



VNIVERSITAT DE VALÈNCIA

**Isocyanoacetates as substrates for
enantioselective addition and
cycloaddition reactions**

Tesi Doctoral

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List of abbreviations

2-CR	Two-component reaction
Å	Angstrom (10^{-10} m)
EtOAc	Ethyl acetate
AIBN	Azobisisobutyronitrile
aq.	Aqueous
ATR	Attenuated total reflectance
$[\alpha]_D^{25}$	Specific rotation at 25 °C
Boc	<i>tert</i> -Butoxycarbonyl
Bs	<i>p</i> -Bromophenylsulfonyl
BSA	Bis(trimethylsilyl)acetamide
cat.	Catalyst
CDC7	Cell division cycle 7
conc.	Concentrated
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
dppe	1,2-Bis(diphenylphosphino)ethane
dr	Diastereomeric ratio
<i>ee</i>	Enantiomeric excess
equiv.	Equivalents
ESI	Electrospray ionization

EWG	Electron-withdrawing group
FTIR	Fourier-transform infrared spectroscopy
HMDS	Hexamethyldisilazane
HPLC	High-performance liquid chromatography
HRMS	High-resolution mass spectrometry
IR	Infrared spectroscopy
L	Ligand
m.p.	Melting point
Mbs	<i>p</i> -Methoxybenzenesulfonyl
Mes	Mesityl
mGlu	Metabotropic glutamate
MS	Molecular sieves
Ms	Mesyl
MW	Microwave
n.d.	Not determined
n.r.	No reaction
NMR	Nuclear Magnetic Resonance
Nos	Nosyl
PG	Protecting group
PMB	<i>p</i> -Methoxybenzyl
quant.	Quantitative
r.t.	Room temperature
sat.	Saturated
TBAF	Tetra- <i>n</i> -butylammonium fluoride

TBDMS	<i>tert</i> -Butyldimethylsilyl
TEMPO	2,2,6,6-Tetramethylpiperidine 1-oxyl
Tf	Triflate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMS	Trimethylsilyl
TosMIC	<i>p</i> -Toluenesulphonylmethyl isocyanide
Ts	Tosyl

1 Introduction

Molecular chirality plays a fundamental role in nature. Biological environments are chiral and each member of a pair of enantiomers interacts in a different way when they are present in living systems, owing to the structural characteristics of enzymes and receptors responsible of controlling biological processes.¹

This particular behavior that is associated with chirality has been progressively bringing interest into asymmetric synthesis, which consists on the stereoselective synthesis of chiral compounds.² This conversion of prochiral groups into chiral moieties contrasts with other synthetic procedures of chiral compounds which make use of the so-called chiral pool, using enantioenriched or enantiopure compounds that may be isolated from natural sources as starting materials, or with resolution protocols.³

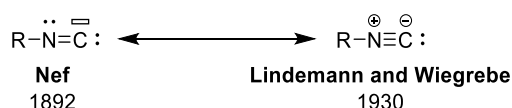
Among asymmetric synthesis methods, the use of chiral catalysts has proven to be a significant advancement in this field. Catalytic methods allow for stereoselective syntheses to be performed using only a small amount of chiral material in the process, as well as avoiding the extra reaction steps that are usually involved in alternatives like the use of chiral auxiliaries, which commonly require its attachment to the reactant and ulterior removal from the product.⁴

Catalytic asymmetric transformations encompass the use of chiral organic molecules as organocatalysts, chiral metallic complexes, as well as enzymatic catalysis.⁵

*

Isocyanides are compounds that contain the isonitrile (—NC) group. This functional group has unique structural characteristics that confer isocyanides a quite particular reactivity, making them emerge as interesting building blocks in the field of Organic Chemistry.⁶

Isocyanides are better represented as a combination of two resonance forms, a carbenic form with a divalent carbon first proposed by Nef,^{7,8} and a zwitterionic form first proposed by Lindemann and Wiegrabe (**Scheme 1**).⁹



Scheme 1: Main isocyanide resonance forms.

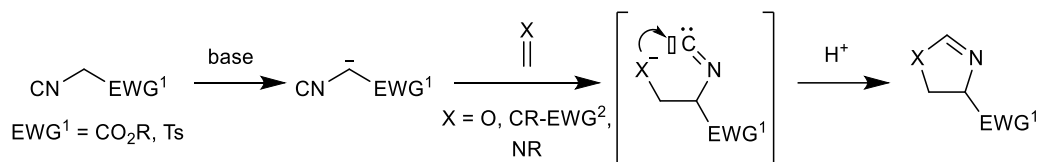
The resonance hybrid resulting from this representation implies a partial triple bond character resulting from the π back-donation of the nitrogen lone pair to the empty orbital of the

terminal carbon of the isonitrile group. This phenomenon allows the understanding of the linear structure of isocyanides.¹⁰

Isocyanides are both nucleophilic and electrophilic at the terminal carbon. The electrophility of this group is better understood considering the carbenic representation of the isonitrile group, with its empty orbital. On the other hand, its nucleophilicity can be visualized thanks to the zwitterionic representation, which provides the terminal carbon with negative charge density.¹¹

Another feature of isocyanides consists in their acidity at the α -carbon, owing to the electron-withdrawing nature of the isonitrile group. This acidity can be further increased by the presence of additional electron-withdrawing groups at this position, such as carboxylic esters. In fact, the versatile reactivity of isocyanoacetate derivatives has been widely studied, especially regarding its potential for the synthesis of *aza*-heterocycles.¹²

The deprotonated isocyano ester can undergo a nucleophilic addition to electrophilic double bonds, originating a carbanion that has inclination to perform an intramolecular attack to the terminal carbon of the isonitrile group. These formal cycloadditions give rise to heterocycles containing nitrogen with one or more chirality centers (**Scheme 2**).¹³



Scheme 2: Formal [3+2] cycloaddition between an isocyanide and an electrophilic double bond.

*

The importance of nitrogenated heterocycles is highlighted by its presence in various compounds of pharmaceutical interest, such as Lincomycin, an antibiotic;¹⁴ Captopril, used for the treatment of cardiovascular diseases;¹⁵ and Zolmitriptan, which showed its applicability for the treatment of migraine (**Figure 1**).¹⁶

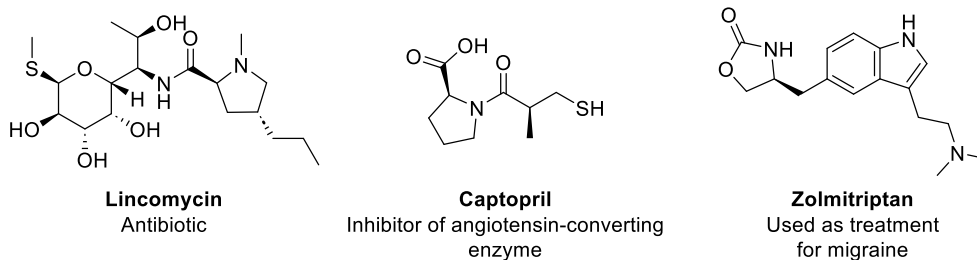


Figure 1: Some examples of compounds of pharmaceutical interest containing *aza*-heterocycles.

On the other hand, a molybdenum-isocyanoacetate complex (**Figure 2**) has been studied for its capacity of delivering CO to the liver in vivo in a targeted fashion, showing therapeutic effect in animal models for the treatment of liver injury.¹⁷

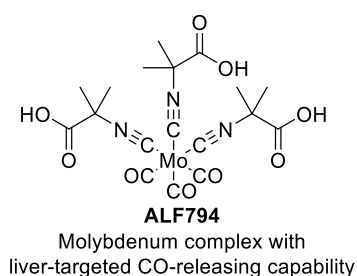


Figure 2: Use of isocyanides as ligands in a complex of pharmaceutical interest.

Finally, there are different examples of derivatives of amino acids with biological activity (**Figure 3**). Notable examples are the antiviral Valacyclovir¹⁸ and L-Dopa methyl ester, an alternative to L-Dopa for the treatment of Parkinson's disease with some pharmacokinetic advantages.¹⁹

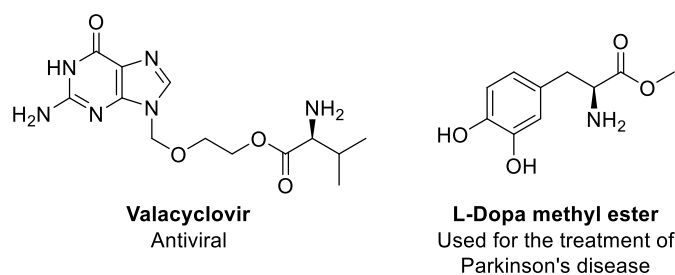


Figure 3: α -Amino acid compounds that feature therapeutic properties.

2 Literature review

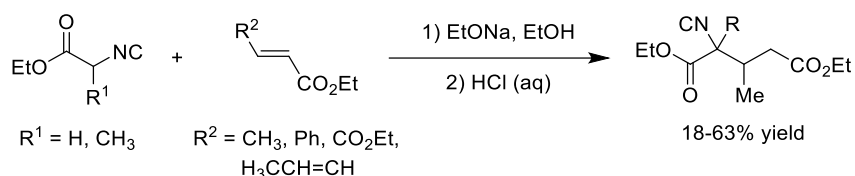
In this chapter, relevant literature regarding reactions of isocyanoacetates with electrophilic double bonds will be reviewed. Given their particular relevance to the experimental work performed in this thesis, we will explore simple isocyanoacetate additions, as well as [3+2] and higher order cycloadditions. A section encompassing previous work in this field by our research group has also been included.

2.1 Synthesis of highly-functionalized isocyanides by the addition of isocyano esters to electrophilic double bonds

Although most examples in the literature focus on the 1,3-dipolar character of isocyano esters in order to take part in cycloaddition reactions, thus using the isonitrile group as an imine adduct precursor,^{12,20} there are some procedures that have focused in keeping the isonitrile moiety in the final product. This has allowed the synthesis of highly-functionalized isonitrile-containing compounds which, considering the aforementioned versatility of isocyanides, can emerge as potential building blocks in organic syntheses. Independent reaction developments, as well as the use of this kind of procedure within total syntheses of natural products or products of pharmaceutical interest are reviewed next.

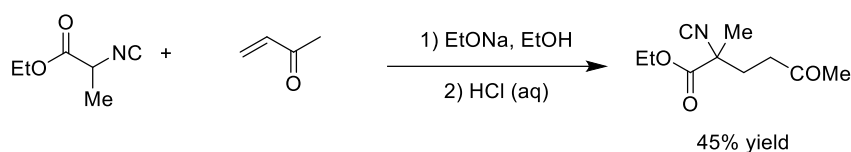
2.1.1 Non-enantioselective examples

In 1973, Schoellkopf and Hantke described the first functionalization of isocyanoacetates, with the synthesis of diethyl α -isocyano glutarates starting from ethyl isocyanoacetates, via a Michael addition to acrylates. Sodium ethoxide was used for the deprotonation of the isocyanoacetates (**Scheme 3**).²¹



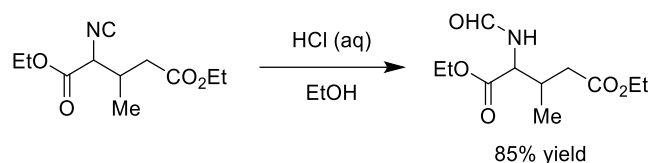
Scheme 3: Michael addition of ethyl isocyanoacetates to acrylates, furnishing more functionalized isocyano glutarates.

The Michael adduct of α -isocyanopropionate with methyl vinyl ketone was also prepared with moderate yield using the same procedure (**Scheme 4**).



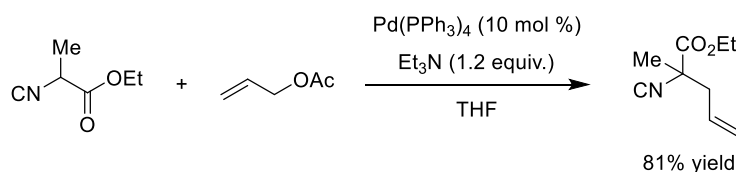
Scheme 4: Applicability of the Michael addition procedure for α,β -unsaturated ketones.

The synthesized isocyano glutarate could also be treated by hydrolysis to furnish an *N*-formyl glutamate (**Scheme 5**).



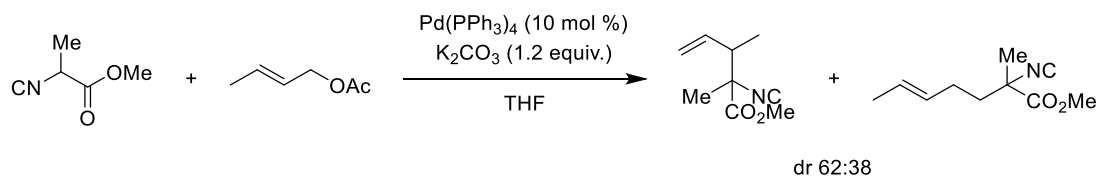
Scheme 5: Hydrolysis of the isonitrile group to give rise to an *N*-formyl amino ester.

In 1987, the group of Ito and Hayashi described the palladium-catalyzed allylation of isocyanoacetates, acting as the nucleophile in basic medium when presented with π -allylpalladium(II) complexes (**Scheme 6**).²²



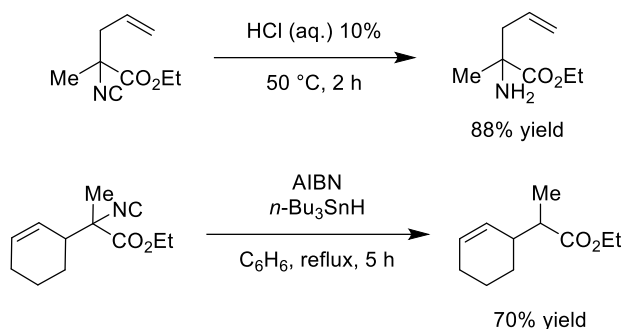
Scheme 6: Example of allylation of isocyanoacetates via a π -allylpalladium(II) complex.

When unsymmetrical π -allylpalladium(II) complex intermediates were involved, however, a mixture of regiomer allylation products was obtained (**Scheme 7**).



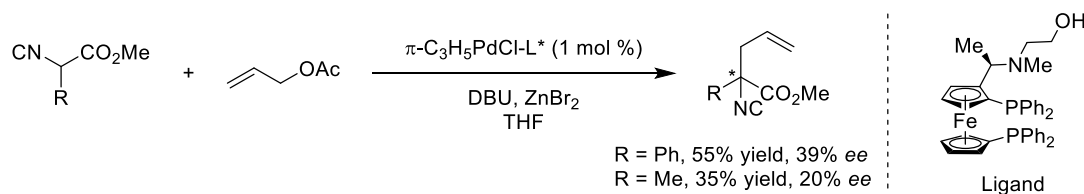
Scheme 7: Example using an unsymmetrical allyl acetate. A regiomer mixture is obtained.

Some synthetic transformations with participation of the isonitrile group were also showcased, like its acidic hydrolysis to obtain an amine, as well as its radical-mediated elimination with tri-*n*-butyl tin and AIBN.



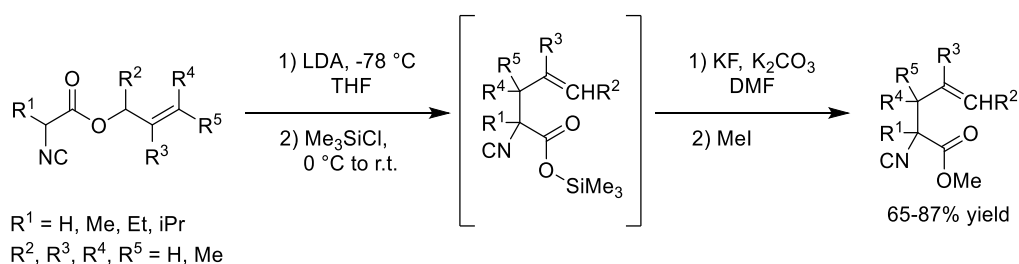
Scheme 8: Synthetic transformations of the allylated isocyanoacetates with participation of the isonitrile group.

Some preliminary findings about an asymmetric version of this reaction were also presented. The use of a palladium catalyst carrying a chiral ferrocene ligand with a 2-hydroxyethylamino group allowed for enantiomeric induction, although the enantiomeric excess was low (**Scheme 9**).



Scheme 9: Preliminary findings about the asymmetric version of the palladium-catalyzed allylation of isocyanoacetates.

A year later, the same group published an alternative regioselective allylation of isocyanoesters via a Claisen rearrangement of allylic isocyanoesters passing by in situ generated silyl ketene acetals (**Scheme 10**).²³

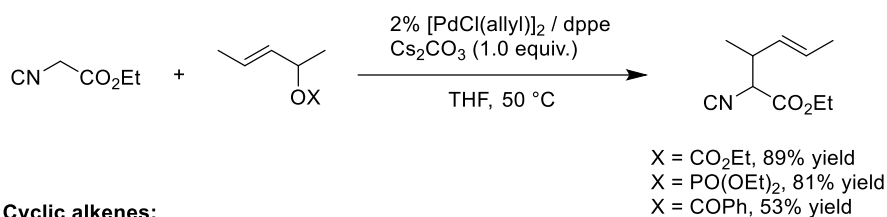


Scheme 10: Regioselective α -allylation of isocyano esters by a Claisen rearrangement of silyl ketene acetals generated in situ.

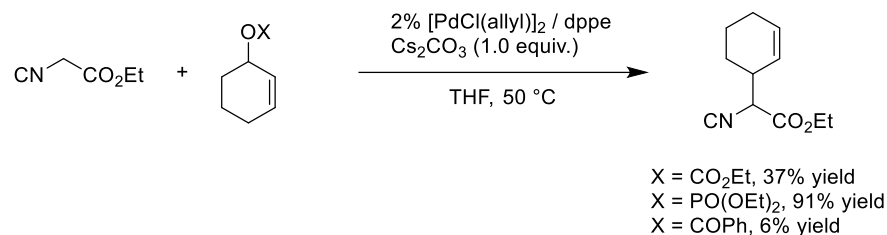
In 2004, Kazmaier and Ackermann revisited the allylation of isocyanoacetates with π -allylpalladium(II) complexes, studying the influence of the leaving group of the allyl alkene starting material.²⁴ They found out that the use of carbonates provided the best results with linear alkenes, although it was better to use allyl phosphonates with cyclic substrates. Allyl benzoates performed poorly in both cases (**Scheme 11**). Unfortunately, as with the case of Ito

and Hayashi, the optimized conditions were shown not to be regioselective with non-symmetric π -allylpalladium(II) complexes.

Linear alkenes:

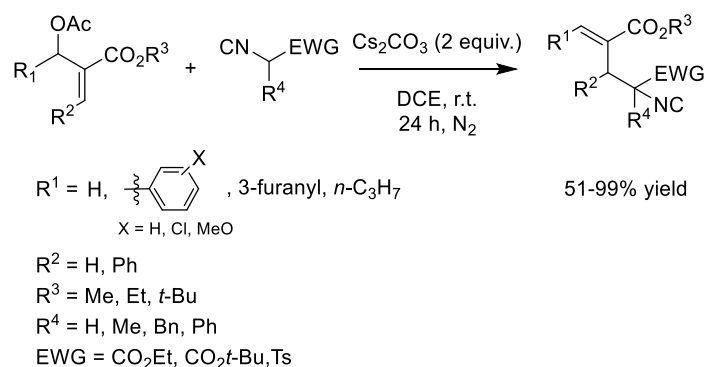


Cyclic alkenes:



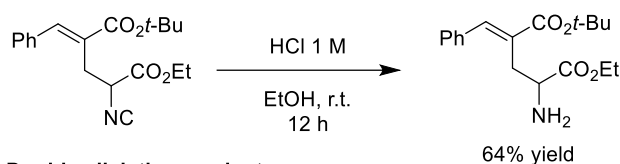
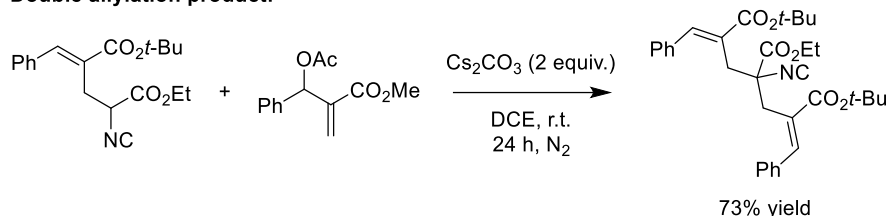
Scheme 11: Influence of the leaving group in the palladium-catalyzed α -allylation of isocyanoacetates.

In 2023, Xie and collaborators described the addition of isocyanoacetates to Morita-Baylis-Hillman adducts, giving rise to α -allylated isocyanoacetates.²⁵ This renewed allylation protocol did not require the use of transition metals, unlike the previous procedures, and used only cesium carbonate as the catalyst (**Scheme 12**).

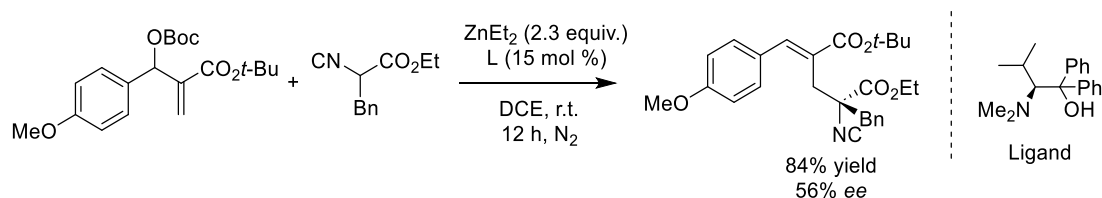


Scheme 12: Allylation of isocyanides without the use of palladium by the use of Morita-Baylis-Hillman adducts.

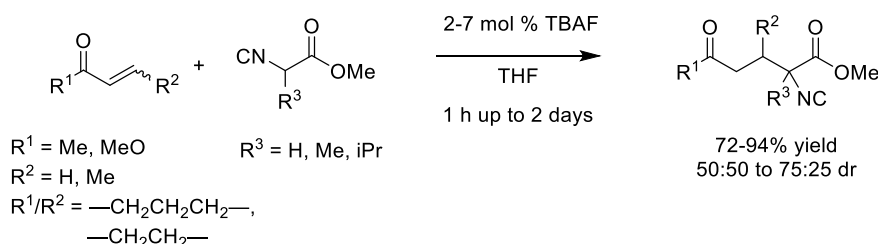
Two transformations of the obtained products were carried out, corresponding to the hydrolysis of the isonitrile group, as well as the formation of the double allylation product by applying the allylation conditions to the mono allylated product (**Scheme 13**).

Formation of the amino ester:**Double allylation product:****Scheme 13:** Synthetic transformation of the allylation products.

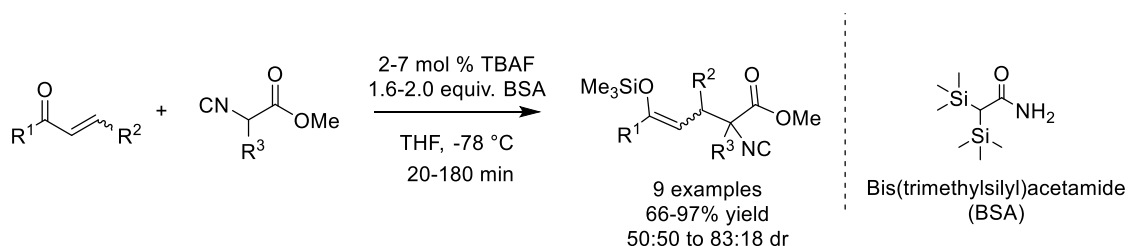
A tentative version of an asymmetric protocol for this reaction was also included. The use of diethylzinc and a chiral amino alcohol ligand provided some asymmetric induction, although the enantioselectivity was moderate (**Scheme 14**).

**Scheme 14:** Initial proposal for an asymmetric version of the allylation reaction.

In 1989, the group of Ito described the fluoride-base-catalyzed Michael addition of methyl isocyanoacetates to α,β -unsaturated ketones and esters, to provide glutamic acid derivatives, which are α -amino acid precursors, with good to excellent yields but poor diastereoselectivity (**Scheme 15**).²⁶

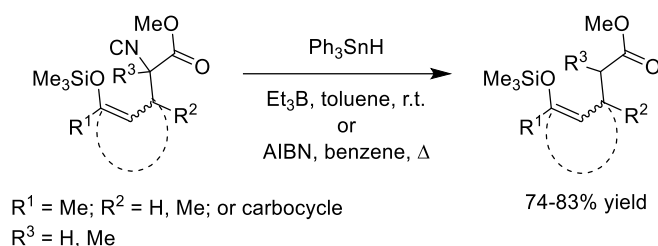
**Scheme 15:** Fluoride-catalyzed Michael addition of isocyanoacetates to α,β -unsaturated ketones and esters.

It was also found out that the procedure could be carried out with a much lower reaction time if the enolate intermediate was captured with a silylating agent. Trimethylsilyl ethers of the Michael products were successfully obtained with good to excellent yields (**Scheme 16**).



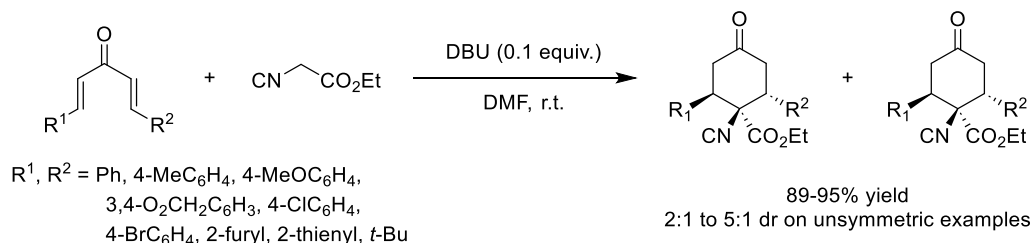
Scheme 16: Lowering the reaction times by capturing the intermediate enolates as silyl enol ethers.

The synthetic utility of the products was demonstrated by their radical-mediated reductive de-isocyanation using organotin hydride and a radical initiator, such as AIBN or triethylborane (**Scheme 17**).



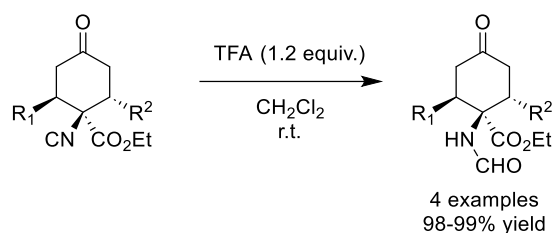
Scheme 17: Removal of the isonitrile group of the silylated Michael addition products.

In 2010, the group of Xu and Liu described the double addition of isocyanoacetates to double α,β -unsaturated ketones, giving rise to [5+1] annulation products, constituting cyclic amino acid precursors (**Scheme 18**).²⁷



Scheme 18: [5+1] Annulation by the double Michael addition reaction of ethyl isocyanoacetate with a dibenzylideneacetone derivatives.

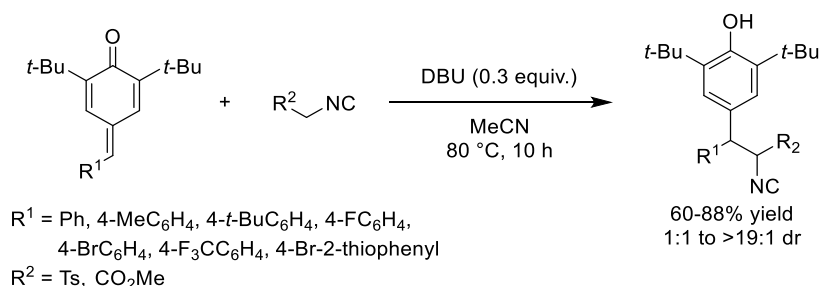
The reaction product could be transformed into *N*-formyl cyclohexane analogues of phenylalanine via an acidic hydrolysis in quantitative yield (**Scheme 19**).



Scheme 19: Hydrolysis of the isonitrile group on the annulation products.

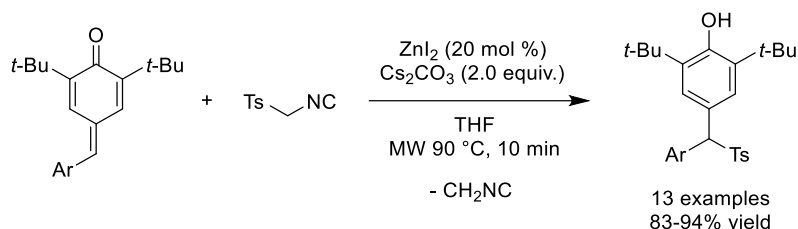
Li and collaborators provided some insight about the crystal structure of these annulation products.^{28,29} Remarkably, both aryl groups as well as the ethoxycarbonyl substituent are in equatorial position, with the six-membered ring adopting a twist-boat conformation.

In 2021, the group of Song published the 1,6-addition of TosMIC to *p*-quinone methides, with DBU as catalyst.³⁰ An example that used methyl isocyanoacetate was also included. The yields were generally good, although the diastereoselectivities were moderate (**Scheme 20**). When methyl isocyanoacetate was used, however, the diastereoisomeric ratio increased to >19:1.



Scheme 20: 1,6-Addition of TosMIC and methyl isocyanoacetate to *p*-quinone methides.

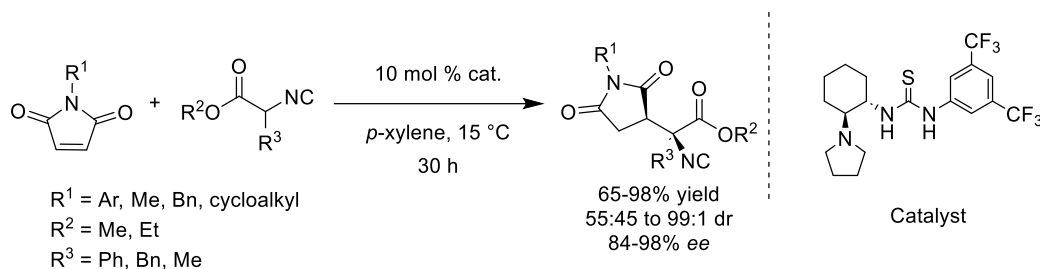
It was also found out that, depending on the conditions, the sulfonylation of the *p*-quinone methide could be obtained, instead of the addition of the isocyanide, in a procedure that globally implies losing —CH₂NC (**Scheme 21**).



Scheme 21: Formal addition of *p*-toluenesulfinate to *p*-quinone methides.

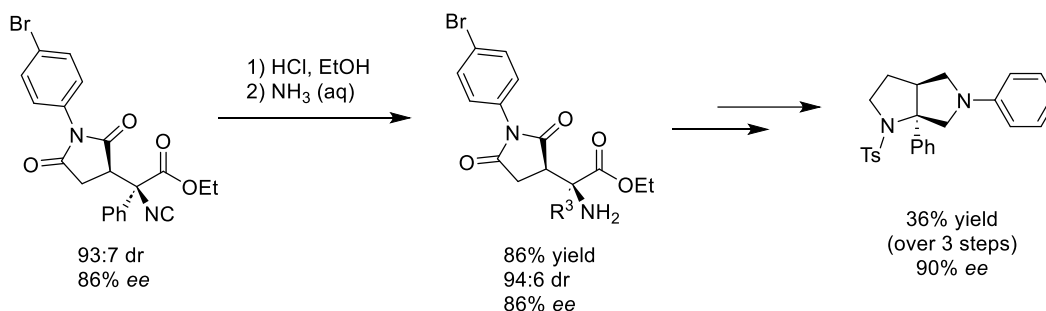
2.1.2 Enantioselective examples

In 2012, the group of Xu and Wang described the first general example of asymmetric isocyanoacetate derivatization by the means of its addition to an electrophilic double bond, in this case maleimides, catalyzed by a thiourea-based chiral organocatalyst, which gave rise to Michael addition adducts in a diastereo- and enantioselective fashion (**Scheme 22**).³¹



Scheme 22: Asymmetric formation of maleimide adducts through the asymmetric Michael addition of isocyanoacetates.

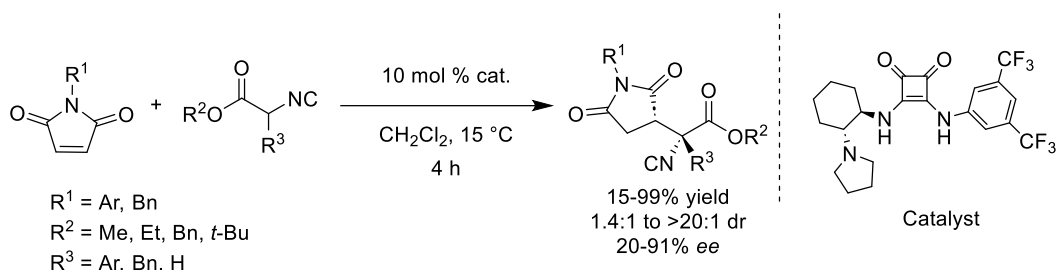
A synthetic route towards a bicyclic γ -lactam derivative, carried out via the amino ester intermediate, was performed, with preservation of the enantiomeric purity (**Scheme 23**).



Scheme 23: Synthetic route towards a chiral bicyclic pyrrolidine derivative.

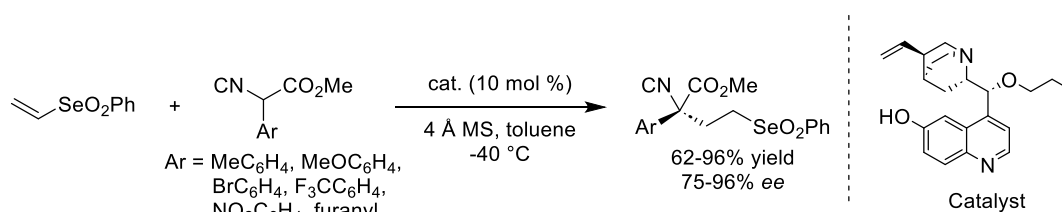
A year later, the group of Zhao and Shi published further studies of the asymmetric addition of isocyanoacetates to maleimides, considering the issues of the previously described synthesis, namely the reaction times.³²

Based on Xu and Wang's work, the authors proposed the use of a 1,2-diaminocyclohexane-derived squaramide catalyst (**Scheme 24**). This catalyst allowed the obtention of the opposite enantiomer of the product from the previous work with overall reduced reaction times and better yield.



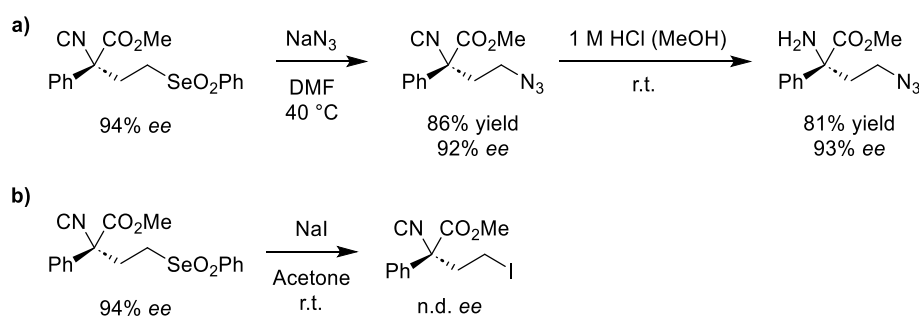
Scheme 24: 1,2-Diaminocyclohexane-derived squaramide organocatalyzed Michael addition of isocyanoacetates to maleimides.

In 2013, the group of Zhu developed the asymmetric Michael addition of isocyanoacetates to α,β -unsaturated vinyl selenones (**Scheme 25**).^{33,34} Owing to the phenylselenonyl properties as a leaving group, combined with the possibility of derivatization of the isonitrile functional group by acidic hydrolysis, the obtained adducts possess broad synthetic versatility.



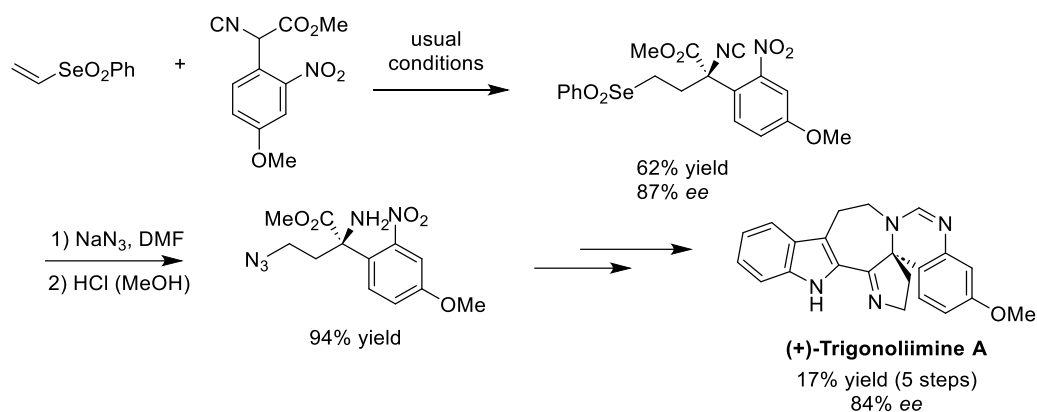
Scheme 25: Asymmetric addition of α -substituted methyl isocyanoacetates to vinyl phenylselenones, via organocatalysis by a cupreine derivative.

Notable synthetic transformations of the Michael addition adducts were the formation of the azide and the iodide from the phenylselenonyl group, as well as the formation of the corresponding amino ester by hydrolysis of the isocyanide (**Scheme 26**).



Scheme 26: Synthetic transformations of the obtained phenylselenonyl adducts. a) Formation of the azide and further hydrolysis of the isonitrile; b) formation of the alkyl iodide.

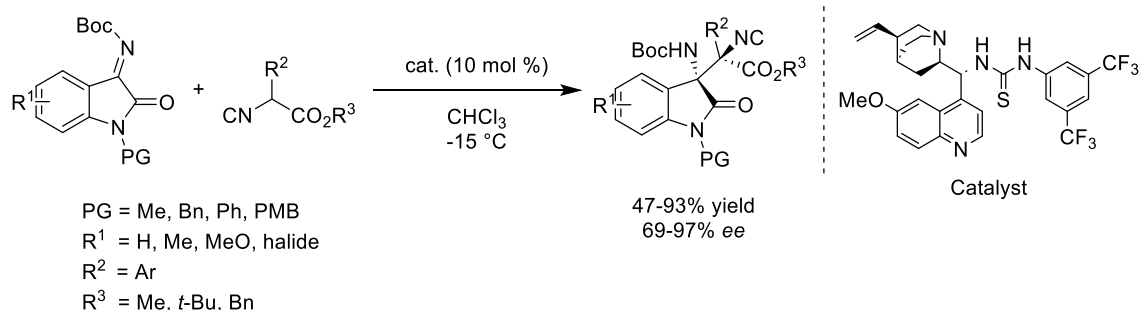
The authors also applied the developed asymmetric methodology as key steps in the total synthesis of (+)-trigonoliimine A (**Scheme 27**).



Scheme 27: Total synthesis of (+)-trigonoliimine A where the developed asymmetric Michael addition occupies a key initial step.

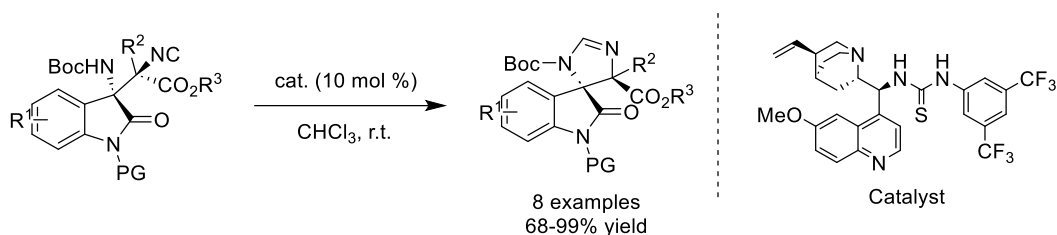
Interestingly, the asymmetric reaction could be carried out with the pseudoenantiomer catalyst derived from cupreidine, with similar enantiomeric induction. This modification also allowed the obtention of (–)-trigonoliimine A with similar results.

In 2015, Zhao, Shi and collaborators described the asymmetric Mannich reaction of isocynoacetates to ketimines derived from isatin.³⁵ This reaction gave rise to 3,3-disubstituted oxindoles with high enantio- and diastereoselectivity. The reaction was catalyzed by a thiourea derived from quinidine (**Scheme 28**).



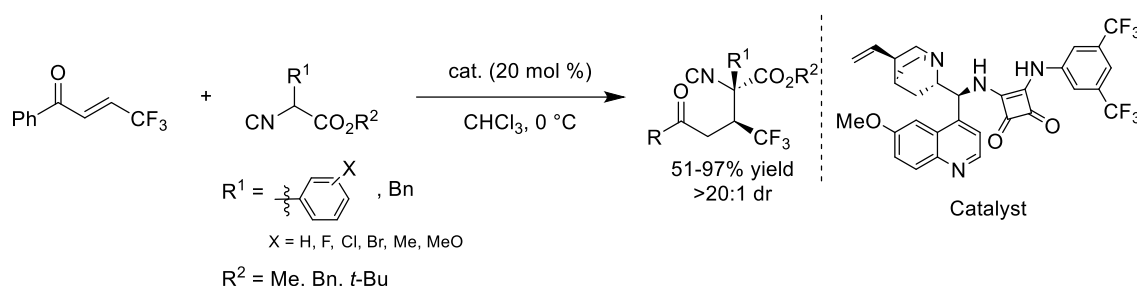
Scheme 28: Synthesis of chiral oxindoles by the Mannich reaction of isocynoacetates to isatin-derived imines.

Remarkably, the obtained product could be intramolecularly cyclized to form a spirooxindole, with preservation of the enantiomeric purity. The cyclization was performed with the opposite pseudoenantiomer of the catalyst used in the asymmetric transformation. In other words, the quinine analogue of the aforementioned thiourea is employed, which provided the adequate chirality match with the Mannich addition adduct to generate an adequate environment for the cyclization.



Scheme 29: Cyclization of the obtained Mannich reaction products to yield chiral spirooxindoles.

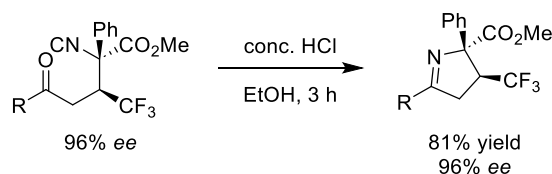
The same research group published the same year the asymmetric Michael addition of isocyanoacetates to β -trifluoromethyl enones, using an organocatalyst derived from quinine (**Scheme 30**).³⁶



Scheme 30: Michael addition of isocyanoacetates to β -trifluoromethyl enones, performed in asymmetric fashion thanks to squaramide organocatalysis.

Excellent enantioselectivities were achieved with aromatic substituents of different character at the α position of the isocyanoacetate, as well as when *tert*-butyl or benzyl isocyanoacetates were used. However, neither α -benzyl substituted isocyanoacetates or *ortho*-substituted phenyl substituents at the α position of the isocyanide yielded the addition product.

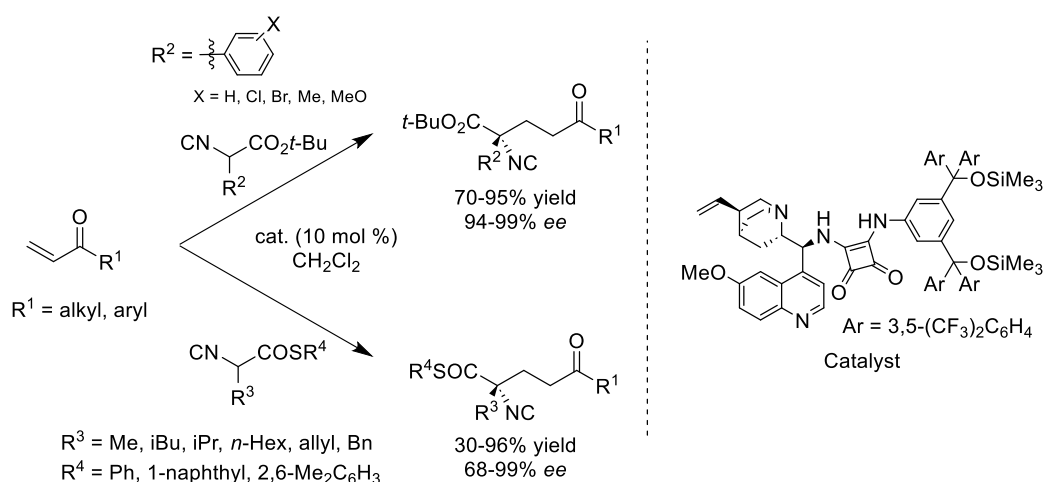
Acidic hydrolysis of the isonitrile group to form the amine induced the imine formation by the addition to the ketone carbonyl. No loss of enantiomeric purity was observed in the obtained pyrrolines, which were formed with good yield (**Scheme 31**).



Scheme 31: Formation of cyclic 1-pyrrolines by the acidic hydrolysis of the isonitrile group and in situ cyclization.

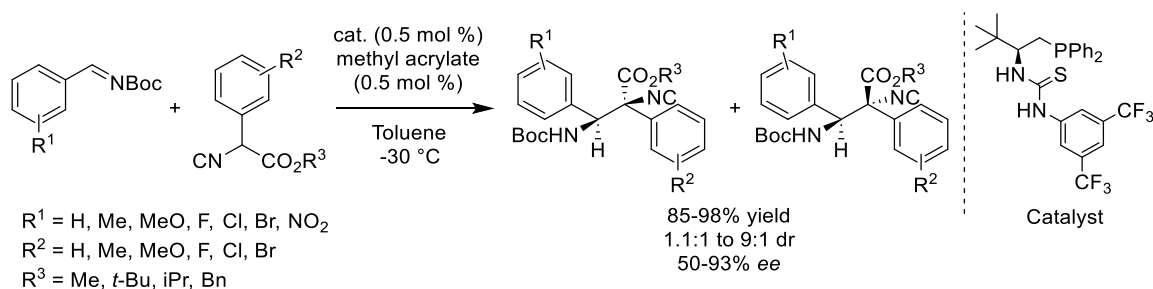
In 2017, the group of Palomo developed the asymmetric addition of α -aryl isocyanoacetates as well as α -alkyl isocyanthioacetates to enones (**Scheme 32**).³⁷ The procedure provided more efficient enantiomeric induction when bulky *Cinchona*-alkaloid derived organocatalysts

were used. In this case, the authors concluded by X-ray measurements of the employed catalyst that the distance of the hydrogen bond donors on the squaramide moiety was lower than the usual squaramide catalyst structure (2.45 Å, compared with the usual ≈ 2.85 Å). Additionally, in the bulky catalyst crystals, the squaramide units were not found to self-aggregate with each other as is generally assumed in this kind of structures. Instead, the squaramide N-H bonds pointed to the quinoline nitrogen of the contiguous molecule. This reduction of the intermolecular interactions also strongly affects the solubility of the bifunctional catalyst in organic solvents, and are presumed to play a significant role in the catalytic activity.



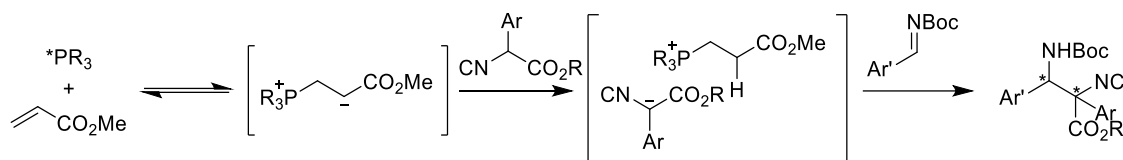
Scheme 32: Asymmetric addition of isocyanoacetates and isocyanothioacetates to enones, catalyzed by a bulky quinine-derived squaramide.

The same year, the group of Cao and Zhao described the asymmetric addition of α -aryl isocyanoacetates to *N*-Boc aldimines, with generally good enantioselectivity, although with poor diastereoselectivity (**Scheme 33**).³⁸ Diastereoselectivity could be improved when a bulky *tert*-butyl isocyanoacetate was used (9:1 dr was obtained in these conditions). The authors also found out that when a single diastereomer was isolated, it had the tendency to partially isomerize, a factor that could also contribute to the reduced diastereoselectivity.



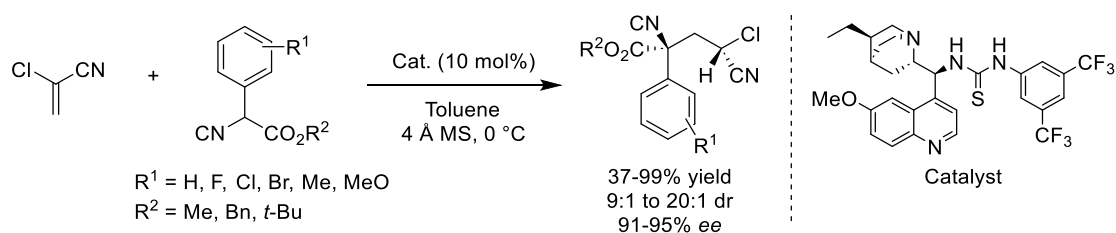
Scheme 33: Asymmetric Mannich addition of isocyanoacetates to *N*-Boc aldimines, with dual-reagent organophosphine organocatalysis.

The so-called dual-reagent catalytic system that was used for this asymmetric transformation involves the use of the zwitterion formed from the phosphine ligand and methyl acrylate as the Brønsted base that serves to deprotonate the pronucleophile which, in turn, forms a chiral ion pair with the phosphonium cation that is generated. This chiral nucleophilic complex allows for facial discrimination when the Mannich addition is produced.³⁹



Scheme 34: Isocyanoacetate asymmetric Mannich addition by dual-reagent organophosphine catalysis with methyl acrylate.

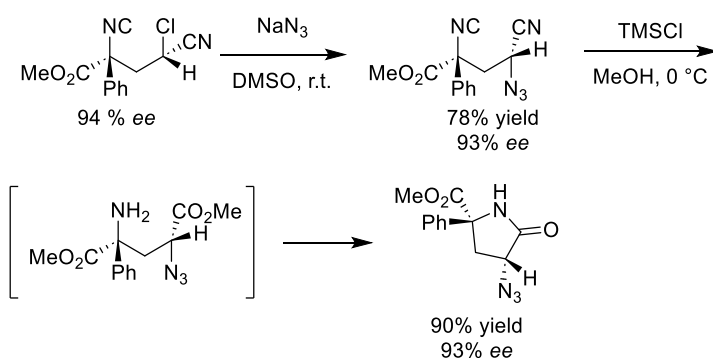
In 2019, the group of Zhao and Shi published the asymmetric addition of isocyanoacetates to 2-chloroacrylonitrile, with a dihydroquinine-derived organocatalyst (**Scheme 35**).⁴⁰



Scheme 35: Organocatalyzed diastereo- and enantioselective addition of α -arylisocyanoacetates to 2-chloroacrylonitrile.

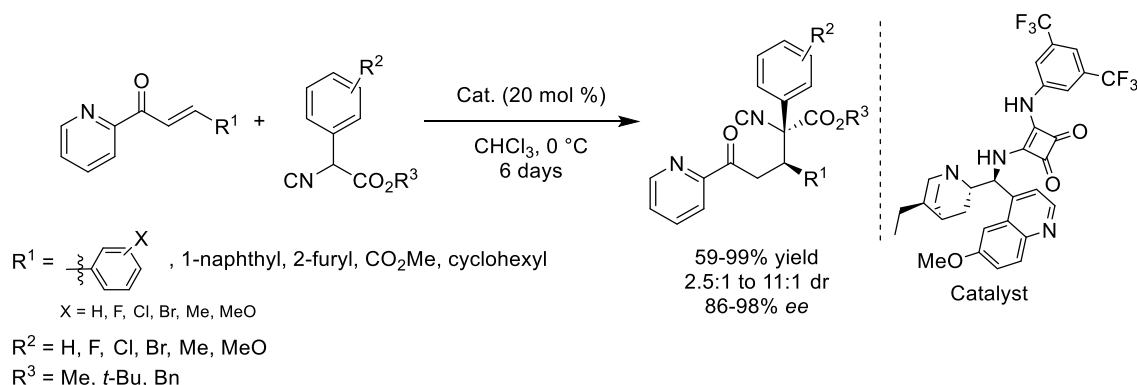
In general, the reaction proceeded with good yield and diastereoselectivity and excellent enantioselectivity irrespective of the substituents in the aromatic ring of the α -arylisocyanoacetate. However, the reaction proceeded poorly when substituents were present at the *ortho* position of the aromatic ring of the isocyanide, and did not perform at all when methyl α -benzylisocyanoacetate was assayed.

Considering the presence of the chloride, which is a good leaving group, as well as the properties of the isonitrile and nitrile groups, the authors designed a transformation pathway that started with the nucleophilic displacement of the chloride atom with sodium azide, followed by treatment with trimethylsilyl chloride in MeOH, which furnished the γ -lactam displayed in **Scheme 36** upon hydrolysis of the isonitrile and methanolysis of the nitrile, giving an amino ester intermediate that spontaneously cyclizes.



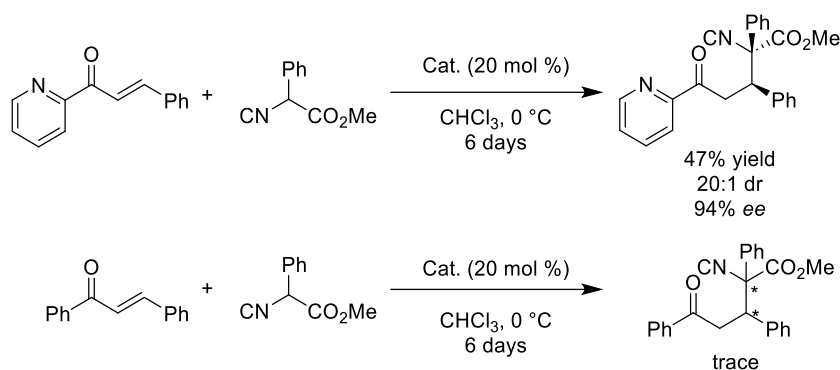
Scheme 36: Synthetic transformations of the obtained isocyano esters.

The same year, this research group published the asymmetric Michael addition of α -aryl isocyanoacetates to 2-enoylpyridines, catalyzed by a dihydroquinine-derived squaramide (Scheme 37).⁴¹ Excellent enantioselectivities and good diastereoselectivities could be obtained, but the reaction showed its limitation regarding the use of α -benzyl isocyanoacetates and α -aryl isocyanoacetates with *ortho* substituents, as it has been shown to be usual with this kind of additions.



Scheme 37: Asymmetric Michael addition of isocyanoacetates to 2-enoylpyridines catalyzed by a dihydroquinine-derived squaramide organocatalyst.

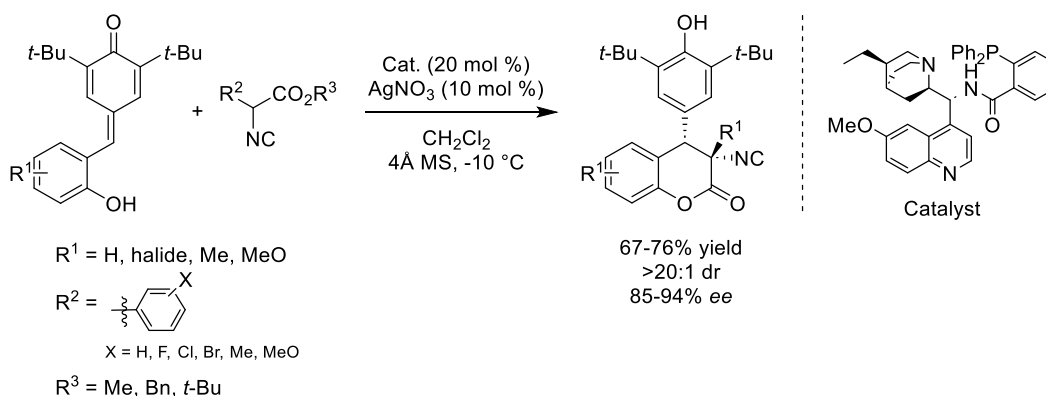
The pyridine moiety of the reactant played a very important role regarding the interaction with the catalytic system, since only a trace amount of addition product was obtained when the structurally similar chalcone was tried (Scheme 38). This finding allowed to hypothesize that the hydrogen donor section of the squaramide moiety was bonding both to the pyridine nitrogen as well as to the lone electron pair of the carbonyl, and this interaction was key for the activation and orientation of the electrophile towards nucleophilic attack by the isocyanide.



Scheme 38: Comparison of the reaction of 3-enoylpyridine and the structurally similar chalcone.

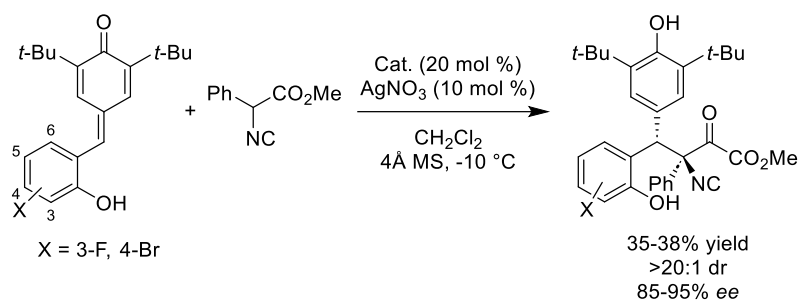
In 2020, the group of Zhao and Shi published the asymmetric addition of α -aryl isocyanoacetates to *ortho*-hydroxyphenyl substituted *para*-quinone methides.⁴² A cascade addition and transesterification reaction was observed, thus obtaining chiral 3,4-dihydrocoumarines.

A cooperative catalytic system comprised of silver acetate and one of Dixon's *Cinchona* alkaloid-derived aminophosphine ligands⁴³ was used to obtain the dihydrocoumarine derivatives with good yield, total diastereoselectivity and good to excellent enantioselectivity (**Scheme 39**). Usual limitations such as the lack of reaction when α -alkyl or α -benzyl isocyanoacetates were used, as well as in the cases that a substituent was present at the *ortho* position of the α -aromatic ring, were noted.



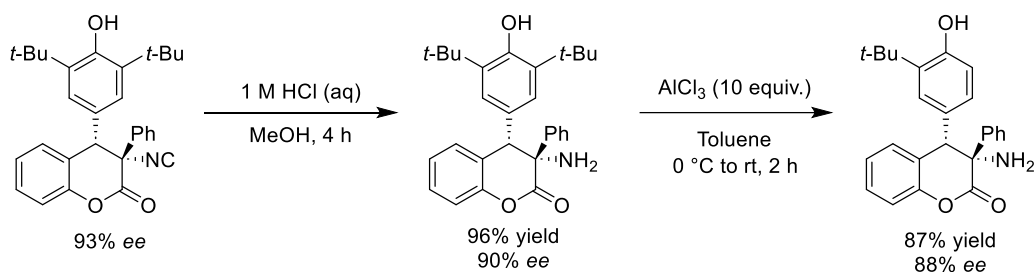
Scheme 39: Asymmetric synthesis of 3,4-dihydrocoumarines via a 1,4-addition and cascade transesterification reaction of *p*-quinone methides and isocyanoacetates.

Interestingly, when a halide substituent was present at either the 3 or 4 position of the phenolic ring, the reaction stopped after the addition of the isocyanide, and the subsequent transesterification was not observed (**Scheme 40**).



Scheme 40: Cascade reaction interruption with halide substituents at 3 or 4.

The obtained products could successfully be transformed into the corresponding α -amino lactones by the means of an acidic hydrolysis of the isonitrile group. Additionally, one of the *tert*-butyl groups of the phenolic ring could be removed using aluminum chloride (**Scheme 41**).

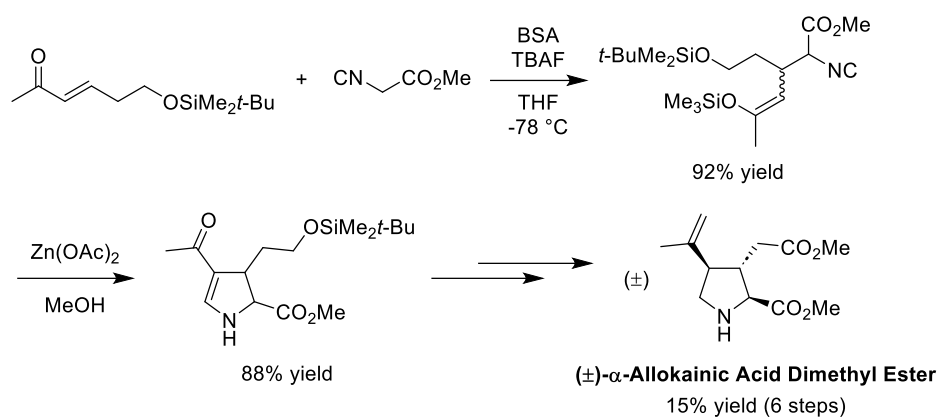


Scheme 41: Synthetic transformations of the obtained 3,4-dihydrocoumarines.

2.1.3 Use in total synthesis

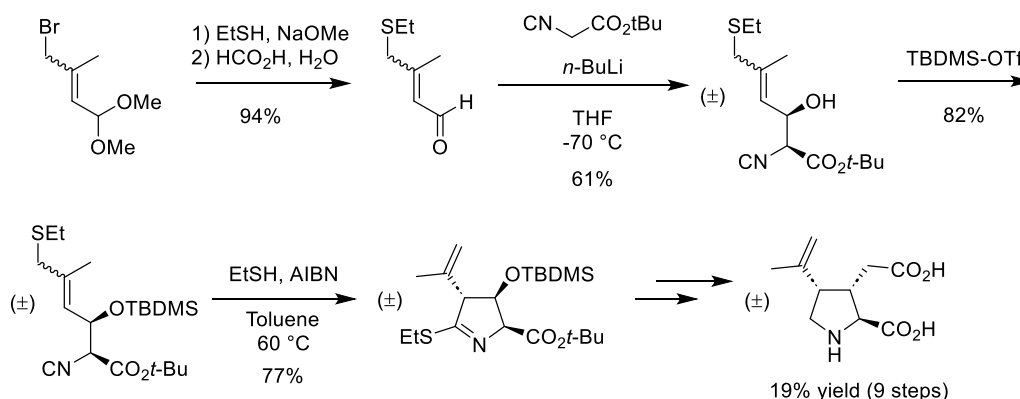
In this section, the synthesis of different natural products and pharmaceuticals in which an addition reaction of isocyanoacetates has been used will be outlined. In general, only the steps where the isocyanoacetate participates, as well as those in which the isocyanide group is transformed or its chemical reactivity takes part in the process will be highlighted.

In 1991, the group of Ito used their fluoride-base-catalyzed Michael addition of methyl isocyanoacetates to α,β -unsaturated ketones, trapping the enolate intermediate as a silyl ether,²⁶ as the initial step for the synthesis of ($\pm$)- α -allokainic acid, a kainoid amino acid with excitotoxic activity.⁴⁴ The obtained isocyano ester could be cyclized by an intramolecular reaction with the newly formed silyl enol ether by using zinc acetate to form the key nitrogen-containing five membered cycle from the desired product (**Scheme 42**).



Scheme 42: Total synthesis of α-alkokainic acid dimethyl ester involving a Michael addition of methyl isocyanoacetate to an α,β-unsaturated ketone.

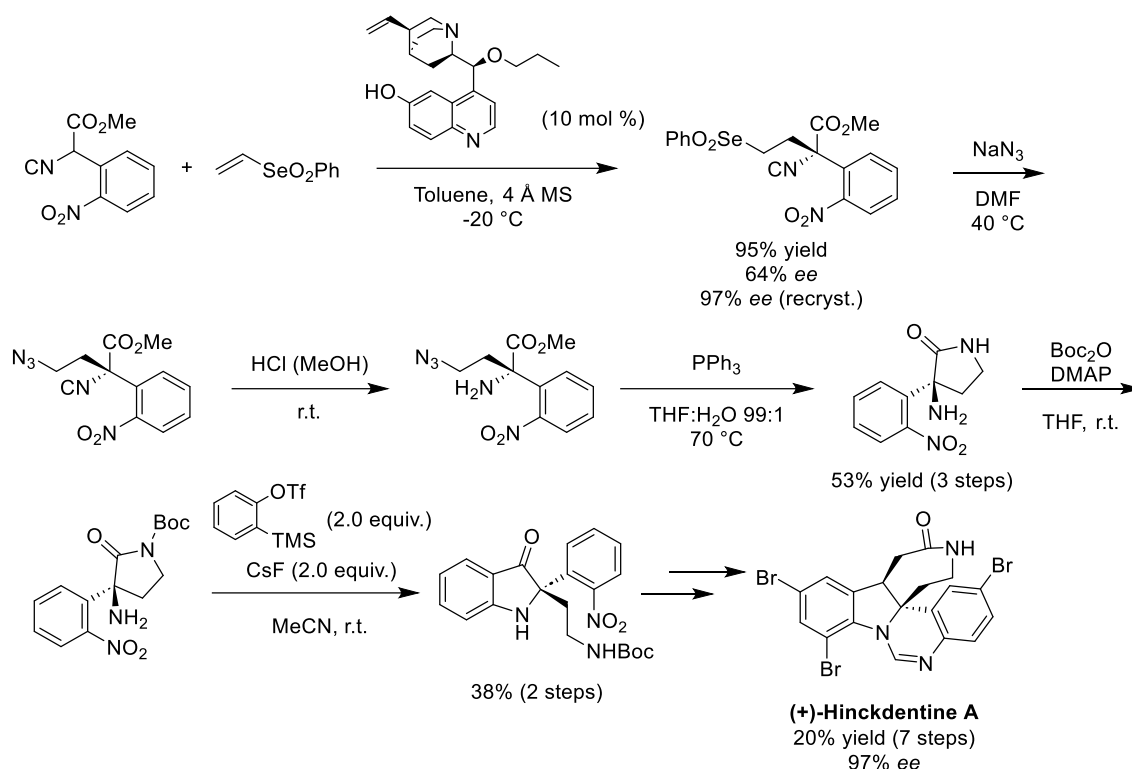
In 1996, Bachi and Melman described the total synthesis of (±)-kainic acid, a diastereoisomer of α-alkokainic acid (see **Scheme 42**), using a synthetic pathway in which the addition of an isocyanoacetate to an aldehyde played a fundamental role (**Scheme 43**).^{45,46} The synthesis started with the bromoacetal of dimethylacrylaldehyde. After substitution of the bromine atom with ethyl ethanethiol and hydrolysis of the acetal, a nucleophilic addition of *tert*-butyl isocyanoacetate to the resulting aldehyde was performed, using *n*-butyllithium as a base. After protection of the resulting alcohol as a *tert*-butyldimethylsilyl ether, a thiyl radical mediated cyclization of the isocyanide was carried out, using a catalytic amount of EtSH and AIBN. The authors claim that the process involves an addition of the EtS· radical to the isocyanide group, followed by cyclization of the resulting carbon-centered imidoyl radical. Subsequent β-elimination of EtS· allows the continuation of the chain reaction. Further steps after formation of the main five-membered skeleton allowed the obtention of the desired product.



Scheme 43: Total synthesis of α-kainic acid, through a synthetic route that includes the 1,2-addition of an isocyanoacetate to an aldehyde and its radical-mediated cyclization.

In 2018, the group of Zhu used their previously described organocatalyzed asymmetric Michael addition of isocyanoacetates to α,β-unsaturated vinyl selenones^{33,34} as the initial step

in the synthesis of (+)-Hinkdentine A, a natural compound that can be isolated in low yields from the bryozoan *Hincksinoflustra denticulata* (Scheme 44).⁴⁷



Scheme 44: Synthesis of (+)-Hinkdentine A starting from the asymmetric addition of an isocyanoacetate to a vinyl selenone.

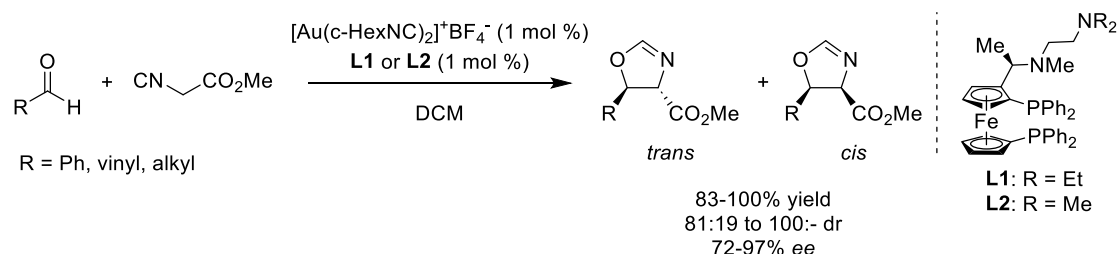
Afterwards, a nucleophilic substitution of the selenonyl group with azide was performed, followed by hydrolysis of the isocyanide to give rise to an amino-azide. Subsequent Staudinger reaction and tandem cyclization allowed to obtain a five-membered lactam, which facilitated the access to the key indolin-3-one moiety by a newly developed heteroannulation reaction with an aryne.

2.2 [3+2] Cycloadditions of isocyanoacetates with electrophilic double bonds

Taking into account the special reactivity of the isocyanide group, there have been multiple examples of formal cycloadditions of isocyanoacetates with dipolarophile compounds. In this section, the most relevant examples regarding [3+2] cycloadditions with electrophilic double bonds will be mentioned. In general, only organocatalytic protocols will be reviewed, although selected relevant metallic catalysis or cooperative metal-organic catalysis procedures are also presented.

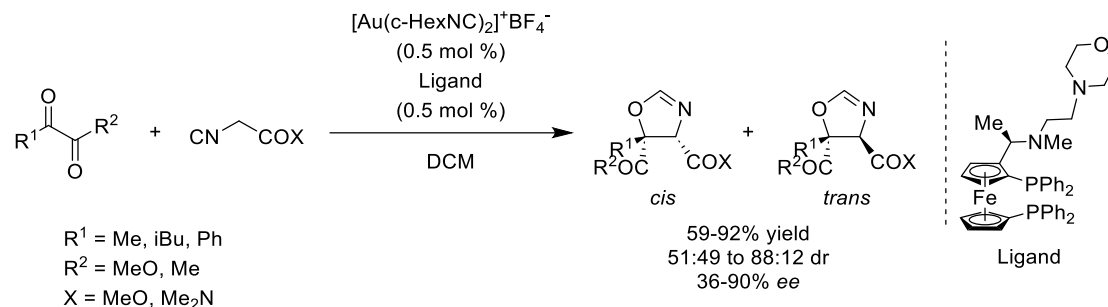
2.2.1 Reactions with aldehydes and ketones

The first example of asymmetric [3+2] cycloadditions of isocyanoacetates and aldehydes was described in 1986 by the group of Ito and Hayashi, using an Au(I) catalyst with a ferrocenylphosphine chiral ligand (**Scheme 45**).⁴⁸



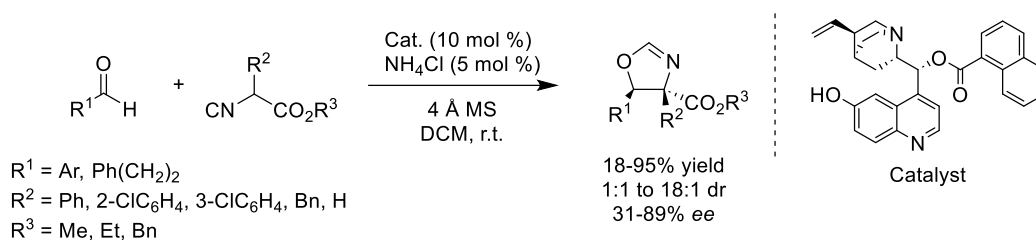
Scheme 45: Asymmetric addition of isocyanoacetates to aldehydes with ulterior cyclization, giving rise to chiral oxazolines.

In the case of ketones, the first asymmetric [3+2] cycloaddition with isocyanoacetates was published a year later by the same research group, describing the reaction with α -ketoesters, using a very similar catalytic system than in the case of aldehydes (**Scheme 46**).⁴⁹ The yields of the obtained oxazolines, as well as their diastereo- and enantioselectivities were, however, lower than in the case of the cycloaddition with aldehydes.



Scheme 46: [3+2] cycloaddition of isocyanoacetates and isocyanoacetamides with α -ketoesters.

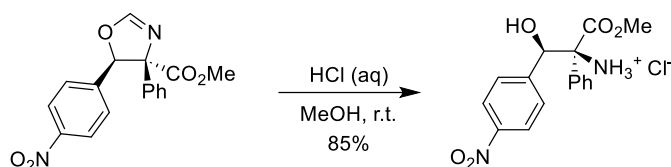
Multiple metallic catalytic methods were developed based on varied metals like Ag(I),⁵⁰ Pt(II)⁵¹ and Pd(II),⁵² but it was not until 2009 that the first purely organocatalytic procedure for the [3+2] cycloaddition of isocyanoacetates, in this case α -aryl substituted, with aldehydes was published by the group of Gong (**Scheme 47**).⁵³ The reaction was catalyzed by a cupreine-derived organocatalyst.



Scheme 47: Organocatalyzed [3+2] cycloaddition of α -aryl isocyanoacetates with aldehydes.

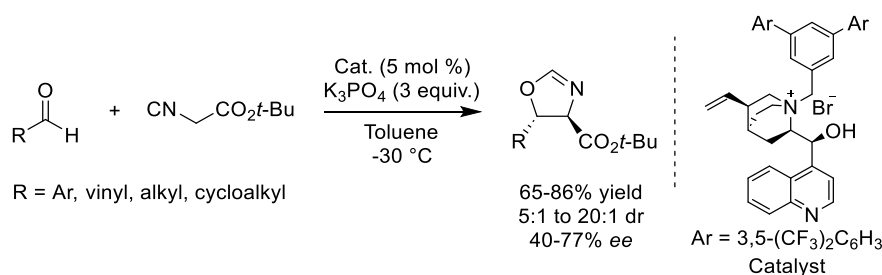
In general, good yields and enantioselectivities were reached, although the reaction conditions showed their limitations when the α -unsubstituted methyl isocyanoacetate or when methyl α -benzyl isocyanoacetate were used, with a marked reduction in the enantioselectivity, showing that the organocatalytic protocol was efficient only with α -aryl isocyanoacetates.

On the other hand, the oxazoline products could be converted to β -hydroxy- α -amino esters by acidic hydrolysis, in good yield (**Scheme 48**).



Scheme 48: Acidic hydrolysis of oxazolines to give rise to β -hydroxy- α -amino esters.

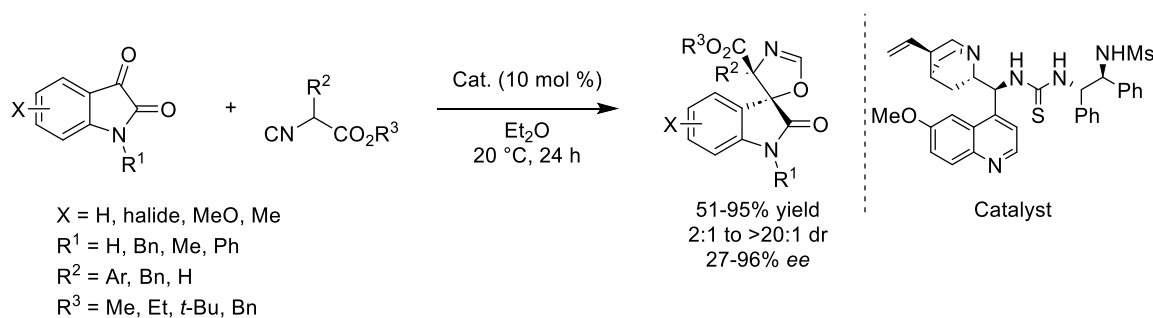
In 2014, the group of Li described an organocatalytic procedure of cycloaddition to aldehydes applied to the α -unsubstituted *tert*-butyl isocyanoacetate (**Scheme 49**).⁵⁴ Although the enantioselectivity oscillated from moderate to good, the described conditions, which made use of a cinchonine-based phase transfer catalyst, allowed a wide scope of aromatic, alkylic or vinyl aldehydes.



Scheme 49: [3+2] cycloaddition of *tert*-butyl isocyanoacetate with aldehydes.

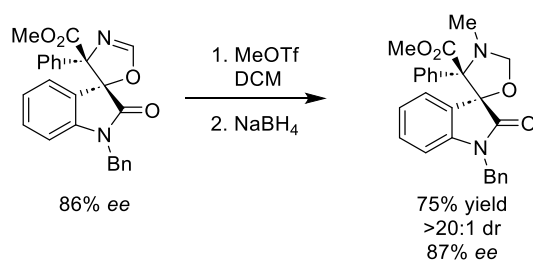
In 2013, the group of Zhao and Shi published the organocatalyzed asymmetric synthesis of spirooxindole oxazolines by the [3+2] cycloaddition of α -aryl isocyanoacetates with isatins.⁵⁵ The reaction was catalyzed by a 1,2-diamine-derived quinine-based thiourea (**Scheme 50**). Good to excellent yields, diastereomeric ratios and enantiomeric excess values were, in

general, obtained. Limitations of the procedure included the use of α -unsubstituted isocyanoacetates as well as *ortho* substitutions in the aromatic ring at the α position of the isocyanoacetate, obtaining poor enantiomeric excess or no reaction at all, respectively. Interestingly, α -benzyl isocyanoacetates were well tolerated, with excellent yield and diastereoselectivity, as well as good enantioselectivity.



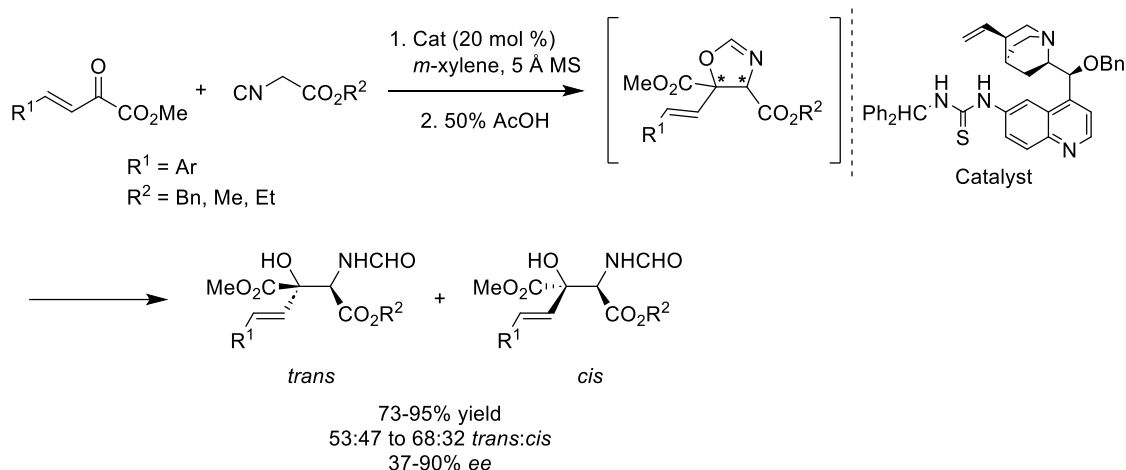
Scheme 50: [3+2] cycloaddition of α -aryl isocyanoacetates with isatins, catalyzed by a quinine-based thiourea.

The spirooxindole products could be methylated at the nitrogen atom of the oxazoline moiety by a Meyers methylation-reduction procedure, with a good yield and without loss of the enantiomeric purity (**Scheme 51**).



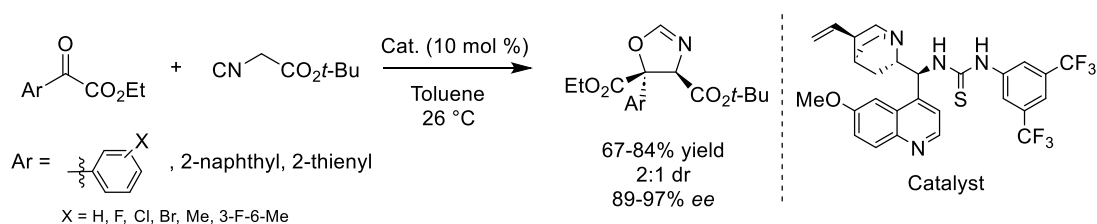
Scheme 51: *N*-methylation and reduction of the oxazoline in the spirooxindole reaction products.

In 2014, the group of Lu described the organocatalytic asymmetric 1,2-addition and cyclization of α -unsubstituted isocyanoacetates to α,β -unsaturated β -ketoesters.⁵⁶ The intermediate oxazolines were hydrolyzed to the corresponding β -hydroxy amino esters in a one pot procedure (**Scheme 52**). Diastereo- and enantioselectivities oscillated from moderate to good.



Scheme 52: Synthesis of α -hydroxy amino esters by the addition of isocyanoacetates to α,β -unsaturated α -ketoesters, using a 6'-thiourea-substituted *Cinchona* alkaloid-derived bifunctional catalyst.

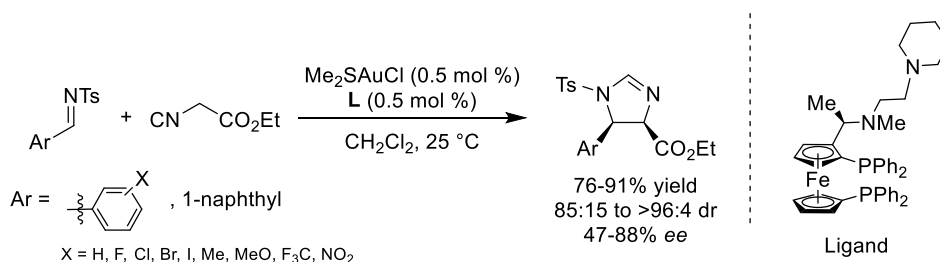
The organocatalytic [3+2] cycloaddition of isocyanoacetates to α -ketoesters was further developed by the group of Chen and Huang in 2017, with the aldol addition of *tert*-butyl isocyanoacetate to aromatic ethyl α -ketoesters, catalyzed by a quinine-derived thiourea (**Scheme 53**).⁵⁷ Although the diastereoselectivity of the reaction was limited, the enantioselectivity for the major diastereomer was excellent.



Scheme 53: Organocatalytic asymmetric synthesis of oxazolines by the [3+2] cycloaddition of *tert*-butyl isocyanoacetates to α -ketoesters.

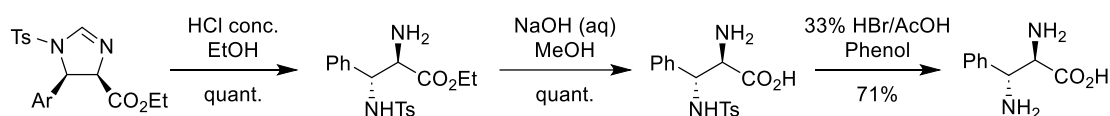
2.2.2 Reactions with imines

The first example of an asymmetric [3+2] cycloaddition of isocyanoacetates with imines was described by Lin and collaborators in 1999, and consisted in the synthesis of chiral 2-imidazolines by the reaction of isocyanoacetates with *N*-sulfonylimines.^{58,59} Based on the conditions previously described by Ito and Hayashi for the cycloaddition of isocyanoacetates with aldehydes,⁴⁸ the authors used a catalytic system comprised of a Au(I) compound with a ferrocene chiral ligand (**Scheme 54**).



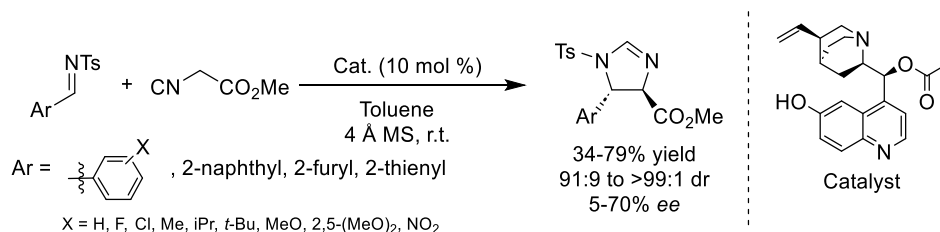
Scheme 54: Asymmetric synthesis of 2-imidazolines by the means of a [3+2] cycloaddition of isocyanoacetates and *N*-sulfonylimines.

Furthermore, the obtained 2-imidazolines could be transformed to the corresponding 2,3-diamino acid derivatives (**Scheme 55**).



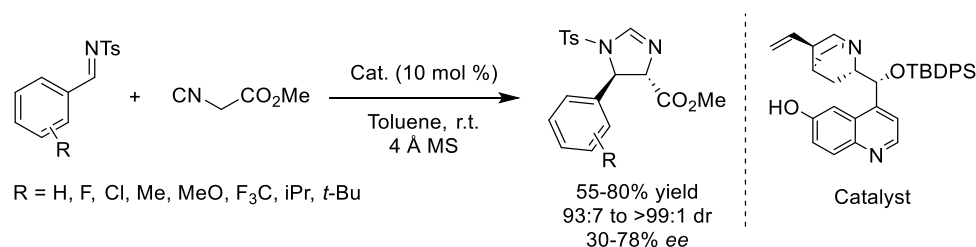
Scheme 55: Synthetic route to access 2,3-diamino acids from 2-imidazolines.

In 2008, another alternative of metallic catalysis for the asymmetric cyclization of isocyanoacetates with *N*-sulfonylimines, using Pd(II) complexes, was published by the group of Szabó.⁶⁰ However, it was not until 2010 that the first organocatalytic protocol for the asymmetric addition and cyclization of isocyanoacetates and imines emerged, with the reaction of methyl isocyanoacetate and aromatic *N*-sulfonylimines, catalyzed by a cupreidine derivative, published by the group of Lu and Chan (**Scheme 56**).⁶¹ Diastereoselectivities were excellent in all cases, although yields and enantioselectivities were only moderate. Strong electron-withdrawing substituents like nitro at the 4 position of the imine aromatic ring were not well tolerated, and provided products with reduced enantioselectivity. Certain heteroaromatic substituents like 2-furyl also reduced the enantiomeric excess of the product, although bulky groups like naphthyl or other heteroaromatics like 2-thienyl provided enantioselectivities comparable to that obtained with the base tosylimine with an unsubstituted phenyl ring.



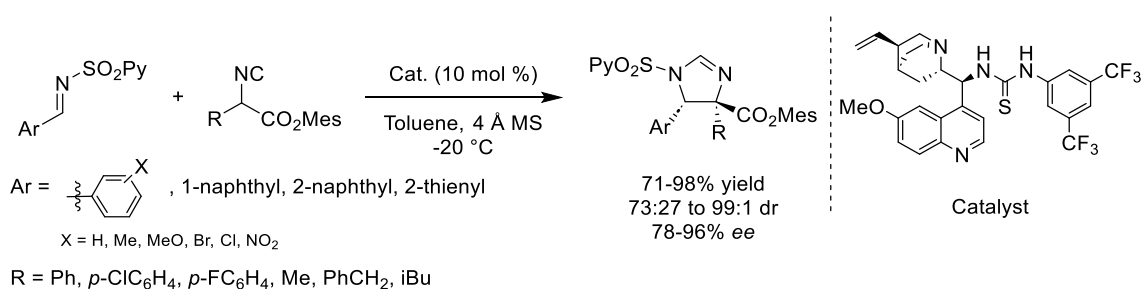
Scheme 56: Asymmetric synthesis of 2-imidazolines by the asymmetric Mannich-type reaction of methyl isocyanoacetate to *N*-tosylimines.

In 2019, the group of Jin also described the Mannich reaction and cyclization of methyl isocyanoacetates with aromatic *N*-tosylimines, this time catalyzed by a cupreine-derived organocatalyst (**Scheme 57**).⁶² This procedure allowed the obtention of the opposite enantiomer of the previous 2-imidazolinones. Electron-withdrawing groups like trifluoromethyl also limited the enantioselectivity of the reaction.



Scheme 57: Asymmetric organocatalyzed synthesis of 2-imidazolinones using a cupreine organocatalyst.

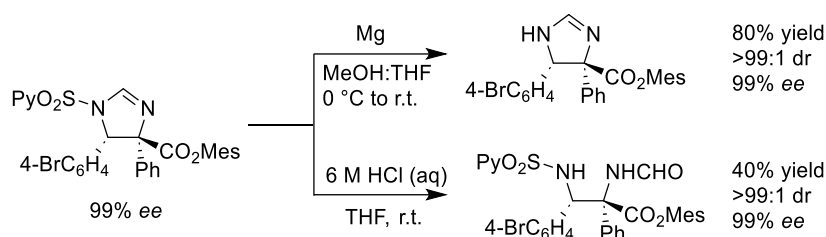
In 2012, Nakamura, Shibata and collaborators developed an asymmetric cycloaddition of α -substituted isocyanoacetates with *N*-(2-pyridinesulfonyl)imines, using a thiourea organocatalyst derived from quinine (**Scheme 58**).⁶³



Scheme 58: [3+2] Cycloaddition of α -substituted isocyanoacetates with *N*-(2-pyridinesulfonyl)imines to give rise to 2-imidazolinones with a quaternary stereocenter.

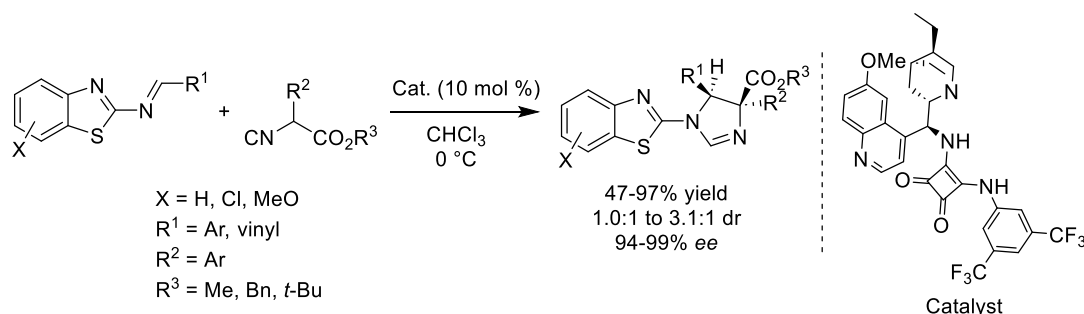
Compared with previously described procedures, the resulting 2-imidazolinones now possess a quaternary chiral stereocenter, because of the use of isocyanoacetates which are α -substituted. Some features of this procedure include the use of *N*-(2-pyridinesulfonyl)imines, which provided higher enantiomeric excess of the 2-imidazolinone products than the analogous *N*-tosylimines and the use of mesityl isocyanoacetate esters, which allowed for an increase in the diastereoselectivity of the process compared with methyl esters.

The pyridinesulfonyl group of the product could be removed by magnesium in MeOH, giving the product of a formal addition to an *N*-unsubstituted imine. Acidic hydrolysis also allowed the obtention of the α,β -diamino ester (**Scheme 59**).



Scheme 59: Synthetic transformation of the 2-imidazolinone products.

In 2023, the group of Zhao and Shi published the enantioselective [3+2] cycloaddition of isocyanoacetates with *N*-(2-benzothiazolyl)imines, giving rise to linked benzothiazole-dihydroimidazole products.⁶⁴ The reaction proceeded organocatalytically, making use of a squaramide derived from the dihydroquinine alkaloid.

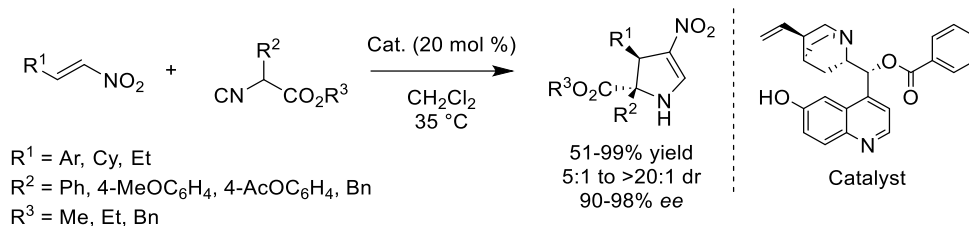


Scheme 60: Asymmetric synthesis of benzothiazole-dihydroimidazole products, via a Mannich-type addition and cyclization of α -substituted isocyanoacetates with *N*-(2-benzothiazolyl)imines.

Enantiomeric excesses for the products were, in general, excellent, although diastereoselectivities were moderate. Limitations of the reaction conditions included the use of isocyanoacetates with *ortho* substituents at its α aromatic ring as well as the use of α -benzylisocyanoacetates. As usual, hydrolysis of the imidazolinone moiety allowed the access to α,β -diamino esters.

2.2.3 Reactions with Michael acceptors

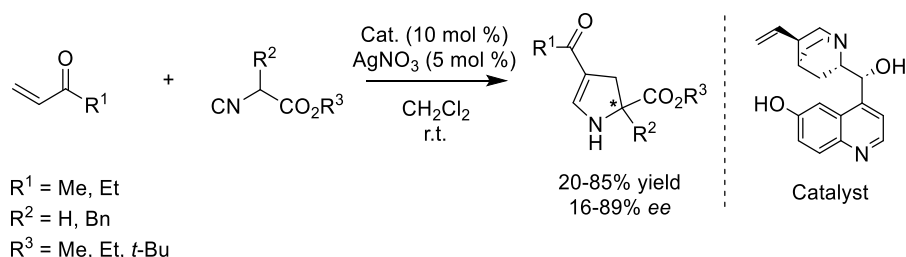
In the realm of organocatalytic asymmetric [3+2] cycloadditions of isocyanoacetates starting with a 1,4-addition followed by intramolecular cyclization, we can find the first example in 2008, when Gong and collaborators published the synthesis of chiral 2-pyrrolines by the reaction of isocyanoacetates and nitroalkenes.⁶⁵ The reaction was catalyzed by a cupreine organocatalyst.



Scheme 61: Organocatalytic asymmetric addition of isocyanoacetates to nitroolefins and intramolecular cyclization.

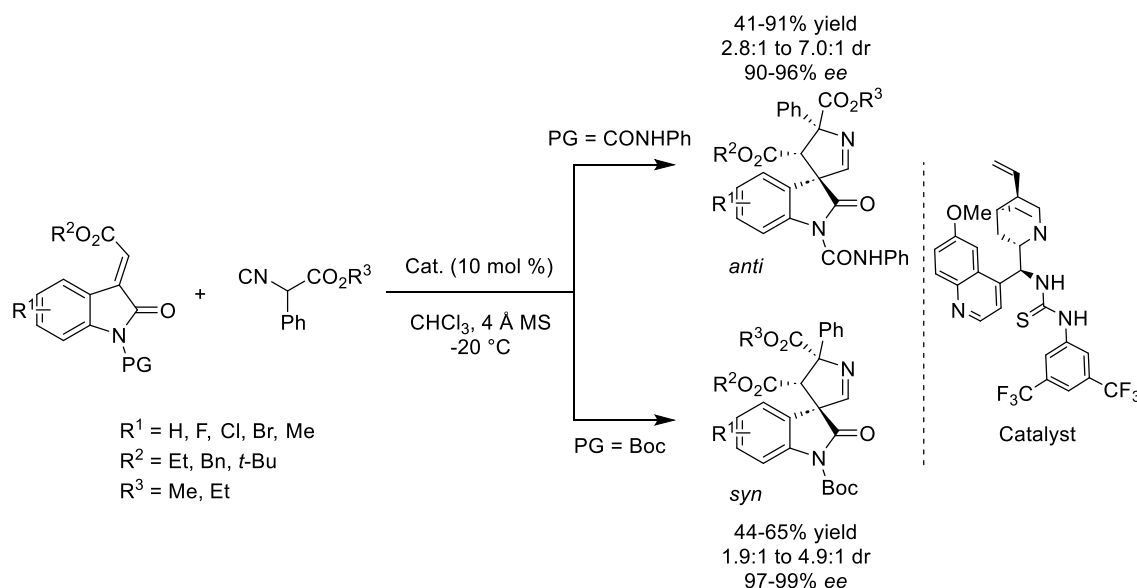
The procedure provided good yields and diastereoselectivities, as well as excellent diastereoselectivities, independently of the substituents at the nitroalkene and at the isocyanoacetate. Nitroalkenes with alkyl substituents as well as α -benzyl isocyanoacetate could be used, providing products with excellent enantioselectivity, although with reduced yield.

The first asymmetric procedure implicating α,β -unsaturated ketones was described in 2011 by the group of Escolano, with a cooperative silver(I)-organocatalyst mediated [3+2] cycloaddition of isocyanoacetates with vinyl ketones.⁶⁶ 2-Pyrrolines were obtained with moderate to good enantiomeric excess (**Scheme 62**).



Scheme 62: Metal-organocatalyst cooperative asymmetric synthesis of 2-pyrrolines from vinyl ketones and isocyanoacetates.

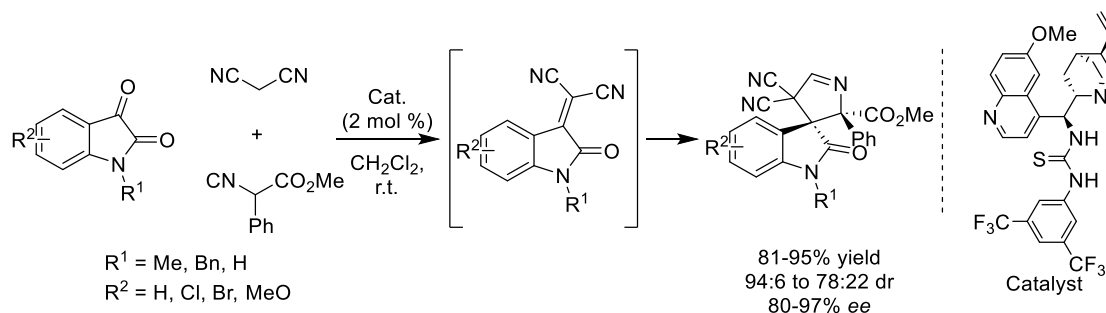
The first organocatalyzed asymmetric reaction of isocyanides with α,β -unsaturated carbonyls came a year later, when the group of Xu and Wang described the synthesis of spirocyclic oxindoles containing a pyrrolidine ring by the [3+2] cycloaddition of isocyanoacetates and indolinones bearing an exocyclic electrophilic double bond, using a thiourea derived from quinine.⁶⁷



Scheme 63: Protecting-group controlled stereocontrol for the asymmetric [3+2] cycloaddition of isocyanoacetates and methyleneindolinones, with quinine-derived thiourea organocatalysis.

An interesting feature of this reaction is the diastereoselectivity switch that occurs when the protecting group of the indolinone ring is replaced from an amide to a *tert*-butoxycarbonyl group, allowing to obtain both the *anti*-4,5-diester as well as the *cis*-4,5-diester pyrroldinyl spirooxindoles (**Scheme 63**).

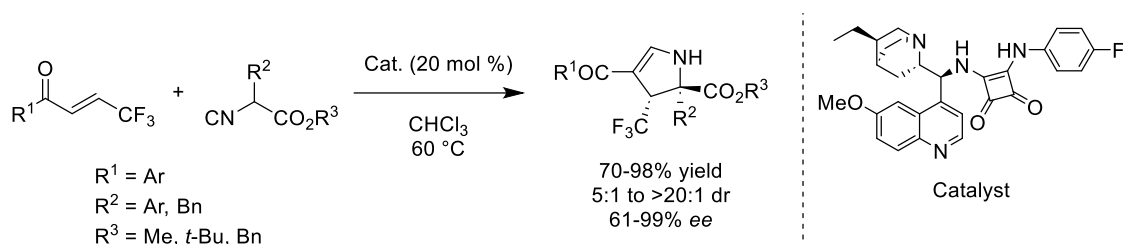
The organocatalytic asymmetric synthesis of 3,3'-pyrroldinyl spirooxindoles was further explored by the group of Yan, with the publication in 2012 of the three-component reaction of isatins, malononitrile and isocyanoacetates.⁶⁸ The synthesis proceeded via a [3+2] cycloaddition to the in situ formed isatylidene malononitriles (**Scheme 64**). Good to excellent yields were, in general, obtained, as well as good diastereoselectivities.



Scheme 64: Three-component asymmetric reaction leading to the formation of chiral 3,3'-dihydropyrryl spirooxindoles, with quinine-derived thiourea catalysis.

Following this trend, organocatalytic asymmetric cycloadditions to α,β -unsaturated ketones were revisited in 2018 by the group of Zhao and Shi, with the [3+2] cycloaddition to β -

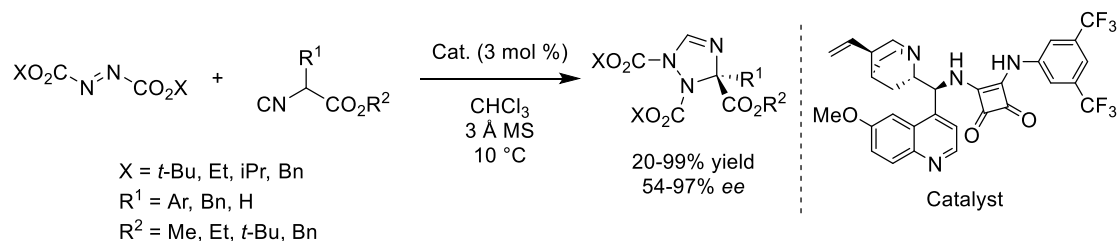
trifluoromethyl enones with isocyanoacetates in order to provide 2-pyrrolines in a diastereo- and enantioselective fashion (**Scheme 65**).⁶⁹



Scheme 65: Asymmetric [3+2] cycloaddition of isocyanoacetates to trifluoromethyl enone Michael acceptors.

The conditions were very similar to the previously mentioned simple Michael addition of isocyanoacetates to β -trifluoromethylenones described by the same research group, performed at 0 °C.³⁶ As such, it was seen that an increase in the temperature of the reaction could result in the cascade consecution of the intramolecular cyclization step after the initial Michael addition.

The first organocatalytic Michael addition to non-carbon double bonds consisted of the cycloaddition of isocyanoacetates with azodicarboxylates to give rise to chiral 1,2,4-triazolines, described in 2013 by the group of Zhao and Shi.⁷⁰

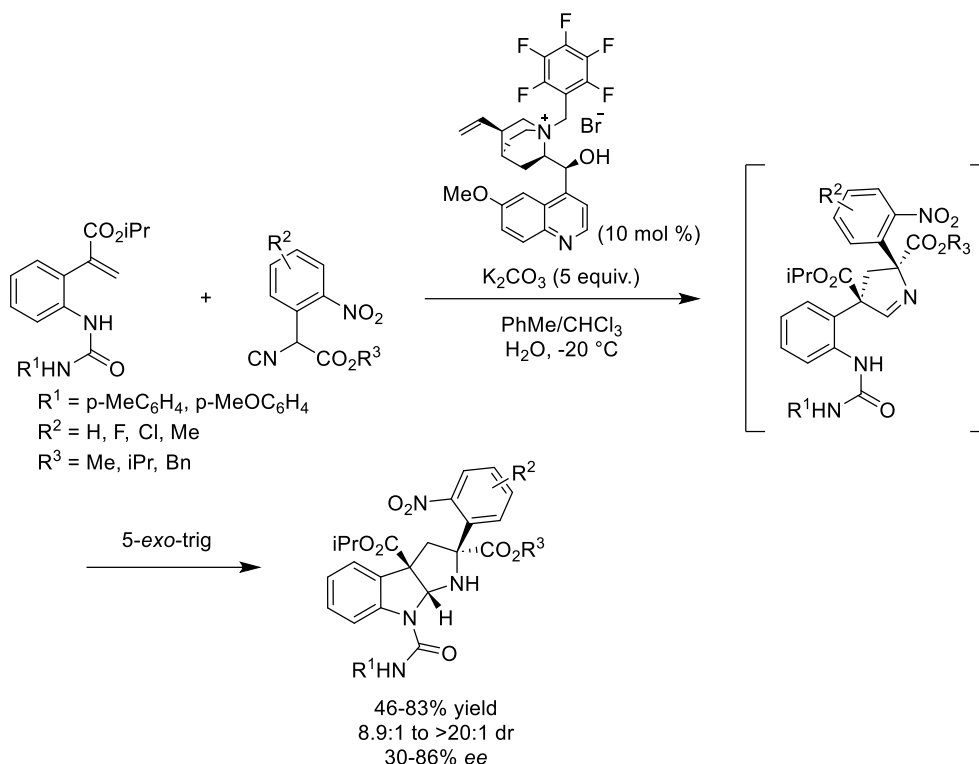


Scheme 66: Synthesis of 1,2,4-triazolines by the [3+2] cycloaddition of isocyanoacetates and azodicarboxylates.

Excellent yields and enantioselectivities were, in general, attained, with the most notable limitations being found in the use of α -alkyl isocyanoacetates and azodicarboxylate amides, which provided no reaction.

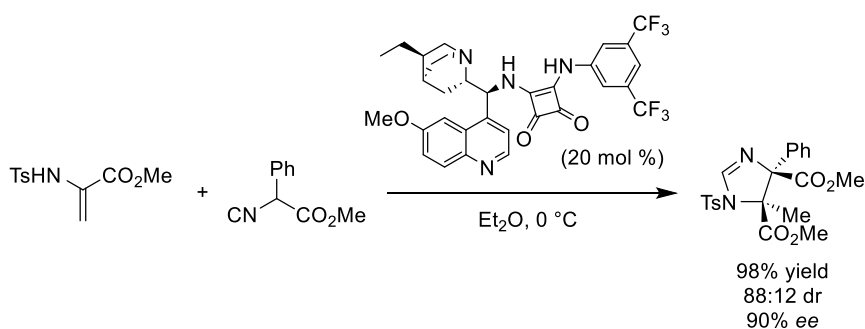
The group of Smith published in 2014 an asymmetric synthesis of pyrroloindolines proceeding via a cascade approach that started with an addition of an isocyanoacetate to a specially designed Michael acceptor.⁷¹ The authors proposed a mechanism implicating an initial [3+2] cycloaddition to the α,β -unsaturated ester moiety of the substrate, followed by a 5-*exo*-trigonal intramolecular cyclization of the amide nitrogen to the resulting pyrroline (**Scheme 67**). The

reaction was performed in phase-transfer conditions with a quaternary amine salt derived from a *Cinchona* alkaloid.



Scheme 67: Cascade reaction resulting in the synthesis of pyrroloindolines, starting by a [3+2] cycloaddition of a Michael acceptor with an isocyanoacetate.

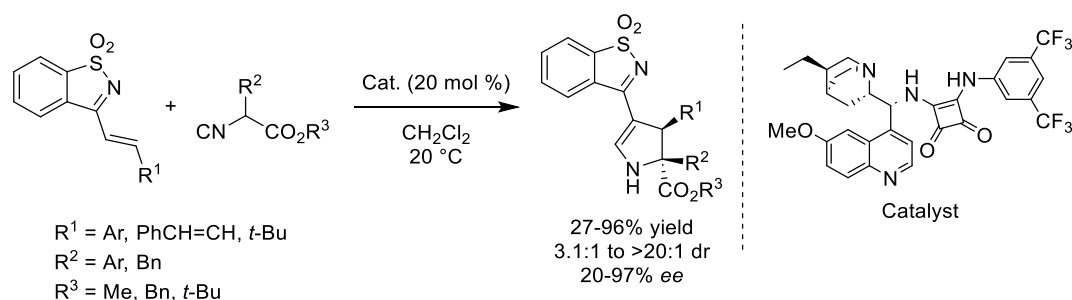
In 2018, Shao, He and collaborators described cycloaddition reactions of isocyanoacetates with different α -substituted acrylates.⁷² Among them, purely organocatalytic conditions could be applied for methyl α -tosylaminoacrylate and methyl α -phenylisocyanoacetate, giving rise to a chiral pyrroline derivative with two consecutive quaternary stereocenters (**Scheme 68**).



Scheme 68: Organocatalytic example for the addition of isocyanoacetates to α -substituted acrylates.

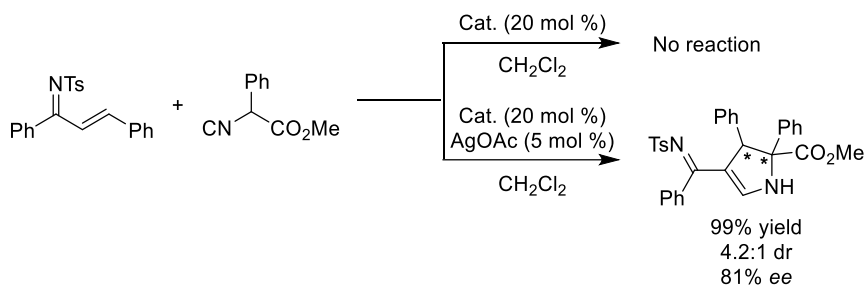
In 2021, the group of Zhao and Shi described the [3+2] cycloaddition of 1-azadienes derived from saccharin and α -substituted isocyanoacetates, with a dihydroquinine-derived squaramide organocatalyt (**Scheme 69**).⁷³ Although diastereoselectivities were moderate,

enantiomeric excesses were excellent in almost all cases, barring the use of α -benzyl isocyanoacetates as well as 1-azadienes with alkyl substituents at the double bond, which provided a product with reduced enantioselectivity. Additionally, the use of *ortho* substituted α -phenyl isocyanoacetates provided no reaction when the substituent was an electron-donating group like methyl, but provided the desired product with excellent diastereo- and enantioselectivity when methyl α -(*o*-fluorophenyl) isocyanoacetate was used.



Scheme 69: Organocatalyzed [3+2] cycloaddition of saccharin-derived 1-azadienes with isocyanoacetates.

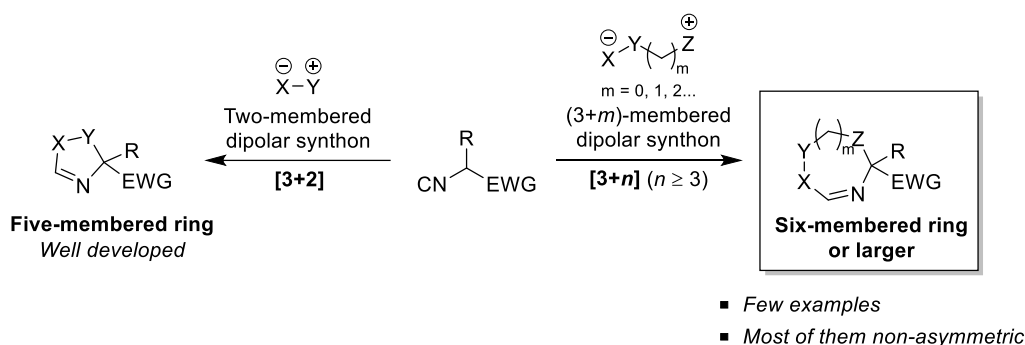
Interestingly, when the reaction was carried out in the optimized reaction conditions with a chalcone-derived 1-azadiene, no reaction took place. However, if the procedure was carried out in cooperative metal-organic catalysis, the expected 2-pyrroline was obtained (**Scheme 70**). Thus, the saccharin moiety of the used 1-azadienes was proved to be crucial for the consecution of the organocatalytic reaction.



Scheme 70: Attempted reaction with chalcone-derived 1-azadienes in organocatalytic conditions and essay with cooperative catalysis conditions.

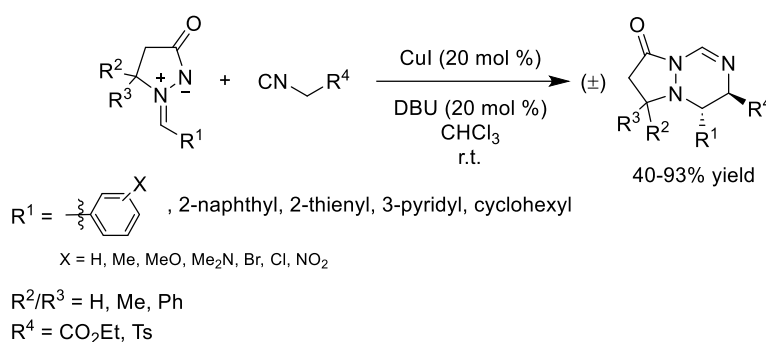
2.3 Higher order cycloadditions involving isocyanoacetates

When compared with [3+2] cycloaddition reactions, [3+*n*] (*n* ≥ 3) cycloadditions involving isocyanoacetates are relatively underdeveloped, with only a few examples published in the literature, and with remarkable minimal presence of enantioselective procedures (**Scheme 71**).



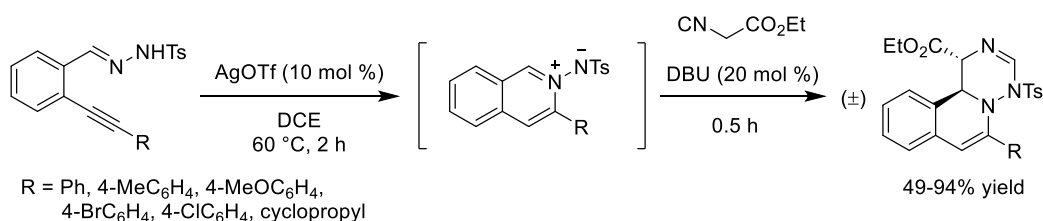
Scheme 71: General perspective comparison of [3+2] and [3+n] ($n \geq 3$) cycloadditions involving isocyanoacetates and related isocyanides.

The first example of a [3+3] cycloaddition with isocyanoacetates was described in 2014 by the group of Xu and Liu, using *N,N'*-cyclic azomethine imines as substrates, in order to obtain pyrazolotriazinones (**Scheme 72**).⁷⁴ Copper(I) iodide was used for the activation of the isocyanide, employing DBU for the initial α -deprotonation.



Scheme 72: [3+3] cycloaddition of isocyanoacetates and TosMIC with *N,N'*-cyclic azomethine imines.

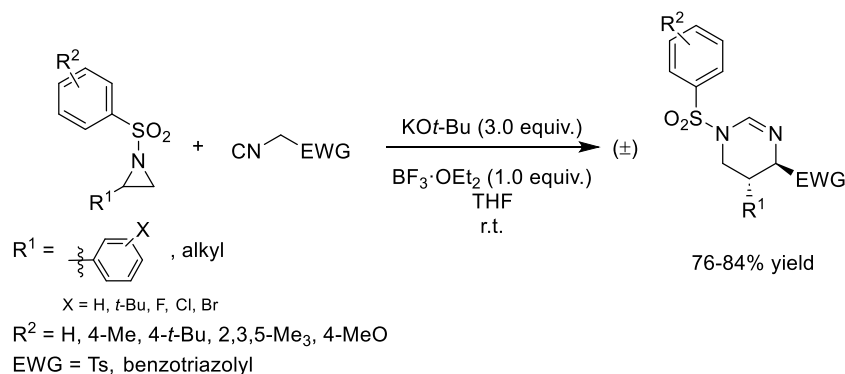
In the same publication, the authors also described the [3+3] cycloaddition of isocyanoacetates to *N*-iminoisoquinolinium ylides, synthesized in situ from (*E*)-*N*-(2-alkynylbenzylidene)-4-methylbenzenesulfonohydrazides, via an AgOTf-mediated cyclization (**Scheme 73**).



Scheme 73: Synthesis of triazinoisoquinolines from in situ synthesized *N*-iminoisoquinolinium ylides.

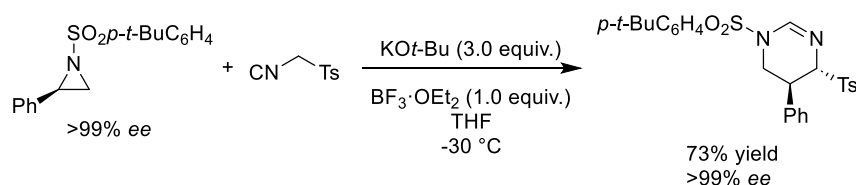
In 2018, the group of Ghorai described a [3+3] cycloaddition of TosMIC and aziridines, proceeding via the ring opening of the aziridine.⁷⁵ The authors coined the global procedure as a domino ring opening cyclization (**Scheme 74**). The procedure involved the use of potassium

tert-butoxide for deprotonating the pronucleophile, as well as boron trifluoride as a Lewis acid catalyst to yield six-membered *aza*-heterocycles containing two nitrogen atoms.



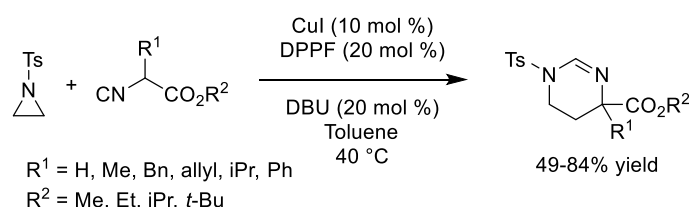
Scheme 74: Domino ring opening cyclization involving TosMIC and aziridines.

Furthermore, when a chiral enantiopure aziridine was used as starting material, the reaction could be carried out in an enantiospecific fashion (**Scheme 75**).



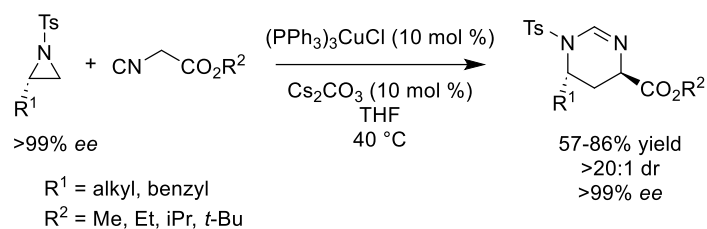
Scheme 75: Enantiospecific example of the [3+3] cyclization of TosMIC with a chiral aziridine.

The same year, the group of Wong and Zhao also published a procedure of [3+3] cycloaddition via ring opening of aziridines, this time with isocyanoacetates instead of TosMIC (**Scheme 76**).⁷⁶ A combination of a Lewis acid, copper(I) iodide, and a phosphine-based ligand, 1,1'-Bis(diphenylphosphino)ferrocene (DPPF), was used. The authors tried to further develop the procedure with the consecution of the enantioselective version using chiral phosphine ligands, though asymmetric induction was not achieved.



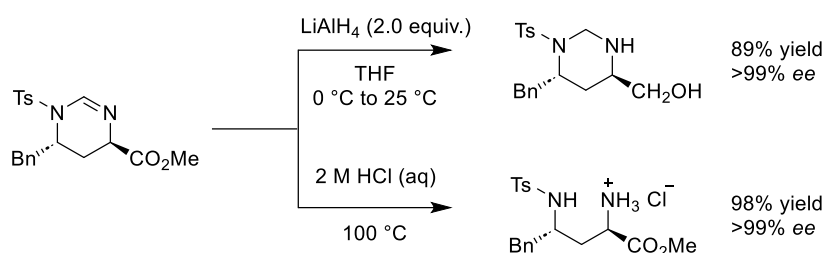
Scheme 76: [3+3] cycloaddition of isocyanoacetates and *N*-tosyl aziridine.

When chiral enantiopure aziridines were used, a completely diastereoselective and enantiospecific reaction was observed (**Scheme 77**).



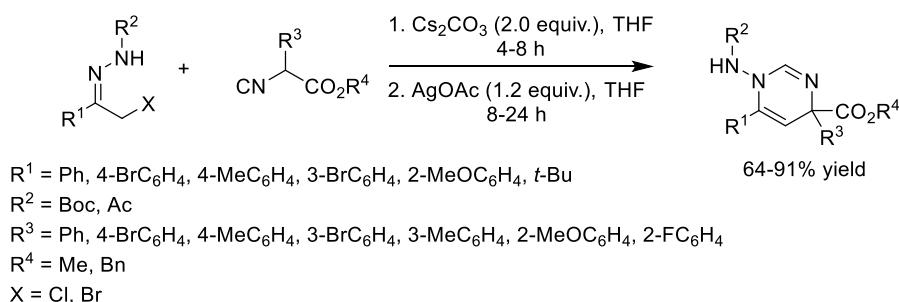
Scheme 77: Reaction with enantiopure aziridines in a completely diastereoselective and enantiospecific fashion.

Furthermore, the obtained tetrahydropyrimidines could be reduced to furnish the corresponding amino alcohol, or hydrolyzed to give rise to α,γ -amino acids, providing a new route to the synthesis of unnatural amino acids (**Scheme 78**).

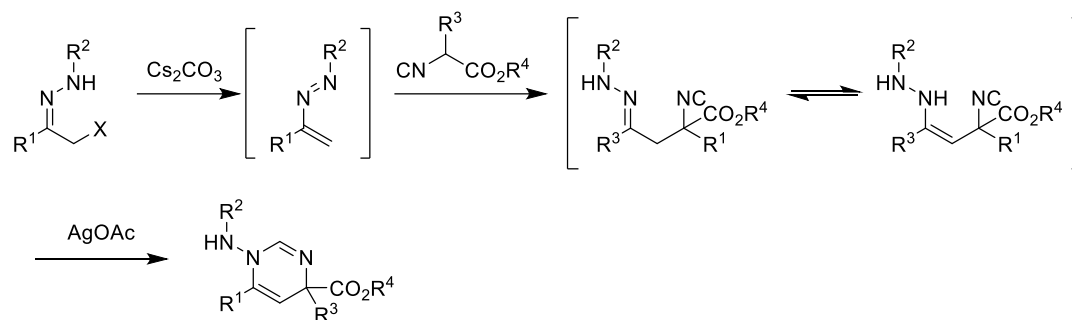


Scheme 78: Reduction and hydrolysis of the obtained tetrahydropyrimidines.

In 2021, the group of Shi and Zhao described the two-step formal [3+3] cycloaddition of isocyanoacetates and in situ generated 1,2-diazadienes (**Scheme 79**).⁷⁷ The first step consisted on the addition of the isocyanoacetate to the 1,2-diazadiene, generated from an α -halohydrazone and a base, while the second step consisted on the isomerization and cyclization of the addition adduct, mediated by silver acetate (**Scheme 80**). Both steps could be carried out one-pot by adding silver acetate to the reaction vessel once the addition step had finished.

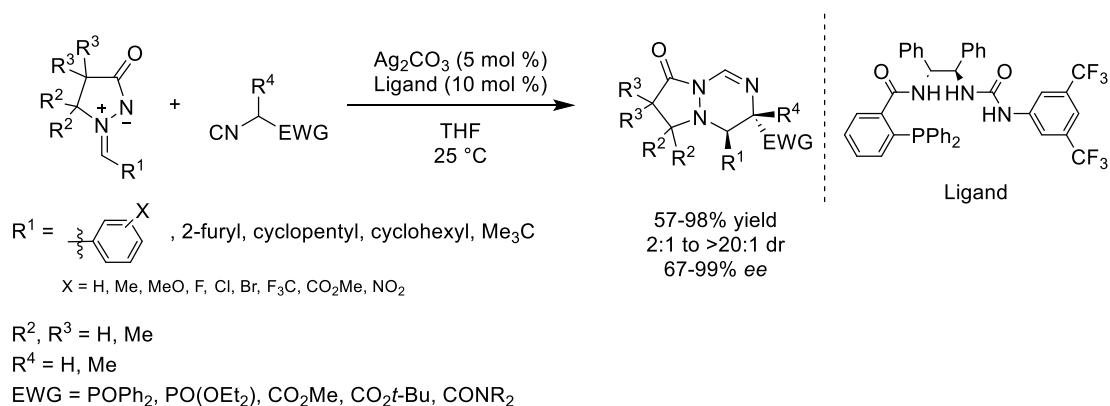


Scheme 79: One pot formal [3+3] cycloaddition of isocyanoacetates and α -halohydrazones.



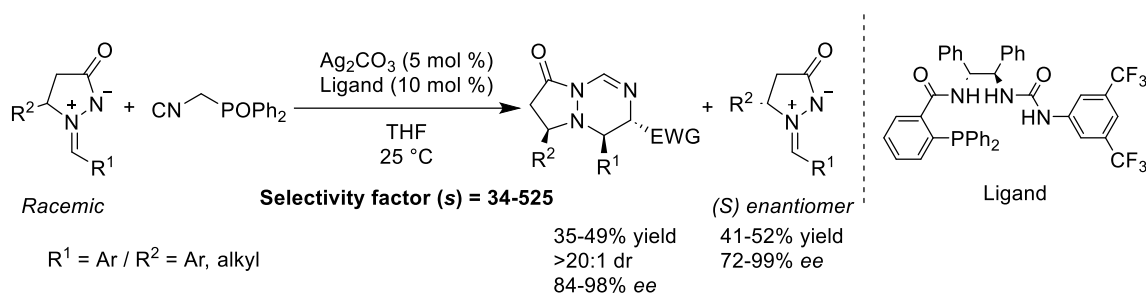
Scheme 80: Mechanistic proposal for the formal [3+3] cycloaddition of isocyanoacetates and in situ generated 1,2-diazadienes.

The first asymmetric procedure involving [3+3] cycloadditions with activated isocyanides was described in 2022, in the reaction with *N,N'*-cyclic azomethine imines, yielding bicyclic 1,2,4-triazines in a diastereo- and enantioselective fashion (**Scheme 81**).^{78,79} Aryl azomethine imines provided excellent diastereoselectivities and good to excellent enantiomeric excesses. Azomethine imines with alkyl substituents at their double bond were also compatible, although with poorer results. Isocyanomethylphosphonates, isocyanoacetates as well as isocyanoacetamides were compatible with the catalytic system, which used a silver(I) salt and a chiral phosphine ligand based on diphenylene-1,2-diamine.



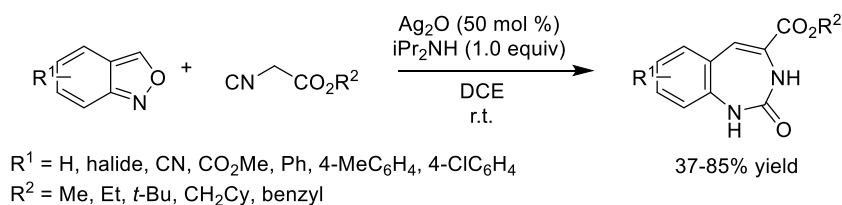
Scheme 81: Diastereo- and enantioselective [3+3] cycloaddition of activated isocyanides and azomethine imines.

Furthermore, the catalytic system could also be employed for the kinetic resolution of racemic 3-substituted azomethine imines. Resolutions were realized with excellent selectivity factors and 1,2,4-triazines were obtained with excellent diastereoselectivity (>20:1 dr) in all cases (**Scheme 82**).



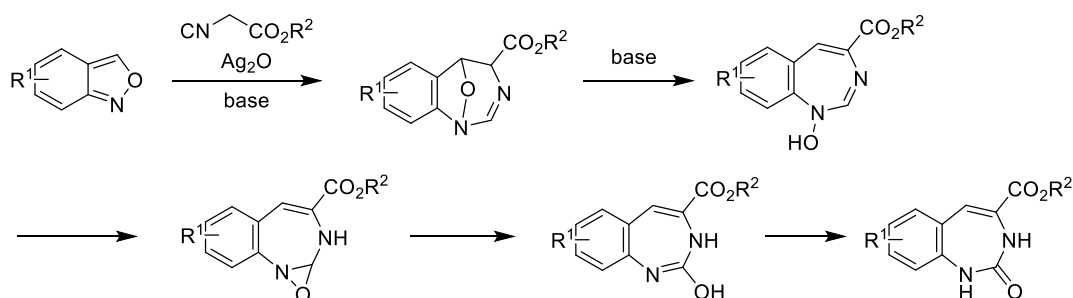
Scheme 82: Kinetic resolution of racemic azomethine imines with the [3+3] cycloaddition catalytic system.

In 2022, the group of Wang and Shang published the first example of [3+4] cycloaddition involving isocyanoacetates, with the silver-promoted dearomative cycloaddition to anthranils (**Scheme 83**).⁸⁰



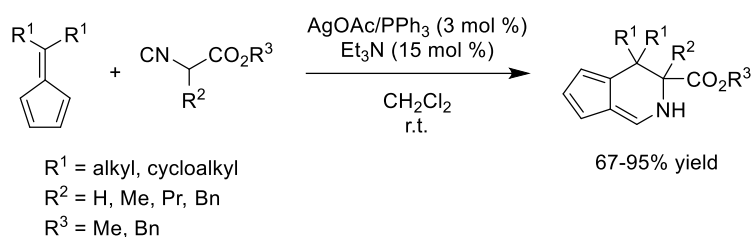
Scheme 83: [3+4] dearomative cycloaddition of isocyanoacetates to anthranils.

The corresponding benzodiazepine products were obtained instead of the “direct” bridged bicycle cycloaddition products because of an internal ring-opening reaction that was followed by an oxygen migration rearrangement pathway (**Scheme 84**).



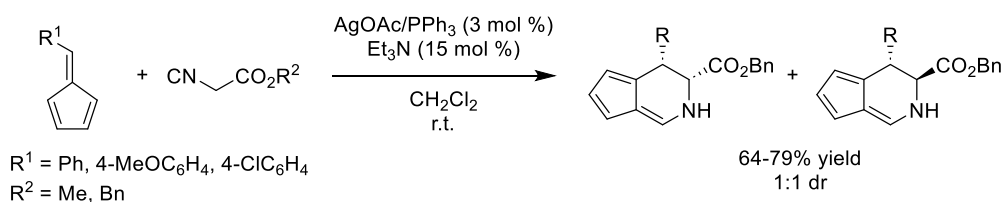
Scheme 84: Simplified mechanistic proposal for the [3+4] cycloaddition procedure.

On the other hand, in 2015, He and Wang described an annulation reaction of isocyanoacetates and fulvenes implicating, from an electronic point of view, a [3+6] cycloaddition.⁸¹ A newly fused six-membered heterocycle containing a nitrogen atom was formed (**Scheme 85**).



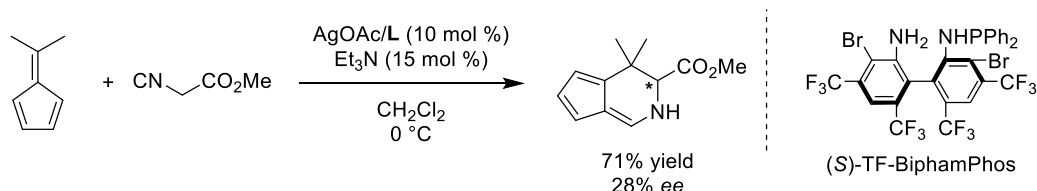
Scheme 85: Cycloaddition of isocyanoacetates with symmetric fulvenes.

The developed reaction conditions were also tested with unsymmetrical fulvenes bearing just one substituent at the exocyclic double bond, thus providing products with two stereogenic centers. Unfortunately, although the reaction proceeded smoothly, a 1:1 mixture of the *syn* and *trans* diastereomers was obtained for all examples (**Scheme 86**).



Scheme 86: [3+6] cycloaddition of unsymmetrical fulvenes and isocyanoacetates.

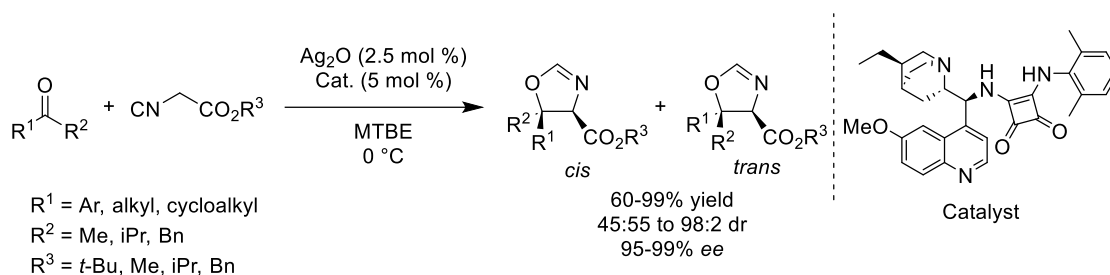
A preliminary result for the enantioselective version of the reaction was presented, using a chiral phosphine ligand, obtaining one example of cycloaddition adduct with 28% *ee* (**Scheme 87**).



Scheme 87: Preliminary results for the enantioselective variant of the [3+6] cycloaddition of isocyanoacetates and fulvenes.

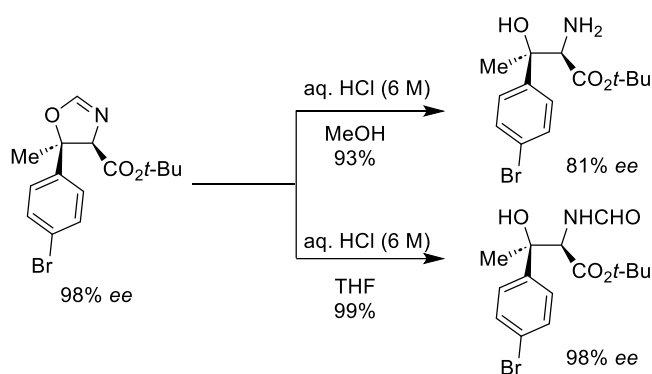
2.4 Previous work by our research group

Our research group has published different asymmetric formal cycloaddition reactions involving isocyanoacetates. The first one was published in 2018, and consisted in the synthesis of chiral oxazolines from ketones and isocyanoacetates by using a metal-organic cooperative catalytic system (**Scheme 88**).⁸² In general, good to excellent yields were obtained, as well as excellent enantioselectivities and moderate to excellent diastereoselectivities.



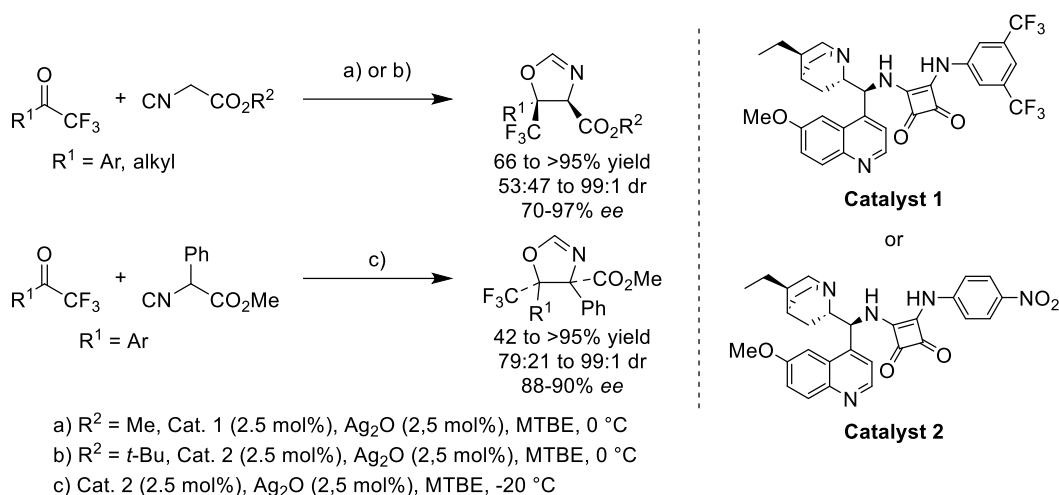
Scheme 88: Synthesis of chiral oxazolines from ketones and isocyanoacetates.

Furthermore, the obtained oxazolines could be hydrolyzed to the corresponding amino alcohol or hydroxy formamide (**Scheme 89**). In the latter case, no loss of enantiomeric excess was observed.



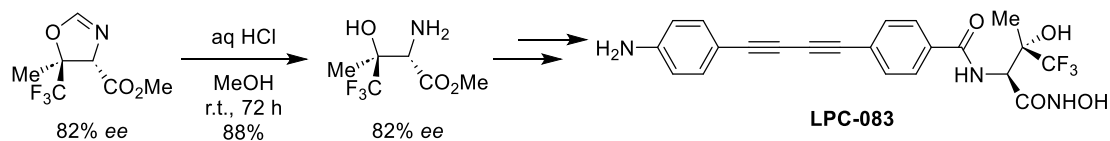
Scheme 89: Hydrolysis pathways of the obtained oxazolines.

In 2019, our research group reported an extension of this reaction to trifluoromethyl ketones, giving rise to chiral 5-trifluoromethyl-2-oxazolines (**Scheme 90**).⁸³ The optimized conditions were different depending on the isocyanoacetate that was used in the cycloaddition. Oxazolines bearing two consecutive quaternary stereocenters could be obtained when an α -phenyl substituted isocyanoacetate was employed.



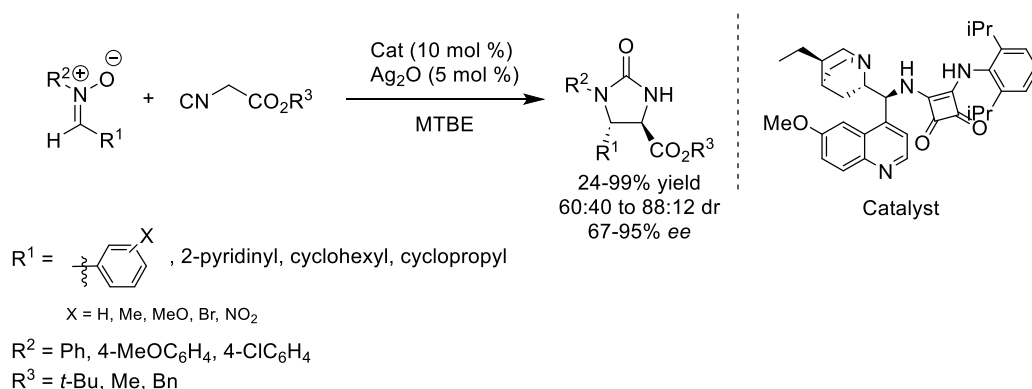
Scheme 90: Synthesis of chiral trifluoromethylated oxazolines via dual silver/organocatalysis conditions.

In a similar fashion to the products from the previous reaction, the trifluoromethyloxazolines could be hydrolyzed to the corresponding amino alcohols or hydroxyformamides with excellent yield and without loss of enantiomeric excess. This allowed for the obtention of a chiral precursor for accessing LPC-083, with antibiotic activity (**Scheme 91**).⁸⁴



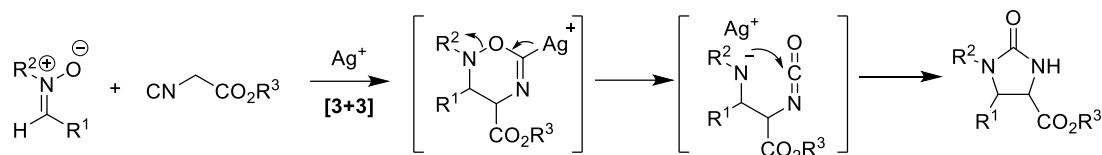
Scheme 91: Hydrolysis of the trifluoromethylated oxazoline *en route* to the synthesis of LPC-083.

The same year, our group also published the asymmetric synthesis of 2-imidazolinones by the reaction of isocyanoacetates and nitrones, using cooperative catalysis conditions, with silver oxide and a dihydroquinine-derived organocatalyst (**Scheme 92**).⁸⁵ In general, the reaction provided better yield and enantioselectivity when *tert*-butyl isocyanoacetate was used, compared with methyl or benzyl esters. Moderate to good diastereoselectivities were obtained.



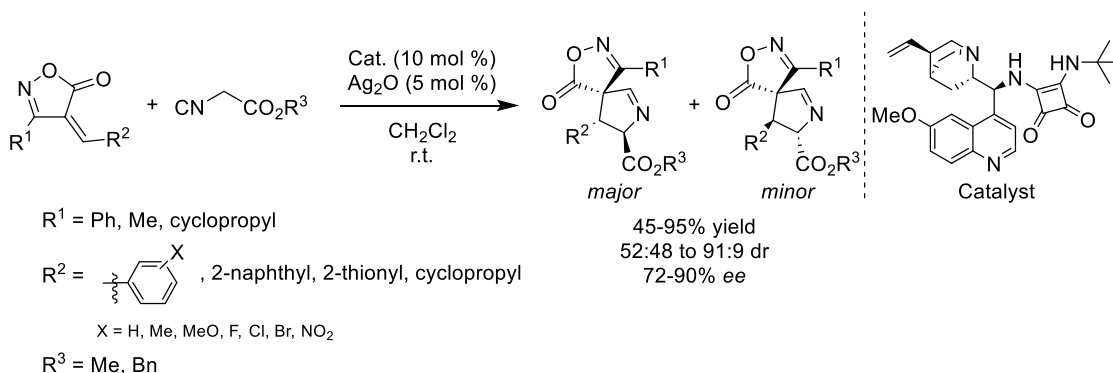
Scheme 92: Synthesis of chiral 2-imidazolinones by the reaction of isocyanoacetates and nitrones.

For the formation of the 2-imidazolinone product, a mechanism was proposed consisting on the initial [3+3] cycloaddition of the nitrone and the isocyanoacetate, followed by spontaneous rearrangement of the formed intermediate to an amino isocyanate. Finally, the observed product could be furnished by the intramolecular addition of the amine to the isocyanate group (**Scheme 93**).



Scheme 93: Simplified mechanistic proposal for the formation of the 2-imidazolinone products.

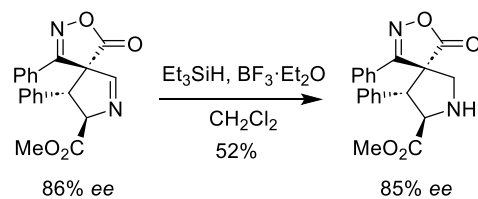
Finally, in 2020, our research group published the formal [3+2] cycloaddition of isocyanoacetates and 4-benzylideneisoxazol-5(4*H*)-ones, using a cooperative metal-organocatalyst system, involving silver oxide and a squaramide derived from quinine (**Scheme 94**).⁸⁶ Chiral diazspirocyclic products were obtained in an enantio- and diastereoselective fashion. In general, diazspirocyclic products were obtained with moderate to excellent yields, moderate diastereoselectivities and high enantiomeric excesses.



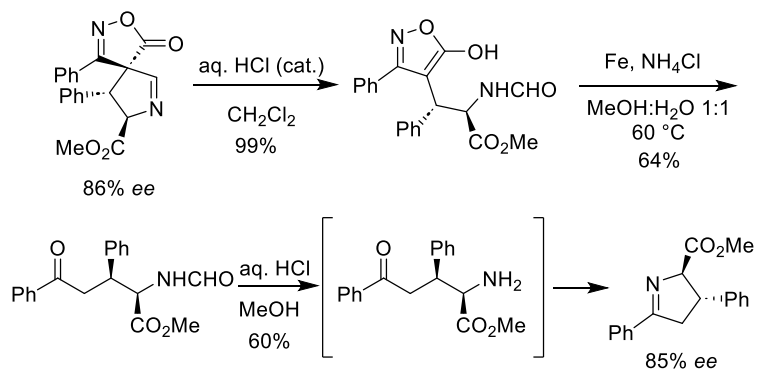
Scheme 94: Enantioselective formal [3+2] cycloaddition of isocyanoacetate esters and 4-benzylideneisoxazol-5(4*H*)-ones.

Two synthetic modifications for the spirocyclic products were developed (**Scheme 95**). On the one hand, reduction of the imine of the pyrroline moiety furnished the corresponding pyrrolidine spirocycle with moderate yield, and without loss of enantiomeric excess. On the other hand, hydrolysis of the imine gave rise to the corresponding hydroxy formamide. Reductive cleavage of the N-O isoxazole bond with spontaneous decarboxylation, followed by further hydrolysis of the formamide gave rise to a chiral pyrroline through the intramolecular cyclization of the resulting amino-ketone intermediate.

a) Reduction of the imine



b) Hydrolysis of the imine and N-O bond cleavage

**Scheme 95:** Synthetic transformations of the spirocyclic products.

3 Objectives

As it has been seen in the previous literature review section, addition reactions to electrophilic double bonds have represented one of the main pathways for the synthesis of highly functionalized isocyanoacetate derivatives which, due to the unique reactivity of the isonitrile group, constitute interesting building blocks for organic synthesis. Furthermore, those functionalized isocyanoacetate derivatives also constitute α -amino acid precursors.

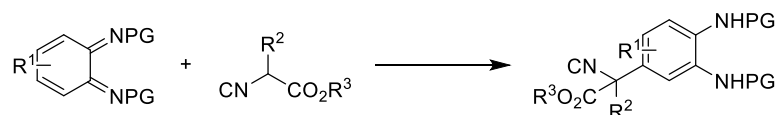
On the other hand, cycloaddition reactions which proceed thanks to the α -H acidity of isocyanoacetates as well as through the electrophilic character of the terminal carbon atom of the isonitrile group owing to its partial carbenic character has been a frequently used method for accessing *aza*-heterocycles. In particular, formal [3+2] cycloadditions that furnish 1- or 2-pyrrolines have seen a rapid development for the synthesis of functionalized heterocycles and polycyclic compounds.

Additionally, despite the advancements seen in the field of [3+2] cycloadditions, there is a notable gap when referring to higher order cycloadditions, with only a few described examples, which are limited to certain families of starting materials and mostly carried out in a non-enantioselective fashion.

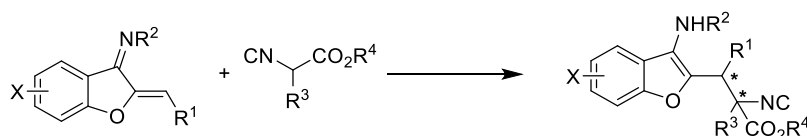
Finally, organocatalytic methods which make use of a small quantity bifunctional chiral catalysts are a very good alternative in the field of asymmetric synthesis, since they allow to access the benefit of asymmetric catalysis without the need to use any kind of metal in the procedure, providing operative simplification as well as sustainability advantages.

Considering the previous developments in these fields, we proposed the following objectives:

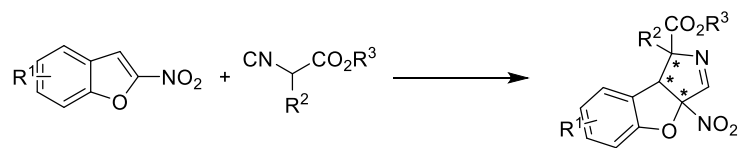
1. *α -Arylation of isocyanoacetate esters:*



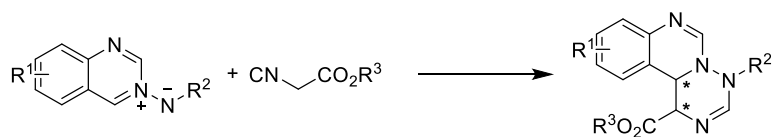
2. *Organocatalytic conjugate addition of isocyanoacetate esters to aurone-derived 1-azadienes:*



3. *Organocatalytic dearomative [3+2] cycloaddition of 2-nitrobenzofurans and isocyanoacetates:*



4. *Organocatalytic asymmetric [3+3] cycloaddition of N-iminoquinazolinium ylides and isocyanoacetates:*



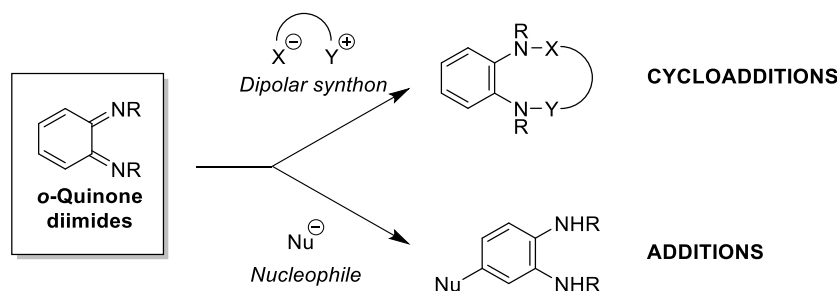
4 Results and discussion

In this chapter, the results obtained for each objective of this thesis will be exposed and discussed. For each section, a brief introduction encompassing the particular state of the art regarding the showcased reaction, as well as its projected importance within its field, is included.

4.1 α -Arylation of isocyanoacetate esters

4.1.1 *o*-Quinone diimides in organic synthesis

o-Quinone diimides are the oxidation product of phenylene-1,2-diamides. The diimides have shown to be more stable than the corresponding *N,N*-unsubstituted and *N,N*-dialkyl diimine analogues. The possibility of decorating the aromatic ring with a variety of substituents, combined with their characteristic reactivity patterns based on the recovery of the aromaticity of the benzene ring, makes them interesting building blocks in organic synthesis.⁸⁷ Since the first reports by Adams and collaborators exploring their reactivity,^{88,89} *o*-quinone diimides have gained increased use in the literature of synthetic organic chemistry (**Scheme 96**).



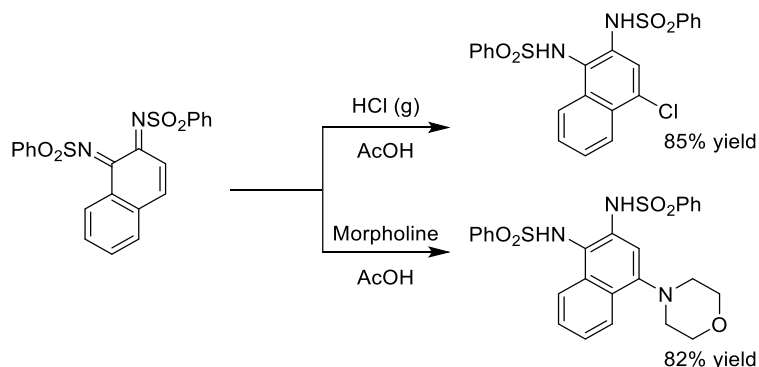
Scheme 96: Most representative reactivity of *o*-quinone diimides explored in the literature.

Since the seminal work performed by Friedrichsen and collaborators investigating the reactivity of *o*-quinone diimides in cycloadditions with varied dipolar synthons like ketenes,⁹⁰ norbornadiene,⁹¹ fulvenes⁹² as well as mesoionic compounds,⁹³ cycloadditions involving *o*-quinone diimides have been increasingly studied in the literature.^{94–100}

In contrast, addition reactions of nucleophiles featuring *o*-quinone diimides as arylating reagents have been limited, with only few examples mainly featuring phosphorus, silicon or tin compounds.

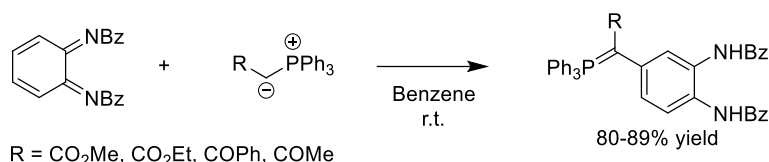
The first addition reactions to *o*-quinone diimides were described by Adams and Wankel in 1951, consisting of the addition of hydrogen chloride and of morpholine to 1,2-

naphthoquinone dibenzenesulfonamide (**Scheme 97**).⁸⁸ In 1954, Adams and Way also studied more additions of this fashion, this time with *o*-quinonedibenzimides.⁸⁹



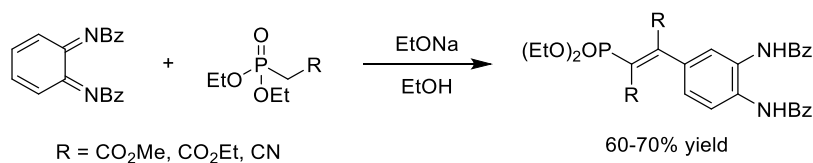
Scheme 97: Addition of hydrogen chloride and morpholine to 1,2-diaminonaphthalene-derived *o*-quinone diimides.

In 1988, Boulos and Arsanious published the addition of phosphorus ylides to *o*-quinone diimides, obtaining the addition products with good yields (**Scheme 98**).¹⁰¹



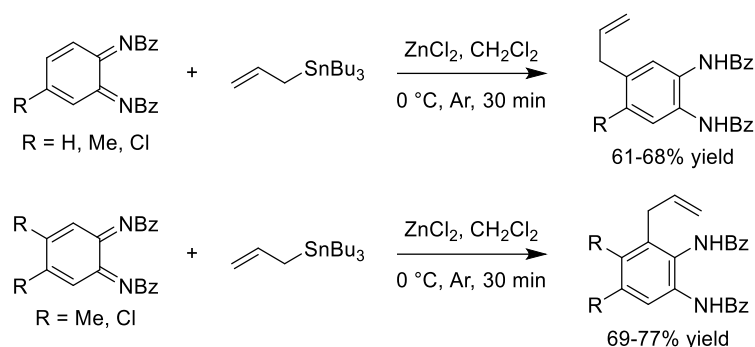
Scheme 98: Obtention of ylid phosphorane adducts by the addition of phosphorus ylides to *o*-quinone diimides.

The same authors described in 1994 the reaction of *o*-quinone diimides with Wittig-Horner reagents.¹⁰² The authors found out that two equivalents of Wittig-Horner reagent reacted with the diimides to give rise to stable phosphonate derivatives with good yield (**Scheme 99**).



Scheme 99: Addition of Wittig-Horner reagents to *o*-quinone diimides.

Later in 2004, Nair and collaborators described the allylation of *o*-quinone benzimides with allylstannane, catalyzed with zinc chloride.⁹⁴ Depending on the substituents of the benzimide, the allylation proceeded in a 1,4- or 1,6-manner (**Scheme 100**). Similar conditions were also applied to the allylation of *o*-quinone benzimides with allylsilane, with very similar results.¹⁰³



4.1.2 Biological relevance of α,α -disubstituted amino acids

On the other hand, α,α -disubstituted α -amino acid and their derivatives, which bear a quaternary alpha carbon, are present in different natural compounds, as well as in compounds with pharmaceutical activity or with interest in the field of catalysis or materials chemistry (**Figure 4**).

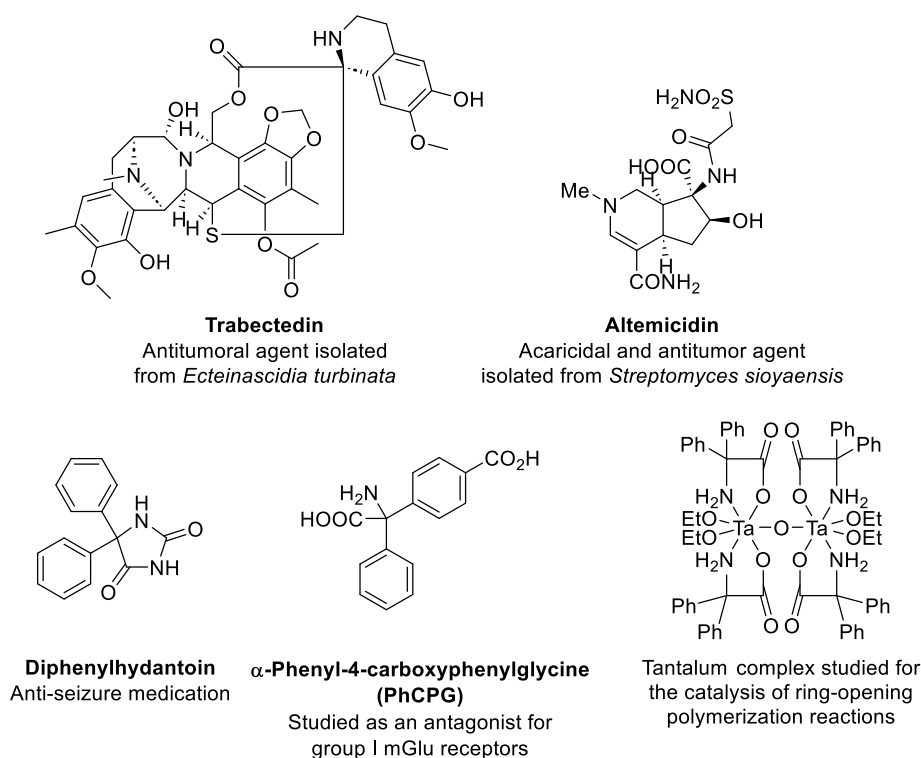


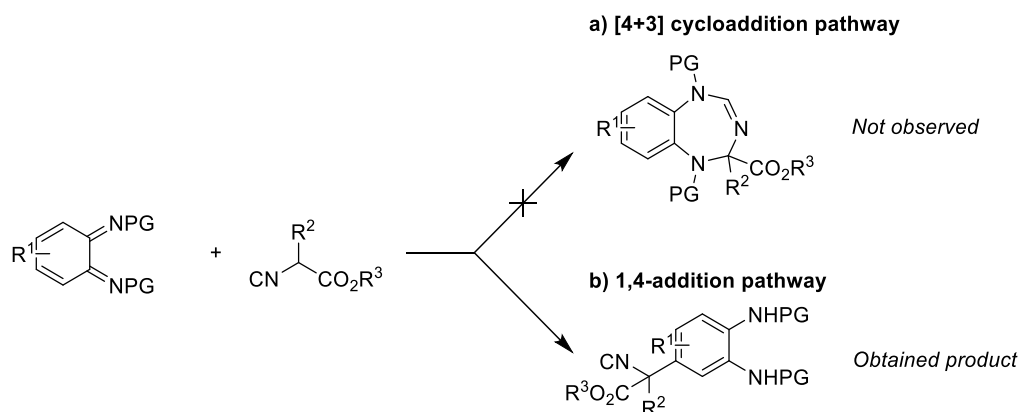
Figure 4: Example of natural products, products with pharmaceutical activity and compounds of chemical interest containing α,α -disubstituted α -amino acid derivative moieties.

Some examples include Trabectedin, isolated from the marine tunicate *Ecteinascidia turbinata*, used as an antitumor medication in chemotherapy;^{104,105} Altemicidin, a compound isolated from the actinomycete *Streptomyces sioyaensis*, present in sea mud, with acaricidal and antitumoral properties;¹⁰⁶ diphenylhydantoin, valuable in the treatment of psychomotor

seizures;¹⁰⁷ PhCPG, studied as a possible antagonist for a family of glutamate receptors which may play a role in long-term depression;¹⁰⁸ as well as metallic complexes studied as promising catalysts for ring-opening polymerization of ϵ -caprolactone, for the synthesis of polyesters.^{109,110}

Moreover, the α,α -disubstitution of amino acids has been shown to have important implications in the secondary structures of the peptides they form.¹¹¹ In this case, α,α -diaryl amino acids prefer extended conformations, while α,α -dialkyl variants favor helical structures.^{112,113}

Encouraged by the versatility of *o*-quinone diimides and the potential interest of highly substituted amino acid derivatives, we were inclined to try reacting isocyanoacetates with *o*-quinone diimides. Considering the electronic characteristics of both reaction partners, two possible reaction pathways were envisioned: a [4+3] cycloaddition process furnishing 1,3,5-triazepines or an arylation pathway consisting on the 1,4-addition of the isocyanoacetate to a carbon atom of the pro-aromatic ring (**Scheme 101**).

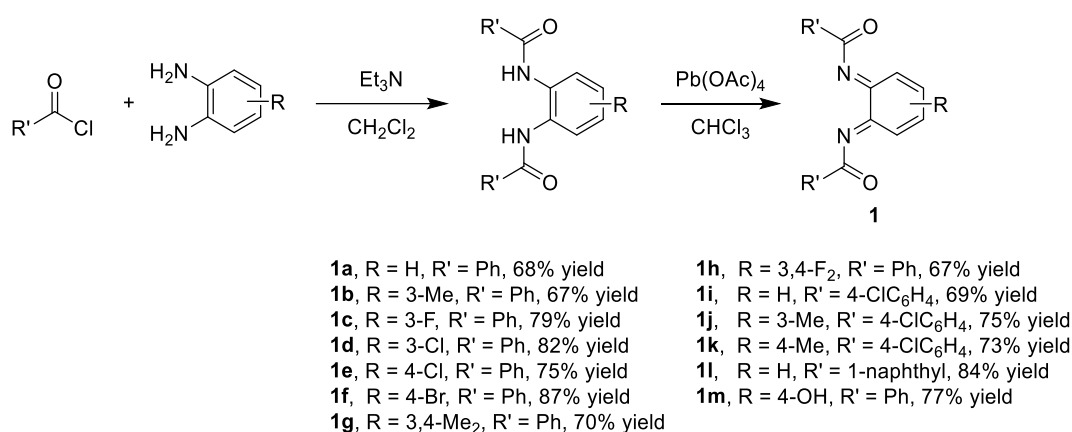


Scheme 101: Possible reaction pathways for the reaction of *o*-quinone diimides with isocyanoacetates.

In this case, we observed that the reaction proceeded via the 1,4-addition pathway (**Scheme 101**, b), giving rise to α,α -diaryl α -amino acid precursors when α -aryl isocyanoacetates were used.

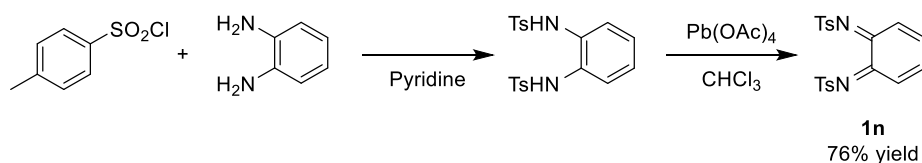
4.1.3 Synthesis of the *o*-quinone diimide starting materials

The *o*-quinone dibenzimide starting materials were synthesized according to a two-step procedure comprising the formation of the diamide of the corresponding phenylene-1,2-diamine, using the appropriate benzyl chloride, followed by lead(IV) tetraacetate-mediated oxidation (**Scheme 102**).



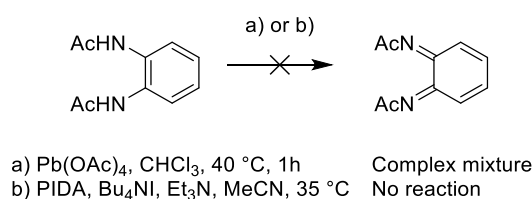
Scheme 102: Synthetic route towards *o*-quinone dibenzimidides. Yields refer only to the second step.

In the case of the *o*-quinone dibenzenesulfonimide, the first step consisted on the double amidation of 1,2-diaminobenzene with *p*-toluenesulfonic acid chloride, using pyridine as the solvent. The second and final step is the usual oxidation of the diamine with Pb(OAc)₄ (**Scheme 103**).



Scheme 103: Synthesis of the *o*-quinone dibenzenesulfonimide **1n**. Yield refers only to the second step.

Attempts to oxidize *N,N'*-(1,2-phenylene)diacetamide with either the usual procedure or with (diacetoxyiodo)benzene were unsuccessful. The first one provided a complex reaction mixture while the second one did not result in any reaction at all, the starting material being recovered (**Scheme 104**).

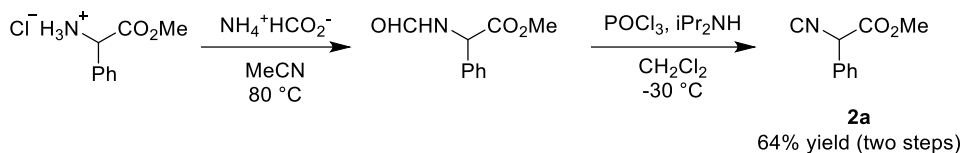


Scheme 104: Unsuccessful attempts to provide *o*-quinone diacetamide.

4.1.4 Synthesis of the isocyanoacetate starting materials

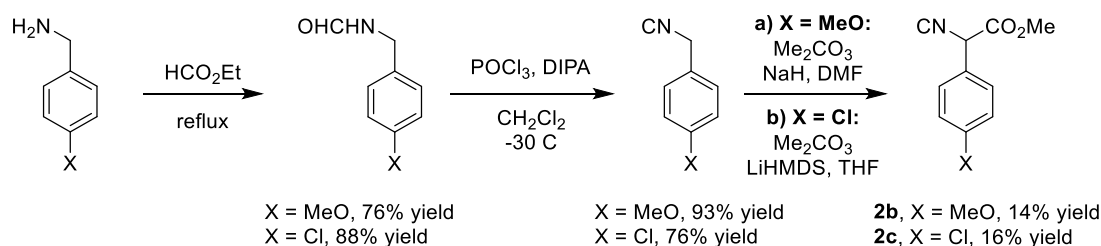
Different α -substituted isocyanoacetates were used for this reaction. Mainly methyl α -phenylisocyanoacetate (**2a**) was employed, but isocyanides with different aryl and alkyl substitutions at the α carbon as well as at the ester moiety were also studied. The synthetic procedure, although similar, varied depending on the specific substituents.

The synthesis of methyl 2-phenylisocyanoacetate (**2a**) started from a racemic mixture of the commercially available 2-phenylglycine methyl ester hydrochloride salt. First, the corresponding formamide was synthesized with ammonium formate. Next, the formamide was dehydrated with phosphoryl chloride to yield the desired isocyanide (**Scheme 105**).



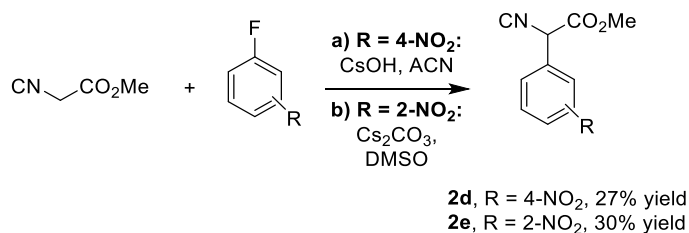
Scheme 105: Two-step protocol for the synthesis of methyl 2-phenylisocyanoacetate.

For accessing methyl 2-(4-methoxyphenyl)isocyanoacetate (**2b**) and methyl 2-(4-chlorophenyl)isocyanoacetate (**2c**), a three step procedure that started with the corresponding substituted benzylamine was followed. The first two steps consisted in the formation of the formamide, in this case with ethyl formate, followed by the synthesis of the isocyanide by dehydration with phosphoryl chloride. Finally, deprotonation of the benzylic position with sodium hydride (for **2b**) or with lithium bis(trimethylsilyl)amide (for **2c**) followed by addition of methyl carbonate gave the expected isocyano esters **2b** and **2c**, respectively (**Scheme 106**).



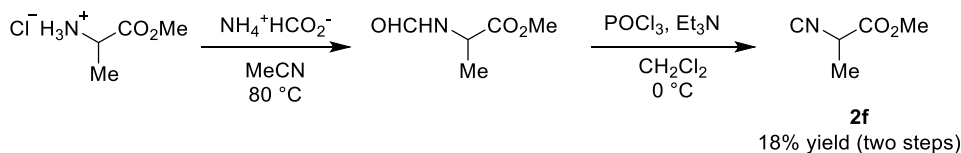
Scheme 106: Synthetic pathway towards methyl 2-(4-methoxyphenyl)isocyanoacetate (**2b**) and methyl 2-(4-chlorophenyl)isocyanoacetate (**2c**).

In the case of methyl 2-(4-nitrophenyl)isocyanoacetate (**2d**) and methyl 2-(2-nitrophenyl)isocyanoacetate (**2e**), the synthesis proceeded through a nucleophilic aromatic substitution of 1-fluoro-4-nitrobenzene with the commercial methyl isocyanoacetate using, depending on the case, cesium hydroxide or cesium carbonate as a base (**Scheme 107**).



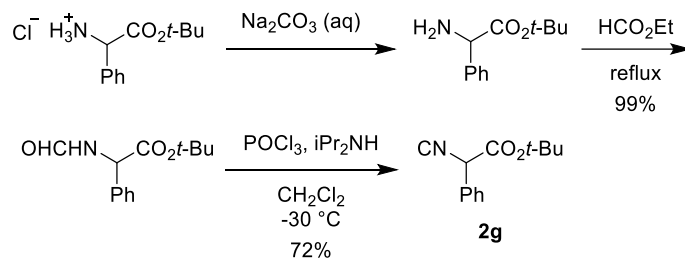
Scheme 107: Synthesis of methyl 2-(4-nitrophenyl)isocyanoacetate (**2d**) via a nucleophilic substitution of methyl isocyanoacetate with 1-fluoro-4-nitrobenzene.

For the α -methyl isocyanoacetate **2f**, the synthesis was very similar to that of **2a**. Starting with an equimolar mixture of the hydrochlorides of D- and L-alanine, formation of the formamide with ammonium formate, followed by the usual phosphoryl chloride-mediated dehydration, yielded the desired isocyanoacetate (**Scheme 108**).



Scheme 108: Synthesis of methyl 2-methylisocyanoacetate (**2f**).

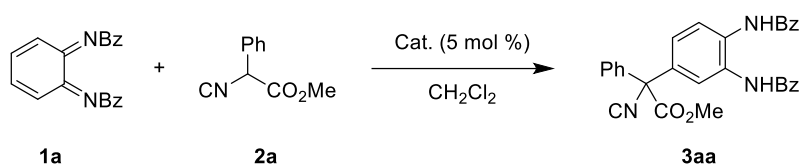
Lastly, regarding *tert*-butyl 2-(4-methoxyphenyl)isocyanoacetate (**2g**), it was synthesized starting from a racemic mixture of the commercially available *tert*-butyl 2-amino-2-phenylacetate hydrochloride. First, the free amine was obtained by the addition of a base. Secondly, the corresponding formamide was formed by refluxing the amine in ethyl formate. Finally, the isocyanide was synthesized by dehydration with phosphoryl chloride (**Scheme 109**).



Scheme 109: Synthesis of *tert*-butyl 2-phenylisocyanoacetate (**2g**).

4.1.5 Selection of the reaction conditions

Firstly, we started trying the reaction between the *o*-quinone dibenzimide **1a** and the α -phenyl substituted isocyanoacetate **2a**, in dichloromethane, at room temperature. Product **3aa** was obtained in 70% yield after 24 hours with total regioselectivity (**Table 1**, entry 1). Encouraged by this result, and considering that Ag^+ coordinates the isonitrile group thus enhancing the acidity of the α -H,¹³ as well as the possibility of electrophilic activation of the bis-imine by monovalent metals as described by Evans and Lectka,^{114,115} 5 mol % of Ag_2O were added to the reaction mixture. In these conditions, we could obtain the corresponding addition product **3aa** with an excellent yield (99%) after 1 hour (entry 2).

Table 1: Results for the addition reaction of **2a** to **1a** with different metallic catalysts and with no catalyst.^a

Entry	Catalyst	Reaction time (h)	Yield (%) ^b
1	-	24	70
2	Ag ₂ O	1	99
3	Cu ₂ O	1.5	47

^a **1a** (57.8 mg, 0.33 mmol), **2a** (36 μ L, 0.25 mmol), catalyst (0.0125 mmol), CH₂Cl₂ (3 mL). ^b Yield of the isolated product.

In this way, it was observed that the incrementation of the basicity of the isocyanide by Ag(I) was crucial for good yields of the addition product as well as for shorter reaction times. Cu₂O also catalyzed the reaction but led to a lower yield (entry 3).

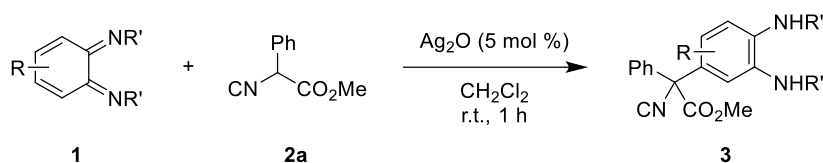
4.1.6 Scope of the reaction

After having established the optimized conditions for the addition reaction as those outlined in **Table 1**, entry 1, we started studying the scope of the reaction, testing differently substituted *o*-quinone diimides as well as varied isocyanoacetates.

First, we tested the addition of different *o*-quinone diimides **1** with the isocyanoacetate **2a**, with the results displayed in **Table 2**. In general, the reaction tolerated the presence of substituents with different electronic character in all positions of the *o*-quinone diimide ring, providing products **3** with good to excellent yields in almost all cases. It needs to be noted that the presence of electron-withdrawing groups in the 3 position like 3-F (entry 3) caused a lowering of the reaction yield (67%). The same effect was observed with 4-Br (entry 6), with 63% yield, presumably because of steric hindrance over the addition position.

On the other side, disubstitution of the *o*-quinone diimide ring with either electron-donating groups such as 3,4-Me₂ (entry 7) or electron-withdrawing groups such as 3,4-F (entry 8) were acceptable substrates, obtaining good yields (71-75%). Moreover, the procedure was also compatible with the substitution of the benzamido moiety. Chlorobenzamides (entries 9 to 11) as well as 1-naphthylbenzamides (entry 12) provided the corresponding products **3** in good yields. In contrast, *o*-quinone dibenzenesulfonamide (**1n**) did not provide observable reaction with isocyanide **2a** (entry 13).

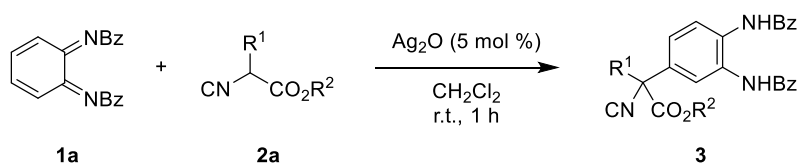
Furthermore, the reaction at a higher scale, using 2.5 mmol of **1a**, also proceeded smoothly with the same reaction time, furnishing product **3aa** in 90% yield (entry 14).

Table 2: Addition of methyl 2-phenyl isocyanoacetate (**2a**) to *o*-quinone diimides **1**. Scope regarding the *o*-quinone diimides.^a

Entry	1	R	R'	3	Yield (%) ^b
1	1a	H	PhCO	3aa	99
2	1b	3-Me	PhCO	3ba	94
3	1c	3-F	PhCO	3ca	67
4	1d	3-Cl	PhCO	3da	99
5	1e	4-Cl	PhCO	3ea	81
6	1f	4-Br	PhCO	3fa	63
7	1g	3,4-Me ₂	PhCO	3ga	75
8	1h	3,4-F ₂	PhCO	3ha	71
9	1i	H	4-ClC ₆ H ₄ CO	3ia	75
10	1j	3-Me	4-ClC ₆ H ₄ CO	3ja	82
11	1k	4-Me	4-ClC ₆ H ₄ CO	3ka	85
12	1l	H	1-naphthylCO	3la	86
13	1n	H	Ts	3na	n.r.
14 ^c	1a	H	PhCO	3aa	90

^a **1** (0.33 mmol), **2a** (36 μ L, 0.25 mmol), Ag₂O (3 mg, 0.0125 mmol), CH₂Cl₂ (3 mL). ^b Yield of the isolated product. ^c Reaction performed with 2.5 mmol of **1a**.

Afterwards, to further expand the study of the reaction scope, isocyanoacetates bearing different substitutions at the α position or at the ester moiety were tested, with the results summarized in **Table 3**.

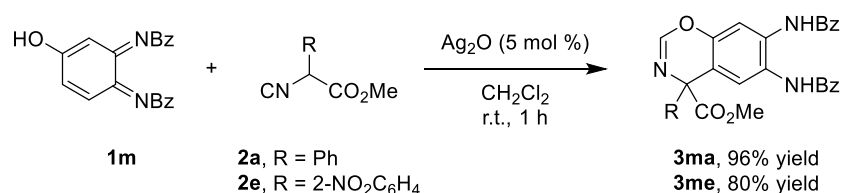
Table 3: Addition of isocyanoacetates **2** to *o*-quinone dibenzimide **1a**. Scope regarding the isocyanides.^a

Entry	2	R ¹	R ²	3	Yield (%) ^b
1	2a	Ph	Me	3aa	99
2	2b	4-MeOC ₆ H ₄	Me	3ab	96
3	2c	4-ClC ₆ H ₄	Me	3ac	74
4	2d	4-NO ₂ C ₆ H ₄	Me	3ad	74
5	2e	2-NO ₂ C ₆ H ₄	Me	3ae	88
6	2f	Me	Me	3af	76
7	2g	Ph	<i>t</i> -Bu	3ag	73

^a **1a** (57.8 mg, 0.33 mmol), **2** (0.25 mmol), Ag₂O (3 mg, 0.0125 mmol), CH₂Cl₂ (3 mL). ^b Yield of the isolated product.

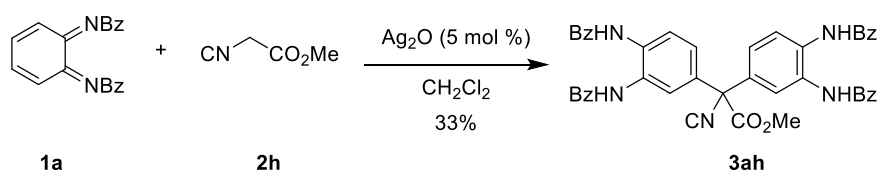
As we can see, the presence of a 4-methoxyphenyl group provided an excellent yield (entry 2). However, when the *para* position was substituted with electron-withdrawing groups such as chloro or nitro, the yield decreased to 74% (entries 3 and 4). The decrease in the yield was less pronounced when the electron-withdrawing group is in the *ortho* position of the phenyl ring, as we can see in the case of compound **2e**, with an 88% yield (entry 5). Besides, α -methyl isocyanide **2f** also successfully provided the corresponding product in 76% yield (entry 6). Finally, when the *tert*-butyl ester **2g** was used, the product **3ag** was obtained in lower yield (entry 7), possibly because of the steric hindrance imposed by the bulky *tert*-butyl group.

Remarkably, when the 4-hydroxy *o*-dibenzimide **1m** was employed, benzoxazines **3m** were obtained due to intramolecular cyclization of the hydroxy group with the terminal carbon of the isonitrile (**Scheme 110**). Reaction with isocyanide **2a** as well as with **2e**, with a *o*-NO₂ substitution, furnished **3ma** and **3me** with very good yields.



Scheme 110: Synthesis of 4*H*-benzo[*e*][1,3]oxazines with the use of the 4-hydroxy-substituted *o*-quinone dibenzimide **1m**. Reaction conditions: **1m** (73.0 mg, 0.33 mmol), **2** (0.25 mmol), Ag₂O (3 mg, 0.0125 mmol), CH₂Cl₂ (3 mL). Yields refer to the isolated product.

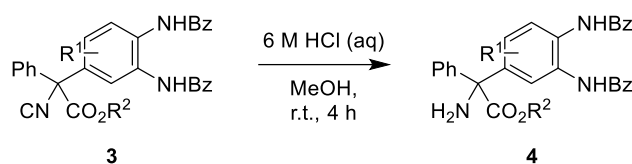
On the other hand, when the α -unsubstituted methyl isocyanoacetate (**2h**) was used, we observed the formation of the double 1,4-addition product **3ah**, in 33% yield (**Scheme 111**).



Scheme 111: Double addition observed when reacting methyl isocyanoacetate (**2h**) with **1a**.

4.1.7 Synthetic transformation of products **3**

The synthetic utility of the obtained addition products **3** was showcased by the hydrolysis of the isocyanide moiety to give rise to α,α -diaryl- α -amino esters **4**. The reaction proceeded smoothly, providing products having different substitutions either at the aromatic ring of the dibenzamide or at the ester moieties (**Table 4**).

Table 4: Hydrolysis of the 1,6-addition products to yield amino esters.^a

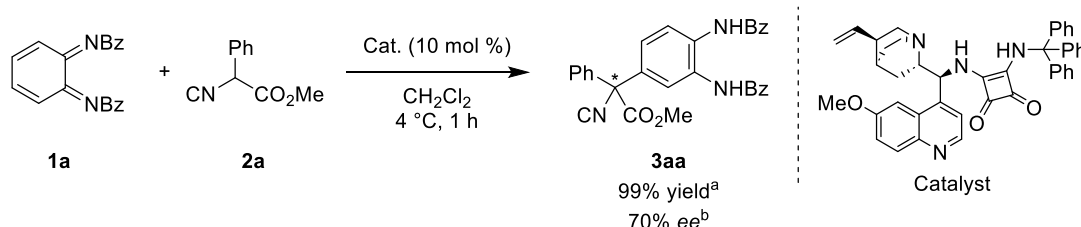
Entry	3	R ¹	R ²	4	Yield (%) ^b
1	3aa	H	Me	4aa	99
2	3ba	3-Me	Me	4ba	99
3	3ea	4-Cl	Me	4ea	99
4	3ag	H	<i>t</i> -Bu	4ag	86

^a **3** (0.2 mmol), 6 M aq. HCl (6 drops), MeOH (2 mL). ^b Yield of the isolated product.

Reactions with methyl esters proceeded in quantitative yield (entries 1 to 3), while the *tert*-butyl ester **3ag** provided the amino ester **4ag** in 86% yield (entry 4).

4.1.8 Preliminary results for the asymmetric variant of the arylation reaction

Considering the potential synthetic utility of this procedure, a preliminary study of an asymmetric version of this addition reaction was carried out. As a result, we found out that the organocatalytic conditions outlined in **Scheme 112**, using a squaramide derived from quinine with a bulky achiral moiety, allowed to obtain product **3aa** in quantitative yield and 70% *ee*.



Scheme 112: Organocatalytic conditions for the asymmetric addition of isocyanoacetates to *o*-quinone dibenzimides. Preliminary results. Reaction conditions: **1a** (57.8 mg, 0.33 mmol), **2a** (36 μ L, 0.25 mmol), catalyst (16.6 mg, 0.025 mmol), CH₂Cl₂ (12.5 mL). ^a Yield of isolated product. ^b Determined by chiral HPLC.

4.1.9 Summary

In this section, we have described a new methodology for the α -arylation of isocyanides to give rise to α,α -disubstituted isocyanoacetates, which are precursors of α,α -disubstituted α -amino acids. Additionally, when using the 4-hydroxy *o*-dibenzimide **1m**, 4*H*-benzo[*e*][1,3]oxazines were also accessible through the developed procedure. On the other hand, α -unsubstituted isocyanide **2h** gave rise to the double addition product **3ah**. Furthermore, the reactivity of *o*-quinone dibenzimides as substrates for conjugate addition reactions, an underdeveloped field compared with their reactivity as 1,4-heterodienes, has been further explored. Good to excellent yields were obtained in almost all cases, with wide applicability even when

substitutions on the *o*-quinone benzamide or on the isocyanoacetate varied. In addition, preliminary results for the enantioselective version of the reaction yielded the addition adduct **3aa** with 70% *ee*. This promising result brings forth the possibility of further development of the asymmetric version of this arylation reaction in future work.

4.2 Organocatalytic conjugate addition of isocyanoacetate esters to aurone-derived 1-azadienes

4.2.1 Benzofuran derivatives as pharmaceuticals

Benzofurans are a family of oxygen-containing heterocycles that are widely found in products of pharmaceutical interest (**Figure 5**).¹¹⁶ Some examples include a particularly active compound in a family of A_{2A} receptor antagonists, which are useful in the treatment of locomotive diseases, depression, cognitive dysfunction, among others;¹¹⁷ XL413, a CDC7 kinase inhibitor which has been studied for the treatment of Ewing sarcoma;¹¹⁸ bufuralol, a nonselective β -adrenoceptor blocking agent;¹¹⁹ and amiodarone, a highly effective antiarrhythmic agent.¹²⁰

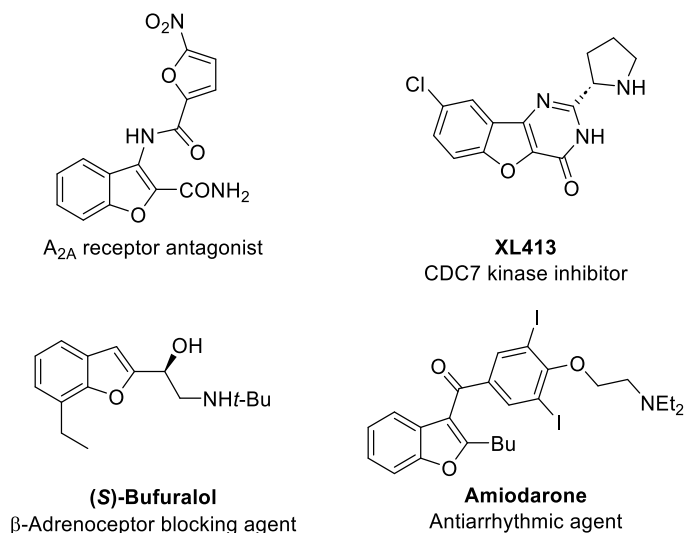
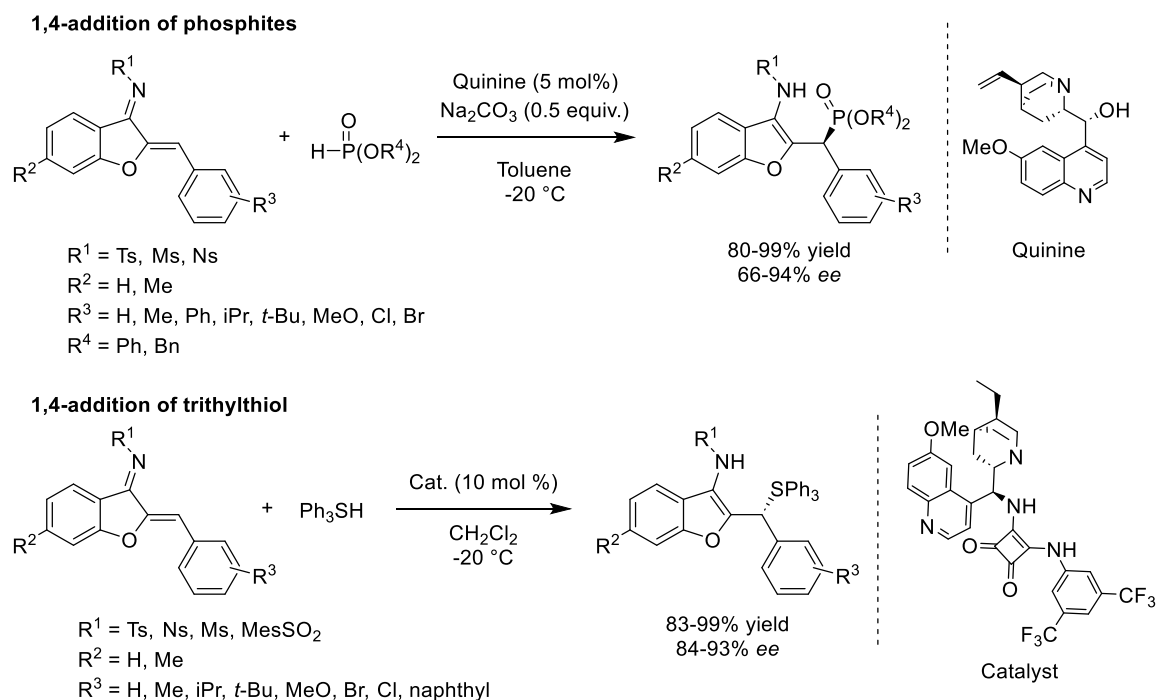


Figure 5: Example of products of pharmaceutical interest containing the benzofuran moiety.

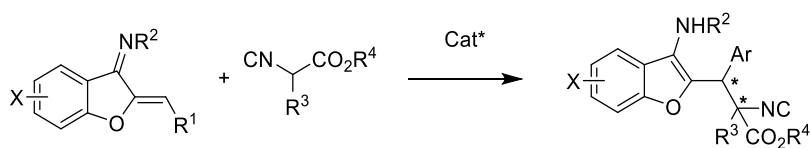
One of the approaches for obtaining benzofuran derivatives consists on the use of benzofuran-derived 1-azadienes. Within this realm, the asymmetric 1,4-addition to imines derived from aurone has been a topic that has received increased interest. Pioneering work in this field include the asymmetric Michael additions developed by the group of Jiang and Zhou, consisting in the asymmetric addition of phosphites¹²¹ and tritylthiols¹²² (**Scheme 113**).



Scheme 113: Initial developments in the field of organocatalyzed Michael additions to benzofuran-derived 1-azadienes by the group of Jiang and Zhou.

Since then, diverse nucleophiles like deconjugated butenolides,¹²³ rhodanines,¹²⁴ indoles,^{125–129} naphthols,^{126,130} pyrazol-5-ones,¹³¹ thiazol-4-ones,¹³² and coumarins¹³³ have been used for the enantioselective synthesis of benzofuran derivatives in this fashion.

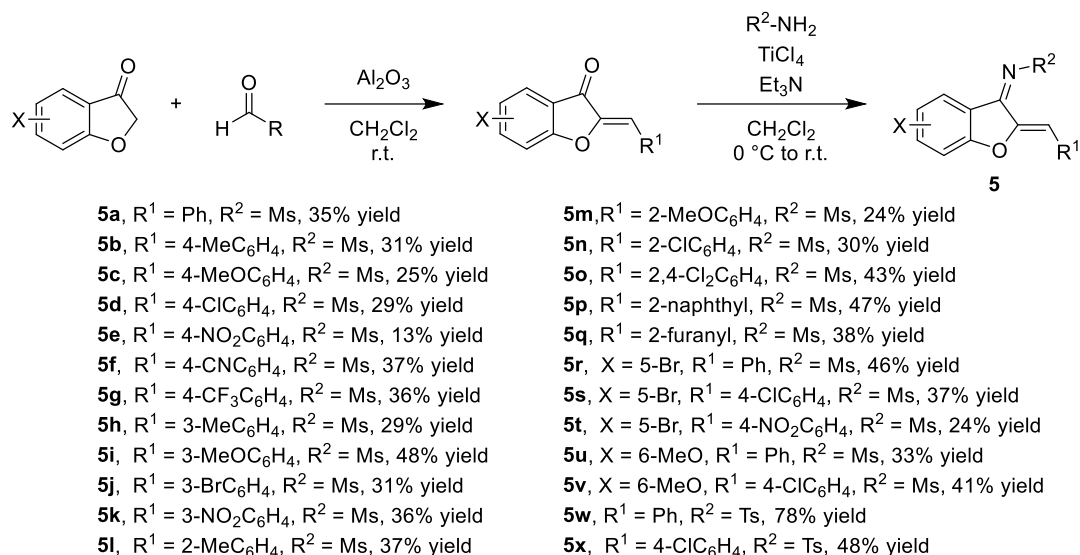
The goal of this section consists on the study of the 1,4-addition reaction of isocyanoacetates to imines derived from aurone, in order to give rise to chiral α,α -difunctionalized isocyanides containing a benzofuran ring moiety (**Scheme 114**).



Scheme 114: Catalytic 1,4-addition of isocyanoacetates to benzofuran derived 1-azadienes.

4.2.2 Synthesis of aurone-derived 1-azadienes **5**

All the aurone-derived 1-azadienes were synthesized in the laboratory. The synthesis was carried out in two steps, involving a Knoevenagel condensation of a benzofuran-3(2*H*)-one derivative with the corresponding aldehyde, followed by condensation of the resulting aurone with the appropriate sulfonylamide (**Scheme 115**).



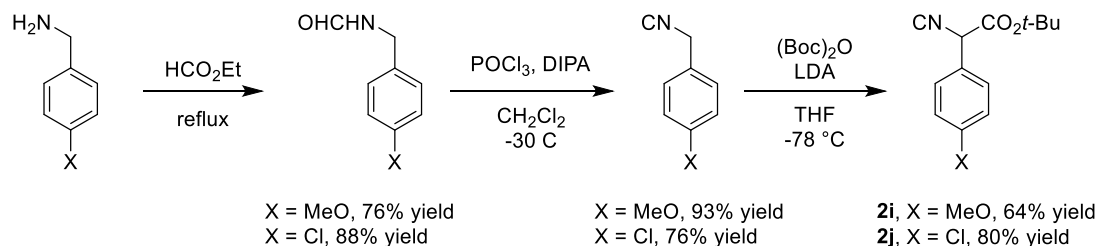
Scheme 115: Two-step synthetic protocol to access benzofuran-derived 1-azadienes. Yields refer only to the second step. Unless otherwise stated, X = H.

The Knoevenagel condensation was catalyzed by basic alumina, previously activated in an oven at 135 °C for about 2 h. Meanwhile, the condensation step was catalyzed by a hard Lewis acid, in this case titanium tetrachloride, in order to prevent the 1,4-addition of the amine.

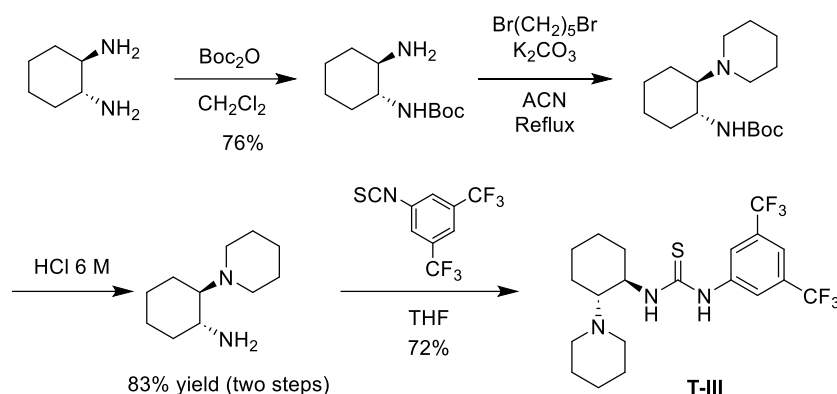
4.2.3 Synthesis of *tert*-butyl isocyanoacetates **2i** and **2j**

Isocyanoacetates were prepared in the laboratory using different procedures depending on each case. Mainly, *tert*-butyl 2-phenylisocyanoacetate (**2g**) was used, but other *tert*-butyl isocyanoacetates were used such as *tert*-butyl 2-(4-methoxyphenyl)isocyanoacetate (**2i**), *tert*-butyl 2-(4-chlorophenyl)isocyanoacetate (**2j**), as well as the methyl ester of 2-phenylisocyanoacetate (**2a**).

For *tert*-butyl 2-(4-methoxyphenyl)isocyanoacetate (**2i**) and *tert*-butyl 2-(4-chlorophenyl)isocyanoacetate (**2j**), the synthesis started from the commercial benzylamines. After synthesizing the corresponding isocyanide through the formation of the formamide and subsequent dehydration, the *tert*-butyl oxycarbonyl group was added at the α-position by deprotonation with LDA and nucleophilic substitution with di-*tert*-butyl dicarbonate (**Scheme 116**).



Scheme 116: Synthesis of *p*-substituted *tert*-butyl phenylisocyanoacetates.

4.2.4 Synthesis of catalyst **T-III**

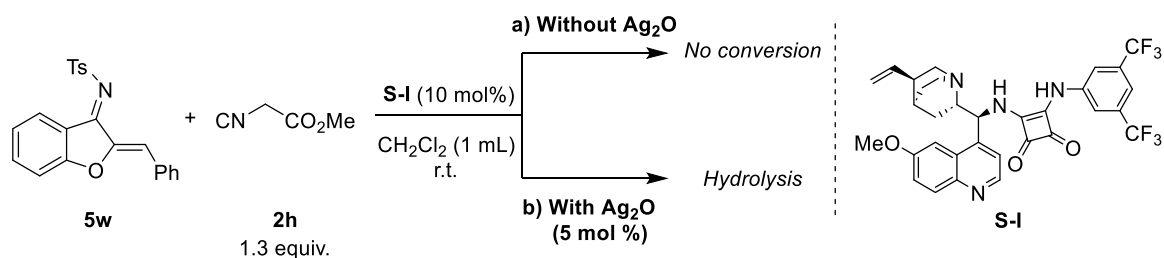
Scheme 117: Synthesis of cyclohexane-1,2-diamine-based thiourea organocatalyst **T-III**.

For the synthesis of the main catalyst used in this section, we started from (1*R*,2*R*)-cyclohexane-1,2-diamine. First, one of the amine groups was protected as a *tert*-butoxycarbonyl amide, in order to dialkylate the other with 1,5-dibromopentane. Afterwards, deprotection of the *N*-Boc protected amine, followed by nucleophilic addition to 3,5-bis(trifluoromethyl)phenyl isothiocyanate allowed to obtain **T-III** in 45% overall yield (**Scheme 117**).

4.2.5 Optimization of the reaction conditions

4.2.5.1 Assessment of the isocyanoacetate ester

In the first place, the reaction of *N*-tosyl imine **5w** with the commercially available α -unsubstituted methyl isocyanoacetate **2h** was tried, using the bifunctional organocatalyst **S-I**, derived from quinine. However, under these conditions, no addition product was observed (**Scheme 118**, a). When adding a catalytic amount of silver oxide (5 mol%), aimed to activating the isocyanoacetate pronucleophile, the hydrolysis of the *N*-tosylimine moiety was instead observed (**Scheme 118**, b).

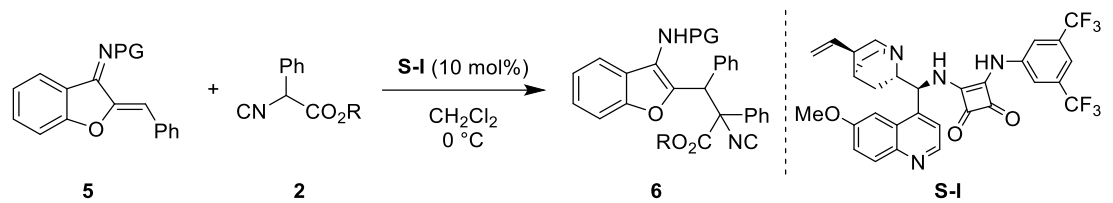


Scheme 118: Initial reaction studies with the 1-azadiene **1w** and methyl isocyanoacetate (**2h**).

Considering these results, taking into account the impossibility of adding silver salts in the reaction mixture, we considered the use of the more acidic methyl α -phenylisocyanoacetate

(**2a**). In this case, the 1,4-addition product was obtained with high yield, although with low diastereo- and enantioselectivity (**Table 5**, entry 1).

Table 5: Preliminary results for the addition of α -phenyl isocyanoacetates to 1-azadienes derived from aurone.^a



Entry	5	2	PG	R	T (°C)	Yield (%) ^b	dr ^c	ee _{major/minor} (%) ^d
1	5w	2a	Ts	Me	r.t.	99	65:35	27/60
2	5w	2a	Ts	Me	0	99	64:36	55/68
3	5w	2g	Ts	<i>t</i> -Bu	0	63	93:7	34/n.d.
4	5a	2g	Ms	<i>t</i> -Bu	0	42	90:10	47/n.d.
5	5a	2g	Ms	<i>t</i> -Bu	r.t.	65	87:13	51/n.d.

^a **5** (0.10 mmol), **2** (0.13 mmol), **S-I** (6.3 mg, 0.01 mmol), CH₂Cl₂ (1 mL). ^b Yield of the isolated product.

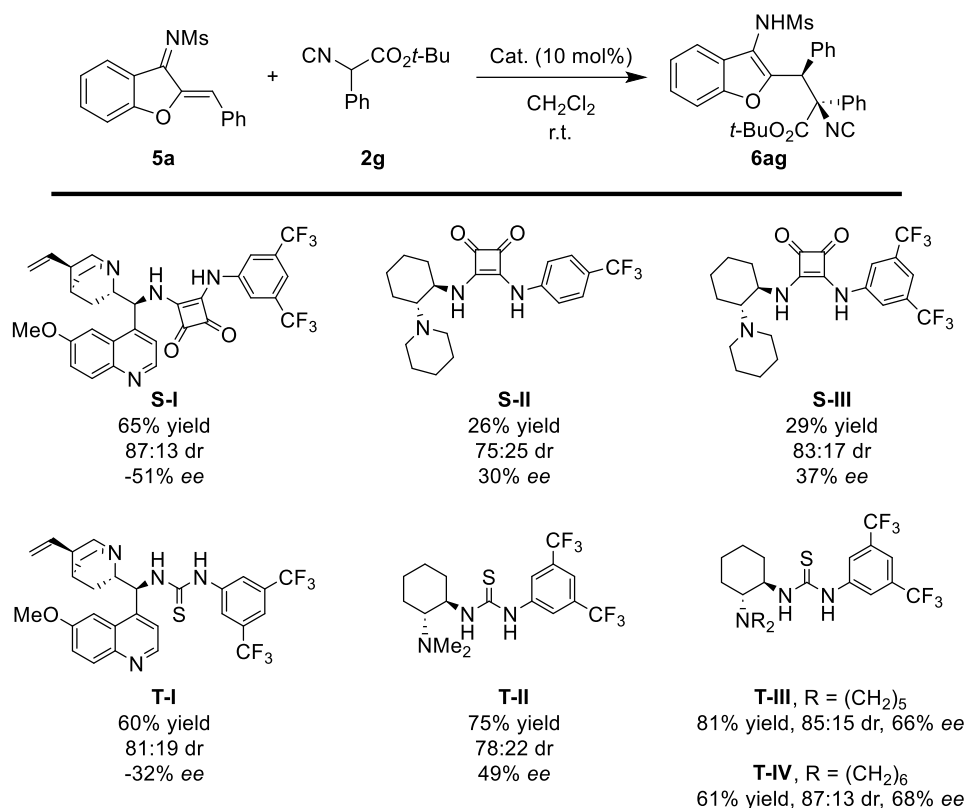
^c Determined by ¹H NMR. ^d Determined by chiral HPLC.

Owing to the low diastereo- and enantioselectivity provided by the initial conditions, we tried lowering the reaction temperature to 0 °C in an attempt to improve the results. Although the enantioselectivity increased, the diastereoselectivity remained low (entry 2). With the aim of improving the diastereoselectivity of the reaction, we considered the use of the bulkier *tert*-butyl ester of α -phenylisocyanoacetate (**2g**). The use of this isocyanide drastically improved the diastereoselectivity of the reaction, although with a reduction of the yield, as well as with an erosion of the enantiomeric excess (entry 3).

When the *N*-mesylamide **5a** was tested, an increase on the enantiomeric excess was observed, while the diastereoselectivity of the reaction was maintained (entry 4). Since the yield was, however, lower, before proceeding with the study of the effect of the structure of the catalyst, we tested the reaction with *tert*-butyl isocyanoacetate **2g** and *N*-mesylamide **5a** at room temperature. As we can see in entry 5, the yield of the product increased without significantly eroding the diastereoselectivity. Meanwhile, the enantioselectivity also increased slightly.

4.2.5.2 Effect of the organocatalyst

After having selected 1-azadiene **5a** and isocyanoacetate **2g** as model substrates for our reaction, we started studying the influence of the structure of the chiral organocatalyst on the results (**Scheme 119**).

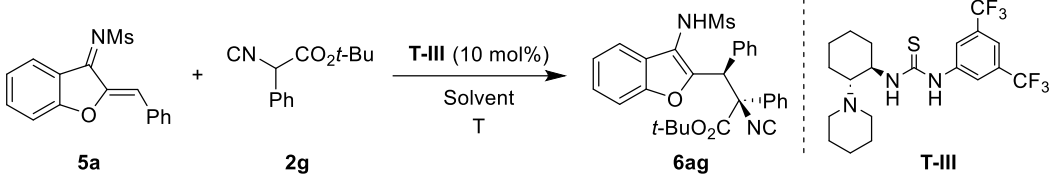


Scheme 119: Effect of the structure of the organocatalyst on the results of the reaction. Reaction conditions: **5a** (29.9 mg, 0.10 mmol), **2g** (27 μL , 0.13 mmol), organocatalyst (0.01 mmol), CH_2Cl_2 (1 mL). Diastereomeric ratios determined by ^1H NMR. Enantiomeric excess values determined by chiral HPLC.

In the first place, organocatalysts **S-I** and **T-I** derived from the *Cinchona* alkaloid quinine were studied. In this case, it was observed that squaramide **S-I** offered better results than **T-I** for product **6ag** with respect to all variables: yield, diastereomeric ratio and enantiomeric excess. Surprisingly, thioureas based on the cyclohexane-1,2-diamine scaffold performed better than the related squaramides. In this case, Takemoto's thiourea¹³⁴ **T-II** provided notably better yield and enantioselectivity than Rawal's squaramide¹³⁵ **S-II** as well as its 3,5- $(\text{CF}_3)_2$ analog **S-III**. According to these results, we considered trying organocatalysts **T-III** and **T-IV**, having a cyclic tertiary amine. This way, we selected the cyclohexane-1,2-diamine-derived thiourea **T-III** as the organocatalyst of choice, which provided the overall best results in terms of yield, diastereoselectivity and enantioselectivity for product **6ag**. Its analogue with the seven-membered ring **T-IV** was discarded because of the 20% decreased product yield, despite it produced a very slight increase in the diastereo- and enantioselectivity of the reaction.

4.2.5.3 Influence of the temperature and the solvent

Using organocatalyst **T-III**, we decided to study the effects of the temperature and the solvent in the reaction.

Table 6: Optimization of the temperature and the solvent of the reaction.^a


Entry	Temp. (°C)	Solvent	Yield (%) ^b	dr ^c	ee (%) ^d
1	r.t.	CH ₂ Cl ₂	81	85:15	66
2	-20	CH ₂ Cl ₂	68	94:6	83
3	-20	CHCl ₃	56	97:3	85
4	-20	ClCH ₂ CH ₂ Cl	54	92:8	81
5	-20	THF	51	83:17	71
6	-20	MeCN	81	69:31	18
7	-20	EtOAc	3	79:21	45
8	-20	Toluene	34	94:6	66

^a **5a** (29.9 mg, 0.10 mmol), **2g** (27 μ L, 0.13 mmol), **T-III** (4.5 mg, 0.01 mmol), solvent (1 mL). ^b Yield of the isolated product. ^c Determined by ¹H NMR. ^d Determined by chiral HPLC.

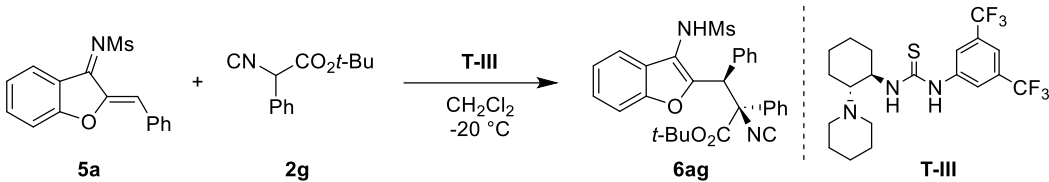
As we can see when comparing the results at different temperatures (**Table 6**, entries 1 and 2), lowering the temperature from room temperature to -20 °C provided an increase in the diastereomeric ratio and in the enantiomeric excess of product **6ag**, albeit with a slight erosion in the yield. Seeing these results, we performed the screening of solvents at this reduced temperature (entries 3 to 8).

As we observed, chlorinated solvents (entries 2, 3 and 4) provided very similar results regarding the diastereo- and enantioselectivity. However, the initially used dichloromethane (entry 2) provided a higher yield for product **6ag**. None of the other ether, polar or aromatic solvents (entries 5 to 8) were able to improve the overall results obtained with dichloromethane. Although acetonitrile (entry 6) allowed for an increase of the yield of the reaction, the enantioselectivity decreased sharply. The use of ethyl acetate and toluene (entries 7 and 8) resulted in very low yield for product **6ag**, probably due to the low solubility of 1-azadiene **5a** in these solvents.

According to these results, we decided to further proceed with the optimization process using dichloromethane, at -20 °C.

4.2.5.4 Effect of the catalytic loading and concentration

Taking the conditions outlined in **Table 6**, entry 2, we decided to study whether the reaction results could be improved by the variation of two other parameters: the catalytic loading and the concentration of the reactants. The combined results are summarized in **Table 7**.

Table 7: Effect of the catalytic loading and concentration.^a


Entry	T-III (mol %)	Conc. of 5a (M)	Yield (%) ^b	dr ^c	ee (%) ^d
1	10	0.10	68	94:6	83
2	15	0.10	86	94:6	82
3	5	0.10	50	95:5	82
4	10	0.20	85	94:6	83
5	10	0.07	44	94:6	82
6 ^e	10	0.20	81	94:6	86

^a **5a** (29.9 mg, 0.10 mmol), **2g** (27 μ L, 0.13 mmol), **T-III**, CH₂Cl₂. ^b Yield of the isolated product. ^c Determined by ¹H NMR. ^d Determined by chiral HPLC. ^e Reaction was carried out at -30 °C.

Regarding the results obtained when the amount of catalyst **T-III** was varied (entries 1 to 3), we can see that catalytic loading did not have appreciable effects on the diastereo- and enantioselectivity of the reaction. However, there was a correlation between the amount of catalyst and the yield of product **6ag**, with the yield increasing when the amount of **T-III** was increased to 15 mol % (entry 2) and decreasing when the catalytic loading was set to 5 mol % (entry 3).

On the other hand, the variation of the concentration of the reaction had a similar effect, showing no significant influence on the diastereomeric ratio or the enantiomeric excess of product **6ag**, but with major variations in the yield. When the concentration of the reaction was doubled from the initial value (entry 4), the yield of the reaction notably increased, without showing negative effects on the asymmetric induction. When the reaction was diluted (entry 5), a significant erosion of the yield was observed.

With the double aim of optimizing the performance of the reaction while reducing, to the extent that was possible, the amount of chiral catalyst and volume of solvent used in the process, we selected the conditions outlined at **Table 7**, entry 4, with a catalytic loading of 10 mol % and a concentration of 0.20 M for **5a**, which also provided a good yield, diastereomeric ratio and enantiomeric excess for the product **6ag**.

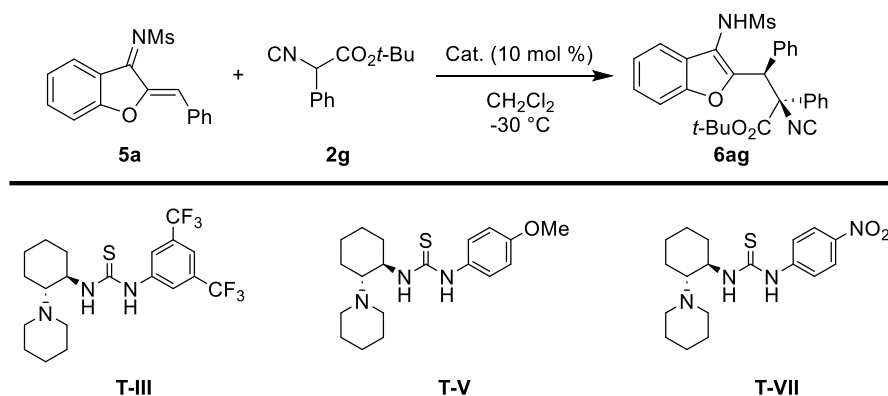
With these conditions in hand, we tried further lowering the temperature at which the reaction was carried out, from -20 °C to -30 °C (**Table 7**, entry 6). This variation resulted in an increase of the enantiomeric excess with only a slight reduction of the yield, without affecting

the diastereoselectivity of the reaction. Thus, we decided to proceed with the optimization of the reaction conditions at this reaction temperature.

4.2.5.5 Effect of the substituents at the aromatic ring of the organocatalyst

To finish the optimization procedure, considering the best conditions for the reaction found at this time (**Table 7**, entry 6), we proceeded to analyze the effect of the variation of the electronic character of the aromatic ring attached to the thiourea.

Table 8: Optimization of the substituents in the aromatic ring of the organocatalyst.^a



Entry	Catalyst	Yield (%) ^b	dr ^c	ee (%) ^d
1	T-III	81	94:6	86
2	T-V	25	87:13	72
3	T-VI	42	88:12	79

^a **5a** (29.9 mg, 0.10 mmol), **2g** (27 μ L, 0.13 mmol), organocatalyst (0.01 mmol), CH₂Cl₂ (0.5 mL). ^b Yield of the isolated product. ^c Determined by ¹H NMR. ^d Determined by chiral HPLC.

As in can be seen in **Table 8**, neither placing strongly electron-donating groups such as methoxy at the 4 position of the aromatic ring (entry 2) nor electron-withdrawing groups such as nitro at the same position (entry 3) resulted in any improvement, with both thioureas **T-V** and **T-VI** giving rise to an overall decrease in the yield, diastereomeric ratio and enantiomeric excess for product **6ag**.

4.2.6 Scope of the reaction

Under the best conditions available, we examined the scope of the procedure with varied 1-azadienes and differently substituted isocyanoacetates.

Table 9: Addition reaction of α -substituted isocyanoacetates **2** to 1-azadienes **5**. Scope of 1-azadienes.^a

Entry	5	R ¹	R ²	X	6	Yield (%) ^b	dr ^c	ee (%) ^d
1	5a	Ph	Ms	H	6ag	86	95:5	84
2	5b	4-MeC ₆ H ₄	Ms	H	6bg	83	95:5	83
3	5c	4-MeOC ₆ H ₄	Ms	H	6cg	trace	75:25	n.d.
4	5d	4-ClC ₆ H ₄	Ms	H	6dg	99	95:5	86
5	5e	4-NO ₂ C ₆ H ₄	Ms	H	6eg	99	95:5	88
6	5f	4-CNC ₆ H ₄	Ms	H	6fg	92	95:5	88
7	5g	4-CF ₃ C ₆ H ₄	Ms	H	6gg	86	95:5	89
8	5h	3-MeC ₆ H ₄	Ms	H	6hg	89	95:5	82
9	5i	3-MeOC ₆ H ₄	Ms	H	6ig	84	95:5	85
10	5j	3-BrC ₆ H ₄	Ms	H	6jg	89	95:5	89
11	5k	3-NO ₂ C ₆ H ₄	Ms	H	6kg	99	95:5	88
12	5l	2-MeC ₆ H ₄	Ms	H	6lg	33	95:5	71
13	5m	2-MeOC ₆ H ₄	Ms	H	6mg	n.r.	-	-
14	5n	2-ClC ₆ H ₄	Ms	H	6ng	36	95:5	81
15	5o	2,4-Cl ₂ C ₆ H ₄	Ms	H	6og	85	95:5	80
16	5p	2-Naphthyl	Ms	H	6pg	45	95:5	67
17	5q	2-Furanyl	Ms	H	6qg	76	95:5	73
18	5r	Ph	Ms	5-Br	6rg	84	95:5	82
19	5s	4-ClC ₆ H ₄	Ms	5-Br	6sg	81	95:5	88
20	5t	4-NO ₂ C ₆ H ₄	Ms	5-Br	6tg	61	95:5	85
21	5u	Ph	Ms	6-MeO	6ug	n.r.	-	-
22	5v	4-ClC ₆ H ₄	Ms	6-MeO	6vg	n.r.	-	-
23	5w	Ph	Ts	H	6wg	84	77:23	65
24	5x	4-ClC ₆ H ₄	Ts	H	6xg	99	79:21	69
25 ^e	5a	Ph	Ms	H	6ag	77	95:5	89

^a **5** (0.20 mmol), **2g** (54 μ L, 0.26 mmol), **T-III** (9.1 mg, 0.02 mmol), CH₂Cl₂ (1.0 mL). ^b Yield of the isolated product. ^c Determined by ¹H NMR. ^d Determined by chiral HPLC. ^e Reaction carried out with 1 mmol of **5a**.

Table 9 summarizes the results for the scope regarding 1-azadienes **5**. In general, we can see that the reaction conditions could be applied for the addition of *tert*-butyl 2-phenylisocyanoacetates to a wide variety of 1-azadienes **5**, bearing substituents of different electronic character in various positions of the aromatic ring at the exocyclic double bond as well as at the benzofuran ring. Benzofurans **6** were obtained, with a few exceptions, with good to excellent yields (33-99%), excellent diastereoselectivity (95:5 in most cases) and good enantioselectivity (65-89% *ee*).

Regarding substitution at the *para* position of the R¹ aromatic ring (entries 2 to 7), it can be seen that electron-withdrawing groups (entries 4 to 6) provided higher yields and enantioselectivities than electron-donating groups (entries 2 and 3). In particular, when the highly electron-donating methoxy group was present on the *para* position, only trace amounts of product **6cg** were obtained (entry 3).

Substitution at the *meta* position of the aromatic ring at the exocyclic double bond (entries 8 to 11) follows a similar trend, with electron-withdrawing groups (entries 10 and 11) providing better combined results than electron-donating groups (entries 8 and 9). However, in this position, the presence of the methoxy group was tolerated, with good yield and enantioselectivity for product **6ig**, as well as excellent diastereoselectivity (entry 9).

Substitution at the *ortho* position of the aromatic ring at the exocyclic double bond was not well tolerated, and yields were very low, with lower than average enantioselectivities (entries 12 and 14). In this case, substitution with methoxy at the *ortho* position also precluded the consecution of the addition reaction (entry 13). Interestingly, the use of the 2,4-dichloro-substituted 1-azadiene **5o** as the substrate (entry 15) allowed the obtention of a good yield for product **6og**, as well as good enantiomeric excess, albeit lower than the *para*-monosubstituted counterpart (entry 4).

Substitution of the exocyclic double bond of the 1-azadiene **5** with bulkier aromatic groups such as 2-naphthyl allowed the obtention of the corresponding product with excellent diastereoselectivity, although with reduced yield and enantioselectivity (entry 16). The presence of the heteroaromatic 2-furanyl (entry 17) provided higher yield and enantioselectivity, although still lower than those obtained with 1-azadiene **5a** (entry 1).

When approaching different substitutions at the benzofuran ring it can be seen that, while the presence of an electron-withdrawing group like bromo at position 5 (entries 18 to 20) furnished the corresponding products with excellent diastereoselectivities and good yields (82-85%), the substitution with strongly electron-donating groups like methoxy at position 6 completely prevented the addition reaction from happening (entries 21 and 22).

When *N*-tosylimines **5w** (entry 23) or **5x** were used (entry 24), the obtained yields were comparable to those obtained with the analogue *N*-mesylimines **5a** (entry 1) and **5d** (entry 4). However, in both cases, a decrease in both the diastereo- and enantioselectivity was observed, showing that our reaction conditions are more adequate for *N*-mesyl 1-azadienes.

Furthermore, we showed that the reaction could be carried out at 1 mmol scale of **5a**, providing product **6ag** with 77% yield, 95:5 dr and 89% *ee* (entry 25).

To continue looking into the scope and limitations of our reaction conditions, we reacted 1-azadiene **5a** with different isocyanoacetates bearing diverse substitutions at the aromatic ring as well as at the ester group. Results are displayed in **Table 10**.

Table 10: Addition reaction of α -substituted isocyanoacetates **2** to 1-azadienes **5**. Scope of isocyanoacetates.^a

Entry	2	R ³	R ⁴	6	Yield (%) ^b	dr ^c	<i>ee</i> (%) ^d
1	2g	Ph	<i>t</i> -Bu	6ag	86	95:5	84
2	2i	4-MeOC ₆ H ₄	<i>t</i> -Bu	6ai	64	95:5	87
3	2j	4-ClC ₆ H ₄	<i>t</i> -Bu	6aj	87	90:10	75
4	2a	Ph	Me	6aa	99	50:50	25/65

^a **5a** (59.9 mg, 0.20 mmol), **2** (0.26 mmol), **T-III** (9.1 mg, 0.02 mmol), CH₂Cl₂ (1.0 mL). ^b Yield of the isolated product. ^c Determined by ¹H NMR. ^d Determined by chiral HPLC.

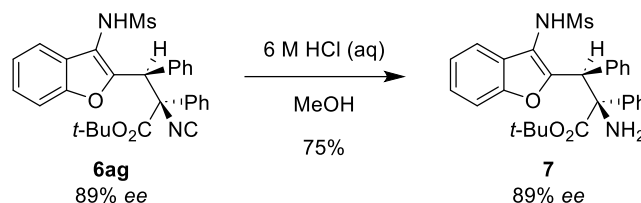
Regarding *tert*-butyl isocyanoacetates, substitution of the aromatic ring with a strongly electron-donating methoxy group at the *para* position provided an increase in the enantioselectivity of the reaction (87% *ee* for entry 2, compared with 84% *ee* for entry 1). In contrast, the yield of the reaction decreased from 86% to 64%, which may be due to the lower basicity of **2i** compared with **2g**. On the other hand, substitution at the aromatic ring with an electron-withdrawing group such as chloro (entry 3) resulted in a decrease of the enantiomeric excess, with 75% *ee*, as well as a decrease in the diastereoselectivity (90:10 dr). However, the yield of **6aj** was comparable to that of **6ag**.

Replacing the *tert*-butyl ester moiety with a methyl ester caused a complete loss of diastereoselectivity, accompanied with an erosion of the enantiomeric excess (entry 4). It can be, then, concluded, that the asymmetric induction is highly dependent on the steric volume provided by the *tert*-butyl ester of the isocyanide reaction partner.

4.2.7 Transformation of product **6ag**

To highlight the synthetic potential of our products **6**, we performed the transformation of **6ag** to the corresponding α -amino ester by acidic hydrolysis of the isocyanide (**Scheme 120**).

This transformation proceeded with a good yield and without any degradation of the enantiomeric excess of the product.



Scheme 120: Synthesis of the amino ester **7** by hydrolysis of the isocyanide.

4.2.8 Determination of the absolute configuration of products **6**

To ascertain the absolute configuration of benzofuran derivatives **6**, we crystallized the 3-methylphenyl derivative **6hg**, which was subjected to X-ray diffraction analysis. In this fashion, the (2*S*, 3*S*) configuration could be assigned to the major diastereomer of **6hg** (**Figure 6**). The absolute stereochemistry of the other compounds **6** was assigned by analogy assuming a common stereogenic mechanism for all of them.

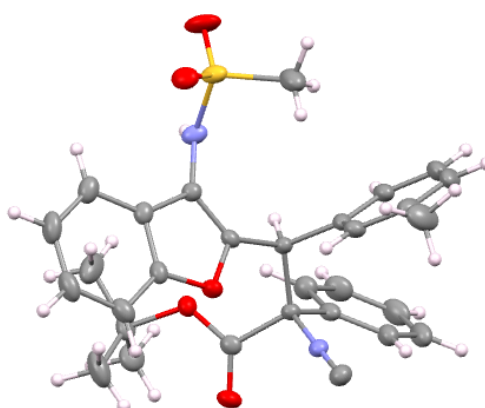


Figure 6: ORTEP plot of the major diastereomer of compound **6hg**. Thermal ellipsoids are represented at the 50% probability level.

4.2.9 Stereochemical model and catalytic function

Thioureas and squaramides act as bifunctional catalysts that exert their catalytic activity with the formation of noncovalent activation transition states through hydrogen bonding.¹³⁶ The dual function makes reference to the simultaneous presence of a hydrogen bond donor moiety and a basic group moiety. The latter can act as a directing group that allows the approach and orientation of the pronucleophile. Both moieties are separated by a chiral spacer that allows for the differentiation of the prochiral faces on the reaction partners.¹³⁷

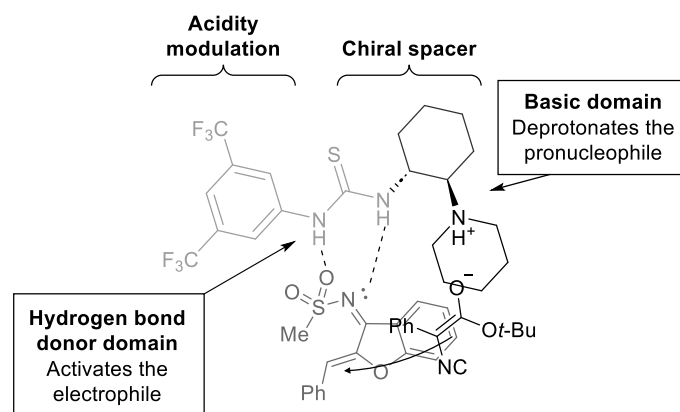


Figure 7: Stereochemical model for the addition reaction.

In this case, based on previous literature reports,^{126,131,133} the thiourea can form hydrogen bond with the 1-azadiene *N*-mesylimine, exerting an electrophilic activation effect, while the isocyanoacetate is deprotonated by the tertiary amine of the organocatalyst. Parallely, the spatial disposition of the different moieties due to the chirality of the catalyst allows for a directed attack of the isocyanide *Re* face to the 1-azadiene *Re* face of the double bond, accounting for the final stereochemistry (**Figure 7**). It needs to be noted that the achiral aromatic moiety also bonded to the thiourea serves to modulate the acidity of the hydrogen-bonding donors, and thus also plays a fundamental role in the catalytic action of the organocatalyst.¹³⁸

4.2.10 Summary

A procedure for the asymmetric addition of α -substituted *tert*-butyl isocyanoacetates to 1-azadienes derived from aurone has been developed. The procedure proceeds on a completely organocatalytic fashion, without the use of any metals. The procedure provides benzofuran derivatives with two consecutive chirality centers, one of them quaternary. The obtained benzofuran derivatives bearing an isonitrile group have, in general, excellent diastereoselectivity and good enantiomeric excess, and are also chiral α -amino acid precursors. The synthesis of the corresponding α -amino esters, without loss of enantiomeric excess, was showcased.

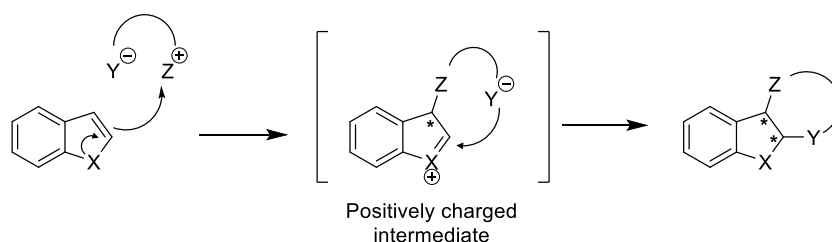
4.3 Dearomative formal [3+2] cycloaddition of 2-nitrobenzofurans and isocyanoacetates

4.3.1 Dearomatization of indoles and related arenes

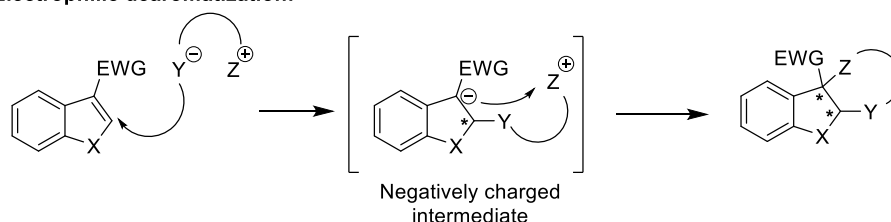
Arene dearomatization-based synthetic strategies have been widely used for the synthesis of polycyclic systems and heterocycles by the introduction of desired substituents onto aromatic rings.¹³⁹ Thus, it has been ultimately a great tool in the total synthesis of natural products, which commonly feature polycyclic skeletons.¹⁴⁰

In the case of indoles and related arenes, dearomative cycloaddition strategies have usually followed two differentiated pathways (**Scheme 121**).¹⁴¹ First, the use of electron-rich arenes that take part in a nucleophilic attack to an electrophile, giving rise to a positively charged intermediate which can be, in turn, attacked by a nucleophilic site of the added species. On the other hand, the introduction of electron-withdrawing groups, forming an electron-poor arene, allow nucleophilic species to act as initiator of cycloaddition reactions when they add to the now electrophilic olefinic carbon positions.

Nucleophilic dearomatization:



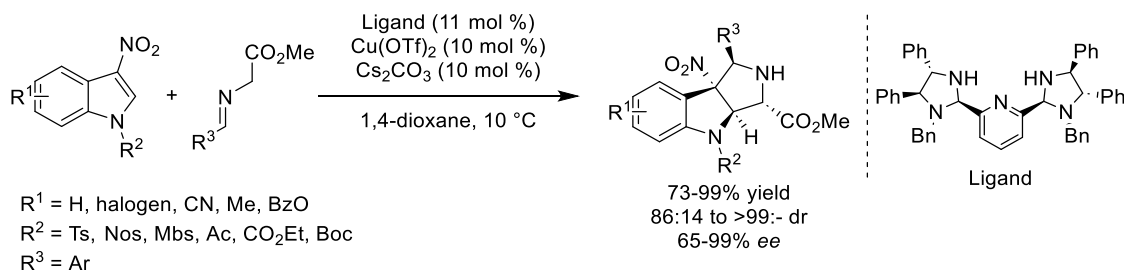
Electrophilic dearomatization:



Scheme 121: Dearomative cycloaddition strategies involving indoles and related heteroarenes.

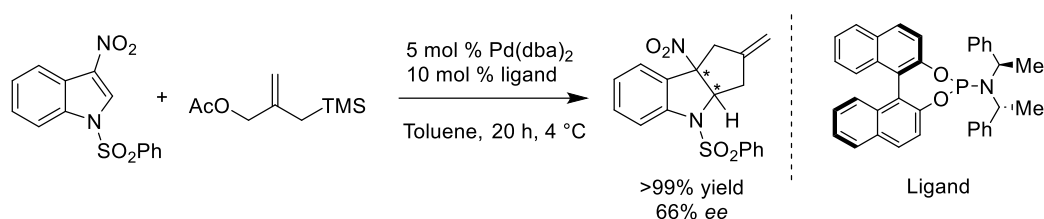
The first general asymmetric procedure covering the aforementioned electrophilic dearomatization pathway was described by Awata and Arai, and consisted in the [3+2] cycloaddition of 3-nitroindoles acting as dipolarophiles with benzyldeneaminoacetates using a chiral catalytic complex comprised of Cu(II) and a bis(imidazoline)pyridine ligand (**Scheme 122**).¹⁴² Irrespective of the presence of substituents of varied electronic behavior on the imino

acetate and on the 3-nitroindole, very high yields, diastereo- and enantioselectivities were, in general, obtained.



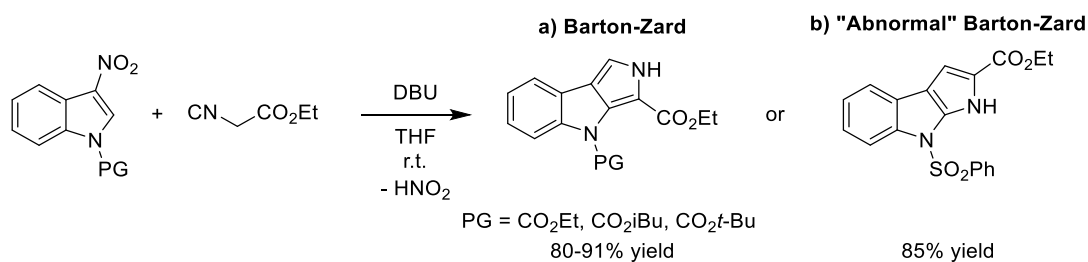
Scheme 122: Diastereo- and enantioselective cycloaddition of 3-nitroindoles and glycine imino esters with metallic catalysis.

Parallely, the group of Trost published an example of a dearomative cycloaddition of a 3-nitroindole with a trimethylenemethane donor, using a $Pd(0)$ chiral catalytic system (**Scheme 123**). Quantitative yield was obtained, albeit with moderate enantioselectivity.¹⁴³



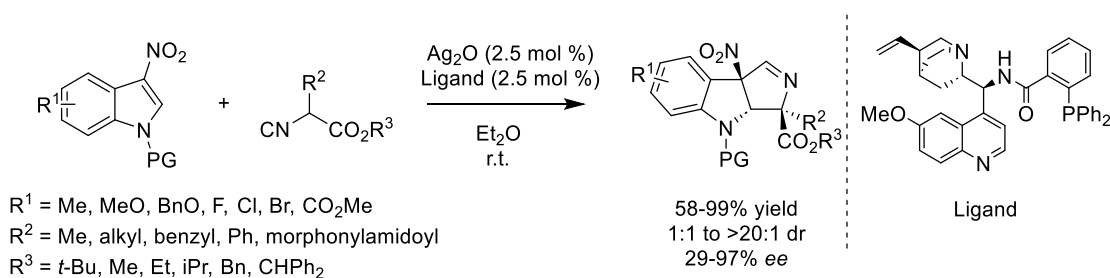
Scheme 123: Enantioselective cycloaddition of a 3-nitroindole with trimethylenemethane diamine, using a catalyst complex of $Pd(0)$ with a phosphoramidite ligand.

On the other hand, the first additions of isocyanoacetates to electron-deficient heterocycles were described by Gribble and collaborators.^{144,145} When attempting to perform Barton-Zard pyrrole synthesis reactions^{146,147} with 3-nitroindoles, the authors discovered that the expected product with a pyrrolo[3,4-*b*]indole ring system was only obtained when moderate electron-withdrawing protecting groups were present in the indole nitrogen atom (**Scheme 124, a**). When more powerful electron-withdrawing groups such as sulfone esters were present, an alternative isomer containing the pyrrolo[2,3-*b*]indole structure resulting from the indole ring fragmentation during the reaction mechanism was obtained (**Scheme 124, b**). The authors coined this reaction mechanism as the “abnormal Barton-Zard”.



Scheme 124: Addition of ethyl isocyanoacetate to *N*-protected 3-nitroindoles. Influence of the protecting group on the structure of the product.

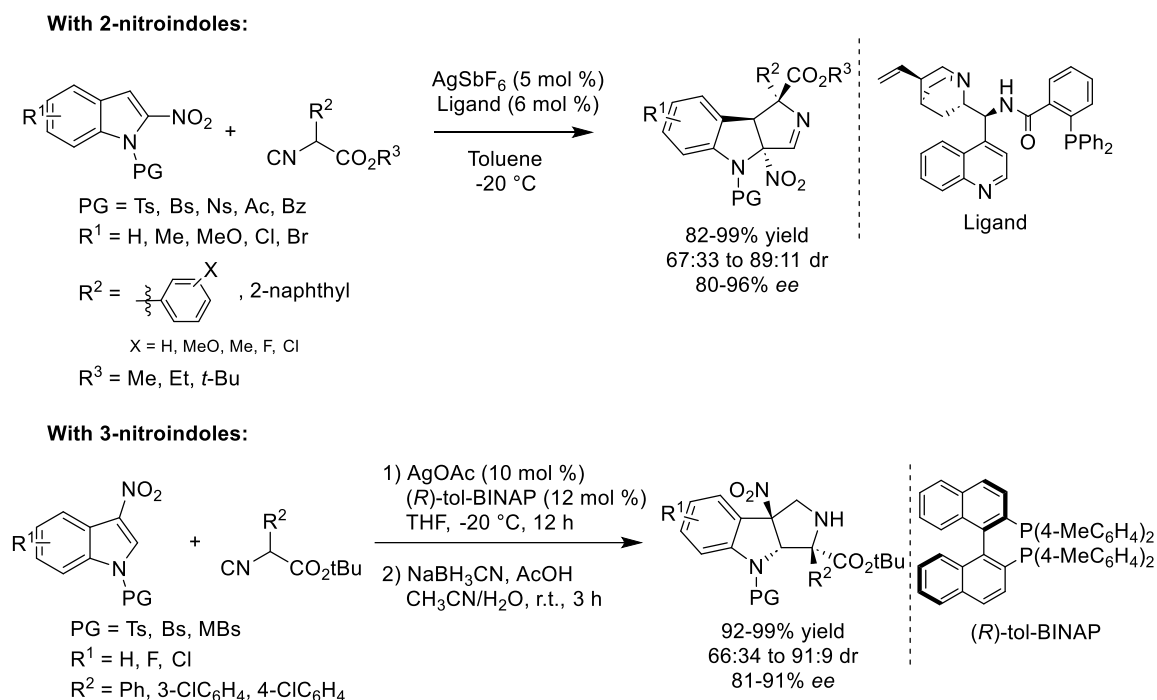
The Barton-Zard reaction can be interrupted at the nitrous acid elimination step if a substituent is placed at the α -position of the isocyanoacetate. The first example of this kind of reaction was described in 2021 by the group of Yuan and You, publishing the asymmetric interrupted Barton-Zard reaction of mainly α -alkyl isocyanoacetates with 3-nitroindoles (**Scheme 125**).¹⁴⁸ The reaction was carried out with a cooperative organic chiral ligand-silver metal catalytic system.



Scheme 125: Cooperative organic ligand-silver metal catalysis for the [3+2] cycloaddition reaction of isocyanoacetates and 3-nitroindoles.

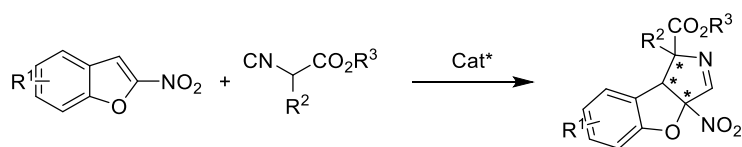
Simultaneously to the consecution of our work, Yuan, Zhao and collaborators described asymmetric interrupted Barton-Zard reactions of 2- and 3-nitroindoles with α -aryl isocyanoacetates,¹⁴⁹ thus increasing the scope of the previously described publication, in which only 3-nitroindoles were employed, and only one example with α -phenyl isocyanoacetate was included with low diastereo- and enantioselectivity.

In the case of 2-nitroindoles, the authors used a catalytic system similar to that used by Yuan and You, consisting in a phosphine ligand derived from cinchonidine with a silver(I) catalyst. For 3-nitroindoles, a cooperative system consisting of binaphthyl phosphine ligand with silver(I) was used. Furthermore, due to the labile nature of the resulting 1-pyrroline structures, the imine moiety had to be reduced with sodium cyanoborohydride before purification (**Scheme 126**).



Scheme 126: Asymmetric dearomative [3+2] cycloaddition of 2- and 3-nitroindoles with α -aryl isocyanoacetates.

Consequently, on the one hand, α -substituted isocyanoacetates have the ability of stopping the Barton-Zard reaction and thus allowing the obtention of fused polycycles with the concomitant generation of chirality centers. On the other hand, the utility and interest of benzofuran-derived structures has been briefed in Section 4.2.1. Taking these facts into consideration, and after realizing that reactions of this fashion were not described in the literature with nitrobenzofurans, to the best of our knowledge, we decided to study the [3+2] cycloaddition reaction of α -substituted isocyanoacetates with 2-nitrobenzofurans, in order to obtain 2,3-dihydrobenzofuran derivatives fused with a 1-pyrroline ring (**Scheme 127**).

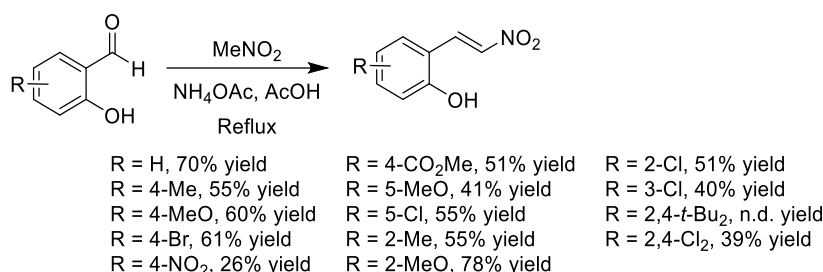


Scheme 127: Interrupted Barton-Zard reaction with 2-nitrobenzofurans.

4.3.2 Synthesis of the 2-nitrobenzofuran starting materials

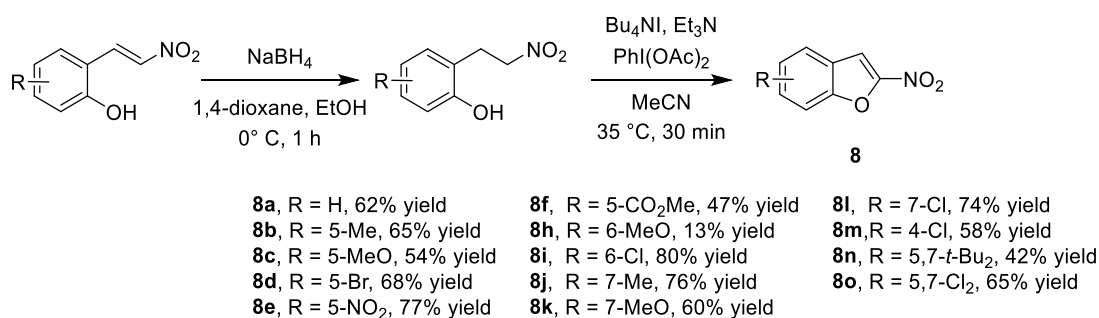
2-Nitrobenzofuranes were synthesized through a three-step procedure involving a nitroaldolic condensation of nitromethane with the corresponding salicylaldehyde, followed by double bond reduction with sodium borohydride and oxidative cyclization.

The nitroaldolic condensation was carried out using nitromethane as the solvent, at reflux, using acidic catalysis (**Scheme 128**). The corresponding *o*-(2-nitrovinyl)phenols were obtained with moderate yield. In the case of the 2,4-di-*tert*-butyl substituted example, a mixture containing the target compound was obtained, which was used for the next step without purification.



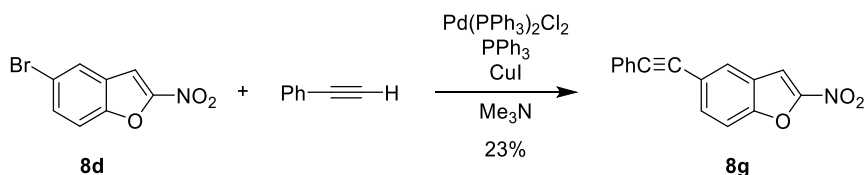
Scheme 128: Obtention of *o*-(2-nitrovinyl)phenols.

Next, the two final steps implicate sodium borohydride reduction of the nitroolefin and (diacetoxyiodo)benzene-mediated oxidative cyclization to give rise to the final 2-nitrobenzofurans **8** (**Scheme 129**).



Scheme 129: Final steps for the synthesis of 2-nitrobenzofuran starting materials. Yields refer to the last two steps.

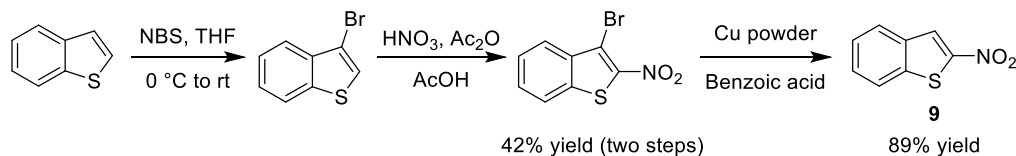
In the case of the 5-phenylethynyl derivative **8g**, the synthesis was carried out through a Sonogashira coupling of 5-bromo-2-nitrobenzofuran (**8d**) with phenylacetylene (**Scheme 130**).



Scheme 130: Synthesis of 5-phenylethynyl-2-nitrobenzofuran.

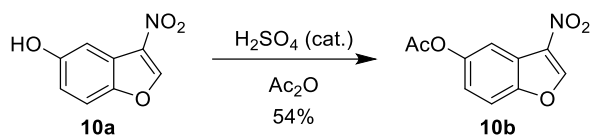
In order to study the reaction with other heterocycles, 2-nitrobenzothiophene (**9**) was also synthesized, following a three-step procedure consisting on the 3-bromination of thianaphthene, using *N*-bromosuccinimide, followed by nitration at the 2 position with nitric acid. Finally,

reduction with metallic copper removed the bromo group to furnish the desired starting material (**Scheme 131**).



Scheme 131: Synthesis of 2-nitrobenzothiophene.

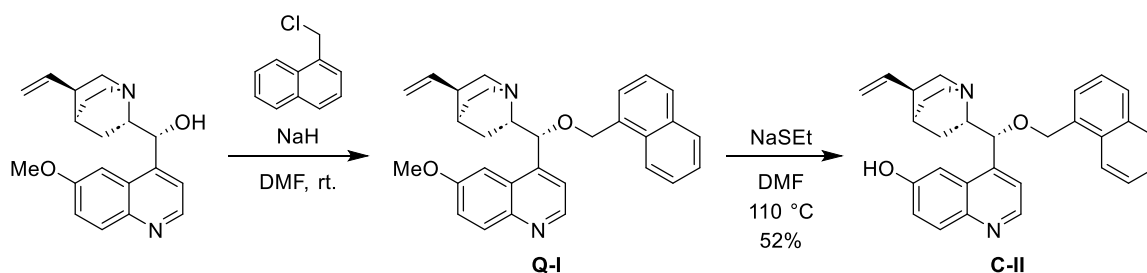
Finally, regarding the less synthetically accessible 3-nitrobenzofurans that were studied, 5-acetoxy-3-nitrobenzofuran (**10b**) was synthesized from the commercially available 5-OH derivative **10a**, by the means of an acetylation with acetic anhydride in acidic conditions (**Scheme 132**).



Scheme 132: Synthesis of 5-acetoxy-3-nitrobenzofuran from the commercially available 5-hydroxy-3-nitrobenzofuran.

4.3.3 Synthesis of catalyst **C-II**

For the synthesis of catalyst **C-II**, a two-step protocol was followed. Starting from quinine, deprotonation with sodium hydride, followed by nucleophilic substitution with 1-(chloromethyl)naphthalene yielded benzylated quinine derivative **Q-I**. Demethylation with sodium ethanethiolate in DMF gave rise to the target cupreine **C-II** (**Scheme 133**).

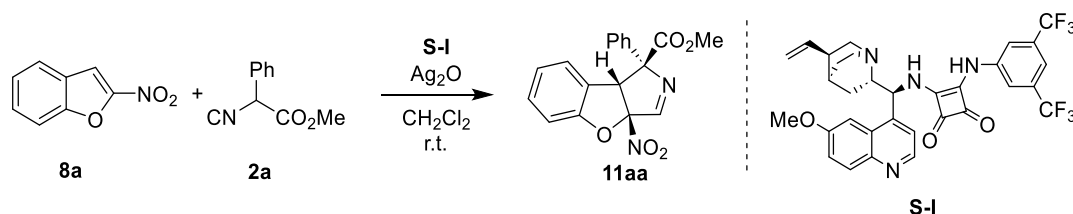


Scheme 133: Synthesis of cupreine-derived catalyst **C-II**.

4.3.4 Optimization of the reaction conditions

4.3.4.1 Initial assessment of the catalytic conditions

As a first step for studying which catalytic system performed better for this cycloaddition reaction, we carried out the reaction both with a cooperative metal-organocatalyst system, as well as with a purely organocatalytic methodology.

Table 11: Initial studies for the selection of the catalytic system.^a

Entry	S-I (mol %)	Ag_2O (mol %)	Time (h)	Yield (%) ^b	dr ^c	ee (%) ^d
1	10	5	24	99	61:39	10/30
2	10	-	48	99	50:50	35/37
3	-	-	72	n.r.	-	-
4	-	5	24	76	29:71	-

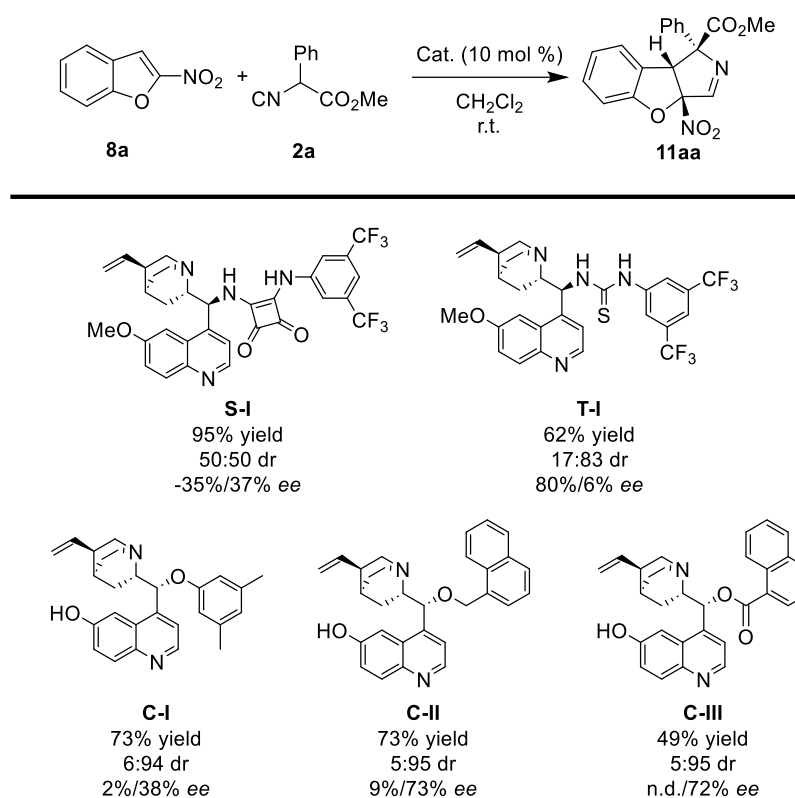
^a **8a** (16.3 mg, 0.1 mmol), **2a** (19 μL , 0.13 mmol), **S-I** (6.3 mg, 0.01 mmol), Ag_2O (1.2 mg, 0.005 mmol), CH_2Cl_2 (1 mL). ^b Yield of the isolated product. ^c Determined by ^1H NMR. ^d Determined by chiral HPLC.

As we can see in **Table 11**, when comparing the results of the reaction carried out with quinine-derived squaramide **S-I** in the presence (entry 1) or absence (entry 2) of silver oxide, the enantioselectivity was better in the second case, although the diastereoselectivity was slightly lower. Furthermore, when the reaction was tested with the absence of both **S-I** and silver oxide no product was observed (entry 3), thus confirming that there was no background reaction. However, the reaction could proceed with a good yield just by the addition of silver oxide (entry 4), exposing a possible background reaction when employing a cooperative catalytic system.

Considering these results, we decided to continue with the optimization procedure using an exclusively organocatalytic system, in order to prevent the decrease of enantioselectivity that the addition of a silver source could originate because of the observed background reaction. Under these conditions, the yield for the product was still excellent (entry 2).

4.3.4.2 Effect of the organocatalyst

Next, we studied the effect of the structure of the organocatalyst, testing multiple families of organocatalysts. The results are displayed in **Scheme 134**.



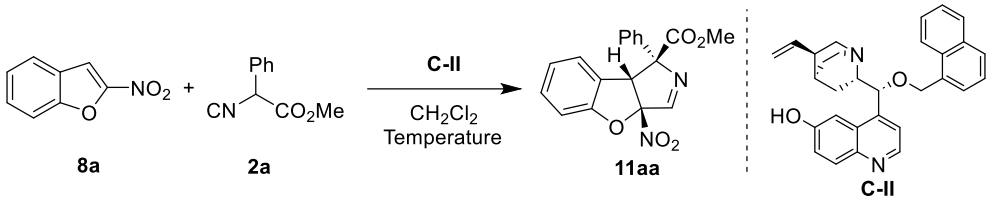
Scheme 134: Effect of the organocatalyst on the reaction results. Reaction conditions: **8a** (16.3 mg, 0.1 mmol), **2a** (19 μL , 0.13 mmol), organocatalyst (0.01 mmol), CH_2Cl_2 (1 mL).

As we can see, thiourea **T-I** provided a remarkable increase of the diastereoselectivity of the reaction compared with squaramide **S-I**. However, the enantioselectivity for the major diastereomer was very low (6% *ee*). The yield of the reaction also decreased when the thiourea was used. In contrast, when cupreine **C-I** was employed, the diastereomeric ratio of product **11aa** improved without affecting the enantiomeric excess of the major diastereomer, compared with thiourea **T-I**. Encouraged by these results, we tested other cupreines as organocatalysts. Cupreine **C-II** provided an increase of the enantioselectivity to 73% *ee* for the major diastereomer, while maintaining the good yield and diastereoselectivity already provided by **C-I**. The structurally similar 1-naphthoic acid ester **C-III**, in turn, was unable to further improve the enantiomeric excess, while causing a significant erosion in the yield of the reaction.

4.3.4.3 Effect of the temperature and catalytic loading

Taking the reaction conditions which provided the best results up to this point, using the organocatalyst **C-II**, we performed a study of the effects that the temperature and the catalytic loading had on the reaction results.

Table 12: Influence of the catalytic loading and the reaction temperature.^a

					
Entry	C-II (mol %)	T (°C)	Yield (%) ^b	dr ^c	ee (%) ^d
1	10	r.t.	73	5:95	9/73
2	15	r.t.	65	5:95	n.d./76
3	15	0	48	5:95	n.d./93

^a **8a** (16.3 mg, 0.1 mmol), **2a** (19 μ L, 0.13 mmol), **C-II**, CH₂Cl₂ (1 mL). ^b Yield of the isolated product. ^c Determined by ¹H NMR. ^d Determined by chiral HPLC.

When the catalytic loading of **C-II** was increased from 10 mol % to 15 mol %, an increase of the enantiomeric excess was observed (**Table 12**, entry 2). Maintaining this catalytic loading, the reaction temperature was decreased to 0 °C (entry 3), what brought forth a marked increase in the enantiomeric excess, to 93% *ee*, while maintaining the diastereoselectivity. The yield of the reaction, however, decreased.

4.3.4.4 Effect of the concentration

Considering that the conditions which resulted in the highest enantiomeric excess up to this point (**Table 12**, entry 3) resulted in a fairly reduced yield, we decided to try increasing the concentration of the reactants in an attempt to obtain a good balance between the yield of product **11aa** and the enantioselectivity of the reaction.

Table 13: Optimization of the concentration of the reaction.^a

Reaction scheme showing the synthesis of **11aa** from **8a** and **2a** using catalyst **C-II** (15 mol %) in CH_2Cl_2 at 0°C .

Entry	Conc. of 8a (M)	Yield (%) ^b	dr ^c	ee (%) ^d
1	0.1	48	5:95	n.d./93
2	0.2	75	5:95	n.d./90
3 ^e	0.2	74	5:95	n.d./90

^a **8a** (16.3 mg, 0.1 mmol), **2a** (19 μL , 0.13 mmol), **C-II** (6.8 mg, 0.015 mmol), CH_2Cl_2 . ^b Yield of the isolated product. ^c Determined by ^1H NMR. ^d Determined by chiral HPLC. ^e Reaction carried out with 10 mol % **C-II**.

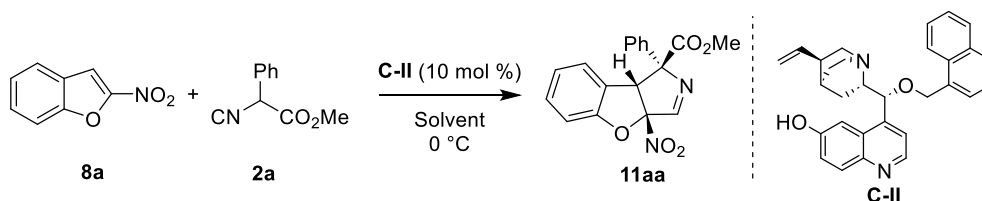
When the concentration of the reaction was doubled (**Table 13**, entry 2), the yield of the reaction increased to 75%, while maintaining the diastereoselectivity and without affecting the enantiomeric excess significantly. With these conditions, we tried to discern whether the

incrementation of the loading of the catalyst was still necessary. Happily, the good results were maintained when the catalyst load was reduced again to 10 mol % (entry 3). Consequently, we decided to continue the optimization of the remaining reaction parameters using these conditions.

4.3.4.5 Effect of the solvent

Taking as a base the conditions which provided better combined results with the use of the least quantity of solvent and organocatalyst that was possible (**Table 13**, entry 3), we proceeded with the optimization of the solvent used for the reaction, obtaining the results displayed on **Table 14**.

Table 14: Influence of the solvent on the results of the reaction.^a



Entry	Solvent	Yield (%) ^b	dr ^c	ee (%) ^d
1	CH ₂ Cl ₂	74	5:95	n.d./90
2	Toluene	40	5:95	n.d./93
3	MTBE	46	5:95	n.d./74
4	ClCH ₂ CH ₂ Cl	58	5:95	n.d./86
5	CHCl ₃	79	5:95	n.d./93

^a **8a** (16.3 mg, 0.1 mmol), **2a** (19 μ L, 0.13 mmol), **C-II** (4.5 mg, 0.01 mmol), solvent (0.5 mL). ^b Yield of the isolated product. ^c Determined by ¹H NMR. ^d Determined by chiral HPLC.

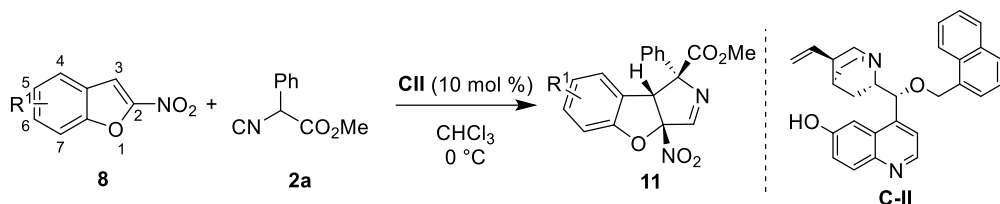
The use of aromatic and ether solvents such as toluene or methyl *tert*-butyl ether (MTBE) caused a decrease of the yield for product **11aa** (**Table 14**, entries 2 and 3). In the case of MTBE, this fact was accompanied by a reduction in the enantioselectivity of the reaction. When other chlorinated solvents were essayed, it could be concluded that, although 1,2-dichloroethane (entry 4) did not result in an improvement compared with dichloromethane, chloroform resulted in an increase of both the yield and the enantioselectivity of the reaction, while maintaining its diastereoselectivity (entry 5). Setting these conditions as optimal, we then proceeded studying the scope of the cycloaddition reaction.

4.3.5 Scope of the reaction

Using the most optimal conditions that had been found (**Table 14**, entry 5), the scope of the reaction using differently substituted 2-nitrobenzofurans **8** as well as isocyanoacetates **2** was studied.

In the first place, the use of 2-nitrobenzofurans **8** with substitutions of different electronic character in the reaction with isocyanoacetate **2a** was studied, with the results that are outlined in **Table 15**.

Table 15: [3+2] cycloaddition of isocyanoacetates **2** to 2-nitrobenzofurans **8**. Scope of 2-nitrobenzofurans.^a



Entry	8	R ¹	11	Yield (%) ^b	dr ^c	ee (%) ^d
1	8a	H	11aa	79	5:95	93
2	8b	5-Me	11ba	67	5:95	88
3	8c	5-MeO	11ca	62	5:95	91
4	8d	5-Br	11da	74	5:95	92
5	8e	5-NO ₂	11ea	99	5:95	92
6	8f	5-CO ₂ Me	11fa	85	5:95	91
7	8g	5-C≡CPh	11ga	55	5:95	89
8	8h	6-MeO	11ha	47	5:95	92
9	8i	6-Cl	11ia	96	5:95	92
10	8j	7-Me	11ja	47	5:95	96
11	8k	7-MeO	11ka	77	5:95	91
12	8l	7-Cl	11la	92	5:95	96
13	8m	4-Cl	11ma	19	5:95	36
14	8n	5,7- <i>t</i> -Bu ₂	11na	30	5:95	82
15	8o	5,7-Cl ₂	11oa	93	5:95	94

^a **8** (0.15 mmol), **2a** (28 μ L, 0.19 mmol), **C-II** (6.8 mg, 0.015 mmol), CHCl₃ (0.75 mL). ^b Yield of the isolated product. ^c Determined by ¹H NMR. ^d Determined by chiral HPLC.

In general terms, the [3+2] cycloaddition products **11** were obtained with excellent diastereoselectivity and good to excellent enantiomeric excess, irrespectively of the position and electronic character of the substituents on the 2-nitrobenzofuran reaction partner. 2-Nitrobenzofurans featuring electron-donating groups provided a lower yield than those featuring electron-withdrawing groups. Regarding substitution at the 5 position of the 2-nitrobenzofuran, the weaker electron-donating group methyl (entry 2) performed with higher yield than the strongly electron-donating group methoxy (entry 3). Electron-withdrawing substituents at this position allowed the obtention of products **11** with higher yield (entries 4 to 6), especially 5-NO₂ (entry 5). The presence of a phenylalkynyl group on position 5 was tolerated, obtaining **11ga** with 55% yield and 89% *ee* (entry 7). Substitution at position 6 followed the same pattern, with the electron-donating 6-MeO (entry 8) providing a moderate yield and 6-Cl (entry 9) providing an excellent yield, although both maintained an excellent enantiomeric excess. Regarding

substitutions at position 7, interestingly, 7-methyl-2-nitrobenzofuran **8j** provided the corresponding product with lower yield than the 7-methoxy derivative (entries 10 and 11), in a reversion of the general trend. In any case, both electron-donating 7-Me (entry 10) and 7-MeO (entry 11) provided excellent enantioselectivity but lower yield than electron-withdrawing 7-Cl (entry 12). Unfortunately, the catalytic system was not compatible with the substitution at position 4 of the 2-nitrobenzofuran ring, obtaining very low yield and enantiomeric excess for product **11ma** (entry 13). With respect to 5,7-disubstituted 2-nitrobenzofurans, di-*tert*-butyl substituted starting material **8n** provided **11na** with a low yield (30%), although with a good enantiomeric excess of 82% (entry 14). On the other hand, dichloro-substituted **8o** allowed the obtention of **11oa** with an excellent yield of 93% and excellent enantioselectivity, with 94% *ee* (entry 15).

Next, we expanded the study of the reaction scope with the use of isocyanoacetates featuring different aromatic and alkyl groups at its α position (Table 16).

Table 16: [3+2] cycloaddition of isocyanoacetates **2** to 2-nitrobenzofurans **8**. Scope of isocyanoacetates.^a

Entry	8	R ¹	2	R ²	11	Yield (%) ^b	dr ^c	<i>ee</i> (%) ^d
1	8a	H	2a	Ph	11aa	79	5:95	93
2	8a	H	2b	4-MeOC ₆ H ₄	11ab	62	5:95	97
3	8a	H	2c	4-ClC ₆ H ₄	11ac	62	5:95	78
4	8a	H	2d	4-NO ₂ C ₆ H ₄	11ad	96	5:95	67
5	8a	H	2f	Me	11af	45	5:95	0
6	8e	5-NO ₂	2a	Ph	11ea	99	5:95	92
7	8e	5-NO ₂	2b	4-MeOC ₆ H ₄	11eb	99	5:95	94
8	8i	6-Cl	2a	Ph	11ia	96	5:95	92
9	8i	6-Cl	2b	4-MeOC ₆ H ₄	11ib	84	5:95	96

^a **8** (0.15 mmol), **2** (0.19 mmol), **C-II** (6.8 mg, 0.015 mmol), CHCl₃ (0.75 mL). ^b Yield of the isolated product.

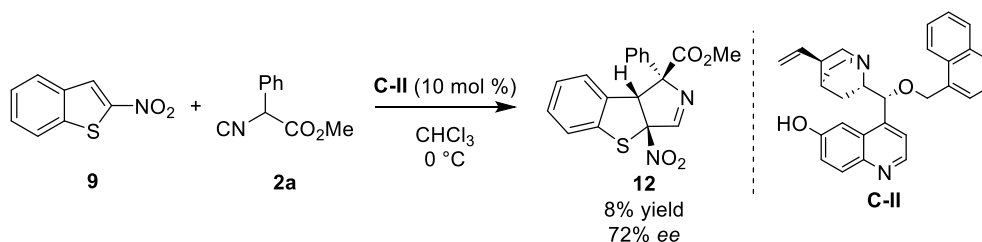
^c Determined by ¹H NMR. ^d Determined by chiral HPLC.

The use of methyl α -(4-methoxyphenyl) isocyanoacetate (**2b**) allowed for an increase of the enantiomeric excess of the cycloaddition product compared with that obtained with **2a**, from 93% to 97% *ee* (entries 1 and 2). However, the use of **2b** was accompanied with an erosion of the yield of the reaction. The presence of electron-withdrawing substitutions at the aromatic ring on the α position of the isocyanoacetate produced a decrease in the enantiomeric excess of the product, with 4-chlorophenyl-substituted **2c** giving 78% *ee* for product **11ac** (entry 3) and

4-nitrophenyl-substituted **2d** giving, in turn, 67% *ee* for product **11ad** (entry 4), compared with the 93% *ee* obtained with **2a** (entry 1). Lastly, asymmetric induction does not occur with α -methyl isocyanoacetate **2f**, providing the corresponding cycloaddition product in a racemic fashion, although maintaining the excellent diastereoselectivity (entry 5).

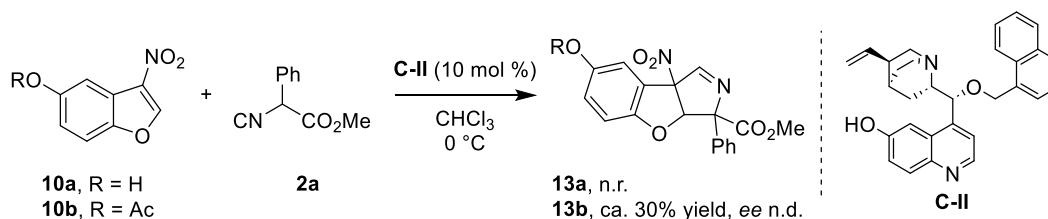
Considering the good results obtained with methyl α -(4-methoxyphenyl) isocyanoacetate (**2b**), this isocyanoacetate was also tested with differently substituted 2-nitrobenzofurans. With benzofuran **8e**, a slight increase in the enantiomeric excess was observed (entries 6 and 7). Similarly, the reaction with the 6-Cl-substituted **8i** also took place with an increase of the enantioselectivity, from 92% to 96% *ee*, although with certain erosion of the yield of the reaction (entries 8 and 9).

The reaction with 2-nitrobenzothiophene (**9**) was also essayed (**Scheme 135**). In this case, the expected [3+2] cycloaddition product **12** was isolated with a good enantiomeric excess, although the yield was very low.



Scheme 135: Reaction with 2-nitrobenzothiophene (**9**).

In the case of the reactions with 3-nitrobenzofurans **10** (**Scheme 136**), it was observed that no reaction took place when using commercially available 5-hydroxy-3-nitrobenzofuran (**10a**), probably due the presence of the free hydroxyl group. In the case of 5-acetoxy-2-nitrobenzofuran (**10b**), although full conversion was observed, the product was highly unstable and a complex mixture containing ca. 30% of **13b** was obtained. All attempts to obtain purer **13b** failed. Owing to these problems with this product, its enantiomeric excess could not be determined.

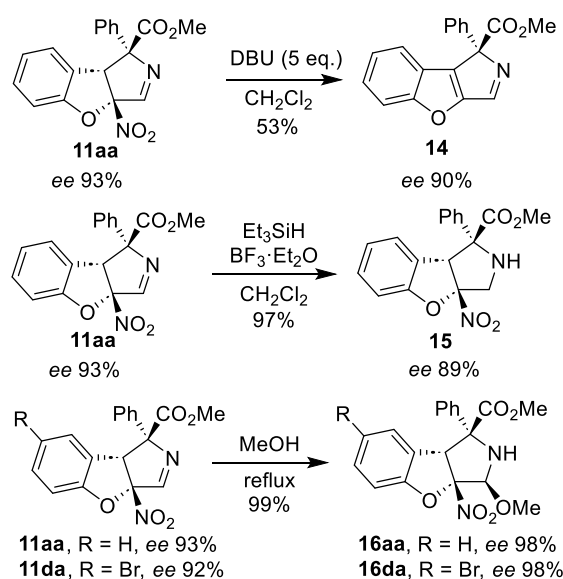


Scheme 136: Reactions with 3-nitrobenzofurans **10**.

4.3.6 Transformations of the cycloaddition product

In order to showcase the synthetic utility of the obtained cycloaddition adducts, we carried out different transformations of products **11** (**Scheme 137**). In the first place, elimination of nitrous acid with DBU gave rise to the 2*H*-pyrrole **14**, with 53% yield and maintaining the enantiomeric excess.

Secondly, reduction of the pyrroline ring C-N double bond with triethylsilane, catalyzed by $\text{BF}_3 \cdot \text{Et}_2\text{O}$ gave rise to the corresponding pyrrolidine **15** in 97% yield, albeit with a slight erosion of the enantiomeric excess. Finally, addition of methanol to the pyrrolynic imine furnished the aminoacetals **16aa** and **16da** with full diastereoselectivity.



Scheme 137: Synthetic transformations of the [3+2] cycloaddition adduct **11**.

4.3.7 Determination of the absolute configuration of products **11**

For the determination of the absolute configuration of the cycloaddition products, X-ray diffraction analysis was performed on product **16da**, which could be crystallized (**Figure 8**). This way, the configuration for product **11da** could be determined as (1*R*,3*aR*,8*bR*). Assuming a common stereochemical pathway, the same configuration was assigned to all compounds **11**.

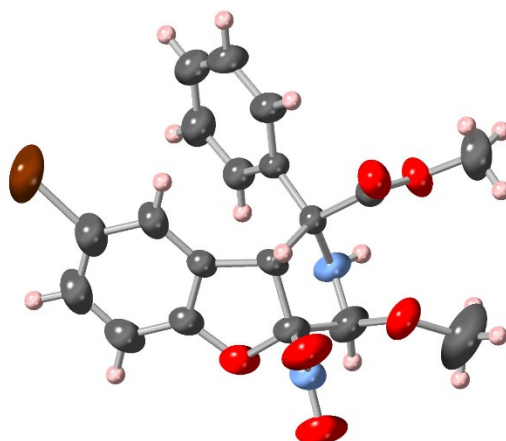
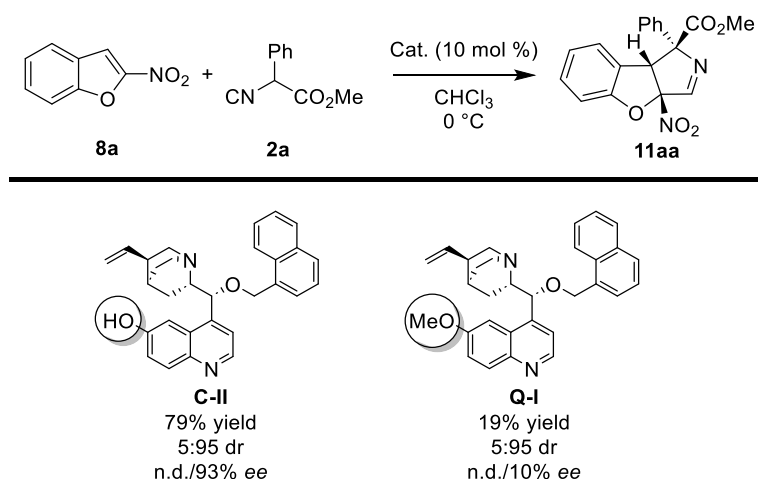


Figure 8: ORTEP plot of aminoacetal **16da**. Thermal ellipsoids are represented at the 50% probability level.

4.3.8 Mechanistic insight

In order to gain more knowledge into the mechanistic activity of the catalyst, we performed a control experiment in which we employed the quinine analogue of our cinchonine organocatalyst **C-II**, with a 6-methoxy group instead of a 6-hydroxy group (**Scheme 138**).



Scheme 138: Control experiment for mechanistic elucidation of the asymmetric interrupted Barton-Zard reaction.

Organocatalyst **Q-I** had notably lower performance than organocatalyst **C-II**, giving product **11aa** with just 19% yield and 10% *ee*, although it maintained the same diastereoselectivity. Thus, it can be deduced that the 6-OH group plays a fundamental role in the asymmetric induction mechanism. Considering this fact, as well as taking into account previously described mechanistic proposals with these kind of organocatalysts,^{150,151} we proposed a stereochemical model in which **C-II** acts as a bifunctional organocatalyst where the free hydroxyl group of the cupreine establishes a hydrogen bond with the nitro group of the 2-nitrobenzofuran, while the ammonium ion of the quinuclidine ring forms an ion pair with the enolate of the

isocyanoacetate, directing the *Si* face of the enolate with the *Si* face of the 2-nitrobenzofuran electrophilic double bond, accounting for the final absolute configuration (**Figure 9**).

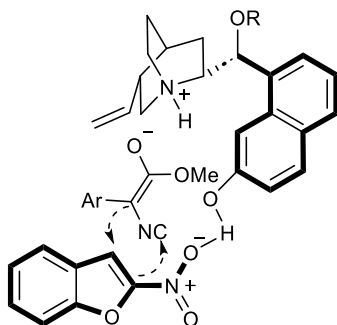


Figure 9: Proposed stereochemical model for the organocatalytic reaction.

4.3.9 Summary

In this section, we developed the interrupted Barton-Zard reaction of α -aryl isocyanoacetates with 2-nitrobenzofurans, giving tricyclic [3+2] cycloaddition adducts which contain the 3*a*,8*b*-dihydro-1*H*-benzofuro[2,3-*c*]pyrrole framework. Products were obtained with generally good to excellent yields, as well as excellent diastereo- and enantioselectivity. The reaction proceeded in a completely organocatalytic fashion, without the use of any metal. Furthermore, the cycloaddition products could be transformed to several different derivative products with good results regarding the preservation of the enantiomeric excess. Mechanistic studies by the utilization of derivative control catalysts were also carried out in order to gain more understanding into the asymmetric induction process.

4.4 Enantioselective [3+3] cycloaddition of isocyanoacetates and *N*-iminoquinazolinium ylides

4.4.1 Azomethine imines as substrates for cycloaddition reactions

Cycloadditions involving 1,3-dipolar compounds have seen wide application for the synthesis of nitrogen-containing heterocycles in an asymmetric manner, with applications spanning wide fields of chemistry such as natural product synthesis, materials science, as well as synthesis of compounds with biological activity.¹⁵²

On the other hand, azomethine imines are a subclass of 1,3-dipolar compounds that are classified in different groups depending on their atom connectivity (**Figure 10**). Since the pioneering use of *N,N'*-cyclic azomethine imines by Fu¹⁵³ and Chen,¹⁵⁴ as well as of *C,N*-cyclic azomethine imines by Maruoka and collaborators^{155,156} for the asymmetric synthesis of pyrrolidine-derived heterocycles, this kind of azomethine imines have been increasingly employed in enantioselective procedures for the obtention of enantiomerically-enriched nitrogen-containing heterocycles.¹⁵⁷ In contrast, acyclic azomethine imines are unstable, and must be generated in situ in harsh conditions that have precluded the development of asymmetric procedures for this variant.^{158–160}

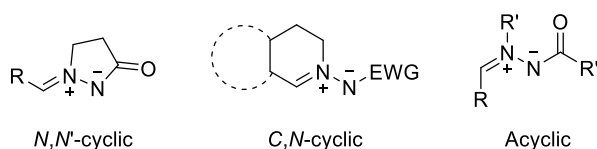
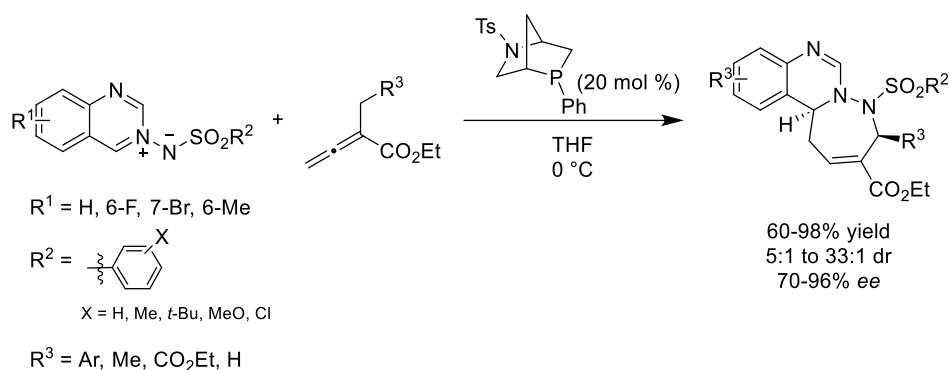


Figure 10: Classification of azomethine imines.

In the case of *N,N'*-cyclic azomethine imines, there have been some non-enantioselective and enantioselective examples of [3+3] cycloadditions involving isocyanoacetates, as summarized in Section 2.3.

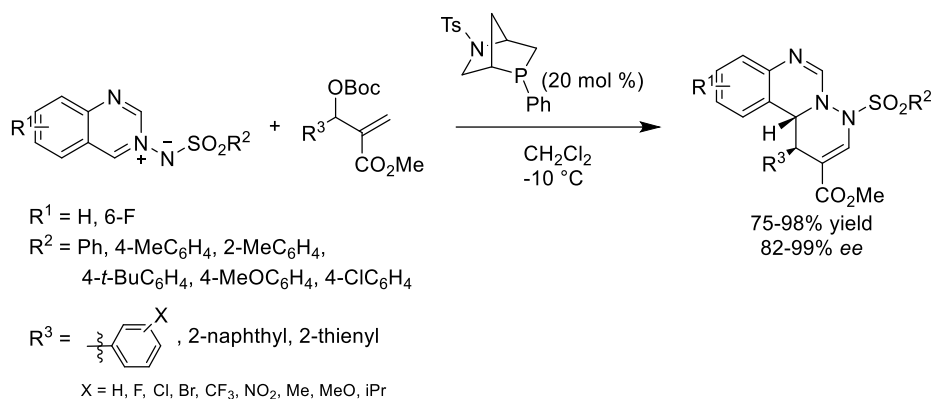
Among *C,N*-cyclic azomethine imines, bicyclic *N*-iminoquinazolinium ylides have recently been used as substrates for enantioselective organocatalyzed cycloadditions.

In 2016, the group of Guo developed an asymmetric [4+3] cycloaddition of *N*-iminoquinazolinium ylides to allenoates, giving rise to tricyclic adducts in a diastereo- and enantioselective fashion.¹⁶¹ The reaction was catalyzed by Kwon's chiral phosphine (**Scheme 139**).^{162,163}



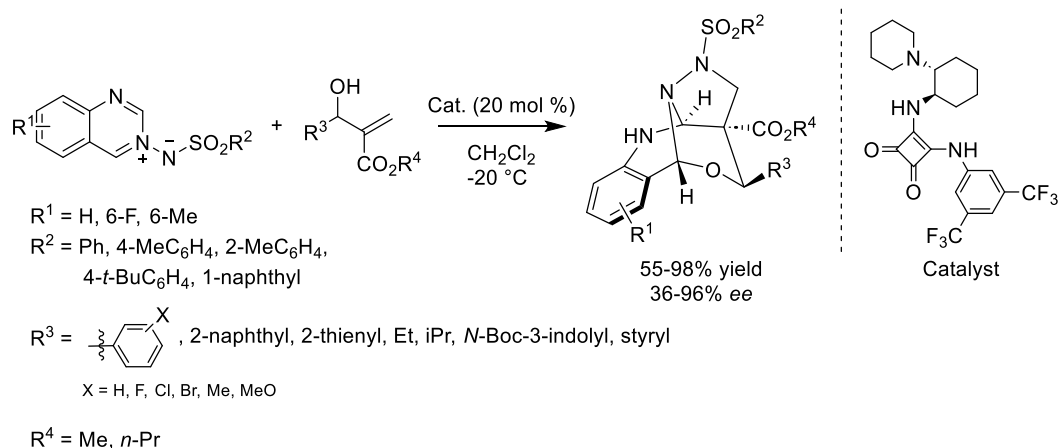
Scheme 139: [4+3] asymmetric cycloaddition of *N*-iminoquinazolinium ylides and allenates, with a chiral phosphine catalyst.

Later in 2017, the group of Guo published an enantioselective [3+3] cycloaddition of *N*-iminoquinazolinium ylides to Morita-Baylis-Hillman (MBH) carbonates, also catalyzed by Kwon's chiral phosphine (**Scheme 140**).¹⁶⁴ Very good yields and good to excellent enantioselectivities were obtained in almost all reported examples. The reaction, however, did not tolerate alkyl substituents on the MBH carbonate, only providing trace amounts of cycloaddition product.



Scheme 140: Enantioselective [3+3] of *N*-iminoquinazolinium ylides and Morita-Baylis-Hillman carbonates.

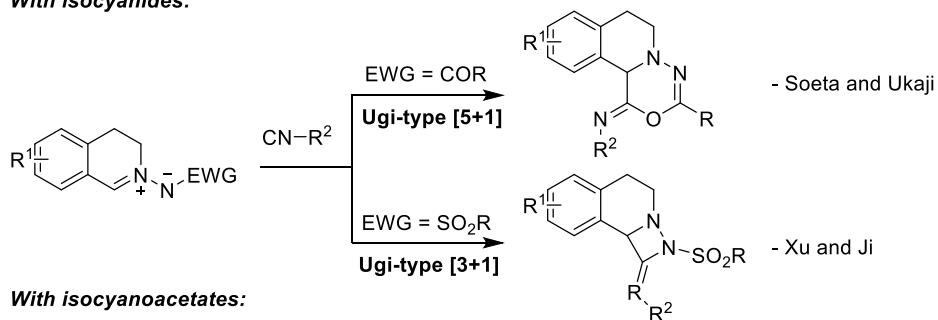
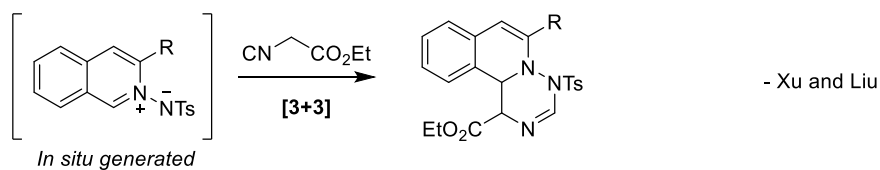
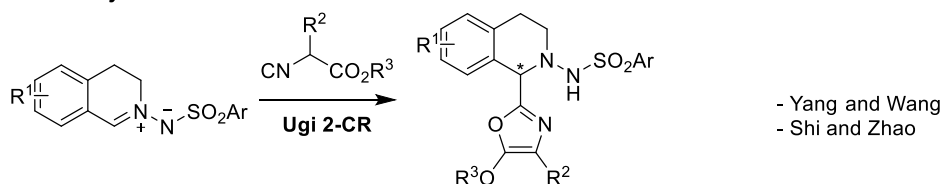
In 2019, Zheng, Guo and collaborators described a dearomative tandem annulation reaction between Morita-Baylis-Hillman alcohols and *N*-iminoquinazolinium ylides, which allowed to furnish functionalized aza-bicyclo[3.3.1]nonane-derived products (**Scheme 141**).¹⁶⁵ The reaction allowed to obtain the polycyclic products enantioselectively through the kinetic resolution of the MBH alcohols, which occurred with high selectivity, except in the cases where the MBH alcohol had alkyl substituents.



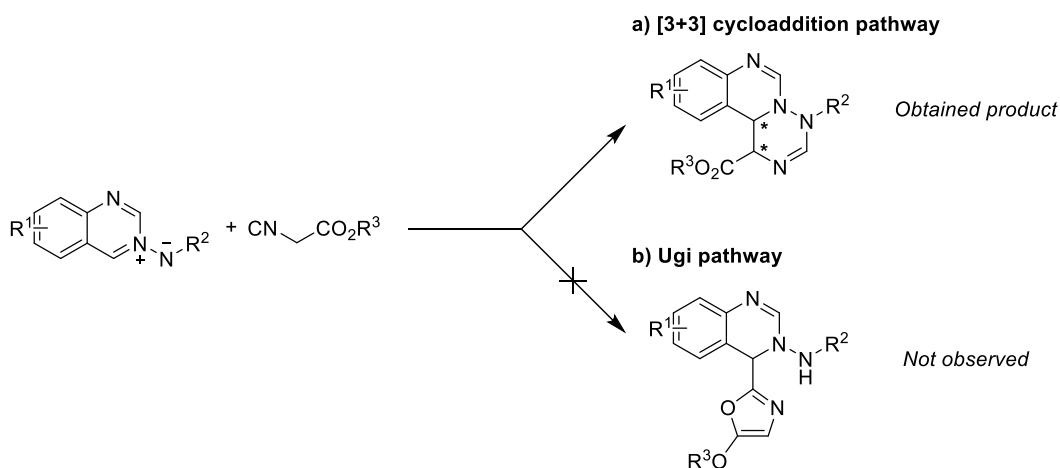
Scheme 141: Kinetic resolution of Morita-Baylis-Hillman alcohols in the dearomative tandem annulation reaction with *N*-iminoquinazolinium ylides.

To the best of our knowledge, there are no examples in the literature involving the reaction of isocyanides and *N*-iminoquinazolinium ylides. A few examples reported in the literature describe the reaction of isocyanides with related *C,N*-cyclic azomethine imines (**Scheme 142**). In particular, non-enantioselective Ugi-type reactions have been developed by Soeta and Ukaji,¹⁶⁶ as well as by Xu and Ji,¹⁶⁷ with the isocyanide providing its terminal carbon thanks to its dual nucleophilic and electrophilic nature in formal $[n+1]$ cycloadditions. Only a non-enantioselective example of [3+3] cycloaddition of isocyanoacetates and in-situ generated *N*-iminoisoquinolinium ylides has been reported by Xu and Liu,⁷⁴ using DBU as a base (see **Scheme 73** in Section 2.3). On the other hand, enantioselective precedents have been limited to Ugi additions of isocyanoacetates followed by cyclization to the isoxazole through the ester carbonyl, like in the examples of Yang and Wang,¹⁶⁸ and Shi and Zhao.¹⁶⁹

In this chapter, we report our effort to develop an enantioselective reaction of *N*-iminoquinazolinium ylides and isocyanoacetates. In this case, the corresponding [3+3] cycloaddition product was obtained, instead of the Ugi-type product (**Scheme 143**).

Non-enantioselective examples:**With isocyanides:****With isocyanoacetates:****Enantioselective examples:****With isocyanoacetates:**

Scheme 142: Summary of the previous examples comprising reactions of isocyanides with *C,N*-cyclic azomethine imines.

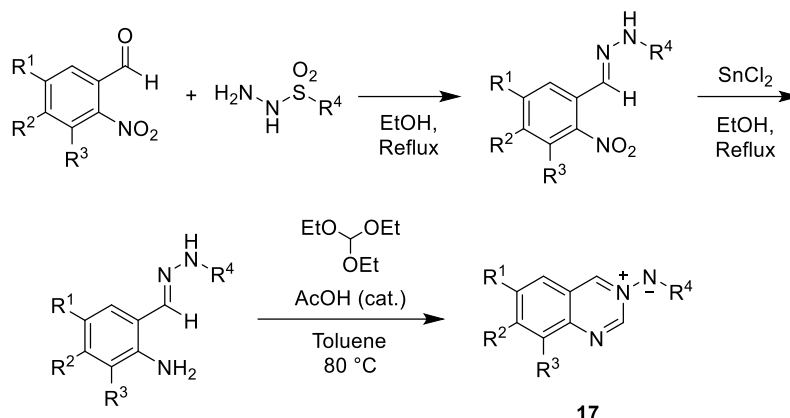


Scheme 143: Reaction of *N*-iminoquinazolinium ylides and isocyanoacetates. Only the [3+3] cycloaddition pathway was observed.

4.4.2 Synthesis of the *N*-iminoquinazolinium ylides

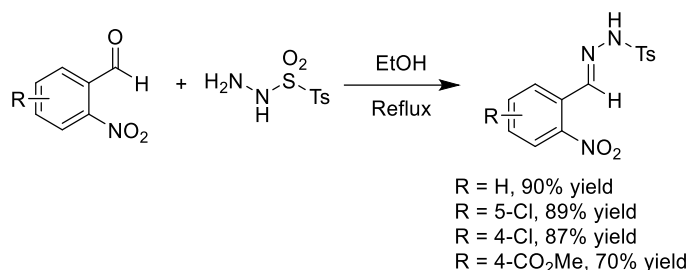
N-Iminoquinazolinium ylides were synthesized via a three-step procedure starting from 2-nitrobenzaldehydes. The corresponding sulfonylhydrazones were formed and, after reduction

of the nitro group, the final ylides were obtained upon treatment with ethyl orthoformate (**Scheme 144**).



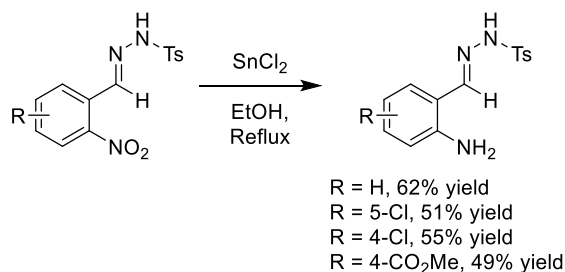
Scheme 144: Synthetic route towards *N*-iminoquinazolinium ylides.

For the formation of tosylhydrazones, the corresponding 2-nitrobenzaldehyde was refluxed in ethanol with tosylhydrazide, giving rise to the desired products in good to excellent yields (**Scheme 145**).



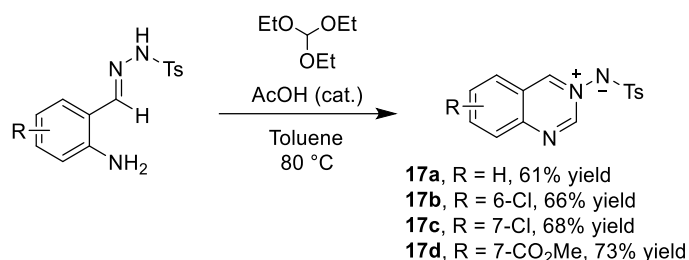
Scheme 145: Synthesis of tosylhydrazones.

For the reduction of the 2-NO₂ group to an amine group, tin(II) chloride was used, refluxing the mixture in ethanol. Reduction products were obtained with moderate yield (**Scheme 146**).



Scheme 146: Reduction of the nitro group of the *N*-tosyl hydrazones.

The final step involved the formation of the ylide by reaction of the aminohydrazone with ethyl orthoformate, under acidic catalysis. Ylides **17** were obtained with moderate to good yield (**Scheme 147**).



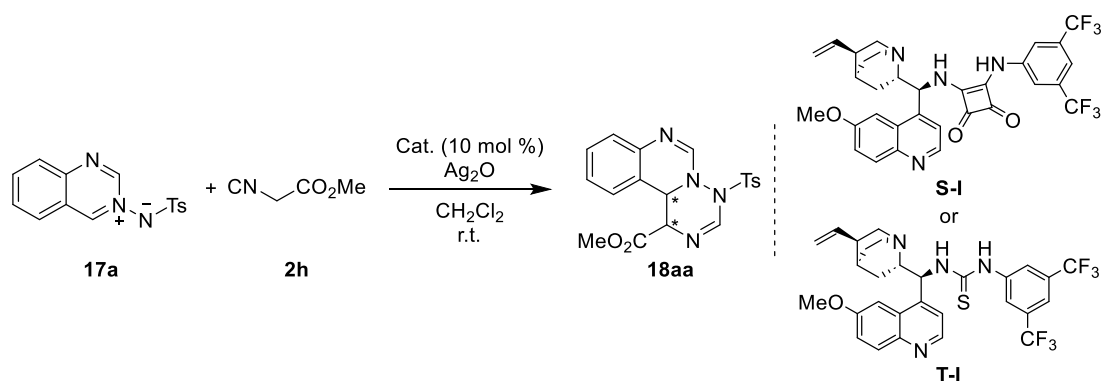
Scheme 147: Final step of the synthesis of *N*-iminoquinazolinium ylides.

4.4.3 Optimization of the reaction conditions

4.4.3.1 Assessment of the catalytic system

In the first place, we tested the reaction of *N*-iminoquinazolinium ylide **17a** and methyl isocyanoacetate (**2h**) in both organocatalytic conditions, as well as in cooperative metal-organic conditions. For these initial investigations, we used squaramide organocatalyst **S-I**, in dichloromethane (**Table 17**). The corresponding [3+3] cycloaddition product **18aa** was obtained in both cases. No Ugi-type products involving the nucleophilic addition of the isocyanide carbon to the electrophilic C-N double bond were observed.

Table 17: Comparison between organocatalytic and cooperative catalysis conditions.^a



Entry	Ag ₂ O (mol %)	Catalyst	Yield (%)	dr	ee (%)
1	5	S-I	76	54:42	11/4
2	0	S-I	70	77:23	63/54
3	0	T-I	90	67:33	28/n.d.

^a **17a** (29.9 mg, 0.1 mmol), **2h** (12 μ L, 0.13 mmol), catalyst (0.01 mmol), Ag₂O (1.2 mg, 0.005 mmol), CH₂Cl₂ (1 mL). ^b Yield of the isolated product. ^c Determined by ¹H NMR. ^d Determined by chiral HPLC.

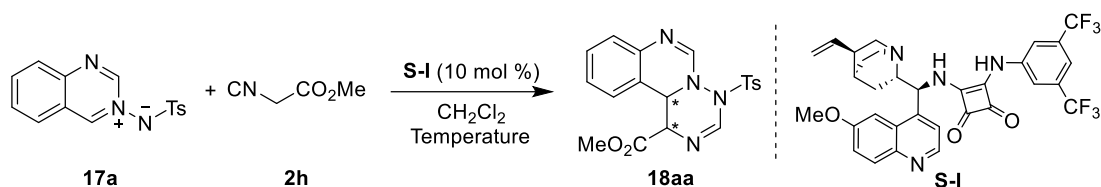
As we can see, the use of silver oxide (entry 1), despite providing higher yield for compound **18aa**, rendered lower diastereo- and enantioselectivity compared with the purely

organocatalytic conditions (entry 2). A test performed in the presence of silver oxide and no organocatalyst revealed that silver oxide may catalyze a non-stereoselective background reaction responsible for the low stereoselectivity observed in entry 1. These results prevented the use of silver oxide and further optimization was carried out under fully organocatalytic conditions. Thiourea **T-I** was also tested and, despite providing a higher yield, diastereo- and enantioselectivity were lower (entry 3).

4.4.3.2 Effect of the temperature

After having decided the catalytic strategy, we investigated the effect of the reaction temperature using squaramide **S-I**. Results are summarized in **Table 18**.

Table 18: Effect of the reaction temperature.



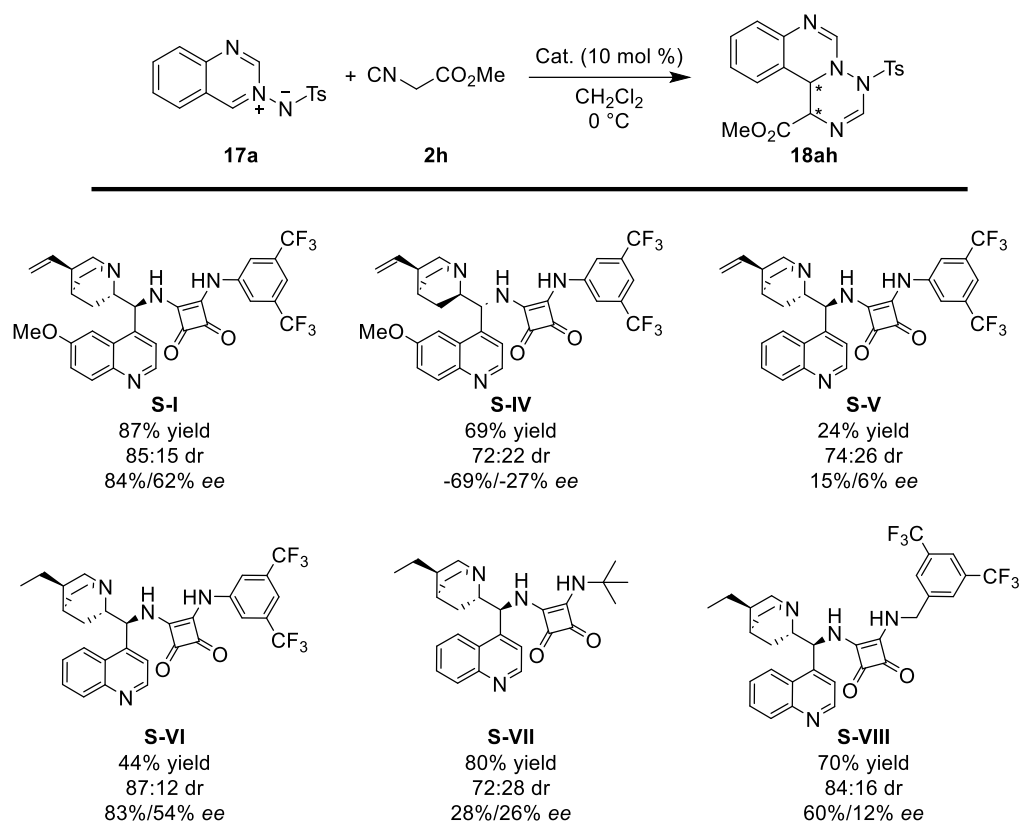
Entry	Temperature (°C)	Yield (%)	dr	ee (%)
1	r.t.	70	77:23	63/54
2	0	87	85:15	84/62
3	-10	81	84:16	75/n.d.

^a **17a** (29.9 mg, 0.1 mmol), **2h** (12 μ L, 0.13 mmol), **S-I** (6.3 mg, 0.01 mmol), CH₂Cl₂ (1 mL). ^b Yield of the isolated product. ^c Determined by ¹H NMR. ^d Determined by chiral HPLC.

Lowering the temperature from room temperature to 0 °C provided an overall improvement of the results, compound **18aa** being obtained with a higher yield, diastereo- and enantioselectivity (entries 1 and 2). However, further decreasing the temperature to -10 °C resulted in a decrease of the enantiomeric excess (entry 3). With these results in hand, we proceeded with the next steps of the optimization with a reaction temperature of 0 °C.

4.4.3.3 Effect of the organocatalyst

After having checked out that squaramides performed better than thioureas and established the best reaction temperature, we tried multiple squaramide organocatalysts with the goal of further improving the reaction results (**Scheme 148**).



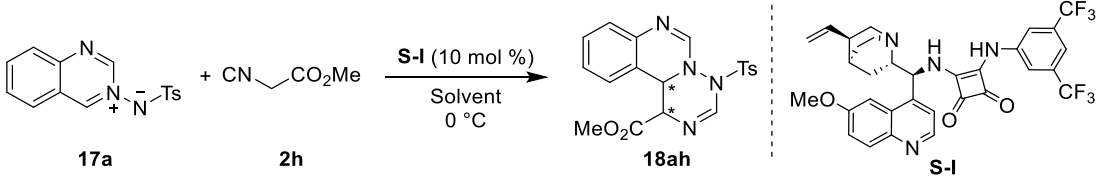
Scheme 148: Effect of the organocatalyst on the reaction results. Reaction conditions: **17a** (29.9 mg, 0.1 mmol), **2h** (12 μL , 0.13 mmol), organocatalyst (0.01 mmol), CH_2Cl_2 (1 mL).

Quinidine-derived catalyst **S-IV** furnished the opposite enantiomer, although with lower yield, diastereo- and diastereoselectivity. Cinchonidine-derived **S-V** did not show any improvement of the results either. In turn, dihydroquinine-based squaramide **S-VI** displayed similar enantioselectivity compared with quinine-based thiourea **S-I** and better diastereoselectivity, although with reduced yield. Other dihydroquinine-derived squaramides (**S-VII** and **S-VIII**) recovered the good reaction yield but unfortunately this was accompanied by an erosion of the enantiomeric excess. With these results, we decided to continue the optimization procedure maintaining **S-I** as the organocatalyst.

4.4.3.4 Effect of the solvent

Taking the best conditions found until now, using catalyst **S-I**, at 0°C , we proceeded to study the effect that the solvent of the reaction had on the results (**Table 19**).

Table 19: Effect of the reaction solvent.

				
Entry	Solvent	Yield (%)	dr	ee (%)
1	CH ₂ Cl ₂	87	85:15	84/62
2	ClCH ₂ CH ₂ Cl	56	83:17	85/64
3	CHCl ₃	65	85:15	66/21
4	Toluene	80	55:45	7/4
5	MTBE	n.r.	-	-

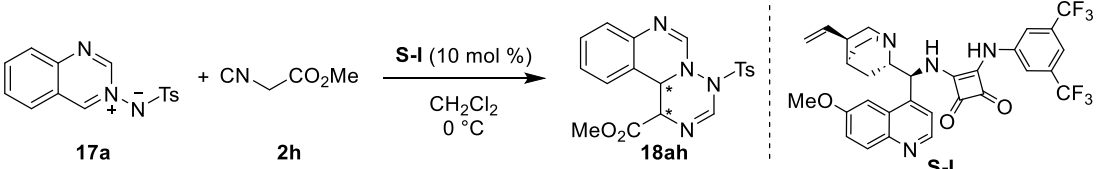
^a **17a** (29.9 mg, 0.1 mmol), **2h** (12 μL, 0.13 mmol), **S-I** (6.3 mg, 0.01 mmol), solvent (1 mL). ^b Yield of the isolated product. ^c Determined by ¹H NMR. ^d Determined by chiral HPLC.

As we can see in **Table 19**, the best results were obtained with chlorinated solvents (entries 1 to 3), although none of them improved the results obtained with dichloromethane (entry 1). Toluene provided product **18ah** with good yield but with very low diastereo- and enantioselectivity and the use of MTBE completely inhibited the reaction.

4.4.3.5 Effect of the concentration

Finally, we decided to test whether the variation of the concentration of the reaction could further improve the results (**Table 20**).

Table 20: Influence of the concentration of the reaction.

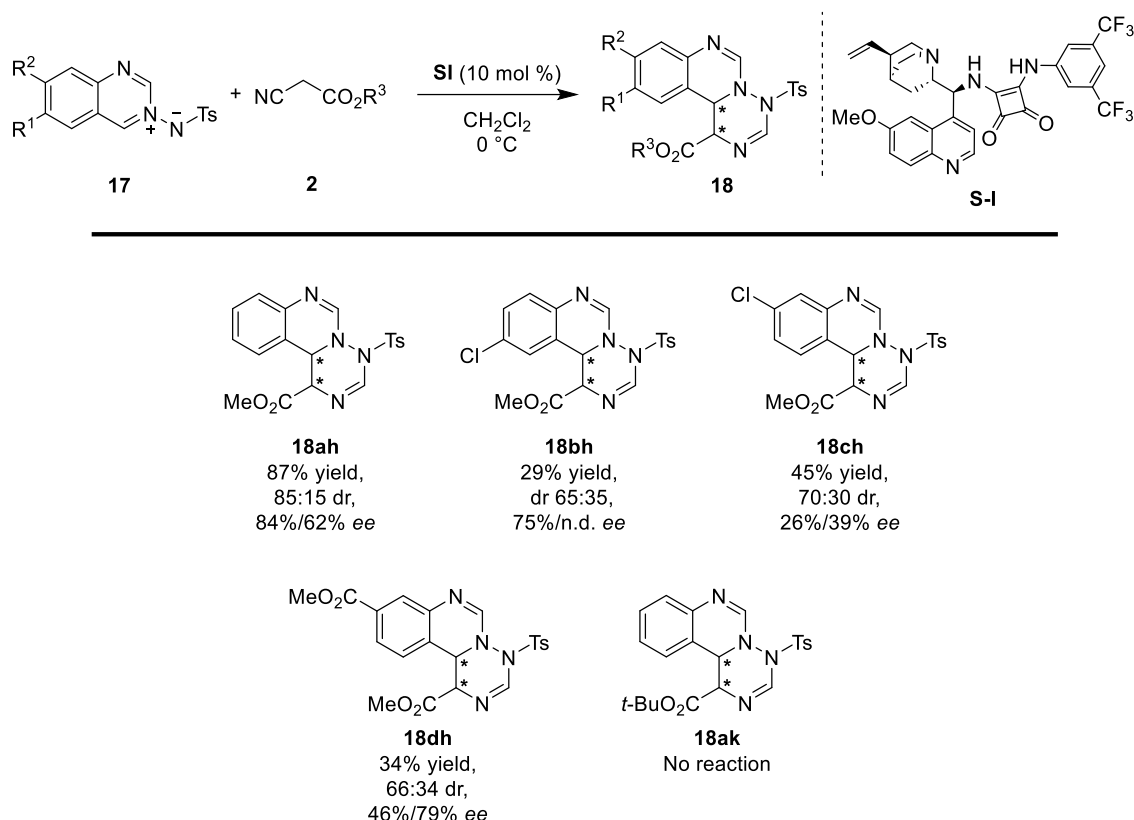
				
Entry	Conc. of 17a (M)	Yield (%)	dr	ee (%)
1	0.10	87	85:15	84/62
2	0.05	75	70:30	12/n.d.
3	0.20	87	82:20	80/64

^a **17a** (29.9 mg, 0.1 mmol), **2h** (12 μL, 0.13 mmol), **S-I** (6.3 mg, 0.01 mmol), CH₂Cl₂. ^b Yield of the isolated product. ^c Determined by ¹H NMR. ^d Determined by chiral HPLC.

The dilution of the reaction (entry 2) caused an erosion of the yield, as well as the diastereo- and enantioselectivity of the reaction. On the other hand, increasing the concentration of the reactants (entry 3) provided very similar overall results with respect to the initial conditions, although both the diastereoselectivity and enantiomeric excess decreased slightly.

4.4.4 Scope of the reaction

With the best reaction conditions available (**Table 20**, entry 1), we proceeded to study the scope of the [3+3] cycloaddition reaction using differently substituted *N*-iminoquinazolinium ylides. Results are displayed in **Scheme 149**.



Scheme 149: Scope for the [3+3] cycloaddition reaction of isocyanoacetates **2** and *N*-iminoquinazolinium ylides **17**. Reaction conditions: **17** (0.1 mmol), **2h** (0.13 mmol), **S-I** (6.3 mg, 0.01 mmol), CH₂Cl₂ (1 mL).

Disappointingly, the developed reaction conditions gave poor results with substituted *N*-iminoquinazolinium ylides. Thus, when a 6-Cl substituent was present at the quinazoline ring (**17b**), product **18bh** was obtained with a fair enantiomeric excess, although the yield was very low and the diastereoselectivity decreased with respect to that of **18ah**. In the case of a 7-Cl substituent at the quinazoline ring (**17c**), product **18ch** was obtained with higher yield and diastereoselectivity, although the enantiomeric excess was very low. Regarding 7-CO₂Me-substituted *N*-iminoquinazolinium ylide **18d**, the corresponding product **18dh** was obtained with a low yield and low diastereoselectivity, as well as reduced enantiomeric excess for the major diastereomer, although it was higher than that obtained in the case of the 7-Cl derivative.

tert-Butyl isocyanoacetate (**2k**) was also tested with ylide **17a**, but no product was observed, showing that the reaction was highly affected by the steric hindrance exerted by the bulky *tert*-butyl group.

At this point we decided to stop our research on this topic and leave a possible re-evaluation of the reaction conditions for the future.

4.4.5 Summary

In this section, the asymmetric [3+3] cycloaddition of isocyanoacetates and *N*-iminoquinazolinium ylides has been preliminarily developed. Unlike previous examples using different *C,N*-cyclic azomethine imines, the Ugi reaction pathway is not observed. The unsubstituted *N*-iminoquinazolinium ylide **17a** furnished the corresponding [3+3] cycloaddition adduct **18ah** with good yield, diastereoselectivity and enantioselectivity of the major diastereomer. However, the studied reaction conditions allowed for a very limited scope. Substitutions at the aromatic ring of the *N*-iminoquinazolinium ylide drastically affected the results, with lower yields, diastereomeric ratios and enantiomeric excesses for the products. In further studies, electron-donating substituents would need to be tried, although there have been synthetic difficulties for their access. The reaction also did not tolerate bulkier *tert*-butyl isocyanoacetate, furnishing no reaction product.

5 Experimental section

5.1 Common procedures and analysis techniques

General procedures

Reactions were monitored using Merck 60 F₂₅₄ (reference 5554 Merck) silica gel thin-layer chromatography plates. The eluted TLC plates were visualized under 254 nm or 365 nm UV light and then revealed using stain solutions of cerium molybdate, potassium permanganate or *p*-anisaldehyde.¹⁷⁰ Flash column chromatography was carried out using Silica Gel Merck 60 as stationary phase (reference 109385 Merck). The eluent was made to flow through the column with an air pump.

Solvents and reagents

Unless otherwise stated, reactants were obtained from commercial sources and used directly without further purification. In the cases where dry solvents were needed, the following procedures were followed:^{171–173}

- For CH₂Cl₂, DCE and toluene, the solvent was distilled over CaH₂ immediately before its use.
- For THF, the solvent was distilled over Na-benzophenone immediately before its use.
- For CHCl₃, the solvent was passed through a short-path plug of basic alumina and then, immediately before its use, distilled over P₂O₅.
- For MTBE, the solvent was stored over activated 4 Å molecular sieves.
- For acetonitrile, the solvent was stored over activated 3 Å molecular sieves.
- For EtOAc, the solvent was stored over activated 4 Å molecular sieves.

Nuclear magnetic resonance (NMR)

NMR spectra were recorded using a Bruker Avance III 300, Bruker AV400 or Bruker Neo500 at, respectively, 300 MHz, 400 MHz or 500 MHz for ¹H, or 75 MHz, 101 MHz or 125 MHz for ¹³C. For ¹⁹F, spectra were recorded at 282 MHz for Bruker Avance III 300 and at 471 MHz for Bruker Neo500. Chemical shifts (δ) are reported in ppm and coupling constants (*J*), in Hz. Carbon multiplicities were determined through DEPT experiments. Signals for non-deuterated residual solvents were used as internal standard:¹⁷⁴

- In chloroform-*d*, 7.26 ppm for ¹H and 77.16 ppm for ¹³C.
- In DMSO-*d*₆, 2.50 ppm for ¹H and 39.52 ppm for ¹³C.

- In benzene-*d*₆, 7.16 ppm for ¹H and 128.06 ppm for ¹³C.
- In methanol-*d*₄, 3.31 ppm for ¹H and 40.00 ppm for ¹³C.

Infrared (IR) spectroscopy

IR spectra were recorded using an Agilent Cary 630 FTIR spectrometer with a diamond ATR sampling module. Wavelengths are reported in reciprocal centimeters (cm⁻¹) and absorptions according to their relative intensities: s (strong), m (medium) or w (weak).

Mass spectrometry (MS)

HRMS were recorded using a Waters Q-TOF spectrometer equipped with an electrospray source with a capillary voltage of 3.3 kV (ESI).

Polarimetry

Specific optical rotations were measured using either a Perkin-Elmer polarimeter equipped with a sodium lamp (D line, 589 nm) and a 1 dm path length cuvette or a Bellingham+Stanley ADP430 polarimeter equipped with a LED light source, measuring at the sodium wavelength (D line, 589 nm) and a 1 dm path length cuvette. Concentrations (*c*) are expressed in g/100 mL.

Chiral HPLC analyses

Enantiomeric excesses were measured through HPLC analysis, using a Hitachi Elite Lachrom chromatograph with a Hitachi L-4500 or L-2455U UV diode array detectors. Daicel or Phenomenex columns with chiral stationary phases were employed, and the samples were eluted with mixtures of HPLC-grade hexane and isopropyl alcohol.

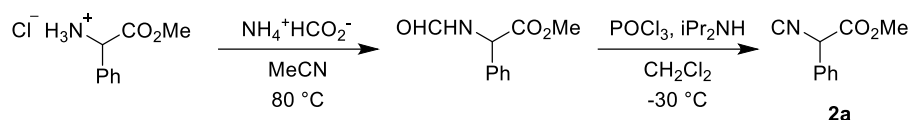
Synthesis of organocatalyst S-I

Catalyst **S-I** is a known compound that was synthesized according to literature procedures.^{175,176}

5.2 Synthesis of isocyanoacetates

Methyl 2-isocyano-2-phenylacetate (2a)³³

A two-step procedure described in the literature was carried out.³³

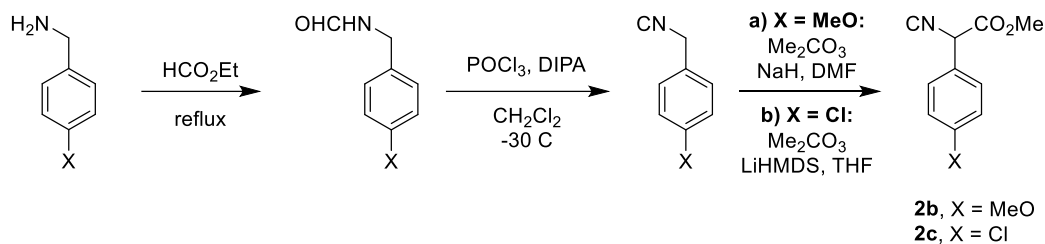


To a suspension of (*S*)-(+)-2-phenylglycine methyl ester hydrochloride (2.0 g, 9.92 mmol) and (*R*)-(-)-2-phenylglycine methyl ester hydrochloride (2.0 g, 9.92 mmol) in acetonitrile (17 mL, 1.1 M) was added ammonium formate (3.2 g, 50 mmol, 2.5 equiv) and the mixture was stirred overnight at 80 °C. After reaction completion (TLC analysis), EtOAc (150 mL) and H₂O (40 mL) were added to the mixture. Phases were separated and the aqueous phase was extracted with EtOAc (3×25 mL). Combined organic phases washed with brine (2×40 mL), dried over Na₂SO₄, and concentrated under reduced pressure to afford crude formamide product as an orange oil, which was used for the next step without further purification.

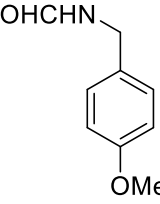
To a solution of crude formamide (3.44 g, 17.8 mmol, 1 equiv) in dichloromethane (60 mL, 0.3 M) was added diisopropylamine (6.8 mL, 48.1 mmol, 2.7 equiv). The mixture was cooled to -30 °C and phosphoryl chloride was added dropwise (1.8 mL, 19.6 mmol, 1.1 equiv). The reaction was stirred at -30 °C until complete consumption of the starting material (TLC, ca. 2 h). The reaction was quenched with saturated aqueous Na₂CO₃ solution (37 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (2×20 mL). The combined organic phases were washed with brine (2×40 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Purification by column chromatography (eluent: hexane:EtOAc 8:2) furnished 2.23 g (64%, over two steps) of the title compound. Light yellow liquid; ¹H NMR (300 MHz, CDCl₃) δ 7.52 – 7.38 (m, 5H), 5.37 (s, 1H), 3.79 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 166.2 (C, C=O), 161.5 (C, NC), 131.9 (C), 129.7 (CH), 129.3 (CH), 126.8 (CH), 60.4 (CH), 53.9 (CH₃).

Synthetic procedure for methyl 2-isocyano-2-(4-methoxyphenyl)acetate and methyl 2-(4-chlorophenyl)-2-isocyanoacetate

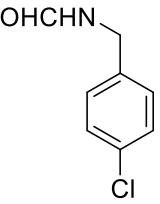
A three-step synthetic procedure was carried out.



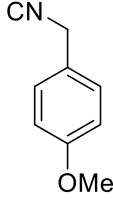
***N*-(4-methoxybenzyl)formamide¹⁷⁷ (representative procedure)**


 A literature procedure was carried out.¹⁷⁷ A mixture of 4-methoxybenzylamine (7.8 mL, 60 mmol, 1.0 equiv) and ethyl formate (25 mL, 309 mmol, 5.0 equiv) was stirred overnight at reflux (oil bath at 60 °C). Hexane (10 mL) was added at room temperature and a white solid precipitated, which was filtered under vacuum and washed with cold hexane to afford 7.56 g (76%) of the title compound as a 84:16 isomeric mixture; ¹H NMR (300 MHz, CDCl₃, for the major isomer) δ 8.19 (s, 1H, CHO), 7.19 (d, *J* = 8.6 Hz, 2H, Ar), 6.85 (d, *J* = 8.6 Hz, 2H, Ar), 6.06 (s, 1H, NH), 4.38 (d, *J* = 5.8 Hz, 2H, CH₂Ar), 3.78 (s, 3H, MeO); ¹³C NMR (75 MHz, CDCl₃, for the major isomer) δ 161.1 (C, CHO), 159.2 (C), 130.2 (C), 129.3 (C), 114.2 (C), 55.4 (CH₃), 41.7 (CH₂).

***N*-(4-chlorobenzyl)formamide¹⁷⁸**

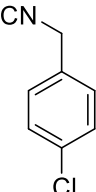

 From 4-chlorobenzylamine (7.3 mL, 60 mmol), 8.91 g (88%) of the title compound were obtained as a 88:12 isomeric mixture. White solid; ¹H NMR (300 MHz, CDCl₃, for the major isomer) δ 8.23 (s, 1H, CHO), 7.35 – 7.26 (m, 2H, Ar), 7.24 – 7.14 (m, 2H, Ar), 6.15 (bs, 1H, NH), 4.42 (d, *J* = 6.1 Hz, 2H, CH₂Ar); ¹³C NMR (75 MHz, CDCl₃, for the major isomer) δ 161.2 (C), 136.3 (C), 133.6 (C), 129.2 (CH), 129.0 (CH), 41.5 (CH₂).

1-(Isocyanomethyl)-4-methoxybenzene¹⁷⁷ (representative procedure)

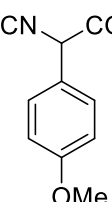

 A modification of a literature procedure was carried out.³³ To a solution of *N*-(4-methoxybenzyl)formamide (3.26 g, 19.8 mmol) in dry DCM, under nitrogen atmosphere, was added diisopropylamine (7.5 mL, 53.5 mmol, 2.7 equiv.) The solution was cooled to -30 °C and POCl₃ (2.0 mL, 21.8 mmol, 1.1 equiv.) was added dropwise. After the reaction had finished (TLC analysis, ca. 1.5 h), it was quenched at -30 °C with an aqueous saturated solution of Na₂CO₃ (35 mL, added portionwise). The mixture was stirred while letting it slowly warm towards room temperature. The mixture was transferred to a separatory funnel, phases were separated, and the aqueous phase was extracted with DCM (2x25 mL). The combined organic phases were washed with brine (2x40 mL) and dried over Na₂SO₄, filtered, and evaporated under reduced pressure at 25 °C. Purification by column

chromatography (eluent: hexane:EtOAc 85:15) yielded 2.71 g (73%) of the title compound. Yellowish liquid; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.26 (d, $J = 8.9$ Hz, 2H), 6.92 (d, $J = 8.7$ Hz, 2H), 4.57 (t, $J = 2.2$ Hz, 2H), 3.82 (s, 3H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 159.8 (C), 157.1 (C, NC), 128.3 (CH), 124.6 (C), 114.5 (CH), 55.5 (CH_3), 45.2 (CH_2).

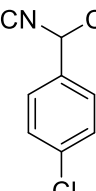
1-Chloro-4-(isocyanomethyl)benzene¹⁷⁸

 From (4-chlorobenzyl)formamide (3.39 g, 20.0 mmol), after purification by column chromatography (eluent: hexane:EtOAc 95:5, 85:15), 2.32 g (76%) of the title compound were obtained. Yellowish liquid; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.38 (d, $J = 8.5$ Hz, 2H, Ar), 7.32 – 7.26 (m, 2H, Ar), 4.62 (s, 2H, CH_2); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 158.3 (C), 134.6 (C), 130.9 (C), 129.3 (CH), 128.1 (CH), 45.1 (CH).

Methyl 2-isocyano-2-(4-methoxyphenyl)acetate (2b)³³

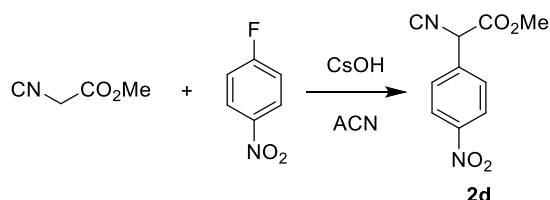
 A modification of a literature procedure was employed.³³ To a solution of 1-(isocyanomethyl)-4-methoxybenzene (2.66 g, 18.1 mmol, 1.0 equiv) in DMF (60 mL, 0.3 M) under nitrogen atmosphere was added NaH (60% dispersion in mineral oil, 1.16 g, 29.0 mmol, 1.6 equiv) portionwise, and dimethylcarbonate (1.83 mL, 21.7 mmol, 1.2 equiv) was added to the resulting mixture. The mixture was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (25 mL) at 0 °C. Water (100 mL) was added and the mixture was extracted with Et_2O (3×150 mL). The organic phase was washed with brine (3×100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (eluent: hexane:EtOAc 9:1) afforded 506 mg (14%) of the title compound as a light yellow liquid. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.38 (d, $J = 8.5$ Hz, 2H, Ar), 6.93 (d, $J = 8.8$ Hz, 2H, Ar), 5.30 (s, 1H, CHAr), 3.82 (s, 3H, MeO), 3.78 (s, 3H, MeO); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 166.5 (C), 161.1 (C), 160.6 (C), 128.2 (CH), 124.0 (C), 114.7 (CH), 59.8 (CH), 55.5 (CH_3), 53.8 (CH_3).

Methyl 2-(4-chlorophenyl)-2-isocyanoacetate (2c)¹⁷⁹

 A modification of a literature procedure was performed.³³ To a solution of 1-chloro-4-(isocyanomethyl)benzene (2.22 g, 14.6 mmol, 1.0 equiv) in THF (50 mL, 0.3 M) under nitrogen atmosphere was added dropwise LiHMDS (17.5 mL, 17.5 mmol, 1.2 equiv, 1.0 M sol. in THF) at -78 °C. After 5 min of stirring, dimethylcarbonate (1.5 mL, 17.5 mmol, 1.2 equiv) was added dropwise at -78 °C, and the reaction was stirred at that temperature for 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution (15 mL) and extracted with EtOAc (3×100 mL). Combined organic

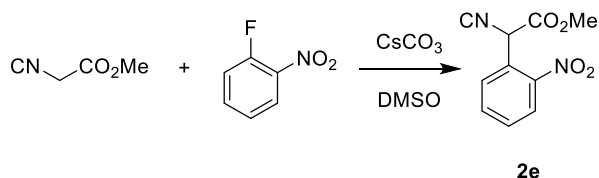
phases were washed with brine (40 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Purification by column chromatography (eluent: hexane:EtOAc 95:5) yielded 477 mg (16%) of the title compound. Light yellow liquid; ¹H NMR (300 MHz, CDCl₃) δ 7.45 – 7.37 (m, 4H), 5.35 (s, 1H), 3.80 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 165.8 (C, C=O), 162.2 (C, NC), 135.9 (C), 130.3 (C), 129.6 (CH), 128.2 (CH), 59.7 (CH), 54.1 (MeO).

Methyl 2-isocyano-2-(4-nitrophenyl)acetate (**2d**)¹⁸⁰



A modification of a literature procedure was carried out.¹⁸⁰ To a solution of methyl isocyanoacetate (0.45 mL, 5.0 mmol, 1.0 equiv) in acetonitrile (5 mL, 1M) under nitrogen atmosphere was added CsOH·x H₂O (15-20% H₂O) (1.20 g, 8.0 mmol, 1.6 equiv) and 1-fluoro-4-nitrobenzene (0.58 mL, 5.5 mmol, 1.1 equiv). The reaction mixture was stirred overnight. EtOAc (150 mL) was added and the mixture was washed with 0.1 M HCl (80 mL, 1.6 equiv), the organic phase changed color from purple to orange. The phases were separated and the aqueous phase was extracted with EtOAc (3×50 mL). The combined organic phases were dried over Na₂SO₄, concentrated under reduced pressure and purified by column chromatography (eluent: hexane:EtOAc 8:2) to afford 293 g (27%) of the title compound. Light yellow solid; ¹H NMR (300 MHz, CDCl₃) δ 8.31 (d, *J* = 8.9 Hz, 2H, Ar), 7.70 (d, *J* = 8.5 Hz, 2H, Ar), 5.51 (s, 1H, CHAr), 3.83 (s, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 165.0 (C, C=O), 163.7 (C, NC), 148.2 (C), 138.1 (C), 128.0 (CH), 124.5 (CH), 54.4 (CH₃), 53.5 (CH).

Methyl 2-isocyano-2-(2-nitrophenyl)acetate (**2e**)³³

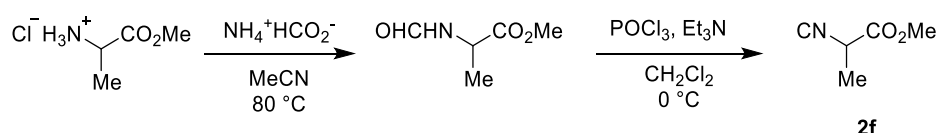


A literature procedure was carried out.³³ To a solution of CsCO₃ (2.26 g, 6.94 mmol) in DMSO (32.5 mL), under nitrogen atmosphere was added methyl isocyanoacetate (0.50 mL, 4.63 mmol). The reaction was stirred for 10 min and 1-fluoro-2-nitrobenzene (0.49 mL, 4.63 mmol) was added. The reaction was stirred overnight and 40 mL of water were added. The mixture was extracted with EtOAc (4×60 mL) and the combined organic phases were washed with brine

(3x60 mL). The organic phase was dried over MgSO_4 , concentrated under reduced pressure and purified by column chromatography (eluent: hexane:EtOAc 9:1, 8:2) to afford 0.31 g (30%) of the title compound as a yellow oil. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.20 (dd, $J = 8.2$, 1.3 Hz, 1H, Ar), 7.91 – 7.75 (m, 2H, Ar), 7.65 (ddd, $J = 8.1$, 7.1, 1.6 Hz, 1H, Ar), 6.39 (s, 1H, CHAr), 3.84 (s, 3H, CH_3).

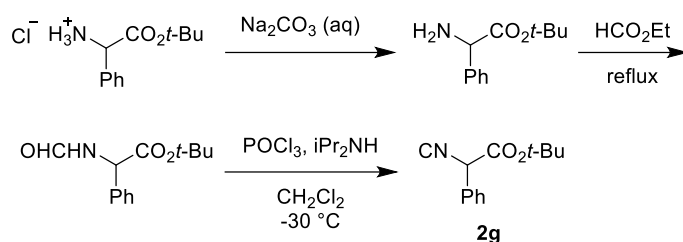
Methyl 2-isocyanopropanoate (2f)¹⁸¹

A modification of a two-step procedure described in the literature was carried out.^{33,177}



To a suspension of D-alanine (2.08 g, 14.9 mmol) and L-alanine (2.08, 14.9 mmol) in acetonitrile (28 mL) was added ammonium formate (2.54 g, 40.2 mmol) and the mixture was stirred overnight at 80 °C. After reaction completion (TLC analysis), EtOAc (250 mL) and H_2O (60 mL) were added to the mixture. Phases were separated and the aqueous phase was extracted with EtOAc (3x25 mL). Combined organic phases washed with brine (2x30 mL), dried over Na_2SO_4 , and concentrated under reduced pressure to afford crude formamide product as an orange oil, which was used for the next step without further purification.

To a solution of crude formamide (1.3 g, 9.9 mmol, 1 equiv) in dichloromethane (30 mL, 0.3 M) was added triethylamine (3.3 mL, 23.8 mmol, 2.4 equiv). The mixture was cooled to -30 °C and phosphoryl chloride was added dropwise (1.0 mL, 10.9 mmol, 1.1 equiv). The reaction was stirred at -30 °C until complete consumption of the starting material (TLC, ca. 2 h). The reaction was quenched with saturated aqueous Na_2CO_3 solution (20 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (2x10 mL). The combined organic phases were washed with brine (2x20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (eluent: pentane:Et₂O 7:3) furnished 0.61 g (18%, over two steps) of the title compound as a grayish liquid. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 4.34 (q, $J = 7.2$ Hz, 1H, CHMe), 3.83 (s, 3H, CO_2Me), 1.66 (d, $J = 7.2$ Hz, 3H, Me).

Synthetic procedure for *tert*-butyl 2-isocyano-2-phenylacetate***tert*-Butyl 2-formamido-2-phenylacetate³⁷**

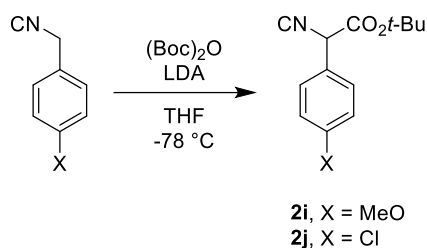
$\text{HOCHNCH}(\text{Ph})\text{CO}_2t\text{-Bu}$ A modification of a literature procedure was carried out.³⁷ A solution of (*R*)-*tert*-butyl 2-amino-2-phenylacetate hydrochloride (2.0 g, 8.21 mmol) and (*S*)-*tert*-butyl 2-amino-2-phenylacetate hydrochloride (2.0 g, 8.21 mmol) in 300 mL H₂O was adjusted to pH 9 with a sat. aq. solution of Na₂CO₃ (ca. 35 mL, a white precipitate appeared while it was added). The mixture was extracted with EtOAc (3x150 mL). The combined organic phases were washed with MgSO₄ and concentrated under reduced pressure to give rise to a yellowish liquid which was dissolved in ethyl formate (50 mL) and stirred overnight at reflux (oil bath at 60 °C). The solvent was evaporated to give rise to 3.87 g (99%) of the title compound as a 94:6 isomeric mixture. White solid; ¹H NMR (300 MHz, CDCl₃, for the major isomer) δ 8.22 (t, *J* = 1.2 Hz, 1H, CHO), 7.39 – 7.28 (m, 5H, Ar), 6.74 (s, 1H, NH), 5.55 (dd, *J* = 7.5, 1.0 Hz, 1H, CHAr), 1.39 (s, 9H, tBu); ¹³C NMR (75 MHz, CDCl₃, for the major isomer) δ 169.7 (C), 160.2 (C), 136.9 (C), 129.0 (CH), 128.4 (CH), 127.1 (CH), 83.1 (C), 55.6 (CH), 27.9 (CH₃).

***tert*-Butyl 2-isocyano-2-phenylacetate (2g)³⁷**

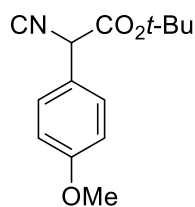
$\text{CNCH}(\text{Ph})\text{CO}_2t\text{-Bu}$ A modification of a literature procedure was carried out.³³ To a solution of crude formamide (3.82 g, 16.2 mmol, 1 equiv) in dichloromethane (54 mL, 0.3 M) was added diisopropylamine (6.1 mL, 43.7 mmol, 2.7 equiv). The mixture was cooled to -30 °C and phosphoryl chloride was added dropwise (1.7 mL, 17.8 mmol, 1.1 equiv). The reaction was stirred at -30 °C until complete consumption of the starting material (TLC, ca. 2 h). The reaction was quenched with saturated aqueous Na₂CO₃ solution (30 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (2x20 mL). The combined organic phases were washed with brine (2x35 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Purification by column chromatography (eluent: hexane:EtOAc 95:5) furnished 2.54 g (72%, over two steps) of the title compound. Yellow liquid; ¹H NMR (300 MHz, CDCl₃) δ 7.50 – 7.36 (m, 5H, Ar), 5.23 (s, 1H, CHAr), 1.42 (s, 9H, tBu); ¹³C NMR

(75 MHz, CDCl₃) δ 164.6 (C), 160.8 (C), 132.5 (C), 129.4 (CH), 129.2 (CH), 126.7 (CH), 84.4 (C), 61.3 (CH), 27.8 (CH₃).

Synthetic procedure for *tert*-butyl 2-isocyano-2-(4-methoxyphenyl)acetate and *tert*-butyl 2-(4-chlorophenyl)-2-isocyanoacetate

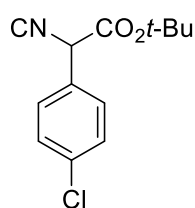


***tert*-butyl 2-isocyano-2-(4-methoxyphenyl)acetate (**2i**)³⁷ (representative procedure)**



A modification of a literature procedure was carried out.³⁷ To a solution of LDA (2 M in THF/heptane/ethylbenzene, 20 mL, 38.3 mmol, 2.5 equiv.) cooled at -78 °C, under nitrogen atmosphere, was added dropwise a solution of 1-(isocyanomethyl)-4-methoxybenzene (2.62 g, 17.8 mmol, 1.0 equiv.) in THF (20 mL). The mixture was allowed to stir at -78 °C for 30 min, and then at room temperature for an additional 30 min. The solution was then cooled down again to -78 °C and a solution of di-*tert*-butyl dicarbonate (4.66 g, 21.4 mmol, 1.2 equiv.) in THF (20 mL) was added dropwise. The mixture was stirred until reaction completion (ca. 1h, TLC analysis). The reaction mixture was quenched with a saturated NH₄Cl aqueous solution (35 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3x80 mL). The combined organic phases were washed with brine (2x25 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure at 25 °C. Purification by column chromatography eluting with hexane:EtOAc 9:1 afforded 2.84 g (64%) of the target compound. Off-white solid; ¹H NMR (300 MHz, CDCl₃) δ 7.36 (d, *J* = 8.4 Hz, 2H, Ar), 6.92 (d, *J* = 8.8 Hz, 2H, Ar), 5.16 (s, 1H, CHAr), 3.82 (s, 3H, OMe), 1.42 (s, 9H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 164.9 (C), 160.4 (C), 128.0 (CH), 124.6 (C), 114.5 (CH), 84.2 (C), 60.7 (CH), 55.5 (CH), 27.8 (CH₃).

***tert*-Butyl 2-(4-chlorophenyl)-2-isocyanoacetate (**2j**)**



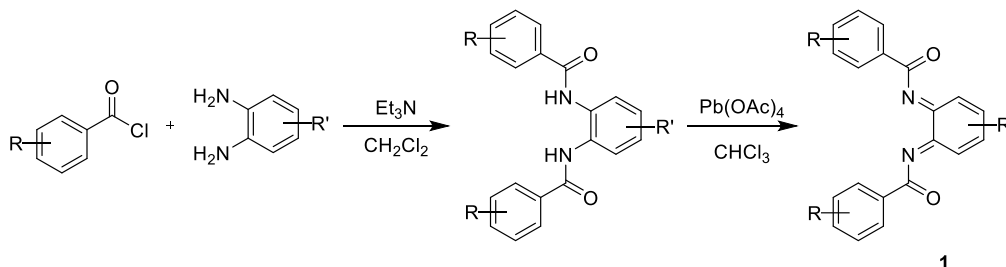
From 1-chloro-4-(isocyanomethyl)benzene (2.32 g, 15.3 mmol), after purification by column chromatography eluting with hexane:EtOAc 95:5, 3.08 g (80%) of the target compound were obtained. Orange liquid; ¹H NMR (300 MHz, CDCl₃) δ 7.40 (s, 4H, Ar), 5.21 (s, 1H, CHAr), 1.42 (s, 9H, tBu); ¹³C NMR (75 MHz, CDCl₃) δ 164.1 (C), 161.4 (C), 135.6 (C), 131.0 (C), 129.4 (CH), 128.1 (CH),

84.7 (C), 28.8 (CH), 27.8 (CH₃); **HRMS** (ESI) m/z : 269.1045 [M+NH₄]⁺, C₁₃H₁₈ClN₂O₂⁺ requires 269.1051.

5.3 α -Arylation of isocyanoacetate esters

5.3.1 Synthesis and characterization data for *o*-quinone diimides **1**

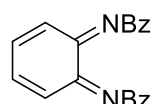
A modification of a two-step procedure described in the literature was employed.⁹⁵



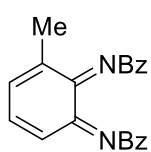
Step 1: A solution of benzoyl chloride (2.81 g, 2.32 mL, 20 mmol, 2.0 equiv) in CH_2Cl_2 (50 mL, 0.4 M) was added to an ice-cooled solution of 1,2-phenylenediamine derivative (10 mmol, 1 equiv) and triethylamine (2.53 g, 3.5 mL, 25 mmol, 2.5 equiv) in CH_2Cl_2 (50 mL, 0.2 M). The reaction was allowed to warm to room temperature and it was stirred at rt until consumption of diamine (TLC). Once completed, the white solid product was collected by filtration, washed with a small amount of CH_2Cl_2 (15 mL) and no further purification was needed.

Step 2: $\text{Pb}(\text{OAc})_4$ (3.10 g, 7 mmol, 1.4 equiv) was added at 0 °C in portions to a suspension of *N,N'*-(1,2-phenylene)dibenzamide derivative (5 mmol, 1 equiv) in CHCl_3 (100 mL, 0.05 M). The mixture was stirred at 40 °C until completion of the reaction (TLC analysis). The suspension was then filtered over celite and washed with 50 mL of CHCl_3 . The filtrate and washings were placed in a separatory funnel and washed with 50 mL of 5% aqueous NaHCO_3 and then with 50 mL of water. The organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure to afford the crude product. Recrystallization from hexane/diethyl ether gave pure compounds **1**.

N,N'-(Cyclohexa-3,5-diene-1,2-diylidene)dibenzamide (**1a**)⁹⁶

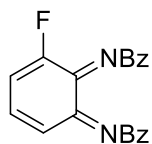


1.07 g (68%) of **1a** were obtained from 1.6 g of *N,N'*-(1,2-phenylene)dibenzamide. Brown solid; m.p. 123.9-124.9 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.72 (d, J = 7.1 Hz, 1H), 7.59 – 7.48 (m, 2H), 7.38 (m, 4H), 6.78 (m, 2H), 6.57 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 180.0 (C), 134.4 (CH), 133.4 (CH), 132.0 (C), 129.0 (CH), 128.7 (CH).

***N,N'*-(3-Methylcyclohexa-3,5-diene-1,2-diylidene)dibenzamide (1b)**

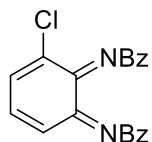
1.1 g (67%) of **1b** were obtained from 1.7 g of *N,N'*-(3-methyl-1,2-phenylene)dibenzamide.

Orange solid; m.p. 125-127 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.80 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.60 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.56 – 7.44 (m, 2H), 7.42 – 7.31 (m, 4H), 6.72 – 6.57 (m, 2H), 6.26 (m, 1H), 2.25 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 180.2 (C), 179.2 (C), 154.6 (C), 150.9 (C), 139.5 (C), 136.0 (CH), 133.8 (CH), 132.6 (CH), 132.18 (C), 132.15 (C), 131.2 (CH), 129.6 (CH), 128.64 (CH), 128.57 (CH), 128.2 (CH), 121.0 (CH), 18.0 (CH₃); HRMS (ESI) *m/z*: 329.1290 [M+H]⁺, C₂₁H₁₇N₂O₂⁺ requires 329.1285.

***N,N'*-(3-Fluorocyclohexa-3,5-diene-1,2-diylidene)dibenzamide (12c)**

1.31 g (79%) of **1c** were obtained from 1.67 g of *N,N'*-(3-fluoro-1,2-phenylene)dibenzamide.

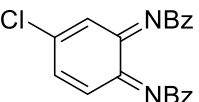
Brown solid; m.p. 72.8-73.5 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.78 (d, *J* = 7.3 Hz, Ar, 2H), 7.68 – 7.61 (m, 2H), 7.59 – 7.50 (m, 3H), 7.44 – 7.35 (m, 3H), 6.69 (ddd, *J* = 9.9, 7.1, 5.9 Hz, 1H), 6.47 (ddd, *J* = 9.3, 7.1, 1.0 Hz, 1H), 6.30 (d, *J* = 9.9 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 179.3 (C), 179.0 (C), 134.0 (CH), 133.4 (CH), 131.9 (C), 131.6 (C), 129.5 (CH), 128.9 (CH), 128.9 (CH), 128.7 (CH), 113.6 (d, ²*J*_{C-F} = 20.3 Hz, CH); ¹⁹F NMR (282 MHz, CDCl₃) δ -123.4; HRMS (ESI) *m/z*: 333.1033 [M+H]⁺, C₂₀H₁₄FN₂O₂⁺ requires 333.1034.

***N,N'*-(3-Chlorocyclohexa-3,5-diene-1,2-diylidene)dibenzamide (1d)**

1.44 g (82%) of **1d** were obtained from 1.8 g of *N,N'*-(3-chloro-1,2-phenylene)dibenzamide.

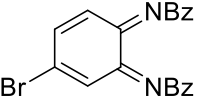
Orange solid; m.p. 139-141 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.81 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.60 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.58 – 7.49 (m, 2H), 7.44 – 7.34 (m, 4H), 7.03 (dd, *J* = 6.8, 1.0 Hz, 1H), 6.66 (dd, *J* = 9.8, 6.8 Hz, 1H), 6.31 (dd, *J* = 9.8, 1.0 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 179.3 (C), 178.6 (C), 150.5 (C), 150.2 (C), 134.9 (C), 134.2 (CH), 134.1 (CH), 133.1 (CH), 132.0 (CH), 131.8 (C), 131.7 (C), 129.6 (CH), 128.8 (CH), 128.7 (CH), 128.3 (CH), 122.3 (CH); HRMS (ESI) *m/z*: 349.0748 [M+H]⁺, C₂₀H₁₄ClN₂O₂⁺ requires 349.0738.

***N,N'*-(4-Chlorocyclohexa-3,5-diene-1,2-diylidene)dibenzamide (1e)⁹⁶**

 1.32 g (75%) of **1e** were obtained from 1.8 g of *N,N'*-(4-chloro-1,2-phenylene)dibenzamide.

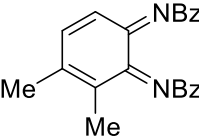
¹H NMR (300 MHz, CDCl₃) δ 7.75–7.62 (m, 4H), 7.54 (t, J = 7.4 Hz, 2H), 7.45 – 7.33 (m, 4H), 6.75 (dd, J = 10.1, 2.0 Hz, 1H), 6.68 (d, J = 10.0 Hz, 1H), 6.67 (s, 1H); **¹³C NMR** (75 MHz, CDCl₃) δ 179.3 (C), 179.0 (C), 136.4 (CH), 133.7 (CH), 133.5 (CH), 131.9 (C), 131.6 (C), 129.2 (CH), 128.8 (CH), 128.7 (CH); **HRMS** (ESI) m/z : 349.0742 [M+H]⁺, C₂₀H₁₄ClN₂O₂⁺ requires 349.0738.

***N,N'*-(4-Bromocyclohexa-3,5-diene-1,2-diylidene)dibenzamide (1f)**

 1.21 g (87%) of **1f** were obtained from 1.4 g of *N,N'*-(4-bromo-1,2-phenylene)dibenzamide.

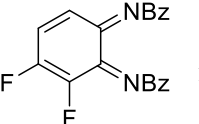
Brown solid; m.p. 71.7–72.5 °C; **¹H NMR** (300 MHz, CDCl₃) δ 7.75 – 7.64 (m, 4H), 7.59 – 7.49 (m, 3H), 7.45 – 7.31 (m, 4H), 6.90 – 6.83 (m, 1H), 6.57 (d, J = 10.1 Hz, 1H); **¹³C NMR** (75 MHz, CDCl₃) δ 179.4 (C), 179.2 (C), 138.5 (CH), 133.9 (CH), 133.6 (CH), 131.9 (C), 131.8 (C), 129.4 (CH), 129.0 (CH), 128.9 (CH); **HRMS** (ESI) m/z : 393.0229 [M+H]⁺, C₂₀H₁₄BrN₂O₂⁺ requires 393.0233.

***N,N'*-(3,4-Dimethylcyclohexa-3,5-diene-1,2-diylidene)dibenzamide (1g)**

 0.47 g (70%) of **1g** were obtained from 0.67 g of *N,N'*-(3,4-dimethyl-1,2-phenylene)dibenzamide.

Brown oil; this compound was highly unstable and was just characterized by **¹H NMR** (300 MHz, CDCl₃) δ 7.82 – 7.77 (m, 2H), 7.64 – 7.56 (m, 2H), 7.55 – 7.45 (m, 2H), 7.41 – 7.31 (m, 4H), 2.21 (s, 3H), 2.12 (s, 3H).

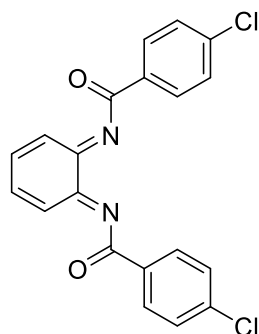
***N,N'*-(3,4-difluorocyclohexa-3,5-diene-1,2-diylidene)dibenzamide (1h)**

 1.2 g (67%) of **1h** were obtained from 1.8 g of *N,N'*-(3,4-difluoro-1,2-phenylene)dibenzamide.

Orange solid; **¹H NMR** (300 MHz, CDCl₃) δ 8.02 – 7.88 (m, 1H), 7.81 – 7.70 (m, 2H), 7.69 – 7.60 (m, 2H), 7.59 – 7.50 (m, 2H), 7.45 – 7.33 (m, 3H), 6.76 (ddd, J = 10.6, 8.7, 7.8 Hz, 1H), 6.50 – 6.33 (m, 1H); **¹³C NMR** (75 MHz, CDCl₃) δ 178.9 (C), 178.6 (C), 167.0 (C), 166.2 (C), 134.2 (CH), 133.6 (CH), 133.0 (CH), 132.4 (CH), 131.6 (C), 129.4 (CH), 129.1 (CH), 129.0 (CH), 128.9 (CH), 128.8 (CH), 127.8 (CH), 127.6 (CH); **¹⁹F NMR** (282

MHz, CDCl₃) δ -139.94 (d, J = 21.4 Hz), -144.15 (d, J = 21.2 Hz); **HRMS** (ESI) m/z : 351.0940 [M+H]⁺, C₂₀H₁₂F₂N₂O₂⁺ requires 351.0943.

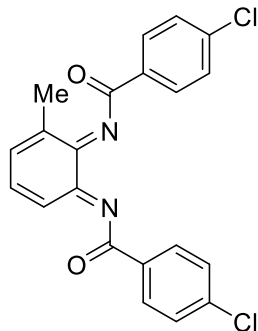
***N,N'*-(Cyclohexa-3,5-diene-1,2-diylidene)bis(4-chlorobenzamide) (1i)**



1.32 g (69%) of **1i** were obtained from 1.9 g of *N,N'*-(1,2-phenylene)bis(4-chlorobenzamide).

Orange solid; m.p. 135-137 °C; **¹H NMR** (300 MHz, CDCl₃) δ 7.66 (d, J = 8.6 Hz, 4H), 7.37 (d, J = 8.6 Hz, 4H), 6.81 (dd, J = 7.7, 3.3 Hz, 2H), 6.54 (dd, J = 7.7, 3.3 Hz, 2H); **¹³C NMR** (75 MHz, CDCl₃) δ 178.4 (C), 152.7 (C), 140.0 (C), 134.9 (CH), 130.3 (CH), 129.1 (CH); **HRMS** (ESI) m/z : 383.0355 [M+H]⁺, C₂₀H₁₃Cl₂N₂O₂⁺ requires 383.0349.

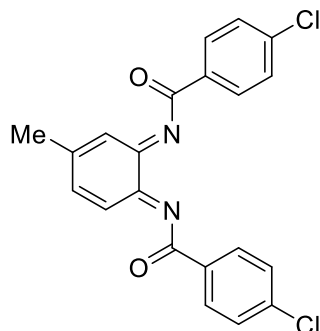
***N,N'*-(3-Methylcyclohexa-3,5-diene-1,2-diylidene)bis(4-chlorobenzamide) (1j)**



1.5 g (75%) of **1j** were obtained from 2.0 g of *N,N'*-(3-methyl-1,2-phenylene)bis(4-chlorobenzamide).

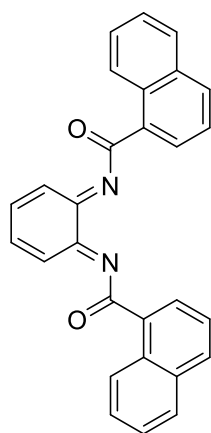
Orange solid; m.p. 136-138 °C; **¹H NMR** (300 MHz, CDCl₃) δ 7.71 (d, J = 8.7 Hz, 2H), 7.57 (d, J = 8.7 Hz, 2H), 7.37 (d, J = 5.7 Hz, 2H), 7.35 (d, J = 5.7 Hz, 2H), 6.71 – 6.62 (m, 2H), 6.22 – 6.11 (m, 1H), 2.23 (s, 3H); **¹³C NMR** (75 MHz, CDCl₃) δ 179.2 (C), 177.9 (C), 155.1 (C), 151.3 (C), 140.5 (C), 139.5 (C), 139.0 (C), 136.5 (CH), 131.5 (CH), 131.0 (CH), 130.6 (C), 130.5 (CH), 129.5 (CH), 129.1 (CH), 129.0 (CH), 120.9 (CH), 17.9 (CH₃); **HRMS** (ESI) m/z : 397.0507 [M+H]⁺, C₂₁H₁₅Cl₂N₂O₂⁺ requires 397.0505.

***N,N'*-(4-Methylcyclohexa-3,5-diene-1,2-diylidene)bis(4-chlorobenzamide) (1k)**



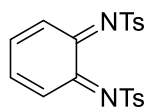
1.46 g (73%) of **1k** were obtained from 2.0 g of *N,N'*-(3-methyl-1,2-phenylene)bis(4-chlorobenzamide).

Orange solid; m.p. 196-198 °C; **¹H NMR** (300 MHz, CDCl₃) δ 7.68 (d, J = 8.7 Hz, 2H), 7.64 (d, J = 8.7 Hz, 2H), 7.40 – 7.34 (m, 4H), 6.68 (1H, dd, J = 9.8, 1.8 Hz, 1H), 6.60 (d, J = 9.9 Hz, 1H), 6.28 (bs, 1H), 2.09 (d, J = 1.8 Hz, 3H); **¹³C NMR** (75 MHz, CDCl₃) δ 178.7 (C), 178.5 (C), 140.0 (C), 139.7 (C), 138.5 (CH), 130.7 (C), 130.6 (CH), 130.5 (C), 130.1 (CH), 129.1 (CH), 22.3 (CH₃); **HRMS** (ESI) m/z : 397.0508 [M+H]⁺, C₂₁H₁₅Cl₂N₂O₂⁺ requires 397.0505.

***N,N'*-(Cyclohexa-3,5-diene-1,2-diylidene)bis(1-naphthamide) (1l)**

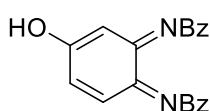
1.77 g (84%) of **1l** were obtained from 2.2 g of *N,N'*-(1,2-phenylene)bis(1-naphthamide).

Orange solid; m.p. 140-142 °C; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.96 (dd, J = 6.3, 3.6 Hz, 2H), 7.96 (d, J = 8.3 Hz, 2H), 7.79 (dd, J = 6.3, 3.6 Hz, 2H), 7.65 (d, J = 6.8 Hz, 2H), 7.40 (dd, J = 6.4, 3.4 Hz, 4H), 7.33 (t, J = 7.8 Hz, 2H), 6.75 (dd, J = 7.7, 3.4 Hz, 2H), 6.61 (d, J = 7.7 Hz, 2H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 181.1 (C), 151.2 (C), 134.3 (CH), 133.9 (CH), 133.8 (C), 131.1 (C), 130.5 (C), 128.4 (CH), 128.1 (CH), 126.3 (CH), 125.8 (CH), 124.2 (CH); **HRMS** (ESI) m/z : 415.1441 $[\text{M}+\text{H}]^+$, $\text{C}_{28}\text{H}_{19}\text{N}_2\text{O}_2^+$ requires 415.1441.

***N,N'*-(Cyclohexa-3,5-diene-1,2-diylidene)bis(4-methylbenzenesulfonamide) (1m)**

1.57 g (76%) of **1m** were obtained from 2.1 g of *N,N'*-(1,2-phenylene)bis(4-methylbenzenesulfonamide).⁴

Brown solid; m.p. 94-95 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.61 – 7.53 (m, 4H), 7.24 – 7.16 (m, 4H), 7.04 – 6.92 (m, 4H), 2.37 (s, 6H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 144.3 (C), 135.6 (C), 130.9 (C), 129.8 (CH), 127.7 (CH), 127.4 (CH), 126.1 (CH), 21.7 (CH_3); **HRMS** (ESI) m/z : (ESI) m/z : 417.0940 $[\text{M}+\text{H}_2+\text{H}]^+$, $\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_4\text{S}_2^+$ requires 417.0937.

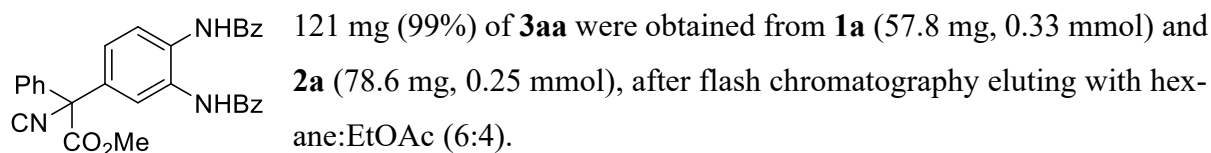
***N,N'*-(4-Hydroxycyclohexa-3,5-diene-1,2-diylidene)dibenzamide (1n)**

1.29 g (77%) of **1n** were obtained from 1.7 g of *N,N'*-(4-hydroxy-1,2-phenylene)dibenzamide.

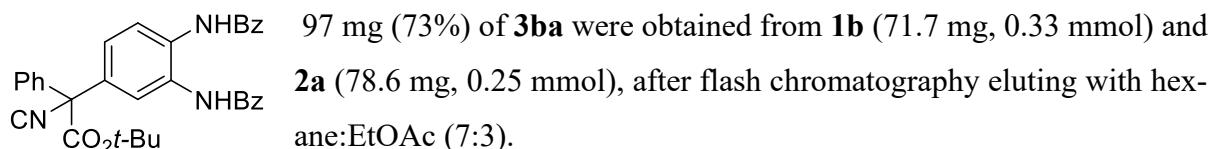
White solid; m.p. 169-171 °C; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 9.32 (bs, 1H), 7.94 – 7.87 (4H, m, 4H), 7.86 (d, J = 2.1 Hz, 1H), 7.67 (t, J = 7.4 Hz, 1H), 7.60 (t, J = 7.3 Hz, 1H), 7.56 – 7.45 (m, 4H), 6.84 (d, J = 10.1 Hz, 1H), 6.51 (dd, J = 10.1, 2.1 Hz, 1H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 187.0 (C), 178.9 (C), 165.5 (C), 153.4 (C), 140.0 (C), 135.4 (CH), 134.7 (CH), 133.3 (C), 132.9 (CH), 131.3 (C), 129.6 (CH), 129.11 (CH), 129.07 (CH), 127.9 (CH), 127.2 (CH), 115.4 (CH); **HRMS** (ESI) m/z : 331.1081 $[\text{M}+\text{H}]^+$, $\text{C}_{20}\text{H}_{15}\text{N}_2\text{O}_3^+$ requires 331.1077.

5.3.2 Synthesis and characterization data for compounds 3

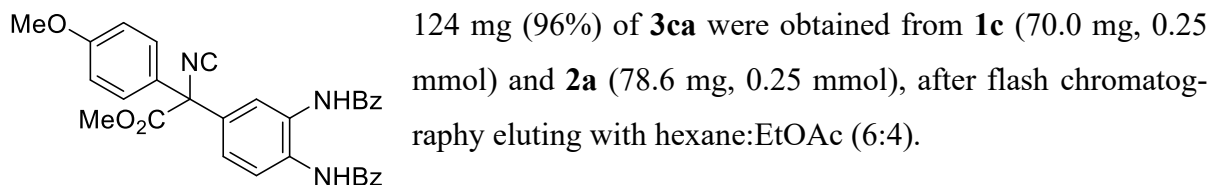
α -Substituted isocyanoacetate **2** (0.33 mmol, 1.3 equiv) was added to a solution of *o*-benzoquinone diimide **1** (0.25 mmol, 1.0 equiv) and silver oxide (3 mg, 0.0125 mmol, 0.05 equiv) in CH_2Cl_2 (3 mL). The mixture was stirred at rt until consumption of diimine **1** (TLC). Then, the reaction mixture was purified by flash column chromatography.

Methyl 2-(3,4-bis(benzamido)phenyl)-2-isocyano-2-phenylacetate (3aa)

Brown solid; m.p. 102-105 °C; ^1H NMR (300 MHz, CDCl_3) δ 9.48 (bs, 1H), 9.33 (bs, 1H), 8.00 – 7.92 (m, 4H), 7.65 (d, J = 8.6 Hz, 1H), 7.60 (d, J = 2.3 Hz, 1H), 7.51 (dd, J = 7.2, 1.6 Hz, 2H), 7.44 (td, J = 7.2, 1.6 Hz, 4H), 7.31 – 7.23 (m, 3H), 7.19 (dd, J = 8.2, 1.6 Hz, 2H), 7.09 (dd, J = 8.6, 2.3 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 167.3 (C), 166.8 (C), 166.5 (C), 161.9 (C), 136.7 (C), 134.0 (C), 133.3 (C), 133.1 (C), 132.3 (CH), 132.2 (CH), 131.9 (C), 130.6 (C), 129.1 (CH), 128.72 (CH), 128.67 (CH), 127.7 (CH), 127.6 (CH), 126.9 (CH), 126.0 (CH), 125.4 (CH), 124.2 (CH), 73.2 (C), 54.2 (CH_3); HRMS (ESI) m/z : 490.1757 $[\text{M}+\text{H}]^+$, $\text{C}_{30}\text{H}_{24}\text{N}_3\text{O}_4^+$ requires 490.1761.

***tert*-Butyl 2-(3,4-bis(benzamido)phenyl)-2-isocyano-2-phenylacetate (3ba)**

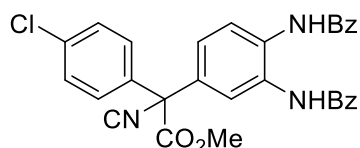
Pink solid; m.p. 125-127 °C; ^1H NMR (300 MHz, CDCl_3) δ 9.38 (bs, 1H), 8.98 (bs, 1H), 7.97 – 7.93 (m, 4H), 7.74 (d, J = 8.6 Hz, 1H), 7.59 (d, J = 2.3 Hz, 1H), 7.55 – 7.41 (m, 6H), 7.34 – 7.27 (m, 4H), 7.31 (dd, J = 8.4, 2.1 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 166.8 (C), 166.3 (C), 165.5 (C), 161.1 (C), 137.3 (C), 134.6 (C), 133.5 (C), 133.2 (C), 132.4 (CH), 132.2 (CH), 131.9 (C), 130.3 (C), 128.9 (CH), 128.80 (CH), 128.76 (CH), 128.6 (CH), 127.6 (CH), 127.5 (CH), 127.0 (CH), 125.8 (CH), 125.6 (CH), 124.3 (CH), 85.2 (C), 73.7 (C), 27.6 (CH_3); HRMS (ESI) m/z : 549.2496 $[\text{M}+\text{NH}_4]^+$, $\text{C}_{33}\text{H}_{33}\text{N}_4\text{O}_4^+$ requires 549.2496.

Methyl 2-(3,4-bis(benzamido)phenyl)-2-isocyano-2-(4-methoxyphenyl)acetate (3ca)

Orange oil; ^1H NMR (300 MHz, CDCl_3) δ 9.48 (bs, 1H), 9.31 (bs, 1H), 8.02 – 7.89 (m, 5H), 7.66 (d, J = 8.7 Hz, 1H), 7.58 (d, J = 2.3 Hz, 1H), 7.55 – 7.39 (m, 6H), 7.14 – 7.03 (m, 3H), 6.74 (d, J = 8.9 Hz, 1H), 3.77 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 167.7 (C), 167.0 (C), 166.6 (C), 161.6 (C), 160.0 (C), 134.4 (C), 133.5 (C), 133.2 (C), 132.5 (CH), 132.4 (CH), 132.1 (C), 130.7 (C), 129.0 (C), 128.9 (CH), 128.5 (CH), 127.8 (CH), 127.7 (CH), 126.1

(CH), 125.5 (CH), 124.3 (CH), 114.1 (CH), 72.9 (C), 55.4 (CH₃), 54.3 (CH₃); **HRMS** (ESI) m/z : 537.2074 [M+NH₄]⁺, C₃₁H₂₉N₄O₅⁺ requires 537.2132.

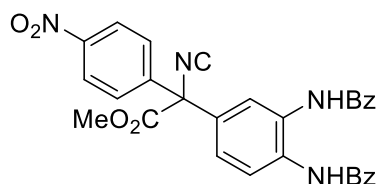
Methyl 2-(3,4-bis(benzamido)phenyl)-2-(4-chlorophenyl)-2-isocyanoacetate (3da)



97 mg (74%) of **3da** were obtained from **1d** (69.2 mg, 0.33 mmol) and **2a** (78.6 mg, 0.25 mmol), after flash chromatography eluting with DCM:EtOAc (95:5).

Yellow solid; m.p. 145-147 °C; **¹H NMR** (300 MHz, DMSO-*d*₆) δ 10.22 (bs, 1H), 10.11 (bs, 1H), 7.98 – 7.91 (m, 4H), 7.83 (d, J = 8.6 Hz, 1H), 7.73 (d, J = 2.4 Hz, 1H), 7.63 – 7.48 (m, 8H), 7.44 (d, J = 8.7 Hz, 2H), 7.28 (dd, J = 8.6, 2.5 Hz, 1H), 3.91 (s, 3H); **¹³C NMR** (75 MHz, DMSO-*d*₆) δ 166.8 (C), 165.8 (C), 165.5 (C), 161.8 (C), 135.6 (C), 134.3 (C), 134.1 (C), 133.9 (C), 133.2 (C), 132.2 (C), 132.0 (CH), 131.5 (C), 129.1 (CH), 129.0 (CH), 128.62 (CH), 128.55 (CH), 127.7 (CH), 127.6 (CH), 126.4 (CH), 123.9 (CH), 72.8 (C), 54.9 (CH₃); **HRMS** (ESI) m/z : 524.1378 [M+H]⁺, C₃₀H₂₃ClN₃O₄⁺ requires 524.1372.

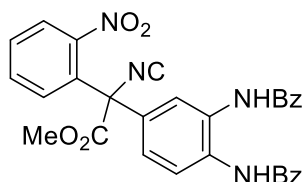
Methyl 2-(3,4-bis(benzamido)phenyl)-2-isocyano-2-(4-nitrophenyl)acetate (3ea)



99 mg (74%) of **3ea** were obtained from **1e** (72.6 mg, 0.33 mmol) and **2a** (78.6 mg, 0.25 mmol), after flash chromatography eluting with hexane:EtOAc (7:3).

White solid; m.p. 186.3-187.7 °C; **¹H NMR** (300 MHz, DMSO) δ 10.20 (bs, 1H), 10.10 (bs, 1H), 8.33 (d, J = 9.0 Hz, 2H), 7.91 (d, J = 8.3 Hz, 4H), 7.81 (s, 1H), 7.71 (d, J = 9.0 Hz, 3H), 7.61 – 7.43 (m, 6H), 7.27 (dd, J = 8.6, 2.4 Hz, 1H), 3.91 (s, 3H); **¹³C NMR** (75 MHz, DMSO) δ 166.3 (C), 165.9 (C), 165.6 (C), 162.6 (C), 148.0 (C), 142.9 (C), 134.0 (C), 133.9 (C), 132.8 (C), 132.4 (C), 132.1 (CH), 131.6 (C), 128.7 (CH), 128.6 (CH), 128.6 (CH), 127.7 (CH), 127.6 (CH), 126.5 (CH), 124.2 (CH), 123.9 (CH), 72.8 (C), 55.1 (CH₃); **HRMS** (ESI) m/z : 535.1583 [M+H]⁺, C₃₀H₂₃N₄O₆⁺ requires 535.1612.

Methyl 2-(3,4-bis(benzamido)phenyl)-2-isocyano-2-(2-nitrophenyl)acetate (3fa)

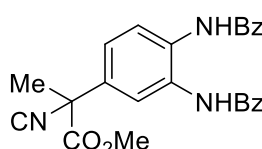


118 mg (88%) of **3fa** were obtained from **1f** (72.5 mg, 0.33 mmol) and **3a** (78.6 mg, 0.25 mmol), after flash chromatography eluting with hexane:EtOAc (6:4).

White solid; m.p. 171.2-171.9 °C; **¹H NMR** (400 MHz, DMSO) δ 10.27 (bs, 1H), 10.17 (bs, 1H), 8.25 – 8.15 (m, 1H), 7.98 – 7.86 (m, 6H), 7.81 – 7.73 (m, 2H), 7.63 – 7.47 (m, 6H), 7.38 (dd, J = 8.6, 2.5 Hz, 1H), 7.02 – 6.95 (m, 1H), 3.82 (s, 3H); **¹³C NMR**

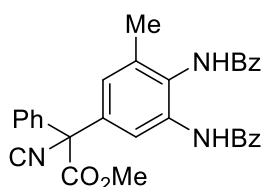
(101 MHz, DMSO) δ 166.0 (C), 165.9 (C), 165.7 (C), 161.7 (C), 147.5 (C), 134.4 (CH), 134.1 (C), 133.9 (C), 132.7 (C), 132.1 (CH), 131.8 (C), 131.6 (CH), 131.5 (C), 131.1 (CH), 130.4 (C), 128.6 (CH), 128.6 (CH), 127.7 (CH), 127.6 (CH), 126.7 (CH), 126.2 (CH), 123.9 (CH), 123.6 (CH), 70.6 (C), 54.4 (CH); **HRMS** (ESI) m/z : 535.1608 $[M+H]^+$, $C_{30}H_{23}N_4O_6^+$ requires 535.1612.

Methyl 2-(3,4-bis(benzamido)phenyl)-2-isocyanopropanoate (**3ga**)

 81 mg (76%) of **3ga** were obtained from **1g** (38.0 mg, 0.33 mmol) and **2a** (78.6 mg, 0.25 mmol), after flash chromatography eluting with hexane:EtOAc (6:4).

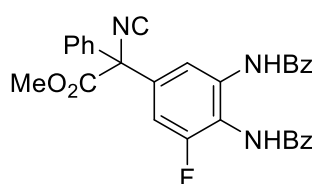
Yellow solid; m.p. 183-186 °C; **¹H NMR** (500 MHz, $CDCl_3$) δ 9.50 (s, 1H), 9.49 (s, 1H), 8.04 – 7.96 (m, 4H), 7.63 – 7.50 (m, 9H), 7.14 (dd, J = 8.5, 2.5 Hz, 1H), 3.64 (s, 3H), 1.68 (s, 3H); **¹³C NMR** (75 MHz, $CDCl_3$) δ 168.0 (C), 166.7 (C), 166.2 (C), 160.4 (C), 134.1 (C), 133.1 (C), 132.9 (C), 132.4 (CH), 132.3 (CH), 131.6 (C), 130.7 (C), 128.8 (CH), 128.7 (CH), 127.5 (CH), 127.4 (CH), 126.3 (CH), 122.8 (CH), 122.0 (CH), 65.5 (C), 53.8 (CH₃), 27.1 (CH₃); **HRMS** (ESI) m/z : 428.1605 $[M+H]^+$, $C_{25}H_{22}N_3O_4^+$ requires 428.1605.

Methyl 2-(3,4-bis(benzamido)-5-methylphenyl)-2-isocyano-2-phenylacetate (**3ab**)

 118 mg (94%) of **3ab** were obtained from **1a** (57.8 mg, 0.33 mmol) and **2b** (82.1 mg, 0.25 mmol), after flash chromatography eluting with hexane:EtOAc (6:4).

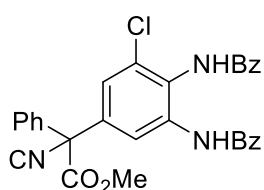
Yellow solid; m.p. 164-166 °C; **¹H NMR** (300 MHz, $CDCl_3$) δ 9.39 (s, 1H), 9.28 (bs, 1H), 7.91 (d, J = 7.0 Hz, 2H), 7.81 (d, J = 7.0 Hz, 2H), 7.50 – 7.45 (m, 3H), 7.44 – 7.34 (m, 4H), 7.31 – 7.15 (m, 6H), 3.70 (s, 3H), 2.37 (s, 3H); **¹³C NMR** (75 MHz, $CDCl_3$) δ 167.3 (C), 166.7 (C), 166.2 (C), 161.9 (C), 136.8 (C), 136.6 (C), 135.1 (C), 133.4 (C), 133.3 (C), 133.0 (C), 132.21 (CH), 132.16 (CH), 130.6 (C), 129.1 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 127.5 (CH), 127.0 (CH), 126.9 (CH), 121.9 (CH), 73.2 (C), 54.1 (CH₃), 19.1 (CH₃); **HRMS** (ESI) m/z : 504.1923 $[M+H]^+$, $C_{31}H_{26}N_3O_4^+$ requires 504.1918.

Methyl 2-(3,4-bis(benzamido)-5-fluorophenyl)-2-isocyano-2-phenylacetate (**3ac**)

 85 mg (67%) of **3ac** were obtained from **1a** (57.8 mg, 0.33 mmol) and **2c** (83.1 mg, 0.25 mmol), after flash chromatography eluting with hexane:EtOAc (7:3).

Orange oil; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 9.61 (bs, 1H), 8.53 (bs, 1H), 8.15 – 8.04 (m, 1H), 8.01 – 7.90 (m, 4H), 7.81 (t, $J = 1.8$ Hz, 1H), 7.62 – 7.32 (m, 10H), 7.07 (dd, $J = 10.8, 2.2$ Hz, 1H), 3.84 (s, 3H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 167.1 (C), 166.1 (C), 162.8 (C), 154.8 (C), 136.3 (C), 136.2 (C), 134.6 (d, $J = 364.2$ Hz, C), 134.2 (C), 134.1 (C), 133.6 (C), 132.9 (CH), 132.4 (CH), 129.5 (CH), 129.1 (CH), 129.0 (CH), 128.8 (CH), 127.8 (CH), 127.7 (CH), 127.0 (CH), 120.1 (d, $J = 3.3$ Hz, CH), 119.7 (d, $J = 14.3$ Hz, C), 111.81 (d, $J = 23.7$ Hz, CH), 73.2 (C), 54.6 (CH_3). $^{19}\text{F NMR}$ (282 MHz, CDCl_3) δ -119.25; **HRMS** (ESI) m/z : 530.1463 $[\text{M}+\text{Na}]^+$, $\text{C}_{30}\text{H}_{22}\text{FN}_3\text{NaO}_4^+$ requires 530.1487.

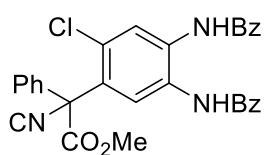
Methyl 2-(3,4-bis(benzamido)-5-chlorophenyl)-2-isocyano-2-phenylacetate (**3ad**)



130 mg (99%) of **3ad** were obtained from **1a** (57.8 mg, 0.33 mmol) and **2d** (87.3 mg, 0.25 mmol), after flash chromatography eluting with hexane:EtOAc (6:4).

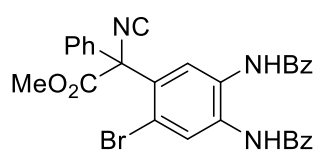
Yellow solid; m.p. 155-157 °C; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 9.67 (bs, 1H), 8.36 (bs, 1H), 8.04 (d, $J = 2.2$ Hz, 1H), 7.97 (d, $J = 7.0$ Hz, 2H), 7.92 (d, $J = 7.0$ Hz, 2H), 7.62 (t, $J = 7.4$ Hz, 1H), 7.56 – 7.48 (m, 3H), 7.47 – 7.40 (m, 8H), 3.91 (s, 3H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 167.1 (C), 167.0 (C), 165.5 (C), 162.8 (C), 136.4 (C), 136.1 (C), 134.2 (C), 133.7 (C), 133.0 (CH), 132.7 (CH), 132.1 (C), 129.7 (C), 129.5 (CH), 129.1 (CH), 129.0 (CH), 128.7 (CH), 127.6 (CH), 127.4 (CH), 127.0 (CH), 124.7 (CH), 124.0 (CH), 73.0 (C), 54.5 (CH_3); **HRMS** (ESI) m/z : 524.1368 $[\text{M}+\text{H}]^+$, $\text{C}_{30}\text{H}_{23}\text{ClN}_3\text{O}_4^+$ requires 524.1372.

Methyl 2-(4,5-bis(benzamido)-2-chlorophenyl)-2-isocyano-2-phenylacetate (**3ae**)



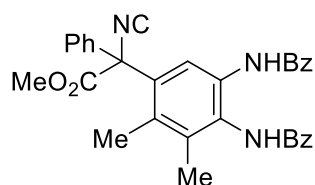
106 mg (81%) of **3ae** were obtained from **1a** (57.8 mg, 0.33 mmol) and **2e** (87 mg, 0.25 mmol), after flash chromatography eluting with hexane:EtOAc (8:2 to 6:4).

Yellow solid; m.p. 160-162 °C; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 9.42 (bs, NH, 1H), 8.91 (1H, bs), 7.94 (d, $J = 7.0$ Hz, 2H), 7.90 (s, 1H), 7.86 (d, $J = 7.0$ Hz, 2H), 7.60 – 7.36 (m, 11H), 6.88 (s, 1H), 3.79 (s, 3H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 167.1 (C), 166.8 (C), 166.4 (C), 161.9 (C), 133.4 (C), 133.2 (C), 133.0 (C), 132.8 (C), 132.53 (CH), 132.51 (CH), 132.4 (C), 131.6 (C), 129.7 (CH), 129.1 (CH), 128.93 (CH), 128.88 (CH), 128.5 (C), 127.6 (CH), 126.94 (CH), 126.91 (CH), 72.0 (C), 54.3 (CH_3); **HRMS** (ESI) m/z : 524.1366 $[\text{M}+\text{H}]^+$, $\text{C}_{30}\text{H}_{23}\text{ClN}_3\text{O}_4^+$ requires 524.1372.

Methyl 2-(4,5-bis(benzamido)-2-bromophenyl)-2-isocyano-2-phenylacetate (3af)

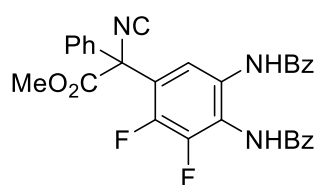
89 mg (63%) of **3af** were obtained from **1a** (57.8 mg, 0.33 mmol) and **2f** (98.2 mg, 0.25 mmol), after flash chromatography eluting with hexane:EtOAc (7:3).

White solid; m.p. 127.0-127.9 °C; ^1H NMR (500 MHz, DMSO) δ 10.11 (bs, 1H), 10.06 (bs, 1H), 8.20 (s, 1H), 7.91 (d, $J = 7.0$ Hz, 1H), 7.84 (d, $J = 7.0$ Hz, 1H), 7.65 – 7.55 (m, 7H), 7.54 – 7.45 (m, 4H), 7.08 (s, 1H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 166.8 (C), 165.7 (C), 165.6 (C), 161.8 (C), 133.8 (C), 133.7 (C), 133.5 (C), 133.4 (C), 132.7 (C), 132.1 (CH), 132.0 (CH), 131.0 (CH), 130.2 (C), 130.0 (CH), 129.5 (CH), 129.1 (CH), 128.6 (CH), 128.5 (CH), 127.7 (CH), 127.4 (CH), 126.6 (CH), 118.4 (C), 73.5 (C), 54.7 (CH₃); HRMS (ESI) m/z : 585.1101 [$\text{M}+\text{NH}_4$]⁺, C₃₀H₂₆BrN₄O₄⁺ requires 585.1132.

Methyl 2-(4,5-bis(benzamido)-2,3-dimethylphenyl)-2-isocyano-2-phenylacetate (3ag)

97 mg (75%) of **3ag** were obtained from **1a** (57.8 mg, 0.33 mmol) and **2g** (85.6 mg, 0.25 mmol), after flash chromatography eluting with hexane:EtOAc (7:3).

Colorless oil; ^1H NMR (300 MHz, CDCl₃) δ 8.77 (bs, 1H, NH), 8.63 (bs, 1H), 7.97 – 7.88 (m, 2H), 7.81 – 7.72 (m, 2H), 7.58 – 7.43 (m, 6H), 7.42 – 7.32 (m, 6H), 6.98 (s, 1H), 3.83 (s, 3H), 2.25 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, CDCl₃) δ 168.3 (C), 166.6 (C), 166.1 (C), 161.9 (C), 137.2 (C), 135.7 (C), 135.0 (C), 134.8 (C), 133.8 (C), 133.5 (C), 132.3 (CH), 132.2 (CH), 130.7 (C), 130.5 (C), 129.4 (CH), 129.1 (CH), 129.0 (CH), 128.8 (CH), 127.6 (CH), 127.5 (CH), 127.2 (CH), 123.1 (CH), 73.6 (C), 54.4 (CH₃), 18.1 (CH₃), 16.3 (CH₃); HRMS (ESI) m/z : 540.1869 [$\text{M}+\text{Na}$]⁺, C₃₂H₂₇N₃NaO₄⁺ requires 540.1894.

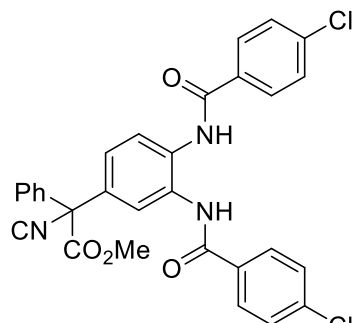
Methyl 2-(4,5-bis(benzamido)-2,3-difluorophenyl)-2-isocyano-2-phenylacetate (3ah)

93 mg (71%) of **3ah** were obtained from **1a** (57.8 mg, 0.33 mmol) and **2h** (87.5 mg, 0.25 mmol), after flash chromatography eluting with hexane:EtOAc (7:3).

White solid; m.p. 94.9-96.0 °C; ^1H NMR (500 MHz, CDCl₃) δ 9.26 (bs, 1H), 8.67 (bs, 1H), 7.97 – 7.90 (m, 2H), 7.86 – 7.80 (m, 2H), 7.63 – 7.56 (m, 1H), 7.53 – 7.46 (m, 5H), 7.45 – 7.38 (m, 5H), 7.13 (d, $J = 4.9$ Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (126 MHz, CDCl₃) δ 166.9 (C), 166.8 (C), 166.1 (C), 162.9 (C), 146.4 (dd, $^1J_{\text{C-F}} = 252.8$, $^2J_{\text{C-F}} = 13.2$ Hz, C), 145.5 (dd, $^1J_{\text{C-F}} = 250.7$, $^2J_{\text{C-F}} = 15.6$ Hz, C), 133.3 (C), 133.1 (CH), 132.5 (CH), 132.5 (C), 132.3 (C), 129.9 (CH), 129.3 (CH), 129.2 (CH), 128.9 (CH), 128.7 (C), 127.9 (CH), 127.5

(CH), 126.7 (CH), 126.2 (d, $^2J_{C-F} = 9.3$ Hz, C), 122.3 (d, $^2J_{C-F} = 11.4$ Hz, C), 120.1 (CH), 69.7 (C), 54.7 (CH₃). ^{19}F NMR (282 MHz, CDCl₃) δ -136.67 (d, $J = 20.5$ Hz), -141.75 (d, $J = 19.6$ Hz); **HRMS** (ESI) m/z : 548.1370 [$\text{M}+\text{Na}$]⁺, C₃₀H₂₁F₂N₃NaO₄⁺ requires 548.1392.

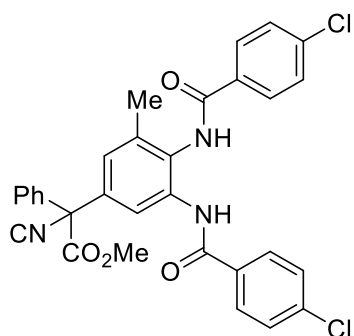
Methyl 2-(3,4-bis(4-chlorobenzamido)phenyl)-2-isocyano-2-phenylacetate (3ai)



105 mg (75%) of **3ai** were obtained from **1a** (57.8 mg, 0.33 mmol) and **2i** (96.0 mg, 0.25 mmol), after flash chromatography eluting with hexane:EtOAc (5:5).

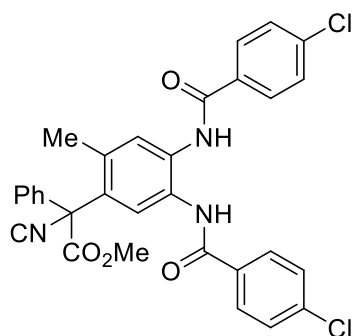
White solid; m.p. 208-210 °C; ^1H NMR (300 MHz, CDCl₃) δ 9.49 (bs, 1H), 9.41 (bs, 1H), 7.94 – 7.88 (m, 4H), 7.57 (d, $J = 8.6$ Hz, 1H), 7.54 (d, $J = 2.3$ Hz, 1H), 7.46-7.39 (m, 4H), 7.35 – 7.21 (m, 3H), 7.13 – 7.08 (m, 2H), 7.02 (dd, $J = 8.6, 2.3$ Hz, 1H), 3.74 (3H, s); ^{13}C NMR (75 MHz, CDCl₃) δ 167.2 (C), 165.9 (C), 165.6 (C), 162.1 (C), 138.9 (C), 138.8 (C), 136.5 (C), 134.3 (C), 134.2 (C), 131.7 (C), 131.5 (C), 131.2 (C), 130.5 (C), 129.3 (CH), 129.2 (CH), 129.1 (CH), 128.7 (CH), 126.7 (CH), 126.1 (CH), 125.7 (CH), 124.1 (CH), 73.0 (C), 54.2 (CH₃); **HRMS** (ESI) m/z : 575.1250 [$\text{M}+\text{NH}_4$]⁺, C₃₀H₂₅Cl₂N₄O₄⁺ requires 575.1247.

Methyl 2-(3,4-bis(4-chlorobenzamido)-5-methylphenyl)-2-isocyano-2-phenylacetate (3aj)



117 mg (82%) of **3aj** were obtained from **1a** (57.8 mg, 0.33 mmol) and **2j** (99.1 mg, 0.25 mmol), after flash chromatography eluting with hexane:EtOAc (5:5).

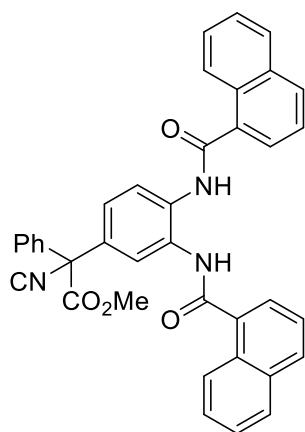
White solid; m.p. 217-219 °C; ^1H NMR (300 MHz, DMSO-*d*₆) δ 10.07 (bs, 1H), 9.86 (bs, 1H), 7.96 (d, $J = 8.7$ Hz, 2H), 7.86 (d, $J = 8.7$ Hz, 2H), 7.62 – 7.47 (m, 8H), 7.47 – 7.38 (m, 2H), 7.17 (d, $J = 1.9$ Hz, 1H), 3.91 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, DMSO-*d*₆) δ 167.1 (C), 164.6 (C), 164.2 (C), 161.4 (C), 137.3 (C), 136.61 (C), 136.56 (C), 136.52 (C), 134.9 (C), 134.8 (C), 133.0 (C), 132.8 (C), 130.8 (C), 129.59 (CH), 129.57 (CH), 129.4 (CH), 129.1 (CH), 128.6 (CH), 128.5 (CH), 126.9 (CH), 125.3 (CH), 121.3 (CH), 73.4 (C), 54.7 (CH₃), 18.6 (CH₃); **HRMS** (ESI) m/z : 589.1405 [$\text{M}+\text{NH}_4$]⁺, C₃₁H₂₇Cl₂N₄O₄⁺ requires 589.1404.

Methyl 2-(4,5-bis(4-chlorobenzamido)-2-methylphenyl)-2-isocyano-2-phenylacetate**(3ak)**

121 mg (85%) of **3ak** were obtained from **1a** (57.8 mg, 0.33 mmol) and **2k** (99.0 mg, 0.25 mmol), after flash chromatography eluting with hexane:EtOAc (5:5).

White solid; m.p. 137-139 °C; ¹H NMR (300 MHz, CDCl₃) δ 9.58 (bs, 1H), 9.42 (bs, 1H), 7.93 (d, *J* = 8.7 Hz, 2H), 7.90 (d, *J* = 8.7 Hz, 2H), 7.46 (t, *J* = 8.4 Hz, 4H), 7.38 (s, 1H), 7.36 – 7.24 (m, 3H), 7.21 – 7.13 (m, 2H), 6.98 (s, 1H), 3.73 (s, 3H),

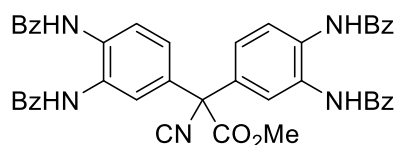
1.78 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 167.5 (C), 165.7 (C), 165.5 (C), 162.0 (C), 138.8 (C), 138.7 (C), 135.6 (C), 134.0 (C), 133.8 (C), 131.4 (C), 131.4 (C), 131.2 (C), 129.23 (CH), 129.18 (CH), 129.15 (CH), 129.1 (CH), 128.7 (CH), 127.7 (C), 126.8 (CH), 72.5 (C), 54.2 (CH₃), 19.6 (CH₃); HRMS (ESI) *m/z*: 589.1406 [M+NH₄]⁺, C₃₁H₂₇Cl₂N₄O₄⁺ requires 589.1404.

Methyl 2-(3,4-bis(1-naphthamido)phenyl)-2-isocyano-2-phenylacetate (3al)

127 mg (86%) of **3al** were obtained from **1a** (57.8 mg, 0.33 mmol) and **2l** (104 mg, 0.25 mmol), after flash chromatography eluting with hexane:EtOAc (6:4).

White solid; m.p. 107-110 °C; ¹H NMR (300 MHz, CDCl₃) δ 9.18 (bs, 1H), 8.81 (bs, 1H), 8.25 (d, *J* = 8.5 Hz, 1H), 8.10 (d, *J* = 8.5 Hz, 1H), 7.87-7.77 (m, 5H), 7.72 (d, *J* = 1.7 Hz, 1H), 7.70 – 7.65 (m, 1H), 7.61 (d, *J* = 6.9 Hz, 1H), 7.48 – 7.23 (m, 13H), 3.87 (s, 3H);

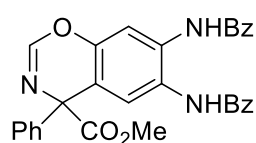
¹³C NMR (75 MHz, CDCl₃) δ 168.6 (C), 168.4 (C), 167.5 (C), 161.9 (C), 136.6 (C), 134.6 (C), 133.62 (C), 133.57 (C), 132.9 (C), 132.5 (C), 131.8 (C), 131.6 (CH), 131.4 (CH), 130.3 (C), 130.0 (C), 129.9 (C), 129.3 (CH), 128.8 (CH), 128.3 (CH), 127.31 (CH), 127.26 (CH), 127.1 (CH), 126.5 (CH), 125.7 (CH), 125.6 (CH), 125.6 (CH), 125.0 (CH), 124.9 (CH), 124.6 (CH), 124.5 (CH), 124.3 (CH), 73.4 (C), 54.3 (CH₃); HRMS (ESI) *m/z*: 607.2343 [M+NH₄]⁺, C₃₈H₃₁N₄O₄⁺ requires 607.2340.

Methyl 2,2-bis(3,4-bis(benzamido)phenyl)-2-isocyanoacetate (3ha)

60 mg (33%) of **3ha** were obtained from **1h** (33 mg, 0.33 mmol) and **2a** (78.6 mg, 0.25 mmol), after flash chromatography eluting with hexane:EtOAc (6:4).

White solid; m.p. 180-181 °C; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.72 (bs, 2H), 9.63 (s, 2H), 8.03 – 7.95 (m, 4H), 7.93 – 7.88 (m, 4H), 7.75 (d, $J = 2.4$ Hz, 2H), 7.58 (d, $J = 8.7$ Hz, 2H), 7.56 – 7.52 (m, 2H), 7.52 – 7.48 (m, 2H), 7.48 – 7.43 (m, 4H), 7.41 – 7.36 (m, 4H), 7.15 (dd, $J = 8.6$, 2.4 Hz, 2H), 3.78 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 167.3 (C), 167.1 (C), 166.7 (C), 162.4 (C), 133.8 (C), 133.8 (C), 133.5 (C), 132.5 (CH), 132.4 (CH), 132.1 (C), 130.5 (C), 128.9 (CH), 128.9 (CH), 127.8 (CH), 127.8 (CH), 125.6 (CH), 125.4 (CH), 125.1 (CH), 72.7 (C), 54.6 (CH_3); **HRMS** (ESI) m/z : 728.2512 $[\text{M}+\text{H}]^+$, $\text{C}_{44}\text{H}_{34}\text{N}_5\text{O}_6^+$ requires 728.2504.

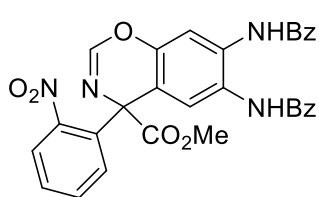
Methyl 6,7-bis(benzamido)-4-phenyl-4H-benzo[e][1,3]oxazine-4-carboxylate (3an)



125 mg (96%) of **3an** were obtained from **1a** (57.8 mg, 0.33 mmol) and **2n** (83.0 mg, 0.25 mmol), after flash chromatography eluting with hexane:EtOAc (5:5).

Pink solid; m.p. 180-182 °C; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 9.46 (bs, 1H), 8.57 (bs, 1H), 7.94 (d, $J = 7.0$ Hz, 2H), 7.89 (d, $J = 7.0$ Hz, 2H), 7.59 (s, 1H), 7.55 – 7.42 (m, 6H), 7.34 (s, 1H), 7.33 (s, 1H), 7.30-7.19 (m, 5H), 3.79 (s, 3H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 171.6 (C), 167.0 (C), 166.0 (C), 145.6 (C), 144.5 (C), 142.8 (C), 133.7 (C), 133.2 (C), 133.1 (C), 132.5 (CH), 132.2 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 127.9 (CH), 127.5 (CH), 127.0 (CH), 126.7 (C), 125.6 (CH), 117.3 (C), 112.7 (CH), 65.4 (C), 53.4 (CH_3); **HRMS** (ESI) m/z : 541.2083 $[\text{M}+\text{H}_2\text{O}+\text{NH}_4]^+$, $\text{C}_{30}\text{H}_{29}\text{N}_4\text{O}_6^+$ requires 541.2082.

Methyl 6,7-bis(benzamido)-4-(2-nitrophenyl)-4H-benzo[e][1,3]oxazine-4-carboxylate (3fn)



113 mg (80%) of **3fn** were obtained from **1f** (73.0 mg, 0.33 mmol) and **2n** (83.1 mg, 0.25 mmol), after flash chromatography eluting with hexane:EtOAc (4:6).

White solid; m.p. 260-262 °C; $^1\text{H NMR}$ (300 MHz, $\text{DMSO}-d_6$) δ 10.19 (bs, 1H), 10.10 (bs, 1H), 8.11-7.84 (m, 5H), 7.81 – 7.48 (m, 11H), 7.32 (d, $J = 7.7$ Hz, 1H), 3.73 (s, 3H); $^{13}\text{C NMR}$ (75 MHz, $\text{DMSO}-d_6$) δ 169.4 (C), 165.9 (C), 165.6 (C), 148.2 (C), 146.6 (C), 144.2 (C), 135.3 (C), 134.0 (C), 133.9 (C), 133.6 (C), 133.0 (CH), 132.1 (CH), 132.0 (CH), 129.9 (CH), 129.7 (CH), 128.7 (CH), 128.5 (CH), 127.9 (C), 127.7 (CH), 127.6 (CH), 125.5 (CH), 125.3 (CH), 114.6 (C), 63.8 (C), 53.0 (CH_3); **HRMS** (ESI) m/z : 586.1930 $[\text{M}+\text{H}_2\text{O}+\text{NH}_4]^+$, $\text{C}_{30}\text{H}_{28}\text{N}_5\text{O}_8^+$ requires 586.1932.

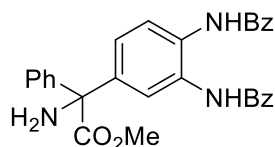
5.3.3 Synthesis of compound **3aa** at 2.5 mmol-scale

α -Phenyl isocyanoacetate **1a** (578 mg, 3.3 mmol, 1.3 equiv) was added to a solution of *o*-benzoquinone diimide **2a** (786 mg, 2.5 mmol, 1.0 equiv) and silver oxide (29 mg, 0.125 mmol, 0.05 equiv) in CH₂Cl₂ (30 mL). The mixture was stirred at rt for 1.5 hours. Then, the reaction mixture was purified by flash column chromatography eluting with hexane:EtOAc (6:4) to give compound **3aa** (1.10 g, 90%) with identical spectroscopic features as those reported for **3aa** in the 0.25 mmol-scale reaction.

5.3.4 Synthesis and characterization data for compounds **4**

To a solution of compounds **3** (0.2 mmol, 1.0 equiv) in MeOH (2 mL, 0.1 M) was added 6 M HCl (aq) (10 drops). The reaction was stirred for 4 h and quenched with NaHCO₃ (aq) sat. until pH 9. The methanol was removed under reduced pressure and the aqueous mixture was extracted with CH₂Cl₂ (3 $\times$ 30 mL). The combined organic phases were washed with brine (40 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The mixture was chromatographed using hexane:EtOAc mixtures as eluent.

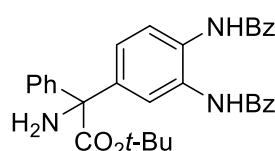
Methyl 2-amino-2-(3,4-bis(benzamido)phenyl)-2-phenylacetate (**4aa**)



95 mg (99%) of **4aa** were obtained from **3aa** (98 mg), after flash chromatography eluting with hexane:EtOAc (5:5).

Brown solid; m.p. 191-194 °C; ¹H NMR (300 MHz, CDCl₃) δ 9.45 (bs, NH, 1H), 9.13 (bs, 1H), 8.04-7.93 (m, 4H), 7.61 (d, *J* = 8.6 Hz, 1H), 7.57 (d, *J* = 2.3 Hz, 1H), 7.55 – 7.39 (m, 6H), 7.22 (d, *J* = 2.3 Hz, 1H), 7.21 – 7.10 (m, 4H), 3.67 (s, 3H), 1.87 (bs, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 174.6 (C), 166.7 (C), 166.2 (C), 143.8 (C), 141.2 (C), 133.6 (C), 133.3 (C), 132.3 (CH), 132.1 (CH), 130.5 (C), 129.9 (C), 128.8 (CH), 128.7 (CH), 128.2 (CH), 127.6 (CH), 127.6 (CH), 127.5 (CH), 127.2 (CH), 126.6 (CH), 125.5 (CH), 124.4 (CH), 67.9 (C), 52.9 (CH₃); HRMS (ESI) *m/z*: 480.1919 [M+H]⁺, C₂₉H₂₆N₃O₄⁺ requires 480.1918.

tert-Butyl 2-amino-2-(3,4-bis(benzamido)phenyl)-2-phenylacetate (**4ba**)

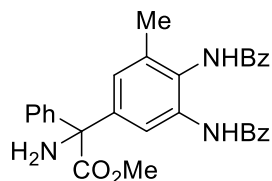


90 mg (86%) of **4ba** were obtained from **3ba** (103 mg), after flash chromatography eluting with hexane:EtOAc (5:5).

Brown solid; m.p. 140-142 °C; ¹H NMR (300 MHz, CDCl₃) δ 9.49 (bs, 1H), 9.12 (bs, 1H), 7.99 (d, *J* = 8.3 Hz, 4H), 7.66 – 7.57 (m, 2H), 7.55 – 7.36 (m, 6H), 7.21 – 7.13 (m, 5H), 1.93 (bs, 2H), 1.37 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 173.0 (C), 166.6 (C), 166.2 (C), 144.3 (C), 141.8 (C), 133.7 (C), 133.4 (C), 132.2 (CH), 132.1 (CH), 130.3 (C), 129.8

(C), 128.8 (CH), 128.7 (CH), 128.0 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 127.2 (CH), 126.7 (CH), 125.1 (CH), 124.5 (CH), 82.6 (C), 68.0 (C), 27.7 (CH₃); **HRMS** (ESI) m/z : 522.2390 [M+H]⁺, C₃₂H₃₂N₃O₄⁺ requires 522.2387.

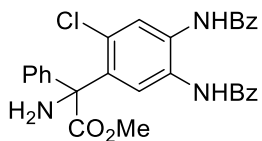
Methyl 2-amino-2-(3,4-bis(benzamido)-5-methylphenyl)-2-phenylacetate (4ab)



98 mg (99%) of **4ab** were obtained from **3ab** (101 mg), after flash chromatography eluting with hexane:EtOAc (5:5).

Yellow solid; m.p. 172-174 °C; **¹H NMR** (300 MHz, CDCl₃) δ 9.40 (bs, 1H), 8.97 (bs, 1H), 7.91 (d, J = 7.0 Hz, 2H), 7.83 (d, J = 7.1 Hz, 2H), 7.55 – 7.31 (m, 8H), 7.23 – 6.99 (m, 6H), 3.54 (s, 3H), 2.36 (s, 3H), 1.76 (bs, 2H); **¹³C NMR** (75 MHz, CDCl₃) δ 174.3 (C), 166.8 (C), 166.0 (C), 143.7 (C), 142.3 (C), 136.0 (C), 133.5 (C), 133.2 (C), 132.9 (C), 132.14 (CH), 132.07 (CH), 129.3 (C), 128.8 (CH), 128.5 (CH), 128.2 (CH), 128.0 (CH), 127.7 (CH), 127.45 (CH), 127.42 (CH), 127.35 (CH), 121.8 (CH), 67.8 (C), 52.7 (CH₃), 19.0 (CH₃); **HRMS** (ESI) m/z : 494.2073 [M+H]⁺, C₃₀H₂₈N₃O₄⁺ requires 494.2074.

Methyl 2-amino-2-(4,5-bis(benzamido)-2-chlorophenyl)-2-phenylacetate (4ae)



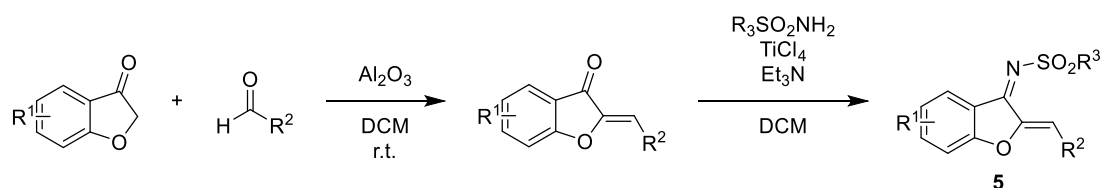
102 mg (99%) of **4ae** were obtained from **3ae** (105 mg), after flash chromatography eluting with hexane:EtOAc (4:6).

Brown solid; m.p. 155-157 °C; **¹H NMR** (300 MHz, CDCl₃) δ 9.56 (bs, 1H), 8.89 (bs, 1H), 7.96 (d, J = 6.9 Hz, 2H), 7.90 (d, J = 7.1 Hz, 2H), 7.81 (s, 1H), 7.60 – 7.40 (m, 8H), 7.30 – 7.27 (m, 2H), 6.96 (s, 1H), 3.63 (s, 3H), 2.18 (bs, 2H); **¹³C NMR** (75 MHz, CDCl₃) δ 174.9 (C), 166.7 (C), 166.1 (C), 139.7 (C), 139.6 (C), 133.3 (C), 133.0 (C), 132.4 (CH), 132.3 (CH), 131.7 (C), 130.8 (C), 128.8 (CH), 128.4 (C), 128.3 (CH), 128.1 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 126.4 (CH), 67.0 (C), 52.9 (CH₃); **HRMS** (ESI) m/z : 514.1532 [M+H]⁺, C₂₉H₂₅ClN₃O₄⁺ requires 514.1528.

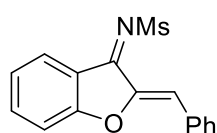
5.4 Organocatalytic conjugate addition of isocyanoacetate esters to aurone-derived 1-azadienes

5.4.1 Synthesis and characterization data for 1-azadienes **5**

Sulfonamides **5** were synthesized via a two-step procedure comprising a Knoevenagel condensation of a benzofuran-3(2*H*)-one derivative with the corresponding aldehyde, followed by condensation of the resulting aurone with the appropriate sulfonylamine.



N-(2-benzylidenebenzofuran-3(2*H*)-ylidene)methanesulfonamide (**5a**)¹⁸² (*representative procedure*)



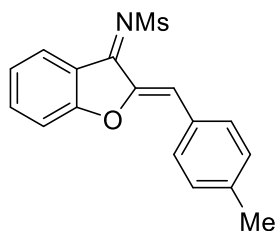
A modification of a literature procedure was carried out.¹⁸³

Step 1: To a solution of benzofuran-3(2*H*)-one (3.0 g, 22.4 mmol) in DCM (220 mL) was added benzaldehyde (2.7 mL, 26.9 mmol) and basic alumina (11.4 g, previously activated for 2 h in an oven set at 135 °C). The reaction mixture was stirred overnight at room temperature. After this time, the mixture was gravity filtered and the solvent was evaporated under reduced pressure. The resulting solid residue was crystallized from hexane:dichloromethane. The solid was filtered under vacuum and washed with cold hexane to afford 4.13 g (83%) of 2-benzylidenebenzofuran-3(2*H*)-one as a yellow solid.

Step 2: To a solution of 2-benzylidenebenzofuran-3(2*H*)-one (2.0 g, 9.0 mmol) and methylsulfonamide (1.3 g, 13.5 mmol, 1.5 equiv.) in dry DCM (90 mL), under nitrogen atmosphere was added Et₃N (2.5 mL, 18.0 mmol, 2.0 equiv.). The solution was then cooled to 0 °C and TiCl₄ (1.0 M soln. in DCM, 9 mL, 9 mmol, 1.0 equiv.) was added. The reaction mixture was allowed to warm towards room temperature and stirred overnight. The reaction was quenched with 20 mL water and the mixture transferred to a separatory funnel. The phases were separated and the aqueous phase was extracted with DCM (4x15 mL). The combined organic phases were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: hexane:EtOAc 8:2, hexane:DCM 5:5, hexane:DCM 1:9) to afford 0.95 g (35%) of the title compound as a yellow solid. ¹H NMR (300 MHz, CDCl₃) δ 8.60 (d, *J* = 8.1 Hz, 1H, Ar), 7.98 – 7.89 (m, 2H, Ar), 7.67 (ddd, *J* = 8.6, 7.3, 1.4 Hz, 1H, Ar), 7.53 – 7.39 (m, 3H, Ar), 7.32 (d, *J* = 8.3 Hz, 1H, Ar), 7.25 (ddd, *J* = 8.2, 7.3,

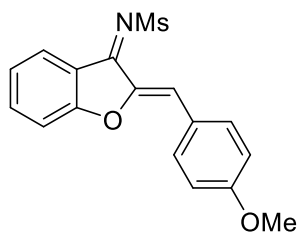
1.0 Hz, 1H, Ar), 7.19 (s, 1H, CH=C), 3.34 (s, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 165.5 (C), 164.8 (C), 137.8 (CH), 132.5 (C), 131.8 (CH), 130.5 (CH), 129.2 (CH), 123.9 (CH), 112.4 (CH), 43.2 (CH₃).

***N*-(2-(4-methylbenzylidene)benzofuran-3(2*H*)-ylidene)methanesulfonamide (5b)¹⁸⁴**



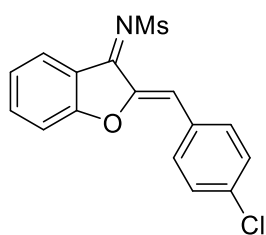
From 2-(4-methylbenzylidene)benzofuran-3(2*H*)-one (2.0 g, 8.5 mmol), 0.83 g (31%) of the title compound were obtained after column chromatography eluting with hexane:EtOAc 8:2 and hexane:DCM 9:1. Yellow solid; ¹H NMR (300 MHz, CDCl₃) δ 8.59 (d, *J* = 8.1 Hz, 1H, Ar), 7.87 – 7.80 (m, 2H, Ar), 7.66 (ddd, *J* = 8.5, 7.3, 1.4 Hz, 1H, Ar), 7.34 – 7.26 (m, 3H, Ar), 7.25 – 7.21 (m, 1H, Ar), 7.19 (s, 1H, CH=C), 3.33 (s, 3H, CH₃), 2.42 (s, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 165.4 (C), 164.7 (C), 141.3 (C), 137.6 (CH), 131.9 (CH), 130.0 (CH), 129.8 (C), 123.8 (CH), 112.4 (CH), 43.2 (CH₃), 21.8 (CH₃).

***N*-(2-(4-methoxybenzylidene)benzofuran-3(2*H*)-ylidene)methanesulfonamide (5c)¹³³**

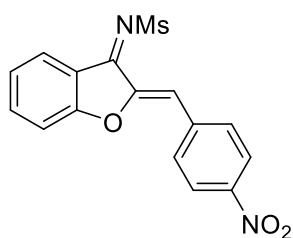


From 2-(4-methoxybenzylidene)benzofuran-3(2*H*)-one (1.8 g, 7.1 mmol), 0.59 g (25%) of the title compound were obtained after column chromatography eluting with hexane:EtOAc 7:3, hexane:DCM 5:95. Yellow solid; ¹H NMR (300 MHz, CDCl₃) δ 8.59 (d, *J* = 8.1 Hz, 1H, Ar), 7.91 (d, *J* = 8.8 Hz, 2H, Ar), 7.65 (ddd, *J* = 8.5, 7.3, 1.4 Hz, 1H, Ar), 7.34 – 7.20 (m, 2H, Ar), 7.20 (s, 1H, CH=C), 6.99 (d, *J* = 8.9 Hz, 2H, Ar), 3.88 (s, 3H, CH₃), 3.32 (s, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 165.2 (C), 164.4 (C), 161.7 (C), 137.4 (C), 133.9 (CH), 125.4 (C), 123.7 (CH), 114.8 (CH), 112.4 (CH), 55.6 (CH₃), 43.2 (CH₃).

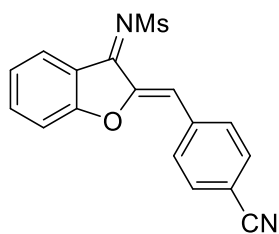
***N*-(2-(4-chlorobenzylidene)benzofuran-3(2*H*)-ylidene)methanesulfonamide (5d)¹⁸⁵**



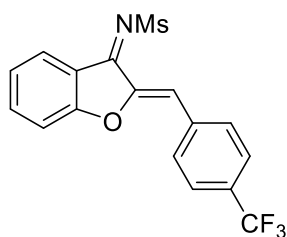
From 2-(4-chlorobenzylidene)benzofuran-3(2*H*)-one (1.6 g, 6.4 mmol), 0.62 g (29%) of the title compound were obtained after column chromatography eluting with hexane:EtOAc 8:2, hexane:DCM 5:95. Yellow solid; ¹H NMR (300 MHz, CDCl₃) δ 8.59 (d, *J* = 8.1 Hz, 1H, Ar), 7.86 (d, *J* = 8.5 Hz, 2H, Ar), 7.67 (ddd, *J* = 8.5, 7.3, 1.4 Hz, 1H, Ar), 7.43 (d, *J* = 8.6 Hz, 2H, Ar), 7.30 (dt, *J* = 8.4, 0.8 Hz, 1H, Ar), 7.25 (ddd, *J* = 8.3, 7.3, 1.0 Hz, 1H, Ar), 7.11 (s, 1H, CH=C), 3.33 (s, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 165.3 (C), 164.6 (C), 137.9 (CH), 136.5 (C), 132.8 (CH), 131.0 (C), 129.5 (CH), 124.1 (CH), 112.4 (CH), 43.2 (CH₃).

***N*-(2-(4-nitrobenzylidene)benzofuran-3(2*H*)-ylidene)methanesulfonamide (5e)¹⁸⁵**

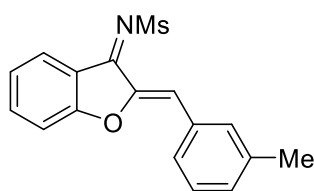
From 2-(4-nitrobenzylidene)benzofuran-3(2*H*)-one (1.4 g, 5.3 mmol), 0.23 g (13%) of the title compound were obtained after column chromatography eluting with hexane:EtOAc 7:3, hexane:DCM 1:9. Yellow solid; ¹H NMR (300 MHz, CDCl₃) δ 8.60 (d, *J* = 8.1 Hz, 1H, Ar), 8.30 (d, *J* = 8.9 Hz, 2H, Ar), 8.06 (d, *J* = 8.6 Hz, 2H, Ar), 7.71 (ddd, *J* = 8.5, 7.3, 1.4 Hz, 1H, Ar), 7.37 – 7.26 (m, 2H, Ar), 7.14 (s, 1H, CH=C), 3.36 (s, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 165.1 (C), 164.7 (C), 147.9 (C), 138.6 (C), 138.4 (CH), 131.9 (CH), 124.5 (CH), 124.2 (CH), 112.5 (CH), 43.2 (CH₃).

***N*-(2-(4-cyanobenzylidene)benzofuran-3(2*H*)-ylidene)methanesulfonamide (5f)**

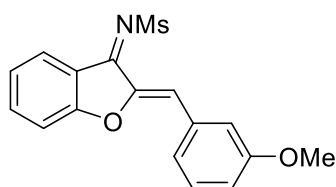
From 2-((3-oxobenzofuran-2(3*H*)-ylidene)methyl)benzonitrile (2.0 g, 8.1 mmol), 0.97 g (37%) of the title compound were obtained after column chromatography eluting with hexane:EtOAc 7:3, hexane:DCM 5:95. Yellow solid; m.p. 232.5-232.8 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.59 (d, *J* = 8.1 Hz, 1H, Ar), 8.05 – 7.94 (m, 2H, Ar), 7.78 – 7.64 (m, 3H, Ar), 7.36 – 7.22 (m, 2H, Ar), 7.09 (s, 1H, CH=C), 3.35 (s, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 165.1 (C), 164.7 (C), 138.3 (CH), 136.7 (C), 132.7 (CH), 131.7 (CH), 124.4 (CH), 118.6 (C), 112.9 (C), 112.4 (CH), 43.1 (CH₃); HRMS (ESI) *m/z*: 325.0643 [M+H]⁺, C₁₇H₁₃N₂O₃S⁺ requires 325.0641.

***N*-(2-(4-(trifluoromethyl)benzylidene)benzofuran-3(2*H*)-ylidene)methanesulfonamide (5g)**

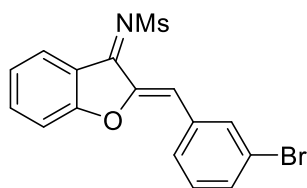
From 2-(4-(trifluoromethyl)benzylidene)benzofuran-3(2*H*)-one (1.9 g, 6.6 mmol), 0.86 g (36%) of the title compound were obtained after column chromatography eluting with hexane:EtOAc 8:2, hexane:DCM 3:7, hexane:DCM 9:1. Yellow solid; m.p. 159.0-160.5 °C; ¹H NMR (500 MHz, CDCl₃) δ 8.60 (d, *J* = 8.1 Hz, 1H, Ar), 8.02 (d, *J* = 8.1 Hz, 2H, Ar), 7.72 – 7.64 (m, 3H, Ar), 7.32 (dt, *J* = 8.3, 0.8 Hz, 1H, Ar), 7.27 (ddd, *J* = 8.1, 7.2, 0.9 Hz, 1H, Ar), 7.14 (s, 1H, CH=C), 3.35 (s, 3H, CH₃); ¹³C NMR (126 MHz, CDCl₃) δ 165.3 (C), 164.8 (C), 138.2 (CH), 135.8 (C), 131.6 (CH), 129.2 (CH), 126.0 (q, ³*J* = 3.8 Hz, CH), 124.3 (CH), 124.0 (q, ¹*J* = 272.7 Hz, C), 112.5 (CH), 43.2 (CH₃); HRMS (ESI) *m/z*: 368.0563 [M+H]⁺, C₁₇H₁₃F₃NO₃S⁺ requires 368.0563.

***N*-(2-(3-methylbenzylidene)benzofuran-3(2*H*)-ylidene)methanesulfonamide (5h)¹⁸⁵**

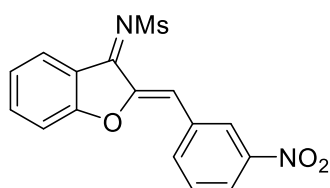
From 2-(3-methylbenzylidene)benzofuran-3(2*H*)-one (2.0 g, 8.4 mmol), 0.76 g (29%) of the title compound were obtained after column chromatography eluting with hexane:EtOAc 8:2, hexane:DCM 5:95. Yellow solid; ¹H NMR (300 MHz, CDCl₃) δ 8.60 (d, *J* = 8.6 Hz, 1H, Ar), 7.77 (d, *J* = 7.7 Hz, 1H, Ar), 7.72 (s, 1H, Ar), 7.66 (ddd, *J* = 8.6, 7.3, 1.4 Hz, 1H, Ar), 7.37 (t, *J* = 7.7 Hz, 1H, Ar), 7.32 (dt, *J* = 8.4, 0.9 Hz, 1H, Ar), 7.28 – 7.20 (m, 2H, Ar), 7.17 (s, 1H, CH=C), 3.33 (s, 3H, CH₃), 2.43 (s, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 165.4 (C), 164.7 (C), 138.8 (C), 137.7 (CH), 132.5 (CH), 132.4 (CH), 131.4 (C), 129.0 (CH), 123.9 (CH), 112.5 (C), 43.2 (CH₃), 21.6 (CH₃).

***N*-(2-(3-methoxybenzylidene)benzofuran-3(2*H*)-ylidene)methanesulfonamide (5i)¹⁸⁵**

From 2-(3-methoxybenzylidene)benzofuran-3(2*H*)-one (0.66 g, 2.6 mmol), 0.42 g (48%) of the title compound were obtained eluting with hexane:EtOAc 8:2, hexane:DCM 5:95. Yellow solid; ¹H NMR (300 MHz, CDCl₃) δ 8.59 (d, *J* = 8.1 Hz, 1H, Ar), 7.66 (ddd, *J* = 8.5, 7.3, 1.4 Hz, 1H, Ar), 7.52 (d, *J* = 1.0 Hz, 2H, Ar), 7.38 (t, *J* = 8.2 Hz, 1H, Ar), 7.30 (dt, *J* = 8.4, 0.8 Hz, 1H, Ar), 7.25 (ddd, *J* = 8.2, 7.3, 1.0 Hz, 1H, Ar), 7.15 (s, 1H, CH=C), 6.98 (ddd, *J* = 8.3, 2.5, 1.2 Hz, 1H, Ar), 3.89 (s, 3H, CH₃), 3.34 (s, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 165.4 (C), 164.7 (C), 160.0 (C), 137.8 (CH), 133.7 (C), 131.1 (CH), 130.1 (CH), 124.6 (CH), 123.9 (CH), 116.7 (CH), 116.4 (CH), 115.4 (CH), 112.4 (CH), 55.5 (CH₃), 43.2 (CH₃).

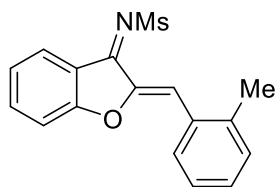
***N*-(2-(3-bromobenzylidene)benzofuran-3(2*H*)-ylidene)methanesulfonamide (5j)¹⁸⁶**

From 2-(3-bromobenzylidene)benzofuran-3(2*H*)-one (0.80 g, 2.7 mmol), 0.31 g (31%) of the title compound were obtained after column chromatography eluting with hexane:EtOAc 85:15, hexane:DCM 5:95. Yellow solid; ¹H NMR (300 MHz, CDCl₃) δ 8.59 (d, *J* = 8.1 Hz, 1H, Ar), 8.09 (t, *J* = 1.8 Hz, 1H, Ar), 7.82 (d, *J* = 7.8 Hz, 1H, Ar), 7.68 (ddd, *J* = 8.5, 7.3, 1.4 Hz, 1H, Ar), 7.54 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H, Ar), 7.41 – 7.28 (m, 2H, Ar), 7.30 – 7.21 (m, 2H, Ar), 7.07 (s, 1H, CH=C), 3.33 (s, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 165.3 (C), 164.7 (C), 138.1 (CH), 134.5 (C), 134.1 (CH), 133.1 (CH), 130.5 (CH), 130.2 (CH), 124.2 (CH), 123.2 (C), 112.5 (CH), 43.2 (CH₃).

***N*-(2-(3-nitrobenzylidene)benzofuran-3(2*H*)-ylidene)methanesulfonamide (5k)¹⁸⁵**

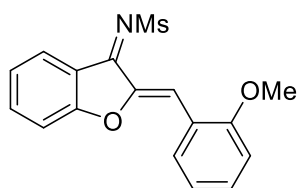
From 2-(3-nitrobenzylidene)benzofuran-3(2*H*)-one (1.42 g, 5.3 mmol), 0.66 g (36%) of the title compound were obtained after column chromatography eluting with hexane:EtOAc 7:3, hexane:DCM 2:8, hexane:DCM 1:9. Yellow solid; ¹H NMR (300

MHz, CDCl₃) δ 8.77 (t, *J* = 1.9 Hz, 1H, Ar), 8.59 (d, *J* = 8.1 Hz, 1H, Ar), 8.24 (ddd, *J* = 8.3, 2.3, 1.0 Hz, 1H, Ar), 8.22 – 8.17 (m, 1H, Ar), 7.70 (ddd, *J* = 8.5, 7.3, 1.4 Hz, 1H, Ar), 7.64 (t, *J* = 8.0 Hz, 1H, Ar), 7.36 (dt, *J* = 8.3, 0.8 Hz, 1H, Ar), 7.28 (ddd, *J* = 8.2, 7.3, 1.0 Hz, 1H, Ar), 7.15 (s, 1H, CH=C), 3.35 (s, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 165.1 (C), 164.7 (C), 148.8 (C), 138.4 (CH), 136.7 (CH), 134.1 (C), 131.3 (CH), 130.1 (CH), 125.8 (CH), 124.4 (CH), 124.3 (CH), 112.6 (CH), 111.5 (CH), 43.2 (CH₃).

***N*-(2-(2-methylbenzylidene)benzofuran-3(2*H*)-ylidene)methanesulfonamide (5l)¹⁸⁴**

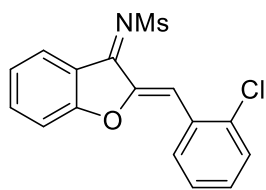
From 2-(2-methylbenzylidene)benzofuran-3(2*H*)-one (1.69 g, 7.2 mmol), 0.82 g (37%) of the title compound were obtained after column chromatography eluting with hexane:EtOAc 8:2, hexane:dichloromethane 5:95. Yellow solid; ¹H NMR (300 MHz, CDCl₃) δ 8.59 (d, *J*

= 7.6 Hz, 1H, Ar), 8.31 – 8.19 (m, 1H, Ar), 7.66 (ddd, *J* = 8.5, 7.3, 1.4 Hz, 1H, Ar), 7.46 (s, 1H, CH=C), 7.40 – 7.19 (m, 5H, Ar), 3.34 (s, 3H, CH₃), 2.53 (s, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 165.5 (C), 164.8 (C), 139.3 (C), 137.8 (CH), 131.5 (CH), 131.1 (C), 130.9 (CH), 130.4 (CH), 126.7 (CH), 123.9 (CH), 112.5 (CH), 43.2 (CH₃), 20.4 (CH₃).

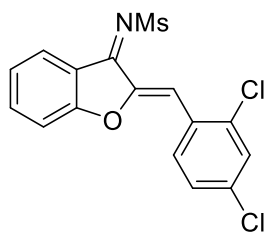
***N*-(2-(2-methoxybenzylidene)benzofuran-3(2*H*)-ylidene)methanesulfonamide (5m)¹³³**

From 2-(2-methoxybenzylidene)benzofuran-3(2*H*)-one (2.0 g, 7.9 mmol), 0.63 g (24%) of the title compound were obtained after column chromatography eluting with hexane:EtOAc 7:3, hexane:DCM 5:95. Yellow solid; ¹H NMR (300 MHz, CDCl₃) δ 8.61 (d, *J* = 8.1

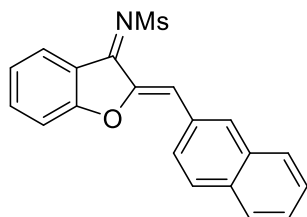
Hz, 1H, Ar), 8.32 (dd, *J* = 7.9, 1.7 Hz, 1H, Ar), 7.75 (s, 1H, CH=C), 7.65 (ddd, *J* = 8.5, 7.3, 1.4 Hz, 1H, Ar), 7.40 (ddd, *J* = 8.4, 7.4, 1.7 Hz, 1H, Ar), 7.34 – 7.18 (m, 2H, Ar), 7.08 (tdd, *J* = 7.4, 1.1, 0.5 Hz, 1H, Ar), 6.94 (dd, *J* = 8.4, 1.1 Hz, 1H, Ar), 3.94 (s, 3H, CH₃), 3.34 (s, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 165.4 (C), 164.6 (C), 158.9 (C), 149.5 (C), 137.5 (CH), 132.4 (CH), 132.2 (CH), 123.7 (CH), 121.6 (C), 121.2 (CH), 118.6 (C), 112.4 (CH), 110.9 (CH), 55.9 (CH₃), 43.2 (CH₃).

***N*-(2-(2-chlorobenzylidene)benzofuran-3(2*H*)-ylidene)methanesulfonamide (5n)¹⁸⁶**

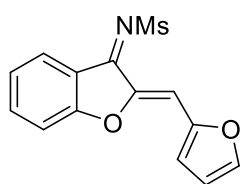
From 2-(2-chlorobenzylidene)benzofuran-3(2*H*)-one (1.4 g, 5.4 mmol), 0.54 g (30%) of the title compound were obtained after column chromatography eluting with hexane:EtOAc 8:2, hexane:DCM 5:95. Yellow solid; ¹H NMR (300 MHz, CDCl₃) δ 8.60 (d, *J* = 7.8 Hz, 1H, Ar), 8.35 (dd, *J* = 7.8, 1.8 Hz, 1H, Ar), 7.73 – 7.61 (m, 2H, Ar+CH=C), 7.48 (dd, *J* = 7.9, 1.4 Hz, 1H, Ar), 7.43 – 7.36 (m, 1H, Ar), 7.34 (dd, *J* = 7.6, 1.9 Hz, 1H, Ar), 7.31 – 7.21 (m, 2H, Ar), 3.36 (s, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 165.3 (C), 164.7 (C), 137.9 (CH), 135.9 (C), 132.5 (CH), 131.3 (CH), 131.1 (CH), 130.5 (C), 130.2 (CH), 127.4 (CH), 124.1 (CH), 112.4 (CH), 110.1 (CH), 43.2 (CH₃).

***N*-(2-(2,4-dichlorobenzylidene)benzofuran-3(2*H*)-ylidene)methanesulfonamide (5o)**

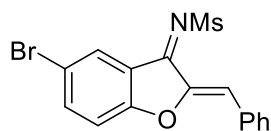
From 2-(2,4-dichlorobenzylidene)benzofuran-3(2*H*)-one (1.25 g, 4.3 mmol), 0.69 g (43%) of the title compound were obtained after column chromatography eluting with hexane:DCM 4:6, hexane:DCM 2:8. Yellow solid; m.p. 176.7–177.7 °C; ¹H NMR (500 MHz, CDCl₃) δ 8.60 (d, *J* = 8.0 Hz, 1H, Ar), 8.29 (d, *J* = 8.6 Hz, 1H, Ar), 7.67 (ddd, *J* = 8.5, 7.3, 1.4 Hz, 1H, Ar), 7.53 (s, 1H, CH=C), 7.49 (d, *J* = 2.1 Hz, 1H, Ar), 7.37 (ddd, *J* = 8.5, 2.2, 0.6 Hz, 1H, Ar), 7.31 – 7.23 (m, 2H, Ar), 3.35 (s, 3H, CH₃); ¹³C NMR (126 MHz, CDCl₃) δ 165.1 (C), 164.6 (C), 150.7 (C), 138.0 (CH), 136.4 (C), 136.3 (C), 133.1 (CH), 131.3 (CH), 130.1 (CH), 129.1 (C), 127.9 (CH), 124.3 (CH), 118.1 (C), 112.4 (CH), 108.7 (CH), 43.2 (CH₃); HRMS (ESI) *m/z*: 367.9911 [M+H]⁺, C₁₆H₁₂Cl₂NO₃S⁺ requires 367.9909.

***N*-(2-(naphthalen-2-ylmethylene)benzofuran-3(2*H*)-ylidene)methanesulfonamide (5p)¹⁸⁶**

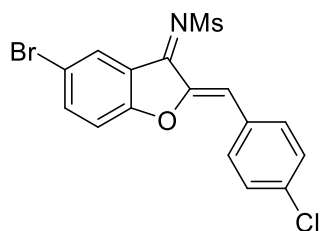
From 2-(naphthalen-2-ylmethylene)benzofuran-3(2*H*)-one (2.10 g, 7.7 mmol), 1.27 g (47%) of the title compound were obtained after column chromatography eluting with hexane:EtOAc 8:2, hexane:DCM 1:9. Yellow solid; ¹H NMR (400 MHz, C₆D₆) δ 9.10 (d, *J* = 8.1 Hz, 1H, Ar), 8.03 – 7.93 (m, 2H, Ar+CH=C), 7.65 – 7.59 (m, 2H, Ar), 7.53 (dd, *J* = 6.1, 3.4 Hz, 1H, Ar), 7.23 (dt, *J* = 6.2, 3.4 Hz, 3H, Ar), 6.88 (ddd, *J* = 8.6, 7.3, 1.4 Hz, 1H, Ar), 6.69 (dtd, *J* = 8.2, 3.5, 1.0 Hz, 2H, Ar), 2.91 (s, 3H, CH₃). Low solubility precluded obtaining a ¹³C NMR spectrum.

***N*-(2-(furan-2-ylmethylene)benzofuran-3(2*H*)-ylidene)methanesulfonamide (5q)**

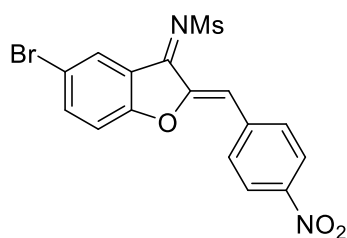
From 2-(furan-2-ylmethylene)benzofuran-3(2*H*)-one (1.20 g, 5.7 mmol), 0.62 g (38%) of the title compound were obtained after column chromatography eluting with hexane:EtOAc 8:2, hexane:DCM 5:95. Orange solid; m.p. 150.5-151.2 °C; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.55 (d, J = 8.0 Hz, 1H, Ar), 7.70 – 7.57 (m, 2H, Ar), 7.32 – 7.26 (m, 1H, Ar), 7.25 – 7.19 (m, 2H, Ar+CH=C), 6.64 (ddd, J = 3.6, 1.8, 0.6 Hz, 1H, Ar), 3.30 (s, 3H, CH_3); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 164.5 (C), 164.2 (C), 162.1 (C), 149.2 (C), 146.1 (CH), 137.5 (CH), 123.9 (CH), 113.8 (CH), 112.4 (CH), 43.1 (CH_3); **HRMS** (ESI) m/z : 290.0484 $[\text{M}+\text{H}]^+$, $\text{C}_{14}\text{H}_{12}\text{NO}_4\text{S}^+$ requires 290.0482.

***N*-(2-benzylidene-5-bromobenzofuran-3(2*H*)-ylidene)methanesulfonamide (5r)**

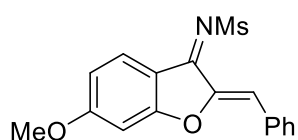
From 2-benzylidene-5-bromobenzofuran-3(2*H*)-one (1.35 g, 4.5 mmol), 0.77 g (46%) of the title compound were obtained after column chromatography eluting with hexane:EtOAc 8:2, hexane:DCM 3:7. Yellow solid; m.p. 224.3-225.1 °C; $^1\text{H NMR}$ (500 MHz, $\text{DMSO}-d_6$) δ 8.55 (s, 1H, Ar), 8.06 – 8.00 (m, 3H, Ar), 7.64 (d, J = 8.9 Hz, 1H, Ar), 7.58 – 7.47 (m, 3H, Ar), 7.31 (s, 1H, CH=C), 3.42 (s, 3H, CH_3); $^{13}\text{C NMR}$ (126 MHz, $\text{DMSO}-d_6$) δ 163.0 (C), 162.8 (C), 140.6 (CH), 131.8 (CH), 130.9 (CH), 129.3 (CH), 115.4 (C), 115.2 (C), 42.7 (CH_3); **HRMS** (ESI) m/z : 377.9786 $[\text{M}+\text{H}]^+$, $\text{C}_{16}\text{H}_{13}\text{BrNO}_3\text{S}^+$ requires 377.9794.

***N*-(5-bromo-2-(4-chlorobenzylidene)benzofuran-3(2*H*)-ylidene)methanesulfonamide (5s)**

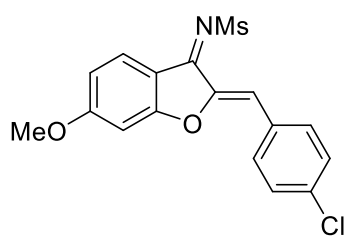
From 5-bromo-2-(4-chlorobenzylidene)benzofuran-3(2*H*)-one (1.5 g, 4.5 mmol), 0.68 g (37%) of the title compound after column chromatography eluting with hexane:EtOAc 8:2, hexane:DCM 4:6. Yellow solid; m.p. 242.1-242.6 °C; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.71 (s, 1H, Ar), 7.84 (d, J = 8.4 Hz, 2H, Ar), 7.76 (dd, J = 8.8, 2.1 Hz, 1H, Ar), 7.44 (d, J = 8.6 Hz, 2H, Ar), 7.21 (dd, J = 8.7, 0.5 Hz, 1H, Ar), 7.13 (s, 1H, CH=C), 3.33 (s, 3H, CH_3); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 163.8 (C), 163.3 (C), 140.5 (CH), 136.9 (C), 133.3 (CH), 133.0 (CH), 130.7 (C), 129.5 (CH), 116.7 (C), 114.7 (CH), 114.0 (CH), 43.1 (CH_3); **HRMS** (ESI) m/z : 411.9395 $[\text{M}+\text{H}]^+$, $\text{C}_{16}\text{H}_{12}\text{BrClNO}_3\text{S}^+$ requires 411.9404.

***N*-(5-bromo-2-(4-nitrobenzylidene)benzofuran-3(2*H*)-ylidene)methanesulfonamide (5t)**

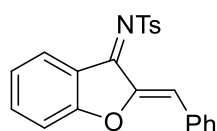
From 5-bromo-2-(4-nitrobenzylidene)benzofuran-3(2*H*)-one (0.4 g, 1.2 mmol), 0.12 g (24%) of the title compound were obtained after column chromatography eluting with hexane:EtOAc 3:7, hexane:DCM 1:9. Yellow solid; m.p. 258.6-259.0 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.73 (s, 1H, Ar), 8.32 (d, *J* = 8.9 Hz, 2H, Ar), 8.06 (d, *J* = 8.8 Hz, 2H, Ar), 7.81 (dd, *J* = 8.8, 2.1 Hz, 1H, Ar), 7.30 – 7.21 (m, 1H, Ar), 7.17 (s, 1H, CH=C), 3.36 (s, 3H, CH₃). Low solubility precluded obtaining a ¹³C NMR spectrum. HRMS (ESI) *m/z*: 422.9634 [M+H]⁺, C₁₆H₁₂BrN₂O₅S⁺ requires 422.9645.

***N*-(2-benzylidene-6-methoxybenzofuran-3(2*H*)-ylidene)methanesulfonamide (5u)**

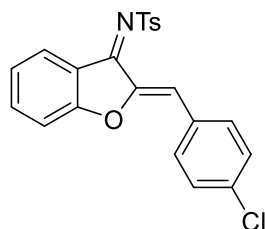
From (*Z*)-2-benzylidene-6-methoxybenzofuran-3(2*H*)-one (1.5 g, 6.0 mmol), 0.64 g (33%) of the title compound were obtained after column chromatography eluting with hexane:EtOAc 7:3, hexane:DCM 1:9. Yellow solid; m.p. 228.6-228.9 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.49 (d, *J* = 9.0 Hz, 1H, Ar), 7.95 – 7.83 (m, 2H, Ar), 7.54 – 7.32 (m, 3H, Ar), 7.09 (s, 1H, CH=C), 6.82 – 6.68 (m, 2H, Ar), 3.93 (s, 3H, CH₃), 3.30 (s, 3H, CH₃); ¹³C NMR (126 MHz, CDCl₃) δ 168.2 (C), 167.6 (C), 163.9 (C), 150.6 (C), 132.5 (C), 132.4 (CH), 131.6 (CH), 130.1 (CH), 129.1 (CH), 114.4 (CH), 112.9 (CH), 111.7 (C), 95.9 (CH), 56.3 (CH₃), 43.0 (CH₃); HRMS (ESI) *m/z*: 330.0792 [M+H]⁺, C₁₇H₁₆NO₄S⁺ requires 330.0795.

***N*-(2-(4-chlorobenzylidene)-6-methoxybenzofuran-3(2*H*)-ylidene)methanesulfonamide (5v)**

From 2-(4-chlorobenzylidene)-6-methoxybenzofuran-3(2*H*)-one (1.7 g, 5.9 mmol), 0.89 g (41%) of the title compound were obtained after column chromatography eluting with hexane:EtOAc 7:3, hexane:DCM 1:9. Yellow solid; m.p. 221.9-222.4 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.48 (d, *J* = 9.0 Hz, 1H, Ar), 7.81 (d, *J* = 8.4 Hz, 2H, Ar), 7.41 (d, *J* = 8.6 Hz, 2H, Ar), 7.00 (s, 1H, CH=C), 6.77 (dd, *J* = 9.0, 2.3 Hz, 1H, Ar), 6.72 (d, *J* = 2.2 Hz, 1H, Ar), 3.93 (s, 3H, CH₃), 3.29 (s, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 168.3 (C), 167.4 (C), 163.7 (C), 150.7 (C), 136.1 (C), 132.6 (CH), 132.4 (CH), 131.0 (C), 129.3 (CH), 113.0 (CH), 112.7 (CH), 111.6 (C), 96.0 (CH), 56.4 (CH₃), 43.0 (CH₃); HRMS (ESI) *m/z*: 364.0402 [M+H]⁺, C₁₇H₁₅ClNO₄S⁺ requires 364.0405.

***N*-(2-benzylidenebenzofuran-3(2*H*)-ylidene)-4-methylbenzenesulfonamide (5w)¹⁸³**

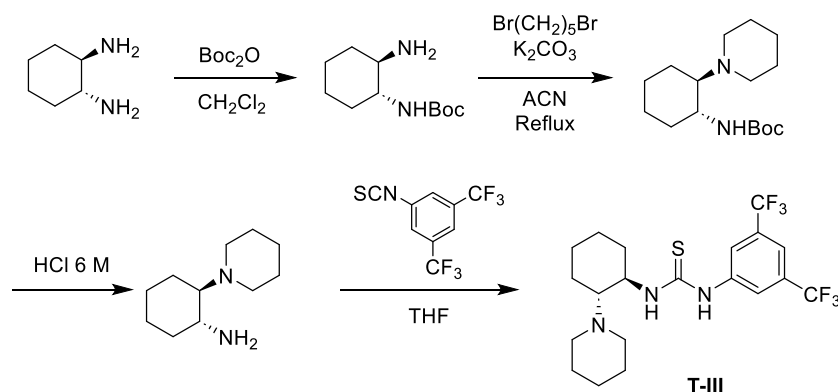
From 2-benzylidenebenzofuran-3(2*H*)-one (4.0 g, 18.0 mmol), 5.27 g (78%) of the title compound were obtained after column chromatography eluting with hexane:EtOAc 8:2, hexane:DCM 95:5. Yellow solid; ¹H NMR (300 MHz, CDCl₃) δ 8.74 (d, *J* = 8.1 Hz, 1H, Ar), 7.96 (d, *J* = 8.3 Hz, 2H, Ar), 7.88 – 7.79 (m, 2H, Ar), 7.63 (ddd, *J* = 8.5, 7.3, 1.4 Hz, 1H, Ar), 7.44 – 7.30 (m, 5H, Ar), 7.30 – 7.20 (m, 2H, Ar), 7.06 (s, 1H, CH=C), 2.43 (s, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 165.3 (C), 164.9 (C), 149.8 (C), 143.5 (C), 139.1 (C), 137.7 (CH), 132.5 (C), 131.8 (CH), 131.2 (CH), 130.4 (CH), 129.6 (CH), 129.1 (CH), 127.2 (CH), 123.9 (CH), 118.5 (C), 115.8 (CH), 112.4 (CH), 21.8 (CH₃).

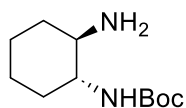
***N*-(2-(4-chlorobenzylidene)benzofuran-3(2*H*)-ylidene)-4-methylbenzenesulfonamide (5x)¹⁸³**

From 2-(4-chlorobenzylidene)benzofuran-3(2*H*)-one (1.5 g, 5.8 mmol), 1.16 g (48%) of the title compound were obtained after column chromatography eluting with hexane:EtOAc 8:2, DCM. Yellow solid; ¹H NMR (300 MHz, CDCl₃) δ 8.77 (d, *J* = 7.8 Hz, 1H, Ar), 7.99 (d, *J* = 8.3 Hz, 2H, Ar), 7.80 (d, *J* = 8.5 Hz, 2H, Ar), 7.68 (ddd, *J* = 8.5, 7.3, 1.4 Hz, 1H, Ar), 7.38 (dd, *J* = 8.3, 3.3 Hz, 4H, Ar), 7.32 (s, 2H, Ar), 7.02 (s, 1H, CH=C), 2.47 (s, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 165.0 (C), 164.8 (C), 149.9 (C), 143.6 (C), 139.0 (C), 137.8 (CH), 136.3 (C), 132.8 (CH), 131.2 (CH), 131.0 (C), 129.6 (CH), 129.4 (CH), 127.2 (CH), 124.1 (CH), 118.4 (C), 114.1 (CH), 112.4 (CH), 21.8 (CH₃).

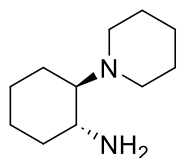
5.4.2 Synthesis and characterization data for catalyst T-III

Catalyst **T-III** was synthesized via a four-step procedure.



***tert*-Butyl ((1*R*,2*R*)-2-aminocyclohexyl)carbamate¹⁸⁷**

A literature procedure was carried out.¹⁸⁸ To a solution of (1*R*,2*R*)-cyclohexane-1,2-diamine (5.0 g, 43.8 mmol, 3.0 equiv.) in dry CH₂Cl₂ (45 mL), at 0 °C, under N₂ atmosphere, was added dropwise, over 30 min, a solution of di-*tert*-butyl decarbonate (3.2 g, 14.6 mmol, 1.0 equiv.) in dry CH₂Cl₂ (35 mL). The reaction was let to warm slowly to room temperature and was stirred overnight. Water (20 ml) and CH₂Cl₂ (18 mL) were added to dissolve the white precipitate that appeared, phases were separated and the organic phase was washed over Na₂SO₄ and concentrated under reduced pressure to give rise to a white solid. The residue was dissolved in water (60 mL) and HCl (aq) 4 M was added until pH 2 (ca. 15 mL). The solution was washed with Et₂O (40 mL) and then basified with NaOH (aq) 4 M until pH > 10. The solution was extracted with EtOAc (4x40 mL) and the organic phase was dried over Na₂SO₄ and concentrated under reduced pressure to yield 2.37 g (76%) of the title compound. White solid; ¹H NMR (300 MHz, CDCl₃) δ 4.47 (bs, 1H, CHN), 3.22 – 3.01 (m, 1H, CHN), 2.38 – 2.23 (m, 1H), 2.04 – 1.87 (m, 2H), 1.76 – 1.61 (m, 2H), 1.43 (s, 9H, *t*-Bu), 1.39 (s, 2H, NH₂), 1.33 – 0.96 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 156.3 (C), 79.4 (C), 57.8 (CH), 55.8 (CH), 35.4 (CH₂), 33.0 (CH₂), 28.5 (CH₃), 25.3 (CH₂), 25.2 (CH₂).

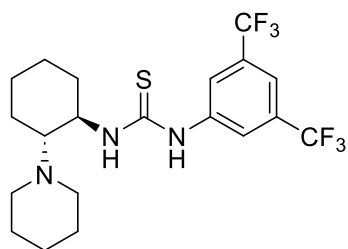
(1*R*,2*R*)-2-(Piperidin-1-yl)cyclohexan-1-amine¹⁸⁷

A modification of a literature procedure was carried out.^{187,189,190} To a mixture of *tert*-butyl ((1*R*,2*R*)-2-aminocyclohexyl)carbamate (1.58 g, 7.37 mmol, 1.0 equiv.) and K₂CO₃ (2.34 g, 16.95 mmol, 2.3 equiv.) in dry acetonitrile (95 mL), under N₂ atmosphere, was added 1,5-dibromopentane (1.2 mL, 8.84 mmol, 1.2 equiv.). The mixture was stirred overnight at reflux and then filtered to remove the insoluble salts. The solution was concentrated under reduced pressure and the crude solid was used without further purification for the next step.

To 1.23 g (3.69 mmol) of the previously obtained crude product was added dropwise HCl (aq) 6 M (4.4 mL, 26.5 mmol) while stirring vigorously. Evolution of gas was observed. The mixture was stirred overnight. The reaction mixture was transferred to a separation funnel and was washed with Et₂O (2x3 mL). 5 mL water were added and the aqueous phase was basified at 0 °C with solid NaOH until pH > 10 (ca. 10 pearls). The mixture was extracted with CH₂Cl₂ (5x30 mL) and the organic phase was washed with brine (10 mL) and dried over Na₂SO₄. Concentration under reduced pressure gave rise to 0.56 g (83%, over two steps) of the title compound as a yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 2.68 – 2.53 (m, 3H), 2.34 – 2.23 (m, 2H), 2.02 – 1.90 (m, 5H), 1.81 – 1.71 (m, 2H), 1.68 – 1.59 (m, 1H), 1.59 – 1.45 (m, 3H), 1.41

(q, $J = 5.1$ Hz, 2H), 1.25 – 1.00 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 71.3 (CH), 50.8 (CH), 49.9 (CH_2), 35.2 (CH_2), 27.0 (CH_2), 26.1 (CH_2), 25.3 (CH_2), 25.2 (CH_2), 22.7 (CH_2).

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((1*R*,2*R*)-2-(piperidin-1-yl)cyclohexyl)thiourea (T-III)¹⁹¹



A modification of a literature procedure was carried out.¹⁹¹ To a solution of (1*R*,2*R*)-2-(piperidin-1-yl)cyclohexan-1-amine (0.6 g, 3.3 mmol) in THF (10 mL), under N_2 atmosphere, was added 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.63 mL, 3.5 mmol, 1.05 equiv.) The mixture was stirred at room temperature for 48

h. Purification by column chromatography (eluent: Hexane:EtOAc 6:4, EtOAc:MeOH 9:1) yielded 1.08 g (72%) of **T-III**. White solid; ^1H NMR (300 MHz, CDCl_3) δ 7.83 (s, 2H, Ar), 7.70 (s, 1H, Ar), 3.89 – 3.62 (m, 1H), 2.83 – 2.51 (m, 3H), 2.47 – 2.25 (m, 3H), 1.99 – 1.66 (m, 3H), 1.47 – 1.08 (m, 10H).

5.4.3 Synthesis and characterization data for compounds **6**

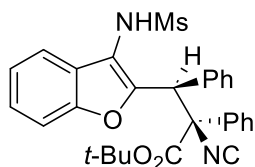
Enantioselective procedure

To a solution of the corresponding sulfonamide **5** (0.20 mmol, 1.0 equiv.) and **T-III** (9.1 mg, 0.02 mmol, 0.1 equiv.) in dry DCM (1.0 mL), at -30°C , was added *tert*-butyl 2-phenylisocyanoacetate (**2g**, 54 μL , 0.26 mmol, 1.3 equiv.) The reaction was stirred for 72 h.

For the determination of the diastereomeric ratio, a short path column chromatography to separate the catalyst **T-III** was carried out and the resulting mixture analyzed by ^1H NMR. Then the product was purified by column chromatography, eluting with hexane:EtOAc mixtures.

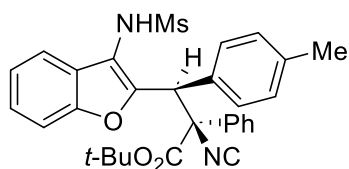
Non-enantioselective procedure

To a solution of the corresponding sulfonamide **5** (0.10 mmol, 1.0 equiv.) and the achiral squaramide 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-((3-(dimethylamino)propyl)amino)cyclobut-3-ene-1,2-dione (4.1 mg, 0.01 mmol, 0.1 equiv.) in DCM (0.5 mL) was added *tert*-butyl 2-phenylisocyanoacetate (**2g**, 27 μL , 0.13 mmol, 1.3 equiv.) The reaction was stirred at room temperature for 48 h and the product was purified by column chromatography, eluting with hexane:EtOAc mixtures.

***tert*-Butyl (2*S*,3*S*)-2-isocyano-3-(3-(methylsulfonamido)benzofuran-2-yl)-2,3-diphenylpropanoate (**6ag**)**

89.1 mg (86%) of **6ag** were obtained from **5a** (59.9 mg, 0.20 mmol) after column chromatography eluting with hexane:EtOAc 8:2, 7:3. Enantiomeric excess (84%) was measured by HPLC (Lux® i-Amylose-1), hexane:iPrOH 80:20, 0.5 mL min⁻¹, major enantiomer: t_r = 26.9 min, minor enantiomer: t_r = 15.4 min.

White solid; m.p. 179.6-180.0 °C; $[\alpha]_D^{25}$ -119.4 (c 0.4, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.73 (ddd, J = 7.7, 1.4, 0.7 Hz, 1H, Ar), 7.62 (dt, J = 8.3, 0.9 Hz, 1H, Ar), 7.49 – 7.43 (m, 2H, Ar), 7.37 (ddd, J = 8.4, 7.3, 1.4 Hz, 1H, Ar), 7.35 – 7.29 (m, 4H, Ar), 7.22 – 7.15 (m, 3H, Ar), 7.12 (t, J = 7.2 Hz, 2H, Ar), 6.50 (s, 1H, NH), 5.23 (s, 1H, CHAr), 2.82 (s, 3H, Me), 1.28 (s, 9H, tBu); ¹³C NMR (75 MHz, CDCl₃) δ 166.5 (C), 164.4 (C), 153.8 (C), 151.1 (C), 133.6 (C), 133.3 (C), 130.3 (CH), 129.2 (CH), 128.8 (CH), 128.3 (CH), 128.2 (CH), 125.6 (CH), 125.4 (CH), 125.4 (C), 123.8 (CH), 120.2 (CH), 115.1 (C), 112.0 (CH), 85.4 (C), 74.0 (C), 50.7 (CH), 39.6 (CH₃), 27.4 (CH₃); IR (ATR) ν 3288 (w), 2978 (w), 2140 (w, NC), 1733 (m), 1454 (m), 1323 (m), 1279 (m), 1148 (s), 958 (m), 842 (w), 757 (s), 716 (s), 626 (m), 507 (m) cm⁻¹; HRMS (ESI) m/z : 517.1784 [M+H]⁺, C₂₉H₂₉N₂O₅S⁺ requires 517.1792.

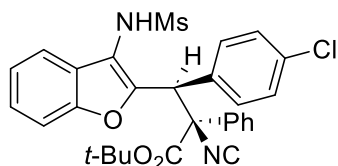
***tert*-Butyl (2*S*,3*S*)-2-isocyano-3-(3-(methylsulfonamido)benzofuran-2-yl)-2-phenyl-3-(*p*-tolyl)propanoate (**6bg**)**

88.6 mg (83%) of **6bg** were obtained from **5b** (62.7 mg, 0.20 mmol) after column chromatography eluting with hexane:EtOAc 8:2, 7:3. Enantiomeric excess (83%) was measured by HPLC (CHIRALPAK® IG), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: t_r = 11.6 min, minor enantiomer: t_r = 10.0 min.

White solid; m.p. 83.5-84.7 °C; $[\alpha]_D^{25}$ -111.3 (c 0.4, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.80 – 7.71 (m, 1H, Ar), 7.66 – 7.57 (m, 1H, Ar), 7.55 – 7.45 (m, 2H, Ar), 7.41 – 7.27 (m, 5H, Ar), 7.07 (d, J = 8.2 Hz, 2H, Ar), 6.92 (d, J = 8.5 Hz, 1H, Ar), 6.63 (s, 1H, NH), 5.24 (s, 1H, CHAr), 2.79 (s, 3H, Me), 2.21 (s, 3H, Me), 1.27 (s, 9H, tBu); ¹³C NMR (75 MHz, CDCl₃) δ 166.5 (C), 164.3 (C), 153.8 (C), 151.3 (C), 138.1 (C), 133.3 (C), 130.5 (CH), 130.1 (CH), 129.2 (CH), 129.0 (CH), 128.8 (CH), 125.6 (CH), 125.4 (C), 125.3 (CH), 123.8 (CH), 120.2 (CH), 115.0 (C), 111.9 (CH), 85.3 (C), 74.0 (C), 50.4 (CH), 39.6 (CH₃), 27.4 (CH₃), 21.1 (CH₃); IR (ATR) ν 3243 (w), 2930 (w), 2978 (w), 2140 (w, NC), 1733 (m), 1618 (w), 1454 (m), 1372

(m), 1320 (m), 1252 (m), 1148 (s), 969 (m), 835 (m), 738 (s), 697 (m), 514 (m) cm^{-1} ; **HRMS** (ESI) m/z : 548.2217 $[\text{M}+\text{NH}_4]^+$, $\text{C}_{30}\text{H}_{34}\text{N}_3\text{O}_5\text{S}^+$ requires 548.2214.

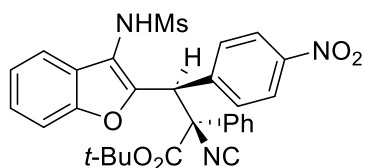
***tert*-Butyl (2*S*,3*S*)-3-(4-chlorophenyl)-2-isocyano-3-(3-(methylsulfonamido)benzofuran-2-yl)-2-phenylpropanoate (6dg)**



110.2 mg (99%) of **6dg** were obtained from **5d** (66.8 mg, 0.20 mmol) after column chromatography eluting with hexane:EtOAc 8:2, 7:3. Enantiomeric excess (86%) was measured by HPLC (CHIRALPAK® AD-H), hexane:iPrOH 80:20, 1.0 mL min^{-1} , major enantiomer: $t_r = 14.3$ min, minor enantiomer: $t_r = 7.7$ min.

Yellowish solid; m.p. 86.0-87.7 $^{\circ}\text{C}$; $[\alpha]_D^{25} -119.4$ (c 0.4, CHCl_3); **$^1\text{H NMR}$** (300 MHz, CDCl_3) δ 7.72 (d, $J = 7.8$ Hz, 1H, Ar), 7.63 (d, $J = 7.7$ Hz, 1H, Ar), 7.51 (dd, $J = 6.8, 3.1$ Hz, 2H, Ar), 7.45 – 7.27 (m, 5H, Ar), 7.23 – 7.04 (m, 4H, Ar), 6.78 (s, 1H, NH), 5.35 (s, 1H, CHAr), 2.86 (s, 3H, Me), 1.26 (s, 9H, tBu); **$^{13}\text{C NMR}$** (75 MHz, CDCl_3) δ 166.2 (C), 164.7 (C), 153.8 (C), 150.9 (C), 134.4 (C), 133.0 (C), 132.2 (C), 131.6 (CH), 129.4 (CH), 129.0 (CH), 128.4 (CH), 125.6 (CH), 125.5 (CH), 125.2 (C), 124.0 (CH), 119.8 (CH), 115.3 (C), 112.1 (CH), 85.5 (C), 73.9 (C), 49.9 (CH), 39.8 (CH_3), 27.4 (CH_3); **IR** (ATR) ν 3235 (w), 2982 (w), 2140 (w, NC), 1733 (m), 1491 (m), 1454 (m), 1319 (m), 1200 (m), 1148 (s), 1092 (m), 1013 (m), 969 (m), 834 (m), 741 (s), 697 (m), 634 (m), 585 (m), 511 (m) cm^{-1} ; **HRMS** (ESI) m/z : 551.1392 $[\text{M}+\text{H}]^+$, $\text{C}_{29}\text{H}_{28}\text{ClN}_2\text{O}_5\text{S}^+$ requires 551.1402.

***tert*-Butyl (2*S*,3*S*)-2-isocyano-3-(3-(methylsulfonamido)benzofuran-2-yl)-3-(4-nitrophenyl)-2-phenylpropanoate (6eg)**

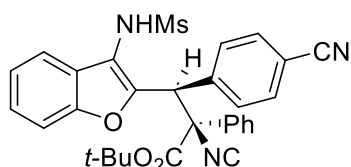


120.0 mg (99%) of **6eg** were obtained from **5c** (68.9 mg, 0.20 mmol) after column chromatography eluting with hexane:EtOAc 8:2, 7:3. Enantiomeric excess (88%) was measured by HPLC (CHIRALPAK® IC), hexane:iPrOH 80:20, 1.0 mL min^{-1} , major enantiomer: $t_r = 37.3$ min, minor enantiomer: $t_r = 19.5$ min.

Yellowish solid; m.p. 82.1-82.9 $^{\circ}\text{C}$; $[\alpha]_D^{25} -102.1$ (c 0.4, CHCl_3); **$^1\text{H NMR}$** (300 MHz, CDCl_3) δ 7.97 (d, $J = 8.9$ Hz, 1H, Ar), 7.72 – 7.63 (m, 1H, Ar), 7.54 – 7.48 (m, 1H, Ar), 7.48 – 7.38 (m, 2H, Ar), 7.38 – 7.30 (m, 4H, Ar), 6.80 (s, 1H, NH), 5.59 (s, 1H, CHAr), 2.93 (s, 3H, Me), 1.26 (s, 9H, tBu); **$^{13}\text{C NMR}$** (75 MHz, CDCl_3) δ 165.8 (C), 165.2 (C), 153.9 (C), 150.4 (C), 147.5 (C), 141.0 (C), 132.6 (C), 131.4 (CH), 129.6 (CH), 129.1 (CH), 125.9 (CH), 125.4 (CH), 124.9 (C), 124.2 (CH), 123.1 (CH), 119.2 (CH), 115.7 (C), 112.3 (CH), 85.7 (C), 73.7 (C), 50.0

(CH), 40.1 (CH₃), 27.4 (CH₃); **IR** (ATR) ν 3243 (w), 2978 (w), 2933 (w), 2140 (w, NC), 1737 (m), 1603 (w), 1521 (m), 1454 (m), 1346 (s), 1252 (m), 1148 (s), 969 (m), 857 (m), 712 (s), 582 (m), 514 (m) cm⁻¹; **HRMS** (ESI) m/z : 579.1901 [M+NH₄]⁺, C₂₉H₃₁N₄O₇S⁺ requires 579.1908.

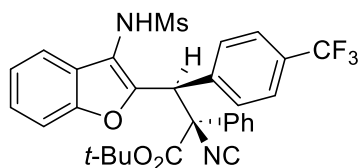
***tert*-Butyl (2*S*,3*S*)-3-(4-cyanophenyl)-2-isocyano-3-(3-(methylsulfonamido)benzofuran-2-yl)-2-phenylpropanoate (6fg)**



99.3 mg (92%) of **6fg** were obtained from **5f** (64.9 mg, 0.20 mmol) after column chromatography eluting with hexane:EtOAc 75:25, 7:3. Enantiomeric excess (88%) was measured by HPLC (CHIRALPAK® AD-H), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: t_r = 17.4 min, minor enantiomer: t_r = 11.4 min.

Yellowish solid; m.p. 101.2-102.0 °C; $[\alpha]_D^{25}$ -133.3 (c 0.4, CHCl₃); **¹H NMR** (300 MHz, CDCl₃) δ 7.72 – 7.60 (m, 2H, Ar), 7.54 – 7.45 (m, 2H, Ar), 7.45 – 7.30 (m, 9H, Ar), 6.76 (s, 1H, NH), 5.50 (s, 1H, CHAr), 2.92 (s, 3H, Me), 1.26 (s, 9H, tBu); **¹³C NMR** (75 MHz, CDCl₃) δ 165.9 (C), 165.1 (C), 153.8 (C), 150.5 (C), 139.0 (C), 132.6 (C), 131.7 (CH), 131.1 (CH), 129.6 (CH), 129.1 (CH), 125.8 (CH), 125.4 (CH), 124.9 (C), 124.1 (CH), 119.3 (CH), 118.5 (CH), 115.7 (C), 112.3 (CH), 112.1 (C), 85.7 (C), 73.7 (C), 50.3 (CH), 40.1 (CH₃), 27.4 (CH₃); **IR** (ATR) ν 3220 (w), 2933 (w), 2978 (w), 2229 (w, CN), 2140 (w, NC), 1737 (m), 1454 (m), 1320 (m), 1256 (m), 1148 (s), 969 (m), 835 (m), 745 (s), 701 (m), 585 (m), 514 (m) cm⁻¹; **HRMS** (ESI) m/z : 559.2003 [M+NH₄]⁺, C₃₀H₃₁N₄O₅S⁺ requires 559.2010.

***tert*-Butyl (2*S*,3*S*)-2-isocyano-3-(3-(methylsulfonamido)benzofuran-2-yl)-2-phenyl-3-(4-(trifluoromethyl)phenyl)propanoate (6gg)**

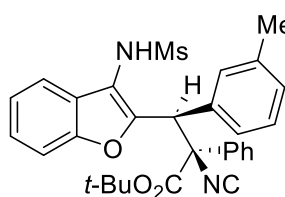


100.3 mg (86%) of **6gg** were obtained from **5g** (73.5 mg, 0.20 mmol) after column chromatography eluting with hexane:EtOAc 8:2. Enantiomeric excess (89%) was measured by HPLC (CHIRALPAK® AD-H), hexane:iPrOH 90:10, 1.0 mL min⁻¹, major enantiomer: t_r = 23.9 min, minor enantiomer: t_r = 10.9 min.

Yellowish solid; m.p. 194.5-194.9 °C; $[\alpha]_D^{25}$ -140.0 (c 0.1, CHCl₃); **¹H NMR** (500 MHz, DMSO-*d*₆) δ 9.49 (s, 1H, NH), 7.77 – 7.71 (m, 1H, Ar), 7.68 (d, J = 8.1 Hz, 1H, Ar), 7.58 – 7.54 (m, 4H, Ar), 7.53 – 7.45 (m, 3H, Ar), 7.43 – 7.37 (m, 1H, Ar), 7.36 – 7.31 (m, 1H, Ar), 7.17 (d, J = 8.1 Hz, 2H, Ar), 5.89 (s, 1H, CHAr), 2.40 (s, 3H, Me), 1.15 (s, 9H, tBu); **¹³C NMR** (75 MHz, DMSO-*d*₆) δ 164.2 (C), 163.8 (C), 152.8 (CH), 148.8 (C), 139.6 (C), 132.8 (C), 130.6

(CH), 129.6 (CH), 129.0 (CH), 128.3 (q, $^2J_{C-F} = 31.5$ Hz, C), 125.5 (CH), 125.3 (CH), 125.0 (C), 124.7 (q, $^3J_{C-F} = 3.8$ Hz, CH), 124.1 (CH), 124.0 (q, $^1J_{C-F} = 271.7$ Hz, C), 123.5 (CH), 120.5 (CH), 116.2 (C), 111.4 (CH), 84.6 (C), 73.9 (C), 48.6 (CH), 26.8 (CH₃); **IR** (ATR) ν 3269 (w), 2982 (w), 2933 (w), 2162 (w, NC), 1756 (m), 1618 (w), 1454 (w), 1327 (s), 1260 (m), 1148 (s), 1066 (s), 1021 (m), 962 (m), 881 (m), 745 (s), 712 (m), 746 (m), 608 (m), 410 (m) cm^{-1} ; **HRMS** (ESI) m/z : 602.1914 $[\text{M}+\text{H}]^+$, $\text{C}_{30}\text{H}_{27}\text{F}_3\text{N}_2\text{O}_5\text{S}^+$ requires 602.1931.

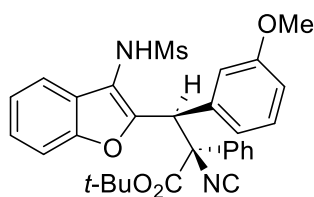
***tert*-Butyl (2*S*,3*S*)-2-isocyano-3-(3-(methylsulfonamido)benzofuran-2-yl)-2-phenyl-3-(*m*-tolyl)propanoate (**6hg**)**



94.4 mg (89%) of **6hg** were obtained from **5h** (62.7 mg, 0.20 mmol) after column chromatography eluting with hexane:EtOAc 8:2, 7:3. Enantiomeric excess (82%) was measured by HPLC (Lux® i-Amylose-1), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: $t_r = 13.3$ min, minor enantiomer: $t_r = 7.5$ min.

Yellowish solid; m.p. 166.5-167.0 °C; $[\alpha]_D^{25} -156.4$ (c 0.4, CHCl_3); **¹H NMR** (300 MHz, CDCl_3) δ 7.77 (d, $J = 7.1$ Hz, 1H, Ar), 7.63 (d, $J = 8.0$ Hz, 1H, Ar), 7.53 – 7.43 (m, 2H, Ar), 7.35 (q, $J = 8.0$ Hz, 5H, Ar), 6.96 (d, $J = 9.5$ Hz, 3H, Ar), 6.63 (s, 1H, NH), 5.23 (s, 1H, CHAr), 2.77 (s, 3H, Me), 2.16 (s, 3H, Me), 1.28 (s, 9H, tBu); **¹³C NMR** (75 MHz, CDCl_3) δ 166.4 (C), 164.2 (C), 153.8 (C), 151.2 (C), 137.8 (C), 133.5 (C), 133.4 (C), 130.9 (CH), 129.2 (CH), 129.1 (CH), 128.8 (CH), 128.0 (CH), 127.3 (CH), 125.6 (CH), 125.4 (C), 125.3 (CH), 123.8 (CH), 120.2 (CH), 115.0 (C), 112.0 (CH), 85.3 (C), 73.9 (C), 50.8 (CH), 39.6 (CH₃), 27.4 (CH₃), 21.4 (CH₃); **IR** (ATR) ν 3239 (w), 2974 (w), 2926 (w), 2147 (w, NC), 1748 (m), 1607 (w), 1450 (m), 1372 (m), 1320 (m), 1252 (m), 1197 (m), 1148 (s), 1103 (m), 973 (m), 839 (m), 757 (s), 693 (m), 634 (m), 440 (m) cm^{-1} ; **HRMS** (ESI) m/z : 548.2189 $[\text{M}+\text{NH}_4]^+$, $\text{C}_{30}\text{H}_{34}\text{N}_3\text{O}_5\text{S}^+$ requires 548.2214. Compound **6gh** was re-crystallized from hexane-DCM to give suitable crystals for X-ray analysis.

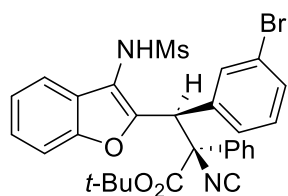
***tert*-Butyl (2*S*,3*S*)-2-isocyano-3-(3-methoxyphenyl)-3-(3-(methylsulfonamido)benzofuran-2-yl)-2-phenylpropanoate (**6ig**)**



86.4 mg (84%) of **6ig** were obtained from **5i** (65.9 mg, 0.20 mmol) after column chromatography eluting with hexane:EtOAc 8:2, 75:25. Enantiomeric excess (88%) was measured by HPLC (CHIRALPAK® AD-H), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: $t_r = 27.9$ min, minor enantiomer: $t_r = 9.5$ min.

Yellowish solid; m.p. 79.1-79.9 °C; $[\alpha]_D^{25} -134.4$ (*c* 0.4, CHCl₃); **¹H NMR** (300 MHz, CDCl₃) δ 7.81 – 7.71 (m, 1H, Ar), 7.65 – 7.58 (m, 1H, Ar), 7.58 – 7.45 (m, 2H, Ar), 7.42 – 7.27 (m, 5H, Ar), 7.08 – 6.96 (m, 1H, Ar), 6.81 – 6.69 (m, 3H, Ar), 6.68 (s, 1H, NH), 5.26 (s, 1H, CHAr), 3.61 (s, 3H, Me), 2.81 (s, 3H, Me), 1.27 (s, 9H, tBu); **¹³C NMR** (75 MHz, CDCl₃) δ 166.4 (C), 164.5 (C), 159.2 (C), 153.8 (C), 150.9 (C), 134.9 (C), 133.3 (C), 129.2 (CH), 129.1 (CH), 128.9 (CH), 125.6 (CH), 125.4 (CH), 125.3 (C), 123.8 (CH), 122.6 (CH), 120.2 (CH), 115.6 (C), 115.2 (CH), 114.2 (CH), 112.0 (CH), 85.4 (C), 73.9 (C), 55.2 (CH₃), 50.7 (CH), 39.6 (CH₃), 27.4 (CH₃); **IR** (ATR) ν 3235 (w), 2978 (w), 2937 (w), 2837 (w), 2140 (w, NC), 1733 (m), 1599 (w), 1491 (w), 1454 (m), 1320 (m), 1256 (m), 1148 (s), 1040 (m), 969 (m), 835 (m), 749 (s), 835 (m), 514 (m) cm⁻¹; **HRMS** (ESI) *m/z*: 564.2118 [M+NH₄]⁺, C₂₉H₃₄N₃O₆S⁺ requires 564.2163.

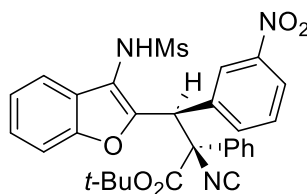
***tert*-Butyl (2*S*,3*S*)-3-(3-bromophenyl)-2-isocyano-3-(3-(methylsulfonamido)benzofuran-2-yl)-2-phenylpropanoate (6jg)**



104.4 mg (88%) of **6jg** were obtained from **5j** (75.6 mg, 0.20 mmol) after column chromatography eluting with hexane:EtOAc 8:2, 7:3. Enantiomeric excess (89%) was measured by HPLC (CHIRALPAK® AD-H), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: *t_r* = 27.7 min, minor enantiomer: *t_r* = 8.5 min.

White foam; m.p. 88.1-88.7 °C; $[\alpha]_D^{25} -126.0$ (*c* 0.4, CHCl₃); **¹H NMR** (300 MHz, CDCl₃) δ 7.74 (d, *J* = 7.6 Hz, 1H, Ar), 7.65 (d, *J* = 7.8 Hz, 1H, Ar), 7.50 (dd, *J* = 6.7, 3.1 Hz, 2H, Ar), 7.45 – 7.33 (m, 4H, Ar), 7.35 – 7.26 (m, 3H, Ar), 7.17 (dt, *J* = 7.9, 1.4 Hz, 2H, Ar), 7.04 – 6.96 (m, 1H, Ar), 6.78 (s, 1H, NH), 5.32 (s, 1H, CHAr), 2.85 (s, 3H, Me), 1.27 (s, 9H, tBu); **¹³C NMR** (75 MHz, CDCl₃) δ 166.1 (C), 164.8 (C), 153.8 (C), 150.6 (C), 135.9 (C), 133.1 (CH), 133.0 (C), 131.4 (CH), 129.6 (CH), 129.4 (CH), 129.0 (CH), 128.9 (CH), 125.6 (CH), 125.5 (CH), 125.1 (C), 124.0 (CH), 122.0 (C), 119.9 (CH), 115.4 (C), 112.2 (CH), 85.5 (C), 73.8 (C), 50.2 (CH), 39.8 (CH₃), 27.4 (CH₃); **IR** (ATR) ν 3239 (w), 2982 (w), 2933 (w), 2140 (w, NC), 1733 (m), 1592 (w), 1450 (m), 1320 (m), 1252 (m), 1148 (s), 969 (m), 835 (m), 745 (s), 693 (m), 574 (m), 514 (m), 436 (m) cm⁻¹; **HRMS** (ESI) *m/z*: 612.1183 [M+NH₄]⁺, C₂₉H₃₁BrN₃O₅S⁺ requires 612.1162.

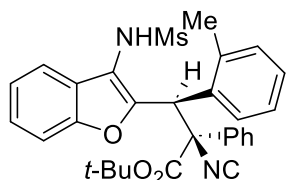
***tert*-Butyl (2*S*,3*S*)-2-isocyano-3-(3-(methylsulfonamido)benzofuran-2-yl)-3-(3-nitrophenyl)-2-phenylpropanoate (**6kg**)**



112.3 mg (99%) of **6kg** were obtained from **5k** (68.9 mg, 0.20 mmol) after column chromatography eluting with hexane:EtOAc 75:25, 7:3. Enantiomeric excess (88%) was measured by HPLC (CHIRALPAK® AD-H), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: t_r = 14.7 min, minor enantiomer: t_r = 10.5 min.

Yellowish solid; m.p. 101.2-101.7 °C; $[\alpha]_D^{25}$ -131.5 (c 0.4, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 8.08 – 7.98 (m, 2H, Ar), 7.69 (t, J = 7.3 Hz, 3H, Ar), 7.55 – 7.48 (m, 2H, Ar), 7.46 – 7.38 (m, 1H, Ar), 7.38 – 7.29 (m, 5H, Ar), 6.84 (s, 1H, NH), 5.58 (s, 1H, CHAr), 2.92 (s, 3H, Me), 1.27 (s, 9H, tBu); ¹³C NMR (75 MHz, CDCl₃) δ 165.8 (C), 165.2 (C), 153.9 (C), 150.3 (C), 147.7 (C), 136.4 (CH), 135.8 (C), 132.6 (C), 129.7 (CH), 129.1 (CH), 129.0 (CH), 125.9 (CH), 125.4 (CH), 125.2 (CH), 124.9 (C), 124.2 (CH), 123.1 (CH), 119.4 (CH), 115.8 (C), 112.3 (CH), 85.7 (C), 73.8 (C), 50.0 (CH), 40.1 (CH₃), 27.4 (CH₃); IR (ATR) ν 3243 (w), 2978 (w), 2933 (w), 2140 (w, NC), 1737 (m), 1528 (m), 1450 (m), 1349 (m), 1320 (m), 1252 (m), 1148 (s), 969 (m), 839 (m), 746 (s), 716 (s), 514 (m), 440 (w) cm⁻¹; HRMS (ESI) m/z : 579.1907 [M+NH₄]⁺, C₂₉H₃₁N₄O₇S⁺ requires 579.1908.

***tert*-Butyl (2*S*,3*S*)-2-isocyano-3-(3-(methylsulfonamido)benzofuran-2-yl)-2-phenyl-3-(*o*-tolyl)propanoate (**6lg**)**

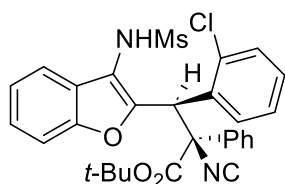


35.1 mg (33%) of **6lg** were obtained from **5l** (62.7 mg, 0.20 mmol) after column chromatography eluting with hexane:EtOAc 8:2, 7:3. Enantiomeric excess (71%) was measured by HPLC (Lux® i-Amylose-1), hexane:iPrOH 85:15, 1.0 mL min⁻¹, major enantiomer: t_r = 20.8 min, minor enantiomer: t_r = 19.2 min.

Orange oil; $[\alpha]_D^{25}$ -115.7 (c 0.6, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.87 (dd, J = 7.8, 1.5 Hz, 1H, Ar), 7.70 – 7.64 (m, 1H, Ar), 7.62 – 7.56 (m, 1H, Ar), 7.40 – 7.27 (m, 6H, Ar), 7.24 – 7.07 (m, 2H, Ar), 6.94 – 6.85 (m, 1H, Ar), 6.09 (s, 1H, NH), 5.53 (s, 1H, CHAr), 2.83 (s, 3H, Me), 1.64 (s, 3H, Me), 1.36 (s, 9H, tBu); ¹³C NMR (75 MHz, CDCl₃) δ 166.4 (C), 163.9 (C), 153.5 (C), 152.9 (C), 137.6 (C), 133.7 (C), 132.2 (C), 130.8 (CH), 130.3 (CH), 129.3 (CH), 128.7 (CH), 128.4 (CH), 126.3 (CH), 125.9 (CH), 125.6 (C), 125.2 (CH), 123.8 (CH), 119.8 (CH), 114.2 (C), 112.0 (CH), 85.3 (C), 73.6 (C), 45.7 (CH), 40.3 (CH₃), 27.5 (CH₃), 19.2 (CH₃); IR (ATR) ν 3228 (w), 3982 (w), 2933 (w), 2140 (w, NC), 1733 (m), 1454 (m), 1372 (m), 1320

(m), 1252 (m), 1148 (s), 969 (m), 835 (m), 738 (s), 701 (m), 589 (m), 462 (m), 514 (m), 462 (m) cm^{-1} ; **HRMS** (ESI) m/z : 531.1919 $[\text{M}+\text{H}]^+$, $\text{C}_{30}\text{H}_{31}\text{N}_2\text{O}_5\text{S}^+$ requires 531.1914.

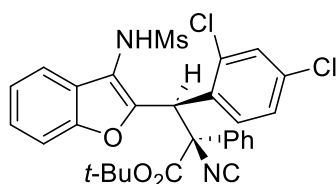
***tert*-Butyl (2*S*,3*S*)-3-(2-chlorophenyl)-2-isocyano-3-(3-(methylsulfonamido)benzofuran-2-yl)-2-phenylpropanoate (**6ng**)**



39.9 mg (36%) of **6ng** were obtained from **5n** (66.8 mg, 0.20 mmol) after column chromatography eluting with hexane:EtOAc 8:2, 7:3. Enantiomeric excess (81%) was measured by HPLC (CHIRALPAK® IG), hexane:iPrOH 80:20, 1.0 mL min^{-1} , major enantiomer: $t_r = 10.3$ min, minor enantiomer: $t_r = 11.9$ min.

Orange oil; $[\alpha]_D^{25} -118.3$ (c 0.2, CHCl_3); **$^1\text{H NMR}$** (300 MHz, CDCl_3) δ 8.36 (dd, $J = 8.0, 1.6$ Hz, 1H, Ar), 7.88 (ddd, $J = 7.5, 1.6, 0.7$ Hz, 1H, Ar), 7.61 – 7.54 (m, 1H, Ar), 7.41 – 7.32 (m, 4H, Ar), 7.32 – 7.22 (m, 3H, Ar), 7.19 – 7.13 (m, 1H, Ar), 7.09 (dd, $J = 8.1, 1.5$ Hz, 1H, Ar), 6.77 (s, 1H, NH), 5.93 (s, 1H, CHAr), 2.98 (s, 3H, Me), 1.32 (s, 9H, tBu); **$^{13}\text{C NMR}$** (75 MHz, CDCl_3) δ 166.8 (C), 165.0 (C), 154.0 (C), 147.9 (C), 134.5 (C), 132.3 (C), 132.1 (CH), 131.3 (C), 129.8 (CH), 129.4 (CH), 129.4 (CH), 128.6 (CH), 127.4 (CH), 125.6 (CH), 125.1 (C), 123.8 (CH), 121.5 (CH), 116.3 (C), 111.7 (CH), 86.2 (C), 73.9 (C), 44.3 (CH), 39.8 (CH_3), 27.5 (CH_3); **IR** (ATR) ν 3235 (w), 2982 (w), 2933 (w), 2140 (w, NC), 1730 (m), 1614 (w), 1566 (w), 1450 (m), 1372 (m), 1323 (m), 1252 (m), 1148 (s), 1040 (m), 969 (m), 835 (m), 742 (s), 697 (m), 507 (m), 585 (m), 507 (m) cm^{-1} ; **HRMS** (ESI) m/z : 551.1367 $[\text{M}+\text{H}]^+$, $\text{C}_{29}\text{H}_{27}\text{ClN}_2\text{O}_5\text{S}^+$ requires 551.1368.

***tert*-Butyl (2*S*,3*S*)-3-(2,4-dichlorophenyl)-2-isocyano-3-(3-(methylsulfonamido)benzofuran-2-yl)-2-phenylpropanoate (**6og**)**

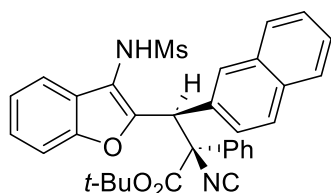


99.7 mg (85%) of **6og** were obtained from **5o** (73.6 mg, 0.20 mmol) after column chromatography eluting with hexane:EtOAc 8:2. Enantiomeric excess (80%) was measured by HPLC (Lux® i-Amylose-1), hexane:iPrOH 80:20, 1.0 mL min^{-1} , major enantiomer: $t_r = 6.0$ min, minor enantiomer: $t_r = 6.8$ min.

White solid; m.p. 110.4–111.0 $^\circ\text{C}$; $[\alpha]_D^{25} -137.3$ (c 0.4, CHCl_3); **$^1\text{H NMR}$** (500 MHz, CDCl_3) δ 8.33 (d, $J = 8.6$ Hz, 1H, Ar), 7.86 (ddd, $J = 7.8, 1.4, 0.7$ Hz, 1H, Ar), 7.57 (dt, $J = 8.3, 0.9$ Hz, 1H, Ar), 7.41 – 7.34 (m, 3H, Ar), 7.35 – 7.26 (m, 5H, Ar), 7.12 (d, $J = 2.2$ Hz, 1H, Ar), 6.82 (s, 1H, NH), 5.88 (s, 1H, CHAr), 3.01 (s, 3H, Me), 1.30 (s, 9H, tBu); **$^{13}\text{C NMR}$** (126 MHz, CDCl_3) δ 166.7 (C), 165.3 (C), 154.1 (C), 147.6 (C), 135.2 (C), 135.2 (C), 132.8 (CH), 132.1

(C), 129.9 (C), 129.6 (CH), 129.2 (CH), 128.8 (CH), 127.7 (CH), 125.8 (CH), 125.6 (CH), 125.0 (C), 123.9 (CH), 121.4 (CH), 116.4 (C), 111.8 (CH), 86.4 (C), 73.8 (C), 43.9 (CH), 40.1 (CH₃), 27.4 (CH₃); **IR** (ATR) ν 3243 (w), 2982 (w), 2933 (w), 2140 (w, NC), 1733 (m), 1588 (w), 1454 (m), 1372 (m), 1323 (m), 1252 (m), 1148 (s), 969 (m), 835 (m), 746 (s), 693 (m), 633 (m), 589 (m), 421 (m) cm⁻¹; **HRMS** (ESI) m/z : 602.1267 [M+NH₄]⁺, C₂₉H₃₀Cl₂N₃O₅S⁺ requires 602.1278.

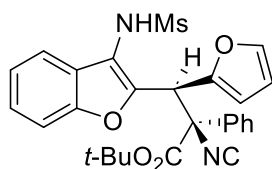
***tert*-Butyl (2*S*,3*S*)-2-isocyano-3-(3-(methylsulfonamido)benzofuran-2-yl)-3-(naphthalen-2-yl)-2-phenylpropanoate (6pg)**



51.1 mg (45%) of **6pg** were obtained from **5p** (69.9 mg, 0.20 mmol) after column chromatography eluting with hexane:EtOAc 8:2. Enantiomeric excess (67%) was measured by HPLC (CHIRALPAK® IC), hexane:iPrOH 90:10, 0.5 mL min⁻¹, major enantiomer: t_r = 33.9 min, minor enantiomer: t_r = 38.3 min.

Yellow solid; m.p. 174.2-174.6 °C; $[\alpha]_D^{25}$ -102.8 (c 0.1, CHCl₃); **¹H NMR** (500 MHz, CDCl₃) δ 7.76 – 7.63 (m, 5H, Ar), 7.57 (d, J = 8.6 Hz, 1H, Ar), 7.49 (d, J = 3.3 Hz, 2H, Ar), 7.44 – 7.37 (m, 3H, Ar), 7.35 – 7.28 (m, 4H, Ar), 7.23 (d, J = 8.6 Hz, 1H, Ar), 6.51 (s, 1H, NH), 5.46 (s, 1H, CHAr), 2.78 (s, 3H, Me), 1.29 (s, 9H, tBu); **¹³C NMR** (126 MHz, CDCl₃) δ 166.5 (C), 164.7 (C), 153.9 (C), 151.5 (C), 133.3 (C), 132.9 (C), 132.8 (C), 131.0 (C), 129.8 (CH), 129.3 (CH), 128.9 (CH), 128.3 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 126.6 (CH), 126.3 (CH), 125.6 (CH), 125.5 (CH), 123.9 (CH), 120.0 (CH), 115.1 (C), 112.1 (CH), 85.5 (C), 74.0 (C), 50.9 (CH), 39.8 (CH₃), 27.5 (CH₃); **IR** (ATR) ν 3228 (w), 3056 (w), 2982 (w), 2933 (w), 2140 (w, NC), 1733 (m), 1554 (w), 1454 (m), 1372 (m), 1320 (m), 1252 (m), 1148 (s), 969 (m), 746 (s), 693 (m), 514 (m) cm⁻¹; **HRMS** (ESI) m/z : 584.2195 [M+NH₄]⁺, C₃₃H₃₄N₃O₅S⁺ requires 584.2214.

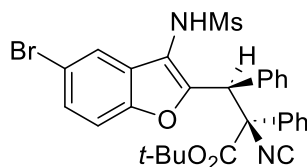
***tert*-Butyl (2*S*,3*R*)-3-(furan-2-yl)-2-isocyano-3-(3-(methylsulfonamido)benzofuran-2-yl)-2-phenylpropanoate (6qg)**



76.7 mg (76%) of **6qg** were obtained from **5q** (57.9 mg, 0.20 mmol) after column chromatography eluting with hexane:EtOAc 8:2, 75:25. Enantiomeric excess (73%) was measured by HPLC (CHIRALPAK® AD-H), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: t_r = 13.8 min, minor enantiomer: t_r = 8.0 min.

Yellowish solid; m.p. 160.7-161.4 °C; $[\alpha]_D^{25}$ -40.5 (*c* 0.4, CHCl₃); **¹H NMR** (300 MHz, CDCl₃) δ 7.85 – 7.75 (m, 1H, Ar), 7.61 – 7.51 (m, 3H, Ar), 7.43 – 7.25 (m, 5H, Ar), 7.11 (dd, *J* = 1.9, 0.8 Hz, 1H, Ar), 6.85 (s, 1H, NH), 6.57 (d, *J* = 3.1 Hz, 1H, Ar), 6.22 (dd, *J* = 3.4, 1.8 Hz, 1H, Ar), 5.45 (s, 1H, CHAr), 2.98 (s, 3H, Me), 1.28 (s, 9H, tBu); **¹³C NMR** (75 MHz, CDCl₃) δ 166.6 (C), 164.6 (C), 154.1 (C), 147.3 (C), 146.6 (C), 142.4 (CH), 132.9 (C), 129.4 (CH), 129.0 (CH), 125.7 (CH), 125.2 (CH), 125.1 (C), 123.8 (CH), 120.7 (CH), 116.1 (C), 112.0 (CH), 111.1 (CH), 110.9 (CH), 86.1 (C), 73.3 (C), 45.1 (CH), 39.5 (CH₃), 27.4 (CH₃); **IR** (ATR) ν 3176 (w), 2982 (w), 2933 (w), 2140 (w, NC), 1730 (m), 1450 (m), 1372 (m), 1282 (m), 1256 (m), 1152 (s), 1018 (m), 965 (m), 835 (m), 746 (s), 630 (m), 459 (m), 429 (m) cm⁻¹; **HRMS** (ESI) *m/z*: 524.1805 [M+NH₄]⁺, C₂₇H₃₀N₃O₆S⁺ requires 524.1850.

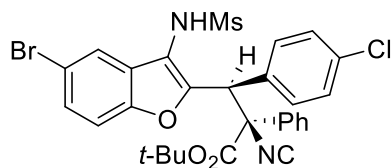
***tert*-Butyl (2*S*,3*S*)-3-(5-bromo-3-(methylsulfonamido)benzofuran-2-yl)-2-isocyano-2,3-diphenylpropanoate (6rg)**



99.8 mg (84%) of **6rg** were obtained from **5r** (75.6 mg, 0.20 mmol) after column chromatography eluting with hexane:EtOAc 85:15. Enantiomeric excess (82%) was measured by HPLC (Lux® i-Amylose-1), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: *t_r* = 5.3 min, minor enantiomer: *t_r* = 7.1 min.

Yellow solid; m.p. 107.3-108.5 °C; $[\alpha]_D^{25}$ -103.1 (*c* 0.4, CHCl₃); **¹H NMR** (300 MHz, CDCl₃) δ 7.89 (dd, *J* = 1.8, 0.8 Hz, 1H, Ar), 7.53 – 7.46 (m, 2H, Ar), 7.46 – 7.39 (m, 2H, Ar), 7.36 – 7.29 (m, 2H, Ar), 7.22 – 7.07 (m, 5H, Ar), 6.57 (s, 1H, NH), 5.19 (s, 1H, CHAr), 2.81 (s, 3H, Me), 1.29 (s, 9H, tBu); **¹³C NMR** (75 MHz, CDCl₃) δ 166.6 (C), 164.7 (C), 152.6 (C), 152.5 (C), 133.2 (C), 133.1 (C), 130.2 (CH), 129.4 (CH), 128.9 (CH), 128.6 (CH), 128.4 (CH), 127.4 (C), 125.4 (CH), 123.0 (CH), 117.2 (C), 114.7 (C), 113.5 (CH), 85.7 (C), 73.8 (C), 50.8 (CH), 39.9 (CH₃), 27.5 (CH₃); **IR** (ATR) ν 3235 (w), 2982 (w), 2933 (w), 2140 (w, NC), 1733 (m), 1446 (m), 1327 (m), 1256 (m), 1148 (s), 969 (m), 835 (m), 705 (s), 600 (m), 514 (s), 432 (w) cm⁻¹; **HRMS** (ESI) *m/z*: 612.1153 [M+NH₄]⁺, C₂₉H₃₁BrN₃O₅S⁺ requires 612.1162.

***tert*-Butyl (2*S*,3*S*)-3-(5-bromo-3-(methylsulfonamido)benzofuran-2-yl)-3-(4-chlorophenyl)-2-isocyano-2-phenylpropanoate (6sg)**

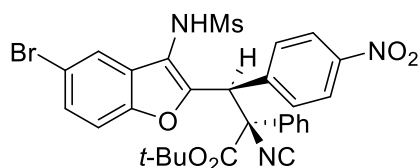


101.5 mg (81%) of **6sg** were obtained from **5r** (82.5 mg, 0.20 mmol) after column chromatography eluting with hexane:EtOAc 85:15, 8:2. Enantiomeric excess (88%) was

measured by HPLC (CHIRALPAK® AD-H), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: t_r = 5.5 min, minor enantiomer: t_r = 7.2 min.

Yellow solid; m.p. 125.1-126.0 °C; $[\alpha]_D^{25}$ -90.6 (c 0.4, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.84 (dd, J = 1.7, 0.9 Hz, 1H, Ar), 7.49 (t, J = 1.5 Hz, 2H, Ar), 7.47 – 7.41 (m, 2H, Ar), 7.38 – 7.32 (m, 3H, Ar), 6.58 (s, 1H, NH), 5.24 (s, 1H, CHAr), 2.89 (s, 3H, Me), 1.27 (s, 9H, tBu); ¹³C NMR (75 MHz, CDCl₃) δ 166.5 (C), 165.0 (C), 152.6 (C), 152.4 (C), 134.7 (C), 132.8 (C), 131.6 (C), 131.5 (CH), 129.5 (CH), 129.1 (CH), 128.7 (CH), 128.6 (CH), 127.3 (C), 125.3 (CH), 122.6 (CH), 117.4 (C), 114.8 (C), 113.6 (CH), 85.9 (C), 73.8 (C), 50.0 (CH), 40.2 (CH₃), 27.5 (CH₃); IR (ATR) ν 3239 (w), 2978 (w), 2930 (w), 2140 (w, NC), 1730 (m), 1491 (m), 1446 (m), 1331 (m), 1256 (m), 1148 (s), 1014 (m), 965 (m), 835 (m), 745 (s), 697 (m), 667 (m), 596 (m), 514 (s), 421 (m) cm⁻¹; HRMS (ESI) m/z : 646.0747 [M+NH₄]⁺, C₂₉H₃₀BrClN₃O₅S⁺ requires 646.0773.

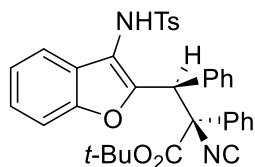
***tert*-butyl (2*S*,3*S*)-3-(5-bromo-3-(methylsulfonamido)benzofuran-2-yl)-2-isocyano-3-(4-nitrophenyl)-2-phenylpropanoate (6tg)**



78.6 mg (61%) of **6tg** were obtained from **5t** (84.6 mg, 0.20 mmol) after column chromatography eluting with hexane:EtOAc 8:2. Enantiomeric excess (85%) was measured by HPLC (CHIRALPAK® AD-H), hexane:iPrOH 80:20,

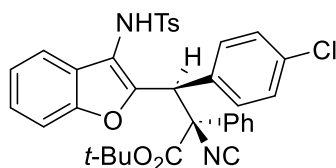
1.0 mL min⁻¹, major enantiomer: t_r = 6.7 min, minor enantiomer: t_r = 9.5 min.

Orange oil; $[\alpha]_D^{25}$ -69.9 (c 0.7, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.98 (d, J = 8.8 Hz, 2H, Ar), 7.80 (dd, J = 1.8, 0.8 Hz, 1H, Ar), 7.52 (dd, J = 2.8, 1.3 Hz, 2H, Ar), 7.48 – 7.41 (m, 4H, Ar), 7.38 – 7.31 (m, 3H, Ar), 6.66 (s, 1H, NH), 5.50 (s, 1H, CHAr), 2.97 (s, 3H, Me), 1.28 (s, 9H, tBu); ¹³C NMR (75 MHz, CDCl₃) δ 166.1 (C), 165.6 (C), 152.7 (C), 151.9 (C), 147.7 (C), 140.4 (C), 132.4 (C), 131.3 (CH), 129.8 (CH), 129.3 (CH), 129.0 (CH), 127.0 (C), 125.2 (CH), 123.2 (CH), 122.1 (CH), 117.6 (C), 115.3 (C), 113.9 (CH), 86.1 (C), 73.6 (C), 50.0 (CH), 40.5 (CH₃), 27.4 (CH₃); IR (ATR) ν 3254 (w), 2982 (w), 2933 (w), 2140 (w, NC), 1733 (m), 1603 (w), 1520 (m), 1446 (m), 1346 (m), 1256 (m), 1148 (s), 965 (m), 910 (m), 861 (m), 805 (m), 723 (s), 581 (m), 514 (s), 418 (m) cm⁻¹; HRMS (ESI) m/z : 657.0987 [M+NH₄]⁺, C₂₉H₃₀BrN₄O₇S⁺ requires 657.1013.

***tert*-Butyl (2*S*,3*S*)-2-isocyano-3-(3-((4-methylphenyl)sulfonamido)benzofuran-2-yl)-2,3-diphenylpropanoate (6wg)**

99.1 mg (84%) of **6wg** were obtained from **5w** (75.1 mg, 0.20 mmol) after column chromatography eluting with hexane:EtOAc 85:15, 75:25. Enantiomeric excess (65%) was measured by HPLC (Lux® Cellulose-2), hexane:iPrOH 80:20, 0.5 mL min⁻¹, major enantiomer: *t_r* = 17.5 min, minor enantiomer: *t_r* = 15.8 min.

Orange solid; m.p. 93.0-93.2 °C; [α]_D²⁵ -68.4 (*c* 0.3, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.69 (ddd, *J* = 7.7, 1.5, 0.7 Hz, 1H, Ar), 7.59 – 7.52 (m, 3H, Ar), 7.34 (ddd, *J* = 8.3, 7.2, 1.5 Hz, 1H, Ar), 7.30 – 7.26 (m, 5H, Ar+NH), 7.23 (d, *J* = 1.1 Hz, 1H, Ar), 7.14 – 7.04 (m, 3H, Ar), 6.97 (t, *J* = 7.6 Hz, 2H, Ar), 6.82 – 6.68 (m, 3H, Ar), 4.52 (s, 1H, CHAr), 2.32 (s, 3H, Me), 1.28 (s, 9H, tBu); ¹³C NMR (75 MHz, CDCl₃) δ 167.1 (C), 164.6 (C), 153.9 (C), 149.5 (C), 143.8 (C), 136.4 (C), 133.0 (C), 132.8 (C), 130.1 (CH), 129.9 (CH), 129.1 (CH), 128.7 (CH), 127.9 (CH), 127.7 (CH), 127.3 (CH), 125.6 (C), 125.3 (CH), 125.2 (CH), 123.6 (CH), 120.9 (CH), 115.7 (C), 111.7 (CH), 85.8 (C), 74.0 (C), 50.4 (CH), 27.4 (CH₃), 21.7 (CH₃); IR (ATR) ν 3247 (w), 3034 (w), 2982 (w), 2930 (w), 2140 (w, NC), 1737 (m), 1595 (w), 1450 (m), 1372 (m), 1252 (m), 1148 (s), 1092 (m), 835 (m), 749 (s), 704 (s), 664 (s), 544 (s), 481 (m), 432 (m) cm⁻¹; HRMS (ESI) *m/z*: 610.2371 [M+NH₄]⁺, C₃₅H₃₆N₃O₅S⁺ requires 610.2370.

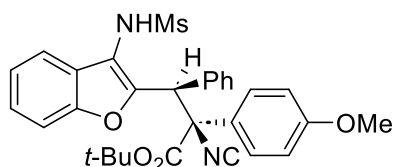
***tert*-Butyl (2*S*,3*S*)-3-(4-chlorophenyl)-2-isocyano-3-(3-((4-methylphenyl)sulfonamido)benzofuran-2-yl)-2-phenylpropanoate (6xg)**

123.6 mg (99%) of **6xg** were obtained from **6x** (82.0 mg, 0.20 mmol) after column chromatography eluting with hexane:EtOAc 85:15, 75:25. Enantiomeric excess (69%) was measured by HPLC (Lux® i-Amylose-1), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: *t_r* = 11.6 min, minor enantiomer: *t_r* = 9.7 min.

Orange solid; m.p. 94.2-94.5 °C; [α]_D²⁵ -74.3 (*c* 0.4, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.63 (ddd, *J* = 7.7, 1.5, 0.7 Hz, 1H, Ar), 7.60 – 7.49 (m, 3H, Ar), 7.39 – 7.27 (m, 7H, Ar), 7.26 – 7.21 (m, 1H, Ar), 7.08 – 7.00 (m, 2H, Ar), 6.95 (d, *J* = 8.6 Hz, 2H, Ar), 6.82 (s, 1H, NH), 6.73 (d, *J* = 8.6 Hz, 2H, Ar), 4.60 (s, 1H, CHAr), 2.30 (s, 3H, Me), 1.25 (s, 9H, tBu); ¹³C NMR (75 MHz, CDCl₃) δ 166.9 (C), 164.9 (C), 153.9 (C), 149.2 (C), 144.0 (C), 136.3 (C), 134.0 (C), 132.8 (C), 131.5 (C), 131.4 (CH), 129.8 (CH), 129.3 (CH), 128.9 (CH), 127.9 (CH), 127.3 (CH), 125.4 (C), 125.4 (CH), 125.3 (CH), 123.7 (CH), 120.8 (CH), 116.0 (C), 111.8 (CH), 86.0

(C), 74.0 (C), 49.7 (CH), 27.4 (CH₃), 21.6 (CH₃); **IR** (ATR) ν 3243 (w), 2982 (w), 2140 (w, NC), 1737 (m), 1595 (w), 1491 (w), 1450 (m), 1372 (m), 1252 (m), 1148 (s), 1088 (m), 835 (m), 746 (s), 967 (m), 664 (s), 544 (s) cm⁻¹; **HRMS** (ESI) m/z : 644.1963 [M+NH₄]⁺, C₃₅H₃₅ClN₃O₅S⁺ requires 644.1980.

***tert*-Butyl (2*S*,3*S*)-2-isocyano-2-(4-methoxyphenyl)-3-(3-(methylsulfonamido)benzofuran-2-yl)-3-phenylpropanoate (6ai)**

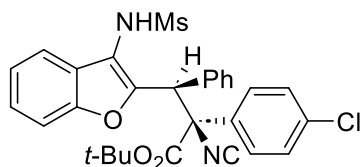


70.5 mg (64%) of **6ai** were obtained from **5a** (59.9 mg, 0.20 mmol) and **2i** (64.3 mg, 0.26 mmol) after column chromatography eluting with hexane:EtOAc 8:2, 7:3. Enantiomeric excess (87%) was measured by HPLC (Lux® i-Amylose-1),

hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: t_r = 16.7 min, minor enantiomer: t_r = 10.6 min.

Orange oil; $[\alpha]_D^{25}$ -137.7 (c 0.2, CHCl₃); **¹H NMR** (300 MHz, CDCl₃) δ 7.77 – 7.72 (m, 1H, Ar), 7.65 – 7.59 (m, 1H, Ar), 7.43 – 7.34 (m, 3H, Ar), 7.30 (td, J = 7.4, 1.2 Hz, 1H, Ar), 7.24 – 7.08 (m, 5H, Ar), 6.84 (d, J = 9.0 Hz, 2H, Ar), 6.67 (s, 1H, NH), 5.24 (s, 1H, CHAr), 3.79 (s, 3H, Me), 2.77 (s, 3H, Me), 1.26 (s, 9H, tBu); **¹³C NMR** (75 MHz, CDCl₃) δ 166.7 (C), 164.1 (C), 160.1 (C), 153.8 (C), 151.2 (C), 133.8 (C), 130.3 (CH), 128.3 (CH), 128.2 (CH), 127.0 (CH), 125.4 (CH), 125.2 (C), 123.8 (CH), 120.1 (CH), 115.1 (C), 114.1 (CH), 112.0 (CH), 85.2 (C), 73.6 (C), 55.4 (CH₃), 50.7 (CH), 39.6 (CH₃), 27.4 (CH₃); **IR** (ATR) ν 3243 (w), 3004 (w), 2978 (w), 2933 (w), 2840 (w), 2140 (w, NC), 1730 (m), 1607 (w), 1510 (m), 1454 (m), 1372 (m), 1320 (m), 1252 (s), 1148 (s), 1032 (m), 969 (m), 835 (m), 746 (s), 704 (s), 567 (m), 514 (m), 439 (m) cm⁻¹; **HRMS** (ESI) m/z : 564.2152 [M+NH₄]⁺, C₃₀H₃₄N₃O₆S⁺ requires 564.2163.

***tert*-Butyl (2*S*,3*S*)-2-(4-chlorophenyl)-2-isocyano-3-(3-(methylsulfonamido)benzofuran-2-yl)-3-phenylpropanoate (6aj)**



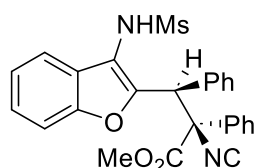
95.6 mg (87%) of **6aj** were obtained from **5a** (59.9 mg, 0.20 mmol) and **2j** (61 μ L, 0.26 mmol) after column chromatography eluting with hexane:EtOAc 8:2, 7:3. Enantiomeric excess (75%) was measured by HPLC (Lux® i-Amylose-1),

hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: t_r = 19.3 min, minor enantiomer: t_r = 8.6 min.

Yellow solid; m.p. 106.8-107.9 °C; $[\alpha]_D^{25}$ -124.6 (c 0.4, CHCl₃); **¹H NMR** (300 MHz, CDCl₃) δ 7.77 – 7.68 (m, 1H), 7.66 – 7.58 (m, 1H), 7.47 – 7.35 (m, 3H), 7.37 – 7.26 (m, 3H), 7.26 – 7.11 (m, 5H), 6.55 (s, 1H), 5.24 (s, 1H), 2.81 (s, 3H), 1.27 (s, 9H); **¹³C NMR** (75 MHz, CDCl₃)

δ 166.3 (C), 165.1 (C), 153.9 (C), 151.0 (C), 135.5 (C), 133.3 (C), 132.0 (C), 130.3 (CH), 129.1 (CH), 128.6 (CH), 128.5 (CH), 127.1 (CH), 125.5 (CH), 125.3 (C), 124.0 (CH), 120.0 (CH), 115.2 (C), 112.1 (CH), 85.8 (C), 73.6 (C), 50.7 (CH), 39.8 (CH₃), 27.4 (CH₃); **IR** (ATR) ν 3243 (w), 2982 (w), 2930 (w), 2140 (w, NC), 1733 (m), 1491 (m), 1454 (m), 1320 (m), 1252 (m), 1148 (s), 1096 (m), 969 (m), 835 (m), 746 (s), 500 (m) cm⁻¹; **HRMS** (ESI) m/z : 568.1663 [M+NH₄]⁺, C₂₉H₃₁ClN₃O₅S⁺ requires 568.1667.

Methyl (2*S*,3*S*)-2-isocyano-3-(3-(methylsulfonamido)benzofuran-2-yl)-2,3-diphenylpropanoate (6aa)



94.9 mg (99%) of **6aa** were obtained from **5a** (59.9 mg, 0.20 mmol) and **2a** (38 μ L, 0.26 mmol) after column chromatography eluting with hexane:EtOAc 7:3. Enantiomeric excess (diastereomer 1: 25%, diastereomer 2: 65%) was measured by HPLC (CHIRALPAK® AD-H), hexane:iPrOH 80:20, 1.0 mL min⁻¹, **diastereomer 1**: major enantiomer: t_r = 43.1 min, minor enantiomer: t_r = 9.2 min, **diastereomer 2**: major enantiomer: t_r = 10.2 min, minor enantiomer: t_r = 29.0 min.

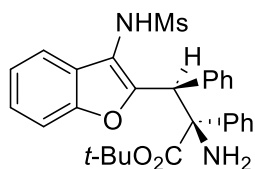
Yellowish solid; m.p. 95.5-95.8 °C; $[\alpha]_D^{25}$ -24.4 (c 0.3, CHCl₃, for the diastereomeric mixture, dr 53:47); **6aa diastereomer 1**: **¹H NMR** (300 MHz, CDCl₃) δ 7.77 – 7.71 (m, 3H, Ar), 7.52 (d, J = 8.3 Hz, 1H, Ar), 7.47 – 7.07 (m, 10H, Ar), 5.68 (s, 1H, CHAr), 5.39 (s, 1H, NH), 3.67 (s, 3H, Me), 2.76 (s, 3H, Me); **¹³C NMR** (75 MHz, CDCl₃) δ 166.84 (C), 165.6 (C), 153.7 (C), 151.7 (C), 134.4 (C), 133.5 (C), 130.6 (CH), 129.5 (CH), 128.8 (CH), 128.7 (CH), 128.7 (CH), 125.7 (CH), 125.5 (CH), 124.6 (C), 123.9 (CH), 118.6 (CH), 115.4 (C), 112.3 (CH), 54.3 (CH₃), 50.3 (CH), 40.0 (CH₃); **6aa diastereomer 2**: **¹H NMR** (300 MHz, CDCl₃) δ 7.86 (dd, J = 8.0, 1.7 Hz, 3H, Ar), 7.66 – 7.60 (m, 1H, Ar), 7.47 – 7.07 (m, 10H, Ar), 6.56 (s, 1H, NH), 5.34 (s, 1H, CHAr), 3.70 (s, 3H, Me), 2.88 (s, 3H, Me); **¹³C NMR** (75 MHz, CDCl₃), significant signals taken from the NMR spectrum of the diastereomeric mixture, δ 168.4 (C), 165.5 (C), 154.0 (C), 151.0 (C), 133.1 (C), 132.9 (C), 130.3 (CH), 129.5 (CH), 129.0 (CH), 128.4 (CH), 128.3 (CH), 125.5 (CH), 125.4 (C), 123.8 (CH), 120.0 (CH), 115.1 (C), 112.2 (CH), 54.6 (CH₃), 50.6 (CH), 40.2 (CH₃); **IR** (ATR) ν 3243 (w), 3064 (w), 3030 (w), 2952 (w), 2140 (w, NC), 1744 (m), 1495 (w), 1450 (m), 1320 (m), 1249 (m), 1133 (m), 969 (m), 746 (s), 708 (s), 574 (m), 514 (m), 440 (m) cm⁻¹; **HRMS** (ESI) m/z : 492.1574 [M+NH₄]⁺, C₂₆H₂₆N₃O₅S⁺ requires 492.1588.

5.4.4 Synthesis of **6ag** at 1 mmol scale

To a solution of **5a** (299.3 mg, 1.0 mmol, 1.0 equiv.) and **T-III** (45.3 mg, 0.1 mmol, 0.1 equiv.) in dry DCM (5.0 mL), at -30 °C, was added *tert*-butyl 2-phenylisocyanoacetate (**2g**, 272 μ L, 1.3 mmol, 1.3 equiv.). The reaction was stirred for 72 h at -30 °C and passed through a short-path column. The resulting mixture was used for the determination of the diastereomeric ratio by ^1H -NMR analysis. The product was then purified by column chromatography (eluent: hexane:EtOAc 85:15, 8:2, 7:3) to furnish 400 mg (77%) of **6ag** as a white solid. Enantiomeric excess (89%) was measured by HPLC (Lux® i-Amylose-1), hexane:iPrOH 80:20, 0.5 mL min^{-1} , major enantiomer: t_r = 28.9 min, minor enantiomer: t_r = 16.7 min.

5.4.5 Transformation of product **6ag**

tert-Butyl (2*S*,3*S*)-2-amino-3-(3-(methylsulfonamido)benzofuran-2-yl)-2,3-diphenylpropanoate (**7**)



To a suspension of **6ag** (30 mg, 0.058 mmol) in MeOH (0.6 mL) was added $\text{HCl}_{(\text{aq.})}$ 6 M (3 drops). The reaction was stirred at room temperature for 4 h and then was quenched with a saturated aqueous solution of NaHCO_3 until pH 8. The MeOH was removed under reduced pressure and the concentrate was extracted with DCM (3x20 mL). Combined organic phases were washed with brine (20 mL) and dried over Na_2SO_4 . The mixture was filtered and concentrated under reduced pressure, and the crude was purified by column chromatography (eluent: hexane:EtOAc 7:3) to yield 21.9 mg (75%) of the title compound. Enantiomeric excess (89%) was measured by HPLC (CHIRALPAK® AD-H), hexane:iPrOH 80:20, 1.0 mL min^{-1} , major enantiomer: t_r = 5.5 min, minor enantiomer: t_r = 19.9 min.

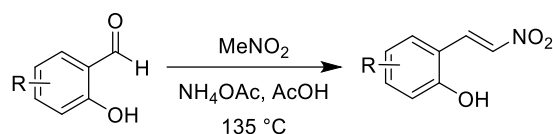
Orange oil; $[\alpha]_D^{25}$ -103.7 (c 0.5, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 9.99 (s, 1H, NHMe), 8.08 – 7.98 (m, 1H, Ar), 7.54 – 7.40 (m, 3H, Ar), 7.37 – 7.27 (m, 5H, Ar), 7.16 – 6.96 (m, 5H, Ar), 5.22 (s, 1H, CHAr), 2.92 (s, 3H, Me), 2.52 (s, 2H, NH_2), 1.21 (s, 9H, tBu); ^{13}C NMR (75 MHz, CDCl_3) δ 172.5 (C), 153.3 (C), 148.5 (C), 140.5 (C), 135.8 (C), 130.0 (CH), 128.5 (CH), 128.2 (CH), 128.2 (CH), 127.6 (CH), 125.9 (CH), 125.0 (CH), 124.5 (C), 123.4 (CH), 121.4 (CH), 116.8 (C), 111.3 (CH), 83.2 (C), 67.7 (C), 52.9 (CH), 40.3 (CH_3), 27.6 (CH_3); IR (ATR) ν 3384 (w), 3247 (w), 3060 (w), 3027 (w), 2978 (w), 2930 (w), 1722 (m), 1618 (w), 1454 (m), 1320 (m), 1249 (m), 1148 (s), 965 (m), 842 (m), 746 (s), 701 (s), 514 (m) cm^{-1} ; HRMS (ESI) m/z : 507.1945 $[\text{M}+\text{H}]^+$, $\text{C}_{28}\text{H}_{31}\text{N}_2\text{O}_5\text{S}^+$ requires 507.1948.

5.5 Dearomative formal [3+2] cycloaddition of 2-nitrobenzofurans and isocyanoacetates

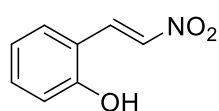
5.5.1 Synthesis and characterization data for 2-nitrobenzofurans **8**

All 2-nitrobenzofurans were synthesized via a three-step procedure comprising a nitroaldolic reaction between salicylaldehydes and nitromethane, followed by a NaBH₄-mediated reduction of the resulting olefin and a final oxidative cyclization.

Nitrovinylphenols

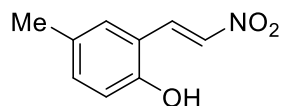


(E)-2-(2-Nitrovinyl)phenol (*Representative procedure*)



A modification of a literature procedure was carried out.¹⁹² A round-bottom flask was charged with nitromethane (8.2 mL, 151 mmol, 18.5 equiv), NH₄OAc (126 mg, 1.64 mmol, 0.2 equiv) and acetic acid (3.3 mL, 57.6 mmol, 7.0 equiv). The mixture was stirred in an oil bath at 90 °C for 15 min and then was added salicylaldehyde (0.87 mL, 8.19 mmol, 1.0 equiv). The temperature of the oil bath was adjusted to 135 °C and the reaction mixture stirred at this temperature overnight. After this time, the reaction mixture was left to reach room temperature, Et₂O (80 mL) was added and the organic phase was washed with brine (3×30 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Purification by column chromatography (eluent: hexane:EtOAc 9:1 to 8:2) yielded 0.95 g (70%) of **(E)-2-(2-nitrovinyl)phenol**. ¹H NMR (300 MHz, CDCl₃) δ 8.14 (d, *J* = 13.6 Hz, 1H, CHNO₂), 7.97 (d, *J* = 13.6 Hz, 1H, CHAr), 7.43 (dd, *J* = 7.7, 1.7 Hz, 1H, Ar), 7.35 (ddd, *J* = 8.1, 7.4, 1.7 Hz, 1H, Ar), 7.01 (td, *J* = 7.6, 1.1 Hz, 1H, Ar), 6.89 (d, *J* = 8.2 Hz, 1H, Ar), 6.06 (s, 1H, OH); ¹³C NMR (75 MHz, CDCl₃) δ 156.2 (C), 138.7 (CH), 135.8 (CH), 133.4 (CH), 132.8 (CH), 121.7 (CH), 117.8 (C), 116.6 (CH).

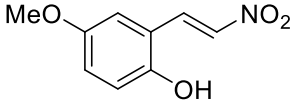
(E)-4-Methyl-2-(2-nitrovinyl)phenol



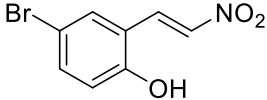
From 5-methylsalicylaldehyde (1.12 g, 8.19 mmol), 801 mg (55%) of the title compound were obtained after column chromatography eluting with hexane:EtOAc (9:1 to 8:2). ¹H NMR (300 MHz, MeOH-*d*₄) δ 8.12 (d, *J* = 13.5 Hz, 1H, CHNO₂), 8.00 (d, *J* = 13.5 Hz, 1H, CHAr), 7.28 (d, *J* = 2.2 Hz, 1H, Ar), 7.13 (ddd, *J* = 8.4, 2.3, 0.7 Hz, 1H, Ar), 6.80 (d, *J* = 8.3 Hz, 1H, Ar), 2.25 (s, 3H, MeO); ¹³C NMR (75 MHz, MeOH-

d_4) δ 157.6 (C), 138.7 (CH), 137.1 (CH), 135.2 (CH), 133.2 (CH), 130.4 (C), 118.4 (C), 117.0 (CH), 20.2 (CH₃).

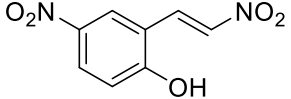
(*E*)-4-Methoxy-2-(2-nitrovinyl)phenol

 From 5-methoxysalicylaldehyde (0.82 mL, 6.57 mmol), 764 mg (60%) of the title compound were obtained after column chromatography eluting with hexane:EtOAc (8:2). **¹H NMR** (300 MHz, MeOH- d_4) δ 8.16 (d, J = 13.6 Hz, 1H, CHNO₂), 8.02 (d, J = 13.6 Hz, 1H, CHAr), 7.04 (d, J = 3.0 Hz, 1H, Ar), 6.93 (dd, J = 8.9, 3.0 Hz, 1H, Ar), 6.83 (d, J = 8.9 Hz, 1H, Ar), 3.76 (s, 3H, MeO); **¹³C NMR** (75 MHz, MeOH- d_4) δ 154.4 (C), 153.9 (C), 139.0 (CH), 136.7 (CH), 121.5 (CH), 118.8 (C), 118.1 (CH), 115.8 (CH), 56.3 (CH₃).

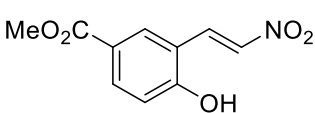
(*E*)-4-Bromo-2-(2-nitrovinyl)phenol

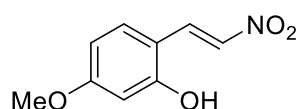
 From 5-bromosalicylaldehyde (1.65 g, 8.20 mmol), 1.22 g (61%) of the title compound were obtained after column chromatography eluting with hexane:EtOAc (9:1). **¹H NMR** (300 MHz, MeOH- d_4) δ 8.08 (d, J = 13.6 Hz, 1H, CHNO₂), 8.02 (d, J = 13.6 Hz, 1H, CHAr), 7.66 (d, J = 2.5 Hz, 1H, Ar), 7.41 (dd, J = 8.8, 2.5 Hz, 1H, Ar), 6.84 (d, J = 8.8 Hz, 1H, Ar); **¹³C NMR** (75 MHz, MeOH- d_4) δ 158.7 (C), 139.9 (CH), 136.6 (CH), 135.2 (CH), 135.1 (CH), 120.8 (C), 118.9 (CH), 112.5 (C).

(*E*)-4-Nitro-2-(2-nitrovinyl)phenol

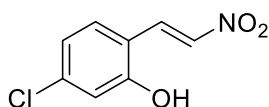
 From 5-nitrosalicylaldehyde (1.20 g, 7.19 mmol), 387 mg (26%) of the title compound were obtained after column chromatography eluting with hexane:EtOAc (8:2). **¹H NMR** (300 MHz, MeOH- d_4) δ 8.46 (d, J = 2.8 Hz, 1H), 8.19 (dd, J = 9.1, 2.8 Hz, 1H), 8.15 (d, J = 13.7 Hz, 1H, CHNO₂), 8.09 (d, J = 13.6 Hz, 1H, CHAr), 7.04 (d, J = 9.1 Hz, 1H); **¹³C NMR** (75 MHz, MeOH- d_4) δ 164.6 (C), 142.0 (C), 140.9 (CH), 134.5 (CH), 129.0 (CH), 129.0 (CH), 119.3 (C), 117.4 (CH).

(*E*)-4-Methoxycarbonyl-2-(2-nitrovinyl)phenol

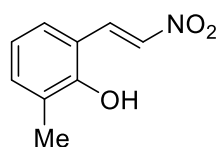
 From 4-methoxycarbonylsalicylaldehyde (1.10 g, 6.1 mmol), 700 mg (51%) of the title compound were obtained after column chromatography eluting with hexane:EtOAc (95:5). **¹H NMR** (300 MHz, MeOH- d_4) δ 8.14 (d, J = 2.1, 1H, Ar), 8.11 (d, J = 11.4 Hz, 1H, CHNO₂), 8.03 (d, J = 11.4 Hz, 1H, CHAr), 7.93 (dd, J = 8.7 Hz, 2.1 Hz, 1H, Ar), 6.95 (d, J = 8.7 Hz, 1H, Ar), 3.87 (s, 3H, MeO); **¹³C NMR** (75 MHz, MeOH- d_4) δ 167.63 (C), 163.42 (C), 139.9 (CH), 135.7 (CH), 135.3 (CH), 135.2 (CH), 123.1 (C), 118.8 (C), 117.1 (CH), 52.5 (CH₃).

(E)-5-Methoxy-2-(2-nitrovinyl)phenol

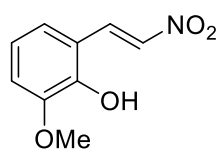
From 4-methoxysalicylaldehyde (1.0 g, 6.57 mmol), 529 mg (41%) of the title compound were obtained after column chromatography eluting with hexane:EtOAc (9:1). ¹H NMR (300 MHz, MeOH-*d*₄) δ 8.11 (d, *J* = 13.4 Hz, 1H, CHNO₂), 7.93 (d, *J* = 13.4 Hz, 1H, CHAr), 7.40 (d, *J* = 8.7 Hz, 1H, Ar), 6.50 (dd, *J* = 8.7, 2.5 Hz, 1H, Ar), 6.44 (d, *J* = 2.5 Hz, 1H, Ar), 3.80 (s, 3H, MeO); ¹³C NMR (75 MHz, MeOH-*d*₄) δ 165.8 (C), 161.6 (C), 137.3 (CH), 136.4 (CH), 135.0 (CH), 112.0 (C), 108.0 (CH), 102.1 (CH), 55.9 (CH₃).

(E)-5-Chloro-2-(2-nitrovinyl)phenol

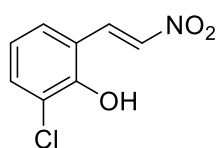
From 4-chlorosalicylaldehyde (700 mg, 4.47 mmol), 487 mg (55%) of the title compound were obtained after column chromatography eluting with hexane:EtOAc (95:5 to 9:1). ¹H NMR (300 MHz, MeOH-*d*₄) δ 8.11 (d, *J* = 13.6 Hz, 1H, CHNO₂), 8.01 (d, *J* = 13.6 Hz, 1H, CHAr), 7.48 (d, *J* = 8.2 Hz, 1H, Ar), 6.99 – 6.86 (m, 2H, Ar); ¹³C NMR (75 MHz, MeOH-*d*₄) δ 160.2 (C), 139.6 (C), 139.2 (CH), 135.6 (CH), 134.3 (CH), 121.4 (CH), 117.8 (C), 117.1 (CH).

(E)-2-Methyl-6-(2-nitrovinyl)phenol

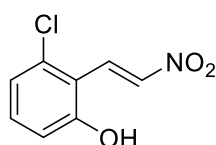
From 3-methylsalicylaldehyde (1.12 g, 8.19 mmol), 801 mg (55%) of compound of the title compound were obtained after column chromatography eluting with hexane:EtOAc (9:1). ¹H NMR (300 MHz, MeOH-*d*₄) δ 8.25 (d, *J* = 13.5 Hz, 1H, CHNO₂), 7.97 (d, *J* = 13.5 Hz, 1H, CHAr), 7.43 – 7.28 (m, 1H, Ar), 7.22 (ddd, *J* = 7.4, 1.7, 0.8 Hz, 1H, Ar), 6.83 (t, *J* = 7.6 Hz, 1H, Ar), 2.25 (s, 3H, Me); ¹³C NMR (75 MHz, MeOH-*d*₄) δ 157.3 (C), 138.7 (CH), 137.0 (CH), 135.8 (CH), 130.0 (CH), 126.8 (C), 121.4 (CH), 119.4 (C), 16.6 (CH₃).

(E)-2-Methoxy-6-(2-nitrovinyl)phenol

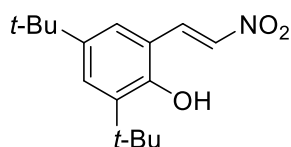
From *o*-vanillin (1.0 g, 6.57 mmol), 1.0 g (78%) of the title compound were obtained after column chromatography eluting with hexane:EtOAc (9:1). ¹H NMR (300 MHz, CDCl₃) δ 8.10 (d, *J* = 13.7 Hz, 1H, CHNO₂), 7.95 (d, *J* = 13.6 Hz, 1H, CHAr), 7.08 – 6.80 (m, 3H, Ar), 6.49 (s, 1H, OH), 3.94 (s, 3H, MeO); ¹³C NMR (75 MHz, CDCl₃) δ 147.0 (C), 146.6 (C), 138.9 (CH), 135.2 (CH), 123.8 (CH), 120.4 (CH), 116.7 (C), 113.5 (CH), 56.5 (CH₃).

(E)-2-Chloro-6-(2-nitrovinyl)phenol

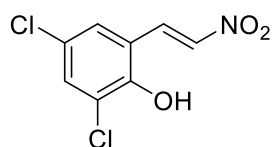
From 3-chlorosalicylaldehyde (700 mg, 4.47 mmol), 457 mg (51%) of the title compound were obtained after column chromatography eluting with hexane:EtOAc (95:5 to 9:1). $^1\text{H NMR}$ (300 MHz, MeOH- d_4) δ 8.19 (d, J = 13.6 Hz, 1H, CHNO₂), 8.02 (d, J = 13.6 Hz, 1H, CHAr), 7.47 (ddd, J = 11.5, 7.9, 1.6 Hz, 2H, Ar), 6.91 (t, J = 7.9 Hz, 1H, Ar); $^{13}\text{C NMR}$ (75 MHz, MeOH- d_4) δ 154.5 (C), 139.9 (CH), 135.7 (CH), 133.9 (CH), 131.4 (CH), 122.9 (C), 121.9 (CH), 121.2 (C).

(E)-3-Chloro-2-(2-nitrovinyl)phenol

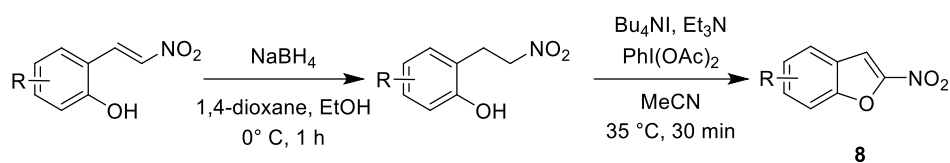
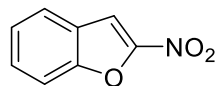
From 6-chlorosalicylaldehyde (1.0 g, 6.39 mmol), 507 mg (40%) of the title compound were obtained after column chromatography eluting with hexane:EtOAc (9:1). $^1\text{H NMR}$ (300 MHz, MeOH- d_4) δ 8.47 (d, J = 13.5 Hz, 1H, CHNO₂), 8.21 (d, J = 13.5 Hz, 1H, CHAr), 7.25 (t, J = 8.2 Hz, 1H, Ar), 7.01 (dd, J = 8.0, 1.1 Hz, 1H, Ar), 6.87 (ddd, J = 8.3, 1.1, 0.6 Hz, 1H, Ar); $^{13}\text{C NMR}$ (75 MHz, MeOH- d_4) δ 161.2 (C), 141.6 (CH), 138.4 (C), 134.0 (CH), 132.4 (CH), 122.2 (CH), 116.9 (C), 115.9 (CH).

(E)-2,4-Di-(tert-butyl)-6-(2-nitrovinyl)phenol

Separation by column chromatography (eluent: hexane:EtOAc 98:2) yielded a mixture containing the title compound, which was used without further purification for the next step.

(E)-2,4-dichloro-6-(2-nitrovinyl)phenol

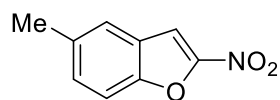
From 3,5-dichlorosalicylaldehyde (700 mg, 3.67 mmol), 337 mg (39%) of the title compound were obtained after column chromatography eluting with hexane:EtOAc (9:1). $^1\text{H NMR}$ (300 MHz, MeOH- d_4) δ 8.14 (d, J = 13.6 Hz, 1H, CHNO₂), 8.03 (d, J = 13.6 Hz, 1H, CHAr), 7.57 (d, J = 2.5 Hz, 1H, Ar), 7.50 (d, J = 2.5 Hz, 1H, Ar); $^{13}\text{C NMR}$ (75 MHz, MeOH- d_4) δ 153.4 (C), 140.9 (CH), 134.3 (CH), 133.0 (CH), 130.4 (CH), 126.0 (C), 123.8 (C), 122.3 (C).

2-Nitrobenzofurans**2-Nitrobenzofuran (8a) (Representative procedure)**

A literature procedure was employed.¹⁹² NaBH₄ (231 mg, 6.1 mmol, 1.2 equiv) was suspended in a mixture of 1,4-dioxane:EtOH 3:1 (20 mL), under nitrogen atmosphere. A solution of (*E*)-2-(2-nitrovinyl)phenol (840 mg, 5.08 mmol, 1.0 equiv) in 1,4-dioxane (15 mL, 0.34 M) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1 h (followed by TLC analysis). The reaction was quenched with NH₄Cl (50 mL) and extracted with Et₂O (3×125 mL). Combined organic phases were washed with brine (3×80 mL) and dried over Na₂SO₄. Concentrated under reduced pressure to furnish an oily crude that was used for the next step without further purification.

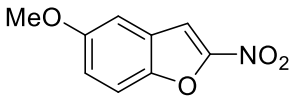
The obtained crude was dissolved in MeCN (50 mL, 0.1 M) and Bu₄NI (4.7 g, 12.7 mmol, 2.5 equiv), triethylamine (1.4 mL, 10.2 mmol, 2.0 equiv), and (diacetoxyiodo)benzene (4.9 g, 15.2 mmol, 3.0 equiv) were added. The mixture was stirred at 35 °C (oil bath) for 30 min (followed by TLC analysis). Et₂O (500 mL) was added and the reaction was washed with brine (3×125 mL). The organic phase was dried over Na₂SO₄ and concentrated under reduced pressure. Purification by column chromatography (eluent: hexane:EtOAc 97:3) yielded 511 mg (62%, over two steps) of 2-nitrobenzofuran (**8a**).¹⁹²

¹H NMR (300 MHz, CDCl₃) δ 7.77 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.68 (d, *J* = 0.7 Hz, 1H), 7.66 – 7.56 (m, 2H), 7.42 (ddd, *J* = 8.1, 6.0, 2.3 Hz, 1H); **¹³C NMR** (75 MHz, CDCl₃) δ 153.5 (C), 130.1 (CH), 126.0 (C), 125.5 (CH), 124.2 (CH), 112.9 (CH), 107.4 (CH).

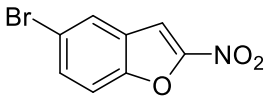
5-Methyl-2-nitrobenzofuran (8b)¹⁹³

From (*E*)-4-methyl-2-(2-nitrovinyl)phenol (700 mg, 3.91 mmol), 514 mg (65%) of **8b** were obtained after column chromatography eluting with hexane:EtOAc (95:5). **¹H NMR** (300 MHz, CDCl₃) δ 7.60 (d, *J* = 0.9 Hz, 1H), 7.53 (dt, *J* = 1.7, 0.9 Hz, 1H), 7.50 (d, *J* = 8.7 Hz, 1H), 7.40 (ddd, *J* = 8.7, 1.8, 0.6 Hz, 1H), 2.48 (s, 3H); **¹³C NMR** (75 MHz, CDCl₃) δ 152.0 (C), 135.4 (C), 131.8 (CH), 126.0 (C), 123.5 (CH), 112.4 (CH), 107.2 (CH), 21.5 (CH₃).

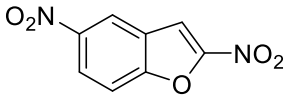
5-Methoxy-2-nitrobenzofuran (8c)¹⁹³


 From (*E*)-4-methoxy-2-(2-nitrovinyl)phenol (620 mg, 3.18 mmol), 330 mg (54%) of **8c** were obtained after column chromatography eluting with hexane:EtOAc (95:5 to 9:1). ¹H NMR (300 MHz, CDCl₃) δ 7.60 (d, *J* = 0.9 Hz, 1H), 7.51 (dt, *J* = 9.3, 0.7 Hz, 1H), 7.20 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.12 (d, *J* = 2.6 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 157.6 (C), 148.6 (C), 126.6 (C), 120.6 (CH), 113.7 (CH), 107.5 (CH), 104.4 (CH), 56.0 (CH₃).

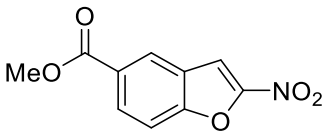
5-Bromo-2-nitrobenzofuran (8d)¹⁹⁴


 From (*E*)-4-bromo-2-(2-nitrovinyl)phenol (700 mg, 2.87 mmol), 474 mg (68%) of **8d** were obtained after column chromatography eluting with hexane:EtOAc (95:5 to 9:1). ¹H NMR (300 MHz, CDCl₃) δ 7.92 (dd, *J* = 2.0, 0.6 Hz, 1H), 7.69 (dd, *J* = 8.9, 2.0 Hz, 1H), 7.61 (d, *J* = 0.9 Hz, 1H), 7.52 (dt, *J* = 9.0, 0.7 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 152.0 (C), 133.2 (CH), 127.7 (C), 126.6 (CH), 118.6 (C), 114.5 (CH), 106.3 (CH).

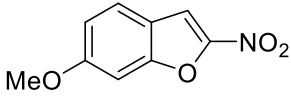
2,5-Dinitrobenzofuran (8e)¹⁹⁵


 From (*E*)-4-nitro-2-(2-nitrovinyl)phenol (340 mg, 1.62 mmol), 187 mg (77%) of **8e** were obtained after column chromatography eluting with hexane:EtOAc (9:1 to 8:2). ¹H NMR (300 MHz, CDCl₃) δ 8.76 (d, *J* = 2.4 Hz, 1H), 8.51 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.86 – 7.75 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 155.5 (C), 145.8 (C), 126.2 (C), 125.1 (CH), 120.8 (CH), 113.9 (CH), 107.4 (CH).

Methyl 2-nitrobenzofuran-5-carboxylate (8f)¹⁹⁶

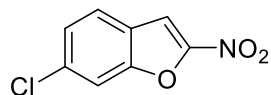

 From (*E*)-4-methoxycarbonyl-2-(2-nitrovinyl)phenol (700 mg, 3.14 mmol), 329 mg (47%) of **8f** were obtained after column chromatography eluting with hexane:EtOAc (9:1 to 8:2). ¹H NMR (300 MHz, CDCl₃) δ 8.52 (dd, *J* = 1.8, 0.7 Hz, 1H, Ar), 8.29 (dd, *J* = 8.9, 1.8 Hz, 1H, Ar), 7.73 (d, *J* = 1.0 Hz, 1H, Ar), 7.68 (dt, *J* = 8.9, 0.8 Hz, 1H, Ar), 3.97 (s, 3H, MeO); ¹³C NMR (75 MHz, CDCl₃) δ 166.1 (C, C=O), 155.5 (C), 131.2 (CH), 128.0 (C), 126.6 (CH), 125.9 (C), 112.9 (CH), 107.5 (CH), 52.7 (CH₃).

6-Methoxy-2-nitrobenzofuran (8h)¹⁹³


 From (*E*)-5-methoxy-2-(2-nitrovinyl)phenol (420 mg, 2.15 mmol), 53 mg (13%) of **8h** were obtained after column chromatography eluting with hexane:EtOAc (95:5 to 9:1). ¹H NMR (300 MHz, CDCl₃) δ 7.62 (dd, *J* = 8.4, 0.9 Hz, 2H),

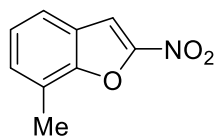
7.07 – 7.01 (m, 2H), 3.90 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 162.5 (C), 155.2 (C), 124.6 (CH), 119.2 (C), 116.2 (CH), 108.3 (CH), 95.8 (CH), 56.0 (CH_3).

6-Chloro-2-nitrobenzofuran (**8i**)¹⁹³



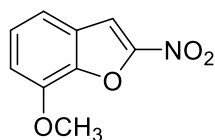
From (*E*)-5-chloro-2-(2-nitrovinyl)phenol (360 mg, 1.80 mmol), 281 mg (80%) of **8i** were obtained after column chromatography eluting with hexane:EtOAc (95:5). Orange solid; m. p. 104.6-105.3 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.71 (dd, J = 8.5, 0.5 Hz, 1H), 7.67 – 7.62 (m, 2H), 7.42 (dd, J = 8.5, 1.8 Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 153.3 (C), 136.2 (C), 126.7 (CH), 124.8 (CH), 124.5 (C), 113.3 (CH), 107.1 (CH).

7-Methyl-2-nitrobenzofuran (**8j**)¹⁹³



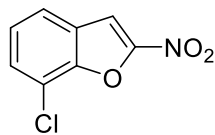
From (*E*)-6-methyl-2-(2-nitrovinyl)phenol (570 mg, 3.18 mmol), 428 mg (76%) of **8j** were obtained after column chromatography eluting with hexane:EtOAc (97:3). ^1H NMR (300 MHz, CDCl_3) δ 7.65 (s, 1H), 7.58 (ddd, J = 7.8, 1.5, 0.7 Hz, 1H), 7.39 (ddd, J = 7.4, 1.5, 0.8 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 2.59 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 152.8 (C), 130.8 (CH), 125.6 (C), 125.5 (CH), 123.3 (C), 121.5 (CH), 107.7 (CH), 15.0 (CH_3).

7-Methoxy-2-nitrobenzofuran (**8k**)¹⁹³

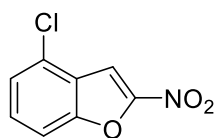


From (*E*)-6-methoxy-2-(2-nitrovinyl)phenol (500 mg, 2.56 mmol), 295 mg (60%) of **8k** were obtained after column chromatography eluting with hexane:EtOAc (95:5 to 9:1). ^1H NMR (300 MHz, CDCl_3) δ 7.64 (s, 1H), 7.39 – 7.27 (m, 2H), 7.05 (dd, J = 5.7, 3.3 Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 146.1 (C), 143.2 (C), 127.5 (C), 126.2 (CH), 115.6 (CH), 111.2 (CH), 107.5 (CH), 56.4 (CH_3).

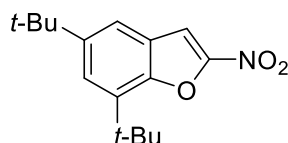
7-Chloro-2-nitrobenzofuran (**8l**)¹⁹³



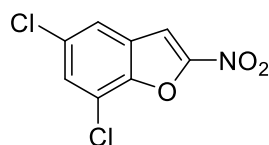
From (*E*)-6-chloro-2-(2-nitrovinyl)phenol (360 mg, 1.80 mmol), 265 mg (74%) of **8l** were obtained after column chromatography eluting with hexane:EtOAc (95:5 to 9:1). Pale yellow solid; m. p. 126.5-127.8 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.72 – 7.66 (m, 2H), 7.60 (dd, J = 7.9, 1.1 Hz, 1H), 7.37 (t, J = 7.9 Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 149.4 (C), 129.9 (CH), 127.4 (C), 126.3 (CH), 122.6 (CH), 118.4 (C), 107.6 (CH).

4-Chloro-2-nitrobenzofuran (8m)¹⁹³

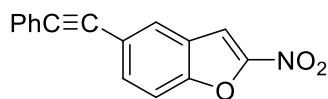
From (*E*)-3-chloro-2-(2-nitrovinyl)phenol (470 mg, 2.36 mmol), 293 mg (58%) of **8k** were obtained after column chromatography eluting with hexane:EtOAc (99:1). Orange solid; m. p. 110.9-111.6 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.75 (d, *J* = 0.6 Hz, 1H), 7.59 – 7.48 (m, 2H), 7.48 – 7.38 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 153.3 (C), 130.5 (CH), 129.3 (C), 125.9 (C), 125.3 (CH), 111.4 (CH), 105.8 (CH).

5,7-Di(*tert*-butyl)-2-nitrobenzofuran (8n)

From (*E*)-4,6-di(*tert*-butyl)-2-(2-nitrovinyl)phenol (408 mg, 1.47 mmol), 171 mg (42%) of **8n** were obtained after column chromatography eluting with hexane:EtOAc (98:2). Light brown solid; m. p. 82.8-84.3 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.61 (s, 1H), 7.55 (s, 2H), 1.53 (s, 9H), 1.38 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 149.9 (C), 148.6 (C), 135.7 (C), 126.4 (C), 125.1 (CH), 117.5 (CH), 107.6 (CH), 35.3 (C), 34.8 (C), 31.7 (CH₃), 29.9 (CH₃).

5,7-Dichloro-2-nitrobenzofuran (8o)¹⁹³

From (*E*)-4,6-dichloro-2-(2-nitrovinyl)phenol (312 mg, 1.33 mmol), 200 mg (65%) of **8o** were obtained after column chromatography eluting with hexane:EtOAc (97:3). ¹H NMR (300 MHz, CDCl₃) δ 7.67 (d, *J* = 1.9 Hz, 1H), 7.64 (s, 1H), 7.61 (d, *J* = 1.9 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 147.9 (C), 131.5 (C), 130.1 (CH), 127.9 (C), 122.0 (CH), 119.3 (C), 106.8 (CH).

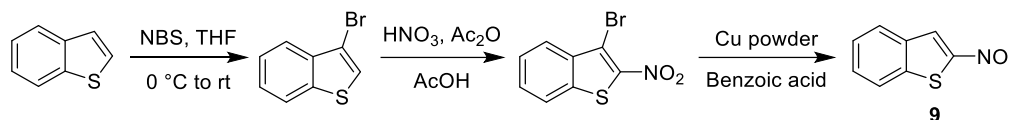
5-(Phenylethynyl)-2-nitrobenzofuran (8g)¹⁹³

A solution of 5-bromo-2-nitrobenzofuran (**8d**, 160 mg, 0.66 mmol, 1.0 equiv) in degassed trimethylamine (2 mL) was added to a mixture of Pd(PPh₃)₂Cl₂ (10 mg, 0.014 mmol, 0.02 equiv), CuI (6 mg, 0.028 mmol, 0.04 equiv) and PPh₃ (8 mg, 0.028 mmol, 4 mol%) under argon. Then, degassed phenylacetylene (80 μL, 0.70 mmol, 1.1 equiv) was added. The resulting mixture was heated at 60 °C overnight under argon. A saturated aqueous NH₄Cl solution (15 mL) was added. The mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with water (15 mL) and brine (15 mL). The organic phase was dried over anhydrous MgSO₄ and concentrated. Purification by column chromatography on silica gel (eluent: hexane:dichloromethane = 9:1) yielded 40.6 mg (23%) of compound **1g**. Yellow solid; ¹H NMR (300 MHz, CDCl₃) δ 7.94 (dd, *J* = 1.7, 0.7 Hz, 1H), 7.74 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.65 (d, *J* = 0.9 Hz, 1H), 7.60 (dt, *J* =

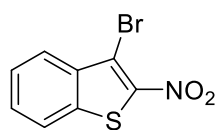
8.8, 0.8 Hz, 1H), 7.58 – 7.51 (m, 2H), 7.41 – 7.33 (m, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 152.8 (C), 133.5 (CH), 131.8 (CH), 128.8 (CH), 128.6 (CH), 127.2 (CH), 126.1 (C), 122.8 (C), 121.1 (C), 113.1 (CH), 107.0 (CH), 90.2 (C), 88.1 (C).

5.5.2 Synthesis and characterization data of 2-nitrobenzothiophene (9)

2-Nitrobenzothiophene was synthesized via a two-step procedure described in the literature.¹⁹³



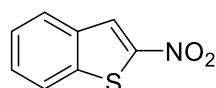
3-Bromo-2-nitrobenzo[b]thiophene¹⁹³



To a solution of thianaphthene (2.5 g, 18.6 mmol, 1.0 equiv) in THF (75 mL, 0.25 M) under nitrogen atmosphere was added NBS (5.0 g, 27.9 mmol, 1.5 equiv) portionwise at 0 °C. The reaction was stirred at 0 °C for 30 min and then stirred at room temperature for 48 h (followed by TLC analysis). The reaction was quenched with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution (10 mL), and the mixture changed color from orange to colorless. The phases were separated and the aqueous phase was extracted with Et_2O (3×20 mL). The combined organic phases were washed with brine (2×15 mL), dried under Na_2SO_4 , filtered and concentrated under reduced pressure. A brownish oil was obtained, which was used without further purification for the next step.

To a solution of the previously obtained crude product in Ac_2O (56 mL, 0.33 M) at 0 °C under nitrogen atmosphere, was added a mixture of 60% HNO_3 (7.8 mL, 95 mmol, 5.1 equiv) and AcOH (6.3 mL, 110 mmol, 5.9 equiv). The reaction was then warmed to room temperature and stirred for 2 h. A yellow precipitate was observed. The reaction was poured into 100 mL ice. The solid was filtered and washed with cold water to obtain 2.0 g (42%, over two steps) of the title compound. Yellow solid; ^1H NMR (300 MHz, CDCl_3) δ 8.07– 8.00 (m, 1H), 7.84 – 7.79 (m, 1H), 7.70 – 7.52 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 137.2 (C), 137.1 (C), 130.5 (CH), 126.9 (CH), 126.9 (CH), 123.0 (CH), 111.4 (C).

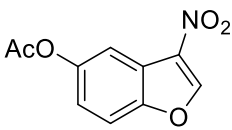
2-Nitrobenzo[b]thiophene (9)¹⁹³



A mixture of 3-bromo-2-nitrobenzo[b]thiophene (0.70 g, 2.71 mmol, 1.0 equiv), benzoic acid (1.17 g, 9.60 mmol, 3.54 equiv) and Cu powder (0.80 g, 12.6 mmol, 4.65 equiv), under nitrogen atmosphere was heated at 150 °C (oil bath) and stirred for 30 min. The melted mixture was allowed to stand at room temperature until solidification. The solid was dissolved in dichloromethane (15 mL) and passed through a short-path

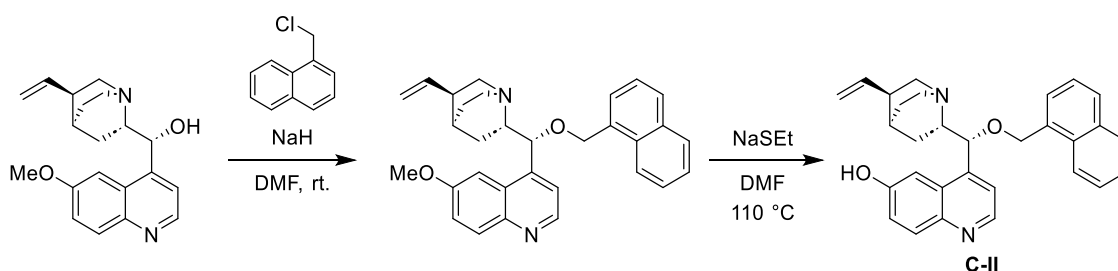
silica gel column, eluting with dichloromethane (100 mL). The filtrate was washed with saturated aqueous NaHCO_3 solution (2×40 mL) and the organic phase changed color from green to yellow. The organic phase was washed with brine (2×40 mL), dried over Na_2SO_4 , and concentrated by reduced pressure. 433 mg (89%) of the title compound were obtained without further purification. Yellow solid; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.21 (s, 1H), 7.93 (d, $J = 8.1$ Hz, 1H), 7.84 (d, $J = 8.3$ Hz, 1H), 7.58 (ddd, $J = 8.3, 7.1, 1.2$ Hz, 1H), 7.49 (ddd, $J = 8.2, 7.1, 1.1$ Hz, 1H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 140.5 (C), 136.3 (C), 129.3 (CH), 127.2 (CH), 126.3 (CH), 125.8 (CH), 123.1 (CH).

5-Acetoxy-3-nitrobenzofuran (10b)¹⁹⁷

 A solution of commercially available 5-hydroxy-3-nitrobenzofuran (**10a**, 90 mg, 0.5 mmol) in acetic anhydride (3.5 mL, 0.15 M) and concentrated H_2SO_4 (2 drops) was stirred overnight at room temperature. The reaction mixture was poured onto ice (ca. 30 g) and extracted with EtOAc (3×50 mL). The organic layer was washed with 5% aqueous NaHCO_3 (20 mL) and brine (20 mL), and dried over Na_2SO_4 . After filtration and removal of the solvent under reduced pressure, column chromatography eluting with hexane:EtOAc (8:2) gave 60 mg (54%) of the title compound. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.59 (s, d, $J = 0.6$ Hz, 1H), 7.89 (dd, $J = 2.4, 0.6$ Hz, 1H), 7.58 (dd, $J = 9.0, 0.6$ Hz, 1H), 7.20 (ddd, $J = 9.0, 2.4, 0.3$ Hz, 1H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 169.7 (C), 152.4 (C), 148.7 (C), 158.07 (CH), 121.5 (CH), 120.0 (C), 114.2 (CH), 113.3 (CH), 21.12 (CH_3).

5.5.3 Synthesis and characterization data for catalyst C-II

A modification of a two-step procedure described in the literature was carried out.¹⁹⁸



To a solution of quinine (1.0 g, 3.08 mmol, 1.0 equiv) in DMF (9 mL, 0.3 M) under nitrogen atmosphere was added NaH (60% dispersion in mineral oil, 0.32 g, 8.02 mmol, 2.6 equiv) portionwise and the mixture was stirred at room temperature for 2 h. A solution of 1-(chloromethyl)naphthalene (0.6 g, 3.38 mmol, 1.1 equiv) in DMF (1 mL) was added dropwise and the reaction was stirred for 24 h at room temperature, until complete consumption of the starting

material (TLC). The reaction was quenched with brine (10 mL) and the mixture was extracted with ethyl acetate (5×30 mL). The organic phase was washed with water (5×25 mL) and brine (25 mL). Dried over Na₂SO₄ and concentrated under reduced pressure to obtain a light-yellow foam that was used without further purification for the next step.

A solution of the crude product previously obtained and sodium ethanethiolate (1.0 g, 12.5 mmol, 4.0 equiv) in DMF (19 mL, 0.16 M) under nitrogen atmosphere was stirred overnight at 110 °C (oil bath) until complete consumption of the starting material (TLC). The reaction was cooled to room temperature and quenched with saturated aqueous NH₄Cl (20 mL) and water (15 mL). The solution was acidified to pH 2 by dropwise addition of conc. HCl. The aqueous solution was washed with EtOAc (2×30 mL) and the organic phase was extracted with aq. HCl 1 M solution (2×15 mL). Combined aqueous phases were brought to pH 8 by the addition of conc. NH₃. The basified aqueous phase was extracted with EtOAc (3×100 mL). Purification by column chromatography (eluent: EtOAc:MeOH 9:1) yielded 726 mg (52%) of **C-II**. Grayish solid; m. p. 141.0-141.9 °C; [α]_D²⁵ -15.8 (*c* 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃): 8.67 (d, *J* = 4.5 Hz, 1H, CH-N), 8.12-8.05 (br s, 2H, Ar), 8.04 (d, *J* = 9.0 Hz, 1H, Ar), 7.96 – 7.82 (m, 2H, Ar), 7.92 – 7.81 (m, 2H, Ar), 7.79 (d, *J* = 8.2 Hz, 1H, Ar), 7.63 – 7.36 (m, 5H, Ar), 7.32 (dd, *J* = 9.1, 2.4 Hz, 1H, Ar), 5.78 (bs, 1H), 5.58 (ddd, *J* = 17.5, 10.3, 7.5 Hz, 1H), 4.98 – 4.78 (m, 3H), 3.70 – 3.47 (m, 1H), 3.27 – 3.00 (m, 2H), 2.85 – 2.55 (m, 2H), 2.38 – 2.24 (m, 1H), 2.16 – 1.96 (m, 1H), 1.90 – 1.68 (m, 2H), 1.59 – 1.40 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 157.0 (C), 146.8 (CH), 144.0 (C), 143.4 (C), 140.4 (CH), 133.67 (C), 133.5 (C), 131.67 (CH), 131.3 (C), 128.8 (CH), 128.6 (CH), 127.9 (C), 126.4 (CH), 126.0 (CH), 125.8 (C), 125.5 (CH), 123.6 (CH), 123.3 (CH), 115.4 (CH₂), 106.6 (CH), 69.3 (CH₂), 59.8 (CH), 56.3 (CH₂), 43.3 (CH₂), 39.2 (CH), 27.7 (CH), 26.7 (CH₂); HRMS (ESI) *m/z*: 451.2369 [M+H]⁺, C₃₀H₃₁N₂O₂⁺ requires 451.2380.

5.5.4 Synthesis and characterization data for compounds **11**

Enantioselective procedure

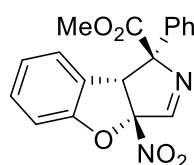
To a solution of the corresponding 2-nitrobenzofuran **8** (0.15 mmol, 1.0 equiv) and **C-II** (6.8 mg, 0.015 mmol, 0.1 equiv) in dry CHCl₃ (0.75 mL, 0.2 M) at 0 °C was added 2-phenylisocyanoacetate (**2a**, 28 μ L, 0.19 mmol, 1.3 equiv). The reaction was stirred until complete consumption of compound **8** or until no more reaction advancement was observed (TLC analysis).

For the determination of the diastereomeric ratio, a short path column chromatography to separate the catalyst **C-II** was carried out and the resulting mixture analyzed by ^1H NMR. Then the product was purified by column chromatography, eluting with hexane:EtOAc mixtures.

Non-enantioselective procedure

To a solution of the corresponding 2-nitrobenzofuran **8** (0.1 mmol, 1.0 equiv) and silver oxide (1.2 mg, 0.005 mmol, 0.05 equiv) in dichloromethane (1 mL, 0.1 M) at room temperature was added 2-phenylisocyanoacetate (**2a**, 19 μL , 0.13 mmol, 1.3 equiv). The reaction was stirred at room temperature for 17 h and the product was purified by column chromatography, eluting with hexane:EtOAc mixtures.

Methyl (1*R*,3*aR*,8*bR*)-3a-nitro-1-phenyl-3a,8b-dihydro-1*H*-benzofuro[2,3-*c*]pyrrole-1-carboxylate (11aa**)**

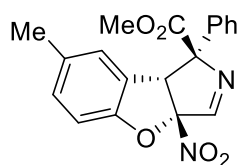


40.1 mg (79%) of **11aa** were obtained from **8a** (24.5 mg, 0.15 mmol) after column chromatography eluting with hexane:EtOAc (95:5). Enantiomeric excess (93%) was measured by HPLC (CHIRALPAK® AD-H), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: t_r = 8.5 min, minor enantiomer: t_r =

24.1 min.

White foam; $[\alpha]_D^{25} +120.5$ (c 1.0, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 8.09 (s, 1H, CH=N), 7.23 – 7.16 (m, 3H, Ar), 7.07 (dddd, J = 8.2, 7.4, 1.4, 0.7 Hz, 1H, Ar), 6.96 – 6.91 (m, 2H, Ar), 6.87 (ddt, J = 8.3, 1.1, 0.6 Hz, 1H, Ar), 6.63 (td, J = 7.6, 1.0 Hz, 1H, Ar), 6.39 (dq, J = 7.6, 0.7 Hz, 1H, Ar), 5.37 (s, 1H), 3.91 (s, 3H, MeO); ^{13}C NMR (75 MHz, CDCl_3) δ 171.1 (C, C=O), 158.7 (CH, C=N), 157.1 (C), 135.7 (C), 129.9 (CH), 128.7 (CH), 128.7 (CH), 126.5 (CH), 125.9 (CH), 124.1 (C), 123.1 (CH), 122.5 (CH), 110.3 (CH), 91.8 (C), 59.2 (CH_3), 54.1 (CH); HRMS (ESI) m/z : 339.0971 $[\text{M}+\text{H}]^+$, $\text{C}_{18}\text{H}_{15}\text{N}_2\text{O}_5^+$ requires 339.0975.

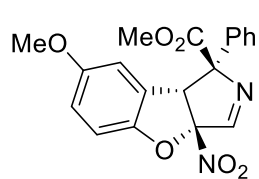
Methyl (1*R*,3*aR*,8*bR*)-7-methyl-3a-nitro-1-phenyl-3a,8b-dihydro-1*H*-benzofuro[2,3-*c*]pyrrole-1-carboxylate (11ba**)**



35.4 mg (67%) of **11ba** were obtained from **8b** (26.6 mg, 0.15 mmol) after column chromatography eluting with hexane:EtOAc (9:1). Enantiomeric excess (88%) was measured by HPLC (CHIRALPAK® AD-H), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: t_r = 7.3 min, minor enantiomer: t_r = 27.0 min.

Colorless oil; $[\alpha]_D^{25} +20.3$ (c 0.5, CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.07 (s, 1H, $\text{CH}=\text{N}$), 7.23 – 7.17 (m, 3H, Ar), 6.96 – 6.90 (m, 2H, Ar), 6.85 (ddt, J = 8.3, 1.8, 0.8 Hz, 1H, Ar), 6.74 (d, J = 8.3 Hz, 1H, Ar), 6.15 (s, 1H, Ar), 5.30 (s, 1H, CHAr), 3.91 (s, 3H, MeO), 1.96 (s, 3H, MeO); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 171.1 (C, $\text{C}=\text{O}$), 158.8 (CH, $\text{C}=\text{N}$), 155.2 (C), 135.8 (C), 132.6 (C), 130.2 (CH), 128.6 (CH), 128.5 (CH), 126.9 (CH), 126.0 (CH), 124.3 (C), 122.4 (C), 109.7 (CH), 91.7 (C), 59.2 (CH_3), 54.0 (CH), 20.6 (CH_3); **HRMS** (ESI) m/z : 353.1128 $[\text{M}+\text{H}]^+$, $\text{C}_{19}\text{H}_{17}\text{N}_2\text{O}_5^+$ requires 353.1132.

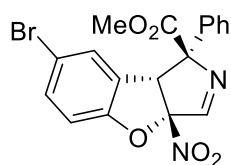
Methyl (1*R*,3*aR*,8*bR*)-7-methoxy-3*a*-nitro-1-phenyl-3*a*,8*b*-dihydro-1*H*-benzofuro[2,3-*c*]pyrrole-1-carboxylate (11*ca*)



34.0 mg (62%) of **11ca** were obtained from **8c** (29.0 mg, 0.15 mmol) after column chromatography eluting with hexane:EtOAc (9:1). Enantiomeric excess (91%) was measured by HPLC (CHIRALPAK® AD-H), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: t_r = 10.4 min, minor enantiomer: t_r = 23.3 min.

Orange oil; $[\alpha]_D^{25} +6.7$ (c 0.8, CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.09 (s, 1H, $\text{CH}=\text{N}$), 7.28 (dd, J = 6.5, 3.2 Hz, 3H, Ar), 7.06 – 6.96 (m, 2H, Ar), 6.81 (d, J = 8.9 Hz, 1H, Ar), 6.65 (ddd, J = 8.9, 2.7, 0.8 Hz, 1H, Ar), 5.88 (dd, J = 2.7, 1.0 Hz, 1H), 5.36 (s, 1H, CHAr), 3.95 (s, 3H, MeO), 3.45 (s, 3H, MeO); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 171.1 (C, $\text{C}=\text{O}$), 158.9 (CH, $\text{CH}=\text{N}$), 155.7 (C), 151.1 (C), 135.7 (C), 128.8 (CH), 128.7 (CH), 126.1 (CH), 124.6 (C), 123.2 (C), 116.6 (CH), 110.9 (CH), 110.7 (CH), 91.6 (C), 59.4 (CH_3), 55.9 (CH_3), 54.1 (CH); **HRMS** (ESI) m/z : 369.1079 $[\text{M}+\text{H}]^+$, $\text{C}_{19}\text{H}_{17}\text{N}_2\text{O}_6^+$ requires 369.1081.

Methyl (1*R*,3*aR*,8*bR*)-7-bromo-3*a*-nitro-1-phenyl-3*a*,8*b*-dihydro-1*H*-benzofuro[2,3-*c*]pyrrole-1-carboxylate (11*da*)

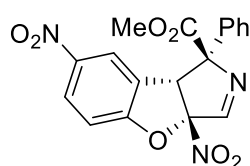


46.5 mg (74%) of **11da** were obtained from **8d** (36.5 mg, 0.15 mmol) after column chromatography eluting with hexane:EtOAc (95:5). Enantiomeric excess (92%) was measured by HPLC (CHIRALPAK® AD-H), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: t_r = 8.7 min, minor enantiomer: t_r = 28.2 min.

Colorless oil; $[\alpha]_D^{25} -21.2$ (c 1.0, CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.08 (s, 1H, $\text{CH}=\text{N}$), 7.28 – 7.23 (m, 3H, Ar), 7.17 (ddd, J = 8.7, 2.1, 0.8 Hz, 1H, Ar), 6.96 – 6.87 (m, 2H, Ar), 6.75 (d, J = 8.6 Hz, 1H, Ar), 6.48 (dd, J = 2.2, 1.0 Hz, 1H, Ar), 5.33 (s, 1H, CHAr), 3.91 (s, 3H, MeO); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 170.8 (C, $\text{C}=\text{O}$), 158.4 (CH, $\text{CH}=\text{N}$), 156.1 (C), 135.3

(C), 132.7 (CH), 129.5 (CH), 129.1 (CH), 128.8 (CH), 125.7 (CH), 124.8 (C), 124.1 (C), 115.3 (C), 111.8, 91.9 (C), 58.9 (CH₃), 54.2 (CH); **HRMS** (ESI) m/z : 417.0079 [M+H]⁺, C₁₈H₁₄BrN₂O₅⁺ requires 417.0081.

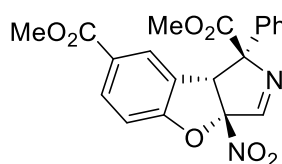
Methyl (1*R*,3*aR*,8*bR*)-3*a*,7-dinitro-1-phenyl-3*a*,8*b*-dihydro-1*H*-benzofuro[2,3-*c*]pyrrole-1-carboxylate (11ea)



58.5 mg (99%) of **11ea** were obtained from **8e** (31.2 mg, 0.15 mmol) after column chromatography eluting with hexane:EtOAc (9:1 to 8:2). Enantiomeric excess (92%) was measured by HPLC (CHIRALPAK® AD-H), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: t_r = 19.4 min, minor enantiomer: t_r = 32.7 min.

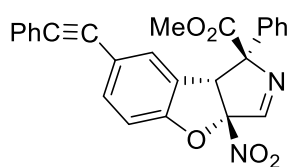
Orange oil; $[\alpha]_D^{25}$ -41.6 (c 1.0, CHCl₃); **¹H NMR** (300 MHz, CDCl₃) δ 8.14 (s, 1H, CH=N), 8.03 (ddd, J = 8.9, 2.4, 0.7 Hz, 1H, Ar), 7.32 (dd, J = 2.4, 1.1 Hz, 1H, Ar), 7.25 – 7.19 (m, 3H, Ar), 6.98 (d, J = 9.0 Hz, 1H, Ar), 6.95 – 6.90 (m, 2H, Ar), 5.43 (s, 1H, CHAr), 3.93 (s, 3H, MeO); **¹³C NMR** (75 MHz, CDCl₃) δ 170.4 (C, C=O), 161.2 (C), 157.9 (CH, C=N), 143.7 (C), 135.0 (C), 129.4 (CH), 129.1 (CH), 126.7 (CH), 125.6 (CH), 124.5 (C), 124.4 (C), 122.8 (CH), 110.6 (CH), 92.1 (C), 58.1 (CH₃), 54.3 (CH); **HRMS** (ESI) m/z : 384.0829 [M+H]⁺, C₁₈H₁₄N₃O₇⁺ requires 384.0826.

Methyl (1*R*,3*aR*,8*bR*)-7-methoxycarbonyl-3*a*-nitro-1-phenyl-3*a*,8*b*-dihydro-1*H*-benzofuro[2,3-*c*]pyrrole-1-carboxylate (11fa)



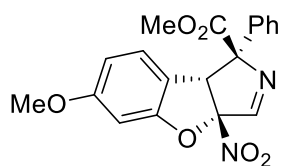
50.8 mg (85%) of **11fa** were obtained from **8f** (33.2 mg, 0.15 mmol) after column chromatography eluting with hexane:EtOAc (9:1). Enantiomeric excess (91%) was measured by HPLC (CHIRALPAK® IC), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: t_r = 14.8 min, minor enantiomer: t_r = 23.5 min.

Colorless oil; $[\alpha]_D^{25}$ -31.1 (c 1.0, CHCl₃); **¹H NMR** (300 MHz, CDCl₃) δ 8.11 (s, 1H, CH=N), 7.80 (ddd, J = 8.6, 1.8, 0.7 Hz, 1H, Ar), 7.24 – 7.10 (m, 4H, Ar), 6.97 – 6.85 (m, 3H, Ar), 5.37 (s, 1H, CHAr), 3.91 (s, 3H, MeO), 3.77 (s, 3H, MeO); **¹³C NMR** (75 MHz, CDCl₃) δ 170.8 (C, C=O), 165.7 (C, C=O), 160.4 (C), 158.2 (CH, CH=N), 135.3 (C), 132.3 (CH), 128.9 (CH), 128.8 (CH), 128.5 (CH), 125.7 (CH), 125.5 (C), 124.3 (C), 123.2 (C), 110.1 (CH), 92.0 (C), 58.5 (CH), 54.1 (CH₃), 52.1 (CH₃); **HRMS** (ESI) m/z : 397.1023 [M+H]⁺, C₂₀H₁₇N₂O₇⁺ requires 397.1030.

Methyl (1*R*,3*aR*,8*bR*)-3*a*-nitro-1-phenyl-7-(phenylethynyl)-3*a*,8*b*-dihydro-1*H*-benzofuro[2,3-*c*]pyrrole-1-carboxylate (11*ga*)

36.2 mg (55%) of **11ga** were obtained from **8g** (39.5 mg, 0.15 mmol) after column chromatography eluting with hexane:EtOAc (95:5). Enantiomeric excess (89%) was measured by HPLC (Lux® i-Amylose-1), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: *t_r* = 12.5 min, minor enantiomer: *t_r* = 22.3 min.

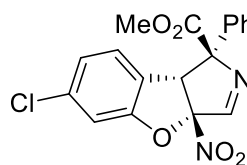
Colorless oil; $[\alpha]_D^{25}$ -88.5 (*c* 1.0, CHCl₃); **¹H NMR** (300 MHz, CDCl₃) δ 8.11 (s, 1H, CH=N), 7.47 – 7.38 (m, 2H, Ar), 7.37 – 7.28 (m, 3H, Ar), 7.30 – 7.24 (m, 1H, Ar), 7.24 (d, *J* = 2.2 Hz, 3H, Ar), 6.99 – 6.90 (m, 2H, Ar), 6.85 (d, *J* = 8.4 Hz, 1H, Ar), 6.60 – 6.57 (m, 1H, Ar), 5.35 (s, 1H, CHAr), 3.93 (s, 3H, MeO); **¹³C NMR** (75 MHz, CDCl₃) δ 170.9 (C, C=O), 158.4 (CH, CH=N), 156.9 (C), 135.4 (C), 133.6 (CH), 131.6 (CH), 129.8 (CH), 129.0 (CH), 128.8 (CH), 128.5 (CH), 128.4 (CH), 125.8 (CH), 124.2 (C), 123.2 (C), 123.2 (C), 118.5 (C), 110.5 (CH), 91.9 (C), 88.7 (C), 88.2 (C), 59.0 (CH), 54.1 (CH₃); **HRMS** (ESI) *m/z*: 439.1283 [M+H]⁺, C₂₆H₁₈N₂O₅⁺ requires 439.1288.

Methyl (1*R*,3*aR*,8*bR*)-6-methoxy-3*a*-nitro-1-phenyl-3*a*,8*b*-dihydro-1*H*-benzofuro[2,3-*c*]pyrrole-1-carboxylate (11*ha*)

26.2 mg (47%) of **11ha** were obtained from **8h** (29.3 mg, 0.15 mmol) after column chromatography eluting with hexane:EtOAc (85:15). Enantiomeric excess (92%) was measured by HPLC (Lux® i-Amylose-1), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: *t_r* = 10.0 min, minor enantiomer: *t_r* = 17.5 min.

Colorless oil; $[\alpha]_D^{25}$ +94.1 (*c* 1.0, CHCl₃); **¹H NMR** (400 MHz, CDCl₃) δ 8.05 (s, 1H, CH=N), 7.25 – 7.20 (m, 3H, Ar), 6.99 – 6.94 (m, 2H, Ar), 6.43 (d, *J* = 2.2 Hz, 1H, Ar), 6.22 – 6.14 (m, 2H, Ar), 5.29 (s, 1H, CHAr), 3.89 (s, 3H, MeO), 3.67 (s, 3H, MeO); **¹³C NMR** (101 MHz, CDCl₃) δ 171.1 (C, C=O), 161.4 (C), 158.7 (CH, CH=N), 158.3 (C), 135.9 (C), 128.7 (C), 126.6 (CH), 126.0 (CH), 124.8 (C), 114.2 (C), 109.5 (CH), 96.4 (CH), 91.5 (C), 58.8 (CH₃), 55.6 (CH₃), 54.0 (CH); **HRMS** (ESI) *m/z*: 369.1080 [M+H]⁺, C₁₉H₁₇N₂O₆⁺ requires 369.1081.

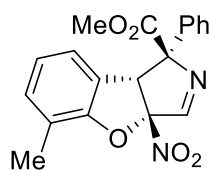
Methyl (1*R*,3*aR*,8*bR*)-6-chloro-3*a*-nitro-1-phenyl-3*a*,8*b*-dihydro-1*H*-benzofuro[2,3-*c*]pyrrole-1-carboxylate (11*ia*)



51.2 mg (92%) of **11ia** were obtained from **8i** (29.6 mg, 0.15 mmol) after column chromatography eluting with hexane:EtOAc (9:1). Enantiomeric excess (92%) was measured by HPLC (CHIRALPAK® AD-H), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: *t_r* = 8.2 min, minor enantiomer: *t_r* = 14.0 min.

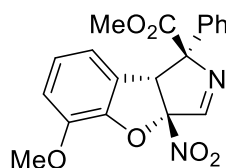
Colorless oil; $[\alpha]_D^{25} +86.0$ (*c* 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 8.08 (s, 1H), 7.28 – 7.20 (m, 3H), 6.96 – 6.91 (m, 2H), 6.90 (d, *J* = 1.9 Hz, 1H), 6.61 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.28 (dd, *J* = 8.2, 1.1 Hz, 1H), 5.32 (s, 1H), 3.90 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 170.9 (C, C=O), 158.4 (CH, CH=N), 157.6 (C), 135.5 (C), 129.0 (CH), 128.9 (C), 128.9 (CH), 127.0 (CH), 125.9 (CH), 124.5 (C), 123.5, 121.3 (C), 111.3, 91.7 (C), 58.6 (CH₃), 54.1 (CH); HRMS (ESI) *m/z*: 373.0581 [M+H]⁺, C₁₈H₁₄ClN₂O₅⁺ requires 373.0586.

Methyl (1*R*,3*aR*,8*bR*)-5-methyl-3*a*-nitro-1-phenyl-3*a*,8*b*-dihydro-1*H*-benzofuro[2,3-*c*]pyrrole-1-carboxylate (11*ja*)



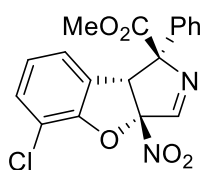
21.6 mg (41%) of **11ja** were obtained from **8j** (26.6 mg, 0.15 mmol) after column chromatography eluting with hexane:EtOAc (95:5). Enantiomeric excess (96%) was measured by HPLC (CHIRALPAK® AD-H), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: *t_r* = 7.4 min, minor enantiomer: *t_r* = 19.3 min.

Colorless oil; $[\alpha]_D^{25} +189.7$ (*c* 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 8.09 (s, 1H, CH=N), 7.24 – 7.17 (m, 3H, Ar), 6.99 – 6.91 (m, 2H, Ar), 6.88 (ddt, *J* = 7.5, 1.4, 0.8 Hz, 1H, Ar), 6.52 (t, *J* = 7.6 Hz, 1H, Ar), 6.18 (d, *J* = 7.7 Hz, 1H, Ar), 5.35 (s, 1H, CHAr), 3.90 (s, 3H, MeO), 2.22 (s, 3H, MeO); ¹³C NMR (75 MHz, CDCl₃) δ 171.2 (C, C=O), 158.9 (CH, CH=N), 155.8 (C), 135.8 (C), 131.1 (CH), 128.7 (CH), 128.6 (CH), 126.0 (CH), 124.0 (C), 123.7 (CH), 122.9 (CH), 121.9 (C), 120.6 (CH), 91.6 (C), 59.5 (CH₃), 54.0 (CH), 15.0 (CH₃); HRMS (ESI) *m/z*: 353.1126 [M+H]⁺, C₁₉H₁₇N₂O₅⁺ requires 353.1132.

Methyl (1*R*,3*aR*,8*bR*)-5-methoxy-3*a*-nitro-1-phenyl-3*a*,8*b*-dihydro-1*H*-benzofuro[2,3-*c*]pyrrole-1-carboxylate (11*ka*)

42.7 mg (77%) of **11ka** were obtained from **8k** (29.0 mg, 0.15 mmol) after column chromatography eluting with hexane:EtOAc (9:1). Enantiomeric excess (91%) was measured by HPLC (Lux® i-Amylose-1), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: *t_r* = 11.8 min, minor enantiomer: *t_r* = 23.3 min.

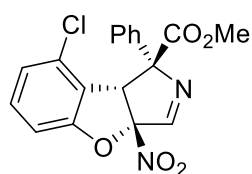
White foam; [α]_D²⁵ +71.0 (*c* 1.1, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 8.09 (s, 1H, CH=N), 7.20 (ddd, *J* = 5.1, 2.6, 1.6 Hz, 3H, Ar), 6.99 – 6.90 (m, 2H, Ar), 6.66 (d, *J* = 8.1 Hz, 1H, Ar), 6.62 – 6.51 (m, 1H, Ar), 5.97 (dt, *J* = 7.6, 1.1 Hz, 1H, Ar), 5.38 (s, 1H, CHAr), 3.90 (s, 3H, MeO), 3.84 (s, 3H, MeO). ¹³C NMR (75 MHz, CDCl₃) δ 171.0 (C, C=O), 158.6 (CH, CH=N), 145.5 (C), 144.2 (C), 135.7 (C), 128.7 (CH), 128.6 (CH), 126.0 (CH), 124.3 (C), 123.8 (CH), 123.8 (C), 118.1 (CH), 112.7 (CH), 91.7 (C), 59.6 (CH₃), 56.2 (CH₃), 54.0 (CH); HRMS (ESI) *m/z*: 369.1080 [M+H]⁺, C₁₉H₁₇N₂O₆⁺ requires 369.1081.

Methyl (1*R*,3*aR*,8*bR*)-5-chloro-3*a*-nitro-1-phenyl-3*a*,8*b*-dihydro-1*H*-benzofuro[2,3-*c*]pyrrole-1-carboxylate (11*la*)

53.9 mg (96%) of **11la** were obtained from **8l** (26.9 mg, 0.15 mmol) after column chromatography eluting with hexane:EtOAc (9:1). Enantiomeric excess (96%) was measured by HPLC (CHIRALPAK® AD-H), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: *t_r* = 8.5 min, minor enantiomer: *t_r* = 22.3 min.

White foam; [α]_D²⁵ +126.0 (*c* 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 8.14 (s, 1H, CH=N), 7.25 – 7.19 (m, 3H, Ar), 7.07 (dt, *J* = 8.1, 1.0 Hz, 1H, Ar), 7.00 – 6.87 (m, 2H, Ar), 6.57 (t, *J* = 7.9 Hz, 1H, Ar), 6.27 (dt, *J* = 7.7, 1.1 Hz, 1H, Ar), 5.42 (s, 1H), 3.91 (s, 3H, MeO); ¹³C NMR (75 MHz, CDCl₃) δ 170.9 (C, C=O), 158.3 (CH, CH=N), 153.1 (C), 135.4 (C), 130.2 (CH), 128.9 (CH), 128.8 (CH), 125.9 (CH), 124.7 (C), 124.3 (C), 124.0 (C), 123.7 (CH), 115.8 (CH), 91.8 (C), 59.6 (CH₃), 54.1 (CH); HRMS (ESI) *m/z*: 373.0579 [M+H]⁺, C₁₈H₁₄ClN₂O₅⁺ requires 373.0586.

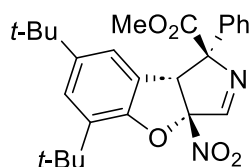
Methyl (1*R*,3*aR*,8*bR*)-8-chloro-3*a*-nitro-1-phenyl-3*a*,8*b*-dihydro-1*H*-benzofuro[2,3-*c*]pyrrole-1-carboxylate (11*ma*)



10.4 mg (19%) of **11ma** were obtained from **8m** (29.6 mg, 0.15 mmol) after column chromatography eluting with hexane:EtOAc (95:5). Enantiomeric excess (36%) was measured by HPLC (Lux® Cellulose-3), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: *t_r* = 12.3 min, minor enantiomer: *t_r* = 20.4 min.

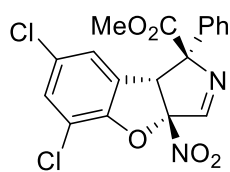
Colorless oil; $[\alpha]_D^{25}$ -15.3 (*c* 0.9, CHCl₃); **¹H NMR** (300 MHz, CDCl₃) δ 8.15 (s, 1H, CH=N), 7.14 – 7.06 (m, 3H, Ar), 7.02 (td, *J* = 8.1, 0.6 Hz, 1H, Ar), 6.89 – 6.83 (m, 2H, Ar), 6.78 (dt, *J* = 8.2, 0.7 Hz, 1H, Ar), 6.68 (dd, *J* = 8.1, 0.8 Hz, 1H, Ar), 5.52 (s, 1H, CHAr), 3.98 (s, 3H, MeO); **¹³C NMR** (75 MHz, CDCl₃) δ 170.5 (C, C=O), 158.2 (C), 157.5 (CH, C=N), 134.6 (C), 131.9 (C), 131.5 (CH), 128.8 (CH), 128.1 (CH), 126.1 (CH), 124.1 (CH), 123.5 (C), 122.7 (C), 108.9 (CH), 93.0 (C), 59.2 (CH₃), 54.0 (CH); **HRMS** (ESI) *m/z*: 373.0583 [M+H]⁺, C₁₈H₁₄ClN₂O₅⁺ requires 373.0586.

Methyl (1*R*,3*aR*,8*bR*)-5,7-di-*tert*-butyl-3*a*-nitro-1-phenyl-3*a*,8*b*-dihydro-1*H*-benzofuro[2,3-*c*]pyrrole-1-carboxylate (11*na*)



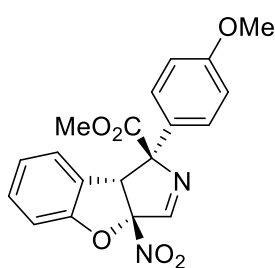
20.5 mg (30%) of **11na** were obtained from **8n** (41.3 mg, 0.15 mmol) after column chromatography eluting with hexane:CH₂Cl₂ (4:6). Enantiomeric excess (82%) was measured by HPLC (CHIRALPAK® AD-H), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: *t_r* = 5.0 min, minor enantiomer: *t_r* = 8.5 min.

Colorless oil; $[\alpha]_D^{25}$ +25.8 (*c* 1.0, CHCl₃); **¹H NMR** (300 MHz, CDCl₃) δ 8.12 (s, 1H), 7.16 – 7.10 (m, 3H), 6.97 (dd, *J* = 2.1, 0.7 Hz, 1H), 6.88 – 6.80 (m, 2H), 6.31 (dd, *J* = 2.0, 0.9 Hz, 1H), 5.25 (t, *J* = 0.8 Hz, 1H), 3.94 (s, 3H), 1.33 (s, 9H), 1.01 (s, 9H); **¹³C NMR** (75 MHz, CDCl₃) δ 171.4 (C), 159.0 (CH, CH=N), 153.0 (C), 145.9 (C), 135.6 (C), 132.9 (C), 128.5 (CH), 125.9 (CH), 124.0 (C), 123.5 (CH), 122.5 (C), 121.0 (CH), 92.1 (C), 59.2 (CH₃), 54.0 (CH₃), 34.5 (C), 34.3 (C), 31.5 (CH₃, MeO), 29.4 (CH); **HRMS** (ESI) *m/z*: 473.2038 [M+H]⁺, C₂₆H₃₀ClN₂NaO₅⁺ requires 473.2047.

Methyl (1*R*,3*aR*,8*bR*)-5,7-dichloro-3*a*-nitro-1-phenyl-3*a*,8*b*-dihydro-1*H*-benzofuro[2,3-*c*]pyrrole-1-carboxylate (11*oa*)

56.6 mg (93%) of **11oa** were obtained from **8o** (34.8 mg, 0.15 mmol) after column chromatography eluting with hexane:EtOAc (9:1). Enantiomeric excess (94%) was measured by HPLC (CHIRALPAK® AD-H), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: *t_r* = 7.5 min, minor enantiomer: *t_r* = 39.5 min.

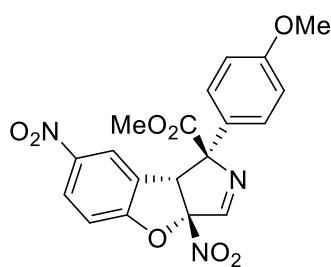
Colorless oil; $[\alpha]_D^{25} +46.6$ (*c* 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 8.13 (s, 1H, CH=N), 7.29 – 7.24 (m, 3H, Ar), 7.08 (dd, *J* = 2.1, 0.8 Hz, 1H, Ar), 6.96 – 6.89 (m, 2H, Ar), 6.24 (dd, *J* = 2.1, 1.1 Hz, 1H, Ar), 5.38 (t, *J* = 0.9 Hz, 1H), 3.91 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 170.6 (C), 158.1 (CH, C=N), 151.9 (C), 135.0 (C), 129.9 (CH), 129.3 (CH), 129.0 (CH), 128.6 (C), 125.7 (CH), 125.5 (C), 124.9 (CH), 123.8 (C), 116.3 (C), 91.9 (C), 59.5 (CH₃), 54.2 (CH); HRMS (ESI) *m/z*: 407.0189 [M+H]⁺, C₁₈H₁₃Cl₂N₂O₅⁺ requires 407.0196.

Methyl (1*R*,3*aR*,8*bR*)-1-(4-methoxyphenyl)-3*a*-nitro-3*a*,8*b*-dihydro-1*H*-benzofuro[2,3-*c*]pyrrole-1-carboxylate (11*ab*)

34.3 mg (92%) of **11ab** were obtained from **8a** (24.5 mg, 0.15 mmol) and methyl 2-(*p*-methoxyphenyl)isocyanoacetate (**2b**, 39 μL, 0.19 mmol) after column chromatography eluting with hexane:EtOAc (9:1). Enantiomeric excess (97%) was measured by HPLC (CHIRALPAK® AD-H), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: *t_r* = 14.4 min, minor enantiomer: *t_r* = 41.4 min.

White foam; $[\alpha]_D^{25} +87.1$ (*c* 1.1, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 8.05 (s, 1H, CH=N), 7.08 (dddd, *J* = 8.2, 7.4, 1.4, 0.8 Hz, 1H, Ar), 6.92 – 6.80 (m, 3H, Ar), 6.75 – 6.62 (m, 3H, Ar), 6.48 – 6.39 (m, 1H, Ar), 5.32 (s, 1H, CHAr), 3.90 (s, 3H, MeO), 3.72 (s, 3H, MeO); ¹³C NMR (75 MHz, CDCl₃) δ 171.3 (C, C=O), 159.7 (C), 158.3 (CH, CH=N), 157.1 (C), 129.8, 127.8 (C), 127.2 (CH), 126.6 (CH), 124.2 (C), 123.2 (CH), 122.7 (C), 113.9 (CH), 110.3 (CH), 91.3 (C), 59.3 (CH₃), 55.4 (CH₃), 54.0 (CH); HRMS (ESI) *m/z*: 369.1066 [M+H]⁺, C₁₉H₁₇N₂O₆⁺ requires 369.1081.

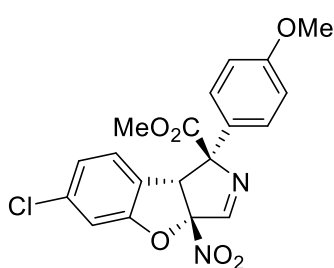
Methyl (1*R*,3*aR*,8*bR*)-1-(4-methoxyphenyl)-3*a*,7-dinitro-3*a*,8*b*-dihydro-1*H*-benzo-furo[2,3-*c*]pyrrole-1-carboxylate (11*eb*)



62.6 mg (99%) of **11eb** were obtained from **8e** (31.2 mg, 0.15 mmol) and methyl 2-(*p*-methoxyphenyl)isocyanoacetate (**2b**, 39 μ L, 0.19 mmol) after column chromatography eluting with hexane:EtOAc (8:2). Enantiomeric excess (94%) was measured by HPLC (CHIRALPAK® AD-H), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: t_r = 33.6 min, minor enantiomer: t_r = 38.5 min.

White foam; $[\alpha]_D^{25}$ -59.4 (c 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 8.10 (s, 1H, CH=N), 8.04 (ddd, J = 8.9, 2.4, 0.7 Hz, 1H, Ar), 7.37 (dd, J = 2.4, 1.1 Hz, 1H, Ar), 6.98 (d, J = 9.0 Hz, 1H, Ar), 6.84 (d, J = 8.9 Hz, 2H, Ar), 6.73 (d, J = 9.0 Hz, 2H, Ar), 5.38 (s, 1H, CHAr), 3.92 (s, 3H, MeO), 3.70 (s, 3H, MeO); ¹³C NMR (75 MHz, CDCl₃) δ 170.7 (C, C=O), 161.2 (C), 160.1 (C), 157.5 (CH, CH=N), 143.8 (C), 127.0 (C), 126.9 (CH), 126.7 (CH), 124.6 (C), 124.5 (C), 122.9 (CH), 114.4 (CH), 110.6 (CH), 91.8 (C), 58.3 (CH₃), 55.5 (CH₃), 54.3 (CH); HRMS (ESI) m/z : 414.0915 [M+H]⁺, C₁₉H₁₆N₃O₈⁺ requires 414.0932.

Methyl (1*R*,3*aR*,8*bR*)-6-chloro-1-(4-methoxyphenyl)-3*a*-nitro-3*a*,8*b*-dihydro-1*H*-benzo-furo[2,3-*c*]pyrrole-1-carboxylate (11*ib*)

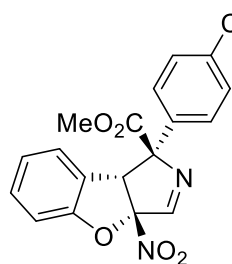


50.8 mg (84%) of **11ib** were obtained from **8i** (29.6 mg, 0.15 mmol) and methyl 2-(*p*-methoxyphenyl)isocyanoacetate (**2b**, 39 μ L, 0.19 mmol) after column chromatography eluting with hexane:EtOAc (9:1). Enantiomeric excess (96%) was measured by HPLC (CHIRALPAK® AD-H), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: t_r = 12.8 min, minor enantiomer: t_r = 26.2

min.

White foam; $[\alpha]_D^{25}$ +88.9 (c 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 8.04 (s, 1H, CH=N), 6.92 – 6.81 (m, 3H, Ar), 6.74 (d, J = 9.0 Hz, 2H, Ar), 6.66 (dd, J = 8.2, 1.9 Hz, 1H, Ar), 6.33 (dd, J = 8.0, 1.0 Hz, 1H, Ar), 5.28 (s, 1H, CHAr), 3.89 (s, 3H, MeO), 3.74 (s, 3H, MeO); ¹³C NMR (75 MHz, CDCl₃) δ 171.1 (C, C=O), 159.8 (C), 158.0 (CH, CH=N), 157.5 (C), 135.4 (C), 127.5 (C), 127.2 (CH), 127.1 (CH), 124.5 (C), 123.5 (CH), 121.5 (C), 114.1 (CH), 111.2 (CH), 91.3 (C), 58.7 (CH₃), 55.4 (CH₃), 54.0 (CH); HRMS (ESI) m/z : 403.0678 [M+H]⁺, C₁₉H₁₆ClN₂O₆⁺ requires 406.0691.

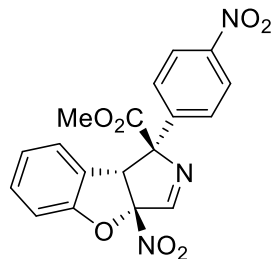
Methyl (1*R*,3*aR*,8*bR*)-1-(4-chlorophenyl)-3*a*-nitro-3*a*,8*b*-dihydro-1*H*-benzofuro[2,3-*c*]pyrrole-1-carboxylate (11ac**)**



34.8 mg (92%) of **11ac** were obtained from **8a** (24.5 mg, 0.15 mmol) and methyl 2-(*p*-chlorophenyl)isocyanoacetate (**2c**, 22 μ L, 0.19 mmol) after column chromatography eluting with hexane:EtOAc (9:1). Enantiomeric excess (78%) was measured by HPLC (CHIRALPAK® AD-H), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: t_r = 12.1 min, minor enantiomer: t_r = 32.4 min.

Colorless oil; $[\alpha]_D^{25}$ +71.5 (c 1.2, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 8.09 (s, 1H, CH=N), 7.19 (d, J = 8.8 Hz, 2H, Ar), 7.11 (dddd, J = 8.2, 7.4, 1.4, 0.7 Hz, 1H, Ar), 6.94 – 6.86 (m, 3H, Ar), 6.70 (td, J = 7.6, 1.0 Hz, 1H, Ar), 6.46 – 6.40 (m, 1H, Ar), 5.34 (s, 1H, CHAr), 3.91 (s, 3H, MeO); ¹³C NMR (75 MHz, CDCl₃) δ 170.8 (C, C=O), 159.1 (CH, CH=N), 157.1 (C), 134.8 (C), 134.3 (C), 130.1 (CH), 128.8 (CH), 127.5 (CH), 126.4 (CH), 124.0 (C), 123.4 (CH), 122.2 (C), 110.5 (CH), 91.2 (C), 59.1 (CH₃), 54.2 (CH); HRMS (ESI) m/z : 373.0573 [M+H]⁺, C₁₈H₁₄ClN₂O₅⁺ requires 373.0586.

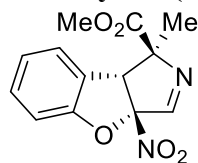
Methyl (1*R*,3*aR*,8*bR*)-3*a*-nitro-1-(4-nitrophenyl)-3*a*,8*b*-dihydro-1*H*-benzofuro[2,3-*c*]pyrrole-1-carboxylate (11ad**)**



55.3 mg (96%) of **11ad** were obtained from **8a** (24.5 mg, 0.15 mmol) and methyl 2-(*p*-nitrophenyl)isocyanoacetate (**2d**, 41.8 mg, 0.19 mmol) after column chromatography eluting with hexane:Et₂O (1:1). Enantiomeric excess (67%) was measured by HPLC (CHIRALPAK® AS-H), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: t_r = 52.6 min, minor enantiomer: t_r = 31.9 min.

Orange oil; $[\alpha]_D^{25}$ +63.1 (c 0.7, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 8.16 (s, 1H, CH=N), 8.07 (d, J = 8.9 Hz, 2H, Ar), 7.19 (d, J = 8.9 Hz, 2H, Ar), 7.16 – 7.04 (m, 1H, Ar), 6.89 (d, J = 8.2 Hz, 1H, Ar), 6.66 (td, J = 7.6, 1.0 Hz, 1H, Ar), 6.43 (d, J = 7.7 Hz, 1H, Ar), 5.39 (s, 1H, CHAr), 3.93 (s, 3H, MeO); ¹³C NMR (75 MHz, CDCl₃) δ 170.2 (C, C=O), 159.9 (CH, CH=N), 157.2 (C), 147.9 (C), 142.6 (C), 130.5 (CH), 127.4 (CH), 126.2 (CH), 123.9 (C), 123.7 (CH), 123.5 (CH), 121.6 (C), 110.8 (CH), 91.2 (C), 59.2 (CH₃), 54.5 (CH); HRMS (ESI) m/z : 384.0822 [M+H]⁺, C₁₈H₁₄N₃O₇⁺ requires 384.0826.

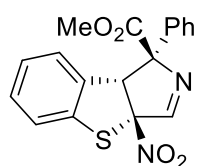
Methyl (1*S*,3*aR*,8*bR*)-1-methyl-3*a*-nitro-3*a*,8*b*-dihydro-1*H*-benzofuro[2,3-*c*]pyrrole-1-carboxylate (11*af*)



18.8 mg (45%) of **11af** were obtained from **8a** (24.5 mg, 0.15 mmol) and 2-methylisocyanoacetate (**2f**, 17 μ L, 0.19 mmol) after column chromatography eluting with hexane:EtOAc (9:1). Enantiomeric excess (0%) was measured by HPLC (CHIRALPAK® AD-H), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: t_r = 11.0 min, minor enantiomer: t_r = 12.5 min.

Orange oil; ¹H NMR (300 MHz, CDCl₃) δ 7.83 (s, 1H, CH=N), 7.31 (t, J = 7.5 Hz, 1H, Ar), 7.15 (d, J = 7.9 Hz, 1H, Ar), 7.03 (t, J = 7.0 Hz, 2H, Ar), 4.18 (s, 1H, CHN), 3.21 (s, 3H, MeO), 1.87 (s, 3H, Me). ¹³C NMR (75 MHz, CDCl₃) δ 169.7 (C, C=O), 157.5 (C), 156.9 (CH, C=N), 130.8 (CH), 125.4 (CH), 125.0 (C), 123.4 (CH), 122.9 (CH), 110.9 (CH), 86.6 (C), 61.5 (CH₃), 52.4 (CH), 25.3 (CH₃); HRMS (ESI) m/z : 277.0819 [M+H]⁺, C₁₃H₁₃N₂O₅⁺ requires 277.0819.

Methyl (1*R*,3*aR*,8*bR*)-3*a*-nitro-1-phenyl-3*a*,8*b*-dihydro-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrole-1-carboxylate (12)



4.4 mg (8%) of **12** were obtained from **9** (26.9 mg, 0.15 mmol) after column chromatography eluting with hexane:EtOAc (9:1). Enantiomeric excess (72%) was measured by HPLC (CHIRALPAK® AD-H), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: t_r = 10.2 min, minor enantiomer: t_r = 39.1 min.

Orange oil; $[\alpha]_D^{25}$ +36.7 (c 0.4, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 8.24 (s, 1H, CH=N), 7.20 (ddt, J = 7.5, 1.5, 0.7 Hz, 1H, Ar), 7.10 – 7.02 (m, 3H, Ar), 7.00 (dd, J = 8.0, 1.5 Hz, 1H, Ar), 6.94 (dd, J = 7.5, 1.3 Hz, 1H, Ar), 6.93 – 6.80 (m, 3H, Ar), 5.65 (s, 1H, CHAr), 3.92 (s, 3H, MeO); ¹³C NMR (75 MHz, CDCl₃) δ 171.8 (C, C=O), 159.7 (CH, CH=N), 137.2 (C), 134.6 (C), 133.7 (CH), 129.4 (CH), 128.5 (CH), 128.0 (CH), 127.7 (CH), 126.1 (CH), 125.6 (CH), 121.2 (CH), 112.0 (CH), 92.6 (C), 64.6 (CH₃), 53.9 (CH); HRMS (ESI) m/z : 355.0752 [M+H]⁺, C₁₈H₁₅N₂O₄⁺S requires 355.0747.

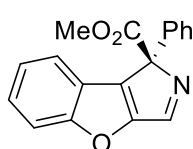
5.5.5 Synthesis of **11aa** at 1 mmol scale

To a solution of **8a** (163.1 mg, 1.0 mmol) and **C-II** (45.1 mg, 0.1 mmol) in dry CHCl₃ (5 mL) was added 2-phenylisocyanoacetate (**2a**, 190 μ L, 1.3 mmol). The reaction was stirred for 6 days at 0 °C and passed through a short-path column. The resulting mixture was used for the determination of the diastereomeric ratio by ¹H-NMR analysis. The product was then purified by column chromatography (eluent: hexane:EtOAc 9:1) to furnish 254 mg (75%) of **11aa** as a

yellowish foam. Enantiomeric excess (91%) was measured by HPLC (CHIRALPAK® AD-H), hexane:*i*PrOH 80:20, 1.0 mL min⁻¹, major enantiomer: *t_r* = 8.5 min, minor enantiomer: *t_r* = 24.1 min.

5.5.6 Transformations of product **11aa**

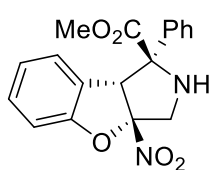
Methyl (*S*)-1-phenyl-1*H*-benzofuro[2,3-*c*]pyrrole-1-carboxylate (**14**)



A modification of a literature procedure was employed.¹⁹⁹ To a solution of **11aa** (31.9 mg, 0.094 mmol, 1.0 equiv, *ee* 93%) in dry dichloromethane (2 mL, 0.05 M) was added DBU (70 μL, 0.470 mmol, 5 equiv). The mixture was stirred at room temperature for 17 h. Purification by column chromatography (hexane:EtOAc 8:2) furnished 14.4 mg (53%) of the title compound. Enantiomeric excess (90%) was measured by HPLC (CHIRALPAK® AD-H), hexane:*i*PrOH 80:20, 1.0 mL min⁻¹, major enantiomer: *t_r* = 11.9 min, minor enantiomer: *t_r* = 8.2 min.

Red oil; [α]_D²⁵ +11.0 (*c* 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 8.52 (s, 1H, CH=N), 7.94 – 7.87 (m, 1H, Ar), 7.73 – 7.67 (m, 2H, Ar), 7.65 – 7.59 (m, 1H, Ar), 7.49 – 7.41 (m, 2H, Ar), 7.40 – 7.32 (m, 3H, Ar), 3.76 (s, 3H, MeO); ¹³C NMR (75 MHz, CDCl₃) δ 168.9 (C, C=O), 161.6 (C), 160.8 (C), 153.2 (CH, CH=N), 140.5 (C), 135.8 (C), 128.9 (CH), 128.8 (CH), 127.9 (CH), 126.5 (CH), 124.6 (C), 124.6 (CH), 121.4 (CH), 113.7 (CH), 82.8 (C), 53.6 (CH₃); HRMS (ESI) *m/z*: 292.0968 [M+H]⁺, C₁₈H₁₄NO₃⁺ requires 292.0968.

Methyl (1*R*,3*aR*,8*bR*)-3*a*-nitro-1-phenyl-2,3,3*a*,8*b*-tetrahydro-1*H*-benzofuro[2,3-*c*]pyrrole-1-carboxylate (**15**)

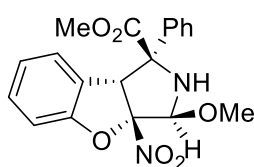


A modification of a literature procedure was employed.²⁰⁰ To a solution of **11aa** (21.1 mg, 0.062 mmol, 1.0 equiv, *ee* 89%) in dry dichloromethane (1.8 mL, 0.034 M) and triethylsilane (30 μL, 0.187 mmol, 3.0 equiv), under nitrogen atmosphere, was added BF₃·Et₂O (25 μL, 0.205 mmol, 3.3 equiv). The mixture was stirred at room temperature until complete consumption of the starting material (TLC, ca. 17 h). The mixture was quenched with saturated aqueous NaHCO₃ (2 mL). CH₂Cl₂ (10 mL) was added and the mixture was transferred to a separatory funnel. The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (3×5 mL). The combined organic phases were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane:EtOAc 8:2) furnished 20.4 mg (97%) of the title compound. Enantiomeric excess (89%) was measured by HPLC

(CHIRALPAK® AD-H), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: t_r = 7.2 min, minor enantiomer: t_r = 17.2 min.

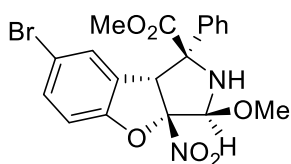
White solid; $[\alpha]_D^{25}$ +180.5 (c 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.37 – 7.28 (m, 2H, Ar), 7.26 (tdd, J = 4.5, 3.1, 1.2 Hz, 3H, Ar), 7.10 (dddd, J = 8.2, 7.5, 1.4, 0.7 Hz, 1H, Ar), 6.93 (d, J = 7.7 Hz, 1H, Ar), 6.55 (td, J = 7.5, 1.1 Hz, 1H, Ar), 6.04 (d, J = 7.7 Hz, 1H, Ar), 5.19 (s, 1H, CHAr), 3.93 (s, 3H, MeO), 3.84 (d, 1H, J = 16.2 Hz), 3.83 (d, J = 15.7 Hz, 1H), 2.87 (s, 1H, NH); ¹³C NMR (75 MHz, CDCl₃) δ 174.0 (C, C=O), 159.2 (C), 135.8 (C), 129.4 (CH), 128.8 (CH), 128.5 (CH), 126.4 (CH), 126.3 (CH), 122.9 (C), 122.2 (CH), 121.6 (C), 109.6 (CH), 77.3 (C), 60.1 (CH₃), 54.9 (CH₂), 53.7 (CH); HRMS (ESI) m/z : 341.1128 [M+H]⁺, C₁₈H₁₇N₂O₅⁺ requires 341.1132.

Methyl (1*R*,3*S*,3*aR*,8*bR*)-3-methoxy-3*a*-nitro-1-phenyl-2,3,3*a*,8*b*-tetrahydro-1*H*-benzofuro[2,3-*c*]pyrrole-1-carboxylate (16aa)



A solution of **11aa** (25.2 mg, 0.075 mmol) dissolved in MeOH (2 mL, 0.04 M) was stirred at reflux for 17 h (oil bath at 70 °C). The solvent was then evaporated to obtain 27.6 mg of **7** (99%). Enantiomeric excess (98%) was measured by HPLC (CHIRALPAK® AD-H), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: t_r = 8.8 min, minor enantiomer: t_r = 16.8 min. White foam; $[\alpha]_D^{25}$ +208.4 (c 1.1, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.24 – 7.15 (m, 5H, Ar), 7.03 (t, J = 7.7 Hz, 1H, Ar), 6.85 (d, J = 8.1 Hz, 1H, Ar), 6.51 (td, J = 7.5, 1.0 Hz, 1H, Ar), 6.13 (d, J = 7.6 Hz, 1H, Ar), 5.77 (s, 1H, CHNH), 5.03 (s, 1H, CHAr), 3.85 (s, 3H, MeO), 3.72 (s, 1H, NH), 3.36 (s, 3H, MeO); ¹³C NMR (75 MHz, CDCl₃) δ 174.9 (C, C=O), 157.7 (C), 136.7 (C), 129.1 (CH), 128.6 (CH), 128.5 (CH), 126.5 (CH), 125.8 (CH), 123.8 (C), 123.4 (C), 122.3 (CH), 109.5 (CH), 92.2 (CH), 75.0 (C), 55.6 (CH), 53.4 (CH₃), 53.2 (CH₃); HRMS (ESI) m/z : 393.1048 [M+Na]⁺, C₁₉H₁₈N₂NaO₆⁺ requires 393.1057.

Methyl (1*R*,3*S*,3*aR*,8*bR*)-7-bromo-3-methoxy-3*a*-nitro-1-phenyl-2,3,3*a*,8*b*-tetrahydro-1*H*-benzofuro[2,3-*c*]pyrrole-1-carboxylate (16da)



Following the same procedure for the synthesis of **16aa**, from **11da** (45.1 mg, 0.11 mmol), 48.5 mg of **16da** (99%) were obtained. Enantiomeric excess (98%) was measured by HPLC (CHIRALPAK® AD-H), hexane:iPrOH 80:20, 1.0 mL min⁻¹, major enantiomer: t_r = 8.5 min, minor enantiomer: t_r = 12.3 min. White solid, m.p. 201.7-203.0; $[\alpha]_D^{25}$ +158.1 (c 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.30 – 7.21 (m, 3H, Ar), 7.21 – 7.12 (m, 3H, Ar), 6.73

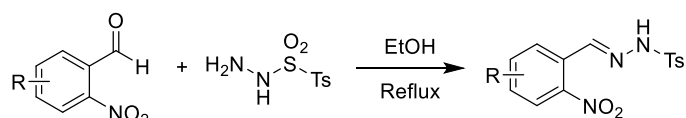
(d, $J = 8.6$ Hz, 1H, Ar), 6.19 (dd, $J = 2.1, 1.0$ Hz, 1H, Ar), 5.73 (s, 1H, CHN), 5.01 (s, 1H, CHAr), 3.86 (s, 3H, MeO), 3.72 (s, 1H, NH), 3.36 (s, 3H, MeO); ^{13}C NMR (75 MHz, CDCl_3) δ 174.5 (C, C=O), 156.7 (C), 136.4 (C), 132.0 (CH), 129.6 (CH), 129.0 (CH), 128.7 (CH), 126.2 (C), 125.6 (CH), 123.6 (C), 114.6 (C), 111.0 (CH), 92.2 (CH), 75.0 (C), 55.7 (CH_3), 53.6 (CH), 53.3 (CH_3); HRMS (ESI) m/z : 471.0153 $[\text{M}+\text{Na}]^+$, $\text{C}_{19}\text{H}_{17}\text{BrN}_2\text{NaO}_6^+$ requires 471.0162. Compound **16da** was re-crystallized from hexane-MeOH to give suitable crystals for X-ray analysis.

5.6 Enantioselective [3+3] cycloaddition of isocyanoacetates and *N*-iminoquinazolinium ylides

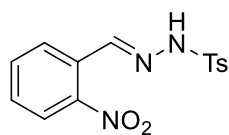
5.6.1 Synthesis and characterization data for *N*-iminoquinazolinium ylides **17**

N-Iminoquinazolinium ylides were synthesized via a three-step procedure consisting in the formation of tosylhydrazones from 2-nitrobenzaldehydes, followed by the reduction of the nitro group to amine and final annulation.

Tosylhydrazones



4-Methyl-*N'*-(2-nitrobenzylidene)benzenesulfonohydrazide²⁰¹ (*representative procedure*)

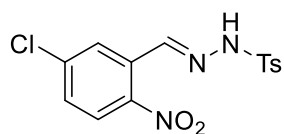


A modification of a procedure described in the literature was carried out.²⁰²

To a solution of 2-nitrobenzaldehyde (3.7 g, 24.6 mmol, 1.0 equiv.) in EtOH (80 mL) was added tosylhydrazine (5.1 g, 27.5 mmol, 1.2 equiv.).

The mixture was stirred at reflux for 1 h, during which a large amount of solid was observed. The mixture was cooled to 0 °C to promote complete precipitation. The solid was filtered and washed with cold ethanol to yield 7.08 g (90%) of the title compound as a pale-yellow solid. ¹H RMN (300 MHz, DMSO-*d*₆) δ 11.90 (s, 1H, NH), 8.28 (s, 1H, CH=N), 8.02 (dd, *J* = 8.1, 1.0 Hz, 1H, Ar), 7.86 – 7.69 (m, 4H, Ar), 7.67 – 7.58 (m, 1H, Ar), 7.42 (d, *J* = 8.1 Hz, 2H, Ar), 2.37 (s, 3H, CH₃).

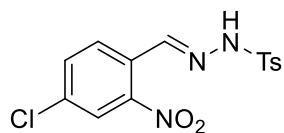
N'-(5-Chloro-2-nitrobenzylidene)-4-methylbenzenesulfonohydrazide²⁰¹



From 5-chloro-2-nitrobenzaldehyde (3.06 g, 16.5 mmol), 5.19 g (89%) of the title compound were obtained. Yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.07 (s, 1H, NH), 8.27 (s, 1H, CH=N), 8.07 (dd,

J = 8.3, 0.9 Hz, 1H, Ar), 7.77 (d, *J* = 8.3 Hz, 2H, Ar), 7.74 – 7.67 (m, 2H, Ar), 7.43 (d, *J* = 8.0 Hz, 2H, Ar), 2.38 (s, 3H, CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 146.3 (C), 143.8 (C), 141.1 (CH), 138.3 (C), 136.0 (C), 130.3 (CH), 130.2 (C), 129.9 (CH), 127.2 (CH), 127.0 (CH), 126.9 (CH), 21.0 (CH₃).

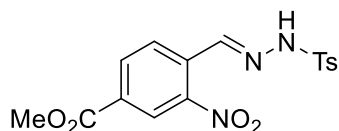
N'-(4-Chloro-2-nitrobenzylidene)-4-methylbenzenesulfonohydrazide²⁰³



From 4-chloro-2-nitrobenzaldehyde (3.05 g, 16.4 mmol), 5.05 g (87%) of the title compound were obtained. Yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.99 (s, 1H, NH), 8.23 (s, 1H, CH=N), 8.12 (dd,

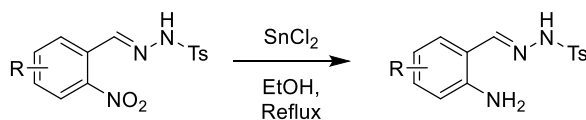
$J = 1.9, 0.7$ Hz, 1H, Ar), 7.84 – 7.82 (m, 2H, Ar), 7.76 (d, $J = 8.3$ Hz, 2H, Ar), 7.46 – 7.37 (m, 2H, Ar), 2.36 (s, 3H, CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 148.2 (C), 143.7 (C), 141.3 (CH), 136.0 (C), 134.5 (C), 133.6 (CH), 129.8 (CH), 129.3 (CH), 127.2 (CH), 126.9 (C), 124.5 (CH), 21.0 (CH₃).

Methyl 3-nitro-4-((2-tosylhydrazineylidene)methyl)benzoate²⁰³

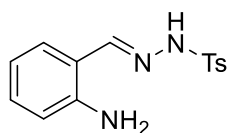


From methyl 4-formyl-3-nitrobenzoate (2.10 g, 16.4 mmol), 2.67 g (70%) of the title compound were obtained. White solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.14 (s, 1H, NH), 8.44 (d, $J = 1.7$ Hz, 1H, Ar), 8.33 (s, 1H, CH=N), 8.25 (ddd, $J = 8.3, 1.8, 0.6$ Hz, 1H, Ar), 8.00 (d, $J = 8.2$ Hz, 1H, Ar), 7.77 (d, $J = 8.3$ Hz, 2H, Ar), 7.46 – 7.39 (m, 2H, Ar), 3.91 (s, 3H, CH₃), 2.37 (s, 3H, CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 164.2 (C), 147.7 (C), 143.8 (C), 141.4 (CH), 136.0 (C), 133.5 (CH), 132.07 (C), 131.0 (C), 129.9 (CH), 128.5 (CH), 127.1 (CH), 125.3 (CH), 52.9 (CH₃), 21.0 (CH₃).

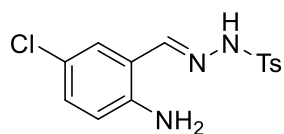
2-Aminobenzylidenehydrazones



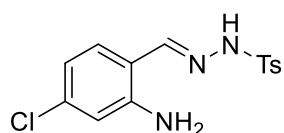
N'-(2-Aminobenzylidene)-4-methylbenzenesulfonohydrazide²⁰¹ (representative procedure)



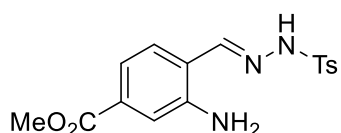
A modification of a literature procedure was employed.²⁰⁴ A solution of 4-methyl-*N'*-(2-nitrobenzylidene)benzenesulfonohydrazide (1.82 g, 5.7 mmol, 1.0 equiv.) and anhydrous 98% SnCl₂ (5.53 g, 28.6 mmol, 5.0 equiv.) in absolute EtOH (23 mL), under nitrogen atmosphere, was stirred at reflux until complete consumption of the starting material (TLC analysis, ca. 2 h). The reaction mixture was poured over 50 mL ice and basified with sat. aq. solution of NaHCO₃ until pH 7-8. The mixture was extracted with EtOAc (3x150 mL) and the combined organic phases were washed with brine (100 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and purified by column chromatography eluting with hexane:EtOAc mixtures to furnish 0.99 g (60%) of the title compound as a pale-yellow solid. ¹H RMN (300 MHz, DMSO-*d*₆) δ 11.16 (s, 1H, NH), 7.97 (s, 1H, CH=N), 7.73 (d, $J = 8.3$ Hz, 2H, Ar), 7.40 (d, $J = 7.7$ Hz, 2H, Ar), 7.11 – 6.99 (m, 2H, Ar), 6.65 (d, $J = 7.9$ Hz, 1H, Ar), 6.56 – 6.45 (m, 3H, Ar+NH₂), 2.36 (s, 3H, CH₃).

***N'*-(2-Amino-5-chlorobenzylidene)-4-methylbenzenesulfonohydrazide²⁰¹**

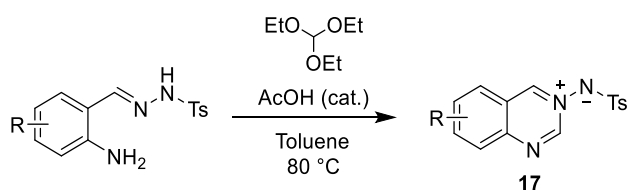
From *N'*-(5-Chloro-2-nitrobenzylidene)-4-methylbenzenesulfonohydrazide (3.08 g, 8.7 mmol), 1.43 g (51%) of the title compound were obtained. Yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.35 (s, 1H, NH), 7.96 (s, 1H, CH=N), 7.73 (d, *J* = 8.3 Hz, 2H, Ar), 7.40 (d, *J* = 7.8 Hz, 2H, Ar), 7.19 (d, *J* = 2.5 Hz, 1H, Ar), 7.07 (dd, *J* = 8.8, 2.5 Hz, 1H, Ar), 6.68 (d, *J* = 8.8 Hz, 1H, Ar), 6.65 (bs, 2H, NH₂), 2.36 (s, 3H, CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 149.8 (CH), 146.2 (C), 143.6 (C), 135.7 (C), 130.7 (CH), 130.0 (CH), 129.7 (CH), 127.2 (CH), 118.1 (C), 116.9 (CH), 115.5 (C), 21.0 (CH₃).

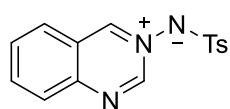
***N'*-(2-Amino-4-chlorobenzylidene)-4-methylbenzenesulfonohydrazide²⁰³**

From *N'*-(4-Chloro-2-nitrobenzylidene)-4-methylbenzenesulfonohydrazide (1.98 g, 5.6 mmol), 1.00 (55%) of the title compound were obtained. Yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.27 (s, 1H, NH), 7.96 (s, 1H, CH=N), 7.73 (d, *J* = 8.3 Hz, 2H, Ar), 7.40 (d, *J* = 8.0 Hz, 2H, Ar), 7.12 (d, *J* = 8.4 Hz, 1H, Ar), 6.76 (bs, 2H, NH₂), 6.71 (d, *J* = 2.1 Hz, 1H, Ar), 6.52 (dd, *J* = 8.3, 2.1 Hz, 1H, Ar), 2.36 (s, 3H, CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 150.2 (CH), 148.4 (C), 143.6 (C), 135.7 (C), 134.9 (C), 133.8 (CH), 129.7 (CH), 127.2 (CH), 114.9 (CH), 114.0 (CH), 113.3 (C), 21.0 (CH₃).

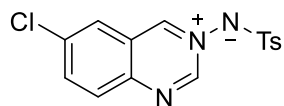
Methyl 3-amino-4-((2-tosylhydrazineylidene)methyl)benzoate²⁰³

From methyl 3-nitro-4-((2-tosylhydrazineylidene)methyl)benzoate (2.00 g, 5.3 mmol), 0.91 g (49%) of the title compound were obtained. Yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.45 (s, 1H, NH), 8.03 (s, 1H, CH=N), 7.74 (d, *J* = 8.3 Hz, 2H, Ar), 7.41 (d, *J* = 7.8 Hz, 2H, Ar), 7.33 (d, *J* = 1.7 Hz, 1H, Ar), 7.23 (d, *J* = 8.1 Hz, 1H, Ar), 7.06 (dd, *J* = 8.1, 1.7 Hz, 1H, Ar), 6.76 (s, 2H, NH₂), 3.80 (s, 3H, CH₃), 2.36 (s, 3H, CH₃); ¹³C NMR (75 MHz, DMSO) δ 166.2 (C), 149.8 (CH), 147.1 (C), 143.7 (C), 135.7 (C), 132.3 (CH), 130.6 (C), 129.8 (CH), 127.1 (CH), 117.8 (C), 116.0 (CH), 115.2 (CH), 52.1 (CH₃), 21.0 (CH₃).

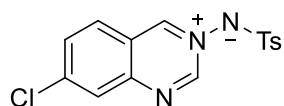
***N*-Iminoquinazolinium ylides**

Quinazolin-3-ium-3-yl(tosyl)amide (17a)²⁰¹ (*representative procedure*)

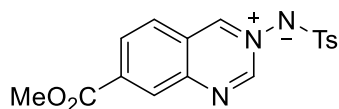
A modification of a literature procedure was carried out.^{201,202} To a solution of *N*-(2-Aminobenzylidene)-4-methylbenzenesulfonohydrazide (363 mg, 0.9 mmol, 1.0 equiv.) in toluene (7 mL), under nitrogen atmosphere, was added triethyl orthoformate (0.75 mL, 4.5 mmol, 5.0 equiv.) and two drops of glacial acetic acid. The mixture was stirred at 80 °C for 1 h. A large amount of solid was observed, which was filtered and washed with cold toluene to yield 160 mg (61%) of the title compound as a white solid. **¹H RMN** (300 MHz, DMSO-*d*₆) δ 9.95 (dd, *J* = 2.0, 0.8 Hz, 1H, N=CH-N), 8.92 (d, *J* = 1.9 Hz, 1H, Ar-CH=N), 8.48 – 8.39 (m, 1H, Ar), 8.28 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H, Ar), 8.18 (dd, *J* = 8.4, 1.0 Hz, 1H, Ar), 8.00 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H, Ar), 7.45 (d, *J* = 8.2 Hz, 2H, Ts), 7.22 (d, *J* = 8.4 Hz, 2H), 2.31 (s, 3H, CH₃).

(6-Chloroquinazolin-3-ium-3-yl)(tosyl)amide (17b)²⁰¹

From *N*-(2-amino-5-chlorobenzylidene)-4-methylbenzenesulfonohydrazide (375 mg, 1.2 mmol), 254 mg (66%) of the title compound was obtained. White solid. Low solubility precluded obtaining an NMR spectrum. **HRMS** (ESI) *m/z*: 366.0674 [M+CH₃OH+H]⁺, C₁₆H₁₈ClN₃O₃S⁺ requires 366.0674.

(7-Chloroquinazolin-3-ium-3-yl)(tosyl)amide (17c)²⁰³

From *N*-(2-amino-4-chlorobenzylidene)-4-methylbenzenesulfonohydrazide (392 mg, 1.2 mmol), 276 mg (68%) of the title compound were obtained. Yellow solid; **¹H NMR** (300 MHz, DMSO-*d*₆) δ 7.65 (d, *J* = 8.3 Hz, 2H, Ar), 7.42 (d, *J* = 8.2 Hz, 2H, Ar), 7.27 – 7.11 (m, 3H, Ar), 6.97 (s, 1H, Ar), 6.86 (s, 1H, Ar), 2.41 (s, 3H, CH₃).

(7-(Methoxycarbonyl)quinazolin-3-ium-3-yl)(tosyl)amide (17d)²⁰³

From methyl 3-amino-4-((2-tosylhydrazineylidene)methyl)benzoate (358 mg, 1.0 mmol), 269 mg (73%) of the title compound were obtained. White solid; **¹H NMR** (300 MHz, DMSO-*d*₆) δ 7.73 (dd, *J* = 8.0, 1.7 Hz, 1H, Ar), 7.67 – 7.60 (m, 3H, Ar), 7.40 (d, *J* = 8.1 Hz, 2H, Ar), 7.27 (d, *J* = 8.0 Hz, 1H, Ar), 7.03 (d, *J* = 7.1 Hz, 1H, Ar), 6.84 (s, 1H, Ar), 3.85 (s, 3H, CH₃), 2.40 (s, 3H, CH₃).

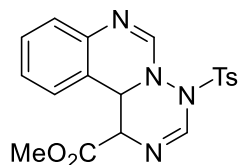
5.6.2 Synthesis and characterization data for compounds **18***Enantioselective procedure*

To a solution of *N*-iminoquinazolium ylide **17** (0.1 mmol, 1.0 equiv.) and **S-I** (6.3 mg, 0.01 mmol, 0.1 equiv.) in dichloromethane (1 mL) was added methyl isocyanoacetate (**2h**, 12 μ L, 0.13 mmol, 1.3 equiv.). The reaction was stirred at room temperature until no further reaction advancement was observed (ca. 72 h, TLC analysis).

For the determination of the diastereomeric ratio, a short path column chromatography to separate the catalyst **SI** was carried out and the resulting mixture analyzed by ^1H NMR. Then the product was purified by column chromatography, eluting with hexane:EtOAc mixtures.

Non-enantioselective procedure

To a solution of *N*-iminoquinazolium ylide **17** (0.1 mmol, 1.0 equiv.) and the achiral squaramide 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-((3-(dimethylamino)propyl)amino)cyclobut-3-ene-1,2-dione (4.1 mg, 0.01 mmol, 0.1 equiv.) in DCM (0.5 mL) was added methyl isocyanoacetate (**2h**, 12 μ L, 0.13 mmol, 1.3 equiv.). The reaction was stirred at room temperature for 48 h and the product was purified by column chromatography, eluting with hexane:EtOAc mixtures.

Methyl 4-tosyl-1,11b-dihydro-4*H*-[1,2,4]triazino[1,6-*c*]quinazoline-1-carboxylate (18ah**)**

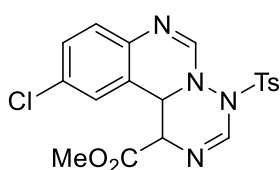
36.0 mg (87%) of **18ah** were obtained from **17a** (32.5 mg, 0.1 mmol).

Diastereomeric ratio (85:15) was determined by ^1H NMR and enantiomeric excess (major diastereomer: 84%, minor diastereomer: 62%) was determined by HPLC, **major diastereomer**: Lux® Cellulose-3, hexane:iPrOH 85:15, 0.5 mL min $^{-1}$, major enantiomer: t_r = 28.2 min, minor enantiomer: t_r = 22.9 min, **minor diastereomer**: CHIRALPAK® AS-H, hexane:iPrOH 80:20, 1.5 mL min $^{-1}$, major enantiomer: t_r = 26.5 min, minor enantiomer: t_r = 67.3 min.

18ah major diastereomer: colorless oil; $[\alpha]_D^{25} +100.0$ (c 1.0, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 8.26 (d, J = 2.5 Hz, 1H, CH=N), 7.80 (d, J = 8.5 Hz, 2H, Ar), 7.38 (d, J = 8.0 Hz, 2H, Ar), 7.33 – 7.21 (m, 3H, Ar+CH=N), 7.06 (td, J = 7.4, 1.5 Hz, 1H, Ar), 6.63 (ddt, J = 7.5, 1.3, 0.6 Hz, 1H, Ar), 4.21 (dd, J = 9.2, 2.5 Hz, 1H, CH), 3.59 (s, 3H, CH_3), 3.37 (dd, J = 9.2, 1.4 Hz, 1H, CH), 2.48 (s, 3H, CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 169.2 (C), 151.0 (CH), 146.9 (C), 140.8 (CH), 139.1 (C), 132.0 (C), 130.6 (CH), 130.3 (CH), 128.6 (CH), 127.1 (CH), 126.5 (CH), 126.38 (CH), 121.0 (C), 58.7 (CH), 52.6 (CH), 52.6 (CH_3), 22.0 (CH_3); **18ah**

minor diastereomer: colorless oil; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.31 (d, $J = 1.4$ Hz, 1H, CH=N), 7.81 (d, $J = 8.4$ Hz, 2H, Ar), 7.37 (d, $J = 8.0$ Hz, 2H, Ar), 7.32 – 7.24 (m, 3H, Ar+CH=N), 7.18 (dd, $J = 7.9, 1.4$ Hz, 1H, Ar), 7.12 (td, $J = 7.5, 1.4$ Hz, 1H, Ar), 6.75 (ddd, $J = 7.6, 1.4, 0.7$ Hz, 1H, Ar), 4.12 (dd, $J = 3.6, 1.4$ Hz, 1H, CH), 3.63 (d, $J = 3.4$ Hz, 1H, CH), 3.42 (s, 3H, CH_3), 2.47 (s, 3H, CH_3); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 168.1 (C), 150.1 (CH), 146.8 (C), 141.7 (CH), 139.0 (C), 132.1 (C), 130.7 (CH), 130.1 (CH), 128.7 (CH), 126.9 (C), 126.5 (CH), 126.4 (CH), 119.8 (C), 60.2 (CH), 53.0 (CH), 52.9 (CH_3), 22.0 (CH_3).

Methyl 10-chloro-4-tosyl-1,11b-dihydro-4*H*-[1,2,4]triazino[1,6-*c*]quinazoline-1-carboxylate (18bh)



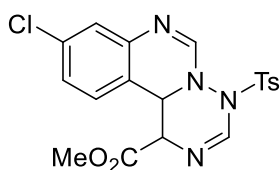
12.6 mg (45%) of **18bh** were obtained from **17b** (32.9 mg, 0.1 mmol).

Diastereomeric ratio (65:35) was determined by $^1\text{H NMR}$ and enantiomeric excess (major diastereomer: 75%, minor diastereomer: n.d.) was determined by HPLC (Lux® i-Amylose-1), hexane:iPrOH 80:20,

1.0 mL min^{-1} , **major diastereomer:** major enantiomer: $t_r = 31.7$ min, minor enantiomer: $t_r = 26.4$ min.

18bh major diastereomer: yellow oil; $[\alpha]_D^{25} -16.0$ (c 0.3, CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.26 (d, $J = 2.5$ Hz, 1H, CH=N), 7.80 (d, $J = 8.4$ Hz, 2H, Ar), 7.41 (d, $J = 7.9$ Hz, 2H, Ar), 7.29 – 7.24 (m, 2H, Ar+CH=N), 7.17 (d, $J = 8.4$ Hz, 1H, Ar), 6.66 (d, $J = 2.3$ Hz, 1H, Ar), 4.21 (dd, $J = 9.3, 2.5$ Hz, 1H, CH), 3.65 (s, 3H, CH_3), 3.34 (dd, $J = 9.3, 1.4$ Hz, 1H, CH), 2.51 (s, 3H, CH_3); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 169.0 (C), 151.2 (CH), 147.1 (C), 140.8 (CH), 137.8 (C), 132.3 (C), 131.9 (C), 130.7 (CH), 130.4 (CH), 128.6 (CH), 127.7 (CH), 126.6 (CH), 122.5 (C), 58.6 (CH), 52.7 (CH), 52.4 (CH_3), 22.1 (CH_3); **HRMS** (ESI) m/z : 433.0721 $[\text{M}+\text{H}]^+$, $\text{C}_{19}\text{H}_{18}\text{ClN}_4\text{O}_4\text{S}^+$ requires 433.0732; **18bh minor diastereomer:** colorless oil; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.31 (d, $J = 1.4$ Hz, 1H, CH=N), 7.80 (d, $J = 8.4$ Hz, 2H, Ar), 7.39 (d, $J = 7.8$ Hz, 2H, Ar), 7.29 – 7.21 (m, 2H, Ar+CH=N), 7.12 (d, $J = 8.5$ Hz, 1H, Ar), 6.74 (d, $J = 2.5$ Hz, 1H, Ar), 4.11 (dd, $J = 3.6, 1.4$ Hz, 1H, CH), 3.57 (d, $J = 3.2$ Hz, 1H, CH), 3.45 (s, 3H, CH_3), 2.50 (s, 3H, CH_3).

Methyl 9-chloro-4-tosyl-1,11b-dihydro-4*H*-[1,2,4]triazino[1,6-*c*]quinazoline-1-carboxylate (18ch)



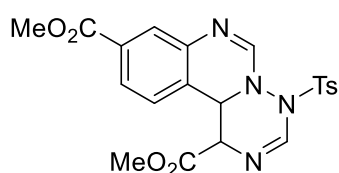
19.5 mg (45%) of **18ch** were obtained from **17c** (33.3 mg, 0.1 mmol).

Diastereomeric ratio (70:30) was determined by $^1\text{H NMR}$ and enantiomeric excess (major diastereomer: 26%, minor diastereomer: 39%)

was determined by HPLC (Lux® Cellulose-3), hexane:iPrOH 85:15, 0.7 mL min⁻¹, **major diastereomer**: major enantiomer: $t_r = 27.0$ min, minor enantiomer: $t_r = 21.5$ min, **minor diastereomer**: major enantiomer: $t_r = 26.5$ min, minor enantiomer: $t_r = 34.4$ min.

18ch major diastereomer: yellow oil; $[\alpha]_D^{25} -44.7$ (c 0.7, CHCl₃); **¹H NMR** (300 MHz, CDCl₃) δ 8.25 (d, $J = 2.5$ Hz, 1H, CH=N), 7.79 (d, $J = 8.4$ Hz, 2H, Ar), 7.38 (d, $J = 7.7$ Hz, 2H, Ar), 7.26 (d, $J = 1.5$ Hz, 1H, CH=N), 7.23 (d, $J = 2.1$ Hz, 1H, Ar), 7.04 (dd, $J = 8.1, 2.1$ Hz, 1H, Ar), 6.59 (d, $J = 8.1$ Hz, 1H, Ar), 4.20 (dd, $J = 9.3, 2.5$ Hz, 1H, CH), 3.62 (s, 3H, CH₃), 3.36 (dd, $J = 9.2, 1.4$ Hz, 1H, CH), 2.48 (s, 3H, CH₃); **¹³C NMR** (75 MHz, CDCl₃) δ 169.0 (C), 151.9 (CH), 147.04 (C), 140.8 (CH), 140.4 (C), 135.9 (C), 131.8 (C), 130.6 (CH), 128.7 (CH), 127.6 (CH), 127.0 (CH), 126.4 (CH), 119.3 (C), 58.7 (CH₃), 52.7 (CH), 52.2 (CH), 22.0 (CH₃); **18ch minor diastereomer**: colorless oil; **¹H NMR** (300 MHz, CDCl₃) δ 8.30 (d, $J = 1.4$ Hz, 1H, CH=N), 7.80 (d, $J = 8.4$ Hz, 2H, Ar), 7.37 (d, $J = 8.0$ Hz, 2H, Ar), 7.29 (d, $J = 1.1$ Hz, 1H, CH=N), 7.17 (d, $J = 2.1$ Hz, 1H, Ar), 7.09 (dd, $J = 8.1, 2.1$ Hz, 1H, Ar), 6.68 (d, $J = 8.1$ Hz, 1H, Ar), 4.10 (dd, $J = 3.7, 1.4$ Hz, 1H, CH), 3.59 (d, $J = 3.7$ Hz, 1H, CH), 3.46 (s, 3H, CH₃), 2.47 (s, 3H, CH₃); **¹³C NMR** (75 MHz, CDCl₃) δ 167.9 (C), 150.9 (CH), 147.0 (C), 141.6 (CH), 140.4 (C), 135.6 (C), 132.0 (C), 130.7 (CH), 128.7 (CH), 127.4 (CH), 126.9 (CH), 126.5 (CH), 118.2 (C), 60.1 (CH₃), 53.0 (CH), 52.7 (CH), 22.0 (CH₃).

Methyl 9-acetoxy-4-tosyl-1,11b-dihydro-4*H*-[1,2,4]triazino[1,6-*c*]quinazoline-1-carboxylate (18dh)



15.2 mg (34%) of **18dh** were obtained from **17d** (35.1 mg, 0.1 mmol). Diastereomeric ratio (66:34) was determined by ¹H NMR and enantiomeric excess (major diastereomer: 46%, minor diastereomer: 79%) was determined by HPLC (Lux® Cellulose-3), hexane:iPrOH 85:15, 0.7 mL min⁻¹, **major diastereomer**: major enantiomer: $t_r = 74.9$ min, minor enantiomer: $t_r = 47.1$ min, **minor diastereomer**: major enantiomer: $t_r = 56.4$ min, minor enantiomer: $t_r = 71.5$ min.

18dh major diastereomer: yellow oil; $[\alpha]_D^{25} +31.1$ (c 0.9, CHCl₃); **¹H NMR** (300 MHz, CDCl₃) δ 8.26 (d, $J = 2.5$ Hz, 1H, CH=N), 7.86 (d, $J = 1.6$ Hz, 1H, Ar), 7.79 (d, $J = 8.4$ Hz, 2H, Ar), 7.73 (dd, $J = 7.9, 1.7$ Hz, 1H, Ar), 7.37 (d, $J = 7.9$ Hz, 2H, Ar), 7.28 (d, $J = 1.4$ Hz, 1H, CH=N), 6.71 (d, $J = 7.9$ Hz, 1H, Ar), 4.23 (dd, $J = 9.3, 2.5$ Hz, 1H, CH), 3.90 (s, 3H, CH₃), 3.59 (s, 3H, CH₃), 3.40 (dd, $J = 9.3, 1.4$ Hz, 1H, CH); **18dh minor diastereomer**: colorless oil; **¹H NMR** (300 MHz, CDCl₃) δ 8.31 (d, $J = 1.4$ Hz, 1H, CH=N), 7.85 – 7.75 (m, 4H, Ar),

7.37 (d, $J = 7.7$ Hz, 2H, Ar), 7.30 (d, $J = 1.1$ Hz, 1H, CH=N), 6.83 (dt, $J = 7.8, 0.6$ Hz, 1H, Ar), 4.14 (dd, $J = 3.6, 1.4$ Hz, 1H, CH), 3.91 (s, 3H, CH₃), 3.65 (d, $J = 3.5$ Hz, 1H, CH), 3.42 (s, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 167.8 (C), 166.3 (C), 150.7 (CH), 147.0 (C), 141.7 (CH), 139.4 (C), 132.2 (C), 132.0 (C), 130.7 (CH), 128.6 (CH), 127.9 (CH), 127.5 (CH), 126.6 (CH), 124.45 (C), 60.0 (CH), 53.0 (CH), 52.9 (CH), 52.5 (CH₃), 22.0 (CH₃).

6 Conclusions

1. New strategies for the synthesis of functionalized isocyanoacetates by the means of addition reactions as well as for the synthesis of polycyclic heterocycles through cycloaddition reactions involving isocyanoacetates have been developed. In the case of the asymmetric syntheses, organocatalytic procedures involving the use of bifunctional organocatalysts have been employed.
2. We have developed a methodology for the α -arylation of isocyanoacetates in order to obtain α,α -diaryl- α -amino esters by the addition of α -substituted isocyanoacetates to *o*-quinonedibenzimides. When 4-OH *o*-quinonebenzimidides were used, bicyclic heterocycles based on the 4*H*-benzo[*e*][1,3]oxazine framework could be obtained. Reaction scope regarding differently substituted *o*-quinonebenzimidides as well as multiple isocyanoacetates was studied. Preliminary results presenting the organocatalyzed version of this reaction were also presented.
3. A procedure for the synthesis of chiral 2-alkyl-3-aminobenzofurans via a thiourea-based organocatalytic procedure of 1,4-addition of isocyanoacetates to aurone-derived 1-azadienes was presented. A wide scope of differently substituted 1-azadienes and isocyanoacetates was explored, with generally excellent diastereoselectivity and good enantiomeric excess for the reaction products. The α -amino ester of the reaction product was obtained via acidic hydrolysis of the isonitrile group.
4. The organocatalyzed dearomative [3+2] cycloaddition between isocyanoacetates and 2-nitrobenzofurans in order to obtain chiral fused tricyclic heterocyclic products containing a newly formed 1-pyrroline ring was developed. A chiral cupreine was used to furnish the aforementioned reaction products with excellent diastereoselectivity as well as, in general, good to excellent enantioselectivity. Multiple transformations of the resulting heterocycles were carried out, without significantly affecting the enantiomeric excess. The reaction conditions were also tested with other electron-deficient heterocycles such as 2-nitrobenzothiophenes and 3-nitrobenzofurans, although they were shown not to be compatible with those alternative substrates.
5. A preliminary study of the asymmetric [3+3] cycloaddition of isocyanoacetates and *N*-iminoquinazolinium ylides has been developed, constituting the first enantioselective example of reaction of isocyanides and *C,N*-cyclic azomethine imines that does not occur through an Ugi pathway. Although the procedure provided reasonable yield, diastereoselectivity and enantiomeric excess with the unsubstituted *N*-

iminoquinazolinium ylide, other examples proceeded with notable lowering of the yield, diastereomeric ratios and enantiomeric excesses, prompting to a necessity of changing the catalytic system for the future continuation of this work.

7 Resum en valencià

7.1 Introducció

La quiralitat de les molècules juga un paper fonamental en la naturalesa. Els entorns biològics són quirals i cada membre d'una parella d'enantiòmers interacciona de diferent manera quan està present als sistemes vius, a causa de les característiques estructurals dels enzims i dels receptors responsables de controlar els processos biològics.¹

Aquest comportament particular que s'associa a la quiralitat ha suscitat de manera progressiva l'interés per la síntesi asimètrica, que consisteix en la síntesi estereoselectiva de composts quirals.² Aquesta conversió de grups proquirals en motius quirals contrasta amb altres procediments de síntesi de composts quirals que fan ús de l'anomenat *chiral pool*, que implica fer servir composts enantioenriquits o enantiopurs que poden ser aïllats de fonts naturals com a materials de partida, així com amb els procediments de resolució.³

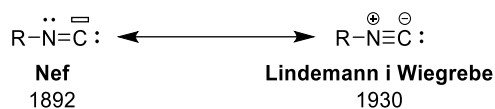
Entre els mètodes de síntesi asimètrica, l'ús de catalitzadors quirals ha comportat un avançament significatiu en aquest camp. Els mètodes catalítics permeten que les síntesis estereoselectives siguin dutes a terme fent servir només una quantitat menuda de material quiral en el procés, així com evitant els passos de reacció addicionals que normalment es requereixen quan es fa ús d'alternatives com ara l'ús d'auxiliars quirals, que normalment n'implica la unió al reactiu i ulterior eliminació del producte.⁴

Les transformacions catalítiques asimètriques comprenen l'ús de molècules orgàniques quirals com a organocatalitzadors, complexos metàl·lics quirals, així com la catàlisi enzimàtica.⁵

*

Els isocianurs són composts que contenen el grup isonitril (—NC). Aquest grup funcional té característiques estructurals úniques que confereixen als isocianurs una reactivitat particular, tot constituint materials de partida interessants en el camp de la Química Orgànica.⁶

Els isocianurs poden ser representats de manera més fidel com a una combinació de dues formes ressonants, una forma carbènica amb un àtom de carboni divalent, proposada per primera vegada per Nef,^{7,8} i una forma zwitteriònica proposada per primera vegada per Lindemann i Wiegrabe (**Esquema 1**).⁹



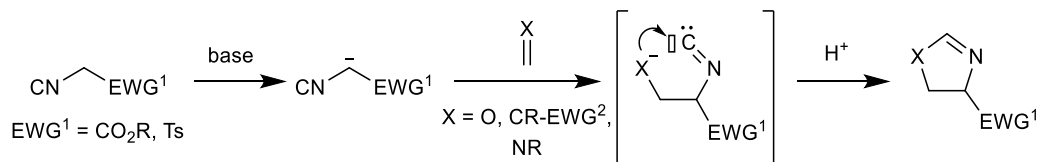
Esquema 1: Formes de ressonància principals dels isocianurs.

L'híbrid de ressonància resultant d'aquesta representació implica un caràcter parcial de triple enllaç resultant de la retrodonació π del parell d'electrons no enllaçant a l'orbital buit del carboni terminal del grup isonitril. Aquest fenomen permet comprendre l'estructura lineal dels isocianurs.¹⁰

Els isocianurs són tant nucleofílics com electrofílics al carboni terminal. L'electrofilia d'aquest grup pot ser explicada tenint en compte la representació carbènica del grup isonitril, amb el seu orbital lliure. Per altra banda, la seua nucleofília pot ser visualitzada gràcies a la representació zwitteriònica, la qual confereix al carboni terminal d'una densitat de càrrega negativa.¹¹

Altra característica dels isocianurs consisteix en la seua acidesa al carboni α , a causa de la naturalesa atraient d'electrons del grup isonitril. Aquesta acidesa pot ser incrementada per la presència de grups atraients d'electrons addicionals en aquesta posició, com ara èsters carboxílics. En aquest sentit, la reactivitat versàtil dels derivats d'isocianoacetat ha estat àmpliament estudiada, especialment en allò que es refereix al seu potencial per a la síntesi d'*aza*-heterocicles.¹²

Els isocianoèsters desprotonats poden participar en reaccions d'addició nucleofílica a dobles enllaços electrofílics, la qual cosa origina un carbanió que té tendència a atacar intramolecularment al carboni terminal del grup isonitril. Aquestes cicloaddicions formals donen lloc a heterocicles que contenen nitrogen amb un o més centres de quiralitat (**Esquema 2**).¹³



Esquema 2: Cicloaddició [3+2] formal entre un isocianur i un doble enllaç electrofílic.

*

La importància dels heterocicles nitrogenats queda palesa per la seua presència en diversos composts d'interés farmacològic, com ara la Lincomicina, un antibiòtic,¹⁴ el Captopril, fet

servir per al tractament de malalties cardiovasculars;¹⁵ i el Zolmitriptan, que ha demostrat ser útil per al tractament de la migranya (**Figura 1**).¹⁶

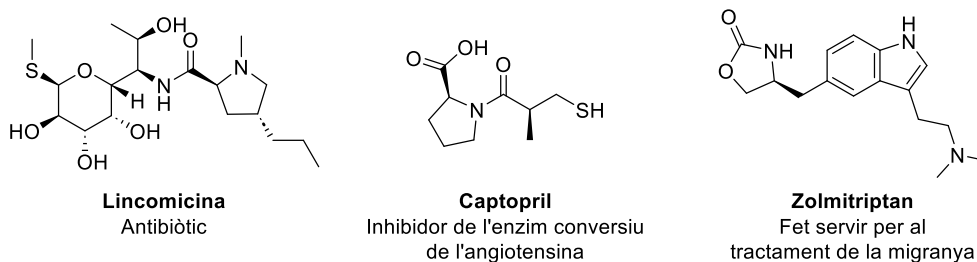


Figura 1: Alguns exemples de composts d'interès farmacològic que contenen *aza*-heterocicles.

Per altra banda, un complex de molibdè-isocianoacetat ha estat estudiat per la seua capacitat de distribuir CO al fetge *in vivo* de manera específica, tot mostrant efectes terapèutics en models animals per al tractament de malalties hepàtiques.¹⁷

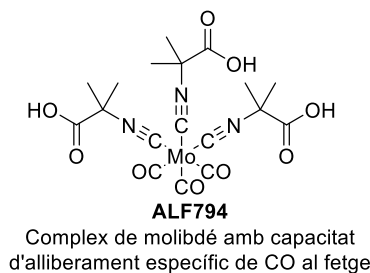


Figura 2: Ús d'isocianurs com a lligands en un complex d'interès farmacèutic.

Finalment, hi ha diferents exemples de derivats d'aminoàcids amb activitat biològica (**Figura 3**). Exemples notables inclouen l'antiviral Valaciclovir¹⁸ i l'èster metílic de l'L-Dopa, una alternativa a l'L-Dopa per al tractament del Parkinson amb certs avantatges farmacocinètics.¹⁹

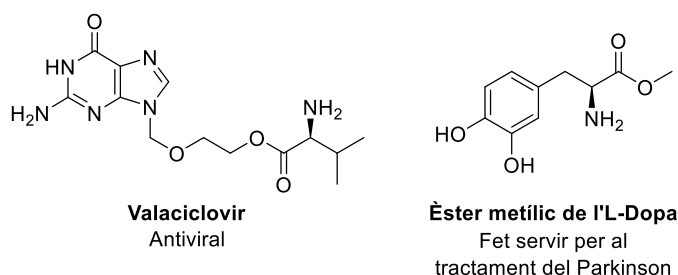
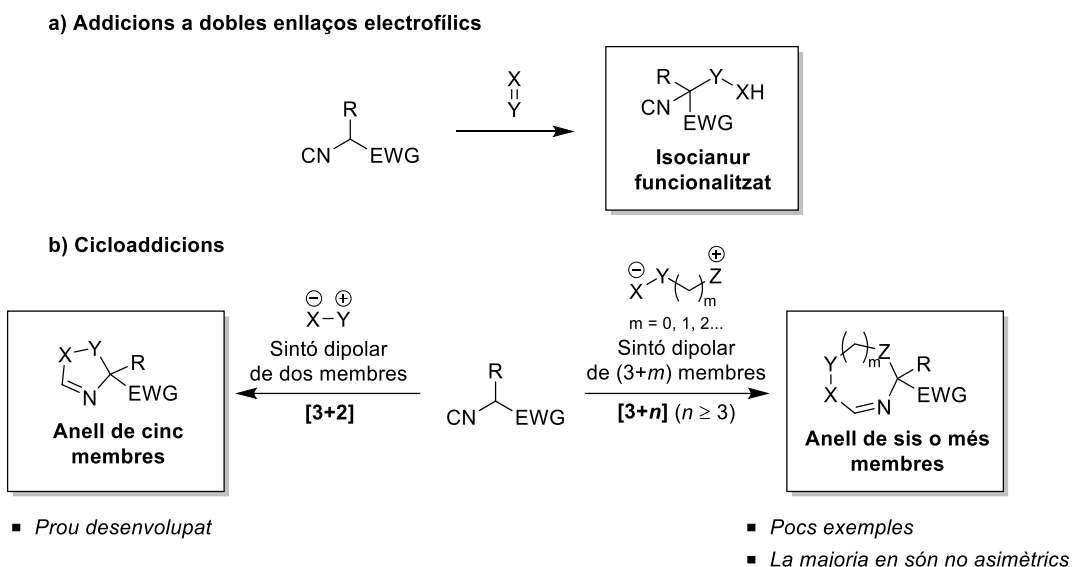


Figura 3: α -Aminoàcids amb propietats terapèutiques.

7.2 Patrons de reactivitat rellevants dels isocianoacetats

A l'**Esquema 3** podem observar un resum de la reactivitat característica dels isocianoacetats respecte reaccions d'addició i cicloaddició que apareixen a la bibliografia de Química Orgànica sintètica ressenyada en detall al Capítol 2 d'aquesta tesi.



Esquema 3: Patrons de reactivitat dels isocianoacetats especialment rellevants en el desenvolupament de la tesi.

Encara que la majoria d'exemples de la literatura se centren en el caràcter 1,3-dipolar dels isocianoèsters per a participar en reaccions de cicloaddició, de manera que fan servir el grup isonitril com un precursor d'adductes d'imina, hi ha també procediments que se centren en mantindre el grup isonitril en el producte final. Açò ha permès la síntesi de composts altament funcionalitzats que contenen l'agrupació isonitril (**Esquema 3**, a). Considerant la versatilitat sintètica dels isocianurs prèviament esmentada, aquests composts poden ser potencials materials de partida per a altres síntesis orgàniques.

Pel que fa a les reaccions de cicloaddició en les quals un isocianoacetat reacciona amb un compost dipolaròfil (**Esquema 3**, b), la majoria d'exemples impliquen l'ús de dipolaròfils de dos membres, per a originar *aza*-heterocicles de cinc membres. En canvi, les cicloaddicions d'ordre superior $[3+n]$ ($n \geq 3$) que impliquen la reacció d'isocianoacetats amb dipolaròfils de tres o més membres es troben comparativament menys desenvolupades, amb només uns pocs exemples descrits a la literatura, i amb una remarcable presència mínima de procediments enantioselectius.

7.3 Objectius

Segons s'observa als antecedents bibliogràfics, les reaccions d'addició a dobles enllaços electrofílics han representat una de les rutes principals per a la síntesi de derivats d'isocianoacetats altament funcionalitzats els quals, gràcies a la reactivitat característica del grup isonitril, constitueixen materials de partida interessants en el camp de la síntesi orgànica. A més, aquests isocianurs funcionalitzats derivats són també precursors d' α -aminoàcids.

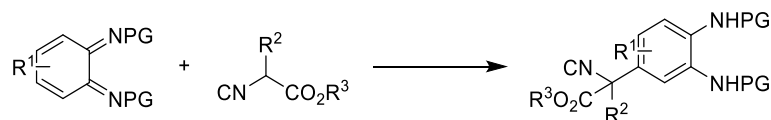
Per altra banda, les reaccions de cicloadició que procedeixen gràcies a la acidesa α -H dels isocianoacetats així com també per mitjà del caràcter electrofílic del carboni terminal del grup isonitril a causa del seu parcial caràcter carbènic, han sigut un mètode fet servir freqüentment per a accedir a *aza*-heterocicles. En particular, les reaccions de cicloadició [3+2] formal que originen 1- o 2-pirrolines han experimentat un desenvolupament ràpid per a la síntesi d'heterocicles funcionalitzats, així com composts policíclics.

Adicionalment, malgrat els avançaments observats en el camp de les cicloadicions [3+2], hi ha un buit notable pel que fa a cicloadicions d'ordre superior, amb només uns pocs exemples descrits, limitats a certes famílies de materials de partida, i majoritàriament duts a terme de forma no enantioselectiva.

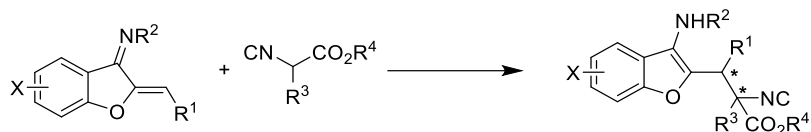
Finalment, els mètodes organocatalítics que fan ús d'una quantitat menuda d'organocatalizador bifuncional quiral són una molt bona alternativa en el camp de la síntesi asimètrica, ja que permeten accedir als beneficis d'aquest tipus de catàlisi sense la necessitat d'usar cap tipus de metall al procediment, de manera que implica una simplificació operativa així com avantatges des del punt de vista de la sostenibilitat.

Considerant els desenvolupaments anteriors en aquests camps, proposarem els objectius que es relacionen tot seguit:

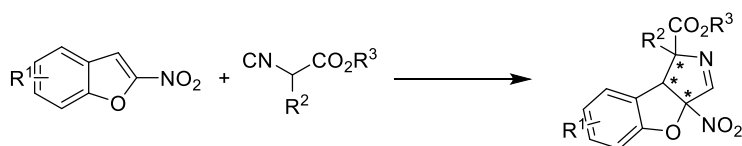
1. α -Arlació d'isocianoacetats:



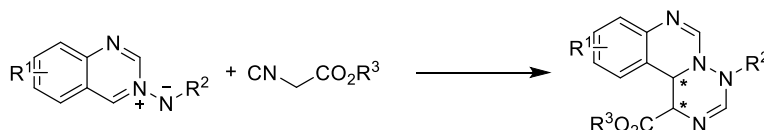
2. *Addició conjugada organocatalítica d'isocianoacetats a 1-azadiens derivats de l'aurona:*



3. *Cicloaddició [3+2] organocatalítica desaromatitzant de 2-nitrobenzofurans i isocianoacetats:*



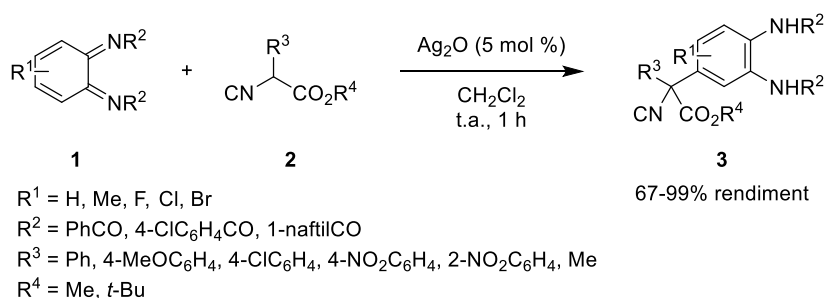
4. *Cicloaddició [3+3] organocatalítica asimètrica d'ilurs d'N-iminoquinazolini i isocianoacetats:*



7.4 Resultats principals

7.4.1 α -Arlació d'isocianoacetats

S'ha desenvolupat l'addició d'isocianoacetats α -substituïts a *o*-quinona diimides, per a donar lloc a productes d'addició que són precursors d' α,α -diaril aminoàcids. El procediment s'ha dut a terme fent servir òxid de plata com a catalitzador (**Esquema 4**).



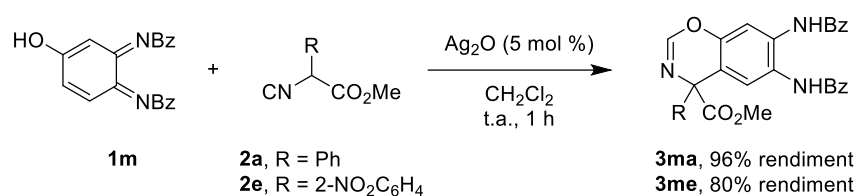
Esquema 4: Addició d'isocianoacetats **2** a *o*-quinone diimides **1**, catalitzada per òxid de plata.

La reacció va demostrar ser compatible amb substituents de diferent caràcter electrònic a totes les posicions de l'anell d'*o*-quinona diimida. Per altra banda, substitucions en el grup benzamido també van ser ben tolerades, fins i tot quan es fan servir grups voluminosos com

ara l'1-naftil. No obstant això, l'*o*-quinona dibenzensulfonamida ($R^2 = Ts$) no va proporcionar reacció observable.

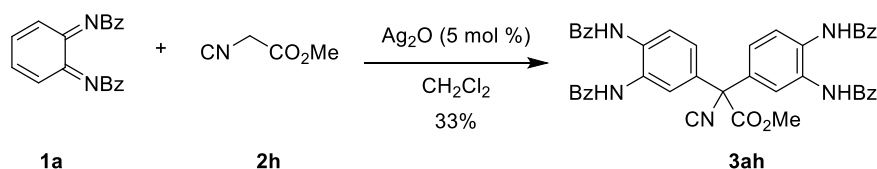
En el cas de les variacions dels substituents de l'isocianoacetat, la presència de grups donadors d'electrons a l'anell aromàtic en posició α proporcionà millor rendiments que la presència de grups atraients d'electrons. La reacció va ser també compatible amb l'ús de l' α -metil isocianoacetat de metil (**2f**), així com amb l' α -fenil isocianoacetat de *tert*-butil (**2g**), tot i que amb un menor rendiment.

Per altra banda, quan es va fer servir la 4-hidroxi *o*-dibenzimida **1m**, se n'obtingueren les benzoxacines **3m**, a través de la ciclació intramolecular del grup hidroxil amb el carboni terminal de l'isonitril (**Esquema 5**).



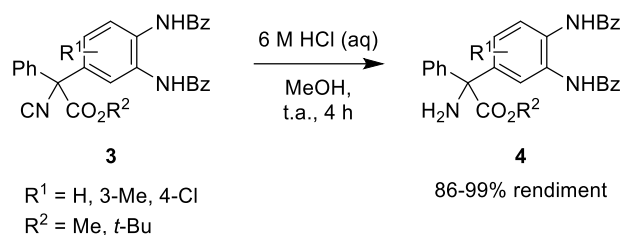
Esquema 5: Síntesi de 4H-benzo[*e*][1,3]oxazines mitjançant l'ús d'*o*-quinona dibenzimides substituïdes amb 4-hidroxi.

A més, quan es va fer servir l'isocianoacetat de metil (**2h**), no substituït en posició α , s'observà la formació del producte de doble addició **2ah**, amb un 33% de rendiment (**Esquema 6**).



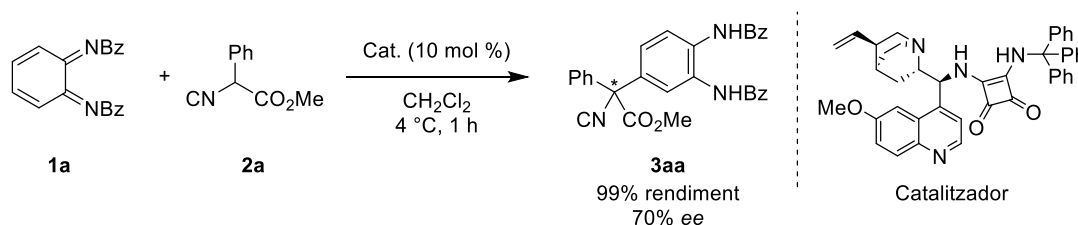
Esquema 6: Doble addició observada quan reacciona l'isocianoacetat de metil (**2h**) amb **1a**.

La utilitat sintètica dels productes d'addició obtinguts va ser demostrada duent a terme una transformació sintètica consistent en la hidròlisi de l'isocianur per a donar lloc a α,α -diaril- α -aminoèsters (**4**), amb rendiments quantitius quan es feien servir productes d'addició amb èsters metílics, i rendiments molt bons quan el producte posseïa un èster *tert*-butílic (**Esquema 7**).



Esquema 7: Hidròlisi dels productes d'addició per a donar lloc a aminoèsters.

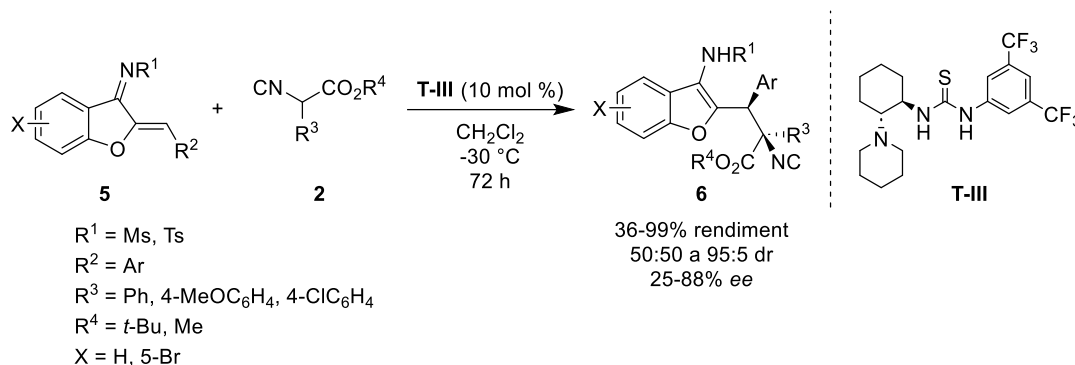
Per últim, es va dur a terme un estudi preliminar de la versió asimètrica d'aquesta reacció d'addició, tenint en compte la potencial utilitat sintètica del procediment. Es va observar que, amb les condicions organocatalítiques que es mostren a l'**Esquema 8**, fent servir una esquaramida derivada de la quinina, amb un grup aquiral voluminós, es podia obtenir el producte d'addició **3aa** amb rendiment quantitatiu i un 70% *ee*.



Esquema 8: Resultats preliminars de les condicions organocatalítiques per a l'addició asimètrica d'isocianoacetats a *o*-quinona dibenzimides.

7.4.2 Addició conjugada organocatalítica d'isocianoacetats a 1-azadiens derivats de l'aurona

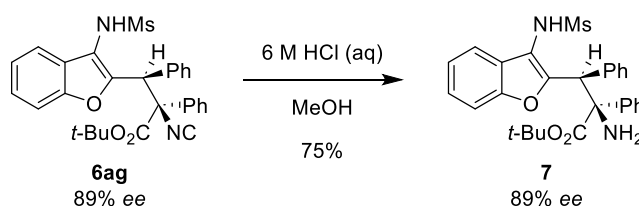
S'ha dut a terme l'addició 1,4 asimètrica d'isocianoacetats a 1-azadiens derivats de l'aurona, la qual cosa proporciona isocianoacetats quirals α,α -difuncionalitzats que contenen un anell de benzofuran (**Esquema 9**). La reacció procedeix de manera enantioselectiva gràcies a un organocatalitzador derivat de la dicitclohexan-1,2-diamina.



Esquema 9: Reacció d'addició asimètrica organocatalítica d'isocianoacetats α -substituïts **2** a 1-azadiens **5**.

En general, les condicions de reacció pogueren ser aplicades a una ampla varietat d'1-azadiens, amb substituents de diferent caràcter electrònic en diverses posicions de l'anell aromàtic al doble enllaç exocíclic així com a l'anell de benzofuran, amb generalment bons rendiments, excel·lent diastereoselectivitat i bona enantioselectivitat. Les limitacions més notables correspongueren a l'ús d'1-azadiens que posseïen substituents en posició *orto* a l'anell aromàtic del doble enllaç exocíclic, amb rendiments menors que la mitjana. Per altra banda, la presència de grups donadors com ara el grup metoxi en posició *orto* o *para* de l'anell aromàtic en posició exocíclica no proporcionà conversió. Aquest comportament també s'observà quan aquest grup era a la posició 6 de l'anell de benzofuran. Per altra banda, les tosylimines proporcionaren una menor diastereoselectivitat i enantioselectivitat que les mesilimines. Pel que fa als isocianoacetats, la reacció tolerà isocianoacetats de *tert*-butil amb bons resultats, però l'ús d'isocianoacetats de metil provocà que la reacció no fora diastereoselectiva.

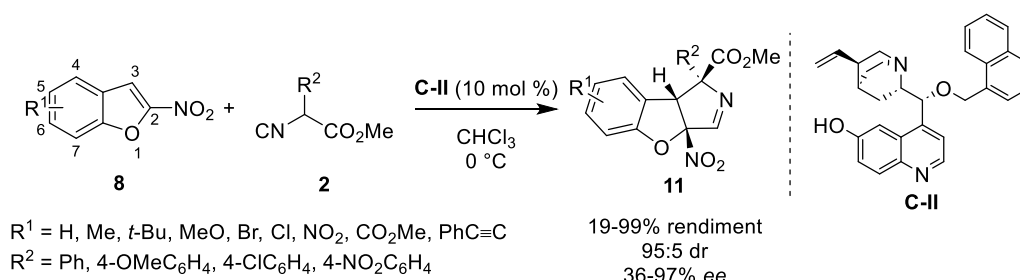
Per altra banda, el grup isonitril del producte va poder ser hidrolitzat per a proporcionar el corresponent α -aminoèster (**Esquema 10**). La transformació va procedir amb un rendiment bo i sense pèrdua d'excés enantiomèric.



Esquema 10: Hidròlisi de l'isocianur per a donar lloc a l'aminoèster **7**.

7.4.3 Cicloaddició [3+2] formal desaromatitzant de 2-nitrobenzofurans i isocianoacetats

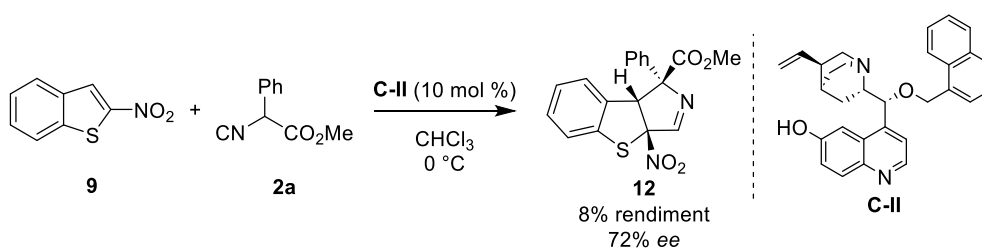
S'ha dut a terme la reacció de Barton-Zard interrompuda¹⁴⁸ asimètrica entre 2-nitrobenzofurans i isocianoacetats α -substituïts, per a obtenir derivats de 2,3-dihidrobenzofuran fusiònats amb un anell d'1-pirrolina (**Esquema 11**). La reacció procedeix de manera organocatalítica, mitjançant l'ús del derivat de cupreïna **C-II**.



Esquema 11: Cicloaddició [3+2] enantioselectiva d'isocianoacetats **2** a 2-nitrobenzofurans **8**.

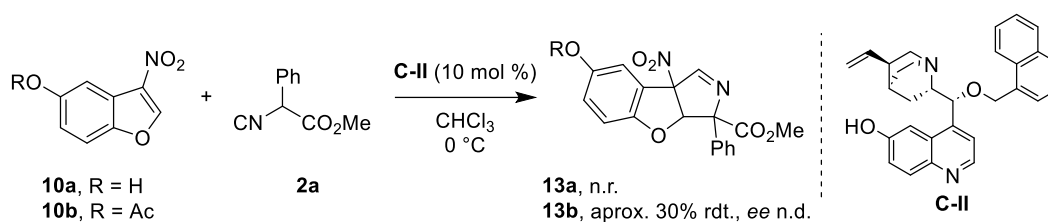
En termes generals, la reacció va suportar l'ús de 2-nitrobenzofurans amb substitucions de diferent caràcter electrònic per a donar lloc als productes de cicloaddició amb excel·lent diastereoselectivitat i enantioselectivitat de bona a excel·lent. És un fet destacable que els 2-nitrobenzofurans amb grups donadors d'electrons van proporcionar un menor rendiment que aquells que posseïen grups atraients de densitat electrònica. Pel que fa a l'ús d'isocianoacetats de diferent naturalesa, la introducció de substituents atraients d'electrons a l'anell aromàtic en posició α provocà una disminució de l'excés enantiomèric. L'efecte contrari va ocórrer quan aquesta posició era substituïda per grups donadors. L'ús de l' α -metil isocianoacetat de metil (**2f**), al seu torn, va proporcionar el producte de forma no enantioselectiva.

També es va assajar la reacció amb el 2-nitrobenzotiofè (**9**). En aquest cas, es va obtenir el producte de cicloaddició [3+2] **12** esperat, amb un bon excés enantiomèric, tot i que el rendiment va ser molt baix (**Esquema 12**).

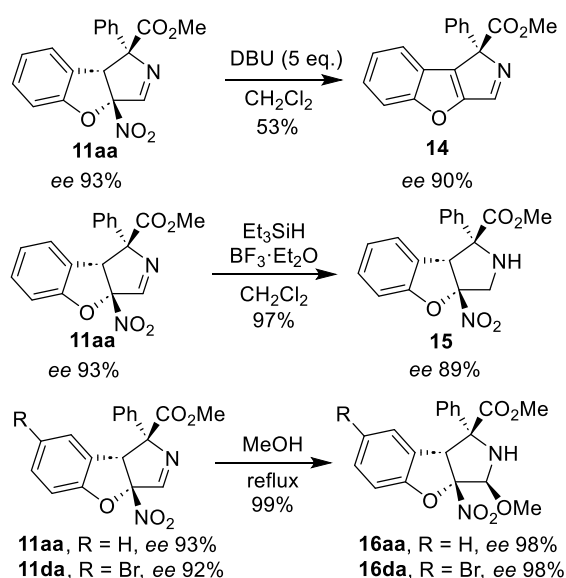


Esquema 12: Reacció amb 2-nitrobenzotiofè (**9**).

Pel que fa a les reaccions amb els 3-nitrobenzofurans **10** (**Esquema 13**), s'observà que no ocorria cap reacció quan s'utilitzà el compost disponible de manera comercial 5-hidroxí-3-nitrobenzofuran (**10a**), probablement a causa de la presència del grup hidroxil lliure. En el cas del 5-acetoxi-2-nitrobenzofuran (**10b**), encara que se'n va observar conversió completa, el producte era altament inestable i es va obtenir una mescla complexa que contenia aproximadament un 30% de **13b**. Tots els intents d'obtenir el producte **13b** de forma més pura van fracassar. A causa dels problemes amb aquest producte, l'excés enantiomèric no pogué ser determinat.

**Esquema 13:** Reaccions amb els 3-nitrobenzofurans **10**.

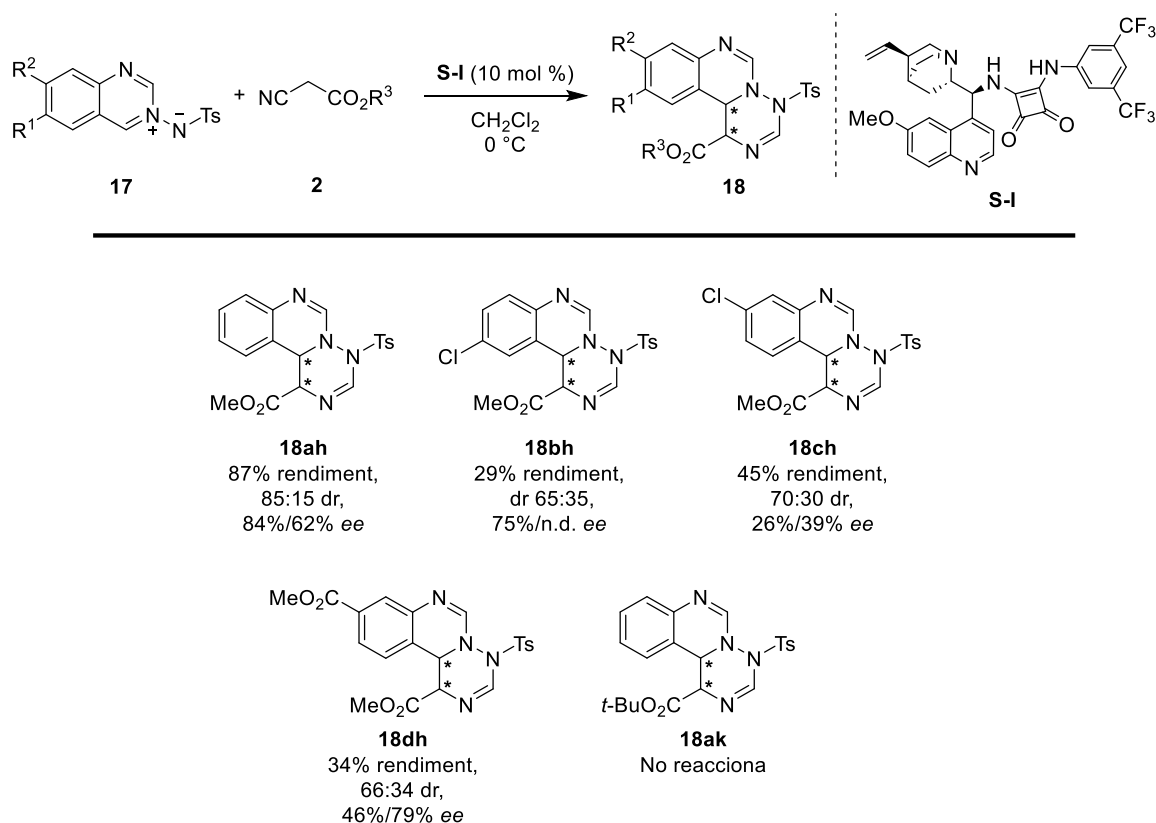
Per altra banda, amb la finalitat de mostrar la utilitat sintètica dels adductes de cicloadició obtinguts, vam dur a terme diferents transformacions dels productes **11** (**Esquema 14**). En primer lloc, l'eliminació d'àcid nitrós amb DBU va donar lloc al 2*H*-pirrol **14**, amb un 53% de rendiment i amb manteniment de l'excés enantiomèric.

**Esquema 14:** Transformacions sintètiques dels productes de cicloadició [3+2] **11**.

En segon lloc, la reducció del doble enllaç C-N de l'anell de pirrolina amb trietilsilà, catalitzat per $\text{BF}_3 \cdot \text{Et}_2\text{O}$ donà lloc a la corresponent pirrolidina **15** amb 97% de rendiment, encara que amb una certa reducció de l'excés enantiomèric. Finalment, l'addició de metanol a la imina pirrolínica proporcionà els aminoacetals **16aa** i **16da** amb completa diastereoselectivitat.

7.4.4 Cicloadició [3+3] enantioselectiva d'isocianoacetats i ilurs d'*N*-iminoquinazolini

Es va assajar la reacció entre isocianoacetats i ilurs d'*N*-iminoquinazolini, un compost de la família de les imines d'azometí *C,N*-cíclics. Es va obtenir el corresponent producte de cicloadició [3+3]. La reacció es va dur a terme de manera enantioselectiva mitjançant l'ús de l'organocatalitzador de tipus esquaramida derivat de la quinina **S-I** (**Esquema 15**).



Esquema 15: Reacció de cicloadició [3+3] asimètrica entre isocianoacetats i ilurs d'*N*-iminoquinazolini. Abast i limitacions de la reacció.

Encara que el producte **18ah** va poder obtindre's amb un bon rendiment i bona diastereoselectivitat, així com un bon excés enantiomèric per al diastereoisòmer majoritari, les condicions de reacció desenvolupades van proporcionar resultats deficients amb ilurs d'*N*-iminoquinazolini substituïts. Quan l'anell de quinazolina presentà un substituent 6-Cl (**17b**), se n'obtingué el producte **18bh** amb un excés enantiomèric moderat, encara que el rendiment va ser molt baix i la diastereoselectivitat va disminuir respecte a **18ah**. En el cas d'una substitució 7-Cl en l'anell de quinolina (**17c**), el producte **18ch** se n'obtingué amb major rendiment i diastereoselectivitat, encara que l'excés enantiomèric va ser molt baix. Respecte l'ús d'un ilur d'*N*-iminoquinazolini amb substitució 7-CO₂Me **18d**, el corresponent producte **18dh** se'n va obtindre amb un baix rendiment i baixa diastereoselectivitat, així com també un excés enantiomèric reduït per al diastereoisòmer majoritari, tot i que va ser superior al cas del derivat 7-Cl.

L'isocianoacetat de *tert*-butil (**2k**) va ser també provat amb l'ilur **17a**, però no es va observar cap producte de reacció, de manera que es pogué visualitzar que la reacció es veia altament afectada per l'impediment estèric exercit pel grup *tert*-butil voluminós.

En aquest punt vam decidir detindre la nostra recerca en aquest tema, tot deixant oberta la possibilitat d'una nova avaluació de les condicions de reacció en un futur.

7.5 Metodologia experimental

7.5.1 Procediments comuns i tècniques d'anàlisi

Procediments generals

Les reaccions van ser monitoritzades fent servir plaques de cromatografia de capa fina de gel de sílice Merck 60 F₂₅₄ (referència 5554 Merck). Les plaques de CCF eluïdes van ser visualitzades sota llum UV de 254 nm o 365 nm i posteriorment revelades fent servir solucions reveladores de molibdat de ceri, permanganat potàssic o *p*-anisaldehid.¹⁷⁰ La cromatografia de columna es va dur a terme fent servir Silica Gel Merck 60 com a fase estacionària (referència 109385 Merck). L'eluent es va fer passar a través de la columna mitjançant una bomba d'aire.

Dissolvents i reactius

Si no s'indica allò contrari, els reactius s'obtingueren de distribuïdors comercials i es feren servir de manera directa sense ulterior purificació. En els casos en què se necessitaren dissolvents secs, se seguiren els següents procediments:^{171–173}

- Per al CH₂Cl₂, DCE i tolué, el dissolvent es destil·là sobre CaH₂ immediatament abans de fer-lo servir.
- Per al THF, el dissolvent es destil·là sobre Na-benzofenona immediatament abans de fer-lo servir.
- Per al CHCl₃, el dissolvent es va fer passar a través d'una columna curta de gel de sílice i després, immediatament abans de fer-lo servir, va ser destil·lat sobre P₂O₅.
- Per a l'MTBE, el dissolvent es va emmagatzemar sobre tamís molecular activat de 4 Å.
- Per a l'acetonitril, el dissolvent s'emmagatzemà sobre tamís molecular activat de 3 Å.
- Per a l'acetat d'etil, el dissolvent s'emmagatzemà sobre tamís molecular activat de 4 Å.

Ressonància magnètica nuclear (RMN)

Els espectres d'RMN van ser enregistrats fent servir un espectròmetre Bruker Avance III 300, Bruker AV400 o Bruker Neo500 a, respectivament, 300 MHz, 400 MHz o 500 MHz per al ¹H; o 75 MHz, 101 MHz o 125 MHz per al ¹³C. Per al ¹⁹F, els espectres van ser enregistrats a 282 MHz per al Bruker Avance III o a 471 MHz per al Bruker Neo500. Els valors de desplaçament químic (δ) s'expressen en ppm i les constants d'acoblament (*J*), en Hz. Les multiplicitats dels

carbonis es determinaren mitjançant experiments DEPT. Els senyals per als dissolvents residu-als no deuterats foren fets servir com a patró intern:¹⁷⁴

- En cloroform-*d*, 7,26 ppm per al ^1H i 77,16 ppm per al ^{13}C .
- En DMSO-*d*₆, 1,50 ppm per al ^1H i 39,52 ppm per al ^{13}C .
- En benzé-*d*₆, 7,16 ppm per al ^1H i 128,06 ppm per al ^{13}C .
- En metanol-*d*₄, 3,31 ppm per al ^1H i 40,00 ppm per al ^{13}C .

Espectroscòpia d'infraroig (IR)

Els espectres d'IR van ser enregistrats amb un espectròmetre FTIR Agilent Cary 630 amb un mòdul de mostreig ATR de diamant. Les longituds d'ona es reporten en centímetres recíprocs (cm^{-1}) i les absorcions d'acord amb la seua intensitat relativa: s (forta), m (mitjana) o w (feble).

Espectroscòpia de masses (MS)

Els HRMS foren enregistrats fent servir un espectròmetre Waters Q-TOF equipat amb una font d'electroesprai amb un voltatge capil·lar de 3,3 kV (ESI).

Polarimetria

Les rotacions òptiques específiques foren mesurades fent servir un polarímetre Perkin-Elmer equipat amb una làmpada de sodi (línia D, 589 nm) i una cubeta d'1 dm de longitud de camí, o bé un polarímetre Bellingham+Stanley ADP430 equipat amb una font de llum LED, mesurant a la longitud d'ona del sodi (línia D, 589 nm) i una cubeta d'1 dm de longitud de camí. Les concentracions (*c*) s'expressen en g/100 mL.

Anàlisis d'HPLC quirals

Els excessos enantiomèrics van ser mesurats mitjançant anàlisis d'HPLC, fent servir un cromatògraf Hitachi Elite Lachrom amb un detector de fila de díodes UV Hitachi L-4500 o L-2455U. Columnes de Daicel o Phenomenex amb fases estacionàries quirals van ser fetes servir, i les mostres s'elüïren amb mescles d'hexà i d'isopropanol de qualitat HPLC.

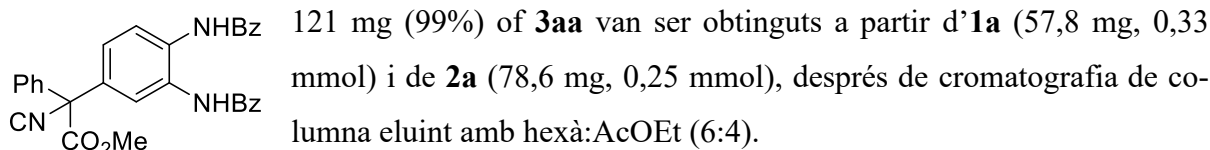
7.5.2 α -Arlació d'isocianoacetats

7.5.2.1 Síntesi i caracterització dels composts 3

L'isocianoacetat α -substituit **2** (0,33 mmol, 1,3 equiv.) va ser addicionat a una dissolució d'*o*-benzoquinona diimida **1** (0,25 mmol, 1,0 equiv.) i d'òxid de plata (3 mg, 0,0125 mmol, 0,05 equiv.) en CH_2Cl_2 (3 mL). La mescla s'agità a t.a. fins a la consumició total de la diimina **1** (CCF). La mescla de reacció va ser després purificada mitjançant cromatografia de columna.

2-(3,4-Bis(benzamido)fenil)-2-fenil-2-isocianoacetat de metil (3aa)

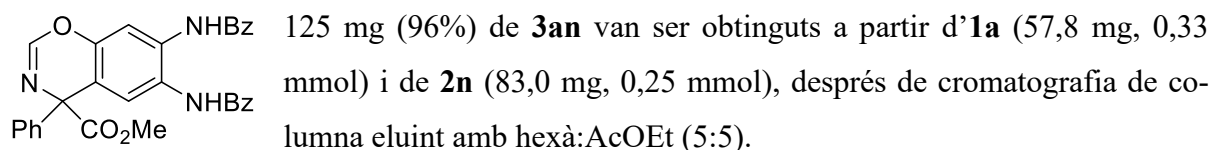
Aquesta descripció es presenta en representació de tota la resta de productes semblants.



Sòlid marró; p.f. 102-105 °C; ¹H RMN (300 MHz, CDCl₃) δ 9,48 (bs, 1H), 9,33 (bs, 1H), 8,00 – 7,92 (m, 4H), 7,65 (d, *J* = 8,6 Hz, 1H), 7,60 (d, *J* = 2,3 Hz, 1H), 7,51 (dd, *J* = 7,2, 1,6 Hz, 2H), 7,44 (td, *J* = 7,2, 1,6 Hz, 4H), 7,31 – 7,23 (m, 3H), 7,19 (dd, *J* = 8,2, 1,6 Hz, 2H), 7,09 (dd, *J* = 8,6, 2,3 Hz, 1H), 3,73 (s, 3H); ¹³C RMN (75 MHz, CDCl₃) δ 167,3 (C), 166,8 (C), 166,5 (C), 161,9 (C), 136,7 (C), 134,0 (C), 133,3 (C), 133,1 (C), 132,3 (CH), 132,2 (CH), 131,9 (C), 130,6 (C), 129,1 (CH), 128,72 (CH), 128,67 (CH), 127,7 (CH), 127,6 (CH), 126,9 (CH), 126,0 (CH), 125,4 (CH), 124,2 (CH), 73,2 (C), 54,2 (CH₃); HRMS (ESI) *m/z*: 490,1757 [M+H]⁺, C₃₀H₂₄N₃O₄⁺ requereix 490,1761.

6,7-Bis(benzamido)-4-fenil-4H-benzo[e][1,3]oxazina-4-carboxilat de metil (3an)

Aquesta descripció es presenta en representació de tota la resta de productes semblants.



Sòlid rosa; p.f. 180-182 °C; ¹H RMN (300 MHz, CDCl₃) δ 9,46 (bs, 1H), 8,57 (bs, 1H), 7,94 (d, *J* = 7,0 Hz, 2H), 7,89 (d, *J* = 7,0 Hz, 2H), 7,59 (s, 1H), 7,55 – 7,42 (m, 6H), 7,34 (s, 1H), 7,33 (s, 1H), 7,30-7,19 (m, 5H), 3,79 (s, 3H); ¹³C RMN (75 MHz, CDCl₃) δ 171,6 (C), 167,0 (C), 166,0 (C), 145,6 (C), 144,5 (C), 142,8 (C), 133,7 (C), 133,2 (C), 133,1 (C), 132,5 (CH), 132,2 (CH), 128,8 (CH), 128,7 (CH), 128,5 (CH), 127,9 (CH), 127,5 (CH), 127,0 (CH), 126,7 (C), 125,6 (CH), 117,3 (C), 112,7 (CH), 65,4 (C), 53,4 (CH₃); HRMS (ESI) *m/z*: 541,2083 [M+H₂O+NH₄]⁺, C₃₀H₂₉N₄O₆⁺ requereix 541,2082.

7.5.2.2 Síntesi del compost 3aa a escala de 2,5 mmol

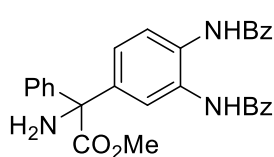
L' α -fenil isocianoacetat **1a** (578 mg, 3,3 mmol, 1,3 equiv.) s'addicionà a una dissolució de l'*o*-benzoquinona diimida **2a** (786 mg, 2,5 mmol, 1,0 equiv.) i òxid de plata (29 mg, 0,125 mmol, 0,05 equiv.) en CH₂Cl₂ (30 mL). La mescla s'agità a temperatura ambient durant 1,5 h. Després, la mescla de reacció es purificà per cromatografia de capa fina eluint amb hexà/AcOEt (6:4) per a donar lloc al compost **3aa** (1,10 g, 90%).

7.5.2.3 Síntesi i caracterització per als composts 4

A una dissolució de compost **3** (0,2 mmol, 1,0 equiv.) en MeOH (2 mL, 0,1 M) s'afegeix HCl (aq) 6 M (10 gotes). La reacció s'agità durant 4 h i es processà amb NaHCO₃ (aq) sat. fins a pH 9. El metanol s'eliminà a pressió reduïda i la mescla aquosa s'extragué amb CH₂Cl₂ (3x30 mL). Les fases orgàniques combinades es rentaren amb salmorra (40 mL), s'assecaren sobre Na₂SO₄ i es concentraren a pressió reduïda. La mescla va ser purificada per cromatografia de columna usant mescles d'hexà i d'acetat d'etil com a eluent.

2-Amino-2-(3,4-Bis(benzamido)fenil)-2-fenilacetat de metil (4aa)

Aquesta descripció es presenta en representació de tota la resta de productes semblants.



95 mg (99%) de **4aa** van ser obtinguts a partir de **3aa** (98 mg), després de cromatografia de columna eluint amb hexà:AcOEt (5:5).

Sòlid marró; p.f. 191-194 °C; ¹H RMN (300 MHz, CDCl₃) δ 9,45 (bs, NH, 1H), 9,13 (bs, 1H), 8,04-7,93 (m, 4H), 7,61 (d, *J* = 8,6 Hz, 1H), 7,57 (d, *J* = 2,3 Hz, 1H), 7,55 – 7,39 (m, 6H), 7,22 (d, *J* = 2,3 Hz, 1H), 7,21 – 7,10 (m, 4H), 3,67 (s, 3H), 1,87 (bs, 2H); ¹³C RMN (75 MHz, CDCl₃) δ 174,6 (C), 166,7 (C), 166,2 (C), 143,8 (C), 141,2 (C), 133,6 (C), 133,3 (C), 132,3 (CH), 132,1 (CH), 130,5 (C), 129,9 (C), 128,8 (CH), 128,7 (CH), 128,2 (CH), 127,6 (CH), 127,6 (CH), 127,5 (CH), 127,2 (CH), 126,6 (CH), 125,5 (CH), 124,4 (CH), 67,9 (C), 52,9 (CH₃); HRMS (ESI) *m/z*: 480,1919 [M+H]⁺, C₂₉H₂₆N₃O₄⁺ requereix 480,1918.

7.5.3 Addició conjugada organocatalítica d'isocianoacetats a 1-azadiens derivats de l'aurona

7.5.3.1 Síntesi i caracterització dels composts 6

Procediment enantioselectiu

A una dissolució de la corresponent sulfonamida **5** (0,20 mmol, 1,0 equiv.) i **T-III** (9,1 mg, 0,02 mmol, 0,1 equiv.) en DCM sec (1.0 mL), a -30 °C, es va afegir 2-fenilisocianoacetat de *tert*-butil (**2g**, 54 µL, 0,26 mmol, 1,3 equiv.) La reacció s'agità durant 72 h.

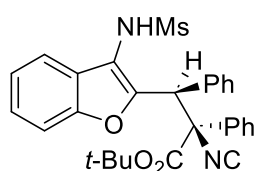
Per a la determinació de la relació diastereoisomèrica, s'utilitzà una columna cromatogràfica de curta longitud per a separar el catalitzador **T-III** i la mescla resultant s'analitzà per ¹H RMN. Després es purificà el producte per cromatografia de columna, eluint amb mescles d'hexà i d'acetat d'etil.

Procediment no enantioselectiu

A una dissolució de la corresponent sulfonamida **5** (0,10 mmol, 1,0 equiv.) i l'esquaramida aquiral 3-((3,5-bis(trifluorometil)fenil)amino)-4-((3-(dimetilamino)propil)amino)ciclobut-3-en-1,2-diona (4,1 mg, 0,01 mmol, 0,1 equiv.) en DCM (0,5 mL) es va afegir 2-fenilisocianoacetat de *tert*-butil (**2g**, 27 µL, 0,13 mmol, 1,3 equiv.) La reacció s'agità a temperatura ambient durant 48 h i el producte es purificà mitjançant cromatografia de capa fina, eluint amb mescles d'hexà i d'acetat d'etil.

(2*S*,3*S*)-2,3-Difenil-2-isocyano-3-(3-(Methylsulfonamido)benzofuran-2-il)propanoat de *tert*-butil (6ag)

Aquesta descripció es presenta en representació de tota la resta de productes semblants.



89.1 mg (86%) de **6ag** van ser obtinguts a partir de **5a** (59,9 mg, 0,20 mmol) després de cromatografia de columna eluint amb hexane:EtOAc 8:2, 7:3. L'excés enantiomèric (84%) va ser mesurat per HPLC (Lux® i-Amylose-1), hexà:iPrOH 80:20, 0,5 mL min⁻¹, enantiòmer majoritari: *t_r* = 26,9 min, enantiòmer minoritari: *t_r* = 15,4 min.

Sòlid blanc; p.f. 179,6-180,0 °C; [α]_D²⁵ -119,4 (*c* 0,4, CHCl₃); ¹H RMN (500 MHz, CDCl₃) δ 7,73 (ddd, *J* = 7,7, 1,4, 0,7 Hz, 1H, Ar), 7,62 (dt, *J* = 8,3, 0,9 Hz, 1H, Ar), 7,49 – 7,43 (m, 2H, Ar), 7,37 (ddd, *J* = 8,4, 7,3, 1,4 Hz, 1H, Ar), 7,35 – 7,29 (m, 4H, Ar), 7,22 – 7,15 (m, 3H, Ar), 7,12 (t, *J* = 7,2 Hz, 2H, Ar), 6,50 (s, 1H, NH), 5,23 (s, 1H, CHAr), 2,82 (s, 3H, Me), 1,28 (s, 9H, tBu); ¹³C RMN (75 MHz, CDCl₃) δ 166,5 (C), 164,4 (C), 153,8 (C), 151,1 (C), 133,6 (C), 133,3 (C), 130,3 (CH), 129,2 (CH), 128,8 (CH), 128,3 (CH), 128,2 (CH), 125,6 (CH), 125,4 (CH), 125,4 (C), 123,8 (CH), 120,2 (CH), 115,1 (C), 112,0 (CH), 85,4 (C), 74,0 (C), 50,7 (CH), 39,6 (CH₃), 27,4 (CH₃); IR (ATR) ν 3288 (w), 2978 (w), 2140 (w, NC), 1733 (m), 1454 (m), 1323 (m), 1279 (m), 1148 (s), 958 (m), 842 (w), 757 (s), 716 (s), 626 (m), 507 (m) cm⁻¹; HRMS (ESI) *m/z*: 517,1784 [M+H]⁺, C₂₉H₂₉N₂O₅S⁺ requereix 517,1792.

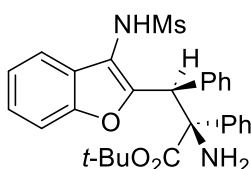
7.5.3.2 Síntesi de **6ag** a escala d'1 mmol

A una dissolució de **5a** (299,3 mg, 1.0 mmol, 1.0 equiv.) i **T-III** (45,3 mg, 0,1 mmol, 0,1 equiv.) en DCM sec (5,0 mL), a -30 °C, es va afegir 2-fenilisocianoacetat de *tert*-butil (**2g**, 272 µL, 1,3 mmol, 1,3 equiv.). La reacció es va agitar durant 72 h a -30 °C i es va passar per una columna curta. La mescla resultant es va fer servir per a la determinació de la relació diastereoisomèrica mitjançant anàlisi per ¹H RMN. El producte va ser posteriorment purificat per cromatografia de columna (eluent: hexà:AcOEt 85:15, 8:2, 7:3) per a proporcionar 400 mg (77%) de **6ag** com

a un sòlid blanc. L'excés enantiomèric (89%) es mesurà per HPLC (Lux® i-Amylose-1), hexà:iPrOH 80:20, 0.5 mL min⁻¹, enantiòmer majoritari: t_r = 28.9 min, enantiòmer minoritari: t_r = 16.7 min.

7.5.3.3 Transformacions del producte **6ag**

(2*S*,3*S*)-2-Amino-2,3-difenil-3-(3-(metilsulfonamido)benzofuran-2-il)propanoat de *tert*-butil (**7**)



A una suspensió de **6ag** (30 mg, 0,058 mmol) en MeOH (0,6 mL) es va afegir HCl (aq) 6 M (3 gotes). La reacció es va agitar a temperatura ambient durant 4 h i posteriorment va ser processada amb una solució aquosa de NaHCO₃ fins a pH 8. El MeOH va ser eliminat a pressió reduïda i el

concentrat es va extraure amb DCM (3x20 mL). Les fases orgàniques combinades van ser rentades amb salmorra (20 mL) i assecades sobre Na₂SO₄. La mescla es va filtrar i es va concentrar a pressió reduïda, i el cru es purificà mitjançant cromatografia de columna (eluent: hexà:AcOEt 7:3) per a donar lloc a 21,9 mg (75%) del compost. L'excés enantiomèric (89%) va ser mesurat per HPLC (CHIRALPAK® AD-H), hexà:iPrOH 80:20, 1,0 mL min⁻¹, enantiòmer majoritari: t_r = 5,5 min, enantiòmer minoritari: t_r = 19,9 min.

Oli taronja; $[\alpha]_D^{25}$ -103,7 (*c* 0,5, CHCl₃); ¹H RMN (300 MHz, CDCl₃) δ 9,99 (s, 1H, NHMs), 8,08 – 7,98 (m, 1H, Ar), 7,54 – 7,40 (m, 3H, Ar), 7,37 – 7,27 (m, 5H, Ar), 7,16 – 6,96 (m, 5H, Ar), 5,22 (s, 1H, CHAr), 2,92 (s, 3H, Me), 2,52 (s, 2H, NH₂), 1,21 (s, 9H, tBu); ¹³C RMN (75 MHz, CDCl₃) δ 172,5 (C), 153,3 (C), 148,5 (C), 140,5 (C), 135,8 (C), 130,0 (CH), 128,5 (CH), 128,2 (CH), 128,2 (CH), 127,6 (CH), 125,9 (CH), 125,0 (CH), 124,5 (C), 123,4 (CH), 121,4 (CH), 116,8 (C), 111,3 (CH), 83,2 (C), 67,7 (C), 52,9 (CH), 40,3 (CH₃), 27,6 (CH₃); IR (ATR) ν 3384 (w), 3247 (w), 3060 (w), 3027 (w), 2978 (w), 2930 (w), 1722 (m), 1618 (w), 1454 (m), 1320 (m), 1249 (m), 1148 (s), 965 (m), 842 (m), 746 (s), 701 (s), 514 (m) cm⁻¹; HRMS (ESI) *m/z*: 507,1945 [M+H]⁺, C₂₈H₃₁N₂O₅S⁺ requereix 507,1948.

7.5.4 Cicloadició [3+2] formal desaromatitzant de 2-nitrobenzofurans i isocianoacetats

7.5.4.1 Síntesi i caracterització dels composts **11**

Procediment enantioselectiu

A una dissolució del corresponent 2-nitrobenzofuran **8** (0,15 mmol, 1,0 equiv.) i **C-II** (6.8 mg, 0,015 mmol, 0,1 equiv.) en CHCl₃ sec (0,75 mL, 0,2 M) a 0 °C es va afegir 2-fenilisocianoacetat

de metil (**2a**, 28 μL , 0,19 mmol, 1,3 equiv.). La reacció es va agitar fins a la consumició completa del compost **8** o fins que no se n'observà més avançament (anàlisi per CCF).

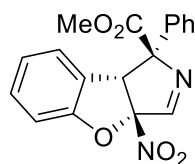
Per a la determinació de la relació diastereoisomèrica, una columna cromatogràfica curta es va fer servir per a separar el catalitzador **C-II** i la mescla resultant va ser analitzada per ^1H RMN. Després el producte va ser purificat per cromatografia de columna, eluint amb mescles d'hexà i d'acetat d'etil.

Procediment no enantioselectiu

A una dissolució del corresponent 2-nitrobenzofuran **8** (0,1 mmol, 1,0 equiv.) i òxid de plata (1,2 mg, 0,005 mmol, 0,05 equiv.) en diclorometà (1,0 mL, 0,1 M), a temperatura ambient, es va afegir 2-fenilisocianoacetat de metil (**2a**, 19 μL , 0,13 mmol, 1,3 equiv.). La reacció es va agitar a temperatura ambient durant 17 h i el producte va ser purificat per cromatografia de columna, eluint amb mescles d'hexà i d'acetat d'etil.

(1*R*,3*aR*,8*bR*)-1-fenil-3*a*-nitro -3*a*,8*b*-dihidro-1*H*-benzofuro[2,3-*c*]pirrole-1-carboxilat de metil (11aa**)**

Aquesta descripció es presenta en representació de tota la resta de productes semblants.



40,1 mg (79%) de **11aa** van ser obtinguts a partir de **8a** (24,5 mg, 0,15 mmol) després de cromatografia de columna eluint amb hexà:AcOEt (95:5). L'excés enantiomèric (93%) va ser mesurat per HPLC (CHIRALPAK® AD-H), hexà:iPrOH 80:20, 1,0 mL min⁻¹, enantiòmer majoritari: t_r = 8,5 min, enantiòmer minoritari: t_r = 24,1 min.

Escuma blanca; $[\alpha]_D^{25} +120,5$ (c 1,0, CHCl_3); ^1H RMN (300 MHz, CDCl_3) δ 8,09 (s, 1H, CH=N), 7,23 – 7,16 (m, 3H, Ar), 7,07 (dddd, J = 8,2, 7,4, 1,4, 0,7 Hz, 1H, Ar), 6,96 – 6,91 (m, 2H, Ar), 6,87 (ddt, J = 8,3, 1,1, 0,6 Hz, 1H, Ar), 6,63 (td, J = 7,6, 1,0 Hz, 1H, Ar), 6,39 (dq, J = 7,6, 0,7 Hz, 1H, Ar), 5,37 (s, 1H), 3,91 (s, 3H, MeO); ^{13}C RMN (75 MHz, CDCl_3) δ 171,1 (C, C=O), 158,7 (CH, C=N), 157,1 (C), 135,7 (C), 129,9 (CH), 128,7 (CH), 128,7 (CH), 126,5 (CH), 125,9 (CH), 124,1 (C), 123,1 (CH), 122,5 (CH), 110,3 (CH), 91,8 (C), 59,2 (CH_3), 54,1 (CH); HRMS (ESI) m/z : 339,0971 $[\text{M}+\text{H}]^+$, $\text{C}_{18}\text{H}_{15}\text{N}_2\text{O}_5^+$ requereix 339,0975.

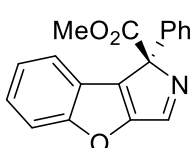
7.5.4.2 Síntesi de **11aa** a escala d'1 mmol

A una dissolució de **8a** (163,1 mg, 1,0 mmol) i **C-II** (45,1 mg, 0,1 mmol) en CHCl_3 sec (5 mL) es va afegir 2-fenilisocianoacetat (**2a**, 190 μL , 1,3 mmol). La reacció s'agità durant 6 dies a 0 °C i es passà a través d'una columna curta. La mescla resultant va ser utilitzada per a la

determinació de la relació diastereoisomèrica mitjançant anàlisi per ^1H RMN. El producte va ser després purificat per cromatografia de columna (eluent: hexà:EtOAc 9:1) per a donar lloc a 254 mg (75%) de **11aa** com a una escuma groguenca. L'excés enantiomèric (91%) va ser mesurat per HPLC (CHIRALPAK® AD-H), hexà:iPrOH 80:20, $1,0\text{ mL min}^{-1}$, enantiòmer majoritari: $t_r = 8,5\text{ min}$, enantiòmer minoritari: $t_r = 24,1\text{ min}$.

7.5.4.3 Transformacions del producte **11aa**

(*S*)-1-Fenil-1*H*-benzofuro[2,3-*c*]pirrole-1-carboxilat de metil(**14**)



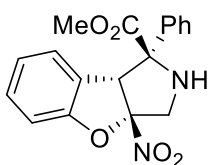
Es va dur a terme una modificació d'un procediment descrit en la literatura.¹⁹⁹

A una dissolució d'**11aa** (31,9 mg, 0,094 mmol, 1,0 equiv, *ee* 93%) en diclorometà sec (2 mL, 0.05 M) es va afegir DBU (70 μL , 0,470 mmol, 5,0 equiv).

La mescla va ser agitada a temperatura ambient durant 17 h. Mitjançant purificació per cromatografia de columna (hexà:EtOAc 8:2) es van obtindre 14,4 mg (53%) del compost. L'excés enantiomèric (90%) va ser mesurat per HPLC (CHIRALPAK® AD-H), hexà:iPrOH 80:20, $1,0\text{ mL min}^{-1}$, enantiòmer majoritari: $t_r = 11,9\text{ min}$, enantiòmer minoritari: $t_r = 8,2\text{ min}$.

Oli roig; $[\alpha]_D^{25} +11,0$ (c 1,0, CHCl_3); ^1H RMN (300 MHz, CDCl_3) δ 8,52 (s, 1H, CH=N), 7,94 – 7,87 (m, 1H, Ar), 7,73 – 7,67 (m, 2H, Ar), 7,65 – 7,59 (m, 1H, Ar), 7,49 – 7,41 (m, 2H, Ar), 7,40 – 7,32 (m, 3H, Ar), 3,76 (s, 3H, MeO); ^{13}C RMN (75 MHz, CDCl_3) δ 168,9 (C, C=O), 161,6 (C), 160,8 (C), 153,2 (CH, CH=N), 140,5 (C), 135,8 (C), 128,9 (CH), 128,8 (CH), 127,9 (CH), 126,5 (CH), 124,6 (C), 124,6 (CH), 121,4 (CH), 113,7 (CH), 82,8 (C), 53,6 (CH_3); HRMS (ESI) m/z : 292,0968 $[\text{M}+\text{H}]^+$, $\text{C}_{18}\text{H}_{14}\text{NO}_3^+$ requereix 292,0968.

(1*R*,3*aR*,8*bR*)-1-Fenil-3*a*-nitro-2,3,3*a*,8*b*-tetrahidro-1*H*-benzofuro[2,3-*c*]pirrole-1-carboxilat de metil (**15**)



Es va dur a terme una modificació d'un procediment descrit en la literatura.²⁰⁰

A una dissolució d'**11aa** (21,1 mg, 0,062 mmol, 1,0 equiv, *ee* 89%) en diclorometà sec (1,8 mL, 0.034 M) i trietilsilà (30 μL , 0,187 mmol, 3,0 equiv), en atmosfera de nitrogen, es va afegir $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (25 μL , 0,205 mmol, 3,3 equiv).

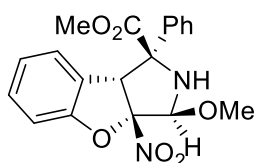
La mescla s'agità a temperatura ambient fins a la completa consumició del material de partida (CCF, aprox. 17 h). La mescla va ser processada amb una solució aquosa saturada de NaHCO_3 (2 mL). S'hi va afegir CH_2Cl_2 (10 mL) i la mescla es va transferir a un embut de decantació. Se separaren les fases i la fase aquosa va ser extreta amb CH_2Cl_2 ($3 \times 5\text{ mL}$). Les fases orgàniques combinades van ser rentades amb salmorra (5 mL) i assecades sobre Na_2SO_4 . Es va filtrar i concentrar a pressió reduïda. La purificació mitjançant columna cromatogràfica

(hexà:EtOAc 8:2) proporciona 20,4 mg (97%) del compost. L'excés enantiomèric (89%) es mesurà per HPLC (CHIRALPAK® AD-H), hexà:iPrOH 80:20, 1,0 mL min⁻¹, enantiòmer majoritari: $t_r = 7,2$ min, enantiòmer minoritari: $t_r = 17,2$ min.

Sòlid blanc; $[\alpha]_D^{25} +180,5$ (c 1,0, CHCl₃); ¹H RMN (300 MHz, CDCl₃) δ 7,37 – 7,28 (m, 2H, Ar), 7,26 (tdd, $J = 4,5, 3,1, 1,2$ Hz, 3H, Ar), 7,10 (dddd, $J = 8,2, 7,5, 1,4, 0,7$ Hz, 1H, Ar), 6,93 (d, $J = 7,7$ Hz, 1H, Ar), 6,55 (td, $J = 7,5, 1,1$ Hz, 1H, Ar), 6,04 (d, $J = 7,7$ Hz, 1H, Ar), 5,19 (s, 1H, CHAr), 3,93 (s, 3H, MeO), 3,84 (d, 1H, $J = 16,2$ Hz), 3,83 (d, $J = 15,7$ Hz, 1H), 2,87 (s, 1H, NH); ¹³C RMN (75 MHz, CDCl₃) δ 174,0 (C, C=O), 159,2 (C), 135,8 (C), 129,4 (CH), 128,8 (CH), 128,5 (CH), 126,4 (CH), 126,3 (CH), 122,9 (C), 122,2 (CH), 121,6 (C), 109,6 (CH), 77,3 (C), 60,1 (CH₃), 54,9 (CH₂), 53,7 (CH); HRMS (ESI) m/z : 341,1128 [M+H]⁺, C₁₈H₁₇N₂O₅⁺ requereix 341,1132.

(1R,3S,3aR,8bR)-1-fenil-3-metoxi-3a-nitro-2,3,3a,8b-tetrahidro-1H-benzofuro[2,3-c]pirrole-1-carboxilat de metil (16aa)

Aquesta descripció es presenta en representació de tota la resta de productes semblants.



Una dissolució d'**11aa** (25,2 mg, 0,075 mmol) dissolt en MeOH (2 mL, 0,04 M) va ser agitada a reflux durant 17 h (bany d'oli a 70 °C). El dissolvent va ser després evaporat per a obtindre 27.6 mg de **7** (99%). L'excés enantiomèric (98%) va ser mesurat per HPLC (CHIRALPAK® AD-

H), hexà:iPrOH 80:20, 1,0 mL min⁻¹, enantiòmer majoritari: $t_r = 8,8$ min, enantiòmer minoritari: $t_r = 16,8$ min. Escuma blanca; $[\alpha]_D^{25} +208,4$ (c 1,1, CHCl₃); ¹H RMN (300 MHz, CDCl₃) δ 7,24 – 7,15 (m, 5H, Ar), 7,03 (t, $J = 7,7$ Hz, 1H, Ar), 6,85 (d, $J = 8,1$ Hz, 1H, Ar), 6,51 (td, $J = 7,5, 1,0$ Hz, 1H, Ar), 6,13 (d, $J = 7,6$ Hz, 1H, Ar), 5,77 (s, 1H, CHNH), 5,03 (s, 1H, CHAr), 3,85 (s, 3H, MeO), 3,72 (s, 1H, NH), 3,36 (s, 3H, MeO); ¹³C RMN (75 MHz, CDCl₃) δ 174,9 (C, C=O), 157,7 (C), 136,7 (C), 129,1 (CH), 128,6 (CH), 128,5 (CH), 126,5 (CH), 125,8 (CH), 123,8 (C), 123,4 (C), 122,3 (CH), 109,5 (CH), 92,2 (CH), 75,0 (C), 55,6 (CH), 53,4 (CH₃), 53,2 (CH₃); HRMS (ESI) m/z : 393,1048 [M+Na]⁺, C₁₉H₁₈N₂NaO₆⁺ requereix 393,1057.

7.5.5 Cicloadició [3+3] enantioselectiva d'isocianoacetats i ilurs d'*N*-iminoquinazolini

7.5.5.1 Síntesi i caracterització dels composts **18**

Procediment enantioselectiu

A una dissolució d'ilur d'*N*-iminoquinazolini **17** (0,1 mmol, 1,0 equiv.) i **S-I** (6,3 mg, 0,01 mmol, 0,1 equiv.) en diclorometà (1 mL) s'afegeix isocianoacetat de metil (**2h**, 12 µL, 0,13 mmol, 1,3 equiv.). La reacció s'agita a temperatura ambient fins que no se'n va observar més avançament (aprox. 72 h, anàlisi CCF).

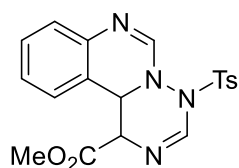
Per a la determinació de la relació diastereoisomèrica, es va dur a terme una columna curta per a separar el catalitzador **S-I** i la mescla resultant va ser analitzada per ¹H RMN. Després el producte va ser purificat mitjançant columna cromatogràfica, eluint amb mescles d'hexà i d'acetat d'etil.

Procediment no enantioselectiu

A una dissolució d'ilur d'*N*-iminoquinazolini **17** (0,1 mmol, 1,0 equiv.) i l'esquaramida aquiral 3-((3,5-bis(trifluorometil)fenil)amino)-4-((3-(dimetilamino)propil)amino)ciclobut-3-en-1,2-diona (4,1 mg, 0,01 mmol, 0,1 equiv.) en DCM (0,5 mL) es va afegir isocianoacetat de metil (**2h**, 12 µL, 0,13 mmol, 1,3 equiv.). La reacció es va agitar a temperatura ambient durant 48 h i producte va ser purificat mitjançant columna cromatogràfica, eluint amb mescles d'hexà i d'acetat d'etil.

4-Tosil-1,11b-dihidro-4*H*-[1,2,4]triazino[1,6-*c*]quinazolin-1-carboxilat de metil (18ah**)**

Aquesta descripció es presenta en representació de tota la resta de productes semblants.



36,0 mg (87%) de **18ah** van ser obtinguts a partir de **17a** (32,5 mg, 0,1 mmol). La relació diastereomèrica (85:15) va ser determinada per ¹H RMN i l'excés enantiomèric (diastereoisòmer majoritari: 84%, diastereoisòmer minoritari: 62%) va ser determinat per HPLC, **diastereoisòmer**

majoritari: Lux® Cellulose-3, hexà:iPrOH 85:15, 0,5 mL min⁻¹, enantiòmer majoritari: *t_r* = 28,2 min, enantiòmer minoritari: *t_r* = 22,9 min, **diastereoisòmer minoritari:** CHIRALPAK® AS-H, hexà:iPrOH 80:20, 1,5 mL min⁻¹, enantiòmer majoritari: *t_r* = 26,5 min, enantiòmer minoritari: *t_r* = 67,3 min.

18ah diastereoisòmer majoritari: oli incolor; [α]_D²⁵ +100,0 (*c* 1,0, CHCl₃); ¹H RMN (300 MHz, CDCl₃) δ 8,26 (d, *J* = 2,5 Hz, 1H, CH=N), 7,80 (d, *J* = 8,5 Hz, 2H, Ar), 7,38 (d, *J* = 8,0

Hz, 2H, Ar), 7,33 – 7,21 (m, 3H, Ar+CH=N), 7,06 (td, $J = 7,4, 1,5$ Hz, 1H, Ar), 6,63 (ddt, $J = 7,5, 1,3, 0,6$ Hz, 1H, Ar), 4,21 (dd, $J = 9,2, 2,5$ Hz, 1H, CH), 3,59 (s, 3H, CH₃), 3,37 (dd, $J = 9,2, 1,4$ Hz, 1H, CH), 2,48 (s, 3H, CH₃); ¹³C RMN (75 MHz, CDCl₃) δ 169,2 (C), 151,0 (CH), 146,9 (C), 140,8 (CH), 139,1 (C), 132,0 (C), 130,6 (CH), 130,3 (CH), 128,6 (CH), 127,1 (CH), 126,5 (CH), 126,38 (CH), 121,0 (C), 58,7 (CH), 52,6 (CH), 52,6 (CH₃), 22,0 (CH₃); **18ah diastereoisòmer minoritari**: oli incolor; ¹H RMN (300 MHz, CDCl₃) δ 8,31 (d, $J = 1,4$ Hz, 1H, CH=N), 7,81 (d, $J = 8,4$ Hz, 2H, Ar), 7,37 (d, $J = 8,0$ Hz, 2H, Ar), 7,32 – 7,24 (m, 3H, Ar+CH=N), 7,18 (dd, $J = 7,9, 1,4$ Hz, 1H, Ar), 7,12 (td, $J = 7,5, 1,4$ Hz, 1H, Ar), 6,75 (ddd, $J = 7,6, 1,4, 0,7$ Hz, 1H, Ar), 4,12 (dd, $J = 3,6, 1,4$ Hz, 1H, CH), 3,63 (d, $J = 3,4$ Hz, 1H, CH), 3,42 (s, 3H, CH₃), 2,47 (s, 3H, CH₃); ¹³C RMN (75 MHz, CDCl₃) δ 168,1 (C), 150,1 (CH), 146,8 (C), 141,7 (CH), 139,0 (C), 132,1 (C), 130,7 (CH), 130,1 (CH), 128,7 (CH), 126,9 (C), 126,5 (CH), 126,4 (CH), 119,8 (C), 60,2 (CH), 53,0 (CH), 52,9 (CH₃), 22,0 (CH₃).

7.6 Conclusions

1. S'han desenvolupat noves estratègies per a la síntesi d'isocianoacetats funcionalitzats mitjançant reaccions d'addició així com per a la síntesi d'heterocicles per mitjà de reaccions de cicloadició que impliquen l'ús d'isocianoacetats. En el cas de les síntesis asimètriques, s'han fet servir procediments organocatalítics que impliquen l'ús d'organocatalitzadors bifuncionals.
2. S'ha desenvolupat una metodologia per a l' α -arilació d'isocianoacetats per a obtenir α,α -diaril- α -aminoèsters mitjançant l'addició d'isocianoacetats α -substituïts a *o*-quinonadibenzimides. Quan s'utilitzaren 4-OH *o*-quinonadibenzimides, heterocicles bicíclics basats en l'estructura de 4*H*-benzo[*e*][1,3]oxazina pogueren ser obtinguts. S'estudià l'abast i limitacions de la reacció respecte a l'ús d'*o*-quinonadibenzimides diferentment substituïdes així com de múltiples isocianoacetats. S'han presentat resultats preliminars relatius a la versió organocatalítica d'aquesta reacció.
3. S'ha presentat un procediment per a la síntesi de 2-alkil-3-aminobenzofurans quirals mitjançant un procediment organocatalític basat en una tiourea per a l'1,4-addició d'isocianoacetats a 1-azadiens derivats de l'aurona. S'ha explorat un ampli abast de la reacció, amb 1-azadiens i isocianoacetats diferentment substituïts, amb generalment excel·lent diastereoselectivitat i un bon excés enantiomèric per als productes de reacció. El corresponent α -aminoèster del producte de reacció s'obtingué mitjançant la hidròlisi àcida del grup isonitril.

4. S'ha desenvolupat la cicloaddició [3+2] organocatalítica desaromatitzant entre isocianoacetats i 2-nitrobenzofurans per a obtenir productes heterocíclics tricíclics fusionats quirals que contenen un cicle d'1-pirrolina de nova formació. Una cupreïna quiral va ser utilitzada per a donar lloc als productes de reacció esmentats prèviament amb excel·lent diastereoselectivitat així com, en general, enantioselectivitat de bona a excel·lent. Transformacions diverses dels heterocicles resultants van poder-se dur a terme sense afectar significativament l'excés enantiomèric. Les condicions de reacció van provar-se també amb altres heterocicles deficients de densitat electrònica, com ara els 2-nitrobenzotiofens o els 3-nitrobenzofurans, encara que van demostrar ser no compatibles.
5. Un estudi preliminar de la cicloaddició [3+3] asimètrica entre isocianoacetats i ilurs d'*N*-iminoquinazolini ha sigut desenvolupat, constituint el primer exemple de reacció entre isocianurs i imines d'azometí *C,N*-cíclics que no ocorre mitjançant un mecanisme de tipus Ugi. Encara que el procediment proporcionà un rendiment, diastereoselectivitat i excés enantiomèric raonables per a l'ilur d'*N*-iminoquinazolini no substituït, els altres exemples procediren amb una notable reducció del rendiment, de la relació diastereomèrica i de l'excés enantiomèric, la qual cosa indica la necessitat de canviar el sistema catalític per a la futura continuació d'aquesta línia de treball.

8 References

- (1) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*, 1st ed.; Baker Lecture Series; John Wiley & Sons: New York, 1994.
- (2) IUPAC. *Compendium of Chemical Terminology, (the "Gold Book")*, 2nd ed.; Blackwell Scientific Publications: Oxford, 1997.
- (3) Morrison, J. D. A Summary of Ways to Obtain Optically Active Compounds. In *Asymmetric Synthesis*; Academic Press: New York, 2012; Vol. 1, pp 1–12.
- (4) Lin, G.-Q.; Li, Y.-M.; Chan, A. S. C. *Principles and Applications of Asymmetric Synthesis*, 1st ed.; John Wiley & Sons: New York, 2001.
- (5) Dalko, P. I. Asymmetric Organocatalysis: A New Stream in Organic Synthesis. In *Enantioselective Organocatalysis: Reactions and Experimental Procedures*; John Wiley & Sons: Weinheim, 2007; pp 1–17.
- (6) Ugi, I. *Isonitrile Chemistry*, 1st ed.; Blomquist, A. T., Ed.; Organic Chemistry: A Series of Monographs; Academic Press: New York, 1971.
- (7) Nef, J. U. *Justus Liebigs Ann. Chem.* **1892**, 270, 267–335.
- (8) Nef, J. U. *Justus Liebigs Ann. Chem.* **1899**, 309, 126–189.
- (9) Lindemann, H.; Wiegand, L. *Chem. Ber.* **1930**, 63, 1650–1657.
- (10) Ramozzi, R.; Chéron, N.; Braïda, B.; Hiberty, P. C.; Fleurat-Lessard, P. *New J. Chem.* **2012**, 36, 1137–1140.
- (11) Mironov, M. A. General Aspects of Isocyanide Reactivity. In *Isocyanide Chemistry*; Nenajdenko, V. G., Ed.; John Wiley & Sons: Weinheim, 2012; pp 35–73.
- (12) Gulevich, A. V.; Zhdanko, A. G.; Orru, R. V. A.; Nenajdenko, V. G. *Chem. Rev.* **2010**, 110, 5235–5331.
- (13) Blay, G.; Vila, C.; Martínez-Pardo, P.; Pedro, J. R. Enantioselective Synthesis of Five-Membered Heterocycles through [3+2]-Cycloadditions with Isocyano Esters. In *Targets in Heterocyclic Systems; Reviews and Accounts on Heterocyclic Chemistry*; Italian Society of Chemistry: Rome, 2018; Vol. 22, pp 165–193.
- (14) Spížek, J.; Řezanka, T. *Appl. Microbiol. Biotechnol.* **2004**, 64, 455–464.
- (15) Duchin, K. L.; McKinstry, D. N.; Cohen, A. I.; Migdalof, B. H. *Clin. Pharmacokinet.* **1988**, 14, 241–259.
- (16) Solomon, G. D.; Cady, R. K.; Klapper, J. A.; Earl, N. L.; Saper, J. R.; Ramadan, N. M. *Neurology* **1997**, 49, 1219–1225.
- (17) Marques, A. R.; Kromer, L.; Gallo, D. J.; Penacho, N.; Rodrigues, S. S.; Seixas, J. D.; Bernardes, G. J. L.; Reis, P. M.; Otterbein, S. L.; Ruggieri, R. A.; Gonçalves, A. S. G.; Gonçalves, A. M. L.; Matos, M. N. D.; Bento, I.; Otterbein, L. E.; Blättler, W. A.; Romão, C. C. *Organometallics* **2012**, 31, 5810–5822.
- (18) Beutner, K. R. *Antiviral Res.* **1995**, 28, 281–290.
- (19) Juncos, J. L.; Mouradian, M. M.; Fabbrini, G.; Serrati, C.; Chase, T. N. *Neurology* **1987**, 37, 1242–1242.
- (20) Giustiniano, M.; Basso, A.; Mercalli, V.; Massarotti, A.; Novellino, E.; Tron, G. C.; Zhu, J. *Chem. Soc. Rev.* **2017**, 46, 1295–1357.
- (21) Schöllkopf, U.; Hantke, K. *Justus Liebigs Ann. Chem.* **1973**, 1973, 1571–1582.
- (22) Ito, Y.; Sawamura, M.; Matsuoka, M.; Matsumoto, Y.; Hayashi, T. *Tetrahedron Lett.* **1987**, 28, 4849–4852.
- (23) Ito, Y.; Higuchi, N.; Murakami, M. *Tetrahedron Lett.* **1988**, 29, 5151–5154.
- (24) Kazmaier, U.; Ackermann, S. *Synlett* **2004**, 2004, 2576–2578.
- (25) Xie, C.; Wu, S.; Zhang, R. *ACS Omega* **2023**, 8, 6854–6859.
- (26) Murakami, M.; Hasegawa, N.; Tomita, I.; Inouye, M.; Ito, Y. *Tetrahedron Lett.* **1989**, 30, 1257–1260.

- (27) Zhang, D.; Xu, X.; Tan, J.; Liu, Q. *Synlett* **2010**, 2010, 917–920.
- (28) Zhang, D.; Yang, P.; Liu, W.; Li, J. *Acta Cryst. E* **2014**, 70, o802–o802.
- (29) Zhang, D.; Hao, L.; Li, J. *Acta Cryst. E* **2014**, 70, o856–o856.
- (30) Qu, C.; Huang, R.; Li, Y.; Liu, T.; Chen, Y.; Song, G. *Beilstein J. Org. Chem.* **2021**, 17, 2822–2831.
- (31) Bai, J.-F.; Wang, L.-L.; Peng, L.; Guo, Y.-L.; Jia, L.-N.; Tian, F.; He, G.-Y.; Xu, X.-Y.; Wang, L.-X. *J. Org. Chem.* **2012**, 77, 2947–2953.
- (32) Zhao, M.-X.; Ji, F.-H.; Wei, D.-K.; Shi, M. *Tetrahedron* **2013**, 69, 10763–10771.
- (33) Buyck, T.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2013**, 52, 12714–12718.
- (34) Buyck, T.; Wang, Q.; Zhu, J. *Chimia* **2014**, 68, 211–211.
- (35) Zhao, M.-X.; Jing, L.; Zhou, H.; Shi, M. *RSC Adv.* **2015**, 5, 75648–75652.
- (36) Zhao, M.-X.; Zhu, H.-K.; Dai, T.-L.; Shi, M. *J. Org. Chem.* **2015**, 80, 11330–11338.
- (37) Odriozola, A.; Oiarbide, M.; Palomo, C. *Chem. Eur. J.* **2017**, 23, 12758–12762.
- (38) Ji, X.; Cao, W.-G.; Zhao, G. *Tetrahedron* **2017**, 73, 5983–5992.
- (39) Wang, H.-Y.; Zhang, K.; Zheng, C.-W.; Chai, Z.; Cao, D.-D.; Zhang, J.-X.; Zhao, G. *Angew. Chem. Int. Ed.* **2015**, 54, 1775–1779.
- (40) Yu, K.-M.; Zhu, H.-K.; Zhao, X.-L.; Shi, M.; Zhao, M.-X. *Org. Biomol. Chem.* **2019**, 17, 639–645.
- (41) Zhao, M.-X.; Zhu, G.-Y.; Zhao, X.-L.; Shi, M. *Tetrahedron* **2019**, 75, 1171–1179.
- (42) Zhao, M.-X.; Xiang, J.; Zhao, Z.-Q.; Zhao, X.-L.; Shi, M. *Org. Biomol. Chem.* **2020**, 18, 1637–1646.
- (43) Sladojevich, F.; Trabocchi, A.; Guarna, A.; Dixon, D. J. *J. Am. Chem. Soc.* **2011**, 133, 1710–1713.
- (44) Murakami, M.; Hasegawa, N.; Hayashi, M.; Ito, Y. *J. Org. Chem.* **1991**, 56, 7356–7360.
- (45) Bachi, M. D.; Melman, A. *Synlett* **1996**, 1996, 60–62.
- (46) Bachi, M. D.; Bar-Ner, N.; Melman, A. *J. Org. Chem.* **1996**, 61, 7116–7124.
- (47) Torres-Ochoa, R. O.; Buyck, T.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2018**, 57, 5679–5683.
- (48) Ito, Yoshihiko.; Sawamura, Masaya.; Hayashi, Tamio. *J. Am. Chem. Soc.* **1986**, 108, 6405–6406.
- (49) Ito, Y.; Sawamura, M.; Hamashima, H.; Emura, T.; Hayashi, T. *Tetrahedron Lett.* **1989**, 30, 4681–4684.
- (50) Hayashi, T.; Uozumi, Y.; Yamazaki, A.; Sawamura, M.; Hamashima, H.; Ito, Y. *Tetrahedron Lett.* **1991**, 32, 2799–2802.
- (51) Gorla, F.; Togni, A.; Venanzi, L. M.; Albinati, A.; Lianza, F. *Organometallics* **1994**, 13, 1607–1616.
- (52) Longmire, J. M.; Zhang, X.; Shang, M. *Organometallics* **1998**, 17, 4374–4379.
- (53) Xue, M.-X.; Guo, C.; Gong, L.-Z. *Synlett* **2009**, 2009, 2191–2197.
- (54) Diao, R.-C.; Zhao, W.-T.; Li, S. *J. Chem. Res.* **2016**, 40, 521–525.
- (55) Zhao, M.-X.; Zhou, H.; Tang, W.-H.; Qu, W.-S.; Shi, M. *Adv. Synth. Catal.* **2013**, 355, 1277–1283.
- (56) Lin, N.; Deng, Y.-Q.; Zhang, Z.-W.; Wang, Q.; Lu, G. *Tetrahedron Asymmetry* **2014**, 25, 650–657.
- (57) Wang, F.; Chen, J.; Huang, Y. *Synlett* **2017**, 28, 1300–1304.
- (58) Zhou, X.-T.; Lin, Y.-R.; Dai, L.-X.; Sun, J.; Xia, L.-J.; Tang, M.-H. *J. Org. Chem.* **1999**, 64, 1331–1334.
- (59) Zhou, X.-T.; Lin, Y.-R.; Dai, L.-X. *Tetrahedron Asymmetry* **1999**, 10, 855–862.
- (60) Aydin, J.; Rydén, A.; Szabó, K. J. *Tetrahedron Asymmetry* **2008**, 19, 1867–1870.
- (61) Zhang, Z.-W.; Lu, G.; Chen, M.-M.; Lin, N.; Li, Y.-B.; Hayashi, T.; Chan, A. S. C. *Tetrahedron Asymmetry* **2010**, 21, 1715–1721.

- (62) Wang, L.; Mu, H.; Lu, D.; Li, X.; Li, T.; Jin, Y. *Chin. J. Appl. Chem.* **2019**, *36*, 758.
- (63) Nakamura, S.; Maeno, Y.; Ohara, M.; Yamamura, A.; Funahashi, Y.; Shibata, N. *Org. Lett.* **2012**, *14*, 2960–2963.
- (64) Yang, T.; Yan, S.; Yu, Z.-J.; Zhao, X.-L.; Shi, M.; Zhao, M.-X. *Eur. J. Org. Chem.* **2023**, *26*, e202300275.
- (65) Guo, C.; Xue, M.-X.; Zhu, M.-K.; Gong, L.-Z. *Angew. Chem. Int. Ed.* **2008**, *47*, 3414–3417.
- (66) Arróniz, C.; Gil-González, A.; Semak, V.; Escolano, C.; Bosch, J.; Amat, M. *Eur. J. Org. Chem.* **2011**, *2011*, 3755–3760.
- (67) Wang, L.-L.; Bai, J.-F.; Peng, L.; Qi, L.-W.; Jia, L.-N.; Guo, Y.-L.; Luo, X.-Y.; Xu, X.-Y.; Wang, L.-X. *Chem. Commun.* **2012**, *48*, 5175.
- (68) Wei, W.-T.; Chen, C.-X.; Lu, R.-J.; Wang, J.-J.; Zhang, X.-J.; Yan, M. *Org. Biomol. Chem.* **2012**, *10*, 5245.
- (69) Zhao, M.-X.; Zhu, G.-Y.; Zhu, H.-K.; Zhao, X.-L.; Ji, M.; Shi, M. *Eur. J. Org. Chem.* **2018**, *2018*, 3997–4005.
- (70) Zhao, M.-X.; Bi, H.-L.; Zhou, H.; Yang, H.; Shi, M. *J. Org. Chem.* **2013**, *78*, 9377–9382.
- (71) Wolstenhulme, J. R.; Cavell, A.; Gredičak, M.; Driver, R. W.; Smith, M. D. *Chem. Commun.* **2014**, *50*, 13585–13588.
- (72) Wang, Z.-P.; Wu, Q.; Jiang, J.; Li, Z.-R.; Peng, X.-J.; Shao, P.-L.; He, Y. *Org. Chem. Front.* **2018**, *5*, 36–40.
- (73) Chang, L.; Zhu, G.-Y.; Yang, T.; Zhao, X.-L.; Shi, M.; Zhao, M.-X. *Org. Biomol. Chem.* **2021**, *19*, 3687–3697.
- (74) Du, J.; Xu, X.; Li, Y.; Pan, L.; Liu, Q. *Org. Lett.* **2014**, *16*, 4004–4007.
- (75) Bhattacharyya, A.; Shahi, C. K.; Pradhan, S.; Ghorai, M. K. *Org. Lett.* **2018**, *20*, 2925–2928.
- (76) Kok, G. P. Y.; Yang, H.; Wong, M. W.; Zhao, Y. *Org. Lett.* **2018**, *20*, 5112–5115.
- (77) Liu, Q.; Chen, J.-H.; Yao, M.; Zhao, Z.-Y.; Liu, X.-Y.; Zhao, X.-L.; Shi, M.; Zhao, M.-X. *Tetrahedron* **2021**, *88*, 132122.
- (78) Tao, L.-F.; Zhang, S.; Huang, F.; Wang, W.-T.; Luo, Z.-H.; Qian, L.; Liao, J.-Y. *Angew. Chem. Int. Ed.* **2022**, *61*, e202202679.
- (79) Tao, L.-F.; Qian, L.; Liao, J.-Y. *Synlett* **2022**, *33*, 1873–1878.
- (80) Shao, R.; Zhao, H.; Ding, S.; Li, L.; Chen, C.; Wang, J.; Shang, Y. *Chem. Commun.* **2022**, *58*, 4771–4774.
- (81) He, Z.-L.; Wang, C.-J. *Chem. Commun.* **2015**, *51*, 534–536.
- (82) Martínez-Pardo, P.; Blay, G.; Muñoz, M. C.; Pedro, J. R.; Sanz-Marco, A.; Vila, C. *Chem. Commun.* **2018**, *54*, 2862–2865.
- (83) Martínez-Pardo, P.; Blay, G.; Vila, C.; Sanz-Marco, A.; Muñoz, M. C.; Pedro, J. R. *J. Org. Chem.* **2019**, *84*, 314–325.
- (84) Lee, C.-J.; Liang, X.; Wu, Q.; Najeeb, J.; Zhao, J.; Gopalaswamy, R.; Titecat, M.; Sebbane, F.; Lemaitre, N.; Toone, E. J.; Zhou, P. *Nat. Commun.* **2016**, *7*, 10638.
- (85) Martínez-Pardo, P.; Blay, G.; Escrivá-Palomo, A.; Sanz-Marco, A.; Vila, C.; Pedro, J. R. *Org. Lett.* **2019**, *21*, 4063–4066.
- (86) Martínez-Pardo, P.; Laviós, A.; Sanz-Marco, A.; Vila, C.; Pedro, J. R.; Blay, G. *Adv. Synth. Catal.* **2020**, *362*, 3564–3569.
- (87) Adams, R.; Nagarkatti, A. S. *J. Am. Chem. Soc.* **1950**, *72*, 4601–4606.
- (88) Adams, R.; Wankel, R. A. *J. Am. Chem. Soc.* **1951**, *73*, 2219–2220.
- (89) Adams, R.; Way, J. W. *J. Am. Chem. Soc.* **1954**, *76*, 2763–2769.
- (90) Friedrichsen, W.; Oeser, H.-G. *Chem. Ber.* **1975**, *108*, 31–47.
- (91) Friedrichsen, W.; Büldt, E.; Schmidt, R. *Tetrahedron Lett.* **1975**, *16*, 1137–1140.
- (92) Friedrichsen, W.; Oeser, H.-G. *Tetrahedron Lett.* **1975**, *16*, 1489–1492.

- (93) Friedrichsen, W.; Schwarz, I. *Tetrahedron Lett.* **1977**, *18*, 3581–3582.
- (94) Nair, V.; Dhanya, R.; Rajesh, C.; Bhadbhade, M. M.; Manoj, K. *Org. Lett.* **2004**, *6*, 4743–4745.
- (95) Abraham, C. J.; Paull, D. H.; Scerba, M. T.; Grebinski, J. W.; Lectka, T. *J. Am. Chem. Soc.* **2006**, *128*, 13370–13371.
- (96) Li, J.-L.; Han, B.; Jiang, K.; Du, W.; Chen, Y.-C. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3952–3954.
- (97) Zhou, S.-L.; Li, J.-L.; Dong, L.; Chen, Y.-C. *Org. Lett.* **2011**, *13*, 5874–5877.
- (98) Fisher, E. L.; Wilkerson-Hill, S. M.; Sarpong, R. *J. Am. Chem. Soc.* **2012**, *134*, 9946–9949.
- (99) Huang, R.; Chen, X.; Mou, C.; Luo, G.; Li, Y.; Li, X.; Xue, W.; Jin, Z.; Chi, Y. R. *Org. Lett.* **2019**, *21*, 4340–4344.
- (100) Wang, D.; Yu, H.; Sun, S.; Zhong, F. *Org. Lett.* **2020**, *22*, 2425–2430.
- (101) Boulos, L. S.; Arsanious, M. H. N. *Phosphorus sulfur relat. elem.* **1988**.
- (102) Boulos, L. S.; Arsanious, M. H. N. *Phosphorus sulfur silicon relat. elem.* **1994**, *89*, 185–191.
- (103) Nair, V.; Dhanya, R.; Vidya, N.; Devipriya, S. *Synthesis* **2006**, *2006*, 107–110.
- (104) Kerr, R. G.; Miranda, N. F. *J. Nat. Prod.* **1995**, *58*, 1618–1621.
- (105) European Medicines Agency. Yondelis <https://www.ema.europa.eu/en/medicines/human/EPAR/yondelis> (accessed Sep 25, 2023).
- (106) Takahashi, A.; Kurasawa, S.; Ikeda, D.; Okami, Y.; Takeuchi, T. *J. Antibiot.* **1989**, *42*, 1556–1561.
- (107) Millichap, J. G. *N. Engl. J. Med.* **1972**, *286*, 464–469.
- (108) Doherty, A. J.; Collingridge, G. L.; Jane, D. E. *Br. J. Pharmacol.* **1999**, *126*, 205–210.
- (109) Collins, J.; Santoro, O.; Prior, T. J.; Chen, K.; Redshaw, C. *J. Mol. Struct.* **2021**, *1224*, 129083.
- (110) Zhang, X.; Prior, T. J.; Redshaw, C. *New J. Chem.* **2022**, *46*, 14146–14154.
- (111) Casanovas, J.; Zanuy, D.; Nussinov, R.; Alemán, C. *J. Org. Chem.* **2007**, *72*, 2174–2181.
- (112) Alemán, C. *J. Phys. Chem. B* **1997**, *101*, 5046–5050.
- (113) Zanuy, D.; Rodríguez-Ropero, F.; Nussinov, R.; Alemán, C. *J. Struct. Biol.* **2007**, *160*, 177–189.
- (114) Evans, D. A.; Lectka, T.; Miller, S. J. *Tetrahedron Lett.* **1993**, *34*, 7027–7030.
- (115) Taggi, A. E.; Hafez, A. M.; Lectka, T. *Acc. Chem. Res.* **2003**, *36*, 10–19.
- (116) Khanam, H.; Shamsuzzaman. *Eur. J. Med. Chem.* **2015**, *97*, 483–504.
- (117) Ozawa T.; Nakamura T.; Misawa K.; Sakamoto S.; Onoda H. New adenosine A2A receptor antagonist. JP2005126374A, May 19, 2005.
- (118) Martin, J. C.; Sims, J. R.; Gupta, A.; Hagoel, T. J.; Gao, L.; Lynch, M. L.; Woloszynska, A.; Melendy, T.; Kane, J. F.; Kuechle, J.; Ohm, J. E. *Cell Death Discov.* **2022**, *8*, 1–10.
- (119) Narimatsu, S.; Takemi, C.; Kuramoto, S.; Tsuzuki, D.; Hichiya, H.; Tamagake, K.; Yamamoto, S. *Chirality* **2003**, *15*, 333–339.
- (120) Spaniol, M.; Bracher, R.; Ha, H. R.; Follath, F.; Krähenbühl, S. *J. Hepatol.* **2001**, *35*, 628–636.
- (121) Gu, Z.; Zhou, J.; Jiang, G.-F.; Zhou, Y.-G. *Org. Chem. Front.* **2018**, *5*, 1148–1151.
- (122) Gu, Z.; Xie, J.-J.; Jiang, G.-F.; Zhou, Y.-G. *Asian J. Org. Chem.* **2018**, *7*, 1561–1564.
- (123) Lin, W.; Lin, X.; Cheng, Y.; Chang, X.; Zhou, S.; Li, P.; Li, W. *Org. Chem. Front.* **2019**, *6*, 2452–2456.
- (124) Lin, W.; Zhang, C.; Xu, W.; Cheng, Y.; Li, P.; Li, W. *Adv. Synth. Catal.* **2019**, *361*, 476–480.
- (125) Xie, H.-P.; Wu, B.; Wang, X.-W.; Zhou, Y.-G. *Chin. J. Catal.* **2019**, *40*, 1566–1575.

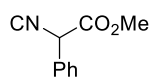
- (126) Wang, C.-J.; Yang, Q.-Q.; Wang, M.-X.; Shang, Y.-H.; Tong, X.-Y.; Deng, Y.-H.; Shao, Z. *Org. Chem. Front.* **2020**, *7*, 609–616.
- (127) Zhou, J.; Li, T.-Z.; Sun, Y.-W.; Du, B.-X.; Tan, W.; Shi, F. *ChemCatChem* **2020**, *12*, 4862–4870.
- (128) Lu, Z.; Hu, J.; Lan, W.; Mo, X.; Zhou, S.; Tang, Y.; Yuan, W.; Zhang, X.; Liao, L. *Tetrahedron Lett.* **2021**, *67*, 152862.
- (129) Huang, W.-J.; Ma, Y.-Y.; Liu, L.-X.; Wu, B.; Jiang, G.-F.; Zhou, Y.-G. *Org. Lett.* **2021**, *23*, 2393–2398.
- (130) Zhang, C.; Cheng, Y.; Li, F.; Luan, Y.; Li, P.; Li, W. *Adv. Synth. Catal.* **2020**, *362*, 1286–1291.
- (131) Huanping, X.; Bo, W.; Muwang, C.; Changbin, Y.; Hongwang, L.; Xiang, L.; Yonggui, Z. *Chin. J. Org. Chem.* **2020**, *40*, 3452–3462.
- (132) Li, F.; Zhang, C.; Cheng, Y.; Jia, Q.; Li, W.; Liu, K.; Li, P. *Asian J. Org. Chem.* **2020**, *9*, 1183–1186.
- (133) Yan, J.; Li, X.; Chen, Y.; Li, Y.; Chen, W.; Zhan, R.; Huang, H. *J. Org. Chem.* **2020**, *85*, 12175–12186.
- (134) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.
- (135) Zhu, Y.; Malerich, J. P.; Rawal, V. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 153–156.
- (136) Marqués-López, E.; Herrera, R. P. Hydrogen Bonds as an Alternative Activation. In *New Strategies in Chemical Synthesis and Catalysis*; Pignataro, B., Ed.; John Wiley & Sons: Weinheim, 2012; pp 175–199.
- (137) Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem. Eur. J.* **2011**, *17*, 6890–6899.
- (138) Jakab, G.; Tancon, C.; Zhang, Z.; Lippert, K. M.; Schreiner, P. R. *Org. Lett.* **2012**, *14*, 1724–1727.
- (139) Zhuo, C.-X.; Zhang, W.; You, S.-L. *Angew. Chem. Int. Ed.* **2012**, *51*, 12662–12686.
- (140) Huck, C. J.; Boyko, Y. D.; Sarlah, D. *Nat. Prod. Rep.* **2022**, *39*, 2231–2291.
- (141) Huang, G.; Yin, B. *Adv. Synth. Catal.* **2019**, *361*, 405–425.
- (142) Awata, A.; Arai, T. *Angew. Chem. Int. Ed.* **2014**, *53*, 10462–10465.
- (143) Trost, B. M.; Ehmke, V.; O’Keefe, B. M.; Bringley, D. A. *J. Am. Chem. Soc.* **2014**, *136*, 8213–8216.
- (144) T. Pelkey, E.; Chang, L.; W. Gribble, G. *Chem. Commun.* **1996**, No. 16, 1909–1910.
- (145) Pelkey, E. T.; Gribble, G. W. *Synthesis* **1999**, *1999*, 1117–1122.
- (146) Barton, D. H. R.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1985**, No. 16, 1098–1100.
- (147) Barton, D. H. R.; Kervagoret, J.; Zard, S. Z. *Tetrahedron* **1990**, *46*, 7587–7598.
- (148) Wan, Q.; Xie, J.-H.; Zheng, C.; Yuan, Y.-F.; You, S.-L. *Angew. Chem. Int. Ed.* **2021**, *60*, 19730–19734.
- (149) Yuan, W.-C.; Chen, X.-M.; Zhao, J.-Q.; Zhang, Y.-P.; Wang, Z.-H.; You, Y. *Org. Lett.* **2022**, *24*, 826–831.
- (150) Li, H.; Wang, Y.; Tang, L.; Wu, F.; Liu, X.; Guo, C.; Foxman, B. M.; Deng, L. *Angew. Chem. Int. Ed.* **2005**, *44*, 105–108.
- (151) Montesinos-Magraner, M.; Cantón, R.; Vila, C.; Blay, G.; Fernández, I.; Muñoz, M. C.; Pedro, J. R. *RSC Adv.* **2015**, *5*, 60101–60105.
- (152) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2015**, *115*, 5366–5412.
- (153) Shintani, R.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 10778–10779.
- (154) Chen, W.; Yuan, X.-H.; Li, R.; Du, W.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Adv. Synth. Catal.* **2006**, *348*, 1818–1822.
- (155) Hashimoto, T.; Maeda, Y.; Omote, M.; Nakatsu, H.; Maruoka, K. *J. Am. Chem. Soc.* **2010**, *132*, 4076–4077.
- (156) Hashimoto, T.; Omote, M.; Maruoka, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 3489–3492.
- (157) Nájera, C.; Sansano, J. M.; Yus, M. *Org. Biomol. Chem.* **2015**, *13*, 8596–8636.

- (158) Oppolzer, W. *Tetrahedron Lett.* **1970**, *11*, 2199–2204.
- (159) Oppolzer, W. *Tetrahedron Lett.* **1970**, *11*, 3091–3094.
- (160) Oppolzer, W. *Angew. Chem. Int. Ed.* **1977**, *16*, 10–23.
- (161) Yuan, C.; Zhou, L.; Xia, M.; Sun, Z.; Wang, D.; Guo, H. *Org. Lett.* **2016**, *18*, 5644–5647.
- (162) Andrews, I. P.; Kwon, O. *Chem. Sci.* **2012**, *3*, 2510–2514.
- (163) Henry, C. E.; Xu, Q.; Fan, Y. C.; Martin, T. J.; Belding, L.; Dudding, T.; Kwon, O. *J. Am. Chem. Soc.* **2014**, *136*, 11890–11893.
- (164) Zhou, L.; Yuan, C.; Zhang, C.; Zhang, L.; Gao, Z.; Wang, C.; Liu, H.; Wu, Y.; Guo, H. *Adv. Synth. Catal.* **2017**, *359*, 2316–2321.
- (165) Zhou, L.; Zeng, Y.; Gao, X.; Wang, Q.; Wang, C.; Wang, B.; Wang, W.; Wu, Y.; Zheng, B.; Guo, H. *Chem. Commun.* **2019**, *55*, 10464–10467.
- (166) Soeta, T.; Tamura, K.; Ukaji, Y. *Org. Lett.* **2012**, *14*, 1226–1229.
- (167) Cao, W.-B.; Jiang, S.; Li, H.-Y.; Xu, X.-P.; Ji, S.-J. *Org. Chem. Front.* **2021**, *8*, 2494–2503.
- (168) Li, D.; Yang, D.; Wang, L.; Liu, X.; Wang, K.; Wang, J.; Wang, P.; Liu, Y.; Zhu, H.; Wang, R. *Chem. Eur. J.* **2017**, *23*, 6974–6978.
- (169) Zhao, Z.-Q.; Zhao, X.-L.; Shi, M.; Zhao, M.-X. *J. Org. Chem.* **2019**, *84*, 14487–14497.
- (170) Li, J. J.; Limberakis, C.; Pflum, D. A. *Modern Organic Synthesis in the Laboratory: A Collection of Standard Experimental Procedures*, 1st ed.; Oxford University Press: New York, 2007.
- (171) Burfield, D. R.; Lee, K.-H.; Smithers, R. H. *J. Org. Chem.* **1977**, *42*, 3060–3065.
- (172) Williams, D. B. G.; Lawton, M. *J. Org. Chem.* **2010**, *75*, 8351–8354.
- (173) Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, 4th ed.; Butterworth-Heinemann: Oxford, 1997.
- (174) Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. *Organometallics* **2010**, *29*, 2176–2179.
- (175) Cassani, C.; Martín-Rapún, R.; Arceo, E.; Bravo, F.; Melchiorre, P. *Nat. Protoc.* **2013**, *8*, 325–344.
- (176) Yang, W.; Du, D.-M. *Org. Lett.* **2010**, *12*, 5450–5453.
- (177) Madej, A.; Paprocki, D.; Koszelewski, D.; Źądło-Dobrowolska, A.; Brzozowska, A.; Walde, P.; Ostaszewski, R. *RSC Adv.* **2017**, *7*, 33344–33354.
- (178) Jacobsen, E. J.; Stelzer, L. S.; Belonga, K. L.; Carter, D. B.; Im, W. B.; Sethy, V. H.; Tang, A. H.; VonVoigtlander, P. F.; Petke, J. D. *J. Med. Chem.* **1996**, *39*, 3820–3836.
- (179) Elders, N.; Ruijter, E.; de Kanter, F. J. J.; Groen, M. B.; Orru, R. V. A. *Chem. Eur. J.* **2008**, *14*, 4961–4973.
- (180) Bonne, D.; Dekhane, M.; Zhu, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 2485–2488.
- (181) Elders, N.; Schmitz, R. F.; de Kanter, F. J. J.; Ruijter, E.; Groen, M. B.; Orru, R. V. A. *J. Org. Chem.* **2007**, *72*, 6135–6142.
- (182) Ni, H.; Tang, X.; Zheng, W.; Yao, W.; Ullah, N.; Lu, Y. *Angew. Chem. Int. Ed.* **2017**, *56*, 14222–14226.
- (183) Feng, Q.; Wu, A.; Zhang, X.; Song, L.; Sun, J. *Chem. Sci.* **2021**, *12*, 7953–7957.
- (184) Li, X.; Yan, J.; Qin, J.; Lin, S.; Chen, W.; Zhan, R.; Huang, H. *J. Org. Chem.* **2019**, *84*, 8035–8045.
- (185) Liu, Y.-Z.; Wang, Z.; Huang, Z.; Zheng, X.; Yang, W.-L.; Deng, W.-P. *Angew. Chem. Int. Ed.* **2020**, *59*, 1238–1242.
- (186) Koay, W. L.; Mei, G.-J.; Lu, Y. *Org. Chem. Front.* **2021**, *8*, 968–974.
- (187) Eröksüz, S.; Neudörfl, J. M.; Berkessel, A. *Synlett* **2017**, *28*, 1278–1281.
- (188) Yu, L.; Li, P. *Tetrahedron Lett.* **2014**, *55*, 3697–3700.

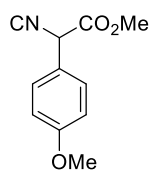
- (189) Yan, L.; Huang, G.; Wang, H.; Xiong, F.; Peng, H.; Chen, F. *Eur. J. Org. Chem.* **2018**, 2018, 99–103.
- (190) Dajek, M.; Kowalczyk, R.; Boratyński, P. J. *Catal. Sci. Technol.* **2018**, 8, 4358–4363.
- (191) Kurimoto, Y.; Nasu, T.; Fujii, Y.; Asano, K.; Matsubara, S. *Org. Lett.* **2019**, 21, 2156–2160.
- (192) Yang, X.-H.; Li, J.-P.; Wang, D.-C.; Xie, M.-S.; Qu, G.-R.; Guo, H.-M. *Chem. Commun.* **2019**, 55, 9144–9147.
- (193) Cheng, Q.; Zhang, H.-J.; Yue, W.-J.; You, S.-L. *Chem* **2017**, 3, 428–436.
- (194) Ling, J.; Laugeois, M.; Michelet, V.; Ratovelomanana-Vidal, V.; Vitale, M. R. *Synlett* **2018**, 29, 928–932.
- (195) Ohishi, Y.; Doi, Y.; Nakanishi, T. *Chem. Pharm. Bull.* **1984**, 32, 4260–4270.
- (196) Tromelin, A.; Demerseman, P.; Royer, R. *Synthesis* **1985**, 1985, 1074–1076.
- (197) Osipov, D. V.; Korzhenko, K. S.; Rashchepkina, D. A.; Artemenko, A. A.; Demidov, O. P.; Shiryaev, V. A.; Osyanin, V. A. *Org. Biomol. Chem.* **2021**, 19, 10156–10168.
- (198) Liu, Y.; Sun, B.; Wang, B.; Wakem, M.; Deng, L. *J. Am. Chem. Soc.* **2009**, 131, 418–419.
- (199) Zhao, J.-Q.; Zhou, X.-J.; Zhou, Y.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2018**, 20, 909–912.
- (200) Han, B.; Li, J.-L.; Ma, C.; Zhang, S.-J.; Chen, Y.-C. *Angew. Chem. Int. Ed.* **2008**, 47, 9971–9974.
- (201) Wang, T.; Luo, J.; Gu, C.; Li, R.; Tang, X.; Yu, D.; Li, J. Preparation Method of One-Class 1,3-Dipole Quinazoline Compound. CN103172575A, June 26, 2013.
- (202) Wang, T.; Shao, A.; Feng, H.; Yang, S.; Gao, M.; Tian, J.; Lei, A. *Tetrahedron* **2015**, 71, 4473–4477.
- (203) Zhang, S.; Tang, A.; Xie, R.; Zhao, Z.; Yao, J.; Miao, M. *Org. Lett.* **2021**, 23, 3701–3705.
- (204) Lill, A. P.; Rödl, C. B.; Steinhilber, D.; Stark, H.; Hofmann, B. *Eur. J. Med. Chem.* **2015**, 89, 503–523.

9 Annexes

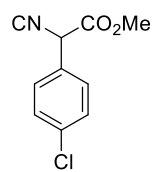
9.1 Isocyanoacetates used throughout this work



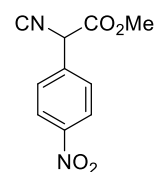
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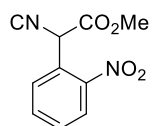
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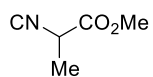
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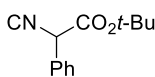
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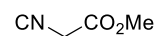
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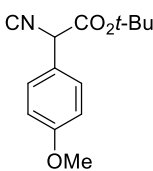
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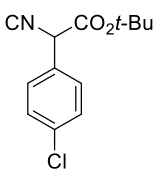
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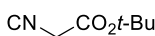
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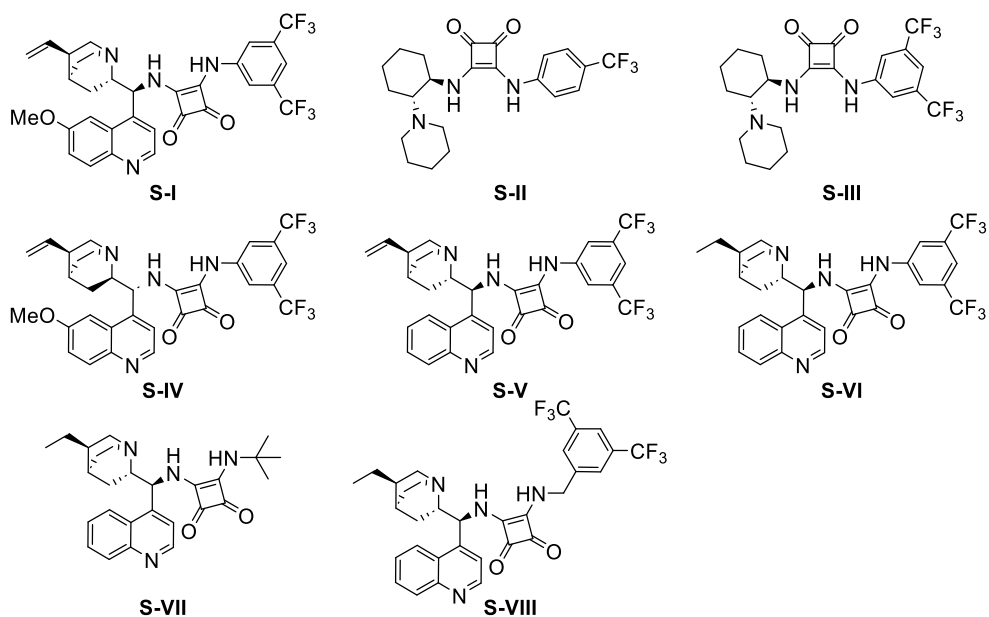
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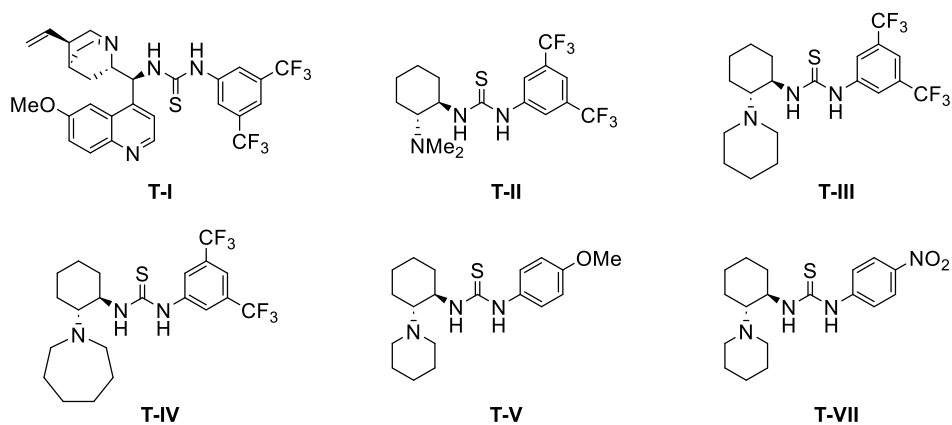
2k

9.2 Organocatalysts used throughout this work

Squaramides



Thioureas



Cupreine and quinine derivatives

