper enantioselective catalytic conditions (Scheme 134).

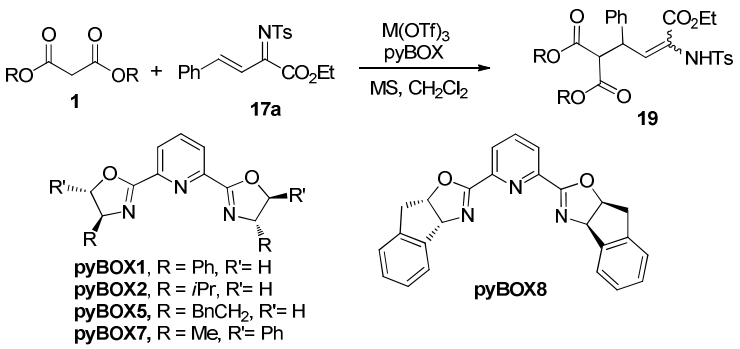


Scheme 134. Conjugate addition of malonate esters to *N*-tosyl imines derived from β,γ-unsaturated α-keto esters

4.4.1. Optimization of the reaction conditions

A preliminary screening of catalytic complexes based on trivalent metal salts and pyBOX ligands was undertaken using the reaction between dimethyl malonate (**1a**, R = Me) and the α,β-unsaturated *N*-tosyl imine **17a** (R^1 = Ph, R^2 = Et) in the presence of 4 Å MS and dichloromethane as the solvent, according to the conditions developed in section 4.1 (Table 13).

Table 13. Enantioselective addition of malonate esters **1** to unsaturated imine **17a** (R^1 = Ph, R^2 = Et) catalyzed by pyBOX-M(III) complexes.[a]



entry	M	pyBOX	1	R	solvent	*t* (h)	19	yield (%)[b]	dr (*E*/*Z*)[c]	ee (%)[d]
1	La	**pyBOX1**	**1a**	Me	CH_2Cl_2	16	**19aa**	94	2:98	-86
2	Yb	**pyBOX1**	**1a**	Me	CH_2Cl_2	44	**19aa**	23	27:73	30
3	Sc	**pyBOX1**	**1a**	Me	CH_2Cl_2	46	**19aa**	-	-	-
4	In	**pyBOX1**	**1a**	Me	CH_2Cl_2	46	**19aa**	-	-	-
5	La	**pyBOX2**	**1a**	Me	CH_2Cl_2	19	**19aa**	90	1:99	-52
6	La	**pyBOX5**	**1a**	Me	CH_2Cl_2	26	**19aa**	91	4:96	-35
7	La	**pyBOX7**	**1a**	Me	CH_2Cl_2	19	**19aa**	96	13:87	26
8	La	**pyBOX8**	**1a**	Me	CH_2Cl_2	26	**19aa**	94	13:87	16
9[e]	La	**pyBOX1**	**1a**	Me	CH_2Cl_2	16	**19aa**	98	7:93	-74
10[f]	La	**pyBOX1**	**1a**	Me	CH_2Cl_2	15	**19aa**	92	8:92	-73
11	La	**pyBOX1**	**1a**	Me	$CHCl_3$	17	**19aa**	99	5:95	-78
12	La	**pyBOX1**	**1a**	Me	DCE	17	**19aa**	89	4:96	-86
13	La	**pyBOX1**	**1a**	Me	toluene	16	**19aa**	93	4:96	-61
14	La	**pyBOX1**	**1a**	Me	THF	16	**19aa**	99	2:98	-83
15	La	**pyBOX1**	**1a**	Me	dioxane	35	**19aa**	96	11:89	-55
16	La	**pyBOX1**	**1a**	Me	Et_2O	18	**19aa**	95	2:98	-86
17	La	**pyBOX1**	**1b**	Et	CH_2Cl_2	18	**19ba**	94	1:99	-91
18	La	**pyBOX1**	**1b**	Et	Et_2O	20	**19ba**	87	3:97	-76
19	La	**pyBOX1**	**1c**	*i*Pr	CH_2Cl_2	16	**19ca**	94	2:98	-73
20	La	**pyBOX1**	**1c**	*i*Pr	Et_2O	15	**19ca**	99	3:97	-25
21[g]	La	**pyBOX1**	**1a**	Me	CH_2Cl_2	41	**19aa**	94	5:95	-87
22[g]	La	**pyBOX1**	**1b**	Et	CH_2Cl_2	64	**19ba**	93	1:99	-86

[a] Reaction conditions: **1** (0.6 mmol), **17a** (0.25 mmol), pyBOX (0.025 mmol), $M(OTf)_3$ (0.025 mmol), 4Å MS (110 mg), solvent (2.2 mL). [b] Yield of isolated product. [c] Determined by ^1H NMR. [d] Only for the major (*Z*)-diastereomer. Determined by HPLC with chiral stationary phases; opposite sign indicates opposite enantiomers. [e] 3 Å MS was used. [f] 5 Å MS was used. [g] Reaction carried out at 0 °C.

The complexes of $Sc(OTf)_3$ or $In(OTf)_3$ with **pyBOX1** were completely inactive and no significative progress of the reaction was observed after 46 hours (Table 13, entries 3 and 4) while the complex with $Yb(OTf)_3$ promoted a sluggish reaction and provided the expected product **19aa** with low yield, fair diastereomeric ratio and low 30% ee (Table 13, entry 2). Pleasantly, the **pyBOX1**-$La(OTf)_3$ complex was more active and, after 16 h, allowed obtaining compound **19aa** in excellent yield, with outstanding diastereoselectivity and high 86% ee (Table 13, entry 1). Other pyBOX

ligands were tested in combination with $La(OTf)_3$ but none of them improved the results obtained with **pyBOX1** (Table 13, entries 5-8). The pore size in the molecular sieves seemed not to have any effect on the performance of the reaction and either 3 Å or 5 Å MS afforded similar results as 4 Å MS (Table 13, entries 9 and 10). Next we studied different solvents. Unfortunately, none of them produced any upturn in the results; only diethyl ether performed similarly to dichloromethane (Table 13, entries 11-16). The influence of the alcoxy group in the malonate ester was also assessed. Slightly enhanced stereoselectivity was obtained with diethyl malonate (**1b**, R = Et, Table 13, entry 17), while diisopropyl malonate (**1c**, R = *i*Pr) gave the reaction product with only 73% ee (Table 13, entry 18). Surprisingly, the use of diethyl ether with these two esters was deleterious unlike with dimethyl malonate (Table 13, entries 19 and 20). Finally, a decrease of temperature to 0 °C resulted in a decrease in the reaction rate and a slight loss of the optical purity in the resulting enamine (Table 13, entry 22)

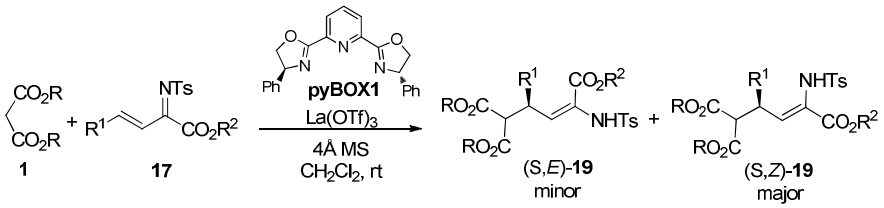
Finally, it is worth remarking that compound **12aa** was obtained as a single diastereomer with excellent diastereoselectivity (dr = 99:1) favoring the *Z* configuration in the double bond (see below).

4.4.2. Scope of the reaction

With the optimized conditions in hand, we studied the scope of the reaction with different imines **17**. Since diethyl malonate was proved to give better results than dimethyl or diisopropyl malonate, most of the research was restricted to this nucleophile. The results are gathered in Table 14.

Different imines **17** having aromatic substitution at the double bond (γ-carbon) of the unsaturated ketimino ester were suitable substrates for the reaction (Table 14, entries 1-10). In general the reaction took place with excellent diastereoselectivity favoring the formation of the isomer having the *Z* configuration at the enamine double bond, with *E/Z* ratios higher than 10:90, except in the case of compound **19bj** that was obtained as an *E/Z* 29:71 mixture (Table 14, entry 10). High enantiomeric excesses above 86% were obtained when R^1 was a phenyl group substituted with either neutral (Me) or electron donating (MeO) substituents at any of the positions (Table 14, entries 2, 5 and 8). The best enantioselectivity was obtained when R^1 was a 2- or 3-clorophenyl ring (Table 14, entries 6 and 9). Nevertheless, when a nitro group is attached to the aromatic ring, a dramatic drop in the enantiomeric excess (Table 14, entries 4, 7 and 10) was observed. The substituent R^1 can also be a heteroaromatic ring (Table 14, entry 11) the corresponding enamine being obtained with excellent diastereoselectivity and still 84% ee. Finally, the alkoxy group in compound **17** was also amenable to variation. Imines **17n** and **17o** derived from methyl or isopropyl keto esters gave the corresponding products with excellent diastereo- and enantioselectivity (Table 14, entries 12 and 13).

Table 14. Enantioselective addition of dialkyl malonates to unsaturated imines **17** catalyzed by **pyBOX1**-La(OTf)$_3$.[a]



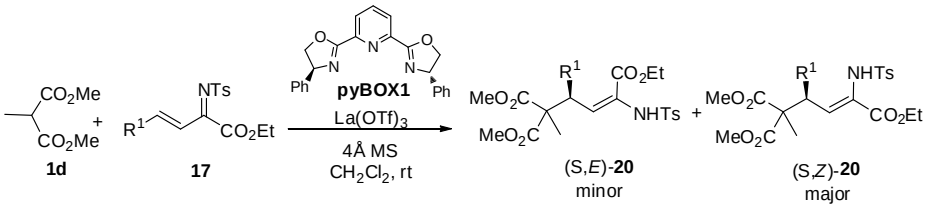
entry	1	R	17	R^1	R^2	*t* (h)	19	yield (%)[b]	dr (*E*/*Z*)[c]	ee (*E*/*Z*)[d]
1	**1b**	Et	**17a**	Ph	Et	18	**19ba**	94	1:99	7/91
2	**1b**	Et	**17b**	4-MeC_6H_4	Et	39	**19bb**	99	1:99	-/88
3	**1b**	Et	**17c**	4-ClC_6H_4	Et	30	**19bc**	97	6:94	21/88
4	**1b**	Et	**17d**	4-$NO_2C_6H_4$	Et	72	**19bd**	99	5:95	24/69
5	**1b**	Et	**17e**	4-MeOC_6H_4	Et	39	**19be**	99	1:99	22/86
6	**1b**	Et	**17f**	3-ClC_6H_4	Et	39	**19bf**	97	1:99	44/90
7	**1b**	Et	**17g**	3-$NO_2C_6H_4$	Et	72	**19bg**	99	7:93	38/52
8	**1b**	Et	**17h**	3-MeOC_6H_4	Et	43	**19bh**	91	7:93	37/88
9	**1b**	Et	**17i**	2-ClC_6H_4	Et	72	**19bi**	99	2:98	23/95
10	**1b**	Et	**17j**	2-$NO_2C_6H_4$	Et	120	**19bj**	95	29:71	60/20
11	**1b**	Et	**17l**	2-furanyl	Et	63	**19bl**	93	2:98	7/84
12	**1b**	Et	**17n**	Ph	Me	21	**19bn**	99	1:99	14/87
13	**1b**	Et	**17o**	Ph	*i*Pr	20	**19bo**	98	1:99	44/89
14	**1a**	Me	**17a**	Ph	Et	16	**19aa**	94	2:98	2/86
15	**1c**	*i*Pr	**17a**	Ph	Et	16	**19ca**	94	3:97	83/73

[a] Reaction conditions: **1** (0.6 mmol), **17** (0.25 mmol), **pyBOX1** (0.025 mmol), La(OTf)$_3$ (0.025 mmol), 4 Å MS (110 mg), solvent (2.2 mL), rt. [b] Yield of isolated product. [c] Determined by ^{1}H NMR. [d] Determined by HPLC with chiral stationary phases.

To complete the study, we assessed the performance of dimethyl 2-methylmalonate (**1d**) in the reaction with four different unsaturated imines **17** (Table15).

The reaction of dimethyl 2-methylmalonate with these imines took place with excellent yields in all the cases but variable results in terms of stereoselectivity. Quite surprisingly, dimethyl 2-methymalonate (**1d**) showed different behavior to that of dimethyl malonate (**1a**). Thus, the best result was obtained with the 4-methoxyphenyl derivative **17e** that provided the conjugate addition product **20de** with excellent diastereoselectivty and 97% ee (Table 15, entry 4). However, the reaction with the *p*-clorophenyl derivative **17c** provided in this case the lower dr (32:68) and ee (Table 15, entry 2), while the nitro derivative **17d** gave the imine with good dr and 81% ee (Table 15, entry 3).

Table 15. Enantioselective addition of dimethyl 2-methylmalonate (**1d**) to unsaturated imines **17** catalyzed **pyBOX1**-La(OTf)$_3$.[a]



entry	17	R^1	*t* (h)	20	yield (%)[b]	dr (*E*/*Z*)[c]	ee (*E*/*Z*)[d]
1	**17a**	Ph	92	**20da**	88	5:95	20/83
2	**17c**	4-ClC_6H_4	67	**20dc**	99	32:68	14/40
3	**17d**	4-$NO_2C_6H_4$	44	**20dd**	99	7:93	34/81
4	**17e**	4-$MeOC_6H_4$	67	**20de**	92	3:97	97/97

[a] Reaction conditions: **1d** (0.6 mmol), **17** (0.25 mmol), **pyBOX1** (0.025 mmol), La(OTf)$_3$ (0.025 mmol), 4 Å MS (110 mg), solvent (2.2 mL), rt. [b] Yield of isolated product. [c] Determined by ^{1}H NMR. [d] Determined by HPLC with chiral stationary phases.

4.4.3. Determination of the stereochemistry of compounds 19

The stereochemistry of the double bond in compounds **19** was initially assigned as *Z* on the basis NOESY experiments carried out with compound **19be**. The spectrum showed an interaction between the NH enamine proton at δ 6.73 and the benzylic proton at δ 4.62, which is only possible if the double bond has the *Z* configuration (Figure 15).

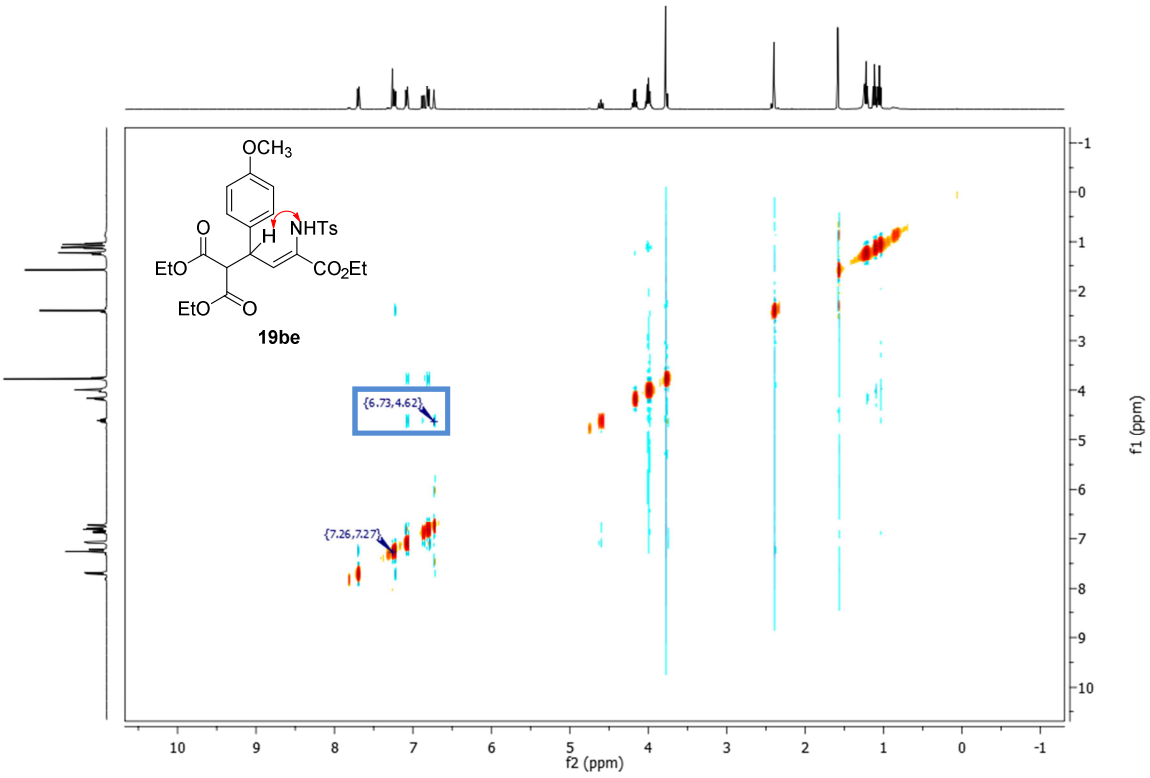


Figure 15. NOESY experiments carried out with compound **19be**

Furthermore, compound **19bn** could be crystallized and subjected to X-ray analysis, which allowed us to confirm the geometry of the double bond as *Z* and also to establish the configuration of the stereogenic center as *S* (Figure 16). The absolute stereochemistry for the other obtained enamines **19** was assigned by analogy upon the assumption of a uniform stereochemical pathway.

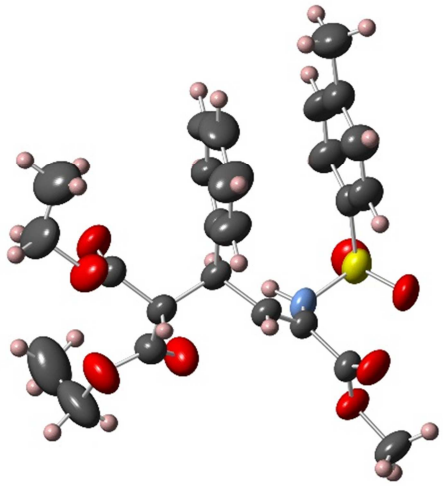
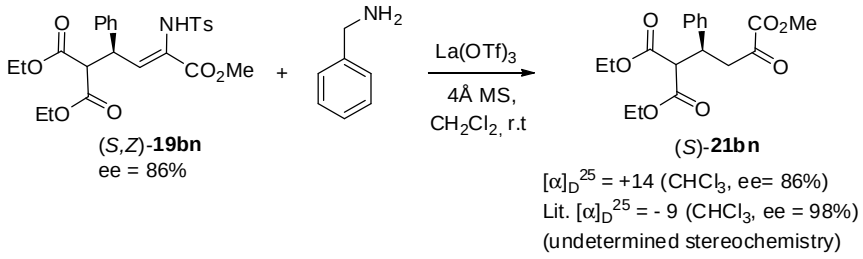


Figure 16. Ortep plot for the X-ray structure of compound **19bn**. The thermal ellipsoids are drawn at the 50% probability level

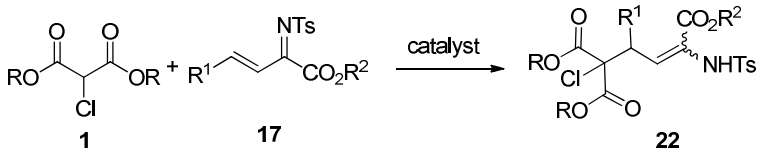
Furthermore, compound **19bn** was hydrolyzed to the known ketone **21**[177] upon treatment with 2 equivalents of benzylamine and a catalytic amount of $La(OTf)_3$ and 4 Å MS in dichloromethane (Scheme 135).



Scheme 135. Hydrolysis of compound **19bn**

4.5. Diastereodivergent enantioselective conjugate addition of 2-chloromalonate esters to *N*-tosyl imines derived from β,γ-unsaturated α-keto esters

The introduction of highly functionalized fragments into an organic molecule is of paramount importance in organic synthesis since this allows increasing the possibilities of further functional or structural modifications in later stages of the synthetic sequence. Following the research on nucleophilic enantioselective addition of malonic acid derivatives to unsaturated imines disclosed in the previous chapter, we decided to study the reaction between dialkyl 2-chloromalonates and *N*-tosyl imines derived from β,γ-unsaturated α-keto esters to give the corresponding highly functionalized chloro-enamino esters (Scheme 136).

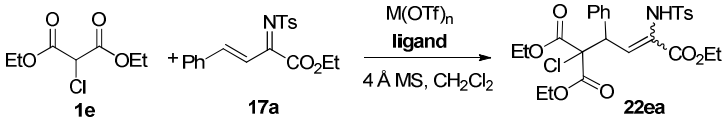


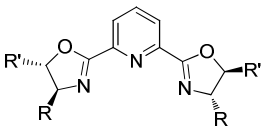
Scheme 136. Conjugate addition of 2-chloromalonate esters to *N*-tosyl imines derived from β,γ-unsaturated α-keto esters

4.5.1. Optimization of the reaction conditions with lanthanum(III) triflate

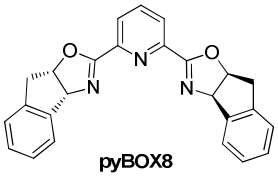
The conditions previously developed for the addition of diethyl malonate with the **pyBOX1**-La(OTf)$_3$ catalyst were initially applied to the reaction between diethyl 2-chloromalonate (**1e**) and imine **17a**, giving the *Z*-enamine **22ea** with high dr (3:97) and 82% ee (Table 16, entry 1). It was also found that the amount of diethyl 2-chloromalonate could be reduced to 1.5 equivalents without any noticeable effect (Table 16, entry 2). Different pyBOX ligands were then tested. All of them led to poorer results than **pyBOX1** (Table 16, entries 3-9) except **pyBOX9,** which performed similarly (Table 16, entry 10). A decrease in the reaction temperature in the presence of **pyBOX1** or **pyBOX9** had little impact on the enantioselectivity, although the **pyBOX9** complex seemed to be slightly more active (Table 16, entries 11 and 12). Decreasing the temperature to -10 °C improved the ee up to 86%, however, further decrease of temperature to -20 °C slowed down the reaction leading to long times without a noticeable effect on the enantioselectivity (Table 16, entry 14). Other pyBOX complexes with trivalent metal triflates such as Yb(OTf)$_3$, Sc(OTf)$_3$ or In(OTf)$_3$ were assessed but proved to be inactive and did not yield enamine **22ea**.

Table 16. Enantioselective addition of diethyl 2-chloromalonate to imine **17a** catalyzed by trivalent metal salts.[a]

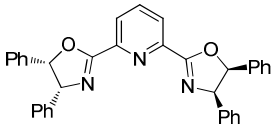




pyBOX1, R = Ph, R'= H
pyBOX2, R = *i*Pr, R'= H
pyBOX3, R = *t*Bu, R' = H
pyBOX4, R = *i*PrCH$_2$, R' = H
pyBOX5, R = BnCH$_2$, R'= H
pyBOX6, R = 1-naphthyl-CH$_2$, R'= H
pyBOX7, R = Me, R'= Ph



pyBOX8



pyBOX9

entry	ligand	*t* (h)	*T* (ºC)	yield (%)[b]	dr (*E:Z*)[c]	ee (%)[d]
1[e]	**pyBOX1**	16	rt	97	3:97	-82
2	**pyBOX1**	14	rt	92	3:97	-82
3	**pyBOX2**	19	rt	89	4:96	-22
4	**pyBOX3**	16	rt	88	9:91	-16
5	**pyBOX4**	39	rt	90	7:93	-3
6	**pyBOX5**	40	rt	87	7:93	-44
7	**pyBOX6**	40	rt	91	8:92	-41
8	**pyBOX7**	16	rt	92	7:93	-46
9	**pyBOX8**	43	rt	92	10:90	13
10	**pyBOX9**	16	rt	93	2:98	82
11	**pyBOX1**	40	0	89	5:95	-82
12	**pyBOX9**	22	0	93	3:97	83
13	**pyBOX9**	40	-10	83	8:92	86
14	**pyBOX9**	92	-20	62	1:99	87
15[e,f]	**BOX1**	16	rt	86	90:10	-73

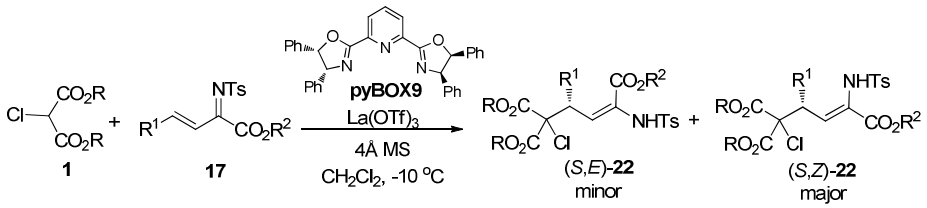
[a] Reaction conditions: **1e** (0.187 mmol), **17a** (0.125 mmol), pyBOX (0.0125 mmol), La(OTf)$_3$ (0.0125 mmol), 4 Å MS (110 mg), CH_2Cl_2 (1.1 mL). [b] Yield of isolated product. [c] Determined by ^{1}H NMR. [d] Only for the major diastereomer. Determined by HPLC analysis with chiral stationary phases; opposite sign indicates opposite enantiomers. [e] Reaction carried out with 0.3 mmol of **1e**/0.125 mmol of **17a**. [f] Reaction carried out with Cu(OTf)$_2$ instead of La(OTf)$_3$.

Furthermore, while performing this study, we also tested the **BOX1**-Cu(OTf)$_2$ complex as catalyst, which allowed obtaining compound **22ea** in 86% yield after 16 h. Quite surprisingly, the *E*- instead of the *Z*-enamine was obtained as the major diastereomer with this catalyst, although with moderate 73% ee (Table 16, entry 15). We will come back to this *E*-selective reaction in a next section of this chapter.

4.5.2. Scope of the reaction catalyzed by the pyBOX9-La(OTf)$_3$ catalyst

With the optimized conditions in hand (Table 16, entry 13), we proceeded to study the scope of this reaction with a number of unsaturated imines **17** (Table 17).

Table 17. Enantioselective addition of dialkyl 2-chloromalonates to unsaturated imines **17** catalyzed by **pyBOX9**-La(OTf)$_3$.[a]



entry	1	R	17	R^1	R^1	*t* (h)	22	yield (%)[b]	dr (*E*:*Z*)[c]	ee (%) (*E*/*Z*)[d]
1	**1e**	Et	**17a**	Ph	Et	40	**22ea**	83	8:92	83/86
2	**1e**	Et	**17b**	4-MeC_6H_4	Et	94	**22eb**	89	5:95	94/86
3	**1e**	Et	**17c**	4-ClC_6H_4	Et	91	**22ec**	89	6:94	52/86
4	**1e**	Et	**17d**	4-$NO_2C_6H_4$	Et	42	**22ed**	93	2:98	69/87
5	**1e**	Et	**17e**	4-MeOC_6H_4	Et	90	**22ee**	99	4:96	76/86
6	**1e**	Et	**17f**	3-ClC_6H_4	Et	91	**22ef**	91	11:89	94/82
7	**1e**	Et	**17g**	3-$NO_2C_6H_4$	Et	40	**22eg**	99	4:96	67/87
8	**1e**	Et	**17h**	3-MeOC_6H_4	Et	67	**22eh**	99	24:76	85/85
9	**1e**	Et	**17i**	2-ClC_6H_4	Et	45	**22ei**	91	3:97	77/88
10	**1e**	Et	**17j**	2-$NO_2C_6H_4$	Et	69	**22ej**	99	6:94	95/88
11	**1e**	Et	**17k**	2-MeOC_6H_4	Et	63	**22ek**	99	1:99	50/87
12	**1e**	Et	**17m**	2-thiophenyl	Et	40	**22em**	94	1:99	61/84
13	**1e**	Et	**17n**	Ph	Me	43	**22en**	91	8:92	84/83
14	**1e**	Et	**17o**	Ph	*i*Pr	43	**22eo**	84	2:98	80/92
15	**1f**	Me	**17a**	Ph	Et	15	**22fa**	82	5:95	64/84

[a] Reaction conditions: **1** (0.187 mmol), **17** (0.125 mmol), **pyBOX9** (0.0125 mmol), La(OTf)$_3$ (0.0125 mmol), 4 Å MS (110 mg), CH_2Cl_2 (1.1 mL), -10 °C. [b] Yield of isolated product. [c] Determined by ^{1}H NMR. [d] Determined by HPLC with chiral stationary phases.

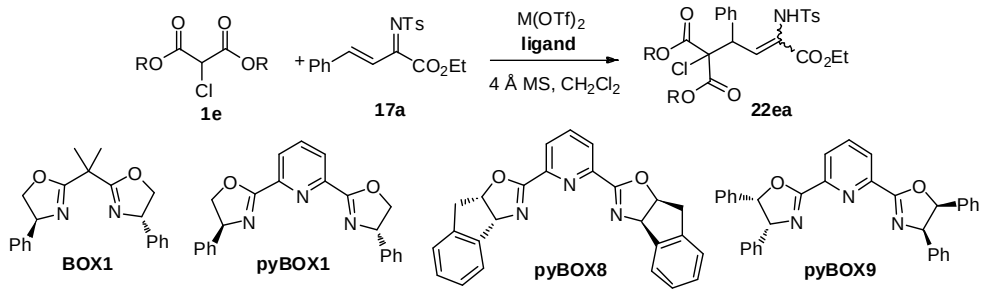
The addition of diethyl 2-chloromalonate (**1e**, R = Et) could be successfully achieved with a number of unsaturated imines having a substituted aromatic ring attached to the double bond (γ-position). Excellent yields were obtained in all the cases regardless the position and electronic nature of the substituent on the aromatic ring (Table 17, entries 1-11). The *Z*-isomer was obtained as the major diastereomer in all the cases with very high diastereoselectivity (dr > 2: 98) except in the cases of the imines substituted with a 3-chloro- or 3-methoxyphenyl group (Table 17, entries 6 and 8). Enantiomeric excesses above 80% were obtained for the major diastereomer in all the cases. It is worth remarking that, unlike in the addition of diethyl malonate, the presence of nitro groups did not lessen the stereoselectivity. The imine also allowed a 2-thiophenyl group attached to the double bond (Table 17, entry 12). A bulkier *i*Pr group at the ester moiety produced a rise in the enantiomeric excess up to 92% ee, while the methyl ester performed similarly to the ethyl derivative (Table 17, entries 13-14).

Finally, dimethyl 2-chloromalonate (**1f**, R = Me) was also tested giving similar results as diethyl 2-chloromalonate (Table 17, entry 15).

4.5.3. Optimization of the reaction conditions with calcium triflate

As it has been advanced in section 4.5.1, the use of the **BOX1**-Cu(OTf)$_2$ instead of **pyBOX9**-La(OTf)$_3$ in the reaction of **1e** and **17a** produced a shift of diastereoselectivity towards the *E*-enamine. Although (*E*)-**22ea** was obtained only with fair enantioselectivity, this change of selectivity prompted us to check other catalysts based on divalent metals (Table 18).

Table 18. Enantioselective addition of diethyl 2-chloromalonate to imine **17a** catalyzed by divalent metal salts.[a]



entry	M	ligand	*t* (h)	*T* (ºC)	yield (%)[b]	dr (*E*/*Z*)[c]	ee (*E*)[d]
1[e]	Cu	**BOX1**	16h	rt	86	90:10	-77
2	Mg	**BOX1**	14h	rt	91	90:10	-91
3	Zn	**BOX1**	88h	rt	69	56:44	-72
4	Ca	**pyBOX1**	14h	rt	89	93:7	-96
5	Ca	**pyBOX1**	40h	0	95	96:4	-98
6	Ca	**pyBOX8**	16h	0	88	93:7	94
7	Ca	**pyBOX9**	39h	0	97	95:5	95
8[f]	Ca	**pyBOX1**	25h	0	85	96:4	-97

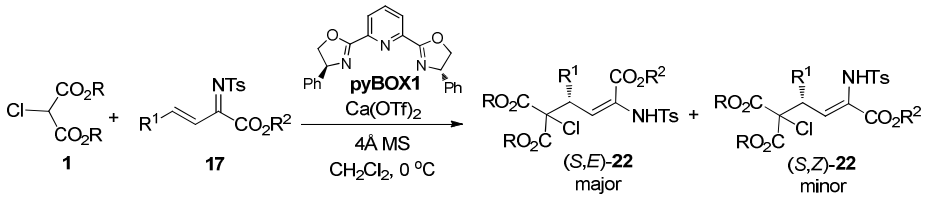
[a] Reaction conditions: **1e** (0.187 mmol), **17a** (0.125 mmol), ligand (0.0125 mmol), M(OTf)$_2$ (0.0125 mmol), 4 Å MS (110 mg), CH_2Cl_2 (1.1 mL). [b] Yield of isolated product. [c] Determined by ^{1}H NMR. [d] Only for the major diastereomer. Determined by HPLC analysis with chiral stationary phases; opposite sign indicates opposite enantiomers. [e] Reaction carried out with 0.3 mmol of **1e**/0.125 mmol of **17a**.[f] Reaction carried out with 0.00625 mmol of **pyBOX1**-Ca(OTf)$_2$ /0.125 mmol of **17a**.

The **BOX1** complexes of Cu(II), Mg(II) and Zn(II) triflates, and **pyBOX1**-Ca(OTf)$_2$ were tested in the reaction of **1e** and **17a**. In all the cases the reaction showed *E*-selectivity, the **pyBOX1**-Ca(OTf)$_2$ catalyst giving the best result (Table 18, entry 4). Decreasing the temperature to 0 °C allowed further improvement of the stereoselectivity (Table 18, entry 5). **pyBOX8** and **pyBOX9** gave similar results to **pyBOX1**. Finally, it should be remarked that the catalyst load could be reduced to 5 mol % without a noticeable impact on the result (Table 18, entry 8). On the view of these results, further optimization was not considered necessary.

4.5.4. Scope of the reaction catalyzed by the pyBOX1-Ca(OTf)$_2$ catalyst

The optimal conditions established for the Ca(OTf)$_2$ catalyzed reaction (Table 18, entry 8) were applied to the same set of *N*-tosyl imines previously studied with La(OTf)$_3$. The results are shown in Table 19.

Table 19. Enantioselective addition of dialkyl 2-chloromalonates to unsaturated imines **17** catalyzed by **pyBOX1**-Ca(OTf)$_2$.[a]

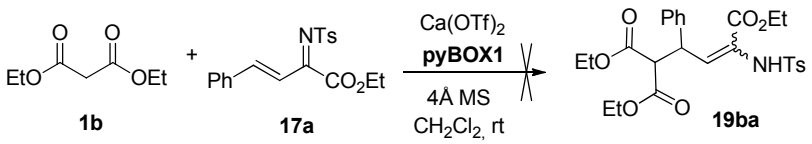


entry	1	R	17	R^1	R^1	*t* (h)	22	yield (%)[b]	dr (*E*/*Z*)[c]	ee (%) (*E*/*Z*)[d]
1	**1e**	Et	**17a**	Ph	Et	25	**22ea**	85	96:4	97/70
2	**1e**	Et	**17b**	4-MeC_6H_4	Et	38	**22eb**	94	96:4	98/61
3	**1e**	Et	**17c**	4-ClC_6H_4	Et	39	**22ec**	95	95:5	98/85
4	**1e**	Et	**17d**	4-$NO_2C_6H_4$	Et	23	**22ed**	99	92:8	98/78
5	**1e**	Et	**17e**	4-MeOC_6H_4	Et	38	**22ee**	99	95:5	98/71
6	**1e**	Et	**17f**	3-ClC_6H_4	Et	39	**22ef**	91	95:5	98/70
7	**1e**	Et	**17g**	3-$NO_2C_6H_4$	Et	40	**22eg**	99	93:7	93/58
8	**1e**	Et	**17h**	3-MeOC_6H_4	Et	44	**22eh**	98	96:4	96/77
9	**1e**	Et	**17i**	2-ClC_6H_4	Et	93	**22ei**	95	95:5	98/92
10	**1e**	Et	**17j**	2-$NO_2C_6H_4$	Et	44	**22ej**	98	97:3	99/22
11	**1e**	Et	**17k**	2-MeOC_6H_4	Et	63	**22ek**	99	95:5	95/8
12	**1e**	Et	**17m**	2-thiophenyl	Et	23	**22em**	99	97:3	97/47
13	**1e**	Et	**17n**	Ph	Me	42	**22en**	91	96:4	98/90
14	**1e**	Et	**17o**	Ph	*i*Pr	66	**22eo**	84	94:6	98/79
15	**1f**	Me	**17a**	Ph	Et	15	**22fa**	92	92:8	98/80

[a] Reaction conditions: **1** (0.187 mmol), **17** (0.125 mmol), **pyBOX1** (0.00625 mmol), Ca(OTf)$_2$ (0.0125 mmol), 4 Å MS (110 mg), CH_2Cl_2 (1.1 mL), 0 °C. [b] Yield of isolated product. [c] Determined by ^{1}H NMR. [d] Determined by HPLC with chiral stationary phases.

In all the cases, products **22** were obtained as the *E*-enamines preferientally with excellent yields, diastereomeric ratios and enantiomeric excesses, regardless of the electronic nature and substitution pattern of the group attached to the double bond and the alkoxy group of the ester moiety. Also, the diastereomeric ratios and enantiomeric excesses were higher than those obtained in the reaction catalyzed by La(OTf)$_3$ as a general trend.

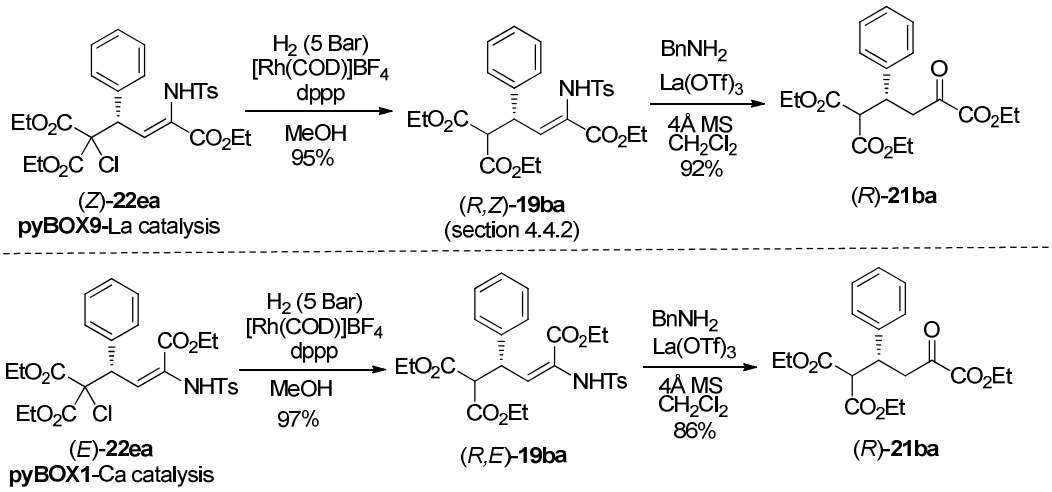
After obtaining these results, we checked the **pyBOX1**-Ca(OTf)$_2$ catalyst in the reaction of diethyl malonate (**1b**) and α,β-unsaturated *N*-tosyl iminoester **17a**. Unfortunately, no advance of the reaction was observed after 5 days at room temperature (Scheme 137).



Scheme 137. Attempted reaction of diethyl malonate (**1b**) and imine **17a** under **pyBOX1**-$Ca(OTf)_2$ catalysis

4.5.5. Determination of the absolute stereochemistry of compounds 22

The absolute stereochemistry of the stereogenic center in the *Z*- or *E*-enamines **22ea** obtained upon catalysis by **pyBOX9**-$La(OTf)_3$ or **pyBOX1**-$Ca(OTf)_2$, respectively, was determined by chemical correlation with compounds of known stereochemistry. For this purpose, enamines **22ea** obtained by any of these two procedures were subjected to a two step sequence involving hydrogenolysis of the C-Cl bond to give enamines **29ba**, followed by hydrolysis to give ketone **21ba** (Scheme 138).



Scheme 138. Determination of the absolute stereochemistry of compound **22ea**

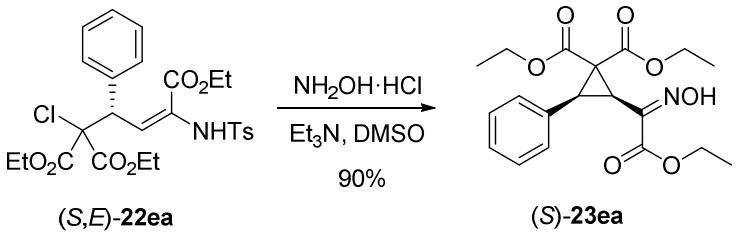
Different attempts to carry out the hydrogenolysis of (*Z*)- or (*E*)-**22ea** such as hydrogenation on Pd/C or treatment with PhSH led to compound **19ba** with considerable isomerization of the double bond. Eventually, transformation of compound **22ea** without isomerization of the double bond nor erosion of the optical purity could be achieved by homogeneous hydrogenation with the $[Rh(COD)]BF_4$-dppp complex. Upon this treatment, compound (*Z*)-**22ea**, resulting from the **pyBOX9**-La(III) catalyzed reaction, was converted into a new enamine that was identified as (*R,Z*)-**19ba** after comparison with the features of the same compound obtained by addition of diethyl malonate to imine **17a** catalyzed by **pyBOX1**-$La(OTf)_3$ (Section 4.4.2). Hydrolysis of (*R,Z*)-**19ba** by treatment with benzylamine gave ketone (*R*)-**21ba** in 92% ee. According to this synthetic correlation we assigned the (*S,Z*) stereochemistry to **22ea**.

A similar sequence carried out with (*E*)-**22ea**, resulting from the **pyBOX1**-Ca(II) catalyzed reaction, gave again ketone (*R*)-**21ba** at the end of the sequence indicating that the stereochemistry of the stereogenic center in the starting compound was *S*.

The *Z*-configuration of the double bond of products (*Z*)-**22** in the La-catalyzed reaction indicates the preference of the unsaturated imines **17** to adopt an s-*cis* conformation in the transition state, while in the Ca-catalyzed reaction imines **17** should adopt the s-*trans* conformation to give the *E*-enamine. The configuration of the stereogenic center in compounds **22** would be the resultant of both: a topological approach of the nucleophile dictated by the stereogenic center of the chiral ligand, and the conformation of the unsaturated imine dictated by the accommodation of the reacting species in the TS (note that the reactions under La or Ca catalysis with the same ligand **pyBOX1** lead to opposite configurations *R* and *S*, respectively, in the final products). At the current stage of the research, it has not been possible to give a reliable explanation of the stereochemical course of the reaction. Further research, including computational calculations, may be required.

4.5.6. Synthetic transformations

Besides the above transformation, we have achieved the reaction between (*E*)-enamine (*S*,*E*)-**22ea** and hydroxylamine to give a chiral cyclopropane oxime **23ea** in 90% yield (Scheme 139). The reaction provided a single diastereomer without any loss of enantiomeric excess with respect to the starting material. The ^{1}H NMR of compound **23ea** showed two doublets at δ 3.67 and 3.27 ppm with a *J* value of 9.0 Hz corresponding to the two cyclopropanic protons. Based on similar *J* values reported in the literature for related cyclopropanes,[178-182] the *cis* geometry was assigned to compound **23ea**.



(*S*,*E*)-**22ea** (*S*)-**23ea**

Scheme 139. Synthesis of a chiral cyclopropane oxime

In summary, in sections 4.4 and 4.5 we have developed procedures for the conjugate addition of different malonate ester derivatives to *N*-tosyl imines derived from β,γ-unsaturated α-keto esters to give chiral α,β-dehydroamino esters. The addition of diethyl malonate and diethyl 2-chloromalonate catalyzed by pyBOX-La(OTf)$_3$ complexes led to the corresponding dehydroamino esters with the *Z*-configuration at the double bond with high enantiomeric excesses. On the other hand, pyBOX-Ca(OTf)$_2$ complexes catalyzed the addition of diethyl 2-chloromalonate favoring the formation of the dehydroamino esters with the *E*-configuration with excellent enantioselectivity. Some synthetic transformation of the resulting products showed their potential applicability in organic synthesis.

4.6. Catalytic asymmetric formal [3+2] cycloaddition of 2-isocyanatomalonate esters and unsaturated imines: synthesis of highly substituted chiral γ-lactams

Pyrrolidinones (γ-lactams) and, in particular, 2-alkoxycarbonylpyrrolidinones (pyroglutamic acid derivatives) have been extensively used as building blocks in synthetic chemistry[183] and as chiral ligands in asymmetric catalysis.[184] They are also structural units frequently encountered in numerous biologically active natural products and pharmaceuticals (Figure 17).[185]

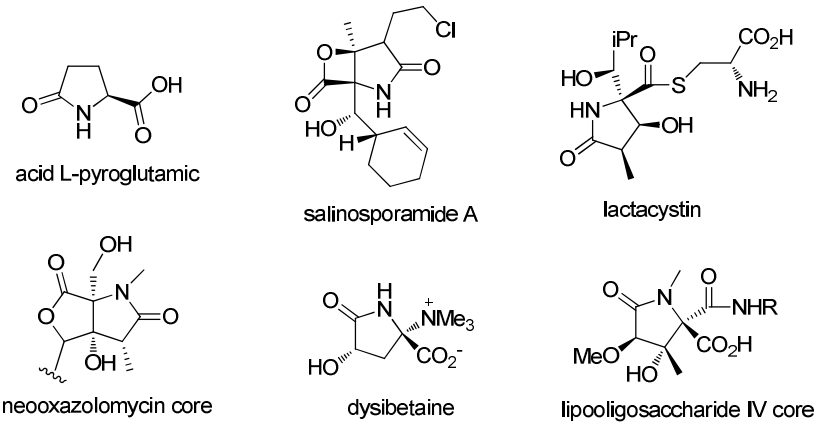
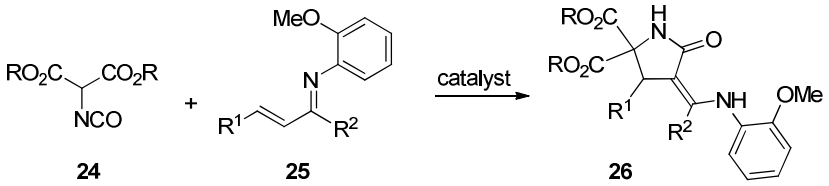


Figure 17. Examples of bioactive natural compounds incorporating a pyrrolidinone unit

Given the widespread chemical significance of these scaffolds, the development of new efficient and atom economy processes for the construction of these heterocyclic systems, especially in an enantioselective manner, constitutes an important challenge in current organic synthesis. Besides procedures based on the structural modification of nitrogen-containing heterocycles such as pyrrolidinones, pyroglutamic acid or succinimides,[186] cyclization procedures in which the pyrrolidinone heterocycle is formed from acyclic precursors in an asymmetric fashion result especially appealing. Examples include the enantioselective Michael addition/lactamization reaction of 2-amino acids and unsaturated acid derivatives,[187] the NHC catalyzed coupling of imines with unsaturated aldehydes[188] or the reaction between 2-aminomalonates and Morita-Baylis-Hillman carbonates catalyzed by chiral Lewis.[189]

On the other hand, the application of isocyano-[190] and isothiocyanato[191] esters in asymmetric synthesis has experienced a growing interest in the last years. These compounds can react with different unsaturated groups to give a variety of five-membered nitrogen containing heterocycles. In particular, several examples involving their participation in asymmetric catalytic [3+2] cycloaddition reactions with conjugate carbonyl compounds to give enantiomerically enriched pyrrolidines[192] or thiopyrrolidinones,[193] respectively, have been reported in the literature.

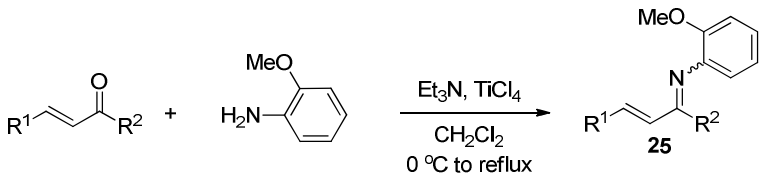
In contrast, the use of isocyanato esters in asymmetric catalysis is almost unknown. The isocyanate group is more reactive than the isothiocyanate and the application of 2-isocyanato esters in reactions that combine both nucleophilic and electrophilic behavior (1,3-dipole-like behavior) is challenging. In fact, 2-isocyanato esters have been mainly used as electrophiles for the preparation of ureas and carbamates,[194] while reactions making use of their 1,3-dipole-like character are very scarce. To the best of our knowledge, the organocatalytic reaction of 2-isocyanatomalonate esters and aldehydes to give oxazolidinones developed by Takemoto[195] is the only example reported in the literature, so far. In this chapter we will disclose the development of the first enantioselective formal [3+2] cycloaddition of 2-isocyanatomalonates with alkenes to give highly substituted α,β-unsaturated γ-lactams (Scheme 140).



Scheme 140. Formal [3+2] cycloaddition between 2-isocyanatomalonate esters and unsaturated imines

4.6.1. Synthesis of α,β-unsaturated *N*-(*o*-methoxyphenyl)imines 25

Preliminary experiments on the reaction of diethyl 2-isocyanatomalonate with chalcone or its *N*-tosyl imine **2a** showed that these were not reactive substrates in the presence of different metal complexes. The reaction was then tested with α,β-unsaturated *N*-(*o*-methoxyphenyl)imines **25** that yielded the expected product. A number of imines **25a-n** having different substitution were then prepared in 32-74% yield from the corresponding enones and *o*-anisidine by treatment with $TiCl_4$ and Et_3N following a similar procedure as described for the previous imines (Scheme 141).[22] Imines **25** have the *E*-geometry at the C=C bond, but were obtained as 2:1 to 7:3 mixtures of C=N geometric isomers and used without separation.



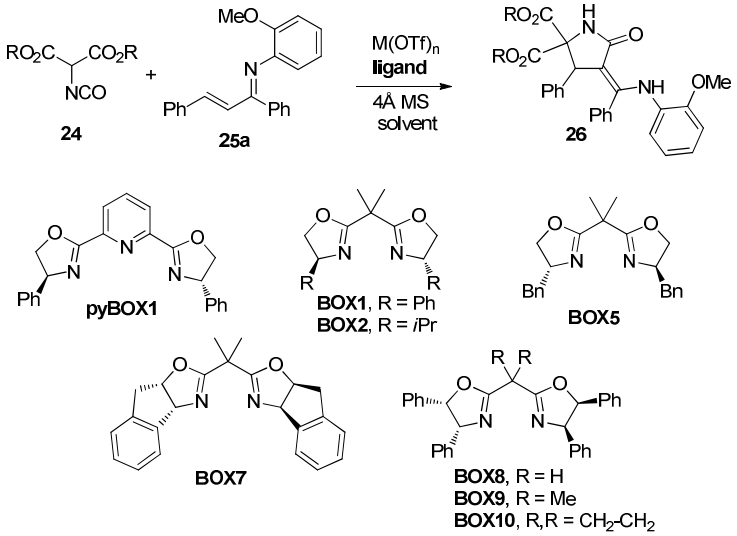
25a, R^1 = Ph, R^2 = Ph
25b, R^1 = 4-ClC_6H_4, R^2 = Ph
25c, R^1 = 4-$NO_2C_6H_4$, R^2 = Ph
25d, R^1 = 4-$MeOC_6H_4$, R^2 = Ph
25e, R^1 = 2-furanyl, R^2 = Ph
25f, R^1 = *t*Bu, R^2 = Ph
25g, R^1 = Ph, R^2 = 4-ClC_6H_4
25h, R^1 = Ph, R^2 = 4-$NO_2C_6H_4$
25i, R^1 = Ph, R^2 = 4-$MeOC_6H_4$
25j, R^1 = Ph, R^2 = 3-$NO_2C_6H_4$
25k, R^1 = Ph, R^2 = 2-ClC_6H_4,
25l, R^1 = Ph, R^2 = 2-$NO_2C_6H_4$
25m, R^1 = Ph, R^2 = 2-furanyl
25n, R^1 = Ph, R^2 = 2-naphthyl

Scheme 141. Synthesis of α,β-unsaturated *N*-(*o*-methoxyphenyl)imines **25**

4.6.2. Optimization of the reaction conditions

We initially investigated the activity of the **pyBOX1**-La(OTf)$_3$, **pyBOX1**-Ca(OTf)$_2$ and **BOX1**-Mg(OTf)$_2$ complexes in the reaction between diethyl 2-isocyanatomalonate (**24b**) and imine **25a** derived from *o*-anisidine and chalcone (Table 20, entries 1-3).

Table 20. Enantioselective [3+2] cycloaddition of 2-isocyanatomalonate esters **24** with unsaturated imine **25a**. Optimization of reaction conditions.[a]



entry	M	ligand	24	R	solvent	*T* (°C)	*t* (h)	26	yield (%)[b]	ee (%)[c]
1	La	**pyBOX1**	**24b**	Et	CH_2Cl_2	rt	3	**26ba**	81	3
2	Ca	**pyBOX1**	**24b**	Et	CH_2Cl_2	rt	3.5	**26ba**	89	-67
3	Mg	**BOX1**	**24b**	Et	CH_2Cl_2	rt	2	**26ba**	97	-67
4	Mg	**BOX2**	**24b**	Et	CH_2Cl_2	rt	2.5	**26ba**	83	-5
5	Mg	**BOX5**	**24b**	Et	CH_2Cl_2	rt	2.5	**26ba**	89	5
6	Mg	**BOX7**	**24b**	Et	CH_2Cl_2	rt	3	**26ba**	94	63
7	Mg	**BOX8**	**24b**	Et	CH_2Cl_2	rt	3	**26ba**	97	29
8	Mg	**BOX9**	**24b**	Et	CH_2Cl_2	rt	2.5	**26ba**	97	71
9	Mg	**BOX9**	**24b**	Et	CH_2Cl_2	0	3	**26ba**	96	80
10	Mg	**BOX9**	**24b**	Et	CH_2Cl_2	-20	45	**26ba**	68	43
11	Mg	**BOX9**	**24a**	Me	CH_2Cl_2	0	2	**26aa**	98	49
12	Mg	**BOX9**	**24c**	*i*Pr	CH_2Cl_2	0	2	**26ca**	98	89
13	Mg	**BOX9**	**24c**	*i*Pr	DCE	0	2.5	**26ca**	98	76
14	Mg	**BOX9**	**24c**	*i*Pr	$CHCl_3$	0	2.5	**26ca**	89	91
15	Mg	**BOX9**	**24c**	*i*Pr	Et_2O	0	2.5	**26ca**	96	91
16	Mg	**BOX10**	**24c**	*i*Pr	Et_2O	0	1.5	**26ca**	97	97

[a] Reaction conditions: **1** (0.19 mmol), **25a** (0.125 mmol), **ligand** (0.0125 mmol), M(OTf)$_n$ (0.0125 mmol), 4 Å MS (110 mg), solvent (1.1 mL). [b] Yield of isolated product. [c] Determined by HPLC with chiral stationary phases; opposite sign indicates opposite enantiomers.

In all the cases, the reaction proceeded smoothly to give pyrrolidinone **26ba**, which features a conjugated exocyclic double bond, a structural moiety that is present in a large number of antitumor compounds. Compound **26ba** was obtained as a single

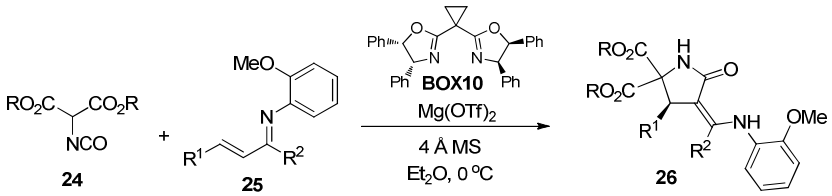
geometric isomer having the *Z* configuration at the double bond. Regarding enantioselectivity, the **pyBOX1**-La(OTf)$_3$ complex gave compound **26ba** in almost racemic form, while the **pyBOX1**-Ca(OTf)$_2$ and **BOX1**-Mg(OTf)$_2$ complexes showed similar enantioselectivities (ee = 67%), although the magnesium complex seemed slightly more active. Further research was, therefore, continued by testing several BOX-Mg complexes. The best result was obtained with **BOX9** that provided compound **26ba** in 98% yield with 71% ee (Table 20, entry 8). A decrease of temperature to 0 °C increased the ee up to 80%, however further decrease of temperature to -20 °C produced a dramatic drop in the enantioselectivity (Table 20, entries 9 and 10). With the optimal temperature (0 °C), the effect of the alkoxy group in the 2-isocyanatomalonate ester was tested (Table 20, entries 9, 11 and 12). It was found that diisopropyl 2-isocyanatomalonate (**24c**) underwent a more enantioselective reaction than dimethyl (**24a**) or diethyl 2-isocyanatomalonates (**24b**), giving lactam **26ca** with 89% ee. Next, the solvent effect was checked. The use of diethyl ether as the solvent in the addition of isocyanate **24c** to imines **25a** allowed increasing the ee of compound **26ca** up to 91% (Table 20, entry 15). Finally, in view of the important effect of the substitution at the central carbon of the BOX ligand on the enantioselectivity of the reaction, compare **BOX8** and **BOX9** (Table 20, entry 7 *vs* entry 8), the cyclopropanic **BOX10** ligand was prepared and tested providing compound **26ca** in excellent 97% yield and 97% ee (Table 20, entry 16).

4.6.3. Scope of the reaction

With the best available conditions, the scope of reaction of diisopropyl 2-isocyanatomalonate (**24c**) and α,β-unsaturated *N*-(*o*-methoxyphenyl)imines **25** using the **BOX10**-Mg(OTf)$_2$ complex as catalyst was studied. The results are gathered in Table 20. The reaction could be carried out with imines bearing at the β-carbon an aromatic ring substituted with either electron-withdrawing (Table 21, entries 2 and 3) or electron-donating groups (Table 21, entry 4), to give the expected products **26cb-cd** with excellent yields and enantioselectivities. R^1 can also be a heterocyclic furanyl ring (Table 21, entry 5). In this case, compound **26ce** was obtained in almost quantitative yield and slightly lower ee (88%). The introduction of a bulky *tert*-butyl group on the β-carbon brought about a decrease on the reaction rate and the expected lactam **26cf** was obtained with low yield and enantioselectivity (Table 21, entry 6). The R^2 group attached to the azomethinic carbon was also amenable to variation (Table 21, entries 7-14). Aromatic rings bearing either electron-withdrawing or electron-donating groups were permitted without showing much influence on the enantioselectivity of the reaction. Again, when R^2 was a 2-furanyl group, compound **26cm** was obtained with lower ee, although with high yield (Table 21, entry 13). A naphthyl group attached to the imine was also tolerated, compound **26cn** being obtained in 98% yield and 98% ee (Table 21, entry 14). As anticipated, dimethyl and diethyl 2-isocyanatomalonates reacted with imine **25a** to give the expected lactams **26aa** and **26ba** with lower enantioselectivity than diisopropyl 2-isocyanatomalonate (Table 21, entries 15 and 16). In all the examples studied compounds **26** were obtained as single diastereomers with

the *Z*-configuration at the exocyclic double bond, except in the cases of imines **25k** and **25l**, bearing an *o*-substituted phenyl ring attached to the azomethinic carbon, which provided *ca.* 1:1 mixtures of diastereomers (Table 21, entries 11 and 12).

Table 21. Enantioselective [3+2] cycloaddition of 2-isocyanatomalonate esters **24** with unsaturated imines **25**.[a]



entry	24	R	25	R^1	R^2	*t* (h)	26	yield (%)[b]	ee (%)[c]
1	**24c**	*i*Pr	**25a**	Ph	Ph	1.5	**26ca**	97	97
2	**24c**	*i*Pr	**25b**	4-ClC_6H_4	Ph	1.5	**26cb**	93	96
3	**24c**	*i*Pr	**25c**	4-$NO_2C_6H_4$	Ph	1.5	**26cc**	98	98
4	**24c**	*i*Pr	**25d**	4-$MeOC_6H_4$	Ph	1.5	**26cd**	98	96
5	**24c**	*i*Pr	**25e**	2-furanyl	Ph	1	**26ce**	98	88
6	**24c**	*i*Pr	**25f**	*t*Bu	Ph	20	**26cf**	26	23
7	**24c**	*i*Pr	**25g**	Ph	4-ClC_6H_4	1.5	**26cg**	94	99
8	**24c**	*i*Pr	**25h**	Ph	4-$NO_2C_6H_4$	1	**26ch**	98	95
9	**24c**	*i*Pr	**25i**	Ph	4-$MeOC_6H_4$	1	**26ci**	97	98
10	**24c**	*i*Pr	**25j**	Ph	3-$NO_2C_6H_4$	3	**26cj**	87	97
11	**24c**	*i*Pr	**25k**	Ph	2-ClC_6H_4	1.5	**26ck**	98[d]	98[e]
12	**24c**	*i*Pr	**25l**	Ph	2-$NO_2C_6H_4$	27	**26cl**	98[d]	99
13	**24c**	*i*Pr	**25m**	Ph	2-furanyl	1	**26cm**	98	83
14	**24c**	*i*Pr	**25n**	Ph	2-naphthyl	1	**26cn**	98	98
16	**24a**	Me	**25a**	Ph	Ph	1	**26aa**	97	76
15	**24b**	Et	**25a**	Ph	Ph	1	**26ba**	96	77
17[f]	**24c**	*i*Pr	**25a**	Ph	Ph	1.5	**26ca**	96	94

[a] Reaction conditions: **24** (0.19 mmol), **25** (0.125 mmol), **BOX10** (0.0125 mmol), $Mg(OTf)_2$ (0.0125 mmol), 4 Å MS (110 mg), Et_2O (1.1 mL), 0 °C. [b] Yield of isolated product. [c] Determined by HPLC with chiral stationary phases. [d] Obtained as a *ca.* 1:1 mixture of *E/Z* isomers. [e] Determined after enamine hydrolysis. [f] Reaction carried out with 1.6 mmol of **25a**.

Remarkably, the reaction of **24c** and **25a** could be carried out on a 1.6 mmol scale (500 mg) to give the expected product **26ca** in 96% yield with minimal erosion in the enantioselectivity (94% ee, Table 21, entry 17), demonstrating the practicality of this newly developed procedure.

4.6.4. Determination of the absolute stereochemistry of compound 26cb

Compound **26cb** could be crystallized and subjected to X-ray analysis (CCDC 1544707), what allowed to stablish the geometry of the enamine double bond as *Z*, and the configuration of the stereogenic center as *R* (Figure 18). The absolute stereochemistry of all compounds **26** was assigned by analogy upon the assumption of a uniform stereochemical pathway, as usually.

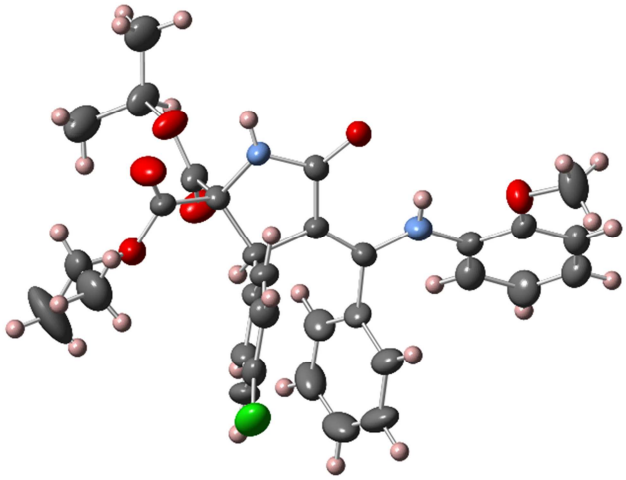
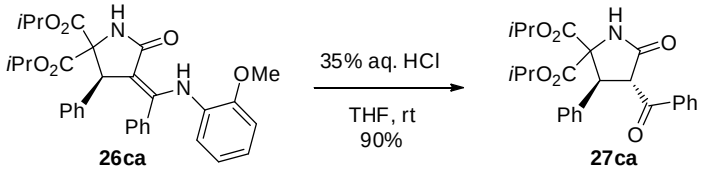


Figure 18. Ortep plot for the X-ray structure of compound **26cb**. The thermal ellipsoids are drawn at the 50% probability level. Flack parameter -0.16(8)

4.6.5. Synthetic transformations

To illustrate the potential application of the γ-lactams resulting from this [3+2] cycloaddition, we carried out some synthetic modifications of compound **26cb.** First, the hydrolysis of the enamine moiety was carried out by treatment with concentrated aqueous HCl in THF to give ketone **27ca** in 90% yield (Scheme 142).



Scheme 142. Hydrolysis of compound **26ca**

The relative stereochemistry of compound **27ca** was determined by NOESY experiments that showed the interaction between proton H4 and one of the protons of the phenyl ring attached to C3 (ring A), indicating that both H4 and this phenyl group are on the same side of the pyrrolidinone ring (Figure 19)

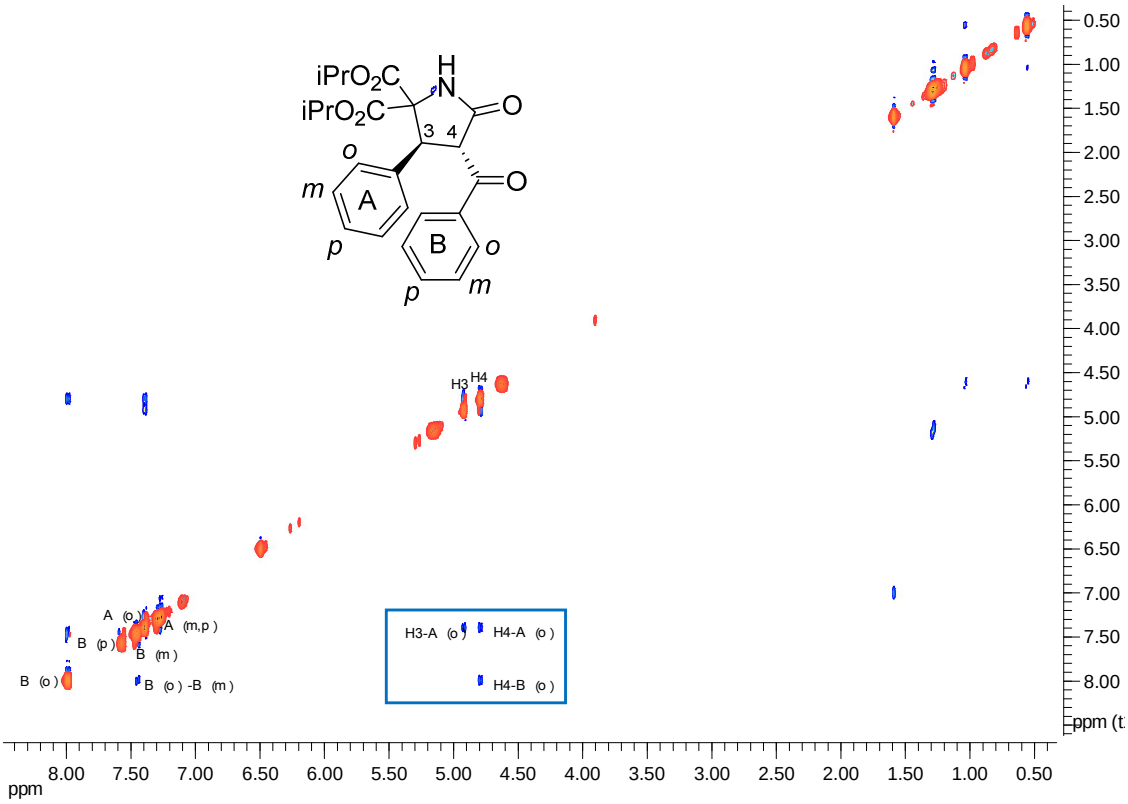
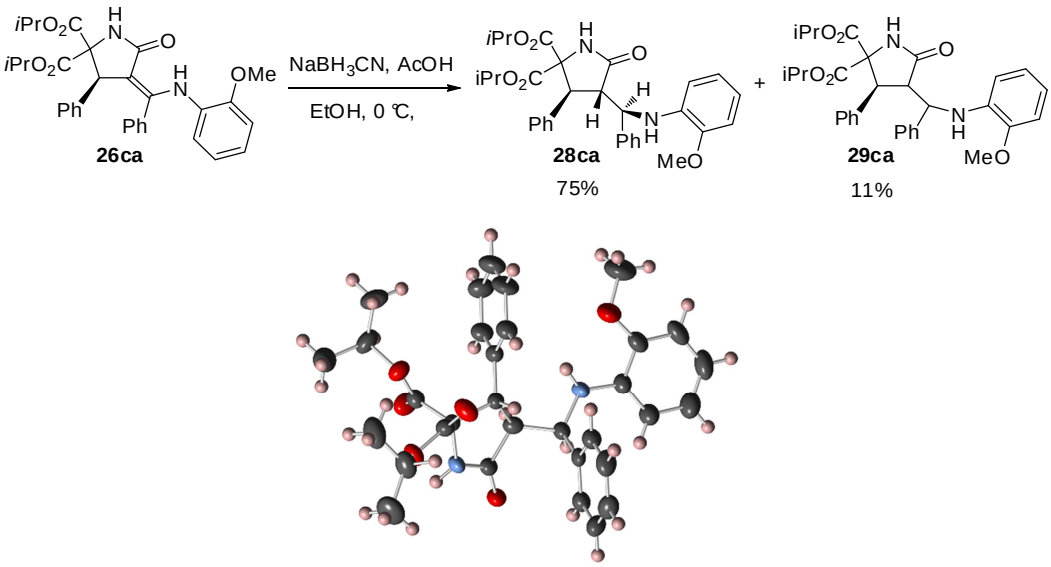


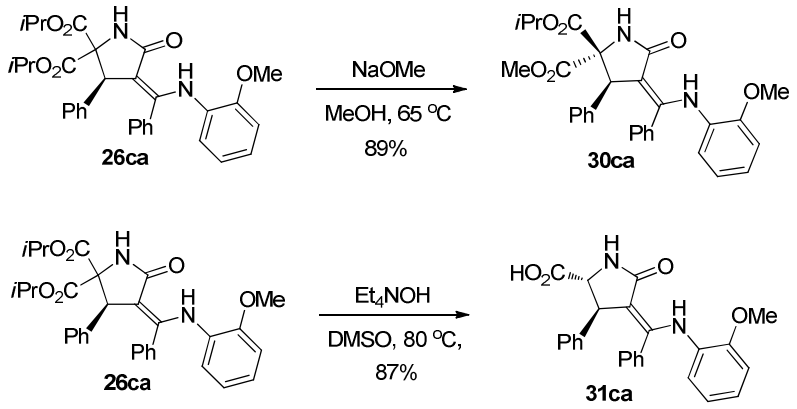
Figure 19. NOESY experiments carried out with compound **27ca**

On the other hand, reduction of the enamine double bond was performed by treatment with $NaBH_3CN$-AcOH in EtOH, which provided two amines **28ca** and **29ca** in 75% and 11% yield, respectively (Scheme 143). The stereochemistry of the major amine could be assigned after crystallization and X-ray analysis (CCDC 1544708). The stereochemistry of the minor amine remains unassigned.



Scheme 143. Reduction of the enamine moiety in compound **26ca** and X-ray structure of compound **28ca**. The thermal ellipsoids drawn at the 50% probability level

Also, the chemoselective transesterification of the diisopropyl ester **26ca** to give the mixed diester **30ca** was efficiently achieved in 89% yield by treatment with NaOMe/MeOH. In the ^{1}H NMR spectra of compounds **30ca** there is a singlet signal at 3.81 ppm corresponding to the new methyl ester group, while both methyls of the remaining isopropyl ester show well separated doublet signals at 0.92 and 0.57 ppm due to the anisotropic effect of the phenyl group attached to C3, which is oriendted to the same side of the molecule (Scheme 144).



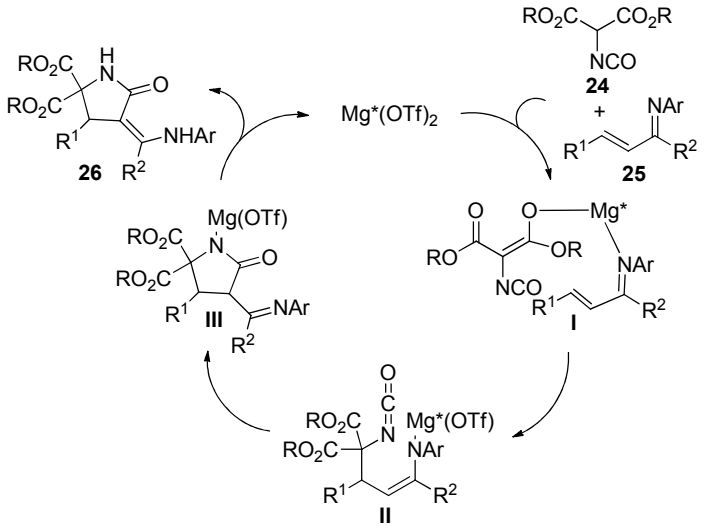
Scheme 144. Chemoselective transesterification and decarboxylation of compound **26ca**

Finally, the pyroglutamic acid derivative **31ca** was obtained in 87% yield after hydrolysis/decarboxylation upon treatment of **26ca** with an excess of tetraethylammonium hydroxyde in DMSO at 80 °C (Scheme 144). The relative stereochemistry (*trans*) was assigned according to the coupling constant values (2.0 Hz) between H2 and H3 by comparison with *J* values reported in the literature for similar compounds.[196]

All the above reactions took place without noticeable loss of enantiomeric excess with respect to starting **26ca**.

4.6.6. Mechanistic proposal

A simplified mechanistic proposal for the formal [3+2] cycloaddition is outlined in Scheme 145. Thus, initial coordination of both reaction partners to the BOX-Mg(OTf)$_2$ complex would result in nucleophilic activation of the malonate ester *via* enolization together with electrophilic activation of the imine (intermediate **I**). Conjugate addition would then lead to enamine intermediate **II** which would undergo nucleophilic addition to the isocyanate group giving lactam **III**. Finally, imine/enamine tautomerization and decoordination would give the final products and release the catalyst.



Scheme 145. Simplified mechanistic proposal. Mg* = Mg-BOX

In summary, we have developed the first enantioselective formal [3+2] cycloaddition of 2-isocyanatomalonate esters with electrophilic alkenes. Using a BOX-Mg(OTf)$_2$ complex as catalyst, diisopropyl 2-isocyanatomalonate reacted with α,β-unsaturated *N*-(*o*-anisidyl) imines to give highly substituted chiral pyrrolidinones featuring a conjugate exocyclic double bond. The reaction products, which are derivatives of pyroglutamic acid, were obtained with excellent yields and high to excellent enantioselectivities for a significative number of unsaturated imines. The use of the *N*-(*o*-anisidyl) group was essential for the success of the reaction as neither the unsaturated ketone nor the unsaturated *N*-tosyl imine were reactive with this catalyst. Furthermore, the reaction does not require the use of diastereomerically pure imines.

5. EXPERIMENTAL SECTION

5. EXPERIMENTAL SECTION

General procedures

All catalytic reactions were carried out in glassware oven-dried overnight at 120 ºC. Reactions were monitored by TLC analysis using Merck Silica Gel 60 F-254 thin layer plates. After elution, TLC plates were observed under UV light and chemically revealed using a solution prepared from $Ce(SO_4)_2$ (10 g), phosphomolibdic acid (25 g) and concentrated H_2SO_4 (80 mL) in water (1L).

Flash column chromatography was performed on Merck silica gel 60, 0.040-0.063 mm.

Solvents and reagents

Analytical quality solvents were used for general purposes. The following solvents were dried and purified when needed: CH_2Cl_2, 1,2-dichloroethane and toluene were freshly distilled from CaH_2 under nitrogen. THF and diethyl ether were freshly distilled from Na/benzophenone under nitrogen. EtOAc, EtOH, *i*PrOH, $CHCl_3$, acetonitrile and 1,4-dioxane were dried and stored on 4 Å molecular sieves, triethylamine and tertiary amines were dried and stored on CaH_2. Most reagents were commercially available and used as purchased without further purification.

4 Å molecular sieves for the enantioselective reactions (8-12 mesh, beads Aldrich 208604) were dried at the flame under vacuum (oil pump) and stored in a closed flask and used before a week.

Melting points

Melting points were measured in capillary tubes in a "Büchi M-560" instrument and are uncorrected.

Nuclear magnetic resonance (NMR)

NMR spectra were run in a Bruker Avance 300 DPX spectrometer (300 MHz for ^{1}H, 75 MHz for ^{13}C and 282 MHz for ^{19}F NMR). In some cases a Bruker Avance 400 spectrometer (400 MHz for ^{1}H) was used, especially for NOE and NOESY experiments.

Samples were dissolved in deuterated solvents as stated, using the residual non-deuterated solvent as internal standard (δ 7.26 for ^{1}H NMR and δ 77.00 for ^{13}C NMR in the case of $CDCl_3$, δ 2.50 for ^{1}H NMR and δ 39.52 for ^{13}C NMR in the case of DMSO-d_6). For ^{19}F NMR experiments, $CFCl_3$ was used as internal standard. Chemical shifts (δ values) are given in ppm. Coupling constants (*J*) are given in Hz. The carbon multiplicity was determined by DEPT experiments.

Polarimetry

Specific optical rotations were measured in a Perkin-Elmer polarimeter using sodium light (D line 589 nm) in a 1 dm cell. Concentrations (*c*) are given in g/100 mL.

Mass spectrometry

Electrospray ionization mass spectra (ESI) were recorded on a Waters Q-TOF premier mass spectrometer equipped with an electrospray source with a capillary voltage of 3.3 kV.

HPLC analyses

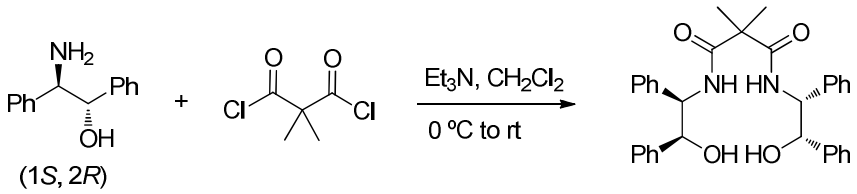
Chiral HPLC analyses were performed in an Agilent 1100 series instrument equipped with a refraction index detector or in a Hitachi Elite Lachrom instrument equipped with a Hitachi UV diode-array L-4500 detector using chiral stationary columns from Daicel or Phenomenex. Variable mixtures of hexane and isopropanol were used as eluents. Retention times (t_r) are expressed in minutes.

Chiral ligands

BOX and pyBOX ligands were commercially available or synthesized following procedures described in the literature. Some typical procedures follow:

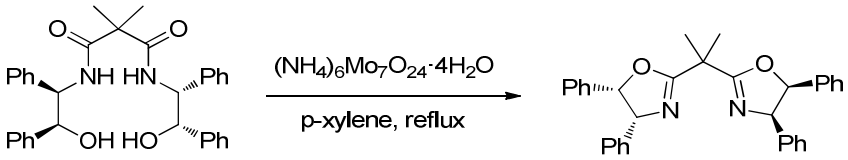
Synthesis of ligands BOX9 and BOX11[197]

***N*^{1},*N*^{3}-bis*((1R,2S)*-2-hydroxy-1,2-diphenylethyl)-2,2-dimethylmalonamide**



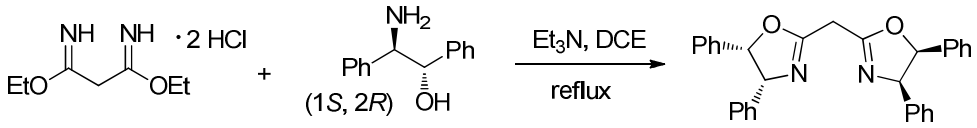
(1*S*,2*R*)-2-Amino-1,2-diphenylethanol (3.0 g, 14.0 mmol) was suspended in dichloromethane (36 mL), triethylamine (3.56 g, 35.0 mmol) was added and the reaction flask was introduced in a bath at 0 °C. After 10 minutes, malonyl dichloride (0.684 mL, 7.03 mmol) was added dropwise, and the mixture was stirred at room temperature overnight. Then, the reaction mixture was diluted with dichloromethane (200 mL), quenched with 2M HCl (2×40 mL) and brine (40 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was used in the next step without further purification.

(4*R*,4'*R*,5*S*,5'*S*)-2,2'-(Propane-2,2-diyl)bis(4,5-diphenyl-4,5-dihydrooxazole) BOX9



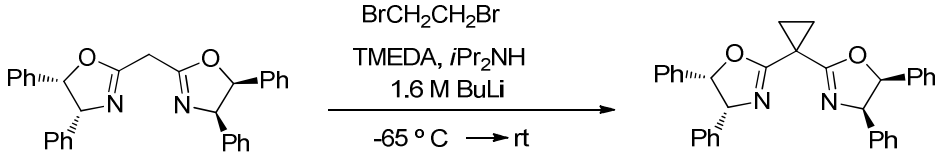
A solution of the previous bis-hydroxyamide (3.74g, 7.16 mmol) and $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (1.13 g, 1.07 mmol) in *p*-xylene (215 mL) was heated at reflux in a Dean-Stark system for 20 h. After cooling to room temperature, the mixture was concentrated under reduced pressure and the chromatographed on silica gel eluting with hexane/EtOAc mixtures to give **BOX9** (3.0g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01-6.96 (m, 20H), 5.97 (d, *J* = 10.2 Hz, 2H), 5.60 (d, *J* = 10.2 Hz, 2H), 1.93 (s, 6H).

Bis((4*R*,5*S*)-4,5-diphenyl-4,5-dihydrooxazol-2-yl)methane (BOX8)



A solution of commercially available diethyl malonimidate dihydrochloride (0.61g, 2.66 mmol) and (1*S*,2*R*)-2-amino-1,2-diphenylethanol (1.15 g, 5.31 mmol) in dry DCE (10.6 mL) was refluxed under N_2 atmosphere for 1 hour. Afterwards, a solution of Et_3N (0.74 mL, 5.31 mmol) dry DCE (2.8 mL) was added to the reaction mixture over 30 minutes, and the mixture was refluxed for additional 3.5 hours. The mixture was cooled down to room temperature until precipitation of a white solid. After filtration, the residue was purified by column chromatography eluting with DCM/MeOH mixtures (98:2 to 95:5) to give **BOX8** (975 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (s, 10H), 6.99 (s, 10H), 5.99 (d, *J* = 10.2 Hz, 2H), 5.65 (dt, *J* = 10.2, 0.9 Hz, 2H), 3.90 (t, *J* = 1.2 Hz, 2H).

(4*R*,4'*R*,5*S*,5'*S*)-2,2'-(cyclopropane-1,1-diyl)bis(4,5-diphenyl-4,5-dihydrooxazole) BOX10[198]

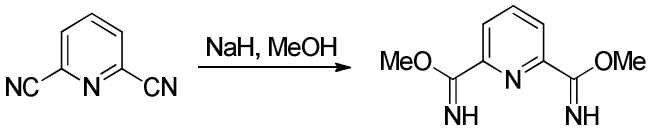


TMEDA (0.73 mL, 4.83 mmol) and diisopropyl amine (0.28 mL, 2.1 mmol) were added to a solution of previously prepared **BOX8** (963 mg, 2.1 mmol) in dry THF (30 mL), under N_2 atmosphere, and the solution was introduced in a bath at -65ºC. After 10 minutes, BuLi 1.6 M in hexanes (2.62 mL, 4.2 mmol) was added to the reaction via syringe and the solution was warmed to -20ºC. After 50 minutes, the solution was cooled again to -65 ºC, 1,2-dibromoethane (0.19 mL, 2.2 mmol) was added and the reaction mixture was stirred for 16 h at room temperature. Then, the reaction was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with methyl *tert*-butyl ether (15 mL). The extract was dried over $MgSO_4$, filtered and concentrated under

reduced pressure and purified by column chromatography eluting with hexane/EtOAc mixtures (50:50 to 40:60) to give **BOX10** (366 mg, 36%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02-6.96 (m, 20H), 5.96 (d, *J* = 10.2 Hz, 2H), 5.60 (d, *J* = 10.2 Hz, 2H), 1.83-1.76 (m, 4H).

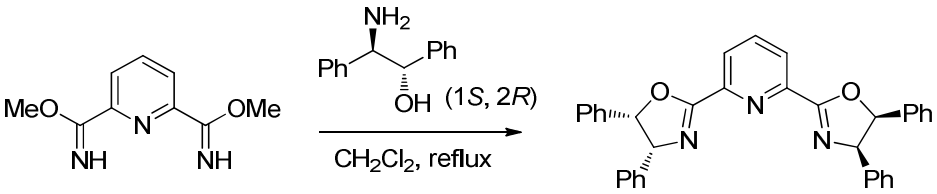
Synthesis of ligands pyBOX9 and pyBOX4

Dimethyl pyridine-2,6-bis(carbimidate)



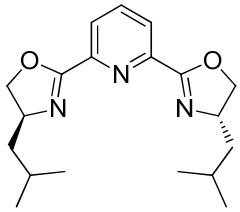
Sodium hydride (60% dispersion in mineral oil, 20.5 mg, 0.51 mmol) was added to a solution of pyridine-2,6-dicarbonitrile (0.6 g, 4.6 mmol) in anhydrous MeOH (5 mL) and the mixture was stirred at rt overnight. Acetic acid (34.6 μL, 0.61 mmol) was added and after 90 minutes, the solvent was removed under reduced pressure to give the title compound which was dried overnight in a desiccator containing P_2O_5 before use.

2,6-Bis((4*R*,5*S*)-4,5-diphenyl-4,5-dihydrooxazol-2-yl)pyridine (pyBOX9)



A solution of dimethyl pyridine-2,6-bis(carbimidate) (361 mg, 1.87 mmol) and (1*S*,2*R*)-2-amino-1,2-diphenylethanol (812 mg, 3.75 mmol) in dichloromethane (20 mL) was heated under reflux for 5 days. The reaction mixture was then cooled to r.t., dichloromethane was evaporated under reduced pressure and the product was filtered and washed with water and methanol. The residue was purified by silica gel column chromatography to give **pyBOX9** (663 mg, 68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, *J* = 8.1 Hz, 2 H), 8.04 (t, *J* = 7.8 Hz, 1 H), 7.06-6.96 (m, 20 H), 6.15 (d, *J* = 10.2 Hz, 2 H), 5.83 (d, *J* = 10.2 Hz, 2 H).

2,6-Bis((*S*)-4-isobutyl-4,5-dihydrooxazol-2-yl)pyridine (pyBOX4)



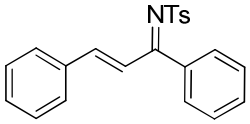
Was prepared in 70% yield following the same procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.8 Hz, 2H), 7.84 (t, *J* =7.5 Hz, 1H), 4.60 (dd, *J* = 9.3, 8.1Hz, 2H), 4.43-4.33 (m, 2H), 4.08 (t, *J* = 8.4 Hz, 2H), 1.89-1.68 (m, 4H), 1.89-1.80 (m, 2H), 1.77-1.68 (m, 2H), 1.43-1.34 (m, 2H), 0.97 (d, *J* = 5.7 Hz, 6H), 0.96 (d, *J* = 5.7 Hz, 6H).

5.1. Asymmetric conjugate addition of malonate esters to α,β-unsaturated *N*-tosyl ketimines catalyzed by pyBOX-La(OTf)$_3$

5.1.1. Synthesis and characterization of α,β-usaturated *N*-tosyl imines 2

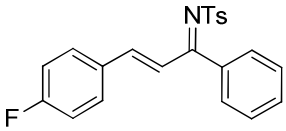
The procedure reported by Carretero was followed:[22] to a solution of enone (4.8 mmol) and *p*-toluenesulfonamide (820 mg, 4.8 mmol) in dry dichloromethane (60 mL) at 0 ºC under nitrogen atmosphere, was added via syringe Et_3N (1.5 mL, 1.07 g, 10.6 mmol) followed by $TiCl_4$ (0.58 mL, 1.0 g, 5.3 mmol). The reaction was heated at reflux temperature for 20 h. Then it was cooled to room temperature and quenched with water (50 mL). The two layers were separated and the aqueous layer was extracted with dichloromethane (3×50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with hexane/EtOAc mixtures afforded the corresponding imine**s 2** (70-85% yield). The imines were recrystallized from *ca.* 1:1 hexane/EtOAc mixtures and stored in the freezer.

(*E*)-1,3-Diphenyl-*N*-tosylprop-2-en-1-imine (2a)[22]



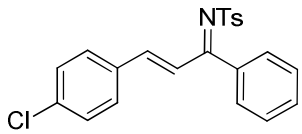
Mp 153-154 °C (hexane-EtOAc); ^{1}H NMR (300 MHz,$CDCl_3$) δ 7.94 (d, *J* = 7.8 Hz, 2H), 7.66 (d, *J* = 7.2 Hz, 2H), 7.59-7.39 (m, 8H), 7.32 (d, *J* = 8.1 Hz , 2H), 7.07 (d. *J* = 15.9 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7 (C), 148.9 (CH), 143.6 (C), 138.8 (C), 134.6 (C), 132.1 (CH), 131.2 (CH), 130.4 (CH), 129.5 (CH), 129.1, (CH) 128.8 (CH), 128.5 (CH), 127.3 (CH), 21.7 (CH_3).

(*E*)-3-(4-Fluorophenyl)-1-phenyl-*N*-tosylprop-2-en-1-imine (2b)[40]



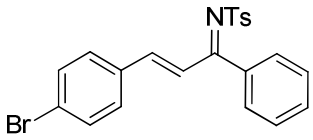
Mp 138-139 °C (hexane-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.8 Hz, 2H), 7.64 (d, *J* = 6.9 Hz, 2H), 7.59-7.52 (m, 3H), 7.46-7.41 (m, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.10 (t, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 16.2 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.5 (C), 164.5 (d, $J_{C\text{-}F}$ = 251.3 Hz, C), 147.5 (CH), 143.6 (C), 138.8 (C), 132.1 (C), 130.96 (d, $J_{C\text{-}F}$ = 3.0 Hz, CH), 130.90 (d, $J_{C\text{-}F}$ = 8.3 Hz, CH), 129.6 (CH), 128.5 (CH), 127.3 (CH), 116.4 (d, $J_{C\text{-}F}$ = 22.5 Hz, CH), 21.7 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ -108.5 (s, 1F);

(*E*)-3-(4-Chlorophenyl)-1-phenyl-*N*-tosylprop-2-en-1-imine (2c)[40]



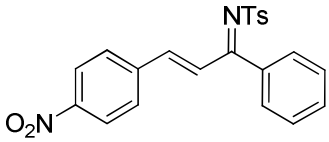
Mp 141-142 °C (hexane-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.5 Hz, 2H), 7.64 (d, *J* = 7.5, 2H), 7.58-7.37 (m, 7H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.01 (d, *J* = 15 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.2 (C), 143.7 (C), 143.4 (C), 138.7 (C), 137.2 (C), 133.1 (CH), 132.2 (CH), 130.2 (CH), 130.0 (CH), 129.7 (CH), 129.6 (CH), 129.5 (CH), 128.8 (CH), 128.5 (CH), 127.3 (CH), 21.7 (CH_3).

(*E*)-3-(4-Bromophenyl)-1-phenyl-*N*-tosylprop-2-en-1-imine (2d)[40]



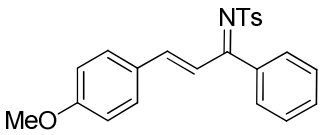
Mp 133-134 °C (hexane-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.8 Hz, 2H), 7.64 (d, *J* = 7.8 Hz, 2H), 7.58-7.53 (m, 3H), 7.44 (dt, *J* = 7.5, 1.2 Hz, 4H), 7.32 (d, *J* = 8.1 Hz, 2H), 6.99 (d, *J* = 16.2 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3 (C), 147.2 (C), 143.7(C), 138.7 (C), 133.6 (C), 132.4 (CH), 132.2 (CH), 130.3 (CH), 130.1 (CH), 129.6 (CH), 128.6 (CH), 127.3 (CH), 125.7 (CH), 123.3 (CH), 21.7 (CH_3).

(*E*)-3-(4-Nitrophenyl)-1-phenyl-*N*-tosylprop-2-en-1-imine (2e)



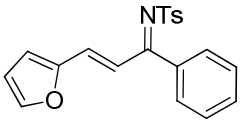
Mp 150-151 °C (hexane-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.7 Hz, 2H), 7.92 (d, *J* = 7.8 Hz, 2H), 7.74-7.67 (m, 4H), 7.58 (tt, *J* = 7.5 Hz, 1.2, 1H), 7.46 (m, 2H), 7.34 (d, *J* = 7.8 Hz, 2H), 7.07 (d, *J* = 16.2 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5 (C), 148.8 (CH), 144.3 (C), 144.0 (C), 140.7 (C), 138.3 (C), 132.7 (C) 130.3 (CH), 129.7 (CH), 129.2 (CH), 128.7 (CH), 127.4 (CH), 126.5 (CH), 124.4 (CH), 21.7 (CH_3); HRMS (ESI) *m/z* 407.1076 $[M]^+$, $C_{22}H_{19}N_2O_4S$ required 407.1060.

(*E*)-3-(4-Methoxyphenyl)-1-phenyl-*N*-tosylprop-2-en-1-imine (2f)[99]



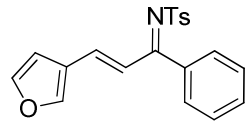
Mp 96-98 °C (hexane-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.8 Hz, 2H), 7.61 (d, *J* = 7.2 Hz, 2H), 7.56-7.50 (m, 3H), 7.45-7.40 (m, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.04 (d, *J* = 10.5 Hz, 1H), 6.92 (dt, *J* = 8.7, 3 Hz, 2H), 3.86 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.1 (C), 162.4 (C), 149.5 (CH), 143.42 (C), 139.0 (C), 131.7 (CH), 130.9 (CH), 130.2 (CH), 129.5 (CH), 128.4 (CH), 127.4 (CH), 127.3 (CH), 114.7 (CH), 55.6 (CH_3), 21.7 (CH_3).

(*E*)-3-(Furan-2-yl)-1-phenyl-*N*-tosylprop-2-en-1-imine (2g)[136]



Mp 125-126 °C (hexane-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.8 Hz, 3H), 7.60-7.58 (m, 3 H), 7.52 (tt, *J* = 7.2, 1.5 Hz, 1H), 7.42 (tt, *J* = 7.5, 1.8 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 2H), 6.83 (d, *J* = 15.7 Hz, 1H), 6.67 (d, *J* = 3.6 Hz, 1H), 6.51 (q, *J* = 1.8 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4 (C), 166.9 (C), 151.1 (CH), 146.4 (C), 143.5 (C), 138.9 (C), 135.0 (CH), 131.8 (CH), 131.7 (CH), 130.0 (CH), 129.5 (CH), 128.5 (CH) , 127.3 (CH), 117.2 (CH), 113.1 (CH), 21.7 (CH_3).

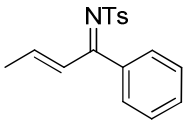
(*E*)-3-(Furan-3-yl)-1-phenyl-*N*-tosylprop-2-en-1-imine (2h)



Mp 120-121 °C (hexane-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.5 Hz, 3H), 7.62-7.58 (m, 3H), 7.53 (tt, *J* = 7.5, 2.4 Hz, 1H), 7.48 (unresolved t, 1H), 7.42 (tt, *J* = 6.9, 1.5 Hz, 2H),

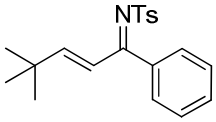
7.31 (d, *J* = 8.1 Hz, 2H), 6.99 (d, *J* = 15.6 Hz, 1H), 6.78 (br, 1H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8 (C), 145.9 (CH), 145.0 (CH), 143.6 (C), 139.5 (CH), 138.8 (C), 131.9 (CH), 130.1 (CH), 129.5 (CH), 128.5 (CH), 127.3 (CH), 123.6 (C), 122.6 (C), 107.7 (CH), 21.7 (CH_3); HRMS (ESI) *m/z* 352.1.013 $[M]^+$, $C_{20}H_{18}NO_3S$ required 352.1002.

(*E*)-1-phenyl-*N*-tosylbut-2-en-1-imine (2i)[92]



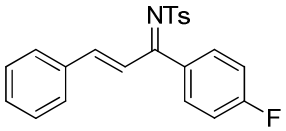
Mp 102-103 °C (hexane-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.8 Hz, 2H), 7.56 (br d, *J* = 7.2 Hz, 2H), 7.49 (tt, *J* = 7.2, 2.4 Hz, 1H), 7.41-7.35 (m, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 6.43 (dq, *J* = 15.9, 6.6 Hz, 1H), 2.42 (s, 3H), 2.04 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9 (C), 150.3 (CH), 143.5 (C), 138.9 (C), 137.5 (C), 132.0 (CH), 130.2 (CH), 129.5 (CH), 128.3 (CH), 127.6 (CH), 127.3 (CH), 21.7 (CH_3), 19.6 (CH_3).

(*E*)-4,4-Dimethyl-1-phenyl-*N*-tosylpent-2-en-1-imine (2j)[157]



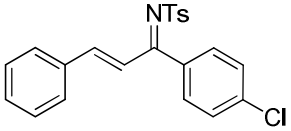
Mp 158-163 °C (hexane-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.8 Hz, 2H), 7.57 (d, *J* = 6.6 Hz, 2H) 7.51 (tt, *J* = 7.2, 2.1 Hz, 1H), 7.39 (tt, *J* = 6.3, 1.2 Hz, 2H), 7.31 (d, *J* = 17.7 Hz, 3H), 6.35 (d, *J* = 15.9 Hz, 1H), 2.42 (s, 3H), 1.13 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.8 (C), 163.9 (CH), 143.5 (C), 138.9 (C), 132.1 (CH), 130.4 (CH), 129.5 (CH), 128.3 (CH), 127.3 (CH), 35.2 (C), 28.7 (CH_3), 21.7 (CH_3). HRMS (ESI) *m/z* 342.1534 $[M]^+$, $C_{20}H_{24}NO_2S$ required 342.1522.

(*E*)-1-(4-Fluorophenyl)-3-phenyl-*N*-tosylprop-2-en-1-imine (2k)



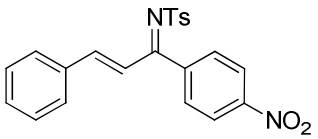
Mp 173-174 °C (hexane-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.1 Hz, 2H), 7.71-7.67 (m, 2H), 7.59-7.56 (m, 2H), 7.46-7.38 (m, 3H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.13 (tt, *J* = 8.7, 2.1 Hz, 2H), 7.04 (d, *J* = 15.9 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4 (C), 165.2 (d, J_{C-F} = 250.0 Hz, C), 148.7 (CH), 143.7 (C), 138.7 (C), 134.5 (C), 133.4 (C), 132.7 (br, CH), 131.3 (CH), 129.6 (CH), 129.2 (CH), 128.9 (CH), 127.3 (CH), 122.6 (br, C), 115.8 (d, J_{C-F} = 21.8 Hz, CH), 21.7 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ -107.2 (s, 1F); HRMS (ESI) *m/z* 380.1132 $[M]^+$, $C_{22}H_{19}FNO_2S$ required 380.1121.

(*E*)-1-(4-Chlorophenyl)-3-phenyl-*N*-tosylprop-2-en-1-imine (2l)[99]



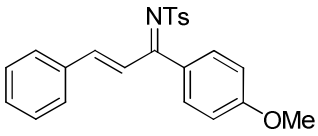
Mp 139-140 °C (hexane-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.1 Hz, 2H), 7.61-7.56 (m, 4H), 7.43-7.38 (m, 5 H), 7.32 (d, *J* = 7.8 Hz, 2H), 7.04 (d, *J* = 15.9 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4 (C), 148.9 (CH), 143.8 (C), 138.6 (C), 138.4 (C), 134.5 (C), 131.6 (CH), 131.4 (CH), 129.6 (CH), 129.2 (CH), 128.9 (CH), 128.8 (CH), 127.3 (CH), 21.7 (CH_3).

(*E*)-1-(4-Nitrophenyl)-3-phenyl-*N*-tosylprop-2-en-1-imine (2m)



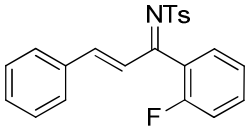
Mp 121-123 °C (hexane-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.4 Hz, 2H), 8.15 (br d, *J* = 15.3 Hz, 1H), 7.92 (br d, *J* = 6 Hz, 2H), 7.79 (br d, *J* = 6.6 Hz, 2H), 7.57 (br s, 2H), 7.44-7.42 (m, 3H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.01 (br d, *J* = 15.6 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1 (C), 150.0 (CH), 149.6 (C), 144.2 (C), 143.2 (C), 138.1 (C), 134.1 (C), 131.9 (CH), 131.1 (CH), 129.7 (CH), 129.3 (CH), 129.1 (CH), 127.4 (CH), 123.6 (CH), 121.9 (CH), 21.7 (CH_3); HRMS (ESI) *m/z* 406.0994 $[M]^+$, $C_{22}H_{18}N_2O_4S$ required 406.0987.

(*E*)-1-(4-Methoxyphenyl)-3-phenyl-*N*-tosylprop-2-en-1-imine (2n)[99]



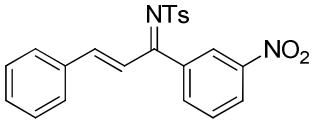
Mp 128-129 °C (hexane-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.7 Hz, 2H), 7.59-7.56 (m, 2H), 7.43-7.40 (m, 3H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.05 (d, *J* = 15.9 Hz, 1H), 6.93 (dt, *J* = 9, 2.1 Hz, 2H), 3.87 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9 (C), 163.4 (C), 147.5 (CH), 143.4 (C), 139.0 (C), 134.8 (C), 132.7 (CH), 130.9 (CH), 129.5 (CH), 129.1 (CH), 128.7 (CH), 127.2 (CH), 113.9 (CH), 55.6 (CH_3), 21.7 (CH_3).

(*E*)-1-(2-Fluorophenyl)-3-phenyl-*N*-tosylprop-2-en-1-imine (2o)



An oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (br s, 1H), 7.80 (br s, 1H), 7.58-7.23 (m, 10H), 7.19-7.13 (m, 1H), 7.10-6.91 (m, 2H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7 (C), 149.7 (CH), 148.9 (CH), 143.8 (C), 134.5 (C), 132.6 (CH), 131.4 (CH, d, $J_{C\text{-}F}$ = 18.0 Hz), 129.6 (CH), 129.1 (CH), 128.8 (CH, d, $J_{C\text{-}F}$ = 7.5 Hz), 127.4 (CH, d, $J_{C\text{-}F}$ = 11.3 Hz), 124.4 (CH), 122.7 (CH), 116.5 (CH), 115.8 (CH), 21.7 (CH3); ^{19}F NMR (282 MHz, $CDCl_3$) δ -112.5 (s, 1F); HRMS (ESI) *m/z* 380.1132 $[M]^+$, $C_{22}H_{19}FNO_2S$ required 380.1121.

(*E*)-1-(3-Nitrophenyl)-3-phenyl-*N*-tosylprop-2-en-1-imine (2p)



Mp 134-135 °C (hexane-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (dq, *J* = 8.4, 1.2 Hz, 1H), 8.15 (d, *J* = 16.5 Hz, 1H), 7.94-7.92 (m, 3H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.63 (br s, 2H), 7.45-7.42 (m, 3H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.03 (d, *J* = 15.6 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8 (C), 149.7 (CH), 148.2 (C), 144.2 (C), 140.0 (C), 138.1 (C), 135.8 (CH), 134.2 (C), 131.8 (CH), 129.8 (CH), 129.7 (CH), 129.3 (CH), 129.1 (CH), 127.4 (CH), 126.3 (CH), 124.9 (CH), 121.9 (CH), 21.7 (CH_3); HRMS (ESI) *m/z* 406.0992 $[M]^+$, $C_{22}H_{18}N_2O_4S$ required 406.0987.

5.1.2. Enantioselective conjugate addition of methyl malonate to α,β-usaturated *N*-tosyl imines 2

5.1.2.1. General procedure for the enantioselective conjugate addition

Anhydrous $La(OTf)_3$ (7.3 mg, 0.0125 mmol) and **pyBOX1** (4.6 mg, 0.012 mmol) were introduced in a Schlenk tube and it was filled with nitrogen. CH_2Cl_2 (0.4 mL) was added *via* syringe and the mixture was stirred for 30 min. Powdered 4Å MS (20 mg) was then added followed by a solution of imine **2** (0.12 mmol) dissolved in dry CH_2Cl_2 (0.4 mL), and dimethyl malonate (**1a**, 35 μL, 0.3 mmol). The mixture was stirred at room temperature for the indicated time and chromatographed on silica gel eluting with hexane/EtOAc mixtures to give compounds **3**. In general the minor *Z*-diastereomer eluted first from the column followed by the major *E*-diastereomer.

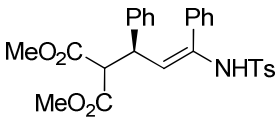
5.1.2.2. General procedure for the synthesis of the racemic products

Racemic compounds for comparative purpose were prepared by following the same procedure, using picolylamine instead of **pyBOX1**.

5.1.2.3. Characterization of products 3

See Table 3 (Page 64) for yield, dr and ee.

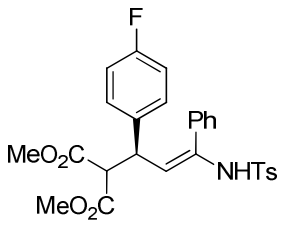
Dimethyl 2-[(*S*,*E*)-1,3-diphenyl-3-(tosylamino)allyl]malonate (3aa).



Chiral HPLC analysis: Chiralpak AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *E*-diastereomer: *major enantiomer* t_r = 13.9 min, *minor enantiomer* t_r = 18.3 min; *Z*-diastereomer unresolved t*r* = 65.3 min.

Major *E*-diastereomer: an oil; $[\alpha]_D^{20}$ -76.0 (*c* 1.0, $CHCl_3$, ee = 86%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.4 Hz, 2H), 7.35-7.18 (m, 6H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.96 (dd, *J* = 8.1, 2.4 Hz, 2H), 6.90 (dd, *J* = 8.1, 1.5 Hz, 2H), 6.05 (s, 1H), 5.95 (d, *J* = 10.8 Hz, 2H), 4.00 (t, *J* = 10.5 Hz, 1H), 3.77 (d, *J* = 10.5 Hz, 1H), 3.67 (s, 3H), 3.40 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0 (C), 167.7 (C), 143.7 (C), 141.2 (C), 136.4 (C), 135.8 (C), 135.3 (CH), 129.6 (CH), 129.1 (CH), 128.70 (CH), 128.69 (CH), 128.6 (CH), 127.7 (CH), 127.0 (CH), 117.2 (CH), 58.1 (CH), 52.6 (CH_3), 52.4 (CH_3), 44.1 (CH), 21.7 (CH_3). **Minor *Z*-diastereomer**: an oil; $[\alpha]_D^{20}$ -23.4 (*c* 0.95, $CHCl_3$, ee = n.d.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.36-7.32 (m, 2H), 7.22-7.05 (m, 8H), 6.70-6.69 (m, 2H), 5.45 (dd, *J* =10.8, 0.3 Hz, 2H), 3.89 (t, *J* = 10.5 Hz, 1H), 3.74 (d, *J* = 10.2 Hz, 1H), 3.63 (s, 3H), 3.37 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7 (C), 167.7 (C), 143.4 (C), 138.8 (C) , 137.8 (C), 137.3 (C), 136.5 (C), 129.7 (CH), 128.8 (CH), 128.6 (CH), 128.1 (CH), 127.8 (CH), 127.6 (CH), 127.4 (CH), 123.0 (CH), 57.8 (CH), 53.3 (CH_3), 52.8 (CH_3), 43.3 (CH), 21.6 (CH_3); HRMS (ESI) *m/z* 516.1453 $[M+Na]^+$, $C_{27}H_{27}NNaO_6S$ required 516.1451.

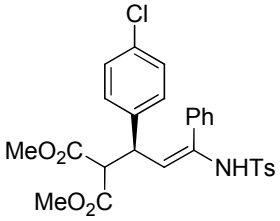
Dimethyl 2-[(*S*,*E*)-1-(4-fluorophenyl)-3-phenyl-3-(tosylamino)allyl]malonate (3ab)



Chiral HPLC analysis: Chiralpak AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *E*-diastereomer: *major enantiomer* t_r = 14.7 min, *minor enantiomer* t_r = 18.0 min.; *Z*-diastereomer: unresolved t_r = 68.3 min.

Major *E*-diastereomer: an oil; $[\alpha]_D^{20}$ -30.6 (*c* 1.0, $CHCl_3$, ee = 86%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.1 Hz, 2H), 7.33-7.24 (m, 4H), 7.19 (d, *J* = 8.1 Hz, 2H), 6.94-6.87 (m, 6H), 6.04 (br s, 1H), 5.90 (d, 10.8 Hz, 1H), 3.98 (t, *J* =10.5 Hz, 1H), 3.72 (d, *J* = 10.5 Hz, 1H), 3.66 (s, 3H), 3.42 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9 (C), 167.7 (C), 161.7 (d, J_{C-F} = 250.0 Hz, C), 143.9 (C), 137.1 (C), 136.4 (C), 136.0 (C), 135.2 (C), 129.7 (CH), 129.3 (d, J_{C-F} = 4.8 Hz, CH), 129.2 (d, J_{C-F} = 7.9 Hz, CH), 128.7 (CH), 128.6 (CH), 127.7 (CH), 116.4 (CH), 115.5 (d, J_{C-F} = 26.2 Hz, CH), 58.1 (CH), 52.7 (CH_3), 52.5 (CH_3), 43.3 (CH), 21.7 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ -115.7 (s, 1F). **Minor *Z*-diastereomer**: an oil; $[\alpha]_D^{20}$ -39.8 (*c* 0.44, $CHCl_3$, ee = n.d.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.29-7.23 (m, 3H), 7.14 (d, *J* = 8.4 Hz, 2H), 6.95-6.83 (m, 2H), 6.77-6.73 (m, 2H), 5.47 (d, *J* = 10.8 Hz, 1H), 4.00 (t, *J* = 10.8 Hz, 1H), 3.72 (s, 3H), 3.70 (d, J = 10.8 Hz, 1H), 3.47 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5 (C), 167.6 (C), 143.5 (C), 137.6 (C), 137.4 (C), 136.7 (C), 134.7 (d, J_{C-F} = 3.0 Hz, CH), 129.7 (CH), 129.3 (d, J_{C-F} = 8.3 Hz, CH), 128.9 (CH), 128.1 (CH), 127.8 (CH), 127.4 (CH), 122.9 (CH), 115.6 (d, J_{C-F} = 21.0 Hz, CH), 57.7 (CH), 53.4 (CH_3), 52.9 (CH_3), 42.8 (CH), 21.6 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ -115.3 (s, 1F); HRMS (ESI) *m/z* 534.1373 $[M+Na]^+$, $C_{27}H_{26}FNNaO_6S$ required 534.1357.

Dimethyl 2-[(*S*,*E*)-1-(4-chlorophenyl)-3-phenyl-3-(tosylamino)allyl]malonate (3ac)

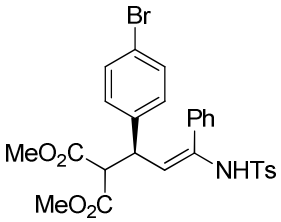


Chiral HPLC analysis: Chiralpak AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *E*-diastereomer: *major enantiomer* t_r = 14.9 min, *minor enantiomer* t_r = 18.0 min.; *Z*-diastereomer: unresolved t_r = 63.5 min.

Major *E*-diastereomer: an oil; $[\alpha]_D^{20}$ -17.6 (*c* 1.0, $CHCl_3$, ee = 86%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.4 Hz, 2H), 7.35-7.16 (m, 7H), 6.91-6.84 (m, 4H), 6.15 (s, 1H), 5.88 (d, *J* = 10.8 Hz, 1H), 3.97 (t, *J* = 10.5 Hz, 1H), 3.74 (d, *J* = 10.5 Hz, 1H), 3.67 (s, 3H), 3.43 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8 (C), 167.6 (C), 144.0 (C), 139.9 (C), 136.3 (C), 136.2 (C), 135.1 (C), 132.7 (C), 129.6 (CH), 129.2 (CH), 129.0 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 127.7 (CH), 116.0 (CH), 57.7 (CH), 52.7 (CH_3), 52.5 (CH_3), 43.4 (CH), 21.7 (CH_3). **Minor *Z*-diastereomer**: an oil; $[\alpha]_D^{20}$ -4.1 (*c* 0.56, $CHCl_3$, ee = n.d.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.56 (d, *J* = 8.1 Hz, 2H), 7.39 (dd, *J* = 7.2, 1.5 Hz, 2H), 7.29-7.12 (m, 8H), 6.72 (d, *J* = 8.4 Hz, 2H), 5.45 (d, *J* = 10.8 Hz, 1H), 3.99 (t, *J* = 10.8 Hz, 1H), 3.71 (s, 3H), 3.70 (d, *J* = 10.8 Hz, 1H), 3.49 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (75

MHz, $CDCl_3$) δ 169.4 (C), 167.6 (C), 143.5 (C), 137.6 (C), 137.4 (C), 137.3 (C), 136.9 (C), 133.2 (C), 129.7 (CH), 129.0 (CH), 128.8 (CH), 128.1 (CH), 127.8 (CH), 127.3 (CH), 122.5 (CH), 57.5 (CH), 53.4 (CH_3), 53.0 (CH_3), 42.8 (CH), 21.7 (CH_3); HRMS (ESI) *m/z* 550.1065 $[M+Na]^+$, $C_{27}H_{26}ClNNaO_6S$ required 550.1062.

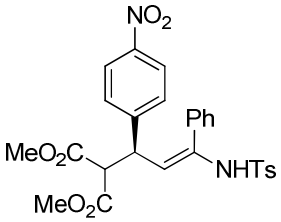
Dimethyl 2-[(*S*,*E*)-1-(4-bromophenyl)-3-phenyl-3-(tosylamino)allyl]malonate (3ad)



Chiral HPLC analysis: Chiralpak AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *E*-diastereomer: major enantiomer t_r = 15.8 min, *minor enantiomer* t_r = 19.3 min.; *Z*-diastereomer: unresolved t_r = 64.0 min.

Major *E*-diastereomer: an oil; $[\alpha]_D^{20}$ -70.5 (*c* 0.9, $CHCl_3$, ee = 85%) for the mixture of diastereomers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.1 Hz, 2H), 7.38-7.25 (m, 6H), 7.18 (d, *J* = 8.7 Hz, 2H), 6.87 (dd, *J* = 6.3, 1.2 Hz, 2H), 6.80 (d, *J* = 8.4, Hz, 2H), 6.07 (s, 1H), 5.88 (d, *J* = 10.5 Hz, 1H), 3.95 (t, *J* = 10.5 Hz, 1H), 3.74 (d, *J* = 10.5 Hz, 1H), 3.68 (s, 3H), 3.44 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8 (C), 167.6 (C), 144.0 (C), 140.5 (C), 136.24 (C), 136.17 (C), 135.1 (C), 131.8 (C), 129.7 (CH), 129.3 (CH), 129.2 (CH), 128.8 (CH), 128.6 (CH), 127.7 (CH), 120.9 (CH), 115.9 (CH), 57.6 (CH), 52.8 (CH_3), 52.6 (CH_3), 43.5 (CH), 21.7 (CH_3). **Minor *Z*-diastereomer:** ^{1}H NMR (300 MHz, $CDCl_3$), significative signals taken from the ^{1}H NMR spectra of the diastereomer mixture, δ 7.86 (s, 1H), 7.14 (d, *J* = 8.7 Hz, 2H), 6.67 (d, *J* = 8.4 Hz, 2H), 5.46 (d, *J* = 11.1 Hz, 1H), 3.98 (t, *J* = 10.5 Hz, 1H), 3.75 (s, 3H), 3.69 (d, J = 10.5 Hz, 1H), 3.49 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), significative signals taken from the ^{13}C NMR spectra of the diastereomer mixture, δ 169.3 (C), 167.5 (C), 143.5 (C), 137.9 (C), 137.5 (C), 137.2 (C), 136.9 (C), 131.8 (CH), 129.7 (CH), 129.3 (CH), 128.9 (CH), 128.1 (CH), 127.8 (CH), 127.3 (CH), 122.4 (CH), 121.3 (CH), 57.4 (CH), 53.4 (CH_3), 53.0 (CH_3), 41.3 (CH), 21.7 (CH_3); HRMS (ESI) *m/z* 594.0546 $[M+Na]^+$, $C_{27}H_{26}BrNNaO_6S$ required 594.0556.

Dimethyl 2-[(*S*,*E*)-1-(4-nitrophenyl)-3-phenyl-3-(tosylamino)allyl]malonate (3ae)

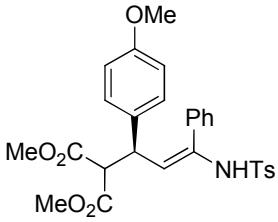


Chiral HPLC analysis: Chiralpak AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *E*-diastereomer: *major enantiomer* t_r = 25.9 min, *minor enantiomer* t_r = 30.3 min.; *Z*-diastereomer: unresolved t_r = 58.9 min.

Major *E*-diastereomer: an oil; $[\alpha]_D^{20}$ 9.4 (*c* 1.1, $CHCl_3$, ee = 90%) for the mixture of diastereomers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.7 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.35-7.31 (m, 2H), 7.07 (d, *J* = 8.7 Hz, 2H), 6.89 (dd, *J* = 6.6, 1.2 Hz, 2H), 6.25 (bs, 1H), 5.88 (d, *J* = 10.5 Hz, 1H), 4.09 (t, *J* = 10.2 Hz, 1H), 3.78 (d, *J* = 10.5 Hz, 1H), 3.69 (s, 3H), 3.45 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5 (C), 167.3 (C), 149.0 (C), 146.8 (C), 144.2 (C), 137.3 (C), 136.3 (C), 134.8 (C), 129.7 (CH), 129.4 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 127.7 (CH), 123.8 (CH), 113.8 (CH), 57.4 (CH), 52.9 (CH_3), 52.7 (CH_3), 43.6 (CH), 21.6 (CH_3). **Minor *Z*-diastereomer:** an oil; ^{1}H NMR (300 MHz, $CDCl_3$), significative signals taken

from the ^{1}H NMR spectra of the diastereomer mixture, δ 7.84 (s, 1H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 9.0 Hz, 2H), 5.48 (d, *J* =11.1 Hz, 1H), 4.29 (t, *J* = 10.5 Hz, 1H), 3.75 (s, 3H), 3.51 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), significative signals taken from the ^{13}C NMR spectra of the diastereomer mixture, δ 169.0 (C), 167.3 (C), 147.1 (C), 146.4 (C), 143.6 (C), 137.7 (C), 137.1 (C), 129.5 (CH), 129.1 (CH), 128.7 (CH), 128.1 (CH), 127.8 (CH), 127.4 (CH), 127.1 (CH), 123.5 (CH), 121.5 (CH), 56.9 (CH), 53.5 (CH_3), 53.1 (CH_3), 43.2 (CH), 21.1 (CH_3); HRMS (ESI) *m/z* 539.1498 $[M+H]^+$, $C_{27}H_{27}N_2O_8S$ required 539.1483.

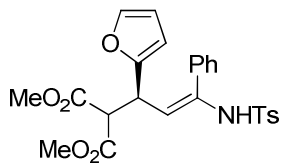
Dimethyl 2-[(*S*,*E*)-1-(4-methoxyphenyl)-3-phenyl-3-(tosylamino)allyl]malonate (3af)



Chiral HPLC analysis: Chiralpak AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *E*-diastereomer: *major enantiomer* t_r = 18.0 min, *minor enantiomer* t_r = 23.4 min.; *Z*-diastereomer: unresolved t_r = 37.3 min.

Major *E*-diastereomer: an oil; $[\alpha]_D^{20}$ -67.8 (*c* 1.0, $CHCl_3$, ee = 69%) for the mixture of diastereomers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.4 Hz, 2H), 7.32-7.29 (m, 3H), 7.18 (d, *J* = 7.8 Hz, 2H), 6.95-6.65 (m, 6H), 5.96 (s, 1H), 5.92 (d, *J* = 10.8 Hz, 1H), 3.96 (t, *J* = 10.5 Hz, 1H), 3.80 (s, 3H), 3.72 (d, *J* = 10.5 Hz, 1H), 3.66 (s, 3H), 3.43 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1 (C), 167.8 (C), 158.5 (C), 143.8 (C), 136.5 (C), 135.4 (C), 135.3 (C), 133.4 (C), 129.6 (CH), 128.70 (CH), 128.67 (CH), 128.61 (CH), 127.7 (CH), 117.5 (CH), 114.1 (CH), 58.3 (CH), 55.3 (CH_3), 52.6 (CH_3), 52.4 (CH_3), 43.3 (CH), 21.7 (CH_3). **Minor *Z*-diastereomer:** an oil; ^{1}H NMR (300 MHz, $CDCl_3$), significative signals taken from the ^{1}H NMR spectra of the diastereomer mixture, δ 7.86 (s, 1H), 7.41 (dd, *J* = 8.1, 1.5 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 5.51 (d, *J* = 10.8 Hz, 1H), 3.94 (t, *J* = 10.5 Hz, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 3.47 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6 (C), 167.7 (C), 158.7 (C), 143.3 (C), 137.8 (C), 137.4 (C), 136.1 (C), 130.8 (C), 129.7 (CH), 129.1 (CH), 128.1 (CH), 127.8 (CH), 127.3 (CH), 123.4 (CH), 114.0 (CH), 57.9 (CH), 55.3 (CH_3), 53.2 (CH_3), 52.8 (CH_3), 53.1 (CH_3), 42.7 (CH), 21.2 (CH_3); HRMS (ESI) *m/z* 524.1742 $[M+H]^+$, $C_{28}H_{30}NO_7S$ required 524.1737.

Dimethyl 2-[(*S*,*E*)-1-(furan-2-yl)-3-phenyl-3-(tosylamino)allyl]malonate (3ag)

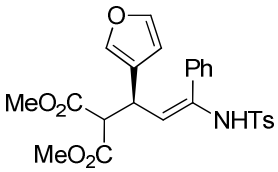


Chiral HPLC analysis: Chiralpak AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *E*-diastereomer: *major enantiomer* t_r = 17.9 min, *minor enantiomer* t_r = 26.6 min.; Z-diastereomer: *major enantiomer* t_r = 20.1 min, *minor enantiomer* t_r = 23.5 min

Major *E*-diastereomer: an oil; $[\alpha]_D^{20}$ -78.8 (*c* 1.0, $CHCl_3$, ee = 94%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.4 Hz, 2H), 7.32-7.25 (m, 6H), 7.09-7.04 (m, 2H), 6.23 (dd, *J* = 3.3, 1.2 Hz, 1H), 6.16 (br s, 1H), 5.83 (dt, *J* = 3.3, 0.6 Hz, 1H), 5.76 (d, *J* = 10.8 Hz, 1H), 4.12 (ddd, *J* = 10.8, 9.3, 0.6 Hz, 1H), 3.77 (d, *J* = 9.3 Hz, 1H), 3.61 (s, 3H), 3.52 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7 (C), 167.6 (C), 153.7

(C), 143.9 (C), 141.9 (CH), 137.1 (C), 136.5 (C), 134.9 (C), 129.7 (CH), 129.2 (CH), 128.7 (CH), 128.6 (CH), 127.8 (CH), 113.4 (CH), 110.3 (CH), 106.3 (CH), 55.6 (CH), 52.6 (CH_3), 38.1 (CH), 21.7 (CH_3). **Minor *Z*-diastereomer:** an oil; $[\alpha]_D^{20}$ -30.2 (*c* 0.8, $CHCl_3$, ee = 52%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.50-7.47 (m, 2H), 7.33-7.25 (m, 5H), 7.11 (d, *J* = 8.1 Hz, 2H), 6.20 (dd, *J* = 5.1, 1.9 Hz, 1H), 5.66 (d, *J* = 3.3 Hz, 1H), 5.58 (dd, *J* = 10.8, 0.6 Hz, 1H), 3.99 (dd, *J* =10.8 9.0 Hz, 1H), 3.76 (d, *J* = 9.0 Hz, 1H), 3.67 (s, 3H), 3.62 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9 (C), 168.1 (C), 151.5 (C), 143.4 (C), 142.1 (CH), 137.62 (C), 137.60 (C), 136.9 (C), 129.6 (CH), 129.0 (CH), 128.1 (CH), 127.8 (CH), 127.2 (CH), 119.5 (CH), 110.2 (CH), 106.7 (CH), 55.8 (CH), 53.2 (CH_3), 53.1 (CH_3), 37.2 (CH), 21.6 (CH_3); HRMS (ESI) *m/z* 506.1237 $[M+Na]^+$, $C_{25}H_{25}NNaO_7S$ required 506.1244.

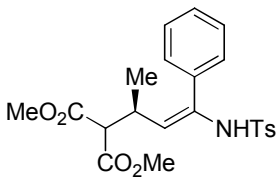
Dimethyl 2-[(*S*,*E*)-1-(furan-3-yl)-3-phenyl-3-(tosylamino)allyl]malonate (3ah)



Chiral HPLC analysis: Chiralpak AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *E*-diastereomer: *major enantiomer* t_r = 15.3 min, *minor enantiomer* t_r = 27.8 min; *Z*-diastereomer: *major enantiomer* t_r = 19.7 min, *minor enantiomer* t_r = 33.8 min

Major *E*-diastereomer: an oil; $[\alpha]_D^{20}$ -49.1 (*c* 0.9, $CHCl_3$, ee = 85%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.1 Hz, 2H), 7.32-7.25 (m, 6H), 7.01-6.96 (m, 3H), 6.13 (dd, *J* = 1.8, 0.9 Hz, 1H), 6.06 (br s, 1H), 5.79 (d, *J* = 10.8 Hz, 1H), 3.97 (dd, *J* = 10.8, 9.0 Hz, 1H), 3.63 (s, 3H), 3.57 (d, *J* = 9.0 Hz), 3.53 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9 (C), 167.8 (C), 144.0 (C), 143.1 (CH), 139.5 (CH), 136.6 (C), 136.1 (C), 135.1 (C), 129.7 (CH), 129.2 (CH), 128.7 (CH), 128.6 (CH), 127.8 (CH), 125.1 (C), 115.9 (CH), 109.5 (CH), 57.5 (CH), 52.6 (CH_3), 52.5 (CH_3), 35.2 (CH), 21.7 (CH_3). **Minor *Z*-diastereomer:** an oil; $[\alpha]_D^{20}$ -3.8 (*c* 0.6, $CHCl_3$, ee = 60%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.44-7.41 (m, 2H), 7.30-7.22 (m, 5H), 7.13 (dd, *J* = 8.1, 0.6 Hz, 2H), 6.84 (t, *J* = 0.6 Hz, 1H), 6.04 (dd, *J* = 1.8, 0.6 Hz, 1H), 5.44 (d, *J* = 10.8 Hz, 1H), 3.94 (t, *J* = 10.8 Hz, 1H), 3.68 (s, 3H), 3.62 (s, 3H), 3.58 (d, *J* = 10.5 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1 (C), 168.2 (C), 143.6 (C), 143.0 (CH), 139.4 (CH), 137.6 (C), 137.2 (C), 136.7 (C), 129.6 (CH), 128.9 (CH), 128.2 (CH), 127.8 (CH), 127.3 (CH), 123.2 (C), 122.3 (CH), 109.3 (CH), 57.2 (CH), 53.2 (CH_3), 53.0 (CH_3), 34.4 (CH), 21.6 (CH_3); HRMS (ESI) *m/z* 506.1241 $[M+Na]^+$, $C_{25}H_{25}NNaO_7S$ required 506.1244.

Dimethyl 2-[(*S*,*E*)-1-methyl-3-phenyl-3-(tosylamino)allyl]malonate (3ai)

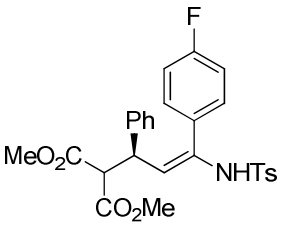


Chiral HPLC analysis: Chiralpak AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *E*-diastereomer: *major enantiomer* t_r = 12.1 min, *minor enantiomer* t_r = 15.5 min.; *Z*-diastereomer: *major enantiomer* t_r = 15.3 min, *minor enantiomer* t_r = 19.8 min.

Major *E*-diastereomer: an oil; $[\alpha]_D^{20}$ 10.4 (*c* 1.0, $CHCl_3$, ee = 74%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.1 Hz, 2H), 7.33-7.29 (m, 5H), 7.07-7.04 (m, 2H), 5.87 (br s, 1H), 5.52 (d, *J* = 10.8 Hz, 1H), 3.66 (s, 3H), 3.62 (s, 3H), 3.24 (d, *J* = 8.7 Hz, 1H),

2.98-2.89 (m, 1H), 2.46 (s, 3H), 0.97 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6 (C), 168.5 (C), 144.0 (C), 136.8 (C), 135.5 (C), 135.0 (C), 129.7 (CH), 129.0 (CH), 128.7 (CH), 128.6 (CH), 127.9 (CH), 119.4 (CH), 57.5 (CH), 52.50 (CH_3), 52.48 (CH_3), 33.1 (CH), 21.7 (CH_3), 19.6 (CH_3). **Minor *Z*-diastereomer:** an oil; $[\alpha]_D^{20}$ -33.6 (*c* 0.45, $CHCl_3$, ee = 44%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (br s, 1H), 7.63 (d, J = 8.4 Hz, 2H), 7.46-7.43 (m, 2H), 7.30-7.27 (m, 3H), 7.25-7.23 (m, 2H), 5.13 (dd, J = 10.5, 0.9 Hz, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 3.19 (d, J = 9.0 Hz, 1H), 2.81-2.72 (m, 1H), 2.40 (s, 3H), 0.57 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6 (C), 168.8 (C), 143.5 (C), 137.7 (C), 137.1 (C), 136.1 (C), 129.5 (CH), 128.7 (CH), 128.1 (CH), 127.7 (CH), 127.6 (CH), 125.8 (CH), 57.4 (CH), 53.0 (CH_3), 52.9 (CH), 32.4 (CH), 21.6 (CH_3), 18.2 (CH_3). HRMS (ESI) *m/z* 454.1301 $[M+Na]^+$, $C_{22}H_{25}NNaO_6S$ required 454.1295.

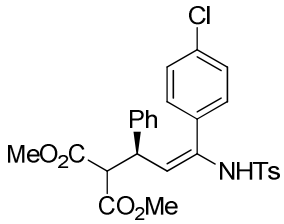
Dimethyl 2-[(*S*,*E*)-3-(4-fluorophenyl)-1-phenyl-3-(tosylamino)allyl]malonate (3ak)



Chiral HPLC analysis: Chiralpak AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *E*-diastereomer: *major enantiomer* t_r = 14.0 min, *minor enantiomer* t_r = 17.1 min.; *Z*-diastereomer: *major enantiomer* t_r = 22.5 min, *minor enantiomer* t_r = 47.4 min.

Major *E*-diastereomer: an oil; $[\alpha]_D^{20}$ -92.9 (*c* 1.0, $CHCl_3$, ee = 86%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 8.4 Hz, 2H), 2.27-7.19 (m, 3H) , 7.15 (d, J = 8.4 Hz, 2H), 6.98-6.87 (m , 6H), 6.02 (br s, 1H), 5.90 (d, J = 10.5 Hz, 1H), 3.95 (t, J = 10.5 Hz, 1H), 3.75 (d, J = 10.5 Hz, 1H), 3.66 (s, 3H), 3.41 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1 (C), 167.7 (C), 163 (d, $J_{C\text{-}F}$ = 247.6 Hz, C), 143.9 (C), 141.0 (C) 136.4 (C), 135.0 (C), 131.20 (d, $J_{C\text{-}F}$ = 3.4 Hz, C), 130.8 (d, $J_{C\text{-}F}$ = 8.3 Hz, CH), 129.7 (CH), 128.8 (CH), 127.6 (CH), 127.2 (CH), 118.2 (CH), 115.7 (d, $J_{C\text{-}F}$ = 21.5 Hz, CH), 58.0 (CH), 52.7 (CH_3), 52.5 (CH_3), 44.1 (CH), 21.7 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ -105.7 (s, 1F). **Minor *Z*-diastereomer:** an oil; $[\alpha]_D^{20}$ -54.9 (*c* 0.4, $CHCl_3$, ee = 55%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.40-7.36 (m, 2H), 7.20-7.14 (m, 5H), 6.94 (t, J = 8.7 Hz, 2H), 6.76-6.73 (m, 2H), 5.46 (d, J = 10.8 Hz, 1H), 3.94 (t, J = 10.2 Hz, 1H), 3.74 (d, J = 10.5 Hz, 1H), 3.71 (s, 3H), 3.45 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9 (C), 168.0 (C), 163.5 (d, $J_{C\text{-}F}$ = 246.2 Hz, C), 143.8 (C), 139.0 (C), 137.5 (C), 135.6 (C), 134.1 (d, $J_{C\text{-}F}$ = 3.1 Hz, C), 130.0 (CH), 129.9 (d, $J_{C\text{-}F}$ = 8.2 Hz, CH), 128.9 (CH), 127.9 (CH), 127.7 (CH), 127.5 (CH), 122.9 (CH), 115.3 (d, $J_{C\text{-}F}$ = 21.6 Hz, CH), 57.9 (CH), 53.6 (CH_3), 53.1 (CH_3), 43.7 (CH), 21.9 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ -113.5 (s, 1F); HRMS (ESI) *m/z* 534.1373 $[M+Na]^+$, $C_{27}H_{26}FNNaO_6S$ required 534.1357.

Dimethyl 2-[(*S*,*E*)-3-(4-chlorophenyl)-1-phenyl-3-(tosylamino)allyl]malonate (3al)

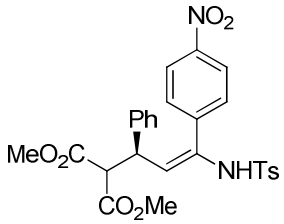


Chiral HPLC analysis: Chiralpak AD-H, hexane-*i*PrOH 90:10, 1 mL/min, *E*-diastereomer: *major enantiomer* t_r = 39.6 min, *minor enantiomer* t_r = 42.0 min.

Chiral HPLC analysis: Chiralpak AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *Z*-diastereomer: *major enantiomer* t_r = 20.8 min, *minor enantiomer* t_r = 43.6 min.

Major *E*-diastereomer: an oil; $[\alpha]_D^{20}$ -111.6 (*c* 1.0, $CHCl_3$, ee = 80%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.4 Hz, 2H), 7.30-7.24 (m, 5H), 7.19 (d, *J* = 8.4 Hz, 2H), 6.99-6.96 (m, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.15 (s, 1H), 5.95 (d, *J* = 10.8 Hz, 1H), 3.99 (t, *J* = 10.8 Hz, 1H), 3.78 (d, *J* = 10.2 Hz, 1H), 3.70 (s, 3H), 3.45 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0 (C), 167.6 (C), 143.9 (C), 140.9 (C), 136.3 (C), 135.1 (C), 134.9 (C), 133.6 (C), 130.2 (CH), 129.7 (CH), 128.8 (CH), 127.6 (CH), 127.2 (CH), 118.8 (CH), 58.0 (CH), 52.7 (CH_3), 52.5 (CH_3), 44.1 (CH), 21.7 (CH_3). **Minor *Z*-diastereomer:** an oil; $[\alpha]_D^{20}$ -56.3 (*c* 0.6, $CHCl_3$, ee = 46%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.7 Hz, 2H), 7.24-7.14 (m, 7H), 6.75-6.71 (m, 2H), 5.51 (dd, *J* = 10.8, 0.6 Hz, 1H), 3.94 (t, *J* = 10.8 Hz, 1H), 3.74 (d, *J* = 10.8 Hz, 1H), 3.71 (s, 3H), 3.45 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6 (C), 167.7 (C), 143.7 (C), 138.6 (C), 137.2 (C), 136.4 (C), 135.6 (C), 134.7 (C), 129.8 (CH), 129.1 (CH), 128.7 (CH), 128.3 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 123.3 (CH), 57.7 (CH), 53.4 (CH_3), 52.8 (CH_3), 43.5 (CH), 21.7 (CH_3). HRMS (ESI) *m/z* 550.1062 $[M+Na]^+$, $C_{27}H_{26}ClNNaO_6S$ required 550.1062.

Dimethyl 2-[(*S*,*E*)-3-(4-nitrophenyl)-1-phenyl-3-(tosylamino)allyl]malonate (3am)

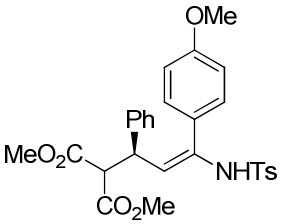


Chiral HPLC analysis: Chiralpak AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *E*-diastereomer: *major enantiomer* t_r = 24.2 min, *minor enantiomer* t_r = 32.0 min; *Z*-diastereomer: *major enantiomer* t_r = 44.6 min, *minor enantiomer* t_r = 76.1 min.

Major *E*-diastereomer: an oil; $[\alpha]_D^{20}$ -87.9 (*c* 1.0, $CHCl_3$, ee = 82%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.7 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.28-7.21 (m, 3H), 7.16 (d, *J* = 9 Hz, 4H), 6.92-6.89 (m, 2H), 6.45 (br s, 1H), 5.96 (d, *J* = 11.1 Hz, 1H), 3.92 (t, *J* = 10.8 Hz, 1H), 3.73 (d, *J* = 9.9 Hz, 1H), 3.65 (s, 3H), 3.41 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9 (C), 167.4 (C), 147.9 (C), 144.2 (C), 141.6 (C), 140.2 (C), 136.0 (C), 134.1 (C), 130.1 (CH), 129.8 (CH), 129.0 (CH), 127.5 (CH), 127.4 (CH), 123.7 (CH), 121.7 (CH), 57.8 (CH), 52.8 (CH_3), 52.6 (CH_3), 44.0 (CH), 21.7 (CH_3). **Minor *Z*-diastereomer:** an oil; $[\alpha]_D^{20}$ -37.8 (*c* 0.6, $CHCl_3$, ee = 49%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.7 Hz, 2H), 8.08 (br s, 1H), 7.59 (d, *J* = 8.4 Hz, 4H), 7.22-7.15 (m, 5H), 6.74-6.70 (m, 2H), 5.70 (d, *J* = 10.8 Hz, 1H), 3.94 (t, *J* = 10.5 Hz, 1H), 3.76 (d, *J* = 9.9 Hz, 1H), 3.72 (s, 3H), 3.46 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6 (C), 167.7 (C), 148.0 (C), 144.5 (C), 144.0 (C), 138.1

(C), 137.0 (C), 134.9 (C), 130.0 (CH), 128.8 (CH), 128.5 (CH), 127.6 (CH), 127.3 (CH), 126.5 (CH), 123.5 (CH), 121.7 (CH), 57.5 (CH), 53.4 (CH_3), 53.0 (CH_3), 43.5 (CH), 21.7 (CH_3); HRMS (ESI) *m/z* 539.1497 $[M+H]^+$, $C_{27}H_{27}N_2O_8S$ required 539.1483.

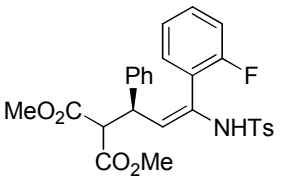
Dimethyl 2-[(*S*,*E*)-3-(4-methoxyphenyl)-1-phenyl-3-(tosylamino)allyl]malonate (3an).



Chiral HPLC analysis: Chiralpak AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *E*-diastereomer: *major enantiomer* t_r = 20.3 min, *minor enantiomer* t_r = 24.6 min.; *Z*-diastereomer: *major enantiomer* t_r = 34.8 min, *minor enantiomer* t_r = 82.7 min.

Major *E*-diastereomer: an oil; $[\alpha]_D^{20}$ -29.6 (*c* 0.9, $CHCl_3$, ee = 80%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.5 Hz, 2H), 7.26-7.19 (m, 3H), 7.14 (d, *J* = 8.5 Hz, 2H), 6.97-6.94 (m, 2H), 6.84 (d, *J* = 9.0 Hz, 2H), 6.77 (dt, *J* = 9.0 Hz, 2H), 5.96 (s, 1H), 5.86 (d, *J* = 10.8 Hz, 1H), 4.01 (t, *J* = 10.5 Hz, 1H), 3.80 (s, 3H), 3.75 (d, *J* = 10.2 Hz, 1H), 3.65 (s, 3H), 3.40 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1 (C), 167.8 (C), 160.0 (C), 143.7 (C), 141.3 (C), 136.5 (C), 135.6 (C), 130.1 (CH), 129.6 (CH), 128.7 (CH), 127.7 (CH), 127.6 (CH), 127.5 (C), 127.0 (CH), 116.8 (CH), 114.0 (CH), 58.1 (CH), 53.4 (CH_3), 52.7 (CH_3), 52.4 (CH_3), 44.2 (CH), 21.7 (CH_3). **Minor *Z*-diastereomer:** $[\alpha]_D^{20}$ -2.0 (*c* 0.74, $CHCl_3$, ee = 42%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 9.0 Hz, 2H), 7.19-7.12 (m, 5H), 6.79 (d, *J* = 9.0 Hz, 2H), 6.73-6.70 (m, 2H), 5.40 (d, *J* = 10.8 Hz, 1H), 3.91 (t, *J* = 10.2 Hz, 1H), 3.86 (d, *J* = 6.0 Hz, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 3.43 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6 (C), 167.8 (C), 160.3 (C), 143.4 (C), 139.0 (C), 137.3 (C), 136.1 (C), 130.3 (CH), 129.7 (CH), 129.2 (CH), 128.6 (CH), 127.6 (CH), 127.3 (CH), 121.1 (CH), 116.8 (CH), 113.5 (CH), 57.9 (CH), 55.4 (CH_3), 53.3 (CH_3), 52.8 (CH_3), 43.5 (CH), 21.7 (CH_3); HRMS (ESI) *m/z* 524.1740 $[M+H]^+$, $C_{28}H_{30}NO_7S$ required 524.1737.

Dimethyl 2-[(*S*,*E*)-3-(2-fluorophenyl)-1-phenyl-3-(tosylamino)allyl]malonate (3ao)

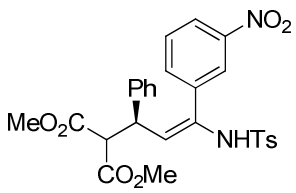


Chiral HPLC analysis: Chiralpak AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *E*-diastereomer: *major enantiomer* t_r = 18.9 min, *minor enantiomer* t_r = 34.1 min.; *Z*-diastereomer: *major enantiomer* t_r = 39.7 min, *minor enantiomer* t_r = 49.7 min.

Major *E*-diastereomer: an oil; $[\alpha]_D^{20}$ -75.4 (*c* 1.0, $CHCl_3$, ee = 82%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.4 Hz, 2H), 7.34-7.27 (m, 1H), 7.25-7.19 (m, 3H), 7.11 (d, *J* = 8.1 Hz, 2H), 7.03 (td, *J* = 7.5, 1.2 Hz, 1H), 7.00-6.94 (m, 3H), 6.83 (td, *J* = 7.5, 1.8 Hz, 1H), 6.15 (br s, 1H), 6.04 (d, *J* = 10.2 Hz, 1H), 3.82 (t, 10.5 Hz, 1H), 3.73 (d, *J* = 10.2 Hz, 1H), 3.62 (s, 3H), 3.39 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8 (C), 167.6 (C), 159.8 (d, $J_{C\text{-}F}$ = 247.7 Hz, C), 143.7 (C), 140.6 (C), 136.1 (C), 131.4 (d, $J_{C\text{-}F}$ = 3.0 Hz, CH), 131.2 (d, $J_{C\text{-}F}$ = 8.1 Hz, CH), 130.4 (CH), 129.5 (CH), 128.7 (CH), 127.8 (CH), 127.7 (CH), 127.1 (CH), 124.1 (d, $J_{C\text{-}F}$ = 3.5 Hz, CH), 122.5

(d, $J_{C\text{-}F}$ = 15.2 Hz, C); 120.3 (CH), 115.9 (d, $J_{C\text{-}F}$ = 21.2 Hz, CH), 58.1 (CH), 25.7 (CH_3), 52.4 (CH_3), 44.4 (CH), 21.6 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ -116.3 (s, 1F). **Minor *Z*-diastereomer:** an oil; $[\alpha]_D^{20}$ -33.3 (*c* 1.0, $CHCl_3$, ee = 28%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (br s, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.32 (td, *J* = 7.5, 1.8 Hz, 1H), 7.25-7.18 (m, 4H), 7.09 (d, *J* = 8.4 Hz, 2H), 7.04 (dt, *J* = 7.5, 1.8 Hz, 1H), 6.92-6.83 (m, 3H), 5.60 (d, *J* = 10.8 Hz, 1H), 4.11 (t, *J* = 9.9 Hz, 1H), 3.75 (d, *J* = 9.9 Hz, 1H), 3.73 (s, 3H), 3.49 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3 (C), 167.8 (C), 160.2 (d, $J_{C\text{-}F}$ = 248.3 Hz, C), 143.3 (C), 138.7 (C), 137.2 (C), 131.4 (d, $J_{C\text{-}F}$ = 2.6 Hz, CH), 130.4 (C), 130.2 (d, $J_{C\text{-}F}$ = 8.4 Hz, CH), 129.6 (CH), 128.7 (CH), 127.6 (CH), 127.4 (CH), 127.2 (CH), 126.2 (d, $J_{C\text{-}F}$ = 3.2 Hz, CH), 123.8 (d, $J_{C\text{-}F}$ = 3.6 Hz, CH), 115.7 (d, $J_{C\text{-}F}$ = 21.9 Hz, CH), 57.6 (CH), 53.2 (CH_3), 52.8 (CH_3), 43.2 (CH), 21.6 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ -113.9 (s, 1F); HRMS (ESI) *m/z* 534.1372 $[M+Na]^+$, $C_{27}H_{26}FNNaO_6S$ required 534.1357.

Dimethyl 2-[(*S*,*E*)-3-(3-nitrophenyl)-1-phenyl-3-(tosylamino)allyl]malonate (3ap)

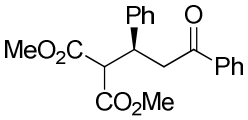


Chiral HPLC analysis: Chiralpak AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *E*-diastereomer: *major enantiomer* t_r = 23.1 min, *minor enantiomer* t_r = 31.7 min.; *Z*-diastereomer: *major enantiomer* t_r = 37.5 min, *minor enantiomer* t_r = 54.8 min.

Major *E*-diastereomer: an oil; $[\alpha]_D^{20}$ -69.5 (*c* 1.0, $CHCl_3$, ee = 84%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18-8.12 (m, 2H), 7.56-7.46 (m, 5H), 7.31-7.22 (m, 3H), 7.14 (d, *J* = 8.4 Hz, 2H), 6.97-6.94 (m, 2H), 6.51 (br s, 1H), 6.00 (d, *J* = 10.8 Hz, 1H), 3.91 (t, *J* = 10.8 Hz, 1H), 3.76 (d, *J* = 10.2 Hz, 1H), 3.67 (s, 3H), 3.41 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9 (C), 167.4 (C), 140.1 (C), 144.3 (C), 140.1 (C), 136.6 (C), 135.9 (C), 135.3 (CH), 133.8 (C), 129.8 (CH), 129.6 (CH), 129.0 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 123.9 (CH), 123.8 (CH), 121.9 (CH), 57.9 (CH), 52.8 (CH_3), 52.5 (CH_3), 44.1 (CH), 21.6 (CH_3). **Minor *Z*-diastereomer:** an oil; $[\alpha]_D^{20}$ -21.8 (*c* 0.5, $CHCl_3$, ee = 48%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13-8.07 (m, 3H), 7.81 (dt, *J* = 8.4, 1.5 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.45 (dd, *J* = 8.7, 1.2 Hz, 1H), 7.25-7.21 (m, 3H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.83-6.77 (m, 2H), 5.67 (dd, *J* = 10.8 Hz, 1H), 4.02 (t, *J* = 10.8, 0.6 Hz, 1H), 3.77 (d, *J* = 9.9 Hz, 1H), 3.73 (s, 3H), 3.47 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6 (C), 167.7 (C), 148.2 (C), 144.0 (C), 139.8 (C), 138.2 (C), 137.0 (C), 134.6 (C), 134.0 (CH), 130.0 (CH), 129.1 (CH), 128.9 (CH), 127.7 (CH), 127.6 (CH), 127.3 (CH), 125.4 (CH), 123.4 (CH), 122.4 (CH), 57.5 (CH), 53.4 (CH_3), 52.9 (CH_3), 43.5 (CH), 21.6 (CH_3); HRMS (ESI) *m/z* 539.1487 $[M+H]^+$, $C_{27}H_{27}N_2O_8S$ required 539.1483.

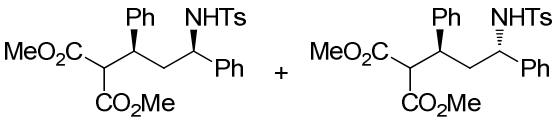
5.1.3. Synthetic transformations from compound 3aa

Dimethyl 2-[(*S*)-3-oxo-1,3-diphenylpropyl]malonate (4)[157]



37% Hydrochloric acid (6 drops) was dropwise added to a solution of compound **3aa** (26.2 mg, 0.053 mmol, ee = 82%) in THF 2mL under nitrogen. The reaction flask was introduced in a bath at 40 °C for 2 h. After this time, the reaction was left at room temperature and water (5 mL) was added. The mixture was extracted with dichloromethane (3 × 20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 18.0 mg (100%) of ketone **4** with identical spectroscopic features as those described in the literature.[157] Chiral HPLC analysis: Chiralpak AS-H, hexane-*i*PrOH 90:10, 1 mL/min, *major enantiomer* t_r = 14.3 min, *minor enantiomer* t_r = 19.1 min. $[\alpha]_D^{20}$ +13.1 (*c* 0.96, $CHCl_3$, ee = 82%), Lit.[157] $[\alpha]_D^{20}$ +18 ($CHCl_3$, ee = 90%) for the *S*-enantiomer.

Dimethyl 2-[(1*S*,3*R*)-1,3-diphenyl-3-(tosylamino)allyl]malonate (5) and dimethyl 2-[(1*S*,3*S*)-1,3-diphenyl-3-(tosylamino)allyl]malonate (6)



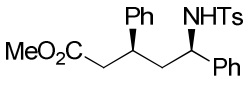
A solution of (*S*,*E*)-**3aa** (140 mg, 0.29 mmol, ee = 86%) in MeOH (12 mL) was stirred under hydrogen atmosphere (balloon) in the presence of 5% Pd/C (4 mg) for 4 h. Then, the reaction mixture was filtered through a short pad of silica gel eluting with EtOAc. The solvent was removed under reduced pressure to give 134 mg (95%) of a *ca.* 25:75 mixture of compounds **5** and **6** which were separated after column chromatography on silica gel eluting with hexane/EtOAc (90:10 to 60:40). Order of elution: compound **6** (minor diastereomer) first, compound **5** (major diastereomer) second.

Chiral HPLC analysis: Chiralpak IC, hexane-*i*PrOH 80:20, 1 mL/min, *Major* diastereomer **5**: *major enantiomer* t_r = 55.6 min, *minor enantiomer* t_r = 63.6 min.; Minor diastereomer **6**: *major enantiomer* t_r = 39.7 min, *minor enantiomer* t_r = 46.6 min.

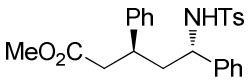
Major diastereomer (1*S*,3*R*)-**5:** an oil; $[\alpha]_D^{20}$ -3.4 (*c* 1.0, $CHCl_3$, ee = 86%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.4 Hz, 2H), 7.30-7.27 (m, 3H), 7.24-7.17 (m, 3H), 7.08 (d, *J* = 8.4 Hz, 2H), 7.00-6.97 (m, 2H), 6.84-6.81 (m, 2H), 4.61 (d, *J* = 6.0 Hz, 1H), 3.77-3.70 (m, 1H), 3.72 (s, 3H), 3.59 (d, *J* = 10.5 Hz, 1H), 3.32 (s, 3H), 2.91 (td, *J* = 11.2 Hz, 1H), 2.45-2.26 (m, 2 H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5 (C), 167.9 (C), 143.2 (C), 138.9 (C), 138.7 (C), 137.0 (C), 129.5 (CH), 129.0 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 127.6 (CH), 127.3 (CH), 127.2 (CH), 58.4 (CH), 56.4 (CH), 52.7 (CH_3), 52.3 (CH_3), 42.3 (CH), 39.7 (CH_2), 21.6 (CH_3). ***Minor diastereomer*** (1*S*,3*S*)-**6:** an oil; $[\alpha]_D^{20}$ -2.0 (*c* 0.6, $CHCl_3$, ee = 86%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.4 Hz, 2H), 7.25-7.21 (m, 3H), 7.15-7.08 (m, 5H), 6.94-6.87 (m, 4H), 5.45 (d, *J* = 6.6 Hz, 1H), 4.08-4.01 (m, 1H), 3.77 (s, 3H), 3.59 (d, *J* = 10.2 Hz, 1H), 3.42 (td, *J* = 10.2, 3.0 Hz, 1H), 3.41 (s, 3H), 2.38 (s, 3H), 2.08-1.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3 (C), 168.0 (C), 143.0 (C), 142.0 (C), 139.5 (C), 137.8 (C), 129.5 (CH),

128.8 (CH), 128.5 (CH), 128.4 (CH), 127.7 (CH), 127.4 (CH), 127.3 (CH), 126.1 (CH), 57.7 (CH), 56.1 (CH), 53.0 (CH_3), 52.5 (CH_3), 43.4 (CH_2), 43.3 (CH), 21.6 (CH_3); HRMS (ESI) *m/z* 518.1613 $[M+Na]^+$, $C_{27}H_{29}NNaO_6S$ required 516.1608.

(3*S*,5*R*)-Methyl 3,5-diphenyl-5-(tosylamino)pentanoate (7) A 25% solution of tetraethylammonium hydroxyde in MeOH (157 μL, 0.23 mmol) was added to a solution of compound **5** (95.4 mg, 0.19 mmol, ee = 82%) in dimethylsulfoxide (5.2 mL) under nitrogen, and the reaction flask was introduced in a bath at 80 °C. Additional tetraethylammonium hydroxyde was added after 6 h (157 μL, 0.23 mmol) and 24 h (53 μL, 0.08 mmol). After a total reaction time of 24h, the reaction mixture was diluted with EtOAc (60 mL), washed with water (3 × 4 mL), brine (4 mL), and dried over $MgSO_4$. Purification by column chromatography eluting with hexane/EtOAc gave 9 mg (10%) of lactam **9**, followed by 58.0 mg (70%) of compound **7**: Chiral HPLC analysis: Chiralpak IC hexane-*i*PrOH 80:20, 1 mL/min, *major enantiomer* t_r = 26.5 min, *minor enantiomer* t_r = 29.1 min. Oil; $[\alpha]_D^{20}$ -9.1 (*c* 1.0, $CHCl_3$, ee = 82%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.4 Hz, 2H), 7.35-7.25 (m, 3H), 7.21-7.12 (m, 3H), 7.08 (d, *J* = 8.4 Hz, 2H), 7.05-6.97 (m, 2H), 6.91-6.82 (m, 2H), 5.09 (d, *J* = 6.6 Hz, 1H), 3.88 (ddd, *J* = 10.5, 6.6, 5.4 Hz, 1H), 3.52 (s, 3H), 2.73 (m. 1H), 2.52 (m, 2H), 2.37 (s, 3H), 2.35-2.12 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2 (C), 143.0 (C), 142.2 (C), 139.6 (C), 137.2 (C), 129.4 (CH), 128.76 (CH), 128.75 (CH), 128.0 (CH), 127.8 (CH), 127.2 (CH), 127.1 (CH), 127.0 (CH), 56.4 (CH), 51.5 (CH_3), 42.2 (CH_2), 41.7 (CH_2), 38.7 (CH), 21.6 (CH_3); HRMS (ESI) *m/z* 460.1560 $[M+Na]^+$, $C_{25}H_{27}NNaO_4S$ required 460.1553.

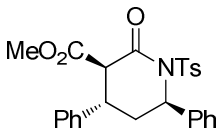


(3*S*,5*S*)-Methyl 3,5-diphenyl-5-(tosylamino)pentanoate (8)



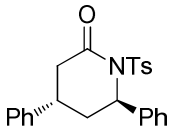
Following the same procedure as for the synthesis of **7**, starting from compound **6** (23.7 mg, 0.058 mmol, ee = 82%), it was obtained 15.9 mg of compound **8** (63%): Chiral HPLC analysis: Chiralpak IC, hexane-*i*PrOH 80:20, 1 mL/min, *major enantiomer* t_r = 55.5 min, *minor enantiomer* t_r = 34.6 min. Oil; $[\alpha]_D^{20}$ -16.3 (*c* 1.0, $CHCl_3$, er = 82%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.4 Hz, 2H), 7.30-7.19 (m, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.13-7.04 (m, 5H), 7.05-6.82 (m, 4H), 5.34 (d, J = 7.2 Hz, 1H), 4.11 (ddd, *J* = 10.8, 7.2, 3.9 Hz, 1H), 3.63 (s, 3H), 3.17 (m, 1H), 2.56 (m, 2H), 2.36 (s, 3H), 2.01 (ddd, *J* = 14.2, 10.2, 3.9 Hz, 1H), 1.93 (ddd, *J* = 14.2, 9.9, 4.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0 (C), 143.0 (C), 142.8 (C), 141.7 (C), 137.8 (C), 129.4 (CH), 128.8 (CH), 128.5 (CH), 127.6 (CH), 127.29 (CH), 127.28 (CH), 127.1 (CH), 126.2 (CH), 56.3 (CH), 51.9 (CH_3), 45.0 (CH_2), 41.0 (CH_2), 38.6 (CH), 21.6 (CH_3); HRMS (ESI) *m/z* 460.1562 $[M+Na]^+$, $C_{25}H_{27}NNaO_4S$ required 460.1553.

(3*R*,4*S*,6*R*)-Methyl 2-oxo-4,6-diphenyl-1-tosylpiperidine-3-carboxylate (9)



A solution of compound **5** (27.7 mg, 0.056 mmol) in toluene (1.2 mL) under nitrogen was treated with 1M LiHMDS in THF (112 μL, 0.112 mmol). The mixture was stirred at 90 °C for 18 h. Then, the reaction was quenched with 1M HCl (1 mL), diluted with water (4 mL), extracted with dichloromethane (3×30 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give 19 mg (73%) of compound **9**: an oil; $[\alpha]_D^{20}$ 2.1 (*c* 0.8, $CHCl_3$, ee = 82%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.4 Hz, 2H), 7.40-7.20 (m, 8H), 7.14 (d, *J* = 8.4 Hz, 2H), 7.10-6.98 (m, 2H), 5.90 (dd, *J* = 5.1, 2.4 Hz, 1H), 3.72 (d, *J* = 12.0 Hz, 1H), 3.58 (s, 3H), 3.50 (td, *J* = 12.0, 3.0 Hz, 1H), 2.59 (td, J = 13.5, 5.4 Hz, 1H), 2.40 (s, 3H), 2.21 (ddd, *J* = 13.5, 3.0, 2.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2 (C), 166.8 (C), 144.3 (C), 140.0 (C), 139.5 (C), 135.9 (C), 129.8 (CH), 128.9 (CH), 128.7 (CH), 128.0 (CH), 127.7 (CH), 126.8 (CH), 59.9 (CH), 58.3 (CH), 52.6 (CH_3), 37.8 (CH_2), 37.4 (CH), 21.6 (CH_3); HRMS (ESI) *m/z* 464.1529 $[M+H]^+$, $C_{26}H_{26}NO_5S$ required 464.1526.

(4*S*,6*R*)-4,6-Diphenyl-1-tosylpiperidin-2-one (10)



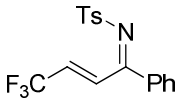
A solution of compound **7** (31.3 mg, 0.072 mmol) in toluene (1.4 mL) under nitrogen was treated with 1M LiHMDS in THF (143 μL, 0.143 mmol). The mixture was stirred at 100 °C for 19h. Then, the reaction was quenched with 1M HCl (4 mL), diluted with water (4 mL), extracted with dichloromethane (3×30 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give 26.2 mg (90%) of compound **10**: Oil; $[\alpha]_D^{20}$ -5.6 (*c* 0.95, $CHCl_3$, ee = 82%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.1 Hz, 2H), 7.32-7.25 (m, 3H), 7.19-7.16 (m, 3H), 7.10-6.90 (m, 4H), 6.86 (m, 2H), 5.30 (dd, *J* = 6.6, 2.7 Hz, 1H), 3.87 (dd, *J* = 14.7, 7.8 Hz, 1H), 2.70 (m, 1H), 2.55 (t, *J* = 7.2 Hz, 1H), 2.60-2.27 (m, 2H overlapped), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3 (C), 143.2 (C), 142.0 (C), 139.5 (C), 137.1 (C), 129.4 (CH), 128.9 (CH), 128.8 (CH), 128,0 (CH), 127.8 (CH), 127.21 (CH), 127.20 (CH), 126.2 (CH), 56.4 (CH), 42.0 (CH), 41.3 (CH_2), 38.5 (CH), 21.6 (CH_3); HRMS (ESI) *m/z* 406.1469 $[M+H]^+$, $C_{24}H_{24}NO_3S$ required 406.1471.

5.2. Enantioselective Michael addition of malonate esters to β-trifluoromethyl-α,β-unsaturated *N*-tosyl imines

5.2.1. Synthesis and characterization of β-trifluoromethyl α,β-unsaturated *N*-tosyl imines 11

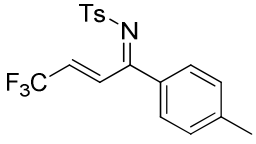
The procedure by A. D. Smith was followed.[103] A solution of the corresponding trifluoromethyl enone[166a,199] (2.8 mmol) and $TsNH_2$ (465 mg, 2.7 mmol) in dry CH_2Cl_2 (15 mL) under nitrogen atmosphere was introduced in a bath at 0 °C (ice-water). After 10 min, dry triethylamine (1.18 mL, 8.4 mmol) was added *via* syringe followed by $TiCl_4$ (0.46 mL, 4.2 mmol). After 15 min, the bath was removed and the reaction mixture was stirred for 24 h at room temperature. Then, the solvent was removed under reduced pressure, water (100 mL) was added and the mixture was extracted with ethyl acetate (3×50 mL). ¡¡ interphases may form !!. The extract was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Imine **11** was obtained after quick column chromatography eluting with hexane-EtOAc mixtures. In most of the cases an additional purification by crystallization from hexane-EtOAc or Et_2O-EtOAc mixtures was required. Nitro-containing imines **11e** and **11i** hydrolyzed almost completely when chromatographed. They could only be obtained in low yield after repeated crystallizations.

4-Methyl-*N*-((1*Z*,2*E*)-4,4,4-trifluoro-1-phenylbut-2-en-1-ylidene)benzene-sulfonamide (11a)[103]



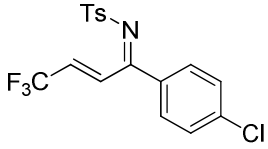
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00-7.65 (5H, m, Ar, =CH), 7.59 (1H, tt, *J* = 7.5, 1.8 Hz, Ar), 7.46 (2H, t, *J* = 7.5 Hz, Ar), 7.35 (2H, d, *J* = 8.1 Hz, Ar), 6.12 (1H, dq, *J* = 16.5, 6.0 Hz, =CH), 2.45 (s, Me-Ar); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -65.6 (s, CF_3).

4-Methyl-N-((1*Z*,2*E*)-4,4,4-trifluoro-1-(*p*-tolyl)but-2-en-1-ylidene)benzene-sulfonamide (11b)[103]



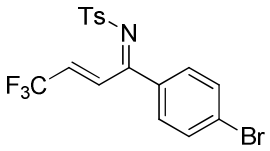
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (2H, d, *J* = 7.8 Hz, Ar), 7.77 (1H, m, =CH), 7.63 (2H, d, *J* = 8.1 Hz, Ar), 7.35 (2H, d, *J* = 7.8 Hz, Ar), 7.25 (2H, d, *J* = 8.1 Hz, Ar), 6.10 (1H, dq, *J* = 16.2, 6.3 Hz, =CH), 2.45 (3H, s, Me-Ar), 2.42 (3H, s, Me-Ar); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -65.5 (s, CF_3).

***N*-((1*E*,2*E*)-1-(4-Chlorophenyl)-4,4,4-trifluorobut-2-en-1-ylidene)-4-methyl-benzenesulfonamide (11c)**



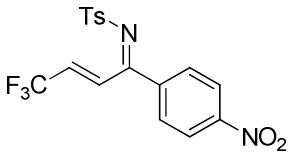
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (2H, d, *J* = 8.1 Hz, Ar), 7.80 (1H, m, =CH), 7.65 (2H, unresolved d, Ar), 7.44 (2H, dd, *J* = 6.9, 2.1 Hz, Ar), 7.37 (2H, d, *J* = 7.8 Hz, Ar), 6.11 (1H, dq, *J* = 16.5, 6.0 Hz, =CH), 2.45 (3H, s, Me-Ar); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -65.6 (s, CF_3); HRMS (ESI) *m/z* 388.0378 $[M+H]^+$, $C_{17}H_{13}ClF_3NO_2S$ requires 388.0380.

_N_-((1_E_,2_E_)-1-(4-Bromophenyl)-4,4,4-trifluorobut-2-en-1-ylidene)-4-methyl-benzenesulfonamide (11d)[103]



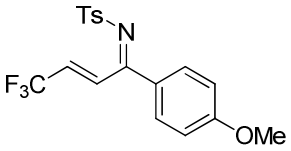
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (2H, d, *J* = 7.5 Hz, Ar), 7.87-7.84 (1H, m, =CH), 7.62-7.58 (4H, m, Ar), 7.36 (2H, d, *J* = 8.4 Hz, Ar), 6.11 (1H, dq, *J* = 16.5, 6.3 Hz, =CH), 2.45 (3H, s, Me-Ar); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -65.6 (s, CF_3).

_N_-((1_E_,2_E_)-1-(4-Nitrophenyl)-4,4,4-trifluorobut-2-en-1-ylidene)-4-methyl-benzenesulfonamide (11e)



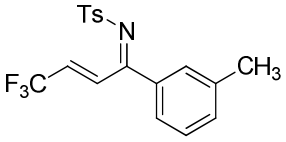
This compound could not be obtained pure and was used contaminated with enone and $TsNH_2$. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (2H, d, *J* = 7.5 Hz, Ar), 8.00-7.80 (5H, m, =CH, Ar), 7.37 (2H, d, *J* = 8.1 Hz, Ar), 6.11 (1H, m, =CH), 2.46 (3H, s, Me-Ar); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -65.6 (s, CF_3).

4-Methyl-_N_-((1_E_,2_E_)-4,4,4-trifluoro-1-(4-methoxyphenyl)but-2-en-1-ylidene)-benzenesulfonamide (11f)



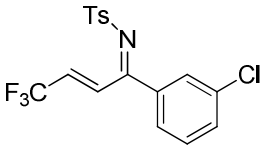
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (2H, d, *J* = 8.4 Hz, Ar), 7.76 (2H, d, *J* = 9,0 Hz, Ar), 7.70-7.60 (1H, m, =CH), 7.34 (2H, d, *J* = 8.4 Hz, Ar), 6.93 (2H, d, *J* = 9.0 Hz, Ar), 6.09 (1H, dq, *J* = 16.5, 6.0 Hz, =CH), 3.87 (3H, s, MeO), 2.44 (3H, s, Me-Ar); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -65.5 (s, CF_3); HRMS (ESI) *m/z* 384.0878 $[M+H]^+$, $C_{18}H_{17}F_3NO_3S$ requires 384.0876.

4-Methyl-_N_-((1_E_,2_E_)-4,4,4-trifluoro-1-(_m_-tolyl)but-2-en-1-ylidene)benzene-sulfonamide (11g)



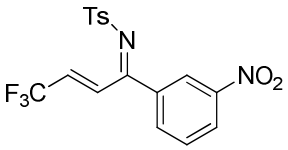
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (2H, d, *J* = 7.8 Hz, Ar), 7.77 (1H, m, =CH), 7-55-7.25 (6H, m, Ar), 6.10 (1H, dq, *J* = 16.2, 6.0 Hz, =CH), 2.45 (3H, s, Me-Ar), 2.39 (3H, s, Me-Ar); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -65.6 (s, CF_3); HRMS (ESI) *m/z* 368.0935 $[M+H]^+$, $C_{18}H_{17}F_3NO_2S$ requires 368.0927.

_N_-((1_E_,2_E_)-1-(3-Chlorophenyl)-4,4,4-trifluorobut-2-en-1-ylidene)-4-methyl-benzenesulfonamide (11h)



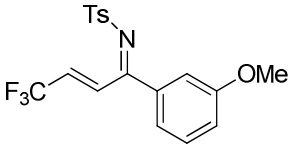
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (2H, d, *J* = 8.7 Hz, Ar), 7.81 (1H, m, =CH), 7.71 (1H, m, Ar), 7.55 (2H, m, Ar), 7.41 (1H, t, *J* = 7.8 Hz, Ar), 7.36 (2H, d, *J* = 8.7 Hz, Ar), 6.13 (1H, dq, *J* = 16.2, 6.0 Hz, =CH), 2.46 (3H, s, Me-Ar); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -65.6 (s, CF_3); HRMS (ESI) *m/z* 388.0378 $[M+H]^+$, $C_{17}H_{14}ClF_3NO_2S$ requires 388.0380.

_N_-((1_E_,2_E_)-1-(3-Nitrophenyl)-4,4,4-trifluorobut-2-en-1-ylidene)-4-methyl-benzenesulfonamide (11i)



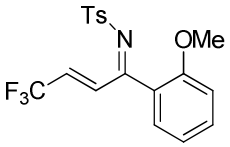
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (1H, s, Ar), 8.43 (1H, ddd, *J* = 8.1, 2.1, 1.0 Hz, Ar), 8.10-7.75 (4H, m, =CH, Ar), 7.69 (1H, t, J = 8.1 Hz, Ar), 7.37 (2H, d, *J* = 8.1 Hz, Ar), 6.15 (1H, dq, *J* = 16.5, 6.0 Hz, =CH), 2.46 (3H, s, Me-Ar); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -65.6 (s, CF_3); HRMS (ESI) *m/z* 399.0628 $[M+H]^+$, $C_{17}H_{14}F_3N_2O_4S$ requires 399.0621

4-Methyl-_N_-((1_E_,2_E_)-4,4,4-trifluoro-1-(3-methoxyphenyl)but-2-en-1-ylidene)-benzenesulfonamide (11j)



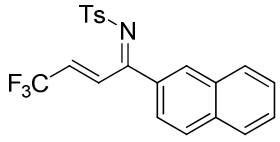
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (2H, d, *J* = 7.8 Hz, Ar), 7.81 (1H, m, =CH), 7.48-7.20 (6H, m, Ar), 7.13 (1H, dd, *J* = 8.1, 2.4 Hz, Ar), 6.13 (1H, dq, *J* = 16.2, 6.3 Hz, =CH), 3.82 (3H, s, MeO), 2.45 (3H, s, Me-Ar); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -65.6 (s, CF_3); HRMS (ESI) *m/z* 384.0877 $[M+H]^+$, $C_{18}H_{17}F_3NO_3S$ requires 384.0876.

4-Methyl-_N_-((1_E_,2_E_)-4,4,4-trifluoro-1-(2-methoxyphenyl)but-2-en-1-ylidene) benzenesulfonamide (11k)



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89-7.53 (2H, m, Ar, =CH), 7.47 (1H, dt, *J* = 8.3, 1.5 Hz, Ar), 7.30-7.20 (3H, m), 7.04-6.89 (3H, m), 6.04 (1H, m, =CH), 3.75 (3H, s, MeO), 2.42 (3H, s, Me-Ar); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -65.4 (s, CF_3); HRMS (ESI) *m/z* 384.0877 $[M+H]^+$, $C_{18}H_{17}F_3NO_3S$ requires 384.0876.

4-Methyl-_N_-((1_E_,2_E_)-4,4,4-trifluoro-1-(naphthalen-2-yl)but-2-en-1-ylidene) benzenesulfonamide (11l)[103]



^{1}H NMR(300 MHz, $CDCl_3$) δ 8.19 (1H, s, Ar), 7.94-7.86 (7H, m, Ar, =CH), 7.64-7.55 (2H, m, Ar), 7.36 (2H, d, *J* = 8.1 Hz , Ar), 6.18 (1H, dq, *J* = 16.4 , 6.0 Hz, =CH), 2.45 (3H, s, Me-Ar). ^{19}F NMR (282 MHz, $CDCl_3$) δ = -65.5 (s, CF_3).

5.2.2. General procedure for the enantioselective conjugate addition of methyl malonate to β-trifluoromethyl α,β-unsaturated *N*-tosyl imines 11

5.2.2.1. General procedure for the enantioselective conjugate addition

$Cu(OTf)_2$ (4.5 mg, 0.0125 mmol) was dried in a Schlenk tube under vacuum. **BOX7** (4.4 mg, 0.0125 mmol) was added and the tube was filled with nitrogen. CH_2Cl_2 (0.55 mL) was added *via* syringe and the mixture was stirred for 30 min. A solution of imine **11** (0.125 mmol) dissolved in dry CH_2Cl_2 (0.5 mL), was added *via* syringe, followed by 4 Å MS (110 mg) and dimethyl malonate (34 μL, 0.3 mmol). The mixture was stirred at room temperature for the indicated time and chromatographed on silica gel eluting with hexane/EtOAc mixtures to give compounds **12**.

For the Mg(II)-catalyzed reaction, $Mg(OTf)_2$ was used instead of $Cu(OTf)_2$. The reaction tube was introduced in a bath at 0 °C before the addition of the imine.

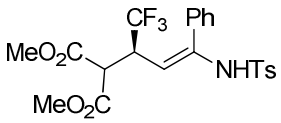
5.2.2.2. General procedure for the synthesis of the racemic products

Racemic compounds for comparative purpose were prepared by following the same procedure, using $La(OTf)_3$-pyBOX (rac) at 40 °C.

5.2.2.3. Characterization of products 12

See Table 6 (Page 73) and Table 8 (Page 75) for yield, dr and ee. The following data refers to products **12** obtained with the **BOX7**-$Cu(OTf)_2$ catalyst.

Dimethyl (*S*,*E*)-2-(1,1,1-trifluoro-4-((4-methylphenyl)sulfonamido)-4-phenylbut-3-en-2-yl)malonate (12aa)



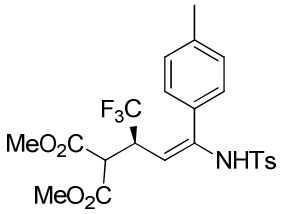
Chiral HPLC analysis: Chiralpak AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *E*-diastereomer: *major enantiomer (S)* t_r = 8.4 min, *minor enantiomer (R)* t_r = 14.0 min; *Z*-diastereomer: *major enantiomer* t_r = 12.4 min, *minor enantiomer* t_r = 9.4 min.

Major *E*-diastereomer: White solid, mp 159-161 °C (hexane-EtOAc); $[\alpha]_D^{20}$ -54.0 (*c* 1.0, $CHCl_3$, ee = 95%) for the mixture of diastereomers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (2H, d, *J* = 8.4 Hz, Ar), 7.40-7.27 (5H, m, Ar), 7.10 (2H, m, Ar), 6.21 (1H, s, NH), 5.57 (1H, d, *J* = 10.8 Hz, =CH), 3.73 (3H, s, MeO), 3.68 (1H, d, *J* = 8.4 Hz, CH-CO_2Me), 3.64 (1H, m, CH-CF_3), 3.63 (3H, s, MeO), 2.45 (3H, s, Me-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7 (C), 166.4 (C), 144.2 (C), 141.3 (C), 135.9 (C), 134.0 (C), 129.6 (CH), 129.5 (CH), 128.7 (CH), 128.6 (CH), 127.7 (CH), 125.4 (C, q, $J_{C\text{-}F}$ = 264.8 Hz), 102.9 (CH, q, $J_{C\text{-}F}$ = 2.4 Hz), 52.93 (CH_3), 52.90 (CH_3), 51.0 (CH), 42.7 (CH, q, $J_{C\text{-}F}$ = 27.9 Hz), 21.5 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -70.1 (s, CF_3); HRMS (ESI) *m/z* 486.1197 $[M+H]^+$, $C_{22}H_{23}F_3NO_6S$ requires 486.1193.

Minor *Z*-diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$, ee = 75%) δ 7.95 (s, 1H), 7.59 (2H, d, *J* = 8.4 Hz, Ar), 7.41 (2H, dd, *J* = 8.1, 1.5 Hz, Ar), 7.36-7.26 (3H, m, Ar), 7.22

(2H, d, *J* = 8.4 Hz, Ar), 5.22 (1H, d, *J* =11.1 Hz, =CH), 3.81 (3H, s, MeO), 3.76-3.48 (2H, m, CH-CF_3, CH-CO_2Me), 3.68 (3H, s, MeO), 2.39 (s, 3H, Me-Ar); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.8 (s, CF_3).

Dimethyl (*S*,*E*)-2-(1,1,1-trifluoro-4-((4-methylphenyl)sulfonamido)-4-(*p*-tolyl)but-3-en-2-yl)malonate (12ab)

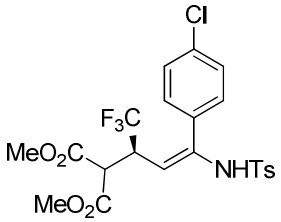


Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 85:15, 1 mL/min, *E*-diastereomer: *major enantiomer (S)* t_r = 13.4 min, *minor enantiomer (R)* t_r = 16.1 min; *Z*-diastereomer: *major enantiomer* t_r = 14.5 min, *minor enantiomer* t_r = 11.9 min.

Major *E*-diastereomer: White solid, mp 138-146 °C (hexane-EtOAc); $[\alpha]_D^{20}$ -38.6 (*c* 0.95, $CHCl_3$, ee = 94%) for the mixture of diastereomers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (2H, d, *J* = 8.4 Hz, Ar), 7.32 (2H, d, *J* = 8.4 Hz, Ar), 7.13 (2H, d, *J* = 8.1 Hz, Ar), 6.97 (2H, d, *J* = 8.1 Hz, Ar), 6.18 (1H, s, NH), 5.52 (1H, d, *J* = 10.8 Hz, =CH), 3.72 (3H, s, MeO), 3.67 (1H, d, *J* = 8.1 Hz, CH-CO_2Me), 3.64 (1H, m, CH-CF_3), 3.63 (3H, s, MeO), 2.45 (3H, s, Me-Ar), 2.33 (3H, s, Me-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8 (C), 166.5 (C), 144.2 (C), 141.3 (C), 139.5 (C), 135.9 (C), 131.2 (C), 129.6 (CH), 129.5 (CH), 128.4 (CH), 127.7 (CH), 125.4 (C, q, $J_{C\text{-}F}$ = 249.7 Hz), 102.6 (CH, q, $J_{C\text{-}F}$ = 2.0 Hz), 52.94 (CH_3), 52.91 (CH_3), 51.0 (CH), 42.7 (CH, q, $J_{C\text{-}F}$ = 27.9 Hz), 21.5 (CH_3), 21.3 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -70.2 (s, CF_3) ppm; HRMS (ESI) *m/z* 500.1356 $[M+H]^+$, $C_{23}H_{25}F_3NO_6S$ requires 500.1349.

Minor *Z*-diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$, ee = 40%), representative signals taken from the ^{1}H NMR of the diastereomer mixtures, δ 7.91 (1H, s, NH), 7.86 (2H, d, *J* = 8.1 Hz, Ar), 7.60 (2H, d, *J* = 8.1 Hz, Ar), 7.25 (2H, d, *J* = 8.1 Hz, Ar), 7.22 (2H, d, *J* = 8.1 Hz, Ar), 5.16 (1H, d, *J* = 10.8 Hz, =CH), 3.82-3.60 (2H, m, CH-CF_3, CH-CO_2Me), 3.76 (3H, s, MeO), 3.67 (3H, s, MeO), 2.43 (3H, s, Me-Ar), 2.39 (3H, s, Me-Ar); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.9 (s, CF_3).

Dimethyl (*S*,*E*)-2-(4-(4-chlorophenyl)-1,1,1-trifluoro-4-((4-methylphenyl)-sulfonamido)-but-3-en-2-yl)malonate (12ac)



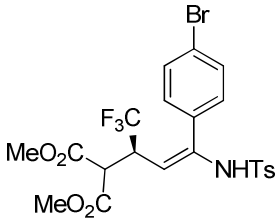
Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 95:05, 1 mL/min, *E*-diastereomer: *major enantiomer (S)* t_r = 38.4 min, *minor enantiomer (R)* t_r = 47.9 min; *Z*-diastereomer: *major enantiomer* t_r = 48.4 min, *minor enantiomer* t_r = 33.9 min.

Major *E*-diastereomer: White solid, mp 142-150 °C (hexane-EtOAc); $[\alpha]_D^{20}$ -21.3 (*c* 0.95, $CHCl_3$, ee = 97%) for the mixture of diastereomers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (2H, d, *J* = 8.4 Hz, Ar), 7.34-7.24 (4H, m, Ar), 7.04 (2H, d, *J* = 8.7 Hz, Ar), 6.42 (1H, s, NH), 5.52 (1H, d, *J* = 10.8 Hz, =CH), 3.72 (3H, s, MeO), 3.67 (1H, d, *J* = 8.4 Hz, CH-CO_2Me), 3.64 (3H, s, MeO), 3.55 (1H, m, CH-CF_3), 2.44 (3H, s, Me-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6 (C), 166.5 (C), 144.3 (C),

140.4 (C), 135.9 (C), 135.6 (C), 132.3 (C), 130.2 (CH), 129.7 (CH), 129.0 (CH), 127.6 (CH), 125.4 (C, q, J_{C-F} = 278 Hz), 104.3 (CH, q, J_{C-F} = 2.5 Hz), 53.04 (CH_3), 52.99 (CH_3), 50.9 (CH), 42.6 (CH, q, J_{C-F} = 28.0 Hz), 21.6 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -70.1 (s, CF_3); HRMS (ESI) *m/z* 520.0795 $[M+H]^+$, $C_{22}H_{22}ClF_3NO_6S$ requires 520.0803.

Minor *Z*-diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$, ee = 32%), representative signals taken from the ^{1}H NMR of the diastereomer mixtures, δ 8.01 (1H, s, NH), 7.57 (2H, d, J = 8.4 Hz, Ar), 7.40-7.19 (6H, m, Ar), 5.19 (1H, d, *J* = 11.4 Hz, =CH), 3.80 (3H, s, MeO), 3.76 (1H, d, J = 7.2 Hz, CH-CO_2Me), 3.68 (3H, s, MeO), 3.51 (1H, m, CH-CF_3), 2.39 (3H, s, Me-Ar); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.8 (s, CF_3).

Dimethyl (*S*,*E*)-2-(4-(4-bromophenyl)-1,1,1-trifluoro-4-((4-methylphenyl) sulfonamido)but-3-en-2-yl)malonate (12ad)

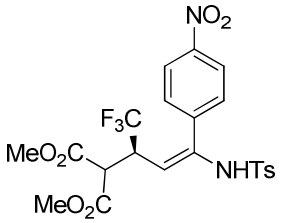


Chiral HPLC analysis: Chiralpak IC, hexane-*i*PrOH 95:05, 1 mL/min, *E*-diastereomer: *major enantiomer (S)* t_r = 47.9 min, *minor enantiomer (R)* t_r = 57.1 min; *Z*-diastereomer: *major enantiomer* t_r = 31.9 min, *minor enantiomer* t_r = 40.2 min.

Major *E*-diastereomer: Yellow solid, mp 130-133 °C (hexane-EtOAc); $[\alpha]_D^{20}$ -12.8 (*c* 1.02 , $CHCl_3$, ee = 95%) for the mixture of diastereomers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (2H, d, *J* = 8.4 Hz, Ar), 7.45 (2H, d, *J* = 8.4 Hz, Ar), 7.31 (2H, d, *J* = 8.4 Hz, Ar), 7.04 (2H, d, *J* = 8.4 Hz, Ar), 6.29 (1H, s, NH), 5.53 (1H, d, *J* = 10.8 Hz, =CH), 3.73 (3H, s, MeO), 3.68 (1H, d, *J* = 8.4 Hz, CH-CO_2Me), 3.65 (3H, s, MeO), 3.55 (1H, m, CH-CF_3), 2.45 (3H, s, Me-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6 (C), 166.5 (C), 144.4 (C), 140.4 (C), 135.9 (C), 132.8 (C), 132.0 (CH), 130.4 (CH), 129.7 (CH), 127.6 (CH), 125.4 (C, q, J_{C-F} = 278 Hz), 124.0 (C), 104.3 (CH, q, J_{C-F} = 2.3 Hz), 53.07 (CH_3), 53.01 (CH_3), 50.9 (CH), 42.6 (CH, q, J_{C-F} = 28.0 Hz), 21.6 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -70.0 (s, CF_3); HRMS (ESI) *m/z* 564.0295 $[M+H]^+$, $C_{22}H_{22}BrF_3NO_6S$ requires 564.0298.

Minor *Z*-diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$, ee = 43%), representative signals taken from the ^{1}H NMR of the diastereomer mixtures, δ 8.01 (1H, s, NH), 7.58 (2H, d, *J* = 8.4 Hz, Ar), 7.41 (2H, d, *J* = 8.4 Hz, Ar), 7.31 (2H, d, *J* = 8.4 Hz, Ar), 7.25 (2H, d, *J* = 8.4 Hz, Ar), 5.21 (1H, d, *J* = 11.4 Hz, =CH), 3.80 (3H, s, MeO), 3.77 (1H, d, J = 7.2 Hz, CH-CO_2Me), 3.68 (3H, s, MeO), 3.52 (1H, m, CH-CF_3), 2.40 (3H, s, Me-Ar); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.8 (s, CF_3).

Dimethyl (*S*,*E*)-2-(1,1,1-trifluoro-4-((4-methylphenyl)sulfonamido)-4-(4-nitrophenyl)but-3-en-2-yl)malonate (12ae)

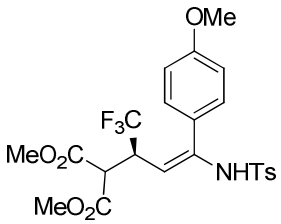


Chiral HPLC analysis: Chiralpak IC, hexane-*i*PrOH 90:10, 1 mL/min, *E*-diastereomer: *major enantiomer (S)* t_r = 60.4 min, *minor enantiomer (R)* t_r = 69.2 min; *Z*-diastereomer: *major enantiomer* t_r = 50.2 min, *minor enantiomer* t_r = 94.8 min.

Major *E*-diastereomer: Orange oil; $[\alpha]_D^{20}$ 1.1 (*c* 1.0, $CHCl_3$, ee = 90%) for the mixture of diastereomers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (2H, d, *J* = 9.0 Hz, Ar), 7.68 (2H, d, *J* = 8.1 Hz, Ar), 7.37.34-7,28 (4H, m, Ar), 6.80 (1H, s, NH), 5.58 (1H, d, *J* = 11.1 Hz, =CH), 3.73 (3H, s, MeO), 3.68 (1H, d, *J* = 8.4 Hz, CH-CO_2Me), 3.65 (3H, s, MeO), 3.49 (1H, m, CH-CF_3), 2.45 (3H, s, Me-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5 (C), 166.4 (C), 148.2 (C), 144.6 (C), 140.1 (C), 139.6 (C), 135.7 (C), 130.2 (CH), 129.7 (CH), 127.6 (CH), 125.2 (C, q, $J_{C\text{-}F}$ = 279 Hz), 123.8 (C), 106.5 (CH, q, $J_{C\text{-}F}$ = 2.1 Hz), 53.2 (CH_3), 53.1 (CH_3), 50.7 (CH), 42.6 (CH, q, $J_{C\text{-}F}$ = 28.2 Hz), 21.6 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.9 (s, CF_3); HRMS (ESI) *m/z* 531.1034 $[M+H]^+$, $C_{22}H_{22}ClF_3N_2O_8S$ requires 531.1043.

Minor *Z*-diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$, ee = 54%), representative signals taken from the ^{1}H NMR of the diastereomer mixture, δ 8.19 (1H, s, NH), 8.14 (2H, d, *J* = 9.0 Hz, Ar), 7.60 (4H, m, Ar), 7.25 (2H, d, *J* = 8.0 Hz, Ar), 5.40 (1H, d, *J* = 10.8 Hz, =CH), 3.83 (3H, s, MeO), 3.80 (1H, d, *J* = 5.7 Hz, CH-CO_2Me), 3.69 (3H, s, MeO), 3.49 (1H, m, CH-CF_3), 2.40 (3H, s, Me-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2 (C), 166.9 (C), 148.2 (C), 144.4 (C), 143.2 (C), 140.0 (C), 136.5 (C), 129.7 (CH), 128.7 (CH), 126.9 (CH), 125.2 (C, q, $J_{C\text{-}F}$ = 279 Hz), 123.3 (C), 114.8 (CH, q, $J_{C\text{-}F}$ = 2.1 Hz), 54.0 (CH_3), 53.4 (CH_3), 50.7 (CH), 41.8 (CH, q, $J_{C\text{-}F}$ = 29.0 Hz), 21.4 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.9 (s, CF_3).

Dimethyl (*S*,*E*)-2-(1,1,1-trifluoro-4-(4-methoxyphenyl)-4-((4-methylphenyl) sulfonamido)but-3-en-2-yl)malonate (12af)



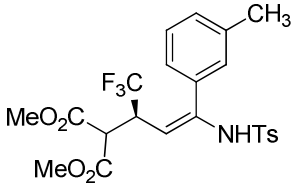
Chiral HPLC analysis: Chiralpak IC, hexane-*i*PrOH 90:10, 1 mL/min, *E*-diastereomer: *major enantiomer (S)* t_r = 44.2 min, *minor enantiomer (R)* t_r = 63.8 min; *Z*-diastereomer: *major enantiomer* t_r = 38.0 min, *minor enantiomer* t_r = 50.9 min.

Major *E*-diastereomer: Yellow oil; $[\alpha]_D^{20}$ -16.3 (*c* 1.0, $CHCl_3$) for the mixture of diastereomers; ^{1}H NMR (300 MHz, $CDCl_3$, ee = 94%) δ 7.75 (2H, d, *J* = 8.1 Hz, Ar), 7.32 (2H, d, *J* = 8.1 Hz, Ar), 7.03 (2H, d, *J* = 8.7 Hz, Ar), 6.84 (2H, d, *J* = 8.7 Hz, Ar), 6.16 (1H, s, NH), 5.48 (1H, d, *J* = 10.8 Hz, =CH), 3.79-3.66 (2H, m, CH-CF_3, CH-CO_2Me), 3.80 (3H, s, MeO), 3.73 (3H, s, MeO), 3.64 (3H, s, MeO), 2.45 (3H, s, Me-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8 (C), 166.5 (C), 160.3 (C), 144.1 (C), 141.2 (C), 136.0 (C), 130.0 (CH), 129.6 (CH), 127.7 (CH), 125.6 (C, q, $J_{C\text{-}F}$ = 279 Hz), 114.1 (CH), 102.7 (C, q, $J_{C\text{-}F}$ = 2.0 Hz), 55.2 (CH_3), 52.96 (CH_3), 52.91 (CH_3), 51.1

(CH), 42.6 (CH, q, $J_{C\text{-}F}$ = 27.8 Hz), 21.6 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -70.2 (s, CF_3); HRMS (ESI) *m/z* 516.1294 $[M+H]^+$, $C_{23}H_{25}F_3NO_7S$ requires 516.1298.

Minor *Z*-diastereomer: ^1H NMR (300 MHz, $CDCl_3$, ee = 56%), representative signals taken from the ^1H NMR of the diastereomer mixture, δ 7.60 (2H, d, *J* = 8.1 Hz, Ar), 7.23 (2H, d, *J* = 8.1 Hz, Ar), 6.93 (2H, d, *J* = 9.0 Hz, Ar), 6.79 (2H, d, *J* = 9.0 Hz, Ar), 5.09 (1H, d, *J* = 11.4 Hz, =CH), 2.43 (3H, s, Me-Ar); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.9 (s, CF_3).

Dimethyl (*S*,*E*)-2-(1,1,1-trifluoro-4-((4-methylphenyl)sulfonamido)-4-(*m*-tolyl)but-3-en-2-yl)malonate (12ag)

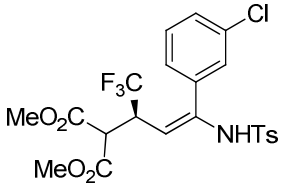


Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 80:20, 1 mL/min, *E*-diastereomer: *major enantiomer (S)* t_r = 7.0 min, *minor enantiomer (R)* t_r = 10.7 min; *Z*-diastereomer: *major enantiomer* t_r = 9.5 min, *minor enantiomer* t_r = 7.8 min.

Major *E*-diastereomer: White solid, mp 117-120 °C (hexane-EtOAc); $[\alpha]_D^{20}$ -40.7 (*c* 1.0, $CHCl_3$, ee = 94%) for the mixture of diastereomers; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (2H, d, *J* = 8.1 Hz, Ar), 7.32 (2H, d, *J* = 8.1 Hz, Ar), 7.21-7.13 (2H, m, Ar), 6.89 (1H, d, *J* = 7,5 Hz, Ar), 6.81 (1H, s, Ar), 6.18 (1H, s, NH), 5.55 (1H, d, *J* = 10.8 Hz, =CH), 3.76-3.67 (2H, m, CH-CF_3, CH-CO_2Me), 3.73 (3H, s, MeO), 3.63 (3H, s, MeO), 2.45 (3H, s, Me-Ar), 2.28 (3H, s, Me-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8 (C), 166.5 (C), 144.2 (C), 141.4 (C), 138.5 (C), 136.0 (C), 134.0 (C), 130.2 (CH), 129.6 (CH), 129.1 (CH), 128.7 (CH), 127.7 (CH), 125.6 (CH), 125.4 (C, q, $J_{C\text{-}F}$ = 255 Hz), 102.9 (CH, q, $J_{C\text{-}F}$ = 2.0 Hz), 52.93 (CH_3), 52.91 (CH_3), 51.1 (CH), 42.6 (CH, q, $J_{C\text{-}F}$ = 27.9 Hz), 21.5 (CH_3), 21.3 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -70.2 (s, CF_3); HRMS (ESI) *m/z* 500.1354 $[M+H]^+$, $C_{23}H_{25}F_3NO_6S$ requires 500.1349.

Minor *Z*-diastereomer: ^1H NMR (300 MHz, $CDCl_3$, ee = 41%), representative signals taken from the ^1H NMR of the diastereomer mixture, δ 7.90 (1H, s, NH), 7.58 (2H, d, *J* = 8.4 Hz, Ar), 7.35-6.75 (6H, m, Ar), 5.22 (1H, d, *J* = 11.4 Hz, =CH), 3.82-3.60 (2H, m, CH-CF_3, CH-CO_2Me), 3.80 (3H, s, MeO), 3.68 (3H, s, MeO), 2.43 (3H, s, Me-Ar), 2.26 (3H, s, Me-Ar); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.8 (s, CF_3).

Dimethyl (*S*,*E*)-2-(4-(3-chlorophenyl)-1,1,1-trifluoro-4-((4-methylphenyl) sulfonamido)but-3-en-2-yl)malonate (12ah)



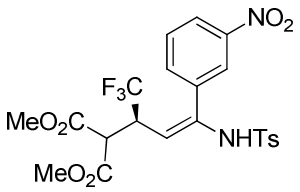
Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 80:20, 1 mL/min, *E*-diastereomer: *major enantiomer (S)* t_r = 7.2 min, *minor enantiomer (R)* t_r = 11.1 min; *Z*-diastereomer: *major enantiomer* t_r = 9.5 min, *minor enantiomer* t_r = 8.2 min.

Major *E*-diastereomer: yellow solid, mp 100-107 °C (hexane-EtOAc); $[\alpha]_D^{20}$ -20.8 (*c* 0.96, $CHCl_3$, ee = 91%) for the mixture of diastereomers; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (2H, d, *J* = 8.4 Hz, Ar), 7.32 (2H, d, *J* = 8.4 Hz, Ar), 7.31-7.17 (2H, m, Ar), 7.05 (1H, dt, *J* = 7.2, 1.5 Hz, Ar), 6.93 (1H, t, *J* = 1.5 Hz, Ar), 6.34 (1H, s, NH), 5.58 (1H, d,

J = 10.8 Hz, =CH), 3.74 (3H, s, MeO), 3.68 (1H, d, J = 8.1 Hz, CH-CO_2Me), 3.64 (3H, s, MeO), 3.56 (1H, m, CH-CF_3), 2.45 (3H, s, Me-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6 (C), 166.4 (C), 144.4 (C), 140.1 (C), 135.8 (C), 135.5 (C), 134.5 (C), 130.0 (CH), 129.7 (CH), 129.6 (CH), 128.8 (CH), 127.6 (CH), 127.0 (CH), 125.4 (C, q, J_{C-F} = 280 Hz), 104.9 (CH, q, J_{C-F} = 2.0 Hz), 53.03 (CH_3), 52.98 (CH_3), 50.9 (CH), 42.6 (CH, q, J_{C-F} = 28.0 Hz), 21.5 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -70.0 (s, CF_3); HRMS (ESI) *m/z* 520.0801 $[M+H]^+$, $C_{22}H_{22}ClF_3NO_6S$ requires 520.0803.

Minor *Z*-diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$, ee = 49%), representative signals taken from the ^{1}H NMR of the diastereomer mixture, δ 8.00 (1H, s, NH), 7.57 (2H, d, *J* = 8.4 Hz, Ar), 7.33-7.20 (6H, m, Ar), 5.26 (1H, dd, *J* = 10.8, 0.6 Hz, =CH), 3.81 (3H, s, MeO), 3.78 (1H, d, *J* = 6.3 Hz, CH-CO_2Me), 3.69 (3H, s, MeO), 3.56 (1H, m, CH-CF_3), 2.39 (3H, s, Me-Ar); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.7 (s, CF_3).

Dimethyl (*S*,*E*)-2-(1,1,1-trifluoro-4-((4-methylphenyl)sulfonamido)-4-(3-nitrophenyl)but-3-en-2-yl)malonate (12ai)

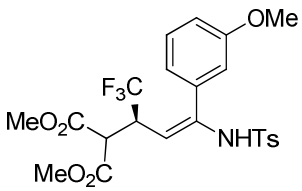


Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 95:05, 2 mL/min, *E*-diastereomer: *major enantiomer (S)* t_r = 42.9 min, *minor enantiomer (R)* t_r = 78.2 min; *Z*-diastereomer: *major enantiomer* t_r = 50.6 min, *minor enantiomer* t_r = 30.9 min.

Major *E*-diastereomer: Yellow oil; $[\alpha]_D^{20}$ -9.5 (*c* 0.97, $CHCl_3$, ee = 83%) for the mixture of diastereomers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (1H, m, Ar), 7.82 (1H, ddd, *J* = 7.8, 1.8, 1.2 Hz, Ar), 7.76 (1H, t, *J* = 1.8 Hz, Ar), 7.65 (2H, d, *J* = 8.0 Hz, Ar), 7.54 (1H, t, *J* = 8.0 Hz, Ar), 7.30 (2H, d, *J* = 8.0 Hz, Ar), 6.62 (1H, s, NH), 5.63 (1H, d, *J* = 11.1 Hz, =CH), 3.76 (3H, s, MeO), 3.67 (1H, d, *J* = 7.4 Hz, CH-CO_2Me), 3.65 (3H, s, MeO), 3.48 (1H, m, CH-CF_3), 2.44 (3H, s, Me-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5 (C), 166.4 (C), 148.1 (C), 144.7 (C), 139.5 (C), 135.7 (C), 135.2 (CH), 135.1 (C), 129.8 (CH, overlaped signals), 127.5 (CH), 125.3 (C, q, J_{C-F} = 279 Hz), 124.2 (CH), 124.1 (CH), 106.9 (CH, q, J_{C-F} = 2.0 Hz), 53.17 (CH_3), 53.12 (CH_3), 50.7 (CH), 42.6 (CH, q, J_{C-F} = 28.2 Hz), 21.5 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.9 (s, CF_3); HRMS (ESI) *m/z* 531.1036 $[M+H]^+$, $C_{22}H_{22}ClF_3N_2O_8S$ requires 531.1043.

Minor *Z*-diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$, ee = 58%), representative signals taken from the ^{1}H NMR of the diastereomer mixture, δ 8.19 (1H, s, NH), 8.16 (1H, m, Ar), 8.11 (1H, t, *J* = 1.9 Hz, Ar), 7.63-7.53 (3H, m, Ar), 7.50 (1H, t, *J* = 8.1 Hz, Ar), 7.23 (2H, d, *J* = 8.0 Hz, Ar), 5.38 (1H, dd, *J* = 10.8, 0.6 Hz, =CH), 3.83 (3H, s, MeO), 3.81 (1H, d, *J* = 6.3 Hz, CH-CO_2Me), 3.71 (3H, s, MeO), 3.58 (1H, m, CH-CF_3), 2.39 (3H, s, Me-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2 (C), 167.0 (C), 148.0 (C), 144.4 (C), 139.8 (C), 138.5 (C), 136.6 (C), 134.1 (CH), 129.7 CH), 129.2 (CH), 126.9 (CH), 125.3 (C, q, J_{C-F} = 279 Hz), 123.9 (CH), 122.7 (CH), 113.8 (CH, q, J_{C-F} = 2.4 Hz), 54.0 (CH_3), 53.4 (CH_3), 50.7 (CH), 41.9 (CH, q, J_{C-F} = 28.29 Hz), 21.4 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.6 (s, CF_3).

Dimethyl (*S*,*E*)-2-(1,1,1-trifluoro-4-(3-methoxyphenyl)-4-((4-methylphenyl) sulfonamido)but-3-en-2-yl)malonate (12aj)

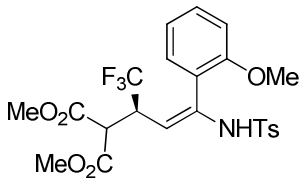


Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 90:10, 1 mL/min, *E*-diastereomer: *major enantiomer (S)* t_r = 19.4 min, *minor enantiomer (R)* t_r = 30.7 min; *Z*-diastereomer: *major enantiomer* t_r = 26.5 min, *minor enantiomer* t_r = 21.8 min.

Major *E*-diastereomer: Yellow solid, mp 102-105 °C (hexane-EtOAc); $[\alpha]_D^{20}$ -40.3 (*c* 0.95, $CHCl_3$, ee = 87%) for the mixture of diastereomers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (2H, d, *J* = 8.4 Hz, Ar), 7.38 (2H, d, *J* = 8.4 Hz, Ar), 7.28-7.25 (1H, m, Ar), 6.93 (1H, ddd, *J* = 8.4, 2.4, 1.2 Hz, Ar), 6.71-6.69 (2H, m, Ar), 6.31 (1H, s, NH), 5.65 (1H, d, *J* = 10.8 Hz, =CH), 3.88 (1H, d, *J* = 8.7 Hz, CH-CO_2Me), 3.80 (3H, s, MeO), 3.79 (3H, s, MeO), 3.76-3.75 (1H, m, CH-CF_3), 3.70 (3H, s, MeO), 2.50 (3H, s, Me-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8 (C), 166.6 (C), 159.6 (C), 144.2 (C), 141.1 (C), 135.9 (C), 135.3 (C), 129.9 (CH), 129.6 (CH), 127.7 (CH), 125.4 (C, q, J_{C-F} = 257.3 Hz), 120.6 (CH), 115.7 (CH), 113.6 (CH), 102.9 (CH, q, J_{C-F} = 2.0 Hz), 55.2 (CH_3), 52.95 (CH_3), 52.94 (CH_3), 51.0 (CH), 42.6 (CH, q, J_{C-F} = 27.9 Hz), 21.5 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -70.2 (s, CF_3); HRMS (ESI) *m/z* 516.1294 $[M+H]^+$, $C_{23}H_{25}F_3NO_7S$ requires 516.1298.

Minor *Z*-diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$, ee = 82%), representative signals taken from the 1H NMR of the diastereomer mixture, δ 7.99 (1H, s, NH), 7.65 (2H, d, *J* = 8.4 Hz, Ar), 7.37-7.32 (1H, m, Ar), 7.06 (dt, *J* = 7,8, 1,2 Hz, Ar), 6.75-6.65 (2H, m, Ar), 5.31 (1H, d, *J* = 11.4 Hz, =CH), 3.89-3.67 (2H, m, CH-CF_3, CH-CO_2Me), 3.86 (3H, s, MeO), 3.80 (3H, s, MeO), 3.75 (3H, s, MeO), 2.45 (3H, s, Me-Ar); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.8 (s, CF_3).

Dimethyl (*S*,*E*)-2-(1,1,1-trifluoro-4-(2-methoxyphenyl)-4-((4-methylphenyl)-sulfonamido)but-3-en-2-yl)malonate (12ak)



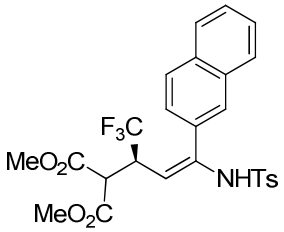
Chiral HPLC analysis: Chiralpak AD-H, hexane-*i*PrOH 90:10, 1 mL/min, *E*-diastereomer: *major enantiomer (S)* t_r = 21.6 min, *minor enantiomer (R)* t_r = 47.2 min; *Z*-diastereomer: *major enantiomer* t_r = 38.3 min, *minor enantiomer* t_r = 32.7 min.

Major *E*-diastereomer: Yellow solid, mp 129-133 °C (hexane-EtOAc); $[\alpha]_D^{20}$ -32.2 (*c* 0.92, $CHCl_3$) for the mixture of diastereomers; ^{1}H NMR (300 MHz, $CDCl_3$, ee = 89%) δ 7.72 (2H, d, *J* = 8.4 Hz, Ar), 7.28-7.25 (2H, m, Ar), 7.03-7.00 (2H, m, Ar), 6.89 (1H, dt, *J* = 7.5, 1.2 Hz, Ar), 6.82 (1H, dd, *J* = 8.4, 1.2 Hz, Ar), 6.18 (1H, s, NH), 5.69 (1H, d, *J* = 10.8 Hz, =CH), 3.75 (3H, s, MeO), 3.69-3.55 (2H, m, CH-CF_3, CH-CO_2Me), 3.65 (3H, s, MeO), 3.60 (3H, s, MeO), 2.42 (3H, s, Me-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8 (C), 166.6 (C), 156.7 (C), 143.8 (C), 138.8 (C), 136.1 (C), 131.2 (C), 131.0 (C), 129.3 (CH), 128.9 (CH), 127.9 (CH), 127.1 (CH), 125.0 (C, q, J_{C-F} = 258.8 Hz), 120.6

(CH), 111.0 (CH), 113.6 (CH), 105.6 (CH, q, J_{C-F} = 2.0 Hz), 55.1 (CH_3), 52.9 (CH_3), 51.1 (CH), 42.8 (CH, q, J_{C-F} = 27.8 Hz), 21.5 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -70.2 (s, CF_3); HRMS (ESI) *m/z* 516.1302 $[M+H]^+$, $C_{23}H_{25}F_3NO_7S$ requires 516.1298.

Minor *Z*-diastereomer: ^1H NMR (300 MHz, $CDCl_3$, ee = 17%), representative signals taken from the ^1H NMR of the diastereomer mixture, δ 7.81 (2H, d, *J* = 8.1 Hz, Ar), 7.38-6.49 (7H, m, Ar, NH), 5.44 (1H, d, *J* = 10.8 Hz, =CH), 3.82-3.60 (2H, m, CH-CF_3, CH-CO_2Me), 3.83 (3H, s, MeO), 3.73 (3H, s, MeO), 3.55 (3H, s, MeO), 2.31 (3H, s, Me-Ar); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.5 (s, CF_3).

Dimethyl (*S*,*E*)-2-(1,1,1-trifluoro-4-((4-methylphenyl)sulfonamido)-4-(naphthalen-2-yl)but-3-en-2-yl)malonate (12al)



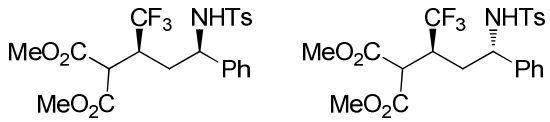
Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 80:20, 1 mL/min, *E*-diastereomer: *major enantiomer (S)* t_r = 11.3 min, *minor enantiomer (R)* t_r = 13.8 min; *Z*-diastereomer: *major enantiomer* t_r = 12.3 min, *minor enantiomer* t_r = 9.4 min

Major *E*-diastereomer: Yellow solid, mp 98-103 °C (hexane-EtOAc); $[\alpha]_D^{20}$ 1.0 (*c* 0.96, $CHCl_3$, ee = 93%) for the mixture of diastereomers; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80-7.74 (5H, m, Ar), 7.59-7.58 (1H, m, Ar), 7.53-7.49 (2H, m, Ar), 7.30 (2H, d, *J* = 8.1 Hz Ar), 7.14 (1H, dd, *J* = 8.1, 1.8 Hz, Ar), 6.38 (1H, s, NH), 5.65 (1H, d, *J* = 10.8 Hz, =CH), 3.82-3.69 (2H, m, CH-CF_3, CH-CO_2Me), 3.76 (3H, s, MeO), 3.60 (3H, s, MeO), 2.44 (3H, s, Me-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7 (C), 166.5 (C), 144.2 (C), 141.4 (C), 136.0 (C), 133.3 (C), 132.8 (C), 131.2 (C), 129.6 (CH), 128.64 (CH), 128.57 (CH), 128.3 (CH), 127.7 (CH), 127.1 (CH), 126.6 (CH), 125.5 (CH), 125.4 (C, q, J_{C-F} = 264.8 Hz), 123.7 (CH), 104.0 (CH, q, J_{C-F} = 2.0 Hz), 53.0 (CH_3), 52.9 (CH_3), 51.1 (CH), 42.7 (CH, q, J_{C-F} = 28.5 Hz), 21.5 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -70.0 (s, CF_3); HRMS (ESI) *m/z* 536.1346 $[M+H]^+$, $C_{26}H_{25}F_3NO_6S$ requires 536.1349.

Minor *Z*-diastereomer: ^1H NMR (300 MHz, $CDCl_3$, ee = 27%), representative signals taken from the ^1H NMR of the diastereomer mixture, δ 8.05 (1H, s, NH), 7.87-6.94 (11H, m, Ar), 5.37 (1H, d, *J* = 11,1 Hz, =CH), 3.82 (3H, s, MeO), 3.80-3.60 (2H, m, CH-CF_3, CHCO_2Me), 3.68 (3H, s, MeO), 2.34 (3H, s, Me-Ar); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.6 (s, CF_3).

5.2.3. Synthetic transformations from compound 12aa

Dimethyl 2-((2*S*,4*R*)-1,1,1-trifluoro-4-((4-methylphenyl)sulfonamido)-4-phenyl-butan-2-yl)malonate (13) and 2-((2*S*,4*S*)-1,1,1-trifluoro-4-((4-methylphenyl)sulfonamido)-4-phenyl-butan-2-yl)malonate (14)

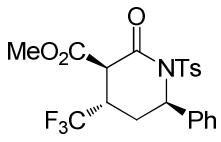


To a sample of compound (*S*,*E*)-**12aa** (52.0 mg, 0.11 mmol, *E/Z* 96:4, ee = 89%/69%), dissolved in dry CH_2Cl_2 (3.3 mL) under nitrogen atmosphere was added triethylsilane (50 μL, 0.428 mmol) followed by $BF_3 \cdot Et_2O$ (67 μL, 0.471 mmol). After stirring for 48 h at room temperature, the mixture was chromatographed on silica gel eluting with hexane/EtOAc (80:20) to give 48.1 mg (92%) of a *ca.* 88:12 mixture of two diastereomeric compounds **13** and **14**. Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 90:10, 1 mL/min, (2*S*,4*R*)-**13** (ee = 87%), *major enantiomer* t_r = 16.4 min, *minor enantiomer* t_r = 15.0 min; (2*S*,4*S*)-**14**, unresolved t_r = 8.3 min. Chiralpak IC, hexane-*i*PrOH 95:05, 2 mL/min, (2*S*,4*R*)-**13**, t_r > 120 min; (2*S*,4*S*)-**14** (ee = 89%), *major enantiomer* t_r = 37.6 min, *minor enantiomer* t_r = 35.8 min;

(2*S*,4*R*)-**13** (major): colorless oil; $[\alpha]_D^{20}$ 7.8 (*c* 0.97, $CHCl_3$) for the diastereomer mixture; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (2H, d, *J* = 8.1 Hz, Ar), 7.20-7.13 (3H, m, Ar), 7.10 (2H, d, *J* = 8.1 Hz, Ar), 7.02-6.90 (2H, m, Ar), 5.13 (1H, d, *J* = 8.1 Hz, NH), 4.47 (1H, q, *J* = 7.8 Hz, CH-Ph), 3.73 (3H, s, MeO), 3.69 (1H, d, *J* = 5.4 Hz, CH-CO_2Me), 2.83 (1H, m, CH-CF_3), 2.34 (3H, s, Me-Ar), 2.32-2.10 (2H, m, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1 (C), 167.0 (C), 143.1 (C), 138.8 (C), 137.2 (C), 129.3 (CH), 128.6 (CH), 128.5 (C), 127.9 (CH), 127.0 (CH), 126.8 (CH), 126.6 (C, q, $J_{C\text{-}F}$ = 278 Hz), 56.4 (CH), 53.1 (CH_3), 52.8 (CH_3), 49.9 (CH), 40.0 (CH, q, $J_{C\text{-}F}$ = 26.8 Hz), 33.4 (CH_2), 21.4 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -68.5 (s, CF_3); HRMS (ESI) *m/z* 488.1357 $[M+H]^+$, $C_{22}H_{25}F_3NO_6S$ requires 488.1349.

(2*S*,4*S*)-**14** (minor): ^{1}H NMR (300 MHz, $CDCl_3$), representative signals taken from the diastereomer mixture δ 7.58 (2H, d, *J* = 8.4 Hz, Ar), 7.40-6.90 (7H, m, Ar), 5.95 (1H, d, *J* = 6.9 Hz, NH), 4.45 (1H, m, CH-Ph), 3.81 (3H, s, MeO), 3.72 (3H, s, MeO), 2.83 (1H, m, CH-CF_3), 2.34 (3H, s, Me-Ar), 2.32-2.10 (2H, m, CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -70.1 (s, CF_3).

Methyl (3*R*,4*S*,6*R*)-2-oxo-6-phenyl-1-tosyl-4-(trifluoromethyl)piperidine-3-carboxylate (15)



A 25% solution of tetraethylammonium hydroxyde in MeOH (24 μL, 0.14 mmol) was added to a solution of compound **13** (28.0 mg, 0.037 mmol, ee = 87%) in dimethylsulfoxide (1.6 mL) under nitrogen, and the reaction flask was introduced in a bath at 80 °C. After 14 h, the reaction mixture was diluted with EtOAc (75 mL), washed with water (5 × 5 mL), brine (5 mL), and dried over $MgSO_4$. Purification by column chromatography eluting with hexane/EtOAc (80:20) gave 13.2 mg (78%) of compound **15**. Chiral HPLC analysis:

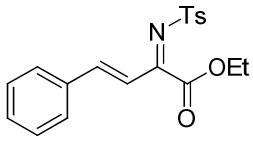
Lux Amylose-1, hexane-*i*PrOH 90:10, 1 mL/min, *major enantiomer* tr = 24.0 min, *minor enantiomer* tr = 22.1 min. White solid, mp 177-179 °C (hexane-EtOAc); $[\alpha]_D^{20}$ -4.5 (*c* 1.0, $CHCl_3$, ee = 87%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (2H, d, *J* = 8.5 Hz, Ar), 7.40-7.32 (3H, m, Ar), 7.20-7.14 (4H, m, Ar), 5.93 (1H, t, J = 3.8 Hz, CH-Ph), 3.78 (3H, s, OMe), 3.65 (1H, d, *J* = 11.4 Hz, CH-CO_2Me), 3.11 (1H, m, CH-CF_3), 2.40 (3H, s, Me-Ar), 2.35-2.28 (2H, m, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3 (C), 164.3 (C), 145.4 (C), 138.1 (C), 134.5 (C), 129.7 (CH), 129.0 (CH), 128.5 (C), 126.5 (CH), 125.6 (C, q, $J_{C\text{-}F}$ = 278 Hz), 58.3 (CH), 53.4 (CH_3), 52.8 (CH_3), 50.2 (CH), 37.1 (CH, q, $J_{C\text{-}F}$ = 28.5 Hz), 29.9 (CH_2), 21.7 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -73.1 (s, CF_3); HRMS (ESI) *m/z* 456.1087 $[M+H]^+$, $C_{21}H_{21}F_3NO_5S$ requires 456.1077.

5.3. Mukaiyama-Michael addition with *N*-tosyl imines derived from β,γ-unsaturated α-keto esters: *E*,*Z*-stereodivergent synthesis of α,β-dehydroamino esters

5.3.1. Synthesis and characterization of α,β-unsaturated *N*-tosyl imines 17

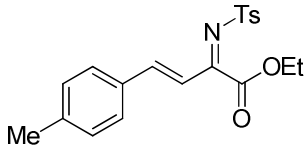
The procedure reported by Carretero was followed:[22] $TiCl_4$ (0.45 mL, 5.6 mmol) was added dropwise to a solution of keto ester (5.6 mmol),[200] *p*-toluensulfonamide (0.95g, 5.6 mmol) and triethylamine (1.55 mL, 11.2 mmol) in dry dichloromethane (17 ml) at 0 ºC under nitrogen. The mixture was heated at reflux temperature for 24 h and, after cooling to room temperature, treated with water (150 ml), extracted with dichloromethane (4 × 80 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography on silica gel eluting with hexane/EtOAc mixtures afforded imines **17**.

Ethyl (2*Z*,3*E*)-4-phenyl-2-(tosylimino)but-3-enoate (17a)



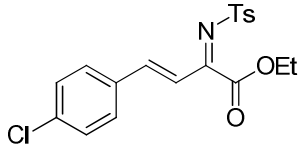
Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.5 Hz, 2H), 7.60-7.28 (m, 6H), 7.36 (d, *J* = 8.5 Hz, 2H), 6.83 (d, J = 16.5 Hz, 1H), 4.54 (q, *J* = 7.2 Hz, 2H), 2.44 (s, 3H), 1.49 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6 (C), 164.4 (C), 149.4 (C), 144.7 (C), 135.8 (C), 133.9 (CH), 131.7 (CH), 129.7 (2CH), 129.6 (3CH), 129.1 (CH), 128.7 (CH), 128.0 (CH), 123.5 (CH), 63.1 (CH_2), 21.6 (CH_3), 14.0 (CH_3); HRMS (ESI) *m/z* 357.1037 $[M]^+$, $C_{19}H_{19}NO_4S$ requires 357.1035.

Ethyl (2*Z*,3*E*)-4-(*p*-tolyl)-2-(tosylimino)but-3-enoate (17b)



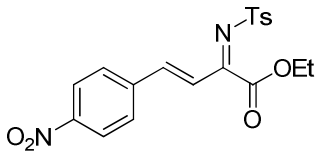
Yellow solid, mp 112-116 ºC (hexane-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.36 (d, J = 16.4 Hz, 1H overlapped), 7.34 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 6.78 (d, *J* = 16.4 Hz, 1H), 4.55 (q, *J* = 7.2 Hz, 2H), 2.43 (s, 3H), 2.38 (s, 3H), 1.48 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0 (C), 164.8 (C), 149.7 (C), 144.7 (C), 142.9 (C), 131.5 (2CH), 130.1 (4CH), 129.8 (2CH), 128.9 (CH), 128.1 (CH), 122.9 (C), 63.3 (CH_2), 21.8 ($2CH_3$), 14.1 (CH_3); HRMS (ESI) *m/z* 371.1195 $[M]^+$, $C_{20}H_{21}NO_4S$ requires 371.1191.

Ethyl (2*Z*,3*E*)-4-(4-chlorophenyl)-2-(tosylimino)but-3-enoate (17c)



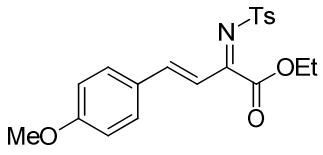
Yellow solid, mp 70-73 ºC (hexane-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.50-7.27 (m, 7H), 6.78 (d, *J* = 16.5 Hz, 1H), 4.54 (q, *J* = 7.2 Hz, 2H), 2.44 (s, 3H), 1.48 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2 (C), 164.4 (C), 147.5 (C), 144.8 (C), 137.8 (C), 135.7 (C), 132.4 (CH), 129.7 (3CH), 129.5 (4CH), 128.0 (CH), 124.0 (CH), 63.3 (CH_2), 21.6 (CH_3), 14.0 (CH_3); HRMS (ESI) *m/z* 391.0645 $[M]^+$, $C_{19}H_{18}ClNO_4S$ requires 391.0645.

Ethyl (2*Z*,3*E*)-4-(4-nitrophenyl)-2-(tosylimino)but-3-enoate (117d)



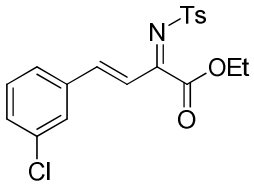
White solid, mp 119-121 ºC (hexane-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.4 Hz, 2H), 7.90 (d, *J* = 8.1, 2H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 16.5 Hz, 1H overlapped), 7.36 (d, *J* = 8.1 Hz, 2H), 6.91 (d, *J* = 16.5 Hz, 1H), 4.56 (q, *J* = 7.0 Hz, 2H), 2.45 (s, 3H), 1.50 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4 (C), 164.0 (C), 149.0 (C), 145.1 (C), 139.7 (C), 129.8 (4CH), 129.1 (CH), 128.2 (CH), 127.4 (C), 124.3 (4CH), 63.5 (CH_2), 21.69 (CH_3), 14.0 (CH_3); HRMS (ESI) *m/z* 425.0083 $[M+Na]^+$, $C_{19}H_{18}N_2NaO_6S$ requires 425.0078.

Ethyl (2*Z*,3*E*)-4-(4-methoxyphenyl)-2-(tosylimino)but-3-enoate (17e)



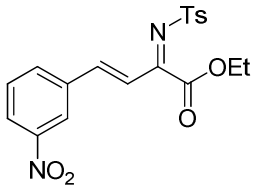
Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 16.5 Hz, 1H overlapped), 7.32 (d, J = 8.3 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.69 (d, *J* = 16.5 Hz, 1H), 4.53 (q, *J* = 7.2 Hz, 2H), 3.83 (s, 3H), 2.42 (s, 3H), 1.47 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9 (C), 164.7 (C), 162.7 (C), 149.4 (C), 144.4 (C), 130.7 (CH), 129.6 (2CH), 127.8 (CH), 126.7 (2CH), 120.9 (C), 114.7 (4CH), 63.0 (CH_2), 55.4 (CH_3), 21.6 (CH_3), 13.9 (CH_3); HRMS (ESI) *m/z* 388.1215 $[M+H]^+$, $C_{20}H_{21}NO_5S$ requires 388.1213.

Ethyl (2*Z*,3*E*)-4-(3-chlorophenyl)-2-(tosylimino)but-3-enoate (17f)



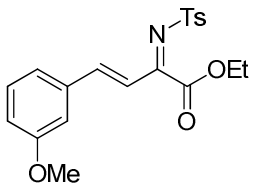
Pale yellow solid, mp 84-86 ºC (hexane-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.47 (s, 1H), 7.41-7.26 (m, 4H), 7.34 (d, *J* = 8.4 Hz, 2H), 6.80 (d, *J* = 16.4 Hz, 1H), 4.54 (q, *J* = 7.1 Hz, 2H), 2.43 (s, 3H), 1.48 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0 (C), 164.2 (C), 147.1 (C), 144.8 (C), 135.6 (C), 135.2 (C), 131.4 (CH), 130.3 (3CH), 129.7 (2CH), 128.3 (CH), 128.0 (CH), 126.6 (CH), 124.8 (CH), 63.3 (CH_2), 21.6 (CH_3), 13.9 (CH_3); HRMS (ESI) *m/z* 391.0646 $[M]^+$, $C_{19}H_{18}ClNO_4S$ requires 391.0645.

Ethyl (2*Z*,3*E*)-4-(3-nitrophenyl)-2-(tosylimino)but-3-enoate (17g)



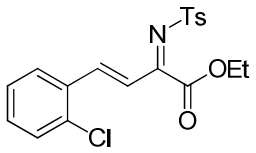
White solid, mp 124-125 ºC (hexane-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.27 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 2H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 16.5 Hz, 1H overlapped), 7.36 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 16.5 Hz, 1H), 4.56 (q, *J* = 7.0 Hz, 2H), 2.45 (s, 3H), 1.49 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5 (C), 164.0 (C), 148.7 (C), 145.3 (C), 145.1 (C), 135.6 (C), 133.7 (2CH), 130.2 (2CH), 129.8 (2CH), 128.1 (CH), 126.3 (CH), 125.6 (CH), 123.0 (CH), 63.5 (CH_2), 21.7 (CH_3), 14.0 (CH_3); HRMS (ESI) *m/z* 425.0080 $[M+Na]^+$, $C_{19}H_{18}N_2NaO_6S$ requires 425.0078.

Ethyl (2*Z*,3*E*)-4-(3-methoxyphenyl)-2-(tosylimino)but-3-enoate (17h)



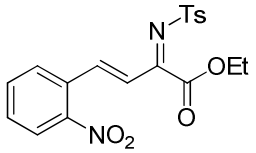
Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.40-7.27 (m, 2H overlapped), 7.09 (d, *J* = 7.2 Hz, 1H), 6.99 (s, 1H overlapped), 6.98 (d, *J* = 8.7 Hz, 1H), 6.81 (d, *J* = 16.5 Hz, 1H), 4.55 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 2.43 (s, 3H), 1.48 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6 (C), 164.4 (C), 160.0 (2C), 149.3 (C), 144.7 (C), 135.4 (CH), 130.1 (2CH), 129.7 (2CH), 128.0 (CH), 123.7 (CH), 121.5 (CH), 117.9 (CH), 113.0 (CH), 63.1 (CH_2), 55.3 (CH_3), 21.6 (CH_3), 14.0 (CH_3); HRMS (ESI) *m/z* 388.1215 $[M+H]^+$, $C_{20}H_{21}NO_5S$ requires 388.1213.

Ethyl (2*Z*,3*E*)-4-(2-chlorophenyl)-2-(tosylimino)but-3-enoate (17i)



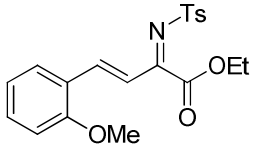
White solid, mp 117-120 ºC (hexane-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.4 Hz, 2H), 7.82 (d, *J* = 16.6 Hz, 1H), 7.61 (d, *J* = 6.9 Hz, 1H), 7.43 (d, *J* = 7.7 Hz, 1H), 7.38-7.28 (m, 2H overlapped), 7.35 (d, *J* = 8.4 Hz, 2H), 6.81 (d, *J* = 16.6 Hz, 1H), 4.57 (q, *J* = 7.2 Hz, 2H), 2.44 (s, 3H), 1.50 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6 (C), 164.2 (C), 144.9 (C), 144.8 (C), 135.6 (C), 135.5 (C), 132.3 (CH), 132.0 (CH), 130.4 (2CH), 129.7 (2CH), 128.1 (CH), 127.5 (CH), 127.4 (CH), 125.8 (CH), 63.2 (CH_2), 21.7 (CH_3), 14.1 (CH_3); HRMS (ESI) *m/z* 391.0647 $[M]^+$, $C_{19}H_{18}ClNO_4S$ requires 391.0645.

Ethyl (2*Z*,3*E*)-4-(2-nitrophenyl)-2-(tosylimino)but-3-enoate (17j)



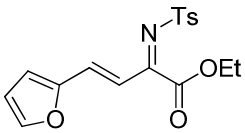
Pale yellow solid, mp 161-162 ºC (hexane-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.8 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 2H), 7.76-7.50 (m, 3H), 7.35 (d, *J* = 8.1 Hz, 2H), 6.72 (d, *J* = 16.4 Hz, 1H), 4.56 (q, *J* = 7.2 Hz, 2H), 2.44 (s, 3H), 1.50 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1 (C), 163.9 (C), 147.9 (C), 145.1 (C), 144.3 (CH), 135.2 (C), 133.9 (CH), 131.3 (CH), 130.0 (C), 129.8 (2CH), 128.9 (CH), 128.2 (2CH), 128.1 (CH), 125.3 (CH), 63.4 (CH_2), 21.7 (CH_3), 14.0 (CH_3); HRMS (ESI) 425.0076 *m/z* $[M+Na]^+$, $C_{19}H_{18}N_2NaO_6S$ requires 425.0078.

Ethyl (2*Z*,3*E*)-4-(2-methoxyphenyl)-2-(tosylimino)but-3-enoate (17k)



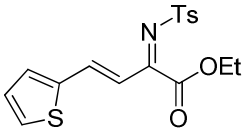
Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 16.5 Hz, 1H), 7.45-7.30 (m, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.03-6.84 (m, 3H), 4.55 (q, *J* = 7.2 Hz, 2H), 3.86 (s, 3H), 2.42 (s, 3H), 1.48 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6 (C), 164.7 (C), 158.7 (C), 145.2 (C), 144.5 (C), 133.3 (CH), 129.6 (2CH), 129.5 (C), 129.1 (CH), 128.0 (CH), 123.8 (CH), 122.9 (CH), 120.9 (CH), 111.3 (2CH), 62.9 (CH_2), 55.6 (CH_3), 21.6 (CH_3), 14.0 (CH_3); HRMS (ESI) 388.1215 *m/z* $[M+H]^+$, $C_{20}H_{21}NO_5S$ requires 388.1213.

Ethyl (2*Z*,3*E*)-4-(furan-2-yl)-2-(tosylimino)but-3-enoate (17l)



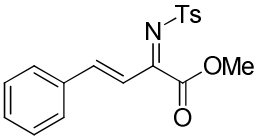
Brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.1 Hz, 2H), 7.55 (s, 1H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 16.1 Hz, 1H), 6.75 (s, 1H overlapped), 6.69 (d, *J* = 16.1 Hz, 1H), 6.53 (s, 1H), 4.51 (q, *J* = 7.0 Hz, 2H), 2.43 (s, 3H), 1.46 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2 (C), 164.5 (C), 150.8 (2CH), 146.7 (CH), 144.8 (C), 136.0 (C), 134.3 (CH), 129.6 (2CH), 127.9 (CH), 120.8 (C), 118.1 (CH), 113.3 (CH), 63.1 (CH_2), 21.6 (CH_3), 14.0 (CH_3); HRMS (ESI) *m/z* 348.0898 $[M+H]^+$, $C_{17}H_{18}NO_5S$ requires 348.0900.

Ethyl (2*Z*,3*E*)-4-(thiophen-2-yl)-2-(tosylimino)but-3-enoate (17m)



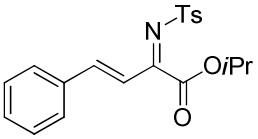
Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.53-7.48 (m, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 4.8 Hz, 1H), 6.60 (d, *J* = 16.2 Hz, 1H), 4.53 (q, *J* = 6.3 Hz, 2H), 2.43 (s, 3H), 1.47 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2 (C), 144.6 (C), 144.5 (C), 141.38 (CH), 141.36 (C), 139.6 (C), 133.2 (CH), 131.5 (CH), 129.7 (2CH), 128.7 (2CH), 127.9 (CH), 122.1 (CH), 63.2 (CH_2), 21.6 (CH_3), 13.9 (CH_3); HRMS (ESI) *m/z* 364.0674 $[M+H]^+$, $C_{17}H_{18}NO_4S_2$ requires 364.0672.

Methyl (2*Z*,3*E*)-4-phenyl-2-(tosylimino)but-3-enoate (17n)



Brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.1 Hz, 2H), 7.66-7.29 (m, 6H), 7.34 (d, *J* = 8.1 Hz, 2H), 6.83 (d, *J* = 16.4 Hz, 1H), 4.07 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4 (C), 164.9 (C), 149.6 (C), 144.8 (C), 135.7 (C), 133.9 (CH), 131.8 (CH), 129.7 (2CH), 129.1 (4CH), 128.7 (CH), 128.0 (CH), 123.4 (CH), 53.0 (CH_3), 21.7 (CH_3); HRMS (ESI) *m/z* 343.0880 $[M]^+$, $C_{18}H_{17}NO_4S$ requires 343.0878.

Isopropyl (2*Z*,3*E*)-4-phenyl-2-(tosylimino)but-3-enoate (17o)



Orange oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.4 Hz, 2H), 7.64-7.29 (m, 6H), 7.34 (d, *J* = 8.4 Hz, 2H), 6.81 (d, *J* = 16.4 Hz, 1H), 5.45 (hept, *J* = 6.3 Hz, 1H), 2.43 (s, 3H), 1.48 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8 (C), 164.0 (C), 149.1 (C), 144.6 (C), 135.9 (C), 133.9 (2CH), 131.7 (CH), 129.7 (2CH), 129.1 (3CH), 128.6 (CH), 128.0 (CH), 123.7 (CH), 71.58 (CH), 21.65 (CH_3), 21.62 (CH_3); HRMS (ESI) *m/z* 371.1196 $[M]^+$, $C_{20}H_{21}NO_4S$ requires 371.1191.

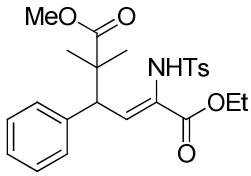
5.3.2. General procedure for the non-catalyzed Mukaiyama-Michael reaction

2-Methyl-1-methoxy-1-trimethylsilyoxyprop-1-ene (**16**, 122 μL, 0.6 mmol) was added to a solution of imine **17** (0.25 mmol) in CH_2Cl_2 (1.2 mL) at rt under nitrogen atmosphere and the mixture was stirred overnight until the reaction was complete (20-24h). The reaction products **18** were isolated by column chromatography on silica gel eluting with hexane/EtOAc mixtures.

5.3.2.1. Characterization of products (Z)-18

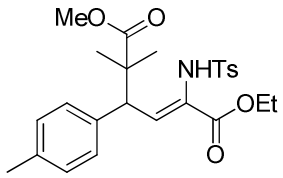
See Table 9 (Page 81) for yield and dr.

(*Z*)-1-Ethyl 6-methyl 5,5-dimethyl-2-(4-methylphenylsulfonamido)-4-phenylhex-2-enedioate (*Z*)-18a



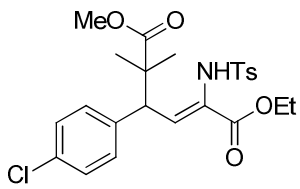
Colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.4 Hz, 2H) 7.31 (d, *J* = 11.4 Hz, 1H overlapped), 7.30-7.27 (m, 3H), 7.17-7.15 (m, 2H overlapped), 7.16 (d, *J* = 8.4 Hz, 2H), 6.20 (s, 1H), 4.41 (d, *J* = 11.4 Hz, 1H), 3.96 (2 overlapped q, *J* = 7.2 Hz, 2H), 3.65 (s, 3H), 2.36 (s, 3H), 1.18 (s, 3H), 1.17 (s, 3H), 1.09 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9 (C), 164.2 (C), 143.7 (C), 140.5 (C), 138.1 (C), 136.0 (C), 129.5 (CH), 129.3 (CH), 128.1 (CH), 127.6 (CH), 127.2 (CH), 125.9 (C), 61.8 (CH_2), 51.9 (CH_3), 50.5 (C), 47.1 (CH), 23.9 (CH_3), 22.4 (CH_3), 21.5 (CH_3), 13.9 (CH_3); HRMS (ESI) *m/z* 458.1641 $[M-H]^-$, $C_{24}H_{28}NO_6S$ requires 458.1643.

(*Z*)-1-Ethyl 6-methyl 5,5-dimethyl-2-(4-methylphenylsulfonamido)-4-(*p*-tolyl)hex-2-enedioate (*Z*)-18b



Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 11.1 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.1 Hz, 2H), 7.03 (d, *J* = 8.1 Hz, 2H), 6.14 (s, 1H), 4.35 (d, *J* = 11.4 Hz, 1H), 3.96 (2 overlapped q, *J* = 7.2 Hz, 2H), 3.64 (s, 3H), 2.36 (s, 3H), 2.33 (s, 3H), 1.16 (s, 6H), 1.08 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0 (C), 164.2 (C), 143.7 (C), 140.9 (C), 136.8 (C), 136.1 (C), 135.0 (C), 129.3 (CH), 128.8 (CH), 127.6 (CH), 125.8 (CH), 61.7 (CH_2), 51.8 (CH_3), 50.1 (C), 47.1 (CH), 23.8 (CH_3), 22.4 (CH_3), 21.5 (CH_3), 21.1 (CH_3), 13.9 (CH_3); HRMS (ESI) *m/z* 472.1782 $[M-H]^-$, $C_{25}H_{30}NO_6S$ requires 472.1799.

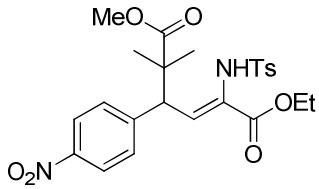
(*Z*)-1-Ethyl 6-methyl 4-(4-chlorophenyl)-5,5-dimethyl-2-(4-methylphenylsulfonamido)hex-2-enedioate (*Z*)-18c



Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 11.4 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.28 (s, 1H), 4.46 (d, *J* = 11.4 Hz, 1H), 3.84 (m, 2H), 3.63 (s, 3H), 2.35 (s, 3H), 1.17 (s, 6H), 1.06 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5 (C), 163.9 (C), 143.8 (C), 139.9 (C), 136.7 (C), 135.7 (CH), 132.9 (C),

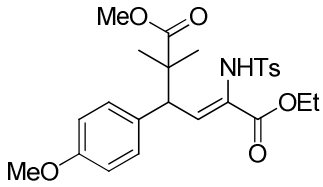
130.7 (CH), 129.3 (CH), 128.1 (CH), 127.5 (CH), 126.1 (C), 61.8 (CH_2), 51.8 (CH_3), 49.8 (CH), 47.0 (C), 23.5 (CH_3), 22.5 (CH_3), 21.4 (CH_3), 13.8 (CH_3); HRMS (ESI) *m/z* 492.1255 $[M-H]^-$, $C_{24}H_{27}ClNO_6S$ requires 492.1253.

(*Z*)-1-Ethyl 6-methyl 5,5-dimethyl-2-(4-methylphenylsulfonamido)-4-(4-nitrophenyl)hex-2-enedioate (*Z*)-18d



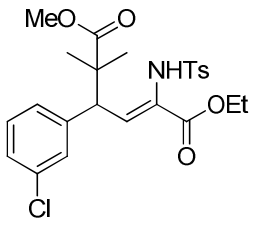
Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 9.0 Hz, 2H), 7.45-7.40 (m, 4H), 7.31 (d, *J* =11.4 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 6.16 (s, 1H), 4.69 (d, *J* = 11.4 Hz, 1H), 3.93 (m, 2H), 3.65 (s, 3H), 2.36 (s, 3H), 1.21 (s, 3H), 1.20 (s, 3H), 1.05 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0 (C), 163.4 (C), 147.0 (C), 146.1 (C), 144.1 (C), 139.1 (CH), 135.5 (C), 130.4 (CH), 129.4 (CH), 127.5 (CH), 126.8 (C), 123.2 (CH), 62.1 (CH_2), 52.0 (CH_3), 50.6 (CH), 47.3 (C), 23.5 (CH_3), 23.0 (CH_3), 21.5 (CH_3), 13.8 (CH_3); HRMS (ESI) *m/z* 503.1489 $[M-H]^-$, $C_{24}H_{27}N_2O_8S$ requires 503.1494.

(*Z*)-1-Ethyl 6-methyl 4-(4-methoxyphenyl)-5,5-dimethyl-2-(4-methylphenylsulfonamido)hex-2-enedioate (*Z*)-18e



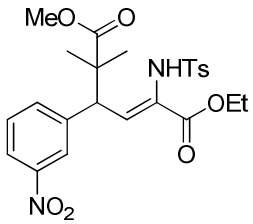
Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 11.4 Hz, 1H), 7.17 (d, *J* = 8.1 Hz, 2H), 7.09 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.18 (s, 1H), 4.35 (d, *J* = 11.4 Hz, 1H), 3.96 (2 overlapped q, *J* = 7.2 Hz, 2H), 3.80 (s, 3H), 3.64 (s, 3H), 2.37 (s, 3H), 1.16 (s, 6H), 1.08 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1 (C), 164.2 (C), 158.6 (C), 143.7 (C), 140.8 (C), 136.0 (C), 130.4 (CH), 130.1(C), 129.3 (CH), 127.6 (CH), 125.6 (CH), 113.5 (CH), 61.7 (CH_2), 55.1 (CH_3), 51.9 (CH_3), 49.7 (C), 47.2 (CH), 23.7 (CH_3), 22.4 (CH_3), 21.5 (CH_3), 13.9 (CH_3); HRMS (ESI) *m/z* 488.1747 $[M-H]^-$, $C_{25}H_{30}NO_7S$ requires 488.1748.

(*Z*)-1-Ethyl 6-methyl 4-(3-chlorophenyl)-5,5-dimethyl-2-(4-methylphenylsulfonamido)hex-2-enedioate (*Z*)-18f



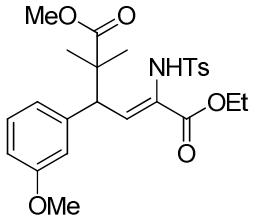
White oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 11.4 Hz, 1H), 7.22-7.03 (m, 4H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.30 (s, 1H), 4.41 (d, *J* = 11.4 Hz, 1H), 3.95 (2 overlapped q, *J* = 7.2 Hz, 2H), 3.62 (s, 3H), 2.35 (s, 3H), 1.16 (s, 6H), 1.07 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5 (C), 163.9 (C), 143.8 (C), 140.2 (C), 139.4 (C), 135.8 (CH), 133.7 (C), 129.3 (CH), 129.18 (CH), 129.15 (CH), 127.8 (CH), 127.5 (CH), 127.3 (CH), 126.4 (CH), 125.2 (C), 61.9 (CH_2), 51.9 (CH_3), 50.1 (CH), 47.1 (C), 23.5 (CH_3), 22.5 (CH_3), 21.4 (CH_3), 13.8 (CH_3); HRMS (ESI) *m/z* 492.1255 $[M-H]^-$, $C_{24}H_{27}ClNO_6S$ requires 492.1253.

(*Z*)-1-Ethyl 6-methyl 5,5-dimethyl-2-(4-methylphenylsulfonamido)-4-(3-nitrophenyl)hex-2-enedioate (*Z*)-18g



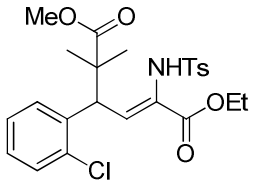
Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (ddd, *J* = 8.1, 2.4, 1.2 Hz, 1H), 8.03 (t, *J* = 2.1 Hz, 1H), 7.61 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.49 (t, *J* = 8.1 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 11.4 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.21 (s, 1H), 4.65 (d, *J* = 11.4 Hz, 1H), 4.10-3.93 (m, 2H), 3.65 (s, 3H), 2.35 (s, 3H), 1.21 (s, 3H), 1.20 (s, 3H), 1.07 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0 (C), 163.6 (C), 147.9 (C), 144.1 (C), 140.5 (C), 138.8 (CH), 136.3 (CH), 135.6 (C), 129.4 (CH), 128.9 (CH), 127.4 (CH), 126.9 (C), 123.6 (CH), 122.2 (CH), 62.1 (CH_2), 52.0 (CH_3), 50.3 (CH), 47.2 (C), 23.2 (CH_3), 23.0 (CH_3), 21.4 (CH_3), 13.8 (CH_3); HRMS (ESI) *m/z* 503.1497 $[M-H]^-$, $C_{24}H_{27}N_2O_8S$ requires 503.1494.

(*Z*)-1-Ethyl 6-methyl 4-(3-methoxyphenyl)-5,5-dimethyl-2-(4-methylphenylsulfonamido)hex-2-enedioate (*Z*)-18h



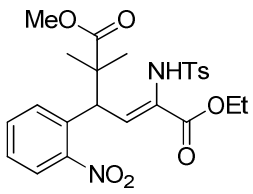
Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 11.1 Hz, 1H), 7.24-7.16 (m, 3H), 6.85-6.70 (m, 3H), 6.18 (s, 1H), 4.37 (d, *J* = 11.1 Hz, 1H), 3.97 (2 overlapped q, *J* = 7.2 Hz, 2H), 3.80 (s, 3H), 3.65 (s, 3H), 2.36 (s, 3H), 1.18 (s, 3H), 1.17 (s, 3H), 1.08 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9 (C), 164.2 (C), 159.2 (C), 143.8 (C), 140.5 (CH), 139.6 (C), 136.0 (C), 129.3 (CH), 128.9 (CH), 127.6 (CH), 126.0 (C), 121.8 (CH), 115.8 (CH), 112.2 (CH), 61.8 (CH_2), 55.1 (CH_3), 51.9 (CH_3), 50.5 (CH_3), 47.1 (C), 23.9 (CH_3), 22.5 (CH_3), 21.5 (CH_3), 13.9 (CH_3); HRMS (ESI) *m/z* 488.1746 $[M-H]^-$, $C_{25}H_{30}NO_7S$ requires 488.1748.

(*Z*)-1-Ethyl 6-methyl 4-(2-chlorophenyl)-5,5-dimethyl-2-(4-methylphenylsulfonamido)hex-2-enedioate (*Z*)-18i



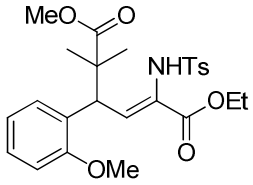
Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.4 Hz, 2H), 7.38-7.35 (m, 1H), 7.35 (d, *J* = 10.5 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.17-7.09 (m, 3H), 6.11 (s, 1H), 5.03 (d, *J* = 10.5 Hz, 1H), 3.95 (2 overlapped q, *J* = 7.2 Hz, 2H), 3.66 (s, 3H), 2.36 (s, 3H), 1.26 (s, 3H), 1.22 (s, 3H), 1.01 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7 (C), 164.1 (C), 143.6 (C), 140.0 (CH), 136.7 (C), 136.6 (C), 135.2 (C), 130.1 (CH), 129.9 (CH), 129.3 (CH), 128.2 (CH), 127.4 (CH), 126.7 (C), 126.4 (CH), 61.7 (CH_2), 52.0 (CH_3), 47.4 (CH), 45.4 (C), 24.5 (CH_3), 22.0 (CH_3), 21.4 (CH_3), 13.8 (CH_3); HRMS (ESI) *m/z* 492.1255 $[M-H]^-$, $C_{24}H_{27}ClNO_6S$ requires 492.1253.

(*Z*)-1-Ethyl 6-methyl 5,5-dimethyl-2-(4-methylphenylsulfonamido)-4-(2-nitrophenyl)hex-2-enedioate (*Z*)-18j



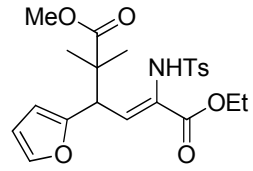
Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.51 (td, *J* = 7.8, 1.5 Hz, 1H), 7.38 (td, *J* = 7.8, 1.5 Hz, 1H), 7.31 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 10.2 Hz, 1H), 6.65 (s, 1H), 4.93 (d, *J* = 10.2 Hz, 1H), 4.06 (q, *J* = 7.2 Hz, 2H), 3.59 (s, 3H), 2.36 (s, 3H), 1.18 (s, 3H), 1.15 (t, *J* = 7.2 Hz, 3H), 1.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9 (C), 164.01 (C), 150.6 (C), 143.7 (C), 136.9 (C), 134.0 (CH), 133.0 (C), 132.1 (CH), 130.6 (CH), 129.3 (CH), 129.1 (C), 128.1 (CH), 127.4 (CH), 124.9 (C), 61.8 (CH_2), 52.1 (CH_3), 47.0 (CH), 42.8 (C), 23.3 (CH_3), 23.2 (CH_3), 21.5 (CH_3), 13.8 (CH_3); HRMS (ESI) *m/z* 503.1496 $[M-H]^-$, $C_{24}H_{27}N_2O_8S$ requires 503.1494.

(*Z*)-1-Ethyl 6-methyl 4-(2-methoxyphenyl)-5,5-dimethyl-2-(4-methylphenylsulfonamido)hex-2-enedioate (*Z*)-18k



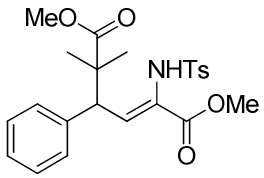
Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 10.8 Hz, 1H), 7.22-7.17 (m, 3H), 7.04 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.86 (2 overlapped t, *J* = 8.1 Hz, 2H), 6.19 (s, 1H), 4.69 (d, *J* = 10.8 Hz, 1H), 4.00 (q, *J* = 6.9 Hz, 2H), 3.82 (s, 3H), 3.64 (s, 3H), 2.37 (s, 3H), 1.15 (s, 3H), 1.13 (s, 3H), 1.09 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2 (C), 164.4 (C), 157.4 (C), 143.4 (C), 140.2 (CH), 136.8 (CH), 130.0 (C), 129.2 (CH), 128.2 (C), 127.5 (CH), 127.0 (CH), 126.1 (C), 120.3 (CH), 111.1 (CH), 61.5 (CH_2), 55.6 (CH_3), 51.8 (CH_3), 46.7 (C), 43.5 (CH), 24.6 (CH_3), 22.3 (CH_3), 21.5 (CH_3), 13.9 (CH_3); HRMS (ESI) *m/z* 488.1752 $[M-H]^-$, $C_{25}H_{30}NO_7S$ requires 488.1748.

(*Z*)-1-Ethyl 6-methyl 4-(furan-2-yl)-5,5-dimethyl-2-(4-methylphenylsulfonamido)hex-2-enedioate (*Z*)-18l



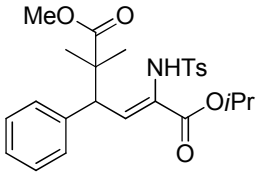
Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.4 Hz, 2H), 7.33 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.18 (d, *J* = 8.7 Hz, 2H), 7.04 (d, *J* = 11.4 Hz, 1H), 6.40 (s, 1H), 6.30 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.12 (dt, *J* = 3.3, 0.6 Hz, 1H), 4.56 (d, *J* = 11.4 Hz, 1H), 4.02-3.90 (m, 2H), 3.66 (s, 3H), 2.36 (s, 3H), 1.19 (s, 3H), 1.15 (s, 3H), 1.08 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8 (C), 164.0 (C), 151.6 (C), 143.8 (C), 141.7 (CH), 137.1 (CH), 136.0 (C), 129.3 (CH), 127.5 (CH), 126.4 (C), 110.1 (CH), 108.3 (CH), 61.8 (CH_2), 52.1 (CH_3), 46.9 (CH), 44.5 (C), 23.5 (CH_3), 22.3 (CH_3), 21.4 (CH_3), 13.8 (CH_3); HRMS (ESI) *m/z* 448.1437 $[M-H]^-$, $C_{22}H_{26}NO_7S$ requires 448.1435.

(*Z*)-Dimethyl 5,5-dimethyl-2-(4-methylphenylsulfonamido)-4-phenylhex-2-enedioate (*Z*)-18n



Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 11.1 Hz, 1H overlapped), 7.30-7.25 (m, 3H), 7.17-7.11 (m, 4H), 6.23 (s, 1H), 4.35 (d, *J* = 11.1 Hz, 1H), 3.64 (s, 3H), 3.52 (s, 3H), 2.37 (s, 3H), 1.17 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0 (C), 164.7 (C), 143.7 (C), 140.6 (CH), 137.9 (C), 136.0 (C), 129.5 (CH), 129.3 (CH), 128.1 (CH), 127.5 (CH), 127.2 (CH), 125.8 (C), 52.5 (CH_3), 51.9 (CH_3), 50.4 (C), 47.1 (CH), 24.0 (CH_3), 22.2 (CH_3), 21.5 (CH_3); HRMS (ESI) *m/z* 444.1492 $[M-H]^-$, $C_{23}H_{26}NO_6S$ requires 444.1486.

(*Z*)-1-Isopropyl 6-methyl 5,5-dimethyl-2-(4-methylphenylsulfonamido)-4-phenylhex-2-enedioate (*Z*)-18o



Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.4 Hz, 2H), 7.31-7.26 (m, 3H), 7.29 (d, *J* = 11.4 Hz, 1H overlapped), 7.19-7.14 (m, 4H), 6.24 (s, 1H), 4.79 (hept, *J* = 6.3 Hz, 1H), 4.45 (d, *J* = 11.4 Hz, 1H), 3.65 (s, 3H), 2.36 (s, 3H), 1.19 (s, 6H), 1.11(d, *J* = 6.3 Hz, 3H), 1.04 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8 (C), 163.7 (C), 143.7 (C), 140.1 (C), 138.2 (C), 135.9 (C), 129.4 (CH), 129.3 (CH), 128.0 (CH), 127.6 (CH), 127.1 (CH), 126.1 (C), 69.7 (CH), 51.8 (CH_3), 50.4 (C), 47.1 (CH), 23.7 (CH_3), 22.5 (CH_3), 21.4 (CH_3), 21.3 (CH_3); HRMS (ESI) *m/z* 472.1784 $[M-H]^-$, $C_{25}H_{30}NO_6S$ requires 472.1799.

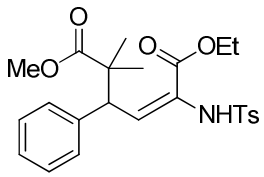
5.3.3. General procedure for the copper-catalyzed Mukaiyama-Michael reaction

A solution of imine **17** (0.25 mmol) in dry CH_2Cl_2 (1 mL) was added to a suspension of anhydrous $Cu(OTf)_2$ (9 mg, 0.025 mmol) in dry CH_2Cl_2 (0.9 mL) contained in a Schlenck tube under nitrogen at rt, followed by 2-methyl-1-methoxy-1-trimethylsilyoxyprop-1-ene (**16**, 122 μL, 0.6 mmol). The mixture was stirred until the reaction was complete (30-90 min). The reaction products (*E*)-**18** were isolated by column chromatography on silica gel eluting with hexane/EtOAc mixtures.

5.3.3.1. Characterization of products (E)-18

See Table 10 (Page 82) for yield and dr.

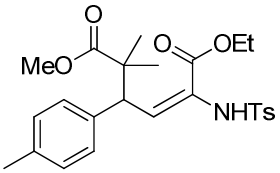
(*E*)-1-Ethyl 6-methyl 5,5-dimethyl-2-(4-methylphenylsulfonamido)-4-phenylhex-2-enedioate (*E*)-18a



Colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.1 Hz, 2H), 7.29-7.22 (m, 3H), 7.14-7.09 (m, 4H), 7.01 (d, *J* = 11.4 Hz, 1H), 6.61 (s, 1H), 4.81 (d, *J* = 11.4 Hz, 1H), 4.00 (q, *J* = 6.9 Hz, 2H), 3.59 (s, 3H), 2.36 (s, 3H), 1.173 (s, 3H), 1.168 (s, 3H), 1.12 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2 (C), 162.9 (C), 143.8 (C), 139.7 (C), 136.3 (C), 135.9 (C), 129.4 (CH), 129.3 (CH), 128.0

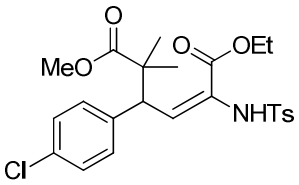
(CH), 127.5 (CH), 127.0 (CH), 124.8 (C), 61.8 (CH_2), 51.7 (CH_3), 50.4 (C), 46.8 (CH), 23.1 (CH_3), 22.3 (CH_3), 21.4 (CH_3), 13.9 (CH_3); HRMS (ESI) *m/z* 458.1644 $[M-H]^-$, $C_{24}H_{28}NO_6S$ requires 458.1643.

(*E*)-1-Ethyl 6-methyl 5,5-dimethyl-2-(4-methylphenylsulfonamido)-4-(p-tolyl)hex-2-enedioate (*E*)-18b



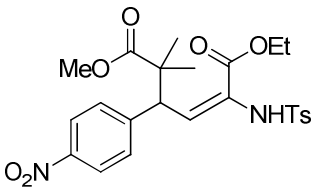
Pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.1 Hz, 2H), 6.974 (d, *J* = 11.4 Hz, 1H), 6.972 (d, *J* = 8.1 Hz, 2H), 6.58 (br s, 1H), 4.77 (d, *J* = 11.4 Hz, 1H), 4.00 (2 overlapped q, *J* = 7.2 Hz, 2H), 3.59 (s, 3H), 2.36 (s, 3H), 2.31 (s, 3H), 1.15 (s, 6H), 1.12 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8 (C), 163.0 (C), 143.7 (C), 136.54 (C), 136.51 (C), 129.4 (CH), 129.1 (CH), 128.7 (CH), 127.5 (CH), 124.6 (CH), 124.5 (CH), 61.8 (CH_2), 51.6 (CH_3), 50.0 (C), 46.8 (CH), 23.2 (CH_3), 22.3 (CH_3), 21.5 (CH_3), 21.0 (CH_3), 13.9 (CH_3); HRMS (ESI) *m/z* 472.1782 $[M-H]^-$, $C_{25}H_{30}NO_6S$ requires 472.1799.

(*E*)-1-Ethyl 6-methyl 4-(4-chlorophenyl)-5,5-dimethyl-2-(4-methylphenylsulfonamido)hex-2-enedioate (*E*)-18c



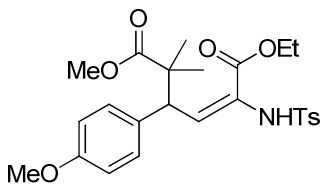
Colourless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.7 Hz, 2H), 7.15 (d, *J* = 8.7 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 11.4 Hz, 1H), 6.62 (s, 1H), 4.77 (d, *J* = 11.4 Hz, 1H), 4.00 (q, *J* = 7.2 Hz, 2H), 3.59 (s, 3H), 2.37 (s, 3H), 1.14 (s, 6H), 1.11 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5 (C), 162.6 (C), 144.0 (C), 138.4 (C), 135.9 (C), 135.3 (CH), 132.8 (C), 130.6 (CH), 129.5 (CH), 128.2 (CH), 127.4 (CH), 125.2 (C), 61.9 (CH_2), 51.8 (CH_3), 49.7 (CH), 46.7 (C), 23.2 (CH_3), 22.1 (CH_3), 21.5 (CH_3), 13.9 (CH_3); HRMS (ESI) *m/z* 492.1257 $[M-H]^-$, $C_{24}H_{27}ClNO_6S$ requires 492.1253.

(*E*)-1-Ethyl 6-methyl 5,5-dimethyl-2-(4-methylphenylsulfonamido)-4-(4-nitrophenyl)hex-2-enedioate (*E*)-18d



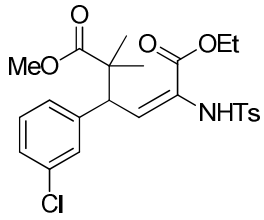
Pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz. 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 10.8 Hz, 1H), 6.71 (s, 1H), 4.88 (d, *J* = 10.8 Hz, 1H), 4.00 (q, *J* = 7.2 Hz, 2H), 3.60 (s, 3H), 2.37 (s, 3H), 1.16 (s, 3H), 1.15 (s, 3H), 1.10 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1 (C), 162.2 (C), 147.7 (C), 146.7 (C), 144.2 (C), 135.9 (C), 133.3 (CH), 130.1 (CH), 129.6 (CH), 127.4 (CH), 126.0 (C), 123.0 (CH), 62.1 (CH_2), 52.0 (CH_3), 50.1 (CH), 46.8 (C), 23.4 (CH_3), 22.1 (CH_3), 21.5 (CH_3), 13.9 (CH_3); HRMS (ESI) *m/z* 503.1491 $[M-H]^-$, $C_{24}H_{27}N_2O_8S$ requires 503.1494.

(*E*)-1-Ethyl 6-methyl 4-(4-methoxyphenyl)-5,5-dimethyl-2-(4-methylphenylsulfonamido)hex-2-enedioate (*E*)-18e



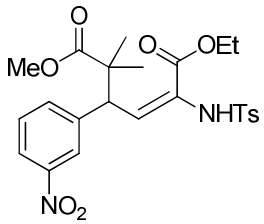
Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 8.7 Hz, 2H), 6.96 (d, *J* = 11.4 Hz, 1H), 6.80 (d, *J* = 8.7 Hz, 2H), 6.58 (s, 1H), 4.76 (d, *J* = 11.4 Hz, 1H), 3.99 (q, *J* = 7.2 Hz, 2H), 3.78 (s, 3H), 2.35 (s, 3H), 1.14 (s, 6H), 1.11 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8 (C), 162.9 (C), 158.5 (C), 143.8 (C), 136.8 (C), 136.0 (C), 131.7 (C), 130.2 (CH), 129.4 (CH), 127.5 (CH), 124.5 (CH), 113.4 (CH), 61.8 (CH_2), 55.2 (CH_3), 51.7 (CH_3), 49.6 (C), 46.8 (CH), 23.1 (CH_3), 22.2 (CH_3), 21.5 (CH_3), 13.9 (CH_3); HRMS (ESI) *m/z* 488.1741 $[M-H]^-$, $C_{25}H_{30}NO_7S$ requires 488.1748.

(*E*)-1-Ethyl 6-methyl 4-(3-chlorophenyl)-5,5-dimethyl-2-(4-methylphenylsulfonamido)hex-2-enedioate (*E*)-18f



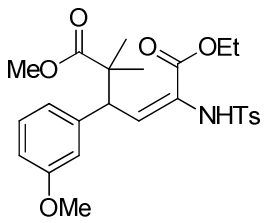
White oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.4 Hz, 2H), 7.20-7.19 (m, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.04 (t, *J* = 0.9 Hz, 1H), 6.98 (m, 1H), 6.89 (d, *J* = 11.1 Hz, 1H), 6.67 (s, 1H), 4.75 (d, *J* = 11.1 Hz, 1H), 4.02 (q, *J* = 7.2 Hz, 2H), 3.60 (s, 3H), 2.36 (s, 3H), 1.16 (s, 3H), 1.15 (s, 3H), 1.12 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4 (C), 162.7 (C), 144.0 (C), 141.9 (C), 135.9 (C), 134.4 (CH), 133.8 (C), 129.5 (CH), 129.4 (CH), 129.2 (CH),127.44 (CH), 127.38 (CH), 127.1 (CH), 125.4 (C), 62.0 (CH_2), 51.8 (CH_3), 50.0 (CH), 46.8 (C), 23.3 (CH_3), 22.1 (CH_3), 21.5 (CH_3), 13.9 (CH_3); HRMS (ESI) *m/z* 492.1255 $[M-H]^-$, $C_{24}H_{27}ClNO_6S$ requires 492.1253.

(*E*)-1-Ethyl 6-methyl 5,5-dimethyl-2-(4-methylphenylsulfonamido)-4-(3-nitrophenyl)hex-2-enedioate (*E*)-18g



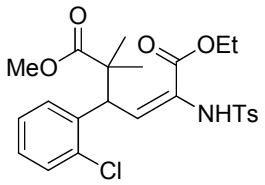
Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09-8.05 (m, 1H), 7.91 (t, *J* = 1.4 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 2H) 7.44-7.42 (m, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 10.8 Hz, 1H), 6.74 (s, 1H), 4.88 (d, *J* = 10.8 Hz, 1H), 4.03 (q, *J* = 6.9 Hz, 2H), 3.62 (s, 3H), 2.36 (s, 3H), 1.16 (s, 6H), 1.12 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1 (C), 162.3 (C), 147.8 (C), 144.2 (C), 142.2 (C), 135.9 (C), 135.3 (CH), 132.8 (CH), 129.6 (CH), 128.8 (CH), 127.3 (CH), 126.1 (C), 124.0 (C), 122.0 (CH), 62.2 (CH_2), 52.0 (CH_3), 50.0 (CH), 46.8 (C), 23.5 (CH_3), 21.9 (CH_3), 21.4 (CH_3), 13.9 (CH_3). HRMS (ESI) *m/z* 503.1495 $[M-H]^-$, $C_{24}H_{27}N_2O_8S$ requires 503.1494.

(*E*)-1-Ethyl 6-methyl 4-(3-methoxyphenyl)-5,5-dimethyl-2-(4-methylphenylsulfonamido)hex-2-enedioate (*E*)-18h



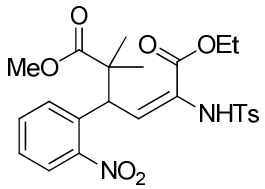
Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.4 Hz, 2H), 7.17 (t, *J* = 8.1 Hz, 1H), 7.12 (d, *J* = 8.7 Hz, 2H), 6.97 (d, *J* = 11.4 Hz, 1H), 6.77 (ddd, *J* = 8.1, 2.7, 0.9 Hz, 1H), 6.67 (d, J = 8.1 Hz, 1H), 6.66 (s, 1H overlapped), 6.59 (s, 1H), 4.79 (d, *J* = 11.4 Hz, 1H), 4.00 (q, *J* = 7.2 Hz, 2H), 3.78 (s, 3H), 3.60 (s, 3H), 2.35 (s, 3H), 1.167 (s, 3H), 1.165 (s, 3H), 1.12 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9 (C), 164.1 (C), 159.2 (C), 143.8 (C), 140.5 (C), 139.6 (CH), 136.0 (C), 129.3 (CH), 128.9 (CH), 127.6 (CH), 126.0 (C), 121.8 (CH), 115.8 (CH), 112.2 (CH), 61.8 (CH_2), 55.1 (CH_3), 51.9 (CH_3), 50.5 (CH_3), 47.1 (C), 23.9 (CH_3), 22.5 (CH_3), 21.5 (CH_3), 13.9 (CH_3); HRMS (ESI) *m/z* 488.1749 $[M-H]^-$, $C_{25}H_{30}NO_7S$ requires 488.1748.

(*E*)-1-Ethyl 6-methyl 4-(2-chlorophenyl)-5,5-dimethyl-2-(4-methylphenylsulfonamido)hex-2-enedioate (*E*)-18i



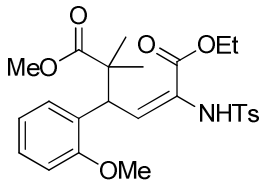
Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.35 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.23-7.14 (m, 3H), 7.11 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 11.4 Hz, 1H), 6.65 (s, 1H), 5.35 (d, *J* = 11.4 Hz, 1H), 4.10 (q, *J* = 7.2 Hz, 2H), 3.62 (s, 3H), 2.35 (s, 3H), 1.22 (s, 3H), 1.20 (s, 3H), 1.10 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3 (C), 163.2 (C), 143.8 (C), 137.7 (C), 135.8 (C), 134.8 (CH), 134.7 (C), 130.4 (CH), 129.8 (CH), 129.4 (CH), 128.1 (CH), 127.5 (CH), 126.5 (CH), 125.2 (C), 62.2 (CH_2), 51.9 (CH_3), 47.4 (CH), 45.4 (C), 24.0 (CH_3), 22.3 (CH_3), 21.5 (CH_3), 13.9 (CH_3); HRMS (ESI) *m/z* 492.1258 $[M-H]^-$, $C_{24}H_{27}ClNO_6S$ requires 492.1253.

(*E*)-1-Ethyl 6-methyl 5,5-dimethyl-2-(4-methylphenylsulfonamido)-4-(2-nitrophenyl)hex-2-enedioate (*E*)-18j



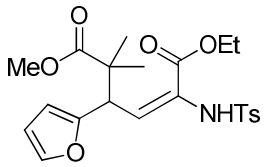
Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 7.8 Hz, 1H), 7.56-7.53 (m, 1H), 7.46-7.31 (m, 3H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 11.4 Hz, 1H), 6.69 (s, 1H), 5.42 (d, *J* = 11.4 Hz, 1H), 4.11 (2 overlapped q, *J* = 7.2 Hz, 2H), 3.60 (s, 3H), 2.34 (s, 3H), 1.24 (s, 3H), 1.18 (s, 3H), 1.13 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9 (C), 163.0 (C), 150.5 (C), 144.0 (C), 135.6 (C), 134.0 (C), 132.6 (CH), 132.0 (CH), 130.4 (CH), 129.5 (CH), 127.8 (CH), 127.4 (CH), 126.0 (C), 124.5 (CH), 62.5 (CH_2), 52.0 (CH_3), 47.3 (CH), 42.9 (C), 23.6 (CH_3), 23.3 (CH_3), 21.5 (CH_3), 13.8 (CH_3); HRMS (ESI) *m/z* 503.1496 $[M-H]^-$, $C_{24}H_{27}N_2O_8S$ requires 503.1494.

(*E*)-1-Ethyl 6-methyl 4-(2-methoxyphenyl)-5,5-dimethyl-2-(4-methylphenylsulfonamido)hex-2-enedioate (*E*)-18k



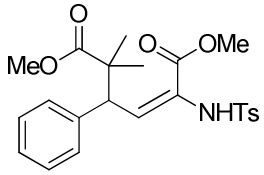
Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.4 Hz, 2H), 7.19 (td, *J* = 7.8, 1.8 Hz, 1H), 7.12 (d, *J* = 8.7 Hz, 2H), 7.06 (d, *J* = 11.1 Hz, 1H), 7.04 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.87 (t, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 6.57 (s, 1H), 5.18 (d, *J* = 11.1 Hz, 1H), 4.00 (q, *J* = 7.2 Hz, 2H), 3.76 (s, 3H), 3.60 (s, 3H), 2.34 (s, 3H), 1.14 (s, 6H), 1.08 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8 (C), 163.4 (C), 157.2 (C), 143.6 (C), 137.0 (CH), 136.0 (C), 130.4 (CH), 129.3 (CH), 128.2 (C), 127.9 (CH), 127.5 (CH), 124.3 (C), 120.1 (CH), 110.5 (CH), 61.7 (CH_2), 55.1 (CH_3), 51.6 (CH_3), 46.8 (C), 43.7 (CH), 23.9 (CH_3), 22.4 (CH_3), 21.4 (CH_3), 13.8 (CH_3); HRMS (ESI) *m/z* 488.1752 $[M-H]^-$, $C_{25}H_{30}NO_7S$ requires 488.1748.

(*E*)-1-Ethyl 6-methyl 4-(furan-2-yl)-5,5-dimethyl-2-(4-methylphenylsulfonamido)hex-2-enedioate (*E*)-18l



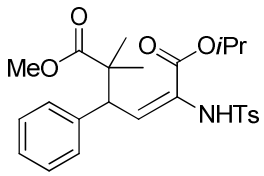
Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 1.8 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.71 (s, 1H overlapped), 6.69 (d, *J* = 11.4 Hz, 1H), 6.26 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.98 (d, *J* = 3.3 Hz, 1H), 5.04 (d, *J* = 11.4 Hz, 1H), 4.07 (2 overlapped q, *J* = 7.2 Hz, 2H), 3.62 (s, 3H), 2.37 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H), 1.13 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6 (C), 163.0 (C), 153.1 (C), 143.9 (C), 141.5 (CH), 135.9 (C), 131.5 (CH), 129.5 (CH), 127.5 (CH), 125.7 (C), 111.0 (CH), 107.2 (CH), 62.1 (CH_2), 51.9 (CH_3), 46.7 (CH), 44.4 (C), 23.3 (CH_3), 21.7 (CH_3), 21.5 (CH_3), 13.8 (CH_3); HRMS (ESI) *m/z* 448.1437 $[M-H]^-$, $C_{22}H_{26}NO_7S$ requires 448.1435.

(*E*)-Dimethyl 5,5-dimethyl-2-(4-methylphenylsulfonamido)-4-phenylhex-2-enedioate (*E*)-18n



Pale yellow solid, mp 126-129 ºC (hexane-CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.4 Hz, 2H), 7.26-7.21 (m, 3H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.07 (dd, *J* = 7.6, 2.4 Hz, 2H), 7.00 (d, *J* = 11.1 Hz, 1H), 6.57 (s, 1H), 4.72 (d, *J* = 11.1 Hz, 1H), 3.59 (s, 3H), 3.52 (s, 3H), 2.37 (s, 3H), 1.17 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7 (C), 163.4 (C), 144.0 (C), 140.0 (CH), 136.8 (C), 136.0 (C), 129.6 (CH), 129.4 (CH), 128.1 (CH), 127.7 (CH), 127.1 (CH), 124.8 (C), 52.4 (CH_3), 51.9 (CH_3), 50.7 (C), 46.9 (CH), 23.1 (CH_3), 22.7 (CH_3), 21.6 (CH_3); HRMS (ESI) *m/z* 444.1491 $[M-H]^-$, $C_{23}H_{26}NO_6S$ requires 444.1486.

(*E*)-1-Isopropyl 6-methyl 5,5-dimethyl-2-(4-methylphenylsulfonamido)-4-phenylhex-2-enedioate (*E*)-18o



Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.4 Hz, 2H), 7.31-7.23 (m, 3H), 7.14-7.08 (m, 4H), 6.98 (d, *J* = 11.7 Hz, 1H), 6.60 (s, 1H), 4.89-4.83 (m, 2H), 3.59 (s, 3H), 2.34 (s, 3H), 1.17 (s, 6H), 1.15 (d, *J* = 6.3 Hz, 3H), 1.04 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7 (C), 162.6 (C), 143.7 (C), 139.6 (C), 136.0 (C), 135.9 (C), 129.4 (CH), 129.3 (CH), 128.0 (CH), 127.5 (CH), 127.0 (CH), 125.0 (C), 70.1 (CH), 51.7 (CH_3), 50.2 (C), 46.8 (CH), 23.3 (CH_3), 22.1 (CH_3), 21.6 (CH_3), 21.43 (CH_3), 21.41 (CH_3); HRMS (ESI) *m/z* 472.1780 $[M-H]^-$, $C_{25}H_{30}NO_6S$ requires 472.1799.

5.4. Enantioselective conjugate addition of malonate esters to *N*-tosyl imines derived from β,γ-unsaturated α-keto esters

5.4.1. General procedure for the enantioselective conjugate addition of diethylmalonate to α,β-usaturated *N*-tosyl imino esters catalyzed by La(OTf)$_3$.

5.4.1.1. General procedure for the enantioselective conjugate addition

La(OTf)$_3$ (14.7 mg, 0.025 mmol) was dried in a Schlenk tube under vacuum. **pyBOX1** (9.24 mg, 0.025 mmol) was added and the tube was filled with nitrogen. CH_2Cl_2 (1.1 mL) was added *via* syringe and the mixture was stirred for 30 min. A solution of imine **17** (0.25 mmol) dissolved in dry CH_2Cl_2 (1.1 mL), was added *via* syringe, followed by 4 Å MS (110 mg) and diethyl malonate (92 μL, 0.63 mmol). The mixture was stirred at room temperature for the indicated time and chromatographed on silica gel eluting with hexane/EtOAc mixtures to give compound **19**.

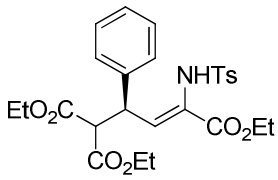
5.4.1.2. General procedure for the synthesis of the racemic products

Racemic compounds for comparative purpose were prepared by following the same procedure, using La(OTf)$_3$-pyBOX (rac) at 40 °C.

5.4.1.3. Characterization of products 19 and 20

See Table 14 (Page 90) and Table 15 (Page 91) for yield, dr and ee.

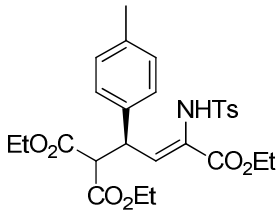
(*S*,*Z*)-Triethyl 4-(4-methylphenylsulfonamido)-2-phenylbut-3-ene-1,1,4-tricarboxylate (19ba)



Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 80:20, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 25.8 min, *minor enantiomer* t_r = 18.6 min. *Z*-isomer: *major enantiomer* t_r = 46.8 min, *minor enantiomer* t_r = 23.8 min.

Colorless oil; $[\alpha]_D^{20}$ 21.5 (*c* 1.0, $CHCl_3$, ee = 91 % *for the major diastereomer*) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.30-7.21 (m, 5H), 7.16-7.13 (m, 2H), 6.90 (d, *J* = 11.1 Hz, 1H), 6.72 (s, 1H), 4.64 (dd, *J* = 11.1, 9.6 Hz, 1H), 4.17 (q, *J* = 7.2 Hz , 2H), 4.01 (q, *J* = 7.2 Hz , 2H), 3.974 (q, *J* = 7.2 Hz, 1H), 3.968 (q, *J* = 6.9 Hz, 1H), 3.81 (d, *J* = 9.6 Hz, 1H), 2.39 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.12 (t, *J* = 6.9 Hz, 3H), 1.02 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1 (C), 166.9 (C), 164.2 (C), 143.6 (C), 138.5 (CH), 137.8 (C), 136.9 (C), 129.4 (CH), 128.6 (CH), 128.4 (CH), 127.53 (CH), 127.49 (CH), 126.4 (C), 62.0 (CH_2), 61.8 (CH_2), 61.6 (CH_2), 57.2 (CH), 43.0 (CH), 21.5 (CH_3), 13.9 (CH_3), 13.7 (CH_3); HRMS (ESI) *m/z* 518.1836 $[M+H]^+$, $C_{26}H_{31}NO_8S$ requires 518.1843.

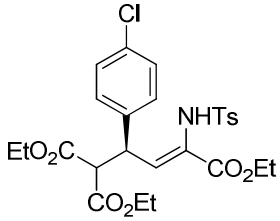
(*S*,*Z*)-Triethyl 4-(4-methylphenylsulfonamido)-2-(p-tolyl)but-3-ene-1,1,4-tricarboxylate (19bb)



Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 25.6 min, *minor enantiomer* t_r = 19.4 min. *Z*-isomer: *major enantiomer* t_r = 57.4 min, *minor enantiomer* t_r = 25.6 min.

Colorless oil; $[\alpha]_D^{20}$ 8.9 (*c* 1.0, $CHCl_3$, ee = 88% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.09-7.01 (m, 4H), 6.88 (d, *J* = 11.1 Hz, 1H), 6.74 (s, 1H), 4.60 (dd, *J* = 11.1, 9.9 Hz, 1H), 4.17 (q, *J* = 7.2 Hz , 2H), 4.04-3.95 (m, 2H), 4.00 (q, *J* = 7.2 Hz, 2H), 3.79 (d, *J* = 9.9 Hz, 1H), 2.39 (s, 3H), 2.30 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.11 (t, *J* = 6.9 Hz, 3H), 1.04 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2 (C), 167.0 (C), 164.3 (C), 143.6 (C), 138.8 (CH), 137.2 (C), 136.9 (C), 134.8 (C), 129.4 (CH), 129.3 (CH), 128.1 (CH), 127.5 (CH), 126.1 (C), 62.0 (CH_2), 61.7 (CH_2), 61.6 (CH_2), 57.3 (CH), 42.7 (CH), 21.5 (CH_3), 21.0 (CH_3), 13.9 (CH_3), 13.7 (CH_3); HRMS (ESI) *m/z* 532.1987 $[M+H]^+$, $C_{27}H_{33}NO_8S$ requires 532.2000.

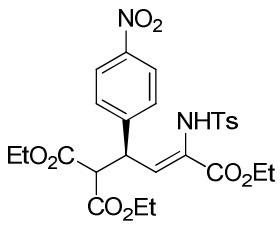
(*S*,*Z*)-Triethyl 2-(4-chlorophenyl)-4-(4-methylphenylsulfonamido)but-3-ene-1,1,4-tricarboxylate (19bc)



Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 80:20, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 21.5 min, *minor enantiomer* t_r = 19.7 min. *Z*-isomer: *major enantiomer* t_r = 67.8 min, *minor enantiomer* t_r = 23.5 min.

Colorless oil; $[\alpha]_D^{20}$ 24.5 (*c* 1.0, $CHCl_3$, ee = 88% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.4 Hz, 2H), 7.27-7.21 (m, 4H), 7.15 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 10.8 Hz, 1H), 6.65 (s, 1H), 4.72 (dd, *J* = 11.1, 9.6 Hz, 1H), 4.17 (q, *J* = 7.2 Hz , 2H), 4.04-3.95 (m, 4H), 3.78 (d, *J* = 9.6 Hz, 1H), 2.39 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.10 (t, *J* = 6.9 Hz, 3H), 1.07 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8 (C), 166.8 (C), 164.0 (C), 143.8 (C), 138.3 (CH), 136.6 (C), 136.5 (C), 133.4 (C), 129.7 (CH), 129.4 (CH), 128.8 (CH), 127.5 (CH), 126.5 (C), 62.1 (CH_2), 61.9 (CH_2), 61.7 (CH_2), 57.1 (CH), 42.4 (CH), 21.5 (CH_3), 13.89 (CH_3), 13.86 (CH_3), 13.76 (CH_3); HRMS (ESI) *m/z* 552.1443 $[M+H]^+$, $C_{26}H_{30}ClNO_8S$ requires 552.1453.

(*S*,*Z*)-Triethyl 4-(4-methylphenylsulfonamido)-2-(4-nitrophenyl)but-3-ene-1,1,4-tricarboxylate (19bd)

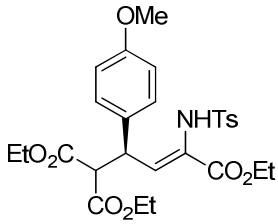


Chiral HPLC analysis: Chiralcel OD-H, hexane-*i*PrOH 90:10, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 38.3 min, *minor enantiomer* t_r = 41.3 min. *Z*-isomer: *major enantiomer* t_r = 80.5 min, *minor enantiomer* t_r = 33.7 min.

Yellow oil; $[\alpha]_D^{20}$ 27,0 (*c* 1.0, $CHCl_3$, ee = 69% *for the major*

diastereomer); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 9.0 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 9.0 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 10.8 Hz, 1H), 6.52 (s, 1H), 5.00 (dd, *J* = 10.8, 9.3 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 1H), 4.04 (q, *J* = 6.9 Hz, 1H), 4.03 (q, *J* = 7.2 Hz, 1H), 3.96 (q, *J* = 7.2 Hz, 1H), 3.95 (q, *J* = 7.2 Hz, 1H), 3.86 (d, *J* = 9.3 Hz, 1H), 2.39 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.10 (t, *J* = 7.2 Hz, 3H), 1.07 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3 (C), 166.6 (C), 163.6 (C), 147.2 (C), 145.7 (C), 144.0 (C), 137.6 (CH), 136.2 (C), 129.5 (2CH), 127.5 (CH), 123.8 (CH), 62.2 (CH_2), 62.1 (CH_2), 61.9 (CH_2), 56.8 (CH), 42.7 (CH), 21.5 (CH_3), 13.9 (CH_3), 13.8 ($2CH_3$); HRMS (ESI) *m/z* 563.1681 $[M+H]^+$, $C_{26}H_{30}N_2O_{10}S$ requires 563.1694.

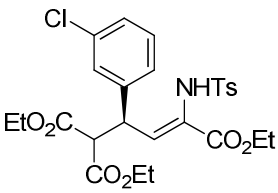
(*S*,*Z*)-Triethyl 2-(4-methoxyphenyl)-4-(4-methylphenylsulfonamido)but-3-ene-1,1,4-tricarboxylate (19be)



Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 90:10 (70 min), 85:15 (5 min), 80:20, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 29.9 min, *minor enantiomer* t_r = 35.2 min. *Z*-isomer: *major enantiomer* t_r = 97.1 min, *minor enantiomer* t_r = 33.0 min.

Yellow oil; $[\alpha]_D^{20}$ 11.6 (*c* 1.0, $CHCl_3$, ee = 86% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.7 Hz, 2H), 7.08 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 11.1 Hz, 1H), 6.80 (d, *J* = 8.7 Hz, 2H), 6.74 (s, 1H), 4.60 (dd, *J* = 11.1, 9.6 Hz, 1H), 4.17 (q, *J* = 7.2 Hz , 2H), 4.04-3.95 (m, 4H), 3.77 (s, 3H), 3.76 (d, *J* = 9.6 Hz, 1H), 2.39 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.11 (t, *J* = 6.9 Hz, 3H), 1.05 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1 (C), 167.0 (C), 164.3 (C), 158.9 (C), 143.6 (C), 138.9 (CH), 136.9 (C), 129.8 (C), 129.4 (CH), 129.3 (CH), 127.5 (CH), 126.0 (C), 114.0 (CH), 62.0 (CH_2), 61.7 (CH_2), 61.6 (CH_2), 57.4 (CH), 55.2 (CH_3), 42.3 (CH), 21.5 (CH_3), 13.9 (CH_3), 13.8 (CH_3); HRMS (ESI) *m/z* 548.1930 $[M+H]^+$, $C_{27}H_{33}NO_9S$ requires 548.1949.

(*S*,*Z*)-Triethyl 2-(3-chlorophenyl)-4-(4-methylphenylsulfonamido)but-3-ene-1,1,4-tricarboxylate (19bf)

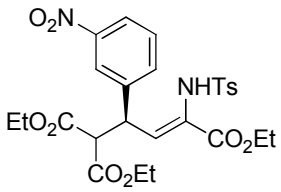


Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 22.7 min, *minor enantiomer* t_r = 17.3 min. *Z*-isomer: *major enantiomer* t_r = 35.7 min, *minor enantiomer* t_r = 28.6 min.

Yellow oil; $[\alpha]_D^{20}$ 20.7 (*c* 1.0, $CHCl_3$, ee = 90% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.4 Hz, 2H), 7.26-7.20 (m, 4H), 7.12-7.09 (m, 2H), 6.87 (d, *J* = 11.1 Hz, 1H), 6.73 (s, 1H), 4.65 (dd, *J* = 11.1, 9.3 Hz, 1H), 4.17 (q, *J* = 6.9 Hz, 2H), 4.05-3.98 (m, 4H), 3.77 (d, *J* = 9.3 Hz, 1H), 2.40 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.12 (t, *J* = 7.2 Hz, 3H), 1.06 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8 (C), 166.7 (C), 164.1 (C), 143.8 (C), 140.0 (CH), 137.6 (CH), 136.7 (C), 134.3 (C), 129.9 (CH), 129.5 (CH), 128.3 (CH), 127.8 (CH), 127.5 (CH), 126.9 (C), 126.6

(CH), 62.1 (CH_2), 61.9 (CH_2), 61.8 (CH_2), 57.1 (CH), 42.6 (CH), 21.5 (CH_3), 13.9 (CH_3), 13.7 (CH_3); HRMS (ESI) *m/z* 552.1445 $[M+H]^+$, $C_{26}H_{30}ClNO_8S$ requires 552,1453.

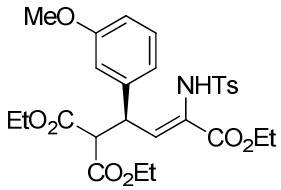
(*S*,*Z*)-Triethyl 4-(4-methylphenylsulfonamido)-2-(3-nitrophenyl)but-3-ene-1,1,4-tricarboxylate (19bg)



Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 80:20, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 28.4 min, *minor enantiomer* t_r = 25.1 min. *Z*-isomer: *major enantiomer* t_r = 58.2 min, *minor enantiomer* t_r = 39.1 min.

Yellow oil; $[\alpha]_D^{20}$ 20.3 (*c* 0.97, $CHCl_3$, ee = 52% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14-8.11 (m, 2H), 7.68 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.52-7.47 (m, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 10.8 Hz, 1H), 6.56 (s, 1H), 4.98 (dd, *J* = 10.8, 9.0 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.043 (q, *J* = 6.9 Hz, 1H), 4.036 (q, *J* = 7.2 Hz, 1H), 3.982 (q, *J* = 7.2 Hz, 1H), 3.978 (q, *J* = 7.2 Hz, 1H), 3.87 (d, *J* = 9 Hz, 1H), 2.38 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.094 (t, *J* = 7.2 Hz, 3H), 1.087 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3 (C), 166.6 (C), 163.7 (C), 148.3 (C), 144.1 (C), 140.5 (C), 137.4 (CH), 136.3 (C), 135.4 (CH), 129.54 (CH), 129.49 (CH), 127.5 (CH), 127.2 (C), 122.9 (CH), 122.6 (CH), 62.15 (CH_2), 62.09 (CH_2), 61.9 (CH_2), 57.0 (CH), 42.5 (CH), 21.5 (CH_3), 13.9 (CH_3), 13.85 (CH_3), 13.80 (CH_3); HRMS (ESI) *m/z* 563,1680 $[M+H]^+$,$C_{26}H_{30}N_2O_{10}S$ requires 563.1694.

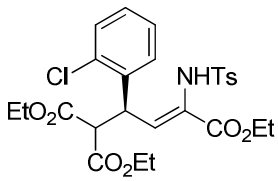
(*S*,*Z*)-Triethyl 2-(3-methoxyphenyl)-4-(4-methylphenylsulfonamido)but-3-ene-1,1,4-tricarboxylate (19bh)



Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 30.2 min, *minor enantiomer* t_r = 21.2 min. *Z*-isomer: *major enantiomer* t_r = 45.4 min, *minor enantiomer* t_r = 33.0 min.

Colorless oil; $[\alpha]_D^{20}$ 15.1 (*c* 0.96, $CHCl_3$, ee = 88% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 7.8 Hz, 1H), 6.88 (d, *J* = 10.8 Hz, 1H), 6.75-6.73 (m, 3H), 4.63 (dd, *J* = 10.8, 9.9 Hz, 1H), 4.17 (q, *J* = 6.9 Hz, 2H), 4.04-3.96 (m, 4H), 3.81 (d, *J* = 9.9 Hz, 1H), 3.79 (s, 3H), 2.39 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.11 (t, *J* = 7.2 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1 (C), 166.9 (C), 164.2 (C), 159.7 (C), 143.7 (C), 139.3 (C), 138.5 (CH), 136.8 (C), 129.6 (CH), 129.4 (CH), 127.5 (CH), 126.4 (C), 120.2 (CH), 114.3 (CH), 112.8 (CH), 62.0 (CH_2), 61.7 (CH_2), 61.6 (CH_2), 57.1 (CH), 55.2 (CH_3), 43.0 (CH), 21.5 (CH_3), 13.9 (CH_3), 13.7 (CH_3); HRMS (ESI) *m/z* 548.1941 $[M+H]^+$, $C_{27}H_{33}NO_9S$ requires 548,1949.

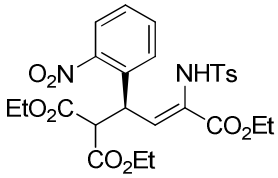
(*S*,*Z*)-Triethyl 2-(2-chlorophenyl)-4-(4-methylphenylsulfonamido)but-3-ene-1,1,4-tricarboxylate (19bi)



Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 23.4 min, *minor enantiomer* t_r = 26.9 min. *Z*-isomer: *major enantiomer* t_r = 58.8 min, *minor enantiomer* t_r = 25.2 min.

Colorless oil; $[\alpha]_D^{20}$ 44.4 (*c* 1.0, $CHCl_3$, ee = 95% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.4 Hz, 2H), 7.35-7.31 (m, 1H), 7.26-7.16 (m, 6H), 6.70 (s, 1H), 5.02 (dd, *J* = 10.5, 8.1 Hz, 1H), 4.19-4.00 (m, 7H), 2.35 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H), 1.13 (t, *J* = 6.9 Hz, 3H), 1.11 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8 (C), 167.3 (C), 164.2 (C), 143.5 (C), 136.8 (C), 136.0 (CH), 135.7 (C), 133.7 (C), 130.5 (CH), 130.2 (CH), 129.3 (CH), 128.7 (CH), 127.5 (C), 127.3 (CH), 126.9 (CH), 61.8 (CH_2), 54.8 (CH), 40.4 (CH), 21.5 (CH_3), 13.90 (CH_3), 13.87 (CH_3), 13.78 (CH_3); HRMS (ESI) *m/z* 552.1441 $[M+H]^+$, $C_{26}H_{30}ClNO_8S$ requires 552.1453.

(*S*,*Z*)-Triethyl 4-(4-methylphenylsulfonamido)-2-(2-nitrophenyl)but-3-ene-1,1,4-tricarboxylate (19bj)



Major *Z*-diastereomer: Chiral HPLC analysis: Chiralcel OD-H, hexane-*i*PrOH 80:20, 1 mL/min, *major enantiomer* t_r = 37.6 min, *minor enantiomer* t_r = 16.1 min.

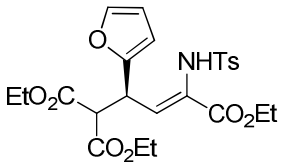
Orange oil; $[\alpha]_D^{20}$ 33.4 (*c* 1.0, $CHCl_3$, ee = 20%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.59-7.49 (m, 4H), 7.45-7.40 (m, 1H), 7.22 (d, *J* = 9.6 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 2H), 6.63 (s, 1H), 5.32 (dd, *J* = 9.6, 7.2 Hz, 1H), 4.21-4.05 (m, 5H), 4.00 (q, *J* = 7.2 Hz, 2H), 2.34 (s, 3H), 1.18 (t, *J* = 7.2 Hz, 3H), 1.14 (t, *J* = 7.2 Hz, 3H), 1.09 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6 (C), 167.3 (C), 163.8 (C), 149.3 (C), 143.7 (C), 136.2 (C), 135.4 (CH), 133.8 (C), 133.0 (CH), 131.2 (CH), 129.2 (CH), 128.4 (CH), 127.7 (C), 127.4 (CH), 125.3 (CH), 61.93 (CH_2), 61.91 (CH_2), 61.8 (CH_2), 56.1 (CH), 38.6 (CH), 21.4 (CH_3), 13.9 (CH_3), 13.82 (CH_3), 13.80 (CH_3); HRMS (ESI) *m/z* 563.1674 $[M+H]^+$, $C_{26}H_{30}N_2O_{10}S$ requires 563.1694.

Minor *E*-diastereomer: Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 80:20, 1 mL/min, *major enantiomer* t_r = 28.2 min, *minor enantiomer* t_r = 55.7 min.

Orange oil; $[\alpha]_D^{20}$ 35.5 (*c* 1.0, $CHCl_3$, ee = 60%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.56 (td, *J* = 7.5, 1.5 Hz, 1H), 7.50-7.46 (m, 3H), 7.43-7.38 (m, 1H), 7.10 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 9.9 Hz, 1H), 6.68 (s, 1H), 5.59 (dd, *J* = 10.2, 7.8 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 1H), 4.14 (q, *J* = 6.9 Hz, 1H), 4.08-3.99 (m, 5H), 2.34 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H), 1.10 (t, *J* = 7.2 Hz, 3H), 1.05 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3 (C), 167.0 (C), 162.6 (C), 149.4 (C), 143.8 (C), 135.6 (C), 135.2 (C), 132.8 (C), 131.5 (CH), 130.4 (CH), 129.4 (CH), 128.0 (CH),

127.4 (CH), 126.2 (C), 124.5 (CH), 62.4 (CH_2), 61.7 (CH_2), 61.6 (CH_2), 56.2 (CH), 37.9 (CH), 21.4 (CH_3), 13.9 (CH_3), 13.74 (CH_3), 13.70 (CH_3); HRMS (ESI) *m/z* 563.1685 $[M+H]^+$, $C_{26}H_{30}N_2O_{10}S$ requires 563,1694 .

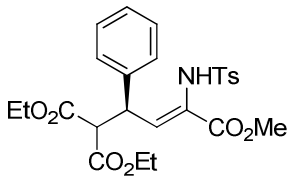
(*S*,*Z*)-Triethyl 4-(4-methylphenylsulfonamido)-2-(thiophen-2-yl)but-3-ene-1,1,4-tricarboxylate (19bl)



Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 17.0 min, *minor enantiomer* t_r = 28.0 min. *Z*-isomer: *major enantiomer* t_r = 23.5 min, *minor enantiomer* t_r = 20.5 min.

Orange oil; $[\alpha]_D^{20}$ 11.9 (*c* 1.01, $CHCl_3$, ee = 84% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (dt, *J* = 8.1 Hz, 2H), 7.32 (dd, *J* = 2.1, 0.9 Hz, 1H), 7.22 (d, *J* = 8.1 Hz, 2H), 6.90 (d, *J* = 10.8 Hz, 1H), 6.72 (s, 1H), 6.28 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.11 (dt, *J* = 3.3, 0.6 Hz, 1H), 4.76 (d, *J* = 10.8, 8.4 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.14-4.07 (m, 2H), 4.02 (q, *J* = 7.2 Hz, 2H), 3.89 (d, *J* = 8.4 Hz, 1H), 2.38 (s, 3H), 1.21 (t, *J* = 6.9 Hz, 3H), 1.17 (t, *J* = 6.9 Hz, 3H), 1.13 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5 (C), 167.1 (C), 164.1 (C), 150.5 (C), 143.7 (C), 142.0 (CH), 136.5 (C), 135.4 (CH), 129.4 (CH), 127.5 (CH), 127.1 (C), 110.4 (CH), 107.8 (CH), 61.88 (CH_2), 61.85 (CH_2), 55.2 (CH), 37.1 (CH), 21.5 (CH_3), 13.89 (CH_3), 13.86 (CH_3); HRMS (ESI) *m/z* 508.1629 $[M+H]^+$, $C_{24}H_{29}NO_9S$ requires 508.1636.

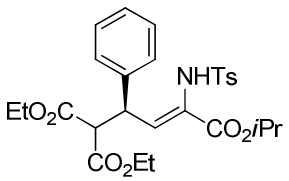
(*S*,*Z*)-1,1-Diethyl 4-methyl 4-(4-methylphenylsulfonamido)-2-phenylbut-3-ene-1,1,4-tricarboxylate (19bn)



Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 28.1 min, *minor enantiomer* t_r = 26.0 min. *Z*-isomer: *major enantiomer* t_r = 76.5 min, *minor enantiomer* t_r = 32.8 min.

White solid, mp 94-95 °C (hexane-EtOAc); $[\alpha]_D^{20}$ 20.2 (*c* 0.98, $CHCl_3$, ee = 87% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4Hz, 2H), 7.32-7.23 (m, 5H), 7.12-7.09 (m, 2H), 6.90 (s, 1H), 6.88 (d, *J* = 11.1Hz, 1H), 4.56 (dd, *J* = 10.8, 9.9 Hz, 1H), 4.179 (q, *J* = 7.2 Hz , 1H), 4.177 (q, *J* = 7.2 Hz , 1H), 3.972 (q, *J* = 7.2 Hz, 1H), 3.966 (q, *J* = 6.9 Hz, 1H), 3.80 (d, *J* = 9.9 Hz, 1H), 3.58 (s, 3H), 2.41 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.01 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2 (C), 166.9 (C), 164.8 (C), 143.6 (C), 138.4 (CH), 137.6 (C), 136.8 (C), 129.5 (CH), 128.6 (CH), 128.2 (CH), 127.6 (CH), 127.4 (CH), 126.3 (C), 62.1 (CH_2), 61.7 (CH_2), 57.1 (CH), 52.5 (CH_3), 43.0 (CH), 21.5 (CH_3), 13.9 (CH_3), 13.7 (CH_3); HRMS (ESI) *m/z* 504.1673 $[M+H]^+$, $C_{25}H_{29}NO_8S$ requires 504.1687.

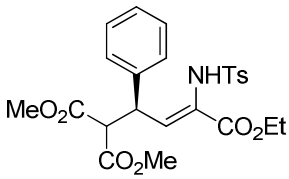
(*S*,*Z*)-1,1-Diethyl 4-isopropyl 4-(4-methylphenylsulfonamido)-2-phenylbut-3-ene-1,1,4-tricarboxylate (19bo)



Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 20.8 min, *minor enantiomer* t_r = 15.0 min. *Z*-isomer: *major enantiomer* t_r = 35.1 min, *minor enantiomer* t_r = 22.4 min.

Colorless oil; $[\alpha]_D^{20}$ 18.4 (*c* 1.0, $CHCl_3$, ee = 89% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (dt, *J* = 8.1 Hz, 2H), 7.32-7.16 (m, 7H), 6.89 (d, *J* = 10.8 Hz, 1H), 6.71 (s, 1H), 4.83 (hept, *J* = 6.3 Hz, 1H), 4.69 (dd, *J* = 10.8, 9.6 Hz, 1H), 4.18 (q, *J* = 6.9 Hz, 2H), 3.983 (q, *J* = 7.2 Hz, 1H), 3.977 (q, *J* = 7.2 Hz, 1H), 3.82 (d, *J* = 9.6 Hz, 1H), 2.39 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.11 (d, *J* = 6.3 Hz, 3H), 1.08 (d, *J* = 6 Hz, 3H), 1.03 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0 (C), 166.9 (C), 163.7 (C), 143.6 (C), 138.3 (CH), 137.9 (C), 136.7 (C), 129.4 (CH), 128.6 (CH), 128.3 (CH), 127.49 (CH), 127.46 (CH), 126.5 (C), 69.7 (CH), 62.0 (CH_2), 61.6 (CH_2), 57.3 (CH), 43.0 (CH), 21.47 (CH_3), 21.43 (CH_3), 21.36 (CH_3), 13.9 (CH_3), 13.7 (CH_3); HRMS (ESI) *m/z* 532.1982 $[M+H]^+$, $C_{27}H_{33}NO_8S$ requires 532.2000.

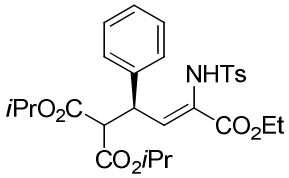
(*S*,*Z*)-4-Ethyl 1,1-dimethyl 4-(4-methylphenylsulfonamido)-2-phenylbut-3-ene-1,1,4-tricarboxylate (19aa)



Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 34.5 min, *minor enantiomer* t_r = 22.9 min. *Z*-isomer: *major enantiomer* t_r = 34.5 min, *minor enantiomer* t_r = 26.8 min.

Colorless oil; $[\alpha]_D^{20}$ 5.5 (*c* 1.0, $CHCl_3$, ee = 86% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.32-7.16 (m, 7H), 6.97 (d, *J* = 11.1 Hz, 1H), 6.60 (s, 1H), 4.75 (dd, *J* = 10.8, 9.6 Hz, 1H), 3.99 (q, *J* = 7.2 Hz, 2H), 3.87 (d, *J* = 9.6 Hz, 1H), 3.72 (s, 3H), 3.54 (s, 3H), 2.39 (s, 3H), 1.11 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4 (C), 167.4 (C), 164.1 (C), 143.7 (C), 138.8 (CH), 137.9 (C), 136.7 (C), 129.5 (CH), 128.7 (CH), 128.1 (CH), 127.6 (CH), 127.5 (CH), 126.3 (C), 61.8 (CH_2), 57.0 (CH), 52.9 (CH_3), 52.6 (CH_3), 43.1 (CH), 21.5 (CH_3), 13.9 (CH_3); HRMS (ESI) *m/z* 490.1524 $[M+H]^+$, $C_{24}H_{27}NO_8S$ requires 490.1530.

(*S*,*Z*)-4-Ethyl 1,1-diisopropyl 4-(4-methylphenylsulfonamido)-2-phenylbut-3-ene-1,1,4-tricarboxylate (19ca)

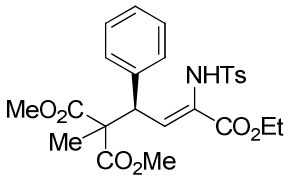


Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 17.2 min, *minor enantiomer* t_r = 14.6 min. *Z*-isomer: *major enantiomer* t_r = 28.9 min, *minor enantiomer* t_r = 18.7 min.

Colorless oil; $[\alpha]_D^{20}$ 25.1 (*c* 1.0, $CHCl_3$, ee = 73% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.28-7.20 (m, 5H), 7.11-7.08 (m, 2H), 6.94 (s, 1H), 6.82 (d, *J* = 10.8 Hz, 1H), 5.02 (hept, *J* = 6 Hz, 1H), 4.79 (hept, *J* =

6.3 Hz, 1H), 4.52 (dd, *J* = 10.8, 9.9 Hz, 1H), 4.04 (q, *J* = 6.9 Hz, 2H), 3.73 (d, *J* = 9.9 Hz, 1H), 2.39 (s, 3H), 1.21 (d, *J* = 6.6 Hz, 3H), 1.18 (d, *J* = 6.3 Hz, 3H), 1.13 (t, *J* = 7.2 Hz, 3H), 1.03 (d, *J* = 6.3 Hz, 3H), 0.99 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8 (C), 166.4 (C), 164.3 (C), 143.5 (C), 138.2 (CH), 137.8 (C), 137.0 (C), 129.4 (CH), 128.5 (CH), 128.3 (CH), 127.4 (CH), 126.5 (C), 69.8 (CH), 69.3 (CH), 61.7 (CH_2), 57.5 (CH), 42.9 (CH), 21.52 (CH_3), 21.48 (CH_3), 21.4 (CH_3), 21.2 (CH_3), 13.9 (CH_3); HRMS (ESI) *m/z* 546.2144 $[M+H]^+$, $C_{28}H_{35}NO_8S$ requires 546.2156.

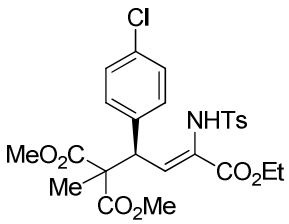
(*R*,*Z*)-Dimethyl 2-(3,3-bis(4-methylphenylsulfonamido)-1-phenylallyl)-2-methylmalonate (20da)



Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 80:20, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 14.2 min, *minor enantiomer* t_r = 23.4 min. *Z*-isomer: *major enantiomer* t_r = 14.9 min, *minor enantiomer* t_r = 12.7 min**.**

Colorless oil; $[\alpha]_D^{20}$ 71.3 (*c* 1.0, $CHCl_3$, ee = 83% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.4 Hz, 2H), 7.26-7.23 (m, 3H), 7.18-7.14 (m, 3H), 7.06-7.03 (m, 2H), 6.94 (s, 1H), 4.52 (d, *J* = 11.1 Hz, 1H), 4.06 (q, *J* = 7.2 Hz, 2H), 3.71 (s, 3H), 3.60 (s, 3H), 2.37 (s, 3H), 1.40 (s, 3H), 1.15 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4 (C), 171.2 (C), 164.5 (C), 143.5 (C), 137.3 (CH), 136.9 (C), 136.5 (C), 129.34 (CH), 129.26 (CH), 128.3 (CH), 127.6 (CH), 127.3 (CH), 126.6 (C), 61.7 (CH_2), 58.6 (C), 52.8 (CH_3), 52.7 (CH_3), 47.6 (CH), 21.5 (CH_3), 18.7 (CH_3), 13.9 (CH_3); HRMS (ESI) *m/z* 504.1684 $[M+H]^+$, $C_{25}H_{29}NO_8S$ requires 504.1687.

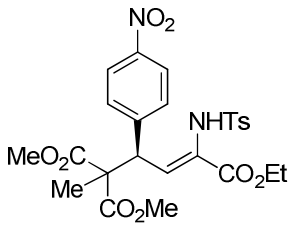
(*R*,*Z*)-1-Ethyl 4,4-dimethyl 3-(4-chlorophenyl)-1-(4-methylphenylsulfonamido)pent-1-ene-1,4,4-tricarboxylate (20dc)



Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 80:20, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 22.4 min, *minor enantiomer* t_r = 48.9 min. *Z*-isomer: *major enantiomer* t_r = 13.1 min, *minor enantiomer* t_r = 13.8 min

Colorless oil; $[\alpha]_D^{20}$ 17.8 (*c* 1.0, $CHCl_3$, ee = 40% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.4 Hz, 2H), 7.27-7.07 (m, 7H), 6.77 (s, 1H), 4.64 (d, *J* = 10.8 Hz, 1H), 4.02 (q, *J* = 6.9 Hz, 2H), 3.72 (s, 3H), 3.64 (s, 3H), 2.38 (s, 3H), 1.42 (s, 3H), 1.12 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2 (C), 171.1 (C), 164.2 (C), 143.7 (C), 137.4 (CH), 136.6 (C), 135.3 (C), 133.6 (C), 130.8 (CH), 129.4 (CH), 128.4 (CH), 127.4 (CH), 126.7 (C), 61.8 (CH_2), 58.5 (C), 52.82 (CH_3), 52.76 (CH_3), 47.1 (CH), 21.5 (CH_3), 18.8 (CH_3), 13.9 (CH_3); HRMS (ESI) *m/z* 538.1298 $[M+H]^+$, $C_{25}H_{28}ClNO_8S$ requires 538.1297.

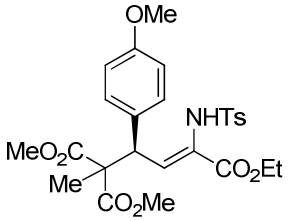
(*R,Z*)-1-Ethyl 4,4-dimethyl 1-(4-methylphenylsulfonamido)-3-(4-nitrophenyl)pent-1-ene-1,4,4-tricarboxylate (20dd)



Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 90:10, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 52.8 min, *minor enantiomer* t_r = 96.5 min. *Z*-isomer: *major enantiomer* t_r = 81.8 min, *minor enantiomer* t_r = 69.5 min.

Pale yellow oil; $[\alpha]_D^{20}$ 77.1 (*c* 1.0, $CHCl_3$, ee = 81% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, *J* = 9 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.7 Hz, 2H), 7.28 (d, *J* = 10.5 Hz, 1H), 7.18 (d, *J* = 8.1 Hz, 2H), 6.56 (s, 1H), 4.93 (d, *J* = 10.8 Hz, 1H), 3.97 (q, *J* = 7.2 Hz, 1H), 3.96 (q, *J* = 7.2 Hz, 2H), 3.70 (s, 3H), 3.66 (s, 3H), 2.36 (s, 3H), 1.45 (s, 3H), 1.07 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8 (C), 170.7 (C), 163.7 (C), 147.2 (C), 144.6 (C), 143.9 (C), 137.2 (CH), 136.1 (C), 130.7 (CH), 129.4 (CH), 127.4 (CH), 127.2 (C), 123.2 (CH), 62.0 (CH_2), 58.4 (C), 52.9 (CH_3), 52.8 (CH_3), 47.6 (CH), 21.4 (CH_3), 19.1 (CH_3), 13.8 (CH_3); HRMS (ESI) *m/z* 549.1542 $[M+H]^+$, $C_{25}H_{28}N_2O_{10}S$ requires 549,1537.

(*R,Z*)-1-Ethyl 4,4-dimethyl 3-(4-methoxyphenyl)-1-(4-methylphenylsulfonamido)pent-1-ene-1,4,4-tricarboxylate (20de)

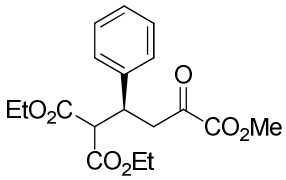


Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 90:10, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 22.4 min, *minor enantiomer* t_r = 39.9 min. *Z*-isomer: *major enantiomer* t_r = 25.6 min, *minor enantiomer* t_r = 34.9 min

Yellow oil; $[\alpha]_D^{20}$ 57.8 (*c* 0.83, $CHCl_3$, ee = 97% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 11.1 Hz, 1H), 6.99 (d, *J* = 8.7 Hz, 2H), 6.90 (s, 1H), 6.78 (d, *J* = 8.7 Hz, 2H), 4.49 (d, *J* = 11.1 Hz, 1H), 4.05 (q, *J* = 6.9 Hz, 2H), 3.78 (s, 3H), 3.71 (s, 3H), 3.62 (s, 3H), 2.38 (s, 3H), 1.40 (s, 3H), 1.14 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6 (C), 171.3 (C), 164.5 (C), 159.0 (C), 143.5 (C), 137.7 (CH), 137.0 (C), 130.4 (CH), 129.4 (CH), 128.5 (C), 127.4 (CH), 126.2 (C), 113.7 (CH), 61.7 (CH_2), 58.7 (C), 55.1 (CH_3), 52.8 (CH_3), 52.7 (CH_3), 46.9 (CH), 21.5 (CH_3), 18.7 (CH_3), 13.9 (CH_3); HRMS (ESI) *m/z* 534.1785 $[M+H]^+$, $C_{26}H_{31}NO_9S$ requires 534.1792.

5.4.2. Synthetic transformations from compound 19bn

(*S*)-1,1-Diethyl 4-methyl 4-oxo-2-phenylbutane-1,1,4-tricarboxylate (21bn)



A solution of (*S*,*Z*)-**19bn** (14.0 mg, 0.04 mmol, ee = 86%) dissolved in dry CH_2Cl_2 (0.8 mL), was added *via* syringe to $La(OTf)_3$ (14.6 mg, 0.025 mmol), previously dried in a Schlenk tube, under nitrogen atmosphere, followed by 4 Å MS (8 mg) and benzylamine (9 μL, 0.08 mmol). The mixture was stirred at rt for 18 hours and chromatographed on silica gel eluting with hexane/EtOAc (85:15) mixture to give compound **21bn** (11.8 mg, 84%). Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *major enantiomer* t_r = 16.5 min, *minor enantiomer* t_r = 13.3 min. Colorless oil; $[\alpha]_D^{20}$ 14.9 (*c* 0.70, $CHCl_3$, *ee* = 86%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 - 7.17 (m, 5H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.08-4.00 (m 1H), 3.95 (q, *J* = 7.2 Hz, 2H), 3.81 (s, 3H), 3.74 (d, *J* = 10.2 Hz, 1H), 3.43 (dd, *J* = 18.0, 8.7 Hz, 1H), 3.33 (q, *J* = 18.0, 5.1 Hz, 1H), 1.26 (t, *J* = 6.9 Hz, 3H), 1.01 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.3 (C), 168.1 (C), 167.4 (C), 160.9 (C), 139.8 (C), 128.5 (CH), 128.2 (CH), 127.4 (CH), 61.8 (CH_2), 61.4 (CH_2), 57.2 (CH), 53.0 (CH_3), 43.4 (CH), 39.9 (CH), 14.0 (CH_3), 13.7 (CH_3); HRMS (ESI) *m/z* 351.1430 $[M+H]^+$, $C_{18}H_{22}O_7$ requires 351.1438.

5.5. Diastereodivergent enantioselective conjugate addition of 2-chloromalonate esters to *N*-tosyl imines derived from β,γ-unsaturated α-keto esters

5.5.1. Enantioselective conjugate addition of diethyl 2-chloromalonate to α,β-unsaturated *N*-tosyl imino esters catalyzed by La(OTf)$_3$

5.5.1.1. General procedure for the enantioselective conjugate addition

La(OTf)$_3$ (7.3 mg, 0.0125 mmol) was dried in a Schlenk tube under vacuum. **pyBOX9** (6.5 mg, 0.0125 mmol) was added and the tube was filled with nitrogen. CH_2Cl_2 (0.55 mL) was added via syringe and the mixture was stirred for 30 min. A solution of imine **17** (0.125 mmol) in dry CH_2Cl_2 (0.5 mL) was added *via* syringe, followed by 4 Å MS (110 mg), and the mixture was introduced in a -10ºC bath. After 10 minutes, diethyl 2-chloromalonate (**1e**, 32 μL, 0.187 mmol) was added to the reaction. The mixture was stirred at -10 ºC for the indicated time and chromatographed on silica gel eluting with hexane/EtOAc mixtures to give compound (*Z*)-**22**.

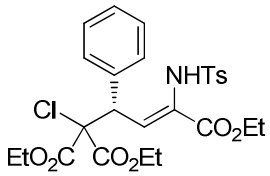
5.5.1.2. General procedure for the synthesis of the racemic products

Racemic compounds for comparative purpose were prepared by following the same procedure, using La(OTf)$_3$ in absence of chiral ligand and performing the reaction at room temperature.

5.5.1.3. Characterization of products (S,Z)-22

See Table 17 (Page 95) for yield, dr and ee.

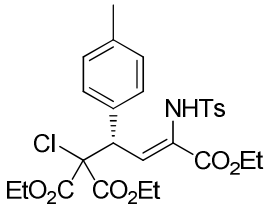
(*S*,*Z*)-Triethyl 1-chloro-4-(4-methylphenylsulfonamido)-2-phenylbut-3-ene-1,1,4-tricarboxylate, (*S*,*Z*)-22ea



Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 90:10, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 54.5 min, *minor enantiomer* t_r = 36.4 min. *Z*-isomer: *major enantiomer* t_r = 29.3 min, *minor enantiomer* t_r = 69.7 min.

White oil; $[\alpha]_D^{20}$ -30.3 (*c* 0.98, $CHCl_3$, *ee* = 86% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (dt, *J* = 8.4, 1.8 Hz, 2H), 7.27-7.26 (m, 5H), 7.21 (d, *J* = 10.2 Hz, 1H), 7.20 (dd, *J* = 8.4, 0.9 Hz, 2H), 6.65 (s, 1H), 5.07 (d, *J* = 9.9 Hz, 1H), 4.34-4.22 (m, 2H), 4.12-4.04 (m, 2H), 4.01 (q, *J* = 7.2 Hz, 1H), 2.38 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.13 (t, *J* = 7.2 Hz, 3H), 1.11 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4 (C), 164.8 (C), 164.1 (C), 143.6 (C), 136.9 (CH), 136.6 (C), 135.2 (C), 129.7 (CH), 129.4 (CH), 128.2 (CH), 127.5 (CH), 126.5 (CH), 74.3 (C), 63.4 (CH_2), 63.3 (CH_2), 61.8 (CH_2), 48.1 (CH), 21.5 (CH_3), 13.9 (CH_3), 13.7 (CH_3), 13.6 (CH_3); HRMS (ESI) *m/z* 552.1459 $[M+H]^+$, $C_{26}H_{30}ClNO_8S$ requires 552.1453.

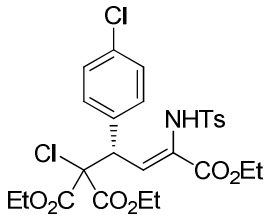
(*S*,*Z*)-Triethyl (Z)-1-chloro-4-((4-methylphenyl)sulfonamido)-2-(p-tolyl)but-3-ene-1,1,4-tricarboxylate, (*S*,*Z*)-22eb



Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 90:10, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 38.8 min, *minor enantiomer* t_r = 26.4 min. *Z*-isomer: *major enantiomer* t_r = 22.7 min, *minor enantiomer* t_r = 44.5 min.

White oil; $[\alpha]_D^{20}$ -31.8 (*c* 0.87, $CHCl_3$, *ee* = 86% *for the major diastereomer*), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (dt, *J* = 8.1, 2.1 Hz, 2H), 7.20 (d, *J* = 9.9 Hz, 3H), 7.15 (d, *J* = 8.4 Hz, 2H), 7. 07 (d, *J* = 8.1 Hz, 2H), 6.64 (s, 1H), 5.02 (d, *J* = 9.9 Hz, 1H), 4.29 (q, *J* = 7.2 Hz, 1H), 4.26 (q, *J* = 7.2 Hz, 1H), 4.09 (q, *J* = 6.9 Hz, 1H), 4.06 (q, *J* = 7.2 Hz, 1H), 4.00 (q, *J* = 7.2 Hz, 2H), 2.38 (s, 3H), 2.30 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.15 (t, *J* = 7.2 Hz, 3H), 1.11 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4 (C), 164.8 (C), 164.1 (C), 143.6 (C), 137.9 (C), 137.2 (CH), 136.6 (C), 132.1 (C), 129.5 (CH), 129.3 (CH), 128.9 (CH), 127.4 (CH), 126.3 (C), 74.4 (C), 63.4 (CH_2), 63.3(CH_2), 61.8 (CH_2), 47.7 (CH), 21.5 (CH_3), 21.1(CH_3), 13.9 (CH_3), 13.71 (CH_3), 13.67 (CH_3); HRMS (ESI) *m/z* 566.1606 $[M+H]^+$, $C_{27}H_{32}ClNO_8S$ requires 566.1610.

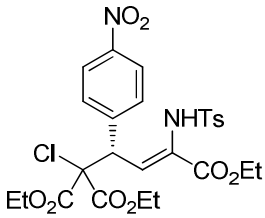
(*S*,*Z*)-Triethyl 1-chloro-2-(4-chlorophenyl)-4-(4-methylphenylsulfonamido)but-3-ene-1,1,4-tricarboxylate, (*S*,*Z*)-22ec



Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 95:05, 1.6 mL/min, *E*-isomer: *major enantiomer* t_r = 93.8 min, *minor enantiomer* t_r = 58.0 min. *Z*-isomer: *major enantiomer* t_r = 47.6 min, *minor enantiomer* t_r = 68.8 min.

White oil; $[\alpha]_D^{20}$ -37.9 (*c* 1.0, $CHCl_3$, *ee* = 86% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (dt, *J* = 8.4, 1.8 Hz, 2H), 7.28-7.25 (m, 4H), 7.21 (dd, *J* = 8.4, 0.9 Hz, 2H), 7.20 (d, *J* = 9.9 Hz, 1H), 6.52 (s, 1H), 5.18 (d, *J* = 9.6 Hz, 1H), 4.29 (q, *J* = 6.9 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 1H), 4.12 (q, *J* = 7.2 Hz, 1H), 4.09 (q, *J* = 7.2 Hz, 1H), 3.98 (q, *J* = 7.2 Hz, 2H), 2.38 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H), 1.09 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1 (C), 164.7 (C), 163.9 (C), 143.8 (C), 136.8 (CH), 136.3 (C), 134.2 (C), 133.9 (C), 131.2 (CH), 129.4 (CH), 128.4 (CH), 127.5 (CH), 126.7 (C), 74.1 (C), 63.5 (CH_2), 63.4 (CH_2), 61.9 (CH_2), 47.5 (CH_3), 21.5 (CH_3), 13.8 (CH_3), 13.7(CH_3); HRMS (ESI) *m/z* 586.1074 $[M+H]^+$, $C_{26}H_{29}Cl_2NO_8S$ requires 586.1064.

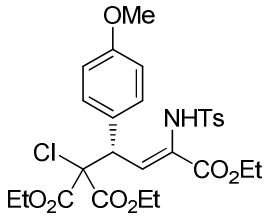
(*S*,*Z*)-Triethyl 1-chloro-4-(4-methylphenylsulfonamido)-2-(4-nitrophenyl)but-3-ene-1,1,4-tricarboxylate, (*S*,*Z*)-22ed



Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 80:20, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 36.7 min, *minor enantiomer* t_r = 21.8 min. *Z*-isomer: *major enantiomer* t_r = 24.6 min, *minor enantiomer* t_r = 43.7 min.

Pale yellow oil; $[\alpha]_D^{20}$ -52.3 (*c* 1.0, $CHCl_3$, *ee* = 87% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (dt, *J* = 8.7, 2.4 Hz, 2H), 7.59 (dt, *J* = 9.0, 2.1 Hz, 2H), 7.56 (dt, *J* = 8.4, 2.1 Hz, 2H), 7.26 (d, *J* = 9.6 Hz, 1H), 7.21 (dd, *J* = 8.7, 0.6 Hz, 2H), 6.41 (s, 1H), 5.46 (d, *J* = 10.2 Hz, 1H), 4.30 (q, *J* = 7.2 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 1H), 4.12 (q, *J* = 6.9 Hz, 1H), 3.95 (q, *J* = 7.2 Hz, 1H), 3.94 (q, *J* = 7.2 Hz, 1H), 2.37 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.19 (t, *J* = 7.2 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6 (C), 164.5 (C), 163.4 (C), 147.5 (C), 144.1 (C), 142.9 (C), 136.4 (CH), 135.8 (C), 131.1 (CH), 129.4 (CH), 127.5 (CH), 127.3 (C), 123.1 (CH), 73.6 (C), 63.64 (CH_2), 63.59 (CH_2), 62.1 (CH_2), 47.8 (CH_3), 21.4 (CH_3), 13.8 (CH_3), 13.7 (CH_3); HRMS (ESI) *m/z* 597.1310 $[M+H]^+$, $C_{26}H_{29}ClN_2O_{10}S$ requires 597.1304.

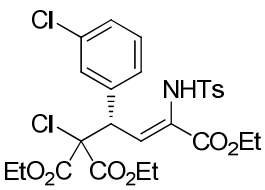
(*S*,*Z*)-Triethyl 1-chloro-2-(4-methoxyphenyl)-4-(4-methylphenylsulfonamido)but-3-ene-1,1,4-tricarboxylate, (*S*,*Z*)-22ee



Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 28.8 min, *minor enantiomer* t_r = 22.9 min. *Z*-isomer: *major enantiomer* t_r = 17.4 min, *minor enantiomer* t_r = 33.5 min.

Yellow oil; $[\alpha]_D^{20}$ -29.3 (*c* 1.0, $CHCl_3$, *ee* = 86% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (dt, *J* = 8.4, 1.8 Hz, 2H), 7.20 (d, *J* = 8.7 Hz, 4H), 7.12 (d, *J* = 9.9 Hz, 1H), 6.79 (dt, *J* = 8.7, 1.8 Hz, 2H), 6.65 (s, 1H), 5.03 (d, *J* = 9.9 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 4.25 (q, *J* = 7.2 Hz, 1H), 4.09 (q, *J* = 6.9 Hz, 1H), 4.06 (q, *J* = 7.2 Hz, 1H), 4.00 (q, *J* = 7.2 Hz, 2H), 3.77 (s, 3H), 2.38 (s, 3H), 1.27 (t, *J* = 6.9 Hz, 3H), 1.15 (t, *J* = 6.9 Hz, 3H), 1.10 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4 (C), 164.8 (C), 164.1 (C), 159.3 (C), 143.6 (C), 137.2 (CH), 136.6 (C), 130.8 (CH), 129.3 (CH), 127.4 (CH), 127.1 (C), 126.1 (C), 113.6 (CH), 74.5 (C), 63.4 (CH_2), 63.2 (CH_2), 61.8 (CH_2), 55.1 (CH_3), 47.4 (CH), 21.4 (CH_3), 13.8 (CH_3), 13.7 (CH_3); HRMS (ESI) *m/z* 582.1565 $[M+H]^+$, $C_{27}H_{32}ClNO_9S$ requires 582.1559.

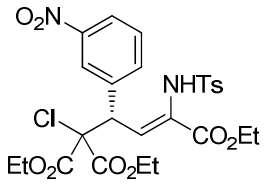
(*S*,*Z*)-Triethyl 1-chloro-2-(3-chlorophenyl)-4-(4-methylphenylsulfonamido)but-3-ene-1,1,4-tricarboxylate, (*S*,*Z*)-22ef



Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 85:15, 0.7 mL/min, *E*-isomer: *major enantiomer* t_r = 33.3 min, *minor enantiomer* t_r = 25.4 min. *Z*-isomer: *major enantiomer* t_r = 27.6 min, *minor enantiomer* t_r = 39.7 min.

White oil; $[\alpha]_D^{20}$ -31.6 (*c* 1.0, $CHCl_3$, ee = 82% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (dt, *J* = 8.1, 1.8 Hz, 2H), 7.25-7.20 (m, 6H), 7.17 (d, *J* = 9.6 Hz, 1H), 6.59 (s, 1H), 5.11 (d, *J* = 9.9 Hz, 1H), 4.29 (q, *J* = 6.9 Hz, 2H), 4.27 (q, *J* = 7.2 Hz, 1H), 4.12 (q, *J* = 7.2 Hz, 1H), 4.10 (q, *J* = 7.2 Hz, 1H), 4.01 (q, *J* = 6.9 Hz, 2H), 2.38 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H), 1.11 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0 (C), 164.6 (C), 163.9 (C), 143.8 (C), 137.3 (C), 136.4 (C), 136.2 (CH), 133.8 (C), 129.8 (CH), 129.4 (CH), 129.3 (C), 128.4 (CH), 128.2 (CH), 127.4 (CH), 127.0 (CH), 74.0 (C), 63.54 (CH_2), 63.46 (CH_2), 62.0 (CH_2), 47.7 (CH_3), 21.5 (CH_3), 13.8 (CH_3), 13.70 (CH_3), 13.68 (CH_3); HRMS (ESI) *m/z* 586.1067 $[M+H]^+$, $C_{26}H_{29}Cl_2NO_8S$ requires 586.1064.

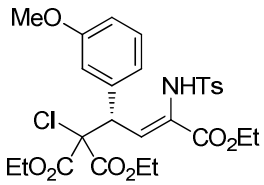
(*S*,*Z*)-Triethyl 1-chloro-4-(4-methylphenylsulfonamido)-2-(3-nitrophenyl)but-3-ene-1,1,4-tricarboxylate, (*S*,*Z*)-22eg



Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 80:20, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 28.0 min, *minor enantiomer* t_r = 20.2 min. *Z*-isomer: *major enantiomer* t_r = 17.3 min, *minor enantiomer* t_r = 24.2 min.

Yellow oil; $[\alpha]_D^{20}$ -59.0 (*c* 1.0, $CHCl_3$, *ee* = 87% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (t, *J* = 2.1 Hz, 1H), 8.15 (dq, *J* = 8.1, 2.4, 1.2 Hz, 1H), 7.75 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.55 (dt, *J* = 8.4, 1.8 Hz, 2H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 9.3 Hz, 1H), 7.20 (dd, *J* = 8.4, 0.9 Hz, 1H), 6.42 (s, 1H), 5.43 (d, *J* = 9.6 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 1H), 3.98 (q, *J* = 7.2 Hz, 1H), 3.97 (q, *J* = 6.9 Hz, 1H), 2.36 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.08 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5 (C), 164.5 (C), 163.5 (C), 147.8 (C), 144.1 (C), 137.6 (C), 136.7 (CH), 136.1 (CH), 135.9 (C), 129.4 (CH), 128.9 (CH), 127.4 (CH), 127.3 (C), 124.6 (CH), 123.1 (CH), 73.8 (C), 63.6 (CH_2), 62.2 (CH_2), 47.7 (CH_3), 21.4 (CH_3), 13.8 (CH_3), 13.7 (CH_3); HRMS (ESI) *m/z* 597.1308 $[M+H]^+$, $C_{26}H_{29}ClN_2O_{10}S$ requires 597.1304.

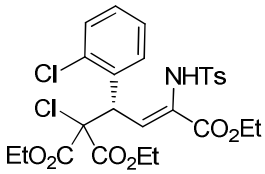
(*S*,*Z*)-Triethyl 1-chloro-2-(3-methoxyphenyl)-4-(4-methylphenylsulfonamido)but-3-ene-1,1,4-tricarboxylate, (*S*,*Z*)-22eh



Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 90:10, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 53.5 min, *minor enantiomer* t_r = 39.6 min. *Z*-isomer: *major enantiomer* t_r = 31.9 min, *minor enantiomer* t_r = 50.0 min.

Yellow oil; $[\alpha]_D^{20}$ -8.7 (*c* 0.98, $CHCl_3$, *ee* = 85% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (dt, *J* = 8.1, 1.8 Hz, 2H), 7.20 (dd, *J* = 8.1, 0.9 Hz, 2H), 7.18 (td, *J* = 7.2, 0.9 Hz, 1H), 7.17 (d, *J* = 9.9 Hz, 1H), 6.88-6.84 (m, 3H), 6.65 (s, 1H), 5.03 (d, *J* = 9.9 Hz, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 4.26 (q, *J* = 7.2 Hz, 1H), 4.10 (q, *J* = 6.9 Hz, 1H), 4.07 (q, *J* = 7.2 Hz, 1H), 4.01 (q, *J* = 7.2 Hz, 1H), 3.78 (s, 3H), 2.38 (s, 3H), 1.27 (t, *J* = 6.9 Hz, 3H), 1.14 (t, *J* = 7.2 Hz, 3H), 1.11 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3 (C), 164.8 (C), 164.1 (C), 159.2 (C), 143.7 (C), 136.8 (CH), 136.64 (C), 136.58 (C), 129.3 (CH), 129.1 (CH), 127.4 (CH), 126.6 (C), 122.0 (CH), 115.9 (CH), 113.3 (CH), 74.2 (C), 63.4 (CH_2), 63.3 (CH_2), 61.8 (CH_2), 55.2 (CH_3), 48.0 (CH), 21.4 (CH_3), 13.9 (CH_3), 13.7 (CH_3), 13.6 (CH_3); HRMS (ESI) *m/z* 582.1566 $[M+H]^+$, $C_{27}H_{32}ClNO_9S$ requires 582.1559.

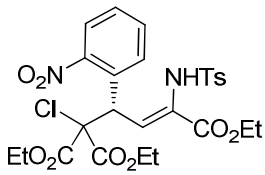
(*S*,*Z*)-Triethyl 1-chloro-2-(2-chlorophenyl)-4-(4-methylphenylsulfonamido)but-3-ene-1,1,4-tricarboxylate, (*S*,*Z*)-22ei



Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 90:10, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 46.1 min, *minor enantiomer* t_r = 54.4 min. *Z*-isomer: *major enantiomer* t_r = 50.3 min, *minor enantiomer* t_r = 71.5 min.

Colorless oil; $[\alpha]_D^{20}$ -37.1 (*c* 0.97, $CHCl_3$, *ee* = 88% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (dt, *J* = 8.4, 1.8 Hz, 2H), 7.65-7.62 (m, 1H), 7.35-7.32 (m, 1H), 7.23-7.20 (m, 4H), 6.99 (s, 1H), 6.94 (d, *J* = 9.9 Hz, 1H), 5.74 (d, *J* = 9.6 Hz, 1H), 4.34 (q, *J* = 7.2 Hz, 1H), 4.30 (q, *J* = 7.2 Hz, H), 4.12 (q, *J* = 7.2 Hz, 1H), 4.06-3.96 (m, 3H), 2.38 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.11 (t, *J* = 6.9Hz, 3H), 1.09 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6 (C), 164.6 (C), 163.9 (C), 143.3 (C), 137.7 (C), 134.8 (C), 133.7 (C), 133.4 (CH), 130.1 (CH), 129.9 (CH), 129.2 (CH), 127.8 (C), 127.2 (CH), 126.8 (CH), 73.9 (C), 63.7 (CH_2), 63.5 (CH_2), 61.7 (CH_2), 43.0 (CH), 21.5 (CH_3), 13.8 (CH_3), 13.7 (CH_3), 13.5 (CH_3); HRMS (ESI) *m/z* 586.1060 $[M+H]^+$, $C_{26}H_{29}Cl_2NO_8S$ requires 586.1064.

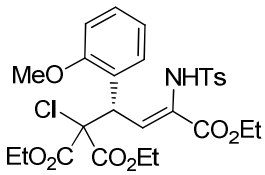
(*S*,*Z*)-Triethyl 1-chloro-4-(4-methylphenylsulfonamido)-2-(2-nitrophenyl)but-3-ene-1,1,4-tricarboxylate, (*S*,*Z*)-22ej



Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 80:20, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 21.5 min, *minor enantiomer* t_r = 18.8 min. *Z*-isomer: *major enantiomer* t_r = 41.1 min, *minor enantiomer* t_r = 53.0 min.

Orange oil; $[\alpha]_D^{20}$ - 37.1 (*c* 0.96, $CHCl_3$, *ee* = 88% *for the major diastereomer*); ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.75 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.61-7.55 (m, 3H), 7.46 (ddd, *J* = 8.1, 7.2, 1.5 Hz, 1H), 7.17 (dd, *J* = 8.1, 0.9 Hz, 2H), 6.97 (d, *J* = 8.7 Hz, 1H), 6.92 (s, 1H), 5.98 (d, *J* = 8.7 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 1H), 4.30 (q, *J* = 7.2 Hz, 1H), 4.18-3.96 (m, 4H), 2.35 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.14 (t, *J* = 7.2 Hz, 3H), 1.12 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5 (C), 164.8 (C), 163.6 (C), 150.1 (C), 143.5 (C), 137.1 (C), 132.5 (CH), 131.5 (CH), 130.7 (C), 130.3 (CH), 129.3 (C), 129.1 (CH), 128.9 (CH), 127.2 (CH), 125.0 (CH), 73.9 (C), 63.8 (CH_2), 63.7 (CH_2), 61.9 (CH_2), 40.7 (CH), 21.4 (CH_3), 13.8 (CH_3), 13.7 (CH_3), 13.5 (CH_3); HRMS (ESI) *m/z* 597.1316 $[M+H]^+$, $C_{26}H_{29}ClN_2O_{10}S$ requires 597.1304.

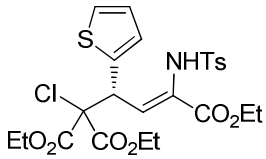
(*S*,*Z*)-Triethyl 1-chloro-2-(2-methoxyphenyl)-4-(4-methylphenylsulfonamido)but-3-ene-1,1,4-tricarboxylate, (*S*,*Z*)-22ek



Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 80:20, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 27.4 min, *minor enantiomer* t_r = 22.1 min. *Z*-isomer: *major enantiomer* t_r = 12.4 min, *minor enantiomer* t_r = 31.4 min.

Yellow oil; $[\alpha]_D^{20}$ -25.2 (*c* 0.98, $CHCl_3$, *ee* = 87% *for the major diastereomer*); ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (dt, *J* = 8.4, 1.8 Hz, 2H), 7.43 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.24-7.20 (m, 3H), 7.03 (s, 1H), 7.02 (d, *J* = 10.2 Hz, 1H), 6.89 (td, *J* = 7.2, 1.2 Hz 1H), 5.55 (d, *J* = 9.9 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 1H), 4.28 (q, *J* = 6.9 Hz, 1H), 4.07 (q, *J* = 7.2 Hz, 1H), 4.030 (q, *J* = 7.2 Hz, 1H), 4.027 (q, *J* = 7.2 Hz, 2H), 3.83 (s, 3H), 2.38 (s, 3H), 1.28 (t, *J* = 6.9 Hz, 3H), 1.11 (t, *J* = 7.2 Hz, 3H), 1.08 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5 (C), 165.2 (C), 164.1 (C), 156.9 (C), 143.1 (C), 138.0 (C), 134.3 (CH), 129.8 (CH), 129.2 (CH), 129.1 (CH), 127.2(CH), 127.0 (C), 124.1 (C), 120.5 (CH), 110.8 (CH), 73.7 (C), 63.3 (CH_2), 63.1 (CH_2), 61.5 (CH_2), 55.6 (CH_3), 40.6 (CH), 21.5 (CH_3), 13.8 (CH_3), 13.7 (CH_3), 13.5 (CH_3); HRMS (ESI) *m/z* 582.1560 $[M+H]^+$, $C_{27}H_{32}ClNO_9S$ requires 582.1559.

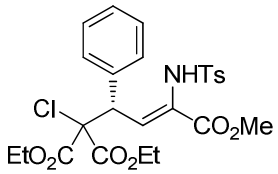
(*S*,*Z*)-Triethyl 1-chloro-4-(4-methylphenylsulfonamido)-2-(thiophen-2-yl)but-3-ene-1,1,4-tricarboxylate, (*S*,*Z*)-22em



Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 90:10, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 70.0 min, *minor enantiomer* t_r = 41.7 min. *Z*-isomer: *major enantiomer* t_r = 32.9 min, *minor enantiomer* t_r = 58.9 min.

Yellow oil; $[\alpha]_D^{20}$ -30.4 (*c* 0.98, $CHCl_3$, *ee* = 84% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (dt, *J* = 8.4, 1.8 Hz, 2H), 7.24 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.20 (dd, *J* = 8.7, 0.9 Hz, 2H), 7.12 (d, *J* = 9.9 Hz, 1H), 7.01 (dq, *J* = 3.6, 0.6 Hz, 1H), 6.93 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.52 (s, 1H), 5.54 (d, *J* = 9.9 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 1H), 4.18 (q, *J* = 6.9 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 1H), 3.99 (q, *J* = 7.2 Hz, 2H), 2.37 (s, 3H), 1.28 (t, *J* = 6.9 Hz, 3H), 1.21 (t, *J* = 6.9 Hz, 3H), 1.09 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8 (C), 164.6 (C), 163.9 (C), 143.8 (C), 136.4 (C), 136.24 (C), 136.21 (CH), 129.3 (CH), 128.4 (CH), 127.5 (CH), 126.4 (C), 126.2 (CH), 125.9 (CH), 74.3 (C), 63.5 (CH_2), 63.4 (CH_2), 61.9 (CH_2), 44.4 (CH_3), 21.4 (CH_3), 13.8 (CH_3), 13.7 (CH_3); HRMS (ESI) *m/z* 558.1019 $[M+H]^+$, $C_{24}H_{28}ClNO_8S_2$ requires 558.1018.

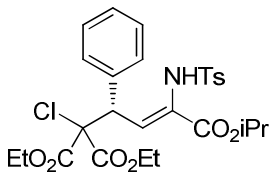
(*S*,*Z*)-1,1-Diethyl 4-methyl 1-chloro-4-(4-methylphenylsulfonamido)-2-phenylbut-3-ene-1,1,4-tricarboxylate, (*S*,*Z*)-22en



Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 26.5 min, *minor enantiomer* t_r = 16.1 min. *Z*-isomer: *major enantiomer* t_r = 14.1 min, *minor enantiomer* t_r = 19.3 min.

Pale yellow oil; $[\alpha]_D^{20}$ -31.9 (*c* 0.98, $CHCl_3$, *ee* = 83% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (dt, *J* = 8.4, 2.1 Hz, 2H), 7.25 (s,5H), 7.20 (dd, *J* = 8.4, 0.6 Hz, 2H), 7.19 (d, *J* = 9.9 Hz, 1H), 6.75 (s, 1H), 5.00 (d, *J* = 9.9 Hz, 1H), 4.34-4.21 (m, 2H), 4.11-3.99 (m, 2H), 3.57 (s, 3H), 2.39 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.12 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4 (C), 164.7 (C), 164.6 (C), 143.6 (C), 136.9 (CH), 136.6 (C), 135.1 (C), 129.6 (CH), 129.4 (CH), 128.2 (CH), 127.4 (CH), 126.4 (C), 74.2 (C), 63.5 (CH_2), 63.3 (CH_2), 52.5 (CH_3), 48.1 (CH), 21.5 (CH_3), 13.7 (CH_3), 13.6 (CH_3); HRMS (ESI) *m/z* 538.1298 $[M+H]^+$, $C_{25}H_{28}ClNO_8S$ requires 538.1297.

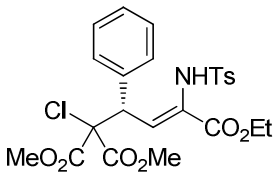
(*S*,*Z*)-1,1-Diethyl 4-isopropyl (Z)-1-chloro-4-((4-methylphenyl)sulfonamido)-2-phenylbut-3-ene-1,1,4-tricarboxylate, (*S*,*Z*)-22eo



Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 80:20, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 16.0 min, *minor enantiomer* t_r = 11.9 min. *Z*-isomer: *major enantiomer* t_r = 10.4 min, *minor enantiomer* t_r = 28.7 min.

Yellow oil; $[\alpha]_D^{20}$ -30.8 (*c* 0.96, $CHCl_3$, *ee* = 92% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (dt, *J* = 8.4, 1.8 Hz, 2H), 7.28-7.26 (m, 5H), 7.21 (d, *J* = 9.9 Hz, 1H), 7.19 (dd, *J* = 8.7, 0.9 Hz, 2H), 6.59 (s, 1H), 5.13 (d, *J* = 9.9 Hz, 1H), 4.82 (quint, *J* = 6.3 Hz, 1H), 4.30 (q, *J* = 7.2 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 1H), 4.08 (q, *J* = 7.2 Hz, 1H), 4.06 (q, *J* = 6.9 Hz, 1H), 2.37 (s, 3H), 1.28 (t, *J* = 6.9 Hz, 3H), 1.14 (t, *J* = 7.2 Hz, 3H), 1.10 (d, *J* = 6.6 Hz, 3H), 1.08 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3 (C), 164.8 (C), 163.6 (C), 143.6 (C), 136.7 (CH), 136.5 (C), 135.4 (C), 129.8 (CH), 129.4 (CH), 128.1 (CH), 127.5 (CH), 126.7 (C), 74.4 (C), 69.8 (CH), 63.4 (CH_2), 63.3 (CH_2), 48.1 (CH), 21.44 (CH_3), 21.40 (CH_3), 21.3 (CH_3), 13.72 (CH_3), 13.66 (CH_3); HRMS (ESI) *m/z* 566.1612 $[M+H]^+$, $C_{27}H_{32}ClNO_8S$ requires 566.1610.

(*S*,*Z*)-4-Ethyl 1,1-dimethyl 1-chloro-4-(4-methylphenylsulfonamido)-2-phenylbut-3-ene-1,1,4-tricarboxylate, (*S*,*Z*)-22fa



Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 80:20, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 24.9 min, *minor enantiomer* t_r = 16.0 min. *Z*-isomer: *major enantiomer* t_r = 17.0 min, *minor enantiomer* t_r = 21.4 min.

Colorless oil; $[\alpha]_D^{20}$ -35.4 (*c* 0.98, $CHCl_3$, *ee* = 84% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (dt, *J* = 8.1, 1.8 Hz, 2H), 7.27-7.25 (m, 5H), 7.24 (d, *J* = 9.9 Hz, 1H), 7.18 (dd, *J* = 8.7, 0.9 Hz, 2H), 6.65 (s, 1H), 5.15 (d, *J* = 9.9 Hz, 1H), 3.98 (q, *J* = 7.2 Hz, 2H), 3.81 (s, 3H), 3.61 (s, 3H), 2.36 (s, 3H), 1.09 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7 (C), 165.3 (C), 164.0 (C), 143.7 (C), 137.1 (CH), 136.4 (C), 135.2 (C), 129.7 (CH), 129.4 (CH), 128.3 (CH), 128.2 (CH), 127.5 (CH), 126.6 (C), 74.2 (C), 61.9 (CH_2), 54.1 (CH_3), 53.8 (CH_3), 48.2 (CH), 21.5 (CH_3), 13.9 (CH_3); HRMS (ESI) *m/z* 524.1143 $[M+H]^+$, $C_{24}H_{26}ClNO_8S$ requires 524.1140.

5.5.2. Enantioselective conjugate addition of diethyl 2-chloromalonate to α,β-unsaturated *N*-tosyl imino esters catalyzed by $Ca(OTf)_2$.

5.5.2.1. General procedure for the enantioselective conjugate addition

$Ca(OTf)_2$ (2.1 mg, 0.00625 mmol) was dried in a Schlenk tube under vacuum. **pyBOX1** (2.3 mg, 0.00625 mmol) was added and the tube was filled with nitrogen. CH_2Cl_2 (0.55 mL) was added via syringe and the mixture was stirred for 30 min. A solution of imine **17** (0.25 mmol) dissolved in dry CH_2Cl_2 (0.5 mL) was added via syringe followed by 4 Å MS (110 mg), and the mixture was introduced in an ice bath. After 10 minutes, diethyl 2-chloromalonate (32 μL, 0.187 mmol) was added to the reaction. The mixture was stirred at 0º C for the indicated time and chromatographed on silica gel eluting with hexane/EtOAc mixtures to give compound (*E*)-**22**.

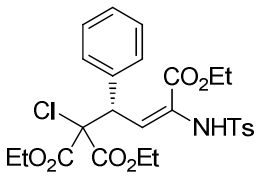
5.5.2.2. General procedure for the synthesis of the racemic products

Racemic compounds for comparative purpose were prepared by following the same procedure, using $La(OTf)_3$ in absence of chiral ligand and performing the reaction at room temperature.

5.5.2.3. Characterization of products (S,E)-22

See Table 19 (Page 97) for yield, dr and ee.

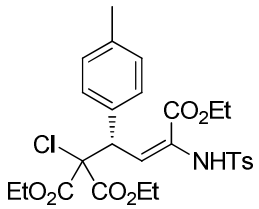
(*S*,*E*)-Triethyl 1-chloro-4-(4-methylphenylsulfonamido)-2-phenylbut-3-ene-1,1,4-tricarboxylate, (*S*,*E*)-22ea



Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 22.2 min, *minor enantiomer* t_r = 15.4 min. *Z*-isomer: *major enantiomer* t_r = 14.1 min, *minor enantiomer* t_r = 28.4 min.

White solid; mp 75-77 ºC; $[\alpha]_D^{20}$ 60.7 (*c* 1.00, $CHCl_3$, *ee* = 97% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (dt, *J* = 8.4, 1.8 Hz, 2H), 7.31-7.25 (m, 5H), 7.12 (d, *J* = 10.2 Hz, 1H), 7.09 (dd, *J* = 7.8, 0.9 Hz, 2H), 6.63 (s, 1H), 5.62 (d, *J* = 10.5 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 4.07 (q, *J* = 7.2 Hz, 1H), 4.06 (q, *J* = 6.9 Hz, 1H), 4.03 (q, *J* = 7.2 Hz, 2H), 2.34 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.12 (t, *J* = 6.9 Hz, 3H), 1.11 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7 (C), 165.1 (C), 162.6 (C), 143.7 (C), 136.8 (C), 135.7(C), 132.8 (CH), 129.8 (CH), 129.4 (CH), 128.1 (CH), 127.9 (CH), 127.6 (CH), 124.9 (C), 74.4 (C), 63.1 (CH_2), 63.0 (CH_2), 62.0 (CH_2), 48.2 (CH), 21.4 (CH_3), 13.9 (CH_3), 13.7 (CH_3), 13.6 (CH_3); HRMS (ESI) *m/z* 552.1456 $[M+H]^+$, $C_{26}H_{30}ClNO_8S$ requires 552.1453.

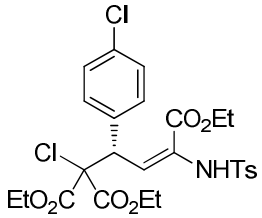
(*S*,*E*)-Triethyl 1-chloro-4-(4-methylphenylsulfonamido)-2-(p-tolyl)but-3-ene-1,1,4-tricarboxylate, (*S*,*E*)-22eb



Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 90:10, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 46.5 min, *minor enantiomer* t_r = 27.9 min. *Z*-isomer: *major enantiomer* t_r = 24.4 min, *minor enantiomer* t_r = 41.3 min.

Pale yellow oil; $[\alpha]_D^{20}$ 70.6 (*c* 0.98, $CHCl_3$, *ee* = 98% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (dt, *J* = 8.4, 1.8 Hz, 2H), 7.16 (dt, *J* = 8.1, 1.8 Hz, 2H), 7.12-7.05 (m, 4H), 7.10 (d, *J* = 10.2 Hz, 1H), 6.64 (s, 1H), 5.59 (d, *J* = 10.2 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 4.09 (q, *J* = 7.2 Hz, 1H), 4.07 (q, *J* = 7.2 Hz, 1H), 4.023 (q, *J* = 7.2 Hz, 1H), 4.022 (q, *J* = 7.2 Hz, 1H), 2.35 (s, 3H), 2.30 (s, 3H), 1.23 (t, *J* = 6.9 Hz, 3H), 1.14 (t, *J* = 7.2 Hz, 3H), 1.12 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7 (C), 165.1 (C), 162.6 (C), 143.6 (C), 137.6 (C), 135.7 (C), 133.7 (C), 132.9 (CH), 129.5 (CH), 129.3 (CH), 128.8 (CH), 127.6 (CH), 124.6 (C), 74.5 (C), 63.1 (CH_2), 62.9 (CH_2), 61.9 (CH_2), 47.7 (CH), 21.4 (CH_3), 21.0 (CH_3), 13.8 (CH_3), 13.69 (CH_3), 13.67 (CH_3); HRMS (ESI) *m/z* 566.1616 $[M+H]^+$, $C_{27}H_{32}ClNO_8S$ requires 566.1610.

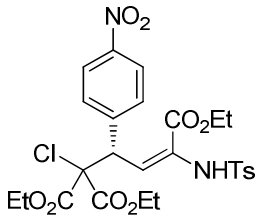
(*S*,*E*)-Triethyl 1-chloro-2-(4-chlorophenyl)-4-(4-methylphenylsulfonamido)but-3-ene-1,1,4-tricarboxylate, (*S*,*E*)-22ec



Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 95:05, 1.6 mL/min, *E*-isomer: *major enantiomer* t_r = 95.9 min, *minor enantiomer* t_r = 61.2 min. *Z*-isomer: *major enantiomer* t_r = 52.3 min, *minor enantiomer* t_r = 73.5 min.

White; mp 87-88 ºC; $[\alpha]_D^{20}$ 77.8 (*c* 1.0, $CHCl_3$, *ee* = 98% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (dt, *J* = 8.4, 1.8 Hz, 2H), 7.23 (s, 4H), 7.13 (dd, *J* = 8.4, 0.9 Hz, 2H), 7.03 (d, *J* = 10.2 Hz, 1H), 6.65 (s, 1H), 5.60 (d, *J* = 10.2 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 4.10 (q, *J* = 7.2 Hz, 1H), 4.09 (q, *J* = 7.2 Hz, 1H), 4.03 (q, *J* = 7.2 Hz, 2H), 2.36 (s, 3H), 1.23 (t, *J* = 6.9 Hz, 3H), 1.14 (t, *J* = 7.2 Hz, 3H), 1.12 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5 (C), 165.0 (C), 162.3 (C), 143.9 (C), 135.8 (C), 135.4 (C), 133.9 (C), 131.9 (CH), 131.2 (CH), 129.4 (CH), 128.2 (CH), 127.5 (CH), 125.2 (C), 74.1 (C), 63.3 (CH_2), 63.2 (CH_2), 62.1 (CH_2), 47.5 (CH_3), 21.5 (CH_3), 13.9 (CH_3), 13.7(CH_3); HRMS (ESI) *m/z* 586.1056 $[M+H]^+$, $C_{26}H_{29}Cl_2NO_8S$ requires 586.1064.

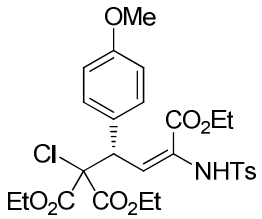
(*S*,*E*)-Triethyl 1-chloro-4-(4-methylphenylsulfonamido)-2-(4-nitrophenyl)but-3-ene-1,1,4-tricarboxylate, (*S*,*E*)-22ed



Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 80:20, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 34.2 min, *minor enantiomer* t_r = 21.1 min. *Z*-isomer: *major enantiomer* t_r = 27.6 min, *minor enantiomer* t_r = 43.5 min.

Yellow solid; Mp 128-129 ºC; $[\alpha]_D^{20}$ 44.8 (*c* 1.0, $CHCl_3$, *ee* = 97% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (dt, *J* = 9.0, 2.1 Hz, 2H), 7.57 (dt, *J* = 8.4, 2.1 Hz, 2H), 7.44 (dt, *J* = 8.7, 1.8 Hz, 2H), 7.17 (dt, *J* = 8.7, 0.9 Hz, 2H), 6.98 (d, *J* = 9.9 Hz, 1H), 6.76 (s, 1H), 5.70 (d, *J* = 9.9 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.11 (q, *J* = 7.2 Hz, 1H), 4.10 (q, *J* = 7.2 Hz, 1H), 4.04 (q, *J* = 7.2 Hz, 2H), 2.37 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.15 (t, *J* = 7.2 Hz, 3H), 1.12 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1 (C), 164.8 (C), 161.9 (C), 147.2 (C), 144.4 (C), 144.1 (C), 135.8 (C), 130.9 (CH), 129.8 (CH), 129.5 (CH), 127.5 (CH), 126.1 (C), 123.0 (CH), 73.7 (C), 63.5 (CH_2), 63.4 (CH_2), 62.2 (CH_2), 47.8 (CH_3), 21.4 (CH_3), 13.8 (CH_3), 13.7 (CH_3); HRMS (ESI) *m/z* 597.1281 $[M+H]^+$, $C_{26}H_{29}ClN_2O_{10}S$ requires 597.1304.

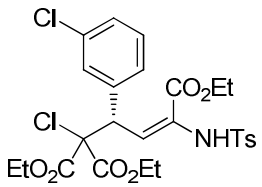
(*S*,*E*)-Triethyl 1-chloro-2-(4-methoxyphenyl)-4-(4-methylphenylsulfonamido)but-3-ene-1,1,4-tricarboxylate, (*S*,*E*)-22ee



Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 28.7 min, *minor enantiomer* t_r = 23.1 min. *Z*-isomer: *major enantiomer* t_r = 18.1 min, *minor enantiomer* t_r = 34.7 min.

Yellow oil; $[\alpha]_D^{20}$ 84.2 (*c* 0.95, $CHCl_3$, *ee* = 98% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (dt, *J* = 8.4, 1.8 Hz, 2H), 7.22 (dt, *J* = 9.0, 3.0 Hz, 2H), 7.12 (dd, *J* = 8.4, 0.9 Hz, 2H), 7.09 (d, *J* = 10.5 Hz, 1H), 6.80 (dt, *J* = 8.7, 3.3 Hz, 2H), 6.60 (s, 1H), 5.59 (d, *J* = 10.5 Hz, 1H), 4.19 (q, *J* = 6.9 Hz, 2H), 4. 09 (q, *J* = 7.2 Hz, 1H), 4.08 (q, *J* = 7.2 Hz, 1H), 4.03 (q, *J* = 7.2 Hz, 2H), 3.78 (s, 3H), 2.35 (s, 3H), 1.23 (t, *J* = 6.9 Hz, 3H), 1.14 (t, *J* = 6.9 Hz, 3H), 1.13 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7 (C), 165.2 (C), 162.6 (C), 159.2 (C), 143.7 (C), 135.8 (C), 133.3 (CH), 130.9 (CH), 129.4 (CH), 128.8 (CH), 127.6 (CH), 124.6 (C), 113.5 (CH), 74.6 (C), 63.1 (CH_2), 63.0 (CH_2), 61.9(CH_2), 55.2 (CH_3), 47.3 (CH), 21.5 (CH_3), 13.9 (CH_3), 13.7 (CH_3); HRMS (ESI) *m/z* 582.1547 $[M+H]^+$, $C_{27}H_{32}ClNO_9S$ requires 582.1559.

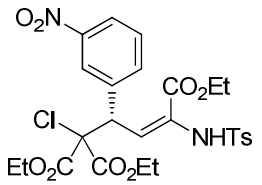
(*S*,*E*)-Triethyl 1-chloro-2-(3-chlorophenyl)-4-(4-methylphenylsulfonamido)but-3-ene-1,1,4-tricarboxylate, (*S*,*E*)-22ef



Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 85:15, 0.7 mL/min, *E*-isomer: *major enantiomer* t_r = 39.2 min, *minor enantiomer* t_r = 29.8 min. *Z*-isomer: *major enantiomer* t_r = 27.9 min, *minor enantiomer* t_r = 33.6 min.

Colorless oil; $[\alpha]_D^{20}$ 44.5 (*c* 1.0, $CHCl_3$, *ee* = 96% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (dt, *J* = 8.4, 1.8 Hz, 2H), 7.25-7.18 (m, 4H), 7.15 (dd, *J* = 8.4, 0.6 Hz, 2H), 7.01 (d, *J* = 10.2 Hz, 1H), 6.71 (s, 1H), 5.57 (d, *J* = 10.2 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.11 (q, *J* = 7.2 Hz, 1H), 4.10 (q, *J* = 6.9 Hz, 1H), 4.05 (q, *J* = 6.9 Hz, 2H), 2.36 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.15 (t, *J* = 6.9 Hz, 3H), 1.13 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4 (C), 164.9 (C), 162.3 (C), 143.9 (C), 138.9 (C), 135.7 (C), 133.7 (C), 131.1 (C), 130.0 (CH), 129.4 (CH), 129.3 (CH), 128.0 (CH), 127.9 (CH), 127.5 (CH), 125.4 (C), 74.1 (C), 63.3 (CH_2), 63.2 (CH_2), 62.1 (CH_2), 47.8 (CH_3), 21.4 (CH_3), 13.8 (CH_3), 13.69 (CH_3), 13.68 (CH_3); HRMS (ESI) *m/z* 586.1057 $[M+H]^+$, $C_{26}H_{29}Cl_2NO_8S$ requires 586.1064.

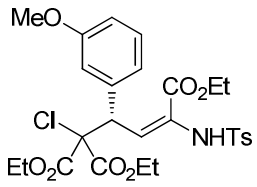
(*S*,*E*)-Triethyl 1-chloro-4-(4-methylphenylsulfonamido)-2-(3-nitrophenyl)but-3-ene-1,1,4-tricarboxylate, (*S*,*E*)-22eg



Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 80:20, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 27.6 min, *minor enantiomer* t_r = 20.0 min. *Z*-isomer: *major enantiomer* t_r = 17.9 min, *minor enantiomer* t_r = 24.5 min.

Yellow solid; Mp 94-96 ºC; $[\alpha]_D^{20}$ 2.6 (*c* 1.0, $CHCl_3$, *ee* = 93% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 -8.08 (m, 2H), 7.67 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.60 (dt, *J* = 8.4, 1.8 Hz, 2H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.17 (dd, *J* = 8.7, 0.6 Hz, 2H), 6.99 (d, *J* = 9.9 Hz, 1H), 6.78 (s, 1H), 5.70 (d, *J* = 9.9 Hz, 1H), 4.212 (q, *J* = 7.2 Hz, 2H), 4.21 (q, *J* = 7.2 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 1H), 4.06 (q, *J* = 7.2 Hz, 2H), 2.36 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H), 1.15 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2 (C), 165.1 (C), 162.2 (C), 149.4 (C), 144.0 (C), 135.6 (C), 132.4 (CH), 132.3 (C), 131.8 (CH), 129.5 (CH), 128.6 (CH), 128.4 (CH), 127.4 (CH), 126.5 (C), 124.5 (CH), 74.1 (C), 63.3 (CH_2), 63.2 (CH_2), 62.5 (CH_2), 40.9 (CH_3), 21.4 (CH_3), 13.8 (CH_3), 13.7 (CH_3), 13.4 (CH_3); HRMS (ESI) *m/z* 597.1302 $[M+H]^+$, $C_{26}H_{29}ClN_2O_{10}S$ requires 597.1304.

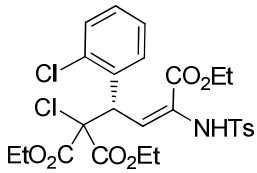
(*S*,*E*)-Triethyl 1-chloro-2-(3-methoxyphenyl)-4-(4-methylphenylsulfonamido)but-3-ene-1,1,4-tricarboxylate, (*S*,*E*)-22eh



Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 90:10, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 53.3 min, *minor enantiomer* t_r = 40.5 min. *Z*-isomer: *major enantiomer* t_r = 34.1 min, *minor enantiomer* t_r = 51.3 min.

Yellow solid; Mp 66-67 ºC; $[\alpha]_D^{20}$ 76.9 (*c* 1.0, $CHCl_3$, *ee* = 96% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (dt, *J* = 8.4, 1.8 Hz, 2H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.10 (dd, *J* = 8.4, 0.9 Hz, 2H), 7.09 (d, *J* = 10.2 Hz, 1H), 6.88-6.80 (m, 3H), 6.63 (s, 1H), 5.61(d, *J* = 10.5 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 4.10 (q, *J* = 7.2 Hz, 1H), 4.08 (q, *J* = 7.2 Hz, 1H), 4.029 (q, *J* = 7.2 Hz, 1H), 4.027 (q, *J* = 7.2 Hz, 1H), 3.78 (s, 3H), 2.34 (s, 3H), 1.23 (t, *J* = 6.9 Hz, 3H), 1.13 (t, *J* = 7.2 Hz, 3H), 1.12 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7 (C), 165.1 (C), 162.6 (C), 159.8 (C), 143.7 (C), 138.1 (C), 135.8 (C), 132.8 (CH), 129.4 (CH), 129.0 (CH), 127.5 (CH), 124.9 (C), 122.1 (CH), 115.5 (CH), 113.0 (CH), 74.4 (C), 63.1 (CH_2), 63.0 (CH_2), 62.0 (CH_2), 55.1 (CH_3), 48.0 (CH), 21.4 (CH_3), 13.9 (CH_3), 13.70 (CH_3), 13.67 (CH_3); HRMS (ESI) *m/z* 582.1545 $[M+H]^+$, $C_{27}H_{32}ClNO_9S$ requires 582.1559.

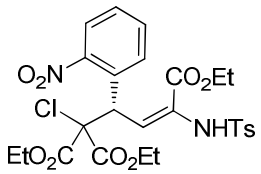
(*S*,*E*)-Triethyl 1-chloro-2-(2-chlorophenyl)-4-(4-methylphenylsulfonamido)but-3-ene-1,1,4-tricarboxylate, (*S*,*E*)-22ei



Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 90:10, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 52.9 min, *minor enantiomer* t_r = 47.9 min. *Z*-isomer: *major enantiomer* t_r = 73.5 min, *minor enantiomer* t_r = 51.6 min.

White solid; Mp 73-75 ºC; $[\alpha]_D^{20}$ 2.7 (*c* 0.97, $CHCl_3$, *ee* = 98% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 6.3, 1.5 Hz, 1H), 7.52 (dt, *J* = 8.4, 1.8 Hz, 2H), 7.33-7.30 (m, 1H), 7.24-7.20 (m, 2H), 7.12 (dd, *J* = 8.4, 0.9 Hz, 2H), 6.74 (s, 1H), 6.13 (d, *J* = 10.2 Hz, 1H), 4.24- 3.99 (m, 6H), 2.35 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.11 (t, *J* = 7.2 Hz, 3H), 1.09 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5 (C), 165.0 (C), 162.7 (C), 143.8 (C), 135.7 (C), 135.1 (C), 134.3 (C), 131.3 (CH), 130.0 (CH), 129.40 (CH), 129.38 (CH), 128.9 (CH), 127.5 (CH), 126.7 (CH), 125.8 (C), 74.1 (C), 63.3 (CH_2), 63.1 (CH_2), 62.4 (CH_2), 55.2 (CH_3), 43.2 (CH), 21.4 (CH_3), 13.9 (CH_3), 13.7 (CH_3), 13.5 (CH_3); HRMS (ESI) *m/z* 586.1056 $[M+H]^+$, $C_{26}H_{29}Cl_2NO_8S$ requires 586.1064.

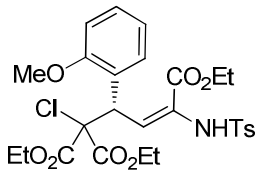
(*S*,*E*)-Triethyl 1-chloro-4-(4-methylphenylsulfonamido)-2-(2-nitrophenyl)but-3-ene-1,1,4-tricarboxylate, (*S*,*E*)-22ej



Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 80:20, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 23.4 min, *minor enantiomer* t_r = 20.4 min. *Z*-isomer: *major enantiomer* t_r = 45.5 min, *minor enantiomer* t_r = 60.1 min.

Orange oil; $[\alpha]_D^{20}$ -117.4 (*c* 1.0, $CHCl_3$, *ee* = 99% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.79 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.59 (td, *J* = 7.5, 1.5 Hz, 1H), 7.49 (dt, *J* = 8.4, 1.8 Hz, 2H), 7.44 (ddd, *J* = 8.1, 7.2, 1.2 Hz, 1H), 7.14 (dd, *J* = 8.7, 0.9 Hz, 2H), 6.92 (d, *J* = 9.9 Hz, 1H), 6.74 (s, 1H), 6.29 (d, *J* = 9.9 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 4.12- 3.98 (m, 4H), 2.36 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.12 (t, *J* = 7.2 Hz, 3H), 1.05(d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2 (C), 165.1 (C), 162.2 (C), 149.4 (C), 144.0 (C), 135.6 (C), 132.4 (CH), 132.3 (C), 131.8 (CH), 129.5 (CH), 128.6 (CH), 128.4 (CH), 127.4 (CH), 126.5 (C), 124.5 (CH), 74.1 (C), 63.3 (CH_2), 63.2 (CH_2), 62.5 (CH_2), 40.9 (CH), 21.4 (CH_3), 13.8 (CH_3), 13.7 (CH_3), 13.4 (CH_3); HRMS (ESI) *m/z* 597.1307 $[M+H]^+$, $C_{26}H_{29}ClN_2O_{10}S$ requires 597.1304.

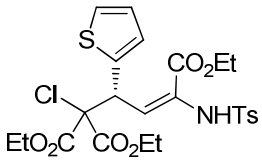
(*S*,*E*)-Triethyl 1-chloro-2-(2-methoxyphenyl)-4-(4-methylphenylsulfonamido)but-3-ene-1,1,4-tricarboxylate, (*S*,*E*)-22ek



Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 80:20, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 26.3 min, *minor enantiomer* t_r = 21.9 min. *Z*-isomer: *major enantiomer* t_r = 12.7 min, *minor enantiomer* t_r = 32.0 min.

Yellow oil; $[\alpha]_D^{20}$ 15.9 (*c* 0.97, $CHCl_3$, *ee* = 95% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (dt, *J* = 8.4, 1.8 Hz, 2H), 7.32 (dd, *J* =7.5, 1.5 Hz, 1H), 7.23 (ddd, *J* = 8.1, 7.5, 1.8 Hz, 1H), 7.12 (dd, *J* = 8.1, 0.9 Hz, 2H), 7.09 (d, *J* = 10.2 Hz, 1H), 6.89 (td, *J* = 7.5, 1.2 Hz 1H), 6.79 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.67 (s, 1H), 5.90 (d, *J* = 9.9 Hz, 1H), 4.17-3.97 (m, 4H), 3.76 (s, 3H), 2.34 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.13 (t, *J* = 6.9 Hz, 3H), 1.06 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8 (C), 165.4 (C), 162.9 (C), 156.8 (C), 143.5 (C), 135.8 (C), 132.4 (CH), 131.2 (CH), 129.3 (CH), 128.8 (CH), 127.6 (CH), 125.6 (C), 124.8 (C), 120.2 (CH), 110.0 (CH), 73.9 (C), 62.8 (CH_2), 62.7 (CH_2), 61.9 (CH_2), 55.2 (CH_3), 41.7 (CH), 21.4 (CH_3), 13.7 (CH_3), 13.69 (CH_3), 13.57 (CH_3); HRMS (ESI) *m/z* 582.1552 $[M+H]^+$, $C_{27}H_{32}ClNO_9S$ requires 582.1559.

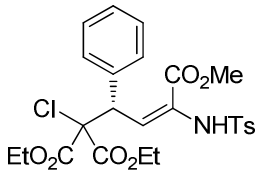
(*S*,*E*)-Triethyl 1-chloro-4-(4-methylphenylsulfonamido)-2-(thiophen-2-yl)but-3-ene-1,1,4-tricarboxylate, (*S*,*E*)-22em



Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 90:10, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 68.7 min, *minor enantiomer* t_r = 42.0 min. *Z*-isomer: *major enantiomer* t_r = 37.5 min, *minor enantiomer* t_r = 63.1 min.

Yellow oil; $[\alpha]_D^{20}$ 64.3 (*c* 1.0, $CHCl_3$, *ee* = 97% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (dt, *J* = 8.4, 2.1 Hz, 2H), 7.21 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.15 (dd, *J* = 8.7, 0.9 Hz, 2H), 7.02 (dq, *J* = 3.9, 0.6 Hz, 1H), 6.94 (d, *J* = 10.5 Hz, 1H), 6.93 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.67 (s, 1H), 6.04 (d, *J* = 10.5 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 4.12 (q, *J* = 7.5 Hz, 2H), 4.11 (q, *J* = 6.9 Hz, 2H), 2.36 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.19 (t, *J* = 7.5 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3 (C), 164.8 (C), 162.7 (C), 143.7 (C), 137.7 (C), 135.7 (C), 130.2 (CH), 129.4 (CH), 127.5 (CH), 126.4 (CH), 125.3 (CH), 125.2 (C), 74.3 (C), 63.3 (CH_2), 63.1 (CH_2), 62.2 (CH_2), 43.9 (CH_3), 21.4 (CH_3), 13.8 (CH_3), 13.7(CH_3); HRMS (ESI) *m/z* 558.1009 $[M+H]^+$, $C_{24}H_{28}ClNO_8S_2$ requires 558.1018.

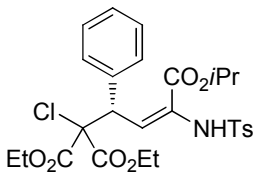
(*S*,*E*)-1,1-Diethyl 4-methyl 1-chloro-4-(4-methylphenylsulfonamido)-2-phenylbut-3-ene-1,1,4-tricarboxylate, (*S*,*E*)-22en



Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 25.9 min, *minor enantiomer* t_r = 16.0 min. *Z*-isomer: *major enantiomer* t_r = 14.7 min, *minor enantiomer* t_r = 19.5 min.

Pale yellow oil; $[\alpha]_D^{20}$ 56.9 (*c* 1.0, $CHCl_3$, *ee* = 98% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (dt, *J* = 8.1, 2.1 Hz, 2H), 7.26 (s, 5H), 7.13 (d, *J* = 9.9 Hz, 1H), 7.12 (d, *J* = 7.8 Hz, 2H), 6.65 (s, 1H), 5.56 (d, *J* = 9.9 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.07 (q, *J* = 7.2 Hz, 1H), 4.06 (q, *J* = 7.2 Hz, 1H), 3.55 (s, 3H), 2.35 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.11 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7 (C), 165.1 (C), 162.8 (C), 143.7 (C), 136.8 (C), 135.6 (C), 133.2 (CH), 129.7 (CH), 129.4 (CH), 128.0 (CH), 127.9 (CH), 127.5 (CH), 124.7 (C), 74.3 (C), 63.1 (CH_2), 63.0 (CH_2), 52.4 (CH_3), 48.2 (CH), 21.4 (CH_3), 13.7 (CH_3), 13.6 (CH_3); HRMS (ESI) *m/z* 538.1288 $[M+H]^+$, $C_{25}H_{28}ClNO_8S$ requires 538.1297.

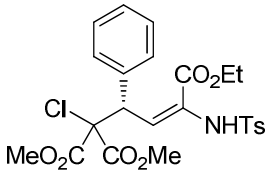
(*S*,*E*)-1,1-Diethyl 4-isopropyl 1-chloro-4-(4-methylphenylsulfonamido)-2-phenylbut-3-ene-1,1,4-tricarboxylate, (*S*,*E*)-22eo



Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 80:20, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 15.1 min, *minor enantiomer* t_r = 11.4 min. *Z*-isomer: *major enantiomer* t_r = 10.2 min, *minor enantiomer* t_r = 26.7 min.

Colorless oil; $[\alpha]_D^{20}$ 66.4 (*c* 0.96, $CHCl_3$, *ee* = 98% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (dt, *J* = 8.1, 2.1 Hz, 2H), 7.31-7.26 (m,5H), 7.10 (d, *J* = 10.5 Hz, 1H), 7.07 (d, *J* = 8.1 Hz, 2H), 6.65 (s, 1H), 5.67 (d, *J* = 10.5 Hz, 1H), 4.90 (quint, *J* = 6.3 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 4.07 (q, *J* = 7.2 Hz, 1H), 4.06 (q, *J* = 6.9 Hz, 1H), 2.33 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.13 (d, *J* = 6.0 Hz, 3H), 1.12 (t, *J* = 6.3 Hz, 3H), 1.04 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6 (C), 165.1 (C), 162.2 (C), 143.6 (C), 136.7 (C), 135.7(C), 132.6 (CH), 129.8 (CH), 129.3 (CH), 128.1 (CH), 127.9 (CH), 127.5 (CH), 125.1 (C), 74.4 (C), 70.2 (CH), 63.1 (CH_2), 63.0 (CH_2), 47.9 (CH), 21.5 (CH_3), 21.46 (CH_3), 21.42 (CH_3), 21.39 (CH_3), 13.71 (CH_3), 13.67 (CH_3); HRMS (ESI) *m/z* 566.1598 $[M+H]^+$, $C_{27}H_{32}ClNO_8S$ requires 566.1610.

(*S*,*E*)-4-ethyl 1,1-dimethyl 1-chloro-4-(4-methylphenylsulfonamido)-2-phenylbut-3-ene-1,1,4-tricarboxylate, (*S*,*E*)-22fa

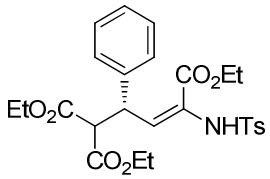


Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 80:20, 1 mL/min, *E*-isomer: *major enantiomer* t_r = 25.9 min, *minor enantiomer* t_r = 16.3 min. *Z*-isomer: *major enantiomer* t_r = 17.5 min, *minor enantiomer* t_r = 22.8 min.

White oil; $[\alpha]_D^{20}$ 50.1 (*c* 1.0, $CHCl_3$, *ee* = 98% *for the major diastereomer*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (dt, *J* = 8.1, 1.8 Hz, 2H), 7.27-7.25 (m, 6H), 7.11 (dd, *J* = 8.1, 0.9 Hz, 2H) 7.08 (d, *J* = 10.2 Hz, 1H), 6.66 (s, 1H), 5.16 (d, *J* = 9.9 Hz, 1H), 4.02 (q, *J* = 7.2 Hz, 2H), 3.73 (s, 3H), 3.61 (s, 3H), 2.34 (s, 3H), 1.10 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1 (C), 165.6 (C), 162.5 (C), 143.7 (C), 136.7 (C), 135.7 (C), 132.3 (CH), 129.6 (CH), 129.4 (CH), 128.1 (CH), 128.0 (CH), 127.6 (CH), 125.2 (C), 74.3 (C), 62.0 (CH_2), 53.8 (CH_3), 53.7 (CH_3), 48.2 (CH), 21.4 (CH_3), 13.8 (CH_3); HRMS (ESI) *m/z* 524.1133 $[M+H]^+$, $C_{24}H_{26}ClNO_8S$ requires 524.1140.

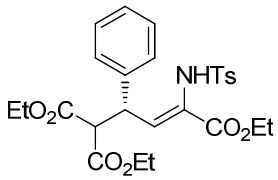
5.5.3. Determination of the absolute stereochemistry of compounds 22

(*R*,*E*)-Triethyl 4-(4-methylphenylsulfonamido)-2-phenylbut-3-ene-1,1,4-tricarboxylate, (*R*,*E*)-19ba



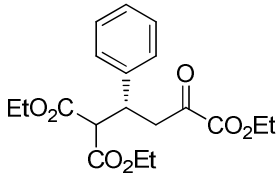
A solution of $Rh(COD)BF_4$ (0.88 mg, 0.0022 mmol) and dppp (0.98 mg, 0.0024 mmol) in MeOH (1.5 mL) was stirred for 30 minutes under nitrogen atmosphere. Then, (*S*,*E*)-**22ea** (30 mg, 0.054 mmol, *E*/*Z* = 96:4, ee = 97%/70%, obtained from the **pyBOX1**-Ca catalyzed reaction) was added and the solution was stirred under H_2 atmosphere (5 atm) for 25 hours. Purification by column chromatography on silica gel eluting with hexane/EtOAc (70:30) mixture gave 27.1 mg (97%) of compound (*R*,*E*)-**19ba (***Z*/*E* : 5:95 ee = 48/97%). Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 80:20, 1 mL/min, *E*-diastereomer: *major enantiomer* t_r = 22.8 min, *minor enantiomer* t_r = 16.7 min; *Z*-diastereomer: *major enantiomer* t_r = 40.4 min, *minor enantiomer* t_r = 21.7 min. Colorless oil; $[\alpha]_D^{20}$ 1.44 (*c* 1.0, $CHCl_3$, *E*/*Z* = 95:5, ee = 97%/48%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (dt, *J* = 8.4, 1.8 Hz, 2H), 7.35-7.23 (m,5H), 7.05 (d, *J* = 8.1 Hz, 2H), 6.72 (d, *J* = 10.8 Hz, 1H), 6.52 (s, 1H), 5.23 (t, *J* = 10.8, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 4.06 (q, *J* = 7.2 Hz, 2H), 3.95 (q, *J* = 7.2, 1H), 3.94 (q, *J* = 7.2 Hz, 1H), 3.81 (d, *J* = 10.5 Hz, 1H), 2.33 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.14 (t, *J* = 7.2 Hz, 3H), 0.99 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4 (C), 167.1 (C), 162.9 (C), 143.6 (C), 139.6 (C), 136.1(CH), 135.6 (C), 129.4 (CH), 128.6 (CH), 128.3 (CH), 127.4 (CH), 127.3 (CH), 124.5 (C), 62.0 (CH_2), 61.7 (CH_2), 61.4 (CH_2), 57.9 (CH), 43.3 (CH), 21.4 (CH_3), 14.0 (CH_3), 13.9 (CH_3), 13.7 (CH_3); HRMS (ESI) *m/z* 518.1850 $[M+H]^+$, $C_{26}H_{31}NO_8S$ requires 518.1843.

(*R*,*Z*)-Triethyl 4-(4-methylphenylsulfonamido)-2-phenylbut-3-ene-1,1,4-tricarboxylate, (*R*,*Z*)-19ba



Following the above procedure (*S*,*Z*)-**22ea** (30 mg, *E*/*Z* = 8:92, ee = 83%/86%, obtained from the **pyBOX9**-La catalyzed reaction) was transformed into (*R*,*Z*)-**19ba (***E*/*Z* = 8:92, *ee* = 80%/86%), which showed the same spectroscopic features but inverted retention times for the major and minor enantiomer as compound (*S*,*Z*)-**19ba** (Section 5.4.1.3).

(*R*)-Triethyl 4-oxo-2-phenylbutane-1,1,4-tricarboxylate (21ba)



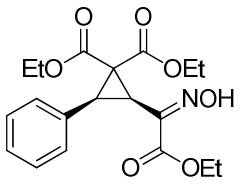
A solution of (*R*,*E*)-**19ba** (17.6 mg, 0.034 mmol) dissolved in dry CH_2Cl_2 (0.8 mL), was added via syringe to $La(OTf)_3$ (2 mg, 0.0034 mmol) previously dried in a Schlenk tube, under nitrogen atmosphere, followed by 4 Å MS (7 mg) and benzylamine (0.068 mmol). The mixture was stirred at rt for 18 hours and chromatographed on silica gel eluting with hexane/EtOAc (85:15) mixture to give 10.7 mg (86%) of compound (*R*)-**21ba.** Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *major enantiomer* t_r = 21.4 min, *minor enantiomer* t_r = 14.0

min. Colorless oil; $[\alpha]_D^{20}$ -18.0 (*c* 0.910, $CHCl_3$, *ee* = 92%); ^1H NMR (300 MHz, $CDCl_3$) δ 7.26-7.17 (m, 5H), 4.232 (q, *J* = 7.2 Hz, 1H), 4.230 (q, *J* = 7.2 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 1H), 4.188 (q, *J* = 6.9 Hz, 1H), 4.06 - 3.98 (m, 1H), 3.93 (q, *J* = 7.2 Hz, 2H), 3.73 (d, *J* = 10.2 Hz, 1H), 3.41 (dd, *J* = 17.7, 8.7 Hz, 1H), 3.30 (q, *J* = 17.7, 5.1 Hz, 1H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.25 (t, *J* = 6.9 Hz, 3H), 0.99 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.6 (C), 168.0 (C), 167.4 (C), 160.4 (C), 139.8 (C), 128.5 (CH), 128.2 (CH), 127.3 (CH), 62.4 (CH_2), 61.7 (CH_2), 61.3 (CH_2), 57.2 (CH), 43.3 (CH), 40.0 (CH), 13.9 (CH_3), 13.8 (CH_3), 13.7 (CH_3); HRMS (ESI) *m/z* 365.1594 $[M+H]^+$, $C_{19}H_{24}O_7$ requires 365.1595.

Hydrolysis of (*R*,*Z*)-**19ba** following a similar procedure gave a product with identical spectroscopic features and retention times in HPLC.

5.5.4. Synthetic transformations

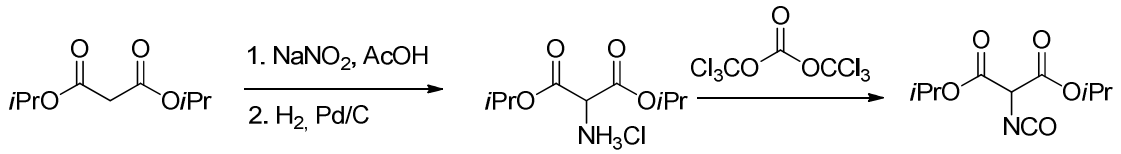
(2*S*,3*S*)-Diethyl 2-(2-ethoxy-1-(hydroxyimino)-2-oxoethyl)-3-phenylcyclopropane-1,1-dicarboxylate (23ea)



A solution of (*S*,*E*)-**22ea** (60 mg, 0.11 mmol, *E/Z* = 94:6, ee = 96%/59%), $NH_2OH \cdot HCl$ (18.1 mg, 0.26 mmol) and Et_3N (37 µL, 0.26 mmol) in DMSO (1.6 mL) was stirred at rt for 4 hours under nitrogen atmosphere. Column chromatography on silica gel eluting with hexane/EtOAc (60:40) mixture gave 37.4 mg (90%) of compound **23ea**. Chiral HPLC analysis: Chiralpak IC, hexane-*i*PrOH 80:20, 1 mL/min, *major enantiomer* t_r = 7.9 min, *minor enantiomer* t_r = 17.2 min. Colorless oil; $[\alpha]_D^{20}$ -11.8 (*c* 1.0, $CHCl_3$, ee = 92%); ^1H NMR (300 MHz, $CDCl_3$) δ 9.68 (br s, 1H), 7.31 - 7.22 (m, 5H), 4.26 (dq, *J* = 7.2, 3.3 Hz, 2H), 4.17 (dq, *J* = 7.2, 4.5 Hz, 2H), 3.90 (dq, *J* = 6.9, 4.8 Hz, 2H), 3.67 (d, *J* = 8.7 Hz, 1H), 3.27 (d, *J* = 9.0 Hz, 1H), 1.28 (t, *J* = 6.9 Hz, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6 (C), 165.8 (C), 162.4 (C), 146.9 (C), 133.8 (C), 128.7 (CH), 128.2 (CH), 127.6 (CH), 61.94 (CH_2), 61.89 (CH_2), 61.5 (CH_2), 42.9 (C), 36.7 (CH), 25.8 (CH), 13.9 ($2CH_3$), 13.7 (CH_3); HRMS (ESI) *m/z* 378.1547 $[M+H]^+$, $C_{19}H_{25}NO_7$ requires 378.1547.

5.6. Catalytic asymmetric formal [3+2] cycloaddition of 2-isocyanatomalonate esters and unsaturated imines: synthesis of highly substituted chiral γ-lactams

5.6.1. Synthesis of dialkyl 2-isocyanatomalonates 24



a) Diisopropyl 2-aminomalonate hydrochloride.[201] A 250 mL round bottom flask containing diisopropyl malonate (30.0 g, 159.4 mmol) was introduced in an ice bath. After 10 min, water (43 ml) was added followed by AcOH (32.8 mL, 569 mmol). $NaNO_2$ (39.6 g, 569 mmol) was added in portions over 1 hour. The mixture was stirred for 24 h at room temperature and extracted with diethyl ether (3×70 mL), washed with aqueous saturated $NaHCO_3$ until basic pH (6×50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude oxime was dissolved in EtOH (130 mL), and hydrogenated over 10% Pd/C (0.25 g) for 24 hours until no remaining oxime was observed in the reaction mixture (TLC). The mixture was filtered through Celite to remove the catalyst. The filtrate was concentrated under reduced pressure and dissolved in diethyl ether (250 mL). Dry HCl was bubbled through the solution for 1 hour. The resulting white precipitate was filtered, washed with diethyl ether and dried under vacuum to give 23.4 g (62%) of diisopropyl 2-aminomalonate hydrochloride.

b) Diisopropyl 2-isocyanatomalonate (**24c**).[195] Diisopropyl 2-aminomalonate hydrochloride (3.53 g, 14.7 mmol), was dissolved in dioxane (11 mL) and cooled to 0 °C under nitrogen atmosphere. Active charcoal (10.8 g) was added followed by triphosgene (4.36 g, 14.7 mmol). The reaction mixture was introduced in a bath at 80 °C for one hour and then heated at reflux temperature overnight. After this time, the reaction mixture was filtered to remove the charcoal and concentrated under reduced pressure. The concentrated was distilled under vacuum (oil pump) in a kugelrohr (T = 160-170 °C) to give 3.17 g (93%) of diisopropyl 2-isocyanatomalonate (**24c**). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.13 (2H, hept, *J* = 6.3 Hz, CHO), 4.44 (1H, s, CH-CO), 1.30 (6H, t, *J* = 6.3 Hz, Me).

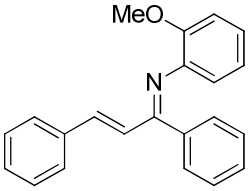
c) Diethyl 2-isocyanatomalonate (**24b**). Starting from commercially available diethyl 2-aminomalonate hydrochloride, it was prepared in 93% yield. (T = 150 °C, oil pump). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.52 (1H, s, CH-CO), 4.32 (2H, q, *J* = 7.2 Hz, CH_2O), 4.31 (2H, q, *J* = 7.2 Hz, CH_2O), 1.32 (6H, t, *J* = 7.2 Hz, Me).

c) Dimethyl 2-isocyanatomalonate (**24a**). Starting from commercially available dimethyl 2-aminomalonate hydrochloride, it was prepared in 82% yield. (T = 145 °C, oil pump). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.58 (1H, s, CH-CO), 3.87 (6H, s, MeO).

5.6.2. Synthesis of α,β-unsaturated *N*-(*o*-methoxyphenyl)imines 25

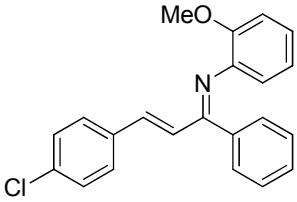
Et_3N (2.96 mL, 2.14 g, 21.3 mmol) followed by $TiCl_4$ (1.16 mL, 2.0 g, 10.6 mmol) were added *via* syringe to a solution of the required *E*-enone (9.6 mmol) and *o*-anisidine (1.18 g, 9.6 mmol) in dry dichloromethane (120 mL) at 0 ºC under nitrogen atmosphere. The reaction was heated at reflux temperature for 16 h. Then it was cooled to room temperature and quenched with water (500 mL). The two layers were separated and the aqueous layer was extracted with ethyl acetate (6×150 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with hexane/EtOAc mixtures afforded the corresponding imines **25** as mixtures of C=N geometric isomers.

_N_-((_E_)-1,3-Diphenylallylidene)-2-methoxyaniline (25a)



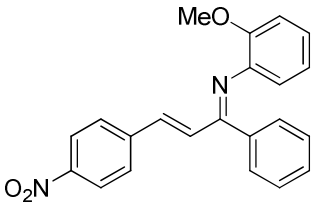
Obtained as a 63:37 diastereomer mixture. Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (significant signals) 3.83 (s, 3H major diastereomer), 3.77 (s, 3H minor diastereomer); HRMS (ESI) *m/z* 314.1532 $[M+H]^+$, $C_{22}H_{19}NO$ requires 314.1539.

_N_-((_E_)-3-(4-Chlorophenyl)-1-phenylallylidene)-2-methoxyaniline (25b)



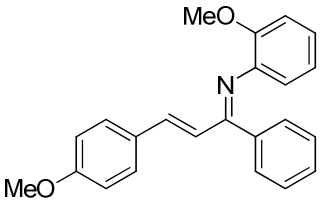
Obtained as a 61:39 diastereomer mixture. Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (significant signals) 3.80 (s, 3H major diastereomer), 3.74 (s, 3H minor diastereomer); HRMS (ESI) *m/z* 348.1145 $[M+H]^+$, $C_{22}H_{18}ClNO$ requires 348.1150.

2-Methoxy-_N_-((_E_)-3-(4-nitrophenyl)-1-phenylallylidene)aniline (25c)



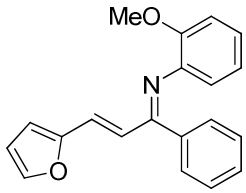
Obtained as a 56:44 diastereomer mixture. Red oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (significant signals) 8.21 (dt, *J* = 8.7, 1.8 Hz, 2H minor diastereomer), 8.15 (dt, *J* = 9.0, 2.1 Hz, 2H major diastereomer), 3.80 (s, 3H major diastereomer), 3.75 (s, 3H minor diastereomer); HRMS (ESI) *m/z* 359.1388 $[M+H]^+$, $C_{22}H_{18}N_2O_3$ requires 359.1390.

2-Methoxy-_N_-((_E_)-3-(4-methoxyphenyl)-1-phenylallylidene)aniline (25d)



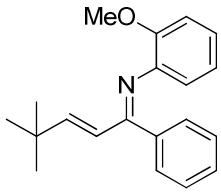
Obtained as a 61:39 diastereomer mixture. Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (significant signals) 3.83 (s, 3H minor diastereomer), 3.80 (s, 3H major diastereomer), 3.79 (s, 3H major diastereomer), 3.74 (s, 3H minor diastereomer); HRMS (ESI) *m/z* 344.1635 $[M+H]^+$, $C_{23}H_{21}NO_2$ requires 344.1645.

_N_-((_E_)-3-(Furan-2-yl)-1-phenylallylidene)-2-methoxyaniline (24e)



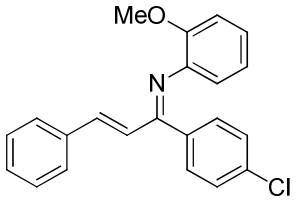
Obtained as a 66:34 diastereomer mixture. Brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (significant signals) 3.80 (s, 3H major diastereomer), 3.73 (s, 3H minor diastereomer); HRMS (ESI) *m/z* 304.1325 $[M+H]^+$, $C_{20}H_{17}NO_2$ requires 304.1332.

_N_-((_E_)-4,4-Dimethyl-1-phenylpent-2-en-1-ylidene)-2-methoxyaniline (25f)



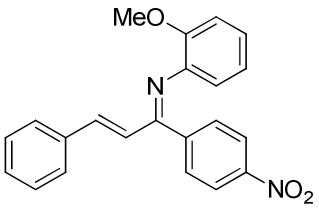
Obtained as a 64:36 diastereomer mixture. Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.79 (s, 3H major diastereomer), 3.72 (s, 3H minor diastereomer), 1.08 (s, 9H minor diastereomer), 0.96 (s, 9H major diastereomer); HRMS (ESI) *m/z* 294.1845 $[M+H]^+$, $C_{26}H_{21}NO$ requires 294.1852.

_N_-((_E_)-1-(4-Chlorophenyl)-3-phenylallylidene)-2-methoxyaniline (25g)



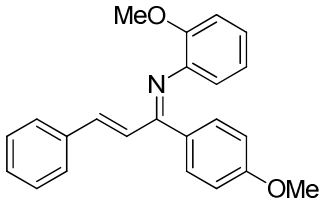
Obtained as a 64:36 diastereomer mixture. Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (significant signals) 7.72 (dt, *J* = 8.4, 2.4 Hz, 2H major diastereomer), 3.80 (s, 3H major diastereomer), 3.74 (s, 3H minor diastereomer); HRMS (ESI) *m/z* 348.1137 $[M+H]^+$, $C_{22}H_{18}ClNO$ requires 348.1150.

2-Methoxy-_N_-((_E_)-1-(4-nitrophenyl)-3-phenylallylidene)aniline (25h)



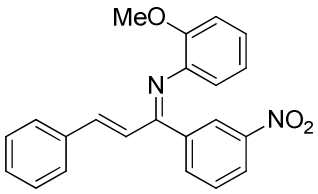
Obtained as a 66:34 diastereomer mixture. Orange oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (significant signals) 8.33 (dt, *J* = 9.0, 2.1 Hz, 2H major diastereomer), 8.13 (dt, *J* = 8.7, 2.1 Hz, 1H major diastereomer), 7.94 (dt, *J* = 8.7, 2.4 Hz, 2H major diastereomer), 3.82 (s, 3H major diastereomer), 3.74 (s, 3H minor diastereomer); HRMS (ESI) *m/z* 359.1385 $[M+H]^+$, $C_{22}H_{18}N_2O_3$ requires 359.1390.

2-Methoxy-_N_-((_E_)-1-(4-methoxyphenyl)-3-phenylallylidene)aniline (25i)



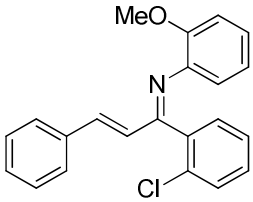
Obtained as a 68:32 diastereomer mixture. Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (significant signals) 7.77 (dt, *J* = 6.9, 2.1 Hz, 2H major diastereomer), 7.49 (dd, *J* = 8.1, 1.8 Hz, 1H major diastereomer), 3.88 (s, 3H major diastereomer), 3.80 (s, 3H major diastereomer), 3.77 (s, 3H minor diastereomer), 3.75 (s, 3H minor diastereomer); HRMS (ESI) *m/z* 344.1640 $[M+H]^+$, $C_{23}H_{21}NO_2$ requires 344.1645.

2-Methoxy-*N*-((*E*)-1-(3-nitrophenyl)-3-phenylallylidene)aniline (25j)



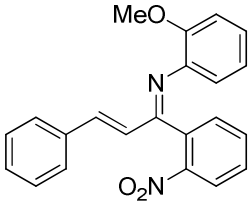
Obtained as a 68:32 diastereomer mixture. Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (significant signals) 8.63 (t, *J* = 1.8 Hz, 1H major diastereomer), 8.35 (dq, *J* = 8.4, 1.2 Hz, 1H major diastereomer), 8.15-8.08 (m, 2H major and minor diastereomers), 7.67 (d, *J* = 8.1 Hz, 1H major diastereomer), 7.65 (d, *J* = 7.8 Hz, 1H minor diastereomer), 3.82 (s, 3H major diastereomer), 3.75 (s, 3H minor diastereomer); HRMS (ESI) *m/z* 359.1384 $[M+H]^+$, $C_{22}H_{18}N_2O_3$ requires 359.1390.

***N*-((*E*)-1-(2-Chlorophenyl)-3-phenylallylidene)-2-methoxyaniline (25k)**



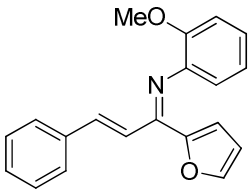
Obtained as a 71:29 diastereomer mixture. Orange oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (significant signals) 3.84 (s, 3H minor diastereomer), 3.80 (s, 3H mayor diastereomer); HRMS (ESI) *m/z* 348.1143 $[M+H]^+$, $C_{22}H_{18}ClNO$ requires 348.1150.

2-Methoxy-*N*-((*E*)-1-(2-nitrophenyl)-3-phenylallylidene)aniline (25l)



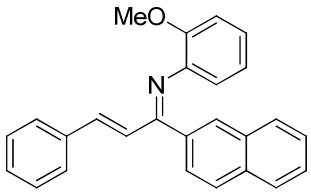
Obtained as a 60:30 diastereomer mixture. Orange solid; mp 48-49 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ (significant signals) 8.16 (dd, *J* = 8.4, 1.2 Hz, 1H minor diastereomer), 8.07 (dd, *J* = 8.1, 1.5 Hz, 1H major diastereomer), 3.85 (s, 3H minor diastereomer), 3.77 (s, 3H major diastereomer); HRMS (ESI) *m/z* 359.1378 $[M+H]^+$, $C_{22}H_{18}N_2O_3$ requires 359.1390.

***N*-((*E*)-1-(Furan-2-yl)-3-phenylallylidene)-2-methoxyaniline (25m)**



Obtained as a 78:22 diastereomer mixture: Brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (significant signals) 7.64 (q, *J* = 0.9 Hz, 1H major diastereomer), 7.46 (d, *J* = 15.9 Hz, 1H minor diastereomer), 7.12 (dd, *J* = 7.2, 1.8 Hz, 1H minor diastereomer), 7.09 (dd, *J* = 7.2, 2.1 Hz, 1H minor diastereomer), 7.00 (dd, *J* = 3.3, 0.6 Hz, 1H major diastereomer), 6.72 (d, *J* = 16.5 Hz, 1H major diastereomer), 6.56 (q, *J* = 1.8 Hz, 1H major diastereomer), 6.30 (q, *J* = 1.8 Hz, 1H minor diastereomer), 6.04 (dd, *J* = 3.6, 0.6 Hz, 1H minor diastereomer), 3.80 (s, 3H major diastereomer), 3.74 (s, 3H minor diastereomer); HRMS (ESI) *m/z* 304.1320 $[M+H]^+$, $C_{20}H_{17}NO_2$ requires 304.1332.

2-Methoxy-*N*-((*E*)-1-(naphthalen-2-yl)-3-phenylallylidene)aniline (25n)



Obtained as a 66:34 diastereomer mixture: Orange solid; mp 53-55 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ (significant signals) 6.99 (dt, *J* = 8.4, 1.5 Hz, 2H major and minor diastereomer), 6.95 (d, *J* = 3.3 Hz, 2H major diastereomer), 6.91 (d, *J* = 1.8 Hz, 2H minor diastereomer), 6.71 (dd, *J* = 8.1, 1.2 Hz, 1H minor diastereomer), 6.64 (dt, *J* = 7.5, 1.2 Hz, 1H minor diastereomer), 6.56 (dd, *J* = 7.8, 1.5 Hz, 1H minor diastereomer), 3.83 (s, 3H major diastereomer), 3.76 (s, 3H minor diastereomer); HRMS (ESI) *m/z* 364.1678 $[M+H]^+$ $C_{26}H_{21}NO$ requires 364.1696.

5.6.3. Enantioselective [3+2] cycloaddition of 2-isocyanatomalonate esters 24 and unsaturated imines 25

5.6.3.1. General procedure for the enantioselective reaction

$Mg(OTf)_2$ (4.0 mg, 0.0125 mmol) was dried in a Schlenk tube under vacuum. **BOX10** (6.1 mg, 0.0125 mmol) was introduced and the Schlenk tube was filled with nitrogen. Et_2O (0.55 mL) was added via syringe and the mixture was stirred for 30 min. The tube was introduced in a bath at 0 °C, 4Å MS (110 mg) was then added followed by the imine **25** (0.125 mmol) dissolved in dry Et_2O (0.5 mL), and by diisopropyl 2-isocyanatomalonate (**24c**, 37 μL, 0.19 mmol). The mixture was stirred at 0 ºC for the indicated time and chromatographed on silica gel eluting with hexane/EtOAc mixtures to give compounds **26**.

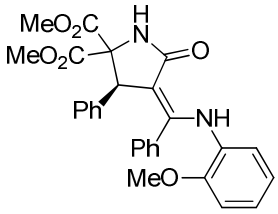
5.6.3.2. General procedure for the synthesis of the racemic products

Racemic compounds for comparative purposes were prepared by following the same procedure, in absence of chiral ligand and performing the reaction at room temperature.

5.6.3.3. Characterization of products 26

See Table 21 (Page 104) for yield, dr and ee.

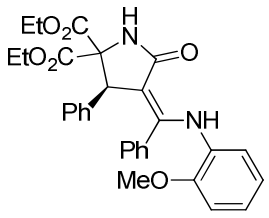
(*R,Z*)-Dimethyl 4-(((2-methoxyphenyl)amino)(phenyl)methylene)-5-oxo-3-phenylpyrrolidine-2,2-dicarboxylate (26aa)



Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 80:20, 1 mL/min. *major enantiomer* t_r = 11.0 min, *minor enantiomer* t_r = 18.9 min.

Yellow solid, mp 72-74 ºC (hexane-EtOAc); $[\alpha]_D^{20}$ -129.5 (*c* 1.0, $CHCl_3$, ee = 76%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.60 (1H, s, NH), 7.22 (1H, t, *J* = 7.5 Hz, Ar), 7.14 (2H, t, *J* = 7.5 Hz, Ar), 7.03-6.99 (m, 5H, Ar), 6.84-6.81 (2H, m, Ar), 6.75-6.73 (2H, m, Ar), 6.38 (1H, m, Ar), 6.14 (1H, s, NH), 6.03 (dd, *J* = 8.1, 1.2 Hz, 1H, Ar), 4.85 (1H, s, CH-Ph), 3.88 (3H, s, MeO), 3.81 (3H, s, MeO), 3.13 (3H, s, MeO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5 (C), 169.0 (C), 167.5 (C), 152.6 (C), 150.0 (C), 140.3 (C), 134.2 (C), 129.7 (C), 128.7 (CH), 128.31 (CH), 128.27 (CH), 127.5 (CH), 126.8 (CH), 121.9 (CH), 119.9 (CH), 119.7 (CH), 110.4 (CH), 101.4 (C), 71.8 (C), 55.7 (CH_3), 53.4 (CH_3), 52.3 (CH_3), 49.2 (CH); HRMS (ESI) *m/z* 487.1880 $[M+H]^+$, $C_{28}H_{26}N_2O_6$ requires 487.1864.

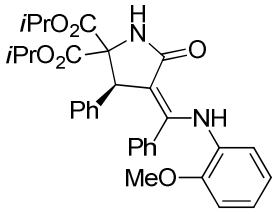
(*R,Z*)-Diethyl 4-(((2-methoxyphenyl)amino)(phenyl)methylene)-5-oxo-3-phenylpyrrolidine-2,2-dicarboxylate (26ba)



Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 80:20, 1 mL/min. *major enantiomer* t_r = 13.1 min, *minor enantiomer* t_r = 22.9 min.

Yellow oil; $[\alpha]_D^{20}$ -148.1 (*c* 1.0, $CHCl_3$, ee = 77%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.58 (1H, s, NH), 7.23 (1H, dt, *J* = 7.5, 1.2 Hz, Ar), 7.15 (2H, t, *J* = 7.5 Hz, Ar), 7.01-6.96 (5H, m, Ar), 6.82-6.79 (2H, m, Ar), 6.74-6.72 (2H, m, Ar), 6.40-6.35 (1H, m, Ar), 6.12 (1H, s, NH), 6.02 (1H, d, *J* = 8.1 Hz, Ar), 4.85 (s, CH-Ph), 4.36-4.20 (2H, m, CH_3-C*H*$_2$O), 3.88 (3H, s, MeO), 3.68-3.45 (2H, m, CH_3-C*H*$_2$O), 1.28 (3H, t, *J* = 7.2 Hz, C*H*$_3$-CH_2O), 0.74 (3H, t, *J* = 7.2 Hz, C*H*$_3$-CH_2O); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5 (C), 168.5 (C), 167.1 (C), 152.4 (C), 149.9 (C), 140.4 (C), 134.3 (C), 129.8 (C), 128.7 (CH), 128.3 (CH), 127.5 (CH), 126.7 (CH), 121.9 (CH), 119.9 (CH), 119.5 (CH), 110.3 (CH), 102.0 (C), 71.6 (C), 62.5 (CH_2), 61.8 (CH_2), 55.7 (CH_3), 48.9 (CH), 13.9 (CH_3), 13.3 (CH_3); HRMS (ESI) *m/z* 515.2177 $[M+H]^+$, $C_{30}H_{30}N_2O_6$ requires 515.2177.

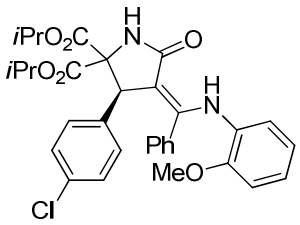
(*R,Z*)-Diisopropyl 4-(((2-methoxyphenyl)amino)(phenyl)methylene)-5-oxo-3-phenylpyrrolidine-2,2-dicarboxylate (26ca)



Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 80:20, 1 mL/min. *major enantiomer* t_r = 10.1 min, *minor enantiomer* t_r = 22.8 min.

Yellow solid, mp 70-72 ºC (hexane-EtOAc); $[\alpha]_D^{20}$ -197.4 (*c* 1.0, $CHCl_3$, ee = 97%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.60 (1H, s, NH), 7.23 (1H, t, *J* = 7.2 Hz, Ar), 7.16 (2H, t, *J* = 7.5 Hz, Ar), 6.99-6.95 (5H, m, Ar), 6.78-6.71 (4H, m, Ar), 6.39-6.34 (1H, m, Ar), 6.16 (1H, s, NH), 6.14 (1H, dd, *J* = 8.1, 1.2 Hz, Ar), 5.09 (1H, hept, *J* = 6.3 Hz, CHO), 4.85 (1H, s, CH-Ph), 4.50 (1H, hept, *J* = 6.3 Hz, CHO), 3.88 (3H, s, MeO), 1.29 (3H, d, *J* = 6.3 Hz, *i*Pr), 1.23 (3H, d, *J* = 6.3 Hz, *i*Pr), 0.95 (3H, d, *J* = 6.3 Hz, *i*Pr), 0.52 (3H, d, *J* = 6.3 Hz, *i*Pr); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4 (C), 168.0 (C), 166.5 (C), 152.1 (C), 149.8 (C), 140.4 (C), 134.4 (C), 129.9 (C), 128.6 (CH), 128.4 (CH), 128.35 (CH), 128.3 (CH), 127.5 (CH), 126.6 (CH), 121.7 (CH), 119.8 (CH), 119.3 (CH), 110.3 (CH), 102.7 (C), 71.4 (C), 70.3 (CH), 69.7 (CH), 55.7 (CH_3), 48.6 (CH), 21.5 (CH_3), 21.3 (CH_3), 21.2 (CH_3), 20.5 (CH_3); HRMS (ESI) *m/z* 543.2491 $[M+H]^+$, $C_{32}H_{34}N_2O_6$ requires 543.2495.

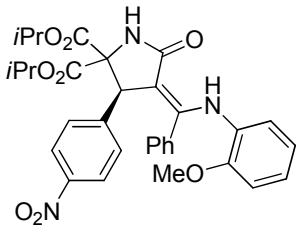
(*R*,*Z*)-Diisopropyl 3-(4-chlorophenyl)-4-(((2-methoxyphenyl)amino)(phenyl) methylene)-5-oxopyrrolidine-2,2-dicarboxylate (26cb)



Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 80:20, 1 mL/min. *major enantiomer* t_r = 7.6 min, *minor enantiomer* t_r = 11.2 min.

White solid, mp 179-181 ºC (hexane-EtOAc); $[\alpha]_D^{20}$ -183.2 (*c* 1.0, $CHCl_3$, *ee* = 96%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.56 (1H, s, NH), 7.25 (1H, t, *J* = 7.2 Hz, Ar), 7.19 (2H, t, *J* = 7.2 Hz, Ar), 7.04-6.97 (2H, m, Ar), 6.94 (2H, dd, *J* = 8.7, 1.2 Hz, Ar), 6.75-6.70 (4H, m, Ar), 6.41-6.40 (1H, m, Ar), 6.18 (1H, s, NH), 6.03 (1H, dd, *J* = 8.1, 1.2 Hz, Ar), 5.09 (1H, hept, *J* = 6.3 Hz, CHO), 4.84 (1H, s, CH-Ar), 4.54 (1H, hept, *J* = 6.3 Hz, CHO), 3.87 (3H, s, MeO), 1.28 (3H, d, *J* = 6.3 Hz, *i*Pr), 1.23 (3H, d, *J* = 6.3 Hz, *i*Pr), 0.97 (3H, d, *J* = 6.3 Hz, *i*Pr), 0.59 (d, *J* = 6.3 Hz, *i*Pr); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2 (C), 167.9 (C), 166.4 (C), 152.5 (C), 150.0 (C), 139.1 (C), 132.4 (C), 129.7 (CH), 129.6 (C), 128.8 (CH), 128.5 (CH), 128.3 (CH), 127.6 (CH), 122.0 (CH), 119.8 (CH), 119.6 (CH), 110.4 (CH), 102.0 (C), 71.3 (C), 70.4 (CH), 69.9 (CH), 55.7 (CH_3), 47.9 (CH), 21.5 (CH_3), 21.3 (CH_3), 21.2 (CH_3), 20.6 (CH_3); HRMS (ESI) *m/z* 577.2108 $[M+H]^+$, $C_{32}H_{33}ClN_2O_6$ requires 577.2100.

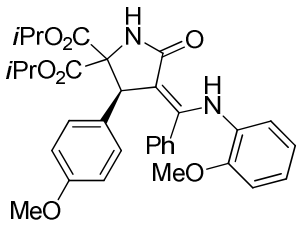
(*R*,*Z*)-Diisopropyl 4-(((2-methoxyphenyl)amino)(phenyl)methylene)-3-(4-nitrophenyl)-5-oxopyrrolidine-2,2-dicarboxylate (26cc)



Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 80:20, 1 mL/min. *major enantiomer* t_r = 10.2 min, *minor enantiomer* t_r = 14.5 min.

Orange solid, mp 225-227 ºC (hexane-EtOAc); $[\alpha]_D^{20}$ -204.0 (*c* 1.0, $CHCl_3$, ee = 98%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.58 (1H, s, NH), 7.83 (2H, d, *J* = 9.0 Hz, Ar), 7.26 (1H, t, *J* = 6.9 Hz, Ar), 7.18 (1H, br s, Ar), 6.93 (2H, d, *J* = 8.1 Hz, Ar), 6.74 (2H, dd, *J* = 5.1, 1.2 Hz, Ar), 6.44 (1H, s, NH), 6.41-6.35 (1H, m, Ar), 6.05 (1H, d, *J* = 7.8 Hz, Ar), 5.10 (1H, hept, *J* = 6.3 Hz, CHO), 5.00 (1H, s, CH-Ar), 4.52 (1H, hept, *J* = 6.3 Hz, CHO), 3.86 (3H, s, MeO), 1.29 (3H, d, *J* = 6 Hz, *i*Pr), 1.23 (3H, d, *J* = 6 Hz, *i*Pr), 0.96 (3H, d, *J* = 6.3 Hz, *i*Pr), 0.53 (3H, d, *J* = 6.3 Hz, *i*Pr); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0 (C), 167.6 (C), 166.2 (C), 153.0 (C), 150.1 (C), 148.2 (C), 146.5 (C), 134.1 (C), 129.2 (C), 129.1 (CH), 129.0 (CH), 128.6 (CH), 128.2 (CH), 122.7 (CH), 122.5 (CH), 120.0 (CH), 119.8 (CH), 110.4 (CH), 101.2 (C), 71.0 (C), 70.7 (CH), 70.1 (CH), 55.7 (CH_3), 48.1 (CH), 21.4 (CH_3), 21.3 (CH_3), 21.1 (CH_3), 20.6 (CH_3); HRMS (ESI) *m/z* 588.2332 $[M+H]^+$, $C_{32}H_{33}N_3O_8$ requires 588.2340.

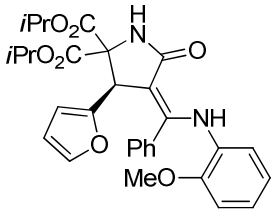
(*R*,*Z*)-Diisopropyl 3-(4-methoxyphenyl)-4-(((2-methoxyphenyl)amino) (phenyl)methylene)-5-oxopyrrolidine-2,2-dicarboxylate (26cd)



Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 80:20, 1 mL/min. *major enantiomer* t_r = 9.1 min, *minor enantiomer* t_r = 16.2 min

Yellow oil; $[\alpha]_D^{20}$ -133.3 (*c* 1.0, $CHCl_3$, ee = 96%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.55 (1H, s, NH), 7.23 (2H, dt, *J* = 6.9, 1.2 Hz, Ar), 7.26 (1H, t, *J* = 6.9 Hz, Ar), 7.18 (1H, br s, Ar), 6.93 (1H, d, *J* = 8.1 Hz, Ar), 7.17 (2H, t, *J* = 6.9 Hz, Ar), 7.02 (2H, d, *J* = 6.9 Hz, Ar), 6.76-6.68 (4H, m, Ar), 6.51 (2H, d, *J* = 9.0 Hz, Ar), 6.39-6.34 (1H, m, Ar), 6.11 (1H, s, NH), 6.01 (1H, dd, *J* = 7.8, 1.2 Hz, Ar), 5.08 (1H, hept, *J* = 6.3 Hz, CHO), 4.78 (1H, s, CH-Ar), 4.53 (1H, hept, *J* = 6.3Hz, CHO), 3.88 (3H, s, MeO), 3.67 (3H, s, MeO), 1.27 (3H, d, *J* = 6.3 Hz, *i*Pr), 1.22 (3H, d, *J* = 6.3 Hz, *i*Pr), 0.97 (3H, d, *J* = 6.3 Hz, *i*Pr), 0.61 (3H, d, *J* = 6 Hz, *i*Pr); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4 (C), 168.1 (C), 166.6 (C), 158.3 (C), 152.0 (C), 149.8 (C), 134.4 (C), 132.7 (C), 129.9 (C), 129.4 (CH), 128.6 (CH), 128.34 (CH), 128.32 (CH), 121.6 (CH), 119.8 (CH), 119.2 (CH), 112.8 (CH), 110.3 (CH), 102.8 (C), 71.6 (C), 70.2 (CH), 69.7 (CH), 55.7 (CH_3), 55.1(CH_3), 47.8 (CH), 21.5 (CH_3), 21.3 (CH_3), 21.2 (CH_3), 20.7 (CH_3); HRMS (ESI) *m/z* 573.2598 $[M+H]^+$, $C_{33}H_{36}N_2O_7$ requires 573.2595.

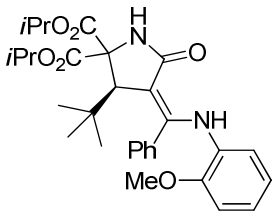
(*R*,*Z*)-Diisopropyl 3-(furan-2-yl)-4-(((2-methoxyphenyl)amino)(phenyl)methylene)-5-oxopyrrolidine-2,2-dicarboxylate (26ce)



Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 80:20, 1 mL/min. *major enantiomer* t_r = 25.8 min, *minor enantiomer* t_r = 49.4 min

Yellow oil; $[\alpha]_D^{20}$ -108.0 (*c* 1.0, $CHCl_3$, ee = 88%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.55 (1H, s, NH), 7.28-7.21 (3H, m, Ar), 7.11 (2H, br s, Ar), 7.04 (1H, q, *J* = 0.9 Hz, Ar), 6.75-6.73 (2H, m, Ar), 6.39 (1H, m, Ar), 6.06-6.02 (3H, m, Ar+ NH), 5.69 (1H, dd, *J* = 3.3, 0.6 Hz, Ar), 5.08 (1H, hept, *J* = 6.3 Hz, CHO), 5.02 (1H, s, CH-fur), 4.72 (1H, hept, *J* = 6.3Hz, CHO), 3.87 (3H, s, MeO), 1.27 (3H, d, *J* = 6.3 Hz, *i*Pr), 1.23 (3H, d, *J* = 6 Hz, *i*Pr), 1.06 (3H, d, *J* = 6.3 Hz, *i*Pr), 0.86 (3H, d, *J* = 6.3 Hz, *i*Pr); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8 (C), 167.7 (C), 166.5 (C), 152.9 (C), 152.2 (C), 150.0 (C), 140.8 (CH), 134.2 (C), 129.8 (C), 128.8 (CH), 128.4 (CH), 128.1 (CH), 122.0 (CH), 119.8 (CH), 119.7 (CH), 110.3 (CH), 110.0 (CH), 107.6 (CH), 99.0 (C), 70.4 (CH), 70.3 (C), 70.0 (CH), 55.7 (CH_3), 42.6 (CH), 21.4 (CH_3), 21.31 (CH_3), 21.28 (CH_3), 21.1 (CH_3); HRMS (ESI) *m/z* 533.2275 $[M+H]^+$, $C_{30}H_{32}N_2O_7$ requires 533.2282.

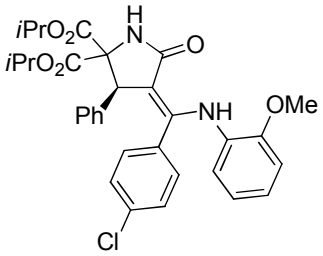
(*R,Z*)-Diisopropyl 3-(*tert*-butyl)-4-(((2-methoxyphenyl)amino)(phenyl)methylene)-5-oxopyrrolidine-2,2-dicarboxylate (26cf)



Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 80:20, 1 mL/min. *major enantiomer* t_r = 18.5 min, *minor enantiomer* t_r = 13.5 min

White solid, mp 60-62 ºC; $[\alpha]_D^{20}$ 52.6 (*c* 0.71, $CHCl_3$, ee = 23%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.29 (1H, s, NH), 7.50-7.30 (5H, m, Ar), 6.77 (1H, dd, *J* = 8.1, 2.1 Hz, Ar), 6.73 (1H, td, *J* = 8.1, 1.2 Hz, Ar), 6.42 (1H, td, *J* = 8.1, 1.8 Hz, Ar), 6.02 (1H, d, J = 7.8 Hz, Ar), 5.92 (1H, s, NH), 5.08 (1H, hept, *J* = 6.3 Hz, CHO), 5.07 (1H, hept, *J* = 6.3 Hz, CHO), 3.98 (1H, *J* = 1.2 Hz, d, CH-*t*Bu), 3.90 (3H, s, MeO), 1.28 (6H, *J* = 6.3Hz, d, *i*Pr), 1.26 (6H, *J* = 6.3 Hz, d, *i*Pr), 0.67 (9H, s, *t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6 (C), 167.6 (C), 168.9 (C), 168.1 (C), 150.33 (C), 1450.30 (C), 135.8 (C), 131.0 (C), 129.9 (CH), 129.0 (CH), 128.5 (CH), 121.3 (CH), 120.2 (CH), 119.8 (CH), 110.3 (CH), 102.9 (C), 71.3 (C), 70.5 (CH), 70.2 (CH), 55.7 (CH_3), 53.8 (CH), 36.7 (C), 28.2 (CH_3), 21.7 (CH_3), 21.5 (CH_3), 21.4 (CH_3), 21.2 (CH_3); HRMS (ESI) *m/z* 523.2800 $[M+H]^+$, $C_{30}H_{38}N_2O_6$ requires 523.2803.

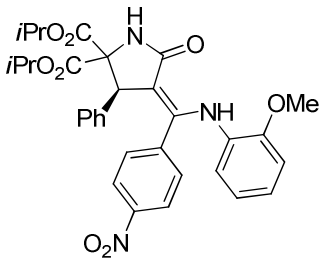
(*R,Z*)-Diisopropyl 4-((4-chlorophenyl)((2-methoxyphenyl)amino)methylene)-5-oxo-3-phenylpyrrolidine-2,2-dicarboxylate (26cg)



Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 80:20, 1 mL/min. *major enantiomer* t_r = 8.0 min, *minor enantiomer* t_r = 18.7 min.

Yellow solid, mp 77-79 ºC (hexane-EtOAc); $[\alpha]_D^{20}$ -167.7 (*c* 1.0, $CHCl_3$, ee = 99%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.46 (1H, s, NH), 7.13 (2H, d, *J* = 8.4 Hz, Ar), 7.01-6.98 (5H, m, Ar), 6.82-6.80 (2H, m, Ar), 6.76-6.73 (2H, m, Ar), 6.45-6.39 (1H, m, Ar), 6.21 (1H, s, NH), 6.07 (1H, dd, *J* = 7.8, 1.2 Hz, Ar), 5.09 (1H, hept, *J* = 6.3Hz, CHO), 4.81 (1H, s, CH-Ph), 4.50 (1H, hept, *J* = 6.3Hz, CHO), 3.86 (3H, s, MeO), 1.28 (3H, d, *J* = 6.3 Hz, *i*Pr), 1.22 (3H, d, *J* = 6.3 Hz, *i*Pr), 0.95 (3H, d, *J* = 6.3 Hz, *i*Pr), 0.53 (3H, d, *J* = 6.3 Hz, *i*Pr); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2 (C), 167.9 (C), 166.4 (C), 150.9 (C), 150.1 (C), 140.2 (C), 134.6 (C), 132.9 (C), 129.8 (CH), 129.6 (C), 128.6 (CH), 128.4 (CH), 127.6 (CH), 126.8 (CH), 122.2 (CH), 119.9 (CH), 119.8 (CH), 110.4(CH), 103.0 (C), 71.4 (C), 70.3 (CH), 69.8 (CH), 55.7 (CH_3), 48.7 (CH), 21.5 (CH_3), 21.3 (CH_3), 21.2 (CH_3), 20.5 (CH_3); HRMS (ESI) *m/z* 577.2109 $[M+H]^+$, $C_{32}H_{33}ClN_2O_6$ requires 577.2100.

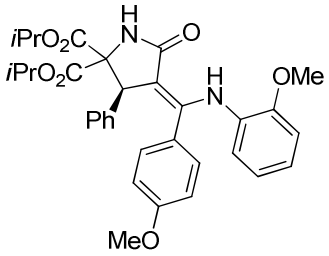
(*R,Z*)-Diisopropyl 4-(((2-methoxyphenyl)amino)(4-nitrophenyl)methylene)-5-oxo-3-phenylpyrrolidine-2,2-dicarboxylate (26ch)



Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 80:20, 1 mL/min. *major enantiomer* t_r = 11.4 min, *minor enantiomer* t_r = 32.9 min.

Orange solid, mp 80-82 ºC (hexane-EtOAc); $[\alpha]_D^{20}$ -189.8 (*c* 1.0, $CHCl_3$, ee = 95%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.40 (1H, s, NH), 7.98 (2H, d, *J* = 8.7 Hz, Ar), 7.19 (1H, br s, Ar), 7.01-6.93 (3H, m, Ar), 6.81-6.71 (4H, m, Ar), 6.44-6.39 (1H, m, Ar), 6.37 (1H, s, NH), 6.07 (1H, dd, *J* = 8.1, 1.2 Hz, Ar), 5.09 (1H, hept, *J* = 6.3Hz, 1H), 4.81 (s, 1H), 4.48 (1H, hept, *J* = 6.3Hz, 1H), 3.84 (3H, s, MeO), 1.28 (3H, d, *J* = 6.3 Hz, *i*Pr), 1.23 (3H, d, *J* = 6.0 Hz, *i*Pr), 0.94 (3H, d, *J* = 6.3 Hz, *i*Pr), 0.51 (3H, d, *J* = 6.3 Hz, *i*Pr); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0 (C), 167.8 (C), 166.3 (C), 150.6 (C), 149.8 (C), 147.5 (C), 141.1 (C), 139.9 (C), 129.7 (CH), 129.0 (C), 128.4 (CH), 127.8 (CH), 127.1 (CH), 123.4 (CH), 123.1 (CH), 120.7 (CH), 119.9 (CH), 110.6 (CH), 103.6 (C), 71.3 (C), 70.5 (CH), 70.0 (CH), 55.6 (CH_3), 48.3 (CH), 21.4 (CH_3), 21.3 (CH_3), 21.2 (CH_3), 20.5 (CH_3); HRMS (ESI) *m/z* 588.2333 $[M+H]^+$, $C_{32}H_{33}N_3O_8$ requires 588.2340.

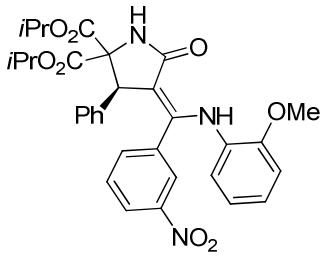
(*R,Z*)-Diisopropyl 4-((4-methoxyphenyl)((2-methoxyphenyl)amino)methylene)-5-oxo-3-phenylpyrrolidine-2,2-dicarboxylate (26ci)



Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 80:20, 1 mL/min. *major enantiomer* t_r = 15.3 min, *minor enantiomer* t_r = 27.5 min.

Yellow oil; $[\alpha]_D^{20}$ -165.1 (*c* 1.0, $CHCl_3$, ee = 98%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.50 (1H, s, NH), 7.00-6.96 (5H, m, Ar), 6.83-6.80 (2H, m, Ar), 6.75-6.68 (4H, m, Ar), 6.42-6.37 (1H, m, Ar), 6.13 (1H, s, NH), 6.05 (1H, dd, *J* = 7.8, 1.2 Hz, Ar), 5.09 (1H, hept, *J* = 6.3 Hz, CHO), 4.86 (1H, s, CHPh), 4.50 (1H, hept, *J* = 6.3Hz, CHO), 3.87 (3H, s, MeO), 3.76 (3H, s, MeO), 1.28 (3H, d, *J* = 6.3 Hz, *i*Pr), 1.22 (3H, d, *J* = 6.3 Hz, *i*Pr), 0.95 (3H, d, *J* = 6.3 Hz, *i*Pr), 0.53 (3H, d, *J* = 6.3 Hz, *i*Pr); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4 (C), 168.1 (C), 166.6 (C), 159.8 (C), 151.9 (C), 149.8 (C), 140.5 (C), 130.1 (C), 129.7 (CH), 129.1 (C), 128.4 (CH), 127.5 (CH), 126.8 (C), 126.6 (CH), 121.5 (CH), 119.9 (CH), 119.3 (CH), 113.7 (CH), 110.3 (CH), 102.74 (C), 71.4 (C), 70.2 (CH), 69.7 (CH), 55.7 (CH_3), 55.1 (CH_3), 48.6 (CH), 21.5 (CH_3), 21.3 (CH_3), 21.2 (CH_3), 20.5 (CH_3); HRMS (ESI) *m/z* 573.2592 $[M+H]^+$, $C_{33}H_{36}N_2O_7$ requires 573.2595.

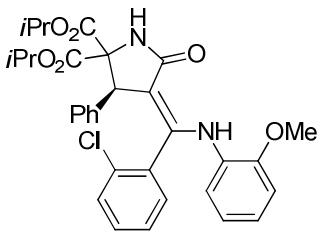
(*R*,*Z*)-Diisopropyl 4-(((2-methoxyphenyl)amino)(3-nitrophenyl)methylene)-5-oxo-3-phenylpyrrolidine-2,2-dicarboxylate (26cj)



Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 80:20, 1 mL/min. *major enantiomer* t_r = 14.2 min, *minor enantiomer* t_r = 48.2 min.

Orange oil; $[\alpha]_D^{20}$ -132.2 (*c* 0.98, $CHCl_3$, ee = 97%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.40 (1H, s, NH), 8.03 (2H, dt, *J* = 7.2, 1.8 Hz, Ar), 7.74 (1H, br s, Ar), 7.36-7.29 (2H, m, Ar), 6.98-6.93 (3H, m, Ar), 6.81-6.71 (4H, m, Ar), 6.42 (1H, dt, *J* = 7.8, 1.8 Hz, Ar), 6.24 (1H, s, NH), 6.13 (1H, dd, *J* = 8.1, 1.2 Hz, Ar), 5.11 (1H, hept, *J* = 6.3 Hz, CHO), 4.78 (1H, s, CH-Ph), 4.48 (1H, hept, *J* = 6.3 Hz, CHO), 3.84 (3H, s, MeO), 1.29 (3H, d, *J* = 6.3 Hz, *i*Pr), 1.24 (3H, d, *J* = 6.3 Hz, *i*Pr), 0.95 (3H, d, *J* = 6.3 Hz, *i*Pr), 0.49 (3H, d, *J* = 6.3 Hz, *i*Pr); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1 (C), 167.8 (C), 166.4 (C), 150.9 (C), 149.9 (C), 147.8 (C), 140.0 (C), 136.2 (C), 134.6 (CH), 129.3 (CH), 129.0 (C), 128.4 (CH), 127.8 (CH), 127.1 (CH), 123.7 (CH), 123.4 (CH), 123.3 (CH), 121.2 (CH), 120.0 (CH), 110.7 (CH), 103.3 (C), 71.3 (C), 70.5 (CH), 70.0 (CH), 55.6 (CH_3), 48.4 (CH), 21.5 (CH_3), 21.3 (CH_3), 21.1 (CH_3), 20.5 (CH_3); HRMS (ESI) *m/z* 588.2338 $[M+H]^+$, $C_{32}H_{33}N_3O_8$ requires 588.2340.

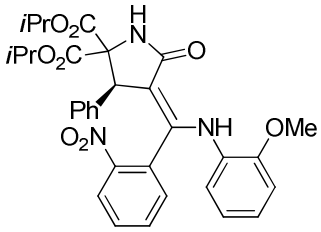
(*R*,*Z*)-Diisopropyl 4-((2-chlorophenyl)((2-methoxyphenyl)amino)methylene)-5-oxo-3-phenylpyrrolidine-2,2-dicarboxylate (26ck)



Obtained as a *ca.*1:1 mixture of diastereomers. Yellow oil; $[\alpha]_D^{20}$ -168.8 (*c* 1.0, $CHCl_3$, *for the diastereomer mixture*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.75 (1H, s, NH), 10.70 (1H, s, NH), 7.62 (1H, dd, *J* = 7.5, 1.5 Hz, Ar), 7.40 (2H, m, Ar), 7.22 (1H, td, *J* = 7.5, 1.2 Hz, Ar), 7.11 (1H, td, *J* = 7.5, 1.2 Hz, Ar), 7.04-6.94 (7H, m, Ar), 6.76-6.70 (m, 6H), 6.63 (1H, td, *J* = 7.5, 1.2 Hz, Ar), 6.43-6.34 (2H, m, Ar), 6.24-6.20 (3H, m, Ar,2NH), 6.07 (1H, d, *J* = 7.5 Hz, Ar), 6.04 (1H, dd, *J* = 7.5, 1.2 Hz, Ar), 5.08 (2H, hept, *J* = 6.3 Hz, 2CHO), 4.71 (1H, s, CH-Ph), 4.69 (1H, s, CH-Ph), 4.47 (2H, hept, *J* = 6.3 Hz, 2CHO), 3.88 (3H, s, MeO), 3.87 (3H, s, MeO), 1.28 (3H, d, *J* = 6.3 Hz, *i*Pr), 1.27 (3H, d, *J* = 6.3 Hz, *i*Pr), 1.22 (3H, d, *J* = 6.3 Hz, *i*Pr), 1.21 (3H, d, *J* = 6.3 Hz, *i*Pr), 0.94 (3H, d, *J* = 6.3 Hz, *i*Pr), 0.93 (3H, d, *J* = 6 Hz, *i*Pr), 0.47 (3H, d, *J* = 6.3 Hz, *i*Pr), 0.45 (3H, d, *J* = 6.3 Hz, *i*Pr); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3 (C), 172.2 (C), 168.0 (C), 167.8 (C), 166.7 (C), 166.5 (C), 149.8 (C), 149.7 (C), 149.5 (C), 145.0 (C), 140.9 (C), 139.5 (C), 133.6 (C), 133.2 (C), 132.9 (C), 132.5 (C), 130.6 (CH), 130.4 (CH), 130.1 (CH), 129.7 (CH), 129.55 (C), 129.52 (CH), 129.4 (CH), 128.3 (CH), 127.5 (CH), 127.0 (CH), 126.8 (CH), 126.6 (CH), 126.2 (CH), 122.1 (CH), 122.0 (CH), 120.1 (CH), 119.9 (CH), 118.3 (CH), 117.7 (CH), 110.5 (CH), 110.3 (CH), 102.9 (C), 101.9 (C), 71.7 (C), 71.4 (C), 70.28 (CH), 70.27 (CH), 69.7 (CH), 69.6 (CH), 55.8 (CH_3), 55.7 (CH_3), 48.8 (CH), 48.6 (CH), 21.5 (CH_3), 21.3 (CH_3), 21.2 (CH_3), 20.4 (CH_3), 20.3 (CH_3); HRMS (ESI) *m/z* 577.2111 $[M+H]^+$, $C_{32}H_{33}ClN_2O_6$ requires 577.2100.

Determination of the ee: Compound **7k** dissolved in THF was treated with 37% hydrochloric acid at 40 °C. The resulting ketone was obtained as a *ca.* 78:22 diastereomer mixture. Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 80:20, 1 mL/min. *major enantiomer (both diastereomers)* t_r = 12.9 min, *minor enantiomer (both diastereomers)* t_r = 19.5 min. Major isomer (*trans*): $[\alpha]_D^{20}$ 32.4 (*c* 1.0, $CHCl_3$, for the diastereomer mixture); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.21 (2H, m, Ar), 7.18 (1H, dd, *J* = 8.1, 1.2 Hz, Ar), 7.12, (td, *J* = 6.9, 1.8 Hz, Ar), 7.08-6.80 (5H, m, Ar), 6.63 (1H, s, NH), 5.11 (2H, hept, *J* = 6.3 Hz, 2CHO), 4.89 (1H, d, *J* = 7.5 Hz , CH-Ph), 4.81 (1H, d, *J* = 7.5 Hz, CH-CO), 4.48 (2H, hept, *J* = 6.3 Hz, 2CHO), 1.30 (3H, d, *J* = 6.3 Hz, *i*Pr), 1.25 (3H, d, *J* = 6.3 Hz, *i*Pr), 0.96 (3H, d, *J* = 6.3 Hz, *i*Pr), 0.42 (3H, d, *J* = 6.3 Hz, *i*Pr); Minor isomer (*cis*): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (1H, ddd, *J* = 7.5, 1.8, 0.9 Hz, Ar), 7.41-6.80 (8H, m, Ar), 6.60 (1H, s, NH), 5.16 (2H, hept, *J* = 6.3 Hz, 2CHO), 4.94 (2H, s, CH-Ph+CH-CO), 4.61 (2H, hept, *J* = 6.3 Hz, 2CHO), 1.31 (3H, d, *J* = 6.3 Hz, *i*Pr), 1.25 (3H, d, *J* = 6.3 Hz, *i*Pr), 1.03 (3H, d, *J* = 6.3 Hz, *i*Pr), 0.56 (3H, d, *J* = 6.3 Hz, *i*Pr).

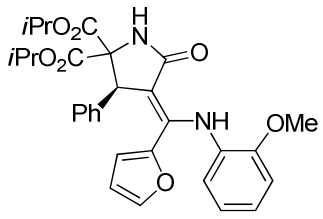
(*R*,*Z*)-Diisopropyl 4-(((2-methoxyphenyl)amino)(2-nitrophenyl)methylene)-5-oxo-3-phenylpyrrolidine-2,2-dicarboxylate (26cl)



Obtained as a *ca.*1:1 mixture of diastereomers. Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 80:20, 1 mL/min. *major enantiomer (both diastereomers)* t_r = 19.7 min, *minor enantiomer (both diastereomers)* t_r = 26.4 min.

Orange solid, mp 98-100 ºC (hexane-EtOAc); $[\alpha]_D^{20}$ -15.1 (*c* 0.97, $CHCl_3$, *for the diastereomer mixture*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.81 (1H, s, NH), 10.70 (1H, s, NH), 8.02 (1H, dd, *J* = 8.1, 1.2 Hz, Ar), 7.74-7.63 (3H, m, Ar), 7.44 (1H, td, *J* = 7.5, 1.5 Hz, Ar), 7.29 (1H, td, *J* = 7.5, 1.5 Hz, Ar), 6.97-6.84 (7H, m, Ar), 6.71-6.60 (6H, m, Ar), 6.35-6.11 (6H, m, Ar+NH), 5.82 (1H, dd, *J* = 8.1, 2.4 Hz, Ar), 5.08 (2H, hept, *J* = 6.3 Hz, 2CHO), 4.51 (1H, s, CHO), 4.40 (2H, hept, *J* = 6.3 Hz, 2CHO), 4.32 (1H, s, CH-Ph), 3.84 (3H, s, MeO), 3.79 (3H, s, MeO), 1.22 (3H, d, *J* = 6 Hz, *i*Pr), 1.20 (3H, d, *J* = 6.3 Hz, *i*Pr), 1.16 (3H, d, *J* = 6.3 Hz, *i*Pr), 1.15 (3H, d, *J* = 6.3 Hz, *i*Pr), 0.86 (3H, d, *J* = 6.3 Hz, *i*Pr), 0.85 (3H, d, *J* = 6.3 Hz, *i*Pr), 0.40 (d, *J* = 6.3 Hz, *i*Pr); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1 (C), 171.8 (C), 168.0 (C), 167.4 (C), 166.4 (C), 150.2 (C), 150.1 (C), 149.9 (C), 148.2 (C), 147.7(C), 146.1 (C), 140.3 (C), 138.7 (C), 134.2 (CH), 132.7 (CH), 131.6 (CH), 130.8 (CH), 130.0 (CH), 129.6 (C), 129.5 (CH), 129.4 (C), 129.3 (CH), 128.5 (CH), 127.7 (CH), 127.1 (CH), 126.9 (CH), 124.5 (CH), 124.4 (CH), 122.8 (CH), 122.3 (CH), 120.0 (CH), 119.8 (CH), 118.4 (CH), 110.8 (CH), 110.5 (CH), 101.5 (C), 99.7 (C), 71.5 (C), 71.4 (C), 70.5 (CH), 70.4 (CH), 69.8 (CH), 55.8 (CH_3), 55.7 (CH_3), 48.9 (CH), 48.3 (CH), 21.43 (CH_3), 21.39 (CH_3), 21.3 (CH_3), 21.1 (CH_3), 20.4 (CH_3); HRMS (ESI) *m/z* 588.2331 $[M+H]^+$, $C_{32}H_{33}N_3O_8$ requires 588.2340.

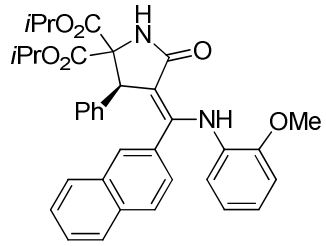
(*R,Z*)-Diisopropyl 4-(furan-2-yl((2-methoxyphenyl)amino)methylene)-5-oxo-3-phenylpyrrolidine-2,2-dicarboxylate (26cm)



Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 80:20, 1 mL/min. *major enantiomer* t_r = 14.3 min, *minor enantiomer* t_r = 26.6 min

Orange oil; $[\alpha]_D^{20}$ -144.8 (*c* 0.97, $CHCl_3$, ee = 83%); ^1H NMR (300 MHz, $CDCl_3$) δ 9.99 (1H, s, NH), 7.28 (1H, q, *J* = 0.9 Hz, Ar), 7.10-7.07 (5H, m, Ar), 6.84-6.77 (2H, m, Ar), 6.56 (1H, m, Ar), 6.25 (1H, s, NH), 6.20 (1H, dd, *J* = 3.6, 1.5 Hz, Ar), 6.16 (1H, dd, *J* = 3.6, 0.9 Hz, Ar), 6.11 (1H, dd, *J* = 8.1, 1.2 Hz, Ar), 5.30 (1H, s, CH-Ph), 5.10 (1H, hept, *J* = 6.3 Hz, CHO), 4.51 (1H, hept, *J* = 6.3Hz, CHO), 3.86 (3H, s, MeO), 1.28 (3H, d, *J* = 6.3 Hz, *i*Pr), 1.24 (3H, d, *J* = 6.4 Hz, *i*Pr), 0.98 (3H, d, *J* = 6.3 Hz, *i*Pr), 0.62 (3H, d, *J* = 6.3 Hz, *i*Pr); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3 (C), 167.9 (C), 166.6 (C), 150.1 (C), 146.4 (C), 142.7 (CH), 140.5 (C), 140.3 (C), 130.8 (C), 128.5 (CH), 127.7 (CH), 127.0 (CH), 122.0 (CH), 120.2 (CH), 118.8 (CH), 113.3 (CH), 110.0 (CH), 110.4 (CH), 104.9 (C), 71.5 (C), 70.4 (CH), 70.0 (CH), 55.7 (CH_3), 48.6 (CH), 21.5 (CH_3), 21.3 (CH_3), 21.2 (CH_3), 20.6 (CH_3); HRMS (ESI) *m/z* 533.2278 $[M+H]^+$, $C_{30}H_{32}N_2O_7$ requires 533.2282.

(*R,Z*)-Diisopropyl 4-(((2-methoxyphenyl)amino)(naphthalen-2-yl)methylene)-5-oxo-3-phenylpyrrolidine-2,2-dicarboxylate (26cn)

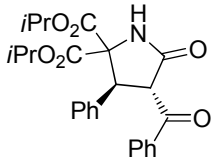


Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 80:20, 1 mL/min. *major enantiomer* t_r = 9.1 min, *minor enantiomer* t_r = 17.5 min

Yellow oil; $[\alpha]_D^{20}$ -99.0 (*c* 0.97, $CHCl_3$, ee = 98%); ^1H NMR (300 MHz, $CDCl_3$) δ 10.67 (1H, s, NH), 7.77 (1H, dd, *J* = 7.8, 1.5 Hz, Ar), 7.62 (2H, d, *J* = 8.4 Hz, Ar), 7.52-7.42 (3H, m, Ar), 7.04 (1H, br s, Ar), 6.97 (1H, dt, *J* = 7.2, 1.2 Hz, Ar), 6.87 (2H, t, *J* = 7.8 Hz, Ar), 6.76-6.67 (4H, m, Ar), 6.26 (1H, td, *J* = 8.1, 1.5 Hz, Ar), 6.21 (1H, s, NH), 6.05 (1H, dd, *J* = 8.1, 1.5 Hz, Ar), 5.11 (1H, hept, *J* = 6.3 Hz, CHO), 4.83 (s, CH-Ph), 4.49 (1H, hept, *J* = 6.3 Hz, CHO), 3.90 (3H, s, MeO), 1.30 (3H, d, *J* = 6.3 Hz, *i*Pr), 1.24 (3H, d, *J* = 6.3 Hz, *i*Pr), 0.93 (3H, d, *J* = 6.3 Hz, *i*Pr), 0.49 (3H, d, *J* = 6 Hz, *i*Pr); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4 (C), 168.0 (C), 166.5 (C), 151.9 (C), 149.8 (C), 140.6 (C), 133.0 (C), 132.7 (C), 132.0 (C), 129.9 (C), 128.5 (CH), 128.3 (CH), 128.1 (CH), 127.6 (CH), 127.5 (CH), 126.7 (CH), 126.5 (CH), 126.0 (CH), 125.5 (CH), 121.7 (CH), 119.9 (CH), 119.2 (CH), 110.3 (CH), 103.2 (C), 71.5 (C), 70.3 (CH), 69.7 (CH), 55.7 (CH_3), 48.6 (CH), 21.5 (CH_3), 21.3 (CH_3), 21.2 (CH_3), 20.5 (CH_3); HRMS (ESI) *m/z* 593.2650 $[M+H]^+$,$C_{36}H_{36}N_2O_6$ requires 593.2646.

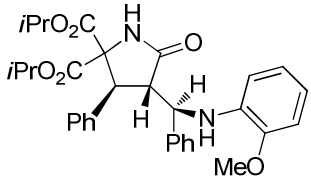
5.6.4. Synthetic transformations

Diisopropyl (3*S*,4*S*)-4-benzoyl-5-oxo-3-phenylpyrrolidine-2,2-dicarboxylate (27ca).



37% Hydrochloric acid (0.3 mL) was added to a solution of compound **26ca** (59.0 mg, 0.11 mmol, ee = 94%) in THF (4.3 mL). The reaction mixture was stirred for 30 min, quenched with water (60 mL), extracted with dichloromethane (4×45 mL) and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, column chromatography eluting with hexane/EtOAc (80:20) gave 43.0 mg (90%) of compound **27ca**. Chiral HPLC analysis: Chiralcel AD-H, hexane-*i*PrOH 85:15, 1 mL/min. *major enantiomer* t_r = 22.1 min, *minor enantiomer* t_r = 39.9 min. White solid, mp 58-60 ºC; $[\alpha]_D^{20}$ 63.2 (*c* 1.0, $CHCl_3$, ee = 92%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (2H, dd, *J* = 6.9, 1.2 Hz, Ar), 7.56 (1H, tt, *J* = 7.5, 1.2 Hz, Ar), 7.46 (1H, d, *J* = 7.8 Hz, Ar), 7.41-7.38 (3H, m, Ar), 7.32-7.19 (3H, m, Ar), 6.81 (1H, s, NH), 5.13 (1H, hept, *J* = 6.3 Hz, CHO), 4.93 (1H, d, *J* = 7.2 Hz, CH-Ph), 4.81 (1H, d, *J* = 7.2 Hz, CH-CO), 4.63 (1H, hept, *J* = 6.3Hz, CHO), 1.26 (3H, d, *J* = 6.3 Hz, *i*Pr), 1.25 (3H, d, *J* = 6.3 Hz, *i*Pr), 1.04 (3H, d, *J* = 6.3 Hz, *i*Pr), 0.55 (3H, d, *J* = 6.3 Hz, *i*Pr); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.4 (C), 171.3 (C), 167.2 (C), 166.7 (C), 136.7 (C), 135.9 (C), 133.7 (CH), 129.4 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.2 (CH), 71.8 (C), 70.7 (CH), 70.6 (CH), 56.5 (CH), 48.1 (CH), 21.4 (CH_3), 21.37 (CH_3), 21.31 (CH_3), 20.5 (CH_3); HRMS (ESI) *m/z* 438.1913 $[M+H]^+$, $C_{25}H_{27}NO_6$ requires 438.1911.

Diisopropyl (3*S*,4*S*)-4-((*R*)-((2-methoxyphenyl)amino)(phenyl)methyl)-5-oxo-3-phenylpyrrolidine-2,2-dicarboxylate (28ca)



$NaBH_3CN$ (41.8 mg, 0.67 mg) and AcOH (14 μL, 0.25 mmol) were successively added to a solution of compound **26ca** (60 mg, 0.11 mmol, ee = 94%) in absolute EtOH (1.2 mL) at 0 ºC under nitrogen atmosphere. The solution was stirred at room temperature for 25 hours and chromatographed on silica gel eluting with hexane/EtOAc (80:20) mixture to give 45.3 mg (75%) of compound **28ca** and 6.6 mg (11%) of its isomer **29ca**.

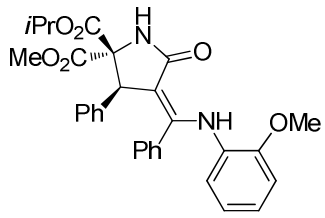
Chiral HPLC analysis: Chiralpak IC, hexane-*i*PrOH 80:20, 1 mL/min. **Major diastereomer**: *major enantiomer* t_r = 11.2 min, *minor enantiomer* t_r = 14.2 min. **Minor diastereomer**: *major enantiomer* t_r = 27.4 min, *minor enantiomer* t_r = 19.9 min.

Major diastereomer 28ca: White solid; mp 93-95 °C (hexane-EtOAc); $[\alpha]_D^{20}$ -1.6 (*c* 1.0, $CHCl_3$, ee = 95%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (2H, dd, *J* = 6.4, 1.5 Hz, Ar), 7.34-7.17 (8 H, m, Ar), 6.66-6.53 (3H, m, Ar), 6.29 (1H, dd, *J* = 7.8, 1.8 Hz, Ar), 6.25 (1H, s, NH), 5.09 (1H, d, *J* = 6.6 Hz, NH), 4.99 (1H, hept, *J* = 6.3 Hz, CHO), 4.94 (1H, dd, *J* = 6.6, 5.1 Hz, CH-NH), 4.59 (1H, hept, *J* = 6.3 Hz, CHO), 4.17 (1H, d, *J* = 9.0 Hz, CH-Ph), 3.67 (3H, s, MeO), 3.50 (1H, dd, *J* = 9.0, 5.1 Hz, CH-CO), 1.20 (3H, d, *J* = 6.3 Hz, *i*Pr), 1.18 (3H, d, *J* = 6.3 Hz, *i*Pr), 1.03 (3H, d, *J* = 6 Hz, *i*Pr), 0.49 (3H, d, *J* = 6.3 Hz, *i*Pr); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8 (C), 167.5 (C), 167.0 (C), 146.9 (C),

139.8 (C), 137.1 (C), 136.6 (C), 129.0 (CH), 128.6 (CH), 128.5 (CH), 127.9 (CH), 127.52 (CH), 127.46 (CH), 121.0 (CH), 116.7 (CH), 111.1 (CH), 109.4 (CH), 71.1 (C), 70.5 (CH), 70.4 (CH), 57.2 (CH), 55.4 (CH_3), 53.2 (CH), 47.3 (CH), 21.41 (CH_3), 21.36 (CH_3), 21.3 (CH_3), 20.5 (CH_3); HRMS (ESI) *m/z* 545.2657 $[M+H]^+$, $C_{32}H_{36}N_2O_6$ requires 545.2646.

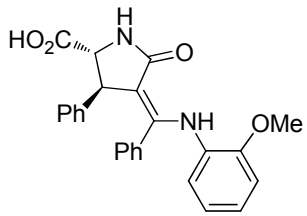
Minor diastereomer 29ca: White solid, mp 83-85 °C (hexane-EtOAc); $[\alpha]_D^{20}$ -12.8 (*c* 0.47, $CHCl_3$, ee = 89%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.15 (11H, m, Ar), 6.61-6.57 (1H, m, Ar), 6.48-6.44 (2H, m, Ar), 6.40 (1H, s, NH), 5.84-5.81 (1H, m, CH-Ph), 5.10 (1H, hept, *J* = 6.3 Hz, CHO), 4.63 (1H, hept, *J* = 6.3 Hz, CHO), 4.56 (1H, d, *J* = 7.5 Hz, CH-Ph), 4.32 (1H, d, *J* = 9.3 Hz, NH), 3.76 (3H, s, MeO), 3.71 (1H, dd, *J* = 8.7, 8.1 Hz, CH-CO), 1.27 (3H, d, *J* = 6.3 Hz, *i*Pr), 1.24 (3H, d, *J* = 6.3 Hz, *i*Pr), 1.02 (3H, d, *J* = 6.3 Hz, *i*Pr), 0.55 (3H, d, *J* = 6.3 Hz, *i*Pr); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0 (C), 167.3 (C), 166.0 (C), 146.7 (C), 141.4 (C), 136.2 (C), 135.0 (C), 128.1 (CH), 128.0 (CH), 127.8 (CH), 127.5 (CH), 127.0 (CH), 120.8 (CH), 116.4 (CH), 111.1 (CH), 109.3 (CH), 70.8 (CH), 70.5 (C), 70.2 (CH), 55.4 (CH_3), 55.0 (CH), 51.3 (CH), 49.8 (CH), 21.5 (CH_3), 21.4 (CH_3), 21.3 (CH_3), 20.5 (CH_3); HRMS (ESI) *m/z* 545.2650 $[M+H]^+$, $C_{32}H_{36}N_2O_6$ requires 545.2646 .

2-Isopropyl 2-methyl (2*R*,3*R*,*Z*)-4-(((2-methoxyphenyl)amino)(phenyl)methylene)-5-oxo-3-phenylpyrrolidine-2,2-dicarboxylate (30ca).



A 1 M solution of NaOMe in MeOH (55 μL, 0.055 mmol) was added to compound **26ca** (30 mg, 0.055 mmol, ee = 94%) dissolved in MeOH (1 mL) under nitrogen atmosphere. The solution was heated at 65 °C for 1 h, diluted with EtOAc (70 mL), washed with water (5×5 mL) and brine (5 mL), dried under $MgSO_4$ and concentrated under reduced pressure to give 25.2 mg (89%) of compound **30ca**: Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 80:20, 1 mL/min. *major enantiomer* t_r = 10.3 min, *minor enantiomer* t_r = 26.0 min. Colorless oil; $[\alpha]_D^{20}$ -184.3 (*c* 1.0, $CHCl_3$, ee = 94%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.55 (1H, s, NH), 7.28-7.20 (1H, m, Ar), 7.17 (2H, t, *J* = 7.5 Hz, Ar), 7.10-6.89 (5H, m, Ar), 6.85-6.63 (4H, m, Ar), 6.38 (1H, ddd, *J* = 8.4, 6.6, 2.7 Hz, Ar), 6.07 (1H, s, NH), 6.03 (1H, dd, *J* = 8.1, 1.2 Hz, Ar), 4.83 (1H, s, CH-Ph), 4.52 (1H, hept, *J* = 6.3Hz, CHO), 3.89 (3H, s, MeO), 3.81 (3H, s, MeO), 0.92 (3H, d, *J* = 6.3 Hz, *i*Pr), 0.57 (3H, d, *J* = 6.3 Hz, *i*Pr); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4 (C), 169.2 (C), 166.4 (C), 152.4 (C), 149.9 (C), 140.4 (C), 129.8 (C), 128.7 (CH), 128.4 (CH), 127.6 (CH), 126.8 (CH), 121.9 (CH), 119.9 (CH), 119.6 (CH), 110.4 (CH), 102.3 (C), 71.5 (C), 70.0 (CH), 55.8 (CH_3), 53.3 (CH_3), 48.9 (CH), 21.2 (CH_3), 20.6 (CH_3); HRMS (ESI) *m/z* 515.2179 $[M+H]^+$, $C_{30}H_{31}N_2O_6$ requires 515.2177.

(2*R*,3*R*,*Z*)-4-(((2-methoxyphenyl)amino)(phenyl)methylene)-5-oxo-3-phenylpyrrolidine-2-carboxylic acid (31ca).



A 25% solution of tetraethylammonium hydroxide in MeOH (38 μL, 0.22 mmol) was added to a solution of compound **26ca** (30.0 mg, 0.055 mmol, ee = 94%) in dimethylsulfoxide (1.5 mL) under nitrogen, and the reaction flask was introduced in a bath at 80 °C. After 36 h, water was added (10 mL). The mixture was acidified with 2M HCl until pH 2 and extracted with dichloromethane (3×30 mL), the organic layer was washed with water (3×5 mL), brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give 19.0 mg (87%) of acid **31ca**. Yellow oil; $[\alpha]_D^{20}$ -88.9 (*c* 1.0, $CHCl_3$, ee = 94%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.53 (1H, s, OH), 8.01 (1H, s, NH), 7.26-7.20 (3H, m, Ar), 7.18-7.13 (1H, m, Ar), 7.11-7.07 (3H, m, Ar), 6.98 (2H, d, *J* = 6.6 Hz, Ar), 6.89 (1H, dd, *J* = 8.1, 1.2 Hz, Ar), 6.80 (2H, dd, *J* = 8.1, 1.8 Hz, Ar), 6.71 (1H, dt, *J* = 7.5, 1.5 Hz, Ar), 6.38 (1H, dd, *J* = 7.8, 1.8 Hz, Ar), 5.96 (1H, dd, *J* = 7.8, 0.9 Hz, Ar), 4.10 (1H, s, CH-Ph), 3.83 (3H, s, MeO), 3.74 (1H, s, CH-CO); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.3 (C), 149.6 (C), 149.3 (C), 145.2 (C), 134.5 (C), 129.4 (C), 128.7 (CH), 128.4 (CH), 128.21 (CH), 128.17 (CH), 126.3 (CH), 126.2 (CH), 121.5 (CH), 119.8 (CH), 119.1 (CH), 110.9 (CH), 104.4 (C), 61.9 (CH), 55.6 (CH_3), 46.8 (CH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.56 (1H, s, NH), 7.25-6.80 (11H, m, Ar), 6.74 (1H, s, NH), 6.72 (1H, m, Ar), 6.37 (1H, ddd, *J* = 8.4, 6.6, 3.0 Hz, Ar), 6.01 (1H, d, *J* = 7.8 Hz, Ar), 4.27 (1H, d, *J* = 2.0 Hz, CH-Ph), 4.04 (1H, d, *J* = 2.0 Hz, CH-CO), 3.87 (3H, s, MeO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9 (C), 152.4 (C), 150.0 (C), 145.3 (C), 134.5 (C), 129.9 (C), 128.5 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 126.7 (CH), 126.2 (CH), 121.8 (CH), 119.8 (CH), 119.7 (CH), 110.4 (CH), 101.9 (C), 62.4 (CH), 55.7 (CH_3), 47.1 (CH); HRMS (ESI) *m/z* 415.1655 $[M+H]^+$, $C_{25}H_{22}N_2O_4$ requires 415.1655

6. CONCLUSIONS

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1. Several new asymmetric conjugate addition reactions of malonate ester derivatives and α,β-unsaturated imines have been developed using different chiral metal complexes as catalysts. In these reactions, the use of molecular sieves as an additive was crucial to obtain the desired products with high yields and stereoselectivity.

2. The enantioselective conjugate addition of dimethyl malonate to α,β-unsaturated *N*-tosyl imines derived from chalcones was carried out in the presence of a catalytic amount of the **pyBOX1**-La(OTf)$_3$ complex, achieving the corresponding chiral *E*-enamines with excellent yields, good diastereomeric ratios and enantiomeric excesses up to 93%. The reaction could be applied to unsaturated imines bearing aromatic and heteroaromatic substituents in both, the β-carbon of the alkene and the azomethinic carbon. Also, the reaction tolerated aliphatic groups yielding the corresponding 1,4-adducts with slightly lower enantiomeric excess. This reaction is the first example of enantioselective conjugate addition of 1,3-dicarbonyl compounds to α,β-unsaturated imines reported in literature. The (*S*,*E*) stereochemistry of the resulting products was established by NOESY experiments and chemical correlation with a compound of known stereochemistry.

3. A similar reaction involving the addition of dimethyl malonate to β-trifluoromethyl α,β-unsaturated *N*-tosyl imines has also been developed. In this case, the reaction performed better in the presence of the **BOX7**-Cu(OTf)$_2$ or **BOX7**-Mg(OTf)$_2$ complexes than with **pyBOX1**-La(OTf)$_3$. Better enantioselectivity was obtained with the copper catalyst while the magnesium complex provided the reaction products with better diastereoselectiviy. In both cases, the trifluoromethylated (*S*,*E*)-enamines were obtained, as it could be determined by X-ray analysis of one of the products.

4. We have developed a diastereodivergent Mukaiyama-Michael reaction of silylketene acetals to conjugated *N*-tosyl ketimines derived from β,γ-unsaturated α-keto esters. Although the reaction could not be carried out in an enantioselective fashion, the *E*- or *Z*-dehydroamino esters were obtained in a stereocontrolled manner starting from a same set of reactants. The non-catalytic reaction favored the *Z*-diastereomer while in the presence of a catalytic amount of copper triflate the *E*-diastereomer was obtained. The stereochemistry of the resulting products was determined by both NOESY experiments and X-ray analysis. Based on these results, we also established a correlation between the ^{1}H NMR chemical shifts and the stereochemistry of the double bond in these compounds.

5. The **pyBOX1**-La(OTf)$_3$ complex catalyzed the enantioselective conjugate addition of dialkyl malonates to conjugated *N*-tosyl imines derived from β,γ-unsaturated α-keto esters to give the corresponding chiral α,β-dehydroamino esters with excellent yields, diastereomeric ratios and high enantiomeric excesses. The reaction could be also performed with dimethyl 2-methylmalonate. In all the cases, the reaction delivered the

products with the *Z* configuration at the enamine double bond as it could be determined by NOESY experiments and X-ray analysis.

6. An extension of the above reaction involved the enantioselective conjugate addition of diethyl 2-chloromalonate to α,β-unsaturated *N*-tosyl imines derived from β,γ-unsaturated α-keto esters. As with diethyl malonate, the addition of diethyl 2-chloromalonate catalyzed by pyBOX-La(OTf)$_3$ complexes led to the corresponding dehydroamino esters with the *Z*-configuration at the double bond. Excellent yields, diasteromeric ratios and good enantiomeric excesses were obtained for a number of imines. On the other hand, the reaction catalyzed by the **pyBOX1**-Ca(OTf)$_2$ complex provided the dehydroamino esters with the *E*-configuration at the double bond, again with excellent yields, high diastereomeric ratios and almost full enantioselectivity. Thus both the *E*- and *Z*- chiral dehydroamino esters were available from the same set of reactants with high enantioselectivity by simply changing the catalyst.

The resulting chloro-derivatives could be subjected to hydrogenolysis in the presence of a Rh-dppp complex without isomerization or erosion of the optical purity. This reaction gave access to compounds (*E*)-**19** which were not directly available from diethyl malonate.

7. The catalytic asymmetric formal [3+2] cycloaddition of diisopropyl 2-isocyanatomalonate and α,β-unsaturated *N*-(*o*-methoxyphenyl)imines to give highly substituted chiral γ-lactams has been developed. The reaction was catalyzed by the **BOX10**-Mg(OTf)$_2$ complex, and the chiral pyrrolidinones featuring a conjugated exocyclic double bond were obtained with excellent yields, full diastereoselectivity and high to excellent enantioselectivities, for a significative number of unsaturated imines. The use of the *N*-(*o*-methoxyphenyl) group was essential for the success of the reaction as neither the unsaturated ketone nor the unsaturated *N*-tosyl imine were reactive with this catalyst. Furthermore, the reaction did not require diastereomerically pure imines as starting materials. Also, the bulky diisopropyl ester was important to achieve high enantioselectivity. The reaction is thought to proceed by a tandem Michael addition/intramolecular addition to isocyanate process. The configuration of the chiral center as well as the geometry of the alkene in the resulting lactams was determined by X-ray analysis.

8. The potential applicability of the products resulting from the above reactions has been proved by performing several synthetic transformations to obtain nitrogen-containing compounds such as δ-amino esters, piperidones, pyrrolidones or cyclopropanic compounds.

7. REFERENCES

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8. RESUMEN EN CASTELLANO

8. RESUMEN EN CASTELLANO

8.1. Objetivos

Las iminas α,β-insaturadas (1-azabutenos) han sido frecuentemente utilizadas como moléculas de partida para la síntesis de diferentes compuestos nitrogenados. La adición conjugada de nucleófilos carbonados a este tipo de compuestos es una manera eficiente de formar nuevos enlaces C-C dando lugar a la síntesis de enaminas con formación concomitante de un nuevo centro estereogénico. No obstante, al contrario de lo que sucede con los compuestos carbonílicos insaturados y los nitroalquenos, la adición conjugada enantioselectiva de nucleófilos carbonados a iminas α,β-insaturadas ha sido mucho menos estudiada y en particular, no existían ejemplos de adición asimétrica de compuestos 1,3-dicarbonílicos antes de del inicio de esta investigación.

El desarrollo de reacciones de adición conjugada enantioselectivas a iminas α,β-insaturadas plantea diferentes retos:

a. Menor reactividad del sustrato debido a la baja electronegatividad del átomo de N.

b. Control de la regioselectividad: los 1-azabutenos a menudo prefieren dar lugar a productos de adición 1,2 o productos de doble adición.

c. Control de la diastereoselectividad: la geometría del doble enlace de las enaminas formadas puede ser tanto *E* como *Z*.

d. Control de la enantioselectividad: el nuevo centro estereogénico debe ser sintetizado preferentemente en una única configuración.

Teniendo en cuenta estos desafíos, esta tesis se centra en el desarrollo de nuevas adiciones conjugadas diastereo- y enantioselectivas de nucleófilos carbonados a iminas α,β-insaturadas mediante catálisis metálica. Las siguientes reacciones han sido estudiadas:

1. Adición conjugada asimétrica de ésteres malónicos a *N*-tosil iminas α,β-insaturadas catalizada por complejos de La(III).

2. Adición conjugada asimétrica de ésteres malónicos a β-trifluorometil *N*-tosil iminas α,β-insaturadas catalizada por complejos de Cu(II) y complejos de Mg(II).

3. Reacción de Mukaiyama-Michael diastereoselectiva de silil acetales de cetena y *N*-tosil iminas derivadas de α-cetoésteres β,γ-insaturados.

4. Adición conjugada asimétrica de ésteres malónicos a *N*-tosil iminas derivadas de α-cetoésteres β,γ-insaturados catalizada por complejos de La(III).

5. Adición conjugada asimétrica diastereodivergente de 2-cloromalonatos a iminas derivadas de α-cetoésteres β,γ-insaturados catalizada por complejos de La(III) o complejos de Ca(II).

6. Cicloadición [3+2] asimétrica entre ésteres 2-isocianatomalónicos e iminas α,β-insaturadas mediante un proceso tándem adición de Michael/adición intramolecular a isocianato.

8.2. Resumen y conclusiones

1. Se han llevado a cabo diferentes reacciones de adición conjugada enantioselectiva de ésteres malónicos a iminas α,β-insaturadas utilizando diferentes complejos metálicos quirales como catalizadores. En estas reacciones el uso de tamiz molecular como aditivo es crucial para obtener los productos deseados con altos rendimientos y estereoselectividades.

2. La adición conjugada enantioselectiva de malonato de dimetilo a *N*-tosil iminas α,β-insaturadas derivadas de chalconas se llevó a cabo en presencia de cantidades catalíticas del complejo **pyBOX1**-La(OTf)$_3$, obteniendo las correspondientes enaminas quirales con excelentes rendimientos, buenas relaciones diastereoisoméricas y excesos enantioméricos de hasta 93% (Tabla 3, página 64). La reacción se puede llevar a cabo con iminas que poseen sustituyentes aromáticos o heteroaromáticos unidos tanto al carbono β como al carbono azometínico. La reacción también tolera sustituyentes alifáticos dando lugar a los correspondientes aductos 1,4 con un ligero descenso en el exceso enantiomérico. Esta reacción representa el primer ejemplo descrito en la literatura de adición conjugada enantioselectiva de compuestos 1,3-dicarbonílicos a iminas α,β-insaturadas. La estereoquímica (*S*,*E*) de los productos resultantes se estableció por experimentos de tipo NOESY y correlación química con un compuestos de estereoquímica conocida.

3. También se ha estudiado una reacción similar consistente en la adición conjugada de malonato de dimetilo a β-trifluorometil *N*-tosil iminas α,β-insaturadas. En este caso, la reacción funciona mejor en presencia de **BOX7**-Cu(OTf)$_2$ o **BOX7**-Mg(OTf)$_2$ que de **pyBOX1**-La(OTf)$_3$. En presencia del complejo de cobre se obtuvieron mejores enantioselectividades (Tabla 6, página 73) mientras que en presencia del complejo de magnesio los productos fueron obtenidos con mejor diastereoselectividad (Tabla 8, página 75). En ambos casos, se obtuvieron las (*S*,*E*)-enaminas trifluorometiladas, tal y como se puedo determinar mediante análisis de rayos X.

4. Hemos desarrollado la reacción de Mukaiyama-Michael diastereodivergente entre silil acetales de cetena y *N*-tosyl cetiminas derivadas de α-cetoésteres β,γ-insaturados. Aunque la reacción no se pudo realizar de manera enantioselectiva, los *E*- o *Z*-dehidroamino ésteres se obtuvieron de manera estereocontrolada, partiendo de los mismos sustratos. La reacción en ausencia de catalizador favoreció la obtención del diastereoisómero *Z* (Tabla 9, página 81) mientras que la presencia de una cantidad catalítica de triflato de cobre favoreció el diastereoisómero *E* (Tabla 10, página 82). La estereoquímica de los productos resultantes se determinó mediante experimentos tipo NOESY. También pudimos establecer una correlación entre los desplazamientos químicos de RMN de ^{1}H y la estereoquímica del doble enlace en estos compuestos.

5. El complejo **pyBOX1**-La(OTf)$_3$ catalizó la adición conjugada enantioselectiva de dialquil malonatos a *N*-tosil cetiminas derivadas de α-cetoésteres β,γ-insaturados dando lugar a los correspondientes α,β-dehidroamino ésteres con excelentes rendimientos y

relaciones diastereoisoméricas, y excesos enantioméricos elevados (Tabla 14, página 90). La reacción también se pudo llevar a cabo utilizando 2-metilmalonato de dimetilo (Tabla 15, página 91). En todos los casos, la reacción proporcionó los productos con la configuración *Z* en el doble enlace de la enamina como se pudo determinar mediante experimentos tipo NOESY y rayos X.

6. Una prolongación de la reacción anterior consistió en la adición conjugada enantioselectiva de 2-cloromalonato de dietilo a *N*-tosil iminas derivadas de α-cetoésteres β,γ-insaturados. Al igual que con malonato de dietilo, la adición conjugada de 2-cloromalonato de dietilo catalizada por complejos de pyBOX-La(OTf)$_3$ dio lugar a los correspondientes dehidroamino ésteres con la configuración *Z* en el doble enlace, obteniéndose excelentes rendimientos y relaciones diastereoisoméricas y buenos excesos enantioméricos para un conjunto de iminas (Tabla 17, página 95). Por otro lado, la reacción catalizada por el complejo **pyBOX1**-Ca(OTf)$_2$ dio lugar a los dehidroamino esteres con la configuración *E* en el doble enlace, con excelentes rendimientos, altas relaciones diastereoisoméricas y excelente enantioselectividad (Tabla 19, página 97). De esta forma fue posible obtener los *E* o *Z* dehidroamino esteres quirales partiendo de los mismos reactivos simplemente cambiando el catalizador.

Los cloro-derivados obtenidos se pudieron someter a hidrogenolisis en presencia del complejo de Rh-dppp sin isomerización en el doble enlace o erosión de la pureza óptica. Esta reacción permitió la obtención de los compuestos (*E*)-**19**, lo cuales no pudieron ser obtenidos directamente a partir de malonato de dietilo.

7. Se ha desarrollado una cicloadición formal [3+2] catalítica enantioselectiva entre 2-isocianatomalonato de diisopropilo y *N*-(*o*-metoxifenil)iminas α,β-insaturadas para dar γ-lactamas quirales altamente sustituidas. La reacción fue catalizada por el complejo **BOX10**-Mg(OTf)$_2$, y las pirrolidinonas con un doble enlace exocíclico resultantes se obtuvieron con excelentes rendimientos, total diastereoselectividad y excelentes excesos enantioméricos (Tabla 21, página 104). El uso del grupo *N*-(*o*-metoxifenilo) fue esencial para el éxito de la reacción, ya que ni las correspondientes enonas ni las *N*-tosil iminas insaturadas reaccionaron en presencia de este catalizador. Además, la reacción no requiere el uso de iminas diastereoisoméricamente puras como sustratos de partida. Igualmente, el uso del éster diisopropílico fue crucial para la obtención de elevada enantioselectividad. La reacción posiblemente transcurre mediante un proceso tándem que implica una adición de Michael seguida de un proceso de adición intramolecular a isocianato. La configuración del centro quiral así como la geometría del doble enlace en las lactamas resultantes se determinó mediante difracción de rayos X.

8. La potencial aplicabilidad de los productos obtenidos en las reacciones anteriores ha sido demostrada mediante varias transformaciones sintéticas obteniendo diferentes compuestos nitrogenados como δ-amino esteres, piperidonas, pirrolidonas o ciclopropanos.

ANNEX

ANNEX. Publications resulting from this thesis at the moment of the lecture

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FULL PAPER

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Asymmetric Conjugate Addition of Malonate Esters to α,β-Unsaturated *N*-Sulfonyl Imines: An Expeditious Route to Chiral δ-Aminoesters and Piperidones

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Abstract: The asymmetric conjugate addition of malonate esters to α,β-unsaturated *N*-sulfonyl imines is catalyzed by PyBOX/La(OTf)$_3$ complexes in the presence of 4 Å MS. The reaction gives the corresponding *E* enamines bearing a stereogenic center at the allylic position with good yields and enantiomeric ratios up to 97:3. This reaction provides a synthetic entry to chiral δ-aminoesters and piperidones.

Keywords: amino acids · asymmetric catalysis · carbanions · conjugate addition · imino compounds

Introduction

Conjugate addition reactions have played a crucial role in organic synthesis. The research on this transformation has been boosted by the wide diversity of compounds that can serve as nucleophiles and electrophiles to generate a varied array of products.[1] Such reactions often result in the generation of a new stereocenter, and consequently a considerable effort has been devoted to the development of asymmetric catalytic versions of 1,4-addition reactions. Unsaturated carbonyl compounds,[2] nitroalkenes,[3] and less frequently unsaturated sulfones[4] have been used as electrophilic partners in asymmetric conjugate additions of easily enolizable nucleophiles, such as 1,3-dicarbonyl and related compounds. In this context, α,β-unsaturated imines (1-azabutenes), readily prepared through condensation of *N*-substituted amines with the parent unsaturated ketones, have emerged as an interesting family of compounds with important applications in the synthesis of nitrogen-containing molecules. Thus, numerous applications of 1-azabutenes as heterodienes in asymmetric cycloaddition reactions have been reported in the literature.[5]

In contrast to carbonyl substrates and nitroalkenes, the asymmetric conjugate addition to α,β-unsaturated imines has been scarcely explored probably due to the lower electrophilicity of these substrates. Furthermore, α,β-unsaturated imines are ambidented electrophiles that can either undergo 1,2- or 1,4-nucleophilic addition processes.[6] However, generally, the control of the regioselectivity is difficult and dependent on the nucleophile and reaction conditions, often 1,2-addition is preferred,[7] or double nucleophilic addition products are obtained.[8] On the other hand, only a much reduced number of examples regarding the enantioselective 1,4-nucleophilic addition of carbon nucleophiles to unsaturated imines have been reported.[9] In 2005, Ellman's group reported the asymmetric conjugate addition of organocuprates to chiral *N*-*tert*-butylsulfinylimines with good yields and diastereomeric ratios (d.r.) of up to 93:7.[10] The first example of catalytic enantioselective conjugate addition was reported by Tomioka's group in 2005. These authors carried out the addition of diethylzinc to *N*-sulfonyl aldimines bearing a bulky group on the azomethinic nitrogen atom in the presence of a phosphine/Cu^{I} complex to give the corresponding 1,4-alkylation products with *ee* values in the 75–91% range. The group of Carretero reported the conjugate addition of diethylzinc to unsaturated *N*-sulfonyl ketimines by using a Cu^{I}/phosphorimidite complex, obtaining the alkylated products with moderate enantioselectivity (*ee* = 70–80%).[11] Later, Palacios described the Cu^{I}-catalyzed conjugate addition of diethylzinc to a reduced number of *N*-aryl imines derived from α-ketoesters, by using a different phosphorimidite ligand with enantiomeric excesses in the 76–88% range.[12] Besides these examples, a conjugate addition of malonate esters or related 1,3-dicarbonyl compounds to unsaturated imines in an enantioselective fashion has not been reported so far, to the best of our knowledge (Scheme 1).[13] In this paper, we describe the first example of asymmetric conjugate addition of methyl malonate to unsaturated *N*-tosyl imines as an efficient procedure to access chiral δ-amino acid derivatives.

Results and Discussion

In this investigation we have used *N*-tosyl imines **2** as electrophiles since the reactivity of imines toward nucleophilic attack is significantly increased by the presence of strong electron-withdrawing groups on the azomethinic nitrogen

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E,Z-Stereodivergent synthesis of *N*-tosyl α,β-dehydroamino esters *via* a Mukaiyama–Michael addition†

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The stereodivergent synthesis of *N*-tosyl α,β-dehydroamino esters *via* a Mukaiyama–Michael addition is reported. The reaction of silylketene acetals with *N*-tosylimines derived from β,γ-unsaturated α-keto esters in dichloromethane provided the corresponding (*Z*)-α,β-dehydroamino esters while the (*E*)-isomers were obtained when the reaction was carried out in the presence of 10 mol% copper(II) triflate.

α,β-Dehydroamino acid derivatives are non-proteinogenic amino acids that are often found as structural subunits in natural products produced by bacteria, fungi, marine organisms and plants, and play an important role in the biosynthesis of other non-proteinogenic amino acids and D-amino acids (Fig. 1).[1] Some of these compounds have shown antibiotic and other intriguing biological activities.[2] The presence of the double bond in the dehydroamino acid residue reduces the conformational flexibility of peptides, a property that is useful for structure–activity studies and for the design of secondary structure in peptides,[3] and it also confers resistance to enzymatic degradation and alters their bioactivity.[4] These properties are affected by the *E*/*Z* configuration of the double bond of the dehydroamino acid moiety.[5] Furthermore, α,β-dehydroamino acid derivatives are widely used as starting materials in the synthesis of natural and unnatural α-amino acids through catalytic hydrogenation,[6] or conjugate addition,[7] as well as in the synthesis of heterocyclic compounds.[8] According to these pharmacological and synthetic potential, much synthetic effort has been devoted to the preparation of dehydroamino acids and their derivatives. Literature antecedents include elimination reactions of β-hydroxy-α-amino acids,[9] Horner–Wadsworth–Emmons and Wittig reactions,[10] condensation of aldehydes with N-protected glycine or 5-(4*H*)-oxazolone (Erlenmeyer synthesis),[11] condensation of carbonyl compounds with isocyano acetates (Schöllkopf method),[12] aminohalogenation of unsaturated esters followed by basic elimination,[13] addition of amines to alkynoates,[14] and Heck reaction.[15] In most of these procedures the thermodynamically stable *Z*-isomer is predominantly formed,[9a,10b,c,11,12b,c,13,14] while the synthesis of the *E*-isomer normally takes place with lower selectivity[9b,10a,12a] or requires the use of stereoisomerically pure starting materials that are usually prepared in multistep sequences or involves difficult isomer separation.[9c,d]

Recently, Palacios described a new approach to α,β-dehydroamino acid esters consisting in the conjugate addition of dialkyl zinc reagents to imines derived from β,γ-unsaturated α-keto esters catalysed by a copper(I)–phosphoramidite complex.[16] A similar strategy has been reported by Liu and Hu

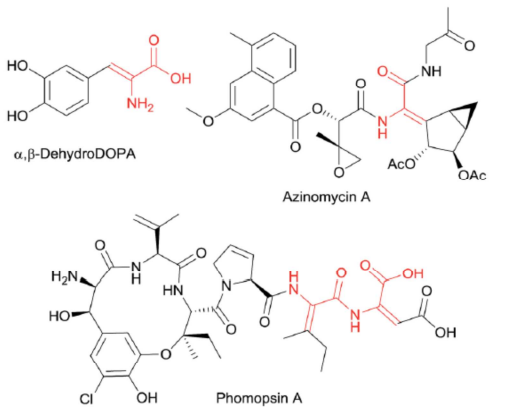

Fig. 1 Examples of natural and bioactive α,β-dehydroamino acid derivatives.

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† Electronic supplementary information (ESI) available: Experimental procedures. Copies of NMR spectra for new compounds. X-ray structures for compounds **1b** and **4m**. CCDC 1442362 and 1442206. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ra27354d

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Copper-catalysed enantioselective Michael addition of malonic esters to β-trifluoromethyl-α,β-unsaturated imines†

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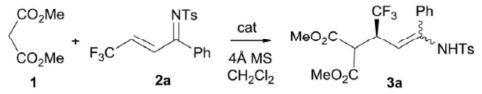
Copper triflate-BOX complexes catalyse the enantioselective conjugate addition of methyl malonate to β-trifluoromethyl-α,β-unsaturated imines to give the corresponding enamines bearing a trifluoromethylated stereogenic centre with good yields, and diastereo- and enantioselectivities. The usefulness of the method has been shown with the synthesis of optically active β-trifluoromethyl δ-amino esters and optically active trifluoromethyl piperidones.

Interest in the chemistry of chiral organofluorine compounds has experienced a tremendous growth in the last few years due to their wide range of applications in medicinal and agricultural chemistry, as well as in materials science.[1] Among organofluorinated compounds, those having a trifluoromethyl group[2] attached to a stereogenic centre deserve special attention due to the occurrence of this structural motif in bioactive compounds[3] and chiral reagents.[4] These stereocentres are most frequently prepared by nucleophilic addition reactions to trifluoromethylated prostereogenic groups such as trifluoromethylketones[5] and trifluoromethylimines.[6] In this context, several carbon nucleophiles have also been reported to undergo enantioselective Michael-type reactions[7] with β-trifluoromethyl α,β-unsaturated carbonyl compounds[8] or with nitroalkenes[9] to obtain compounds with a trifluoromethylated stereogenic centre not connected to a heteroatom.

In the last few years, α,β-unsaturated imines (1-aza-butadienes) have emerged as interesting Michael acceptors[10,11] that have been used in several enantioselective conjugate addition reactions providing chiral nitrogenated compounds.[12,13] Following our interest in the chemistry of 1-aza-butadienes,[12d,e,13b] and considering the importance of fluorine-containing amino acids in medicinal chemistry,[14] we report in this communication the first example of enantioselective conjugate addition of malonate esters to β-trifluoromethyl α,β-unsaturated *N*-tosyl imines as an efficient procedure to access the chiral β-trifluoromethyl-δ-amino acid derivatives, a reaction that has no precedent in the literature.

Our group has previously reported the enantioselective conjugate addition of dimethyl malonate to unsaturated *N*-tosyl imines derived from chalcone, using La(OTf)$_3$-pyBOX complexes in the presence of 4 Å molecular sieves (MS), with good yields and stereoselectivity.[12d,e] When this catalytic system was applied to the reaction (Scheme 1) between dimethyl malonate (**1**) and (*E*,*E*)-*N*-tosyl-4,4,4-trifluoro-1-phenylbut-2-en-1-imine (**2a**),‡ the expected Michael reaction product **3a** was obtained with good yields but low enantioselectivities with different La(OTf)$_3$-pyBOX complexes (see the ESI†). Other pyBOX complexes with trivalent metal triflates such as Yb(OTf)$_3$, Sc(OTf)$_3$ or In(OTf)$_3$ performed similarly or worse than La(OTf)$_3$. Due to the low stereocontrol obtained with trivalent metal-pyBOX complexes, we proceeded to test the reaction in the presence of Cu(OTf)$_2$-BOX complexes (Fig. 1 and Table 1).[15]

The reaction requires the presence of 4 Å molecular sieves (MS) to proceed (Table 1, entries 1 and 2). 4 Å MS probably work as an effective proton scavenger favouring the generation of the dimethyl malonate enolate in sufficient concentration.[16] Under these reaction conditions, several BOX ligands were tested (Table 1, entries 2–11). All BOX ligands with the exception of **BOX8** favoured the formation of the *E*-enamine. Indene-derived bisoxazoline (**BOX7**) led to the best results in terms of yield and stereoselectivity providing enamine **3a** in 93% yield, as a *ca.* 90 : 10 mixture of *E*/*Z*-diastereomers and



Scheme 1 Conjugate addition of dimethyl malonate (**1**) to imine **2a**.

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†Electronic supplementary information (ESI) available: Experimental procedures and characterization data for compounds 3. CCDC 1535016 and 1535017. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7ob00595d