UNIVERSITY OF SALERNO

DEPARTMENT OF CHEMISTRY AND BIOLOGY

Ph. D. Course in "Chemistry" - XXXI Cycle

Ph. D. Thesis in Chemistry

Enantioselective construction of new heterocyclic scaffolds via organocatalyzed cascade reactions

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To my family

ABSTRACT

Chirality plays a vital role in human daily life. After the famous but tragic case regarding the Thalidomide, Food and Drug Administration (FDA) gave a guide in relation to the submission of new drug applications. As a consequence, the use of enantiomeric drugs has hugely been increased and substantial efforts have been done to develop new asymmetric syntheses of chiral drugs. In this context, the goal of this PhD project has been to design, plan and develop new organocatalytic domino methodologies for the synthesis of optically active, densely functionalized, organic molecules. The target products represent notable motifs present in many biologically active natural and non-natural substances. All the processes studied have involved a non-covalent activation of the substrates provided by chiral organic promoters. Catalysts employed are generally able to synergistically activate both the electrophile and the nucleophile through multiple hydrogen-bonding interactions and/or ion-pair formation.

In order to access chiral heterocyclic compounds, the organocatalytic cascade approaches developed allowed us to obtain enantioenriched 3-amino-substituted isoindolinones thanks to an efficient reaction of 2-formylbenzonitriles and primary amines catalyzed by multifunctional Cinchona alkaloid-derivative ammonium salts. Moreover, the use of 2-cyano-*N*-tosylbenzylidenimine led to a new class of multi-heteroatomic cyclic scaffolds containing the important *N,S*-acetal functionality, which afforded 3-thio-substituted isoindolinones by a mild acidic hydrolysis. Furthermore, during this PhD project, a useful one-pot approach to the synthesis of 2-acetylbenzonitriles was developed and these substrates were successfully used as electrophiles in a new tandem methodology for the access to 3,3-disubstituted isoindolinones under very mild conditions. Finally, another objective of this project was the synthesis of novel highly functionalized β-amino acid derivatives, which required the use of easily available Morita-Baylis-Hillman carbonates and 4-substituted isoxazolidin-5-ones.

The work contained within this thesis is partially described in the following publications:

"*Asymmetric tandem hemiaminal-heterocyclization-aza-Mannich reaction of 2-formylbenzonitriles and amines using chiral phase transfer catalysis: an experimental and theoretical study*"
A. Capobianco, A. Di Mola, V. Intintoli, A. Massa, V. Capaccio, L. Roiser, M. Waser, L. Palombi, *RSC Adv*. **2016**, *6*, 31861.

"Organocatalytic Heterocyclization Driven by Dynamic Kinetic Resolution: Enantioselective Access to Multi-heteroatomic Cyclic Structures Mediated by Cinchona Alkaloid-based Catalysts"

V. Capaccio, A. Capobianco, A. Stanzione, G. Pierri, C. Tedesco, A. Di Mola, A. Massa, L. Palombi, *Adv. Synth. Catal.* **2017***, 359,* 2874.

"Synthesis of 2-Acetylbenzonitriles and Their Reactivity in Tandem Reactions with Carbon and Hetero Nucleophiles: Easy Access to 3,3-Disubstituted Isoindolinones"

A. Di Mola, M. Di Martino, V. Capaccio, G. Pierri, L. Palombi, C. Tedesco, A. Massa, *Eur. J. Org. Chem.* **2018**, 1699.

"Asymmetric phase-transfer catalysed β-addition of isoxazolidin-5-ones to MBH carbonates"
V. Capaccio, K. Zielke, A. Eitzinger, A. Massa, L. Palombi, K. Faustc, M. Waser, *Org. Chem. Front.* **2018**, *5*, 3336.

CONTRIBUTION TO CONFERENCES

V. Capaccio, A. Capobianco, L. Palombi, *Merck young Chemists Symposium, Rimini (Italy), 25-27th October*, **2016**. **Flash communication and poster**.

V. Capaccio, L. Palombi, *XXVI Congresso Nazionale della Società Chimica Italiana (SCI), Paestum (IT), 10-14th September,* **2017**. **Poster**.

V. Capaccio, L. Palombi, *XXII International Conference on Organic Synthesis-22-ICOS, 16-21th September*, **2018. Poster.**

RESEARCH STAY ABROAD

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LIST OF ABBREVIATIONS

Ac	acetyl
acac	acetylacetonate
AcOH	Acetic acid
AIBN	2,2'-azobis (2-methylpropionitrile)
Alk	alkyl
aq.	aqueous
BA*	Brønsted Acid
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	tert-buthoxycarbonyl
BPO	dibenzoyl peroxide
br	broad
Bu	butyl
C	concentration
c	cyclic
cat.	catalyst(s)
Cp	cyclopentadienyl
d	days
d	doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	double doublet
ddd	doublet of double doublets
de	diastereoisomeric excess
DFT	density functional theory
diast.	diastereomer
DKR	dynamic kinetic resolution

DMAP	4-(Dimethylamino) pyridine
dmdba	3,5,3′,5′-dimethoxydibenzylideneacetone
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DNA	DeoxyriboNucleic Acid
dr	diastereoisomeric ratio
DTR	dynamic thermodynamic resolution
EDC	N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide
ee	enantiomeric excess
El	electrophile
eq.	equivalent(s)
equiv.	equivalent(s)
er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
FDA	Food and Drug Administration
G	Gibbs energy
H	hydrogen
h	hour(s)
hex	hexyl
HOBt	1-Hydroxybenzotriazole
HOMO	Higher Occupied Molecular Orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Herz
i	iso
IR	infrared spectroscopy
IUPAC	International Union of Pure and Applied Chemistry
KHMDS	hexamethyldisilazane potassium salt
KR	kinetic resolution
LDA	lithium diisopropylamide

LUMO	Lower Unoccupied Molecular Orbital
m	*meta*
m	multiplet
M	molar (concentration)
MALDI	Matrix-assisted laser desorption/ionization
MBH	Morita-Baylis-Hillman
MBHc	Morita-Baylis-Hillman carbonates
*m*CPBA	*meta*-Chloroperbenzoicacid
MCR	Multicomponent reaction
Me	methyl
min	minutes
mp	melting point
MS	mass spectrometry
MS	molecular sieves
MTBE	methyl *tert*-butyl ether
m/z	atomic mass units per charge
NaH	sodium hydride
Naph	naphthyl
n-BuLi	*n*-Butyllithium
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance spectroscopy
NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
o	*ortho*
OC	organocatalysis
p	*para*
PCC	Pyridinium chlorochromate
$Pd(tfa)_2$	Palladium trifluoroacetate
PG	protecting group
Ph	phenyl
PMB	(acetate) *p*-methoxy benzylacetate

Pr	propyl
PTC	Phase Transfer Catalyst/ or catalysis
PTSA	*p*-toluenesulfonic acid
*p*TSOH	*p*-toluenesulfonic acid
q	quartet
rac	racemic
RNA	RiboNucleic Acid
r.t.	room temperature
s	singlet
s	*sec*
SOMO	Singly Occupied Molecular Orbital
S_N	nucleophilic substitution
t	tert
t	time
t	triplet
T	Temperature
TADDOL	α,α,α',α'-tetraaryl-1,3-dioxolan-4,5-dimethanol
TBAB	tetrabutylammonium bromide
TBSCl	*tert*-butyldimethylsilyl chloride
$TEABF_4$	tetraethylammonium tetrafluoroborate
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic Acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TMS	tetramethylsilyl
TMSCl	trimethylsilyl chloride
tol	*p*-tolyl
Tol.	toluene
Ts	*para*-toluenesulfonyl
TS	transition state
TSA	*p*-toluenesulfonic acid

CHAPTER 1

1.1 Chirality and Life

Molecules that are not superimposable with their mirror images and thus exist in two enantiomeric forms are said to be chiral (from the Greek word *cheir*, "hand").[1] The molecular chirality was discovered by Luis Pasteur in 1848[2] when he separated by hand the two isomers of sodium ammonium tartrate. It's very intriguing that the chiral molecules in every life form on Earth exist almost exclusively as single enantiomers and this bizarre phenomenon is known as "homochirality", or single-handedness, and is one of life's greatest mysteries.

"Breaking the mirror"

Several theories are trying to explain this discrepancy in symmetry, "breaking the mirror", from a primordial chemical soup to the origin of life, and shed light on the question of amplification of the enantiomeric excess. Physical or chemical processes are possible, and Pasteur himself hypothesized that molecular chirality in the living world is the product of some universal chiral force or influence in nature.[3] Only in the 1956 an asymmetry in the laws of physics was found with the discovery of parity violation in the weak interaction[4], and one of its consequences is that two enantiomers have a very small energy difference between them. Thus, it was estimated that the difference in energy between the L and D isomers of amino acids could lead to an excess of the L form of about one molecule in 10^{17}. In addition, the circular dichroism, that is a difference in absorption for left and right circularly polarized light, can lead to an disproportion between left and right enantiomeric molecules because in photochemistry the rate of a reaction depends on the amount of light absorbed. Therefore, under circularly polarized light, reaction rates will be different for left and right-handed enantiomers. It was also suggested a possible extraterrestrial origin: chondritic meteor deposits contain small enantiomeric excesses in amino acid, as demonstrated by Pizzarello.[5] Obviously, the next question would be "why is there asymmetry on meteorites?", but that's another story…

Moreover, chiral symmetry breaking could derive from the different solubility of racemates and their corresponding enantiomers.[6] So, during evaporation or mechanical

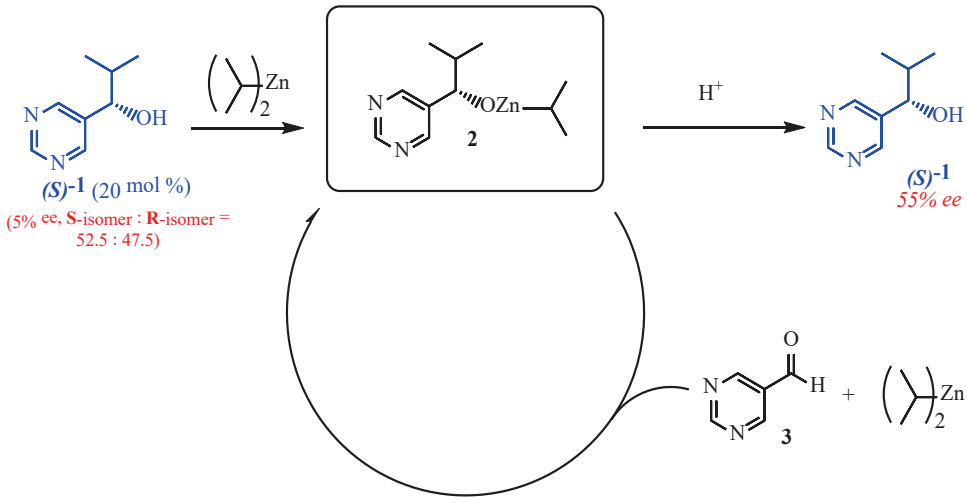
stirring in solution, they display different behaviours in crystallization and lead to a very small enantiomeric excess (*ee*) (that could be amplified upon repeated crystallizations).

"Asymmetric Amplification"

As seen above, physics demonstrates a slight natural discrepancy in symmetry. But now the question is: how is it possible to achieve complete homochirality from a so small *ee*? Of course, some mechanisms to increase any initial imbalance in chirality are necessary. In 1953, Frank[7] developed a mathematical model of autocatalysis for a chemical rationalization of the achievement of high enantioselectivities in organic molecules from a small initial imbalance. The basic idea is very simple: starting from small fluctuations in an initially racemic mixture, a reaction product can act as a catalyst to produce more of itself and at the same time acts to inhibit production of its enantiomer to yield almost exclusively one enantiomeric product. Frank concludes his paper with a challenge to experimental chemists to discover a reaction with this features:

"spontaneous asymmetric synthesis is a natural property of life: a laboratory demonstration is not necessarily impossible".

Only about forty years later, a first asymmetric autocatalytic reaction was found by Soai[8] and coworkers. The authors reported an asymmetric amplification in the autocatalytic alkylation of pyrimidyl aldehydes **3** with dialkylzincs by using 20% of pyrimidyl alcohol **1** (the reaction product) with only 5% *ee* (that is, *S*-isomer : *R*-isomer = 52.5:47.5) (Scheme 1). Pyrimidyl alcohol (*S*)-**1** reacts with an equimolar amount of diisopropylzinc to form *in situ* a dimeric specie of chiral isopropylzinc alkoxide **2**, which catalyses the enantioselective addition of diisopropylzinc to aldehyde **3** to give **2** with increased *ee*.[8,9] After, acid hydrolysis of **2** affords (*S*)-**1** with notable amplified *ee* (the newly formed pyrimidyl alcohol (*S*)-**1** was obtained with a 42% yield and 55% *ee*) (Figure 1).



Scheme 1. *Proposed reaction scheme of Soai reaction.*

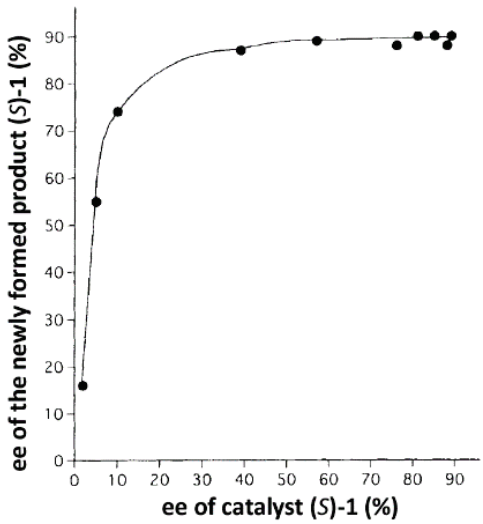


Figure 1. *Relation between the enantiomeric excess (ee) of catalyst (S)-**1** and that of the newly formed product (S)-**1** in asymmetric autocatalytic reaction of (S)-**1**.*

After the discovery of Soai reaction, the same group continued to explore this reaction and shaw an asymmetric amplification by means of circularly polarized light.[10] Moreover, they reported the first example of asymmetric amplification of an organic compound with high enantiomeric excess initiated by inorganic chiral materials such as quartz.[11] Most recently Soai[12] has exploited the very small difference between carbon

isotope ($^{13}C/^{12}C$) chirality to trigger autocatalysis, demonstrating that the reaction needs only an extremely small nudge to high selectivities.

As seen above, the mechanism to generate homochirality can be divided into two steps: the formation of an initial chiral imbalance and its subsequent amplification to homochirality. However, it will take some time to resolve the intriguing matter of the true nature of homochirality, but it seems to be essential for the development of life itself on our planet.

1.2 Chirality and Daily Life

From a molecular point of view, chirality is a geometric property of a particular class of stereoisomers, but it has a very strong repercussion on our daily life regarding the use of chiral bioactive compounds such as pharmaceuticals, agrochemicals or flavours and fragrances. Indeed, the basic components of proteins, enzymes, polysaccharides are chiral and occur in enantiopure form. Thus, biological systems have a chiral environment and enantiomers of a chiral compound can exhibit specific stereoselective interactions due to their three-dimensional structures. This feature is essential for molecular recognition and replication processes. For example, receptors of the smells in the human body react differently with chiral molecules, giving different responses to the brain based on its absolute configurations. In fact, natural L-asparagine is bitter, whereas artificial D-asparagine is sweet (Figure 2).[13]

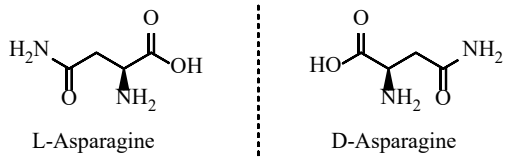


Figure 2. *L and D-Asparagine.*

An even more important aspect is the role of chirality in drug development. In 1894, the famous scientist Emil Fischer introduced the lock-and-key concept to explain the interactions of enzymes and substrates:[14]

"I would like to say that enzyme and glucoside have to fit together like lock and key in order to exert a chemical effect on each other"

Now we know that this model can be extended for example to receptors. Receptor molecules in the body are proteins that show high affinities for the binding of molecules with definite structures. This is totally similar to enzyme-substrate binding.

Obviously, if a chiral drug is directed towards a biological target, the two enantiomers should be recognized as different compounds and thus could have different pharmacological activity. For a chiral drug, the isomer having greater pharmacological activity is called eutomer, the opposite isomer could be less active (distomer), inactive, otherwise, in the worst case, toxic, or have other desired or undesired properties.[15]

A famous but tragic case concerns the Thalidomide (Figure 3).[15] On October 1, 1957, this drug was marketed as a sedative and prescribed for morning sickness treatment during pregnancy. But only after 4 years later thalidomide was associated with serious teratogenic malformations.[16]

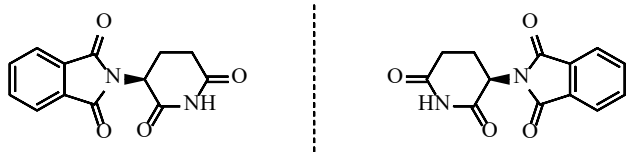


Figure 3. *The two enantiomers of Thalidomide.*

While the *R*-enantiomer of thalidomide (at that time drugs were marketed as racemates. Only natural drugs were sold under single enantiomeric form) has pharmacological activity, the *S*-enantiomer shows teratogenic effects and was responsible for thousands of birth defects and deaths.[17] After these sad events, Food and Drug Administration (FDA) gave a guide in relation to the submission of new drug applications.[18] As a consequence, the use of enantiomeric drugs has hugely been increased[19] and different chiral drug development processes have been developed.

1.1 Asymmetric Synthesis

Enantioselective or asymmetric synthesis is defined IUPAC as: "*a chemical reaction (or reaction sequence) in which one or more new elements of chirality are formed in a substrate molecule and which produces the stereoisomeric (enantiomeric or diastereoisomeric) products in unequal amounts*".[20]

While naturally occurring products or their semi-synthetic variations occur in enantiomerically pure form, compounds from achiral chemical reactions are necessarily present as a racemic mixture. Enantioselective syntheses are difficult to achieve because the reaction path involved must have a diastereoisomeric transition state with different energy (Figure 4, b) leading the formation of one enantiomer over the other.[21]

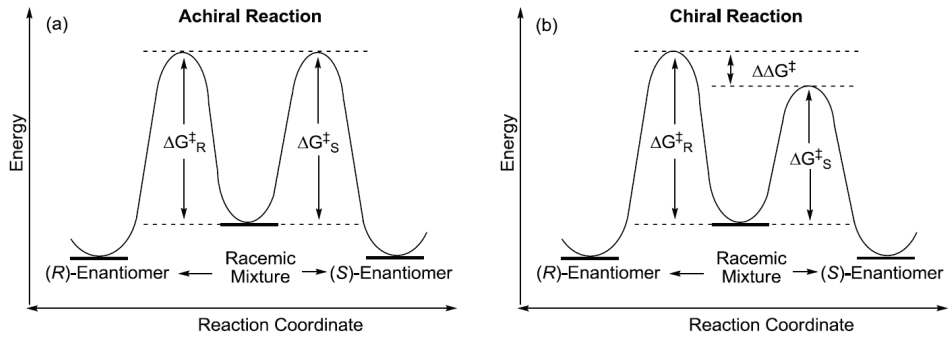


Figure 4. *Energy profiles of (a) non steroselective and (b) stereoselective reaction.*

Thus, a stereoselective reaction needs chiral features in the substrate, reagent, catalyst or environment to make the activation energy required to form one enantiomer lower than that of the opposing enantiomer.[22] This aspect is known as asymmetric induction and is the key element in asymmetric synthesis.[20]

There are several approaches to access to enantiopure or enantioenriched compounds[19,23] and some of these are described below.

1.2.1 Resolution of Racemates

The process of separating a racemic mixture into its enantiomers is called resolution. Nowadays, it is still the most used method, but it is expensive and purification needs a long time. Separation takes place through crystallization of diastereomeric adducts (usually salts) or chromatographic methods (HPLC, high-performance liquid chromatography) using a chiral stationary phase. Another classical approach is the enzymatic or kinetic resolution (KR), a process where the two enantiomers of a racemate **A** and *epi*-**A**, which cannot be interconverted with each other, react at different rates in the presence of an enantiomerically pure reagent or a catalyst ($k_1 = k_{-1} = 0$, $k_2 \neq k_3$) (Figure 5).[24]

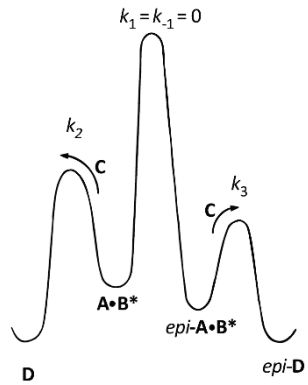


Figure 5. *Energy profile for a kinetic resolution of a racemate.* ***A****, epi-****A*** *= substrate enantiomers;* ***B**** *= a chiral specie;* ***A•B****, epi-****A•B**** *= diasteroisomeric complexes;* ***C*** *= reagent;* ***D****, epi-****D****= enantiomeric products.*

To obtain an efficient kinetic resolution, the reaction rate of one enantiomer has to be much greater than that of the other (e.g., $k_2 >> k_3$), so that it could be possible recover the unreacted enantiomer *epi*-**A** and the highly enantiomerically enriched product **D** of the other enantiomer. However, the main limitation of this technique is exactly that theoretical yield can never exceed the maximum theoretical of 50%, and this is a considerable disadvantage above all for practical applications considering that the unreacted enantiomer have to be separated and discarded (or recycled) and this step may be not easy. Moreover, the enantiomeric excess of the product dramatically decreases

beyond a conversion of 50%.[25] All these limits can be overcome in a process which allows the complete transformation of a racemate into a single stereoisomeric product, that is a Dynamic Kinetic Resolution (DKR). In DKR the substrate is subject to an equilibration or racemization process combined with a kinetic resolution step (Figure 6).

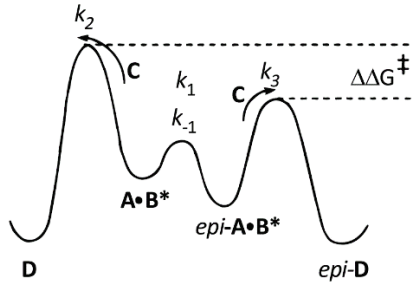
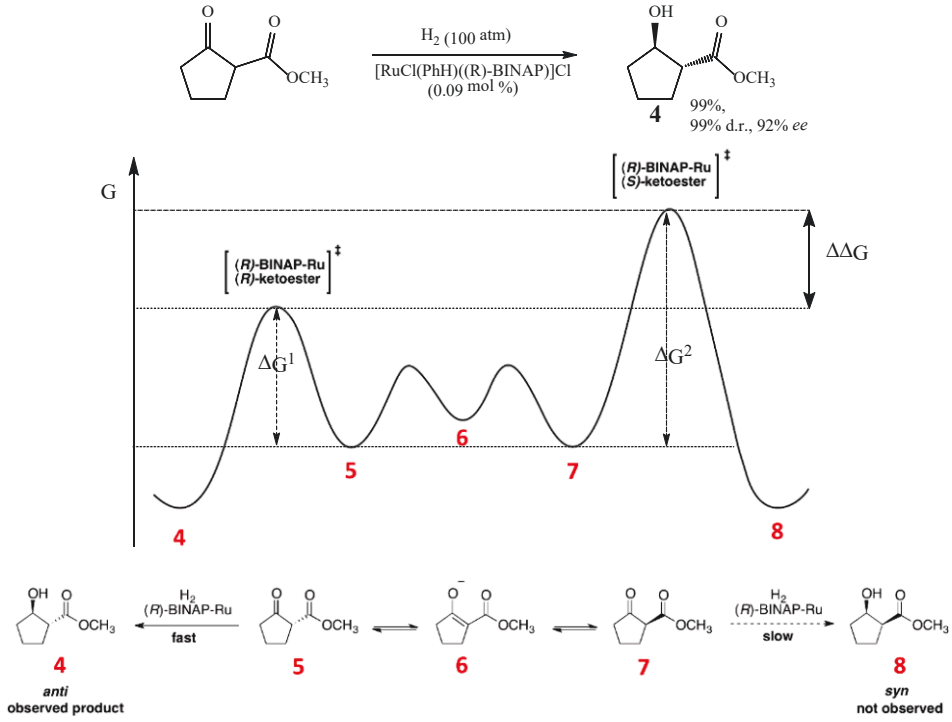


Figure 6**. Energy diagram for a dynamic kinetic resolution of a racemate. **A**, epi-**A** = substrate enantiomers; **B = a chiral specie; **A•B***, epi-**A•B*** = diasteroisomeric complexes; **C** = reagent; **D**, epi-**D**= enantiomeric products.*

If the rate constants for racemization are greater than the rates of substrate transformation (k_1, k_{-1} >> k_2, k_3), a single stereoisomeric product in 100% theoretical yield can be obtained.[26] This kind of resolution follows the Curtin–Hammett principle and product distribution reflects the difference in energy between the diastereomeric transition states of the irreversible derivatization step ($\Delta\Delta G^{\ddagger}$) (Figure 6). Noyori's asymmetric hydrogenation is a classic example of the application of DKR (Scheme 2).[27] In this reaction, the presence of an acidic center in β-keto esters allows for easy epimerization at the chiral center under conditions compatible with (*R*)(BINAP)$RuCl_2$-catalyzed asymmetric hydrogenation. Moreover, the catalytic system selectively reduces the (*R*)-enantiomer of methyl cyclopentanone-2-carboxylate **5**, which is constantly regenerated from the less reactive (*S*)-enantiomer **7** via enolization. As a result, (1*R*,2*R*)-trans-β-hydroxy ester **4** is obtained mainly as a single diastereomer in very high enantioselectivity.



Scheme 2. *Noyori's asymmetric hydrogenation of methyl cyclopentanone-2-carboxylate driven by DKR.*

In a third scenario, called dynamic thermodynamic resolution (DTR), the diastereoisomeric complexes of substrate **A•B*** and *epi*-**A•B*** can interconvert but do not equilibrate in the presence of the reagent **C** (k_1, $k_{-1} \neq 0$, k_2, $k_3 >> k_1$, k_{-1}), as represented in Figure 7.[28]

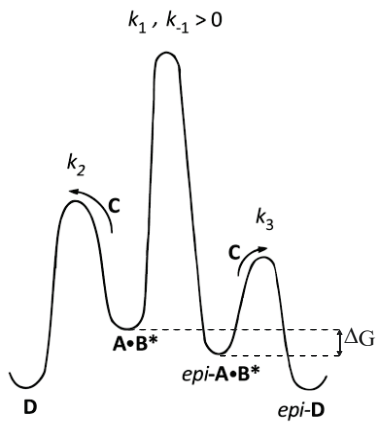
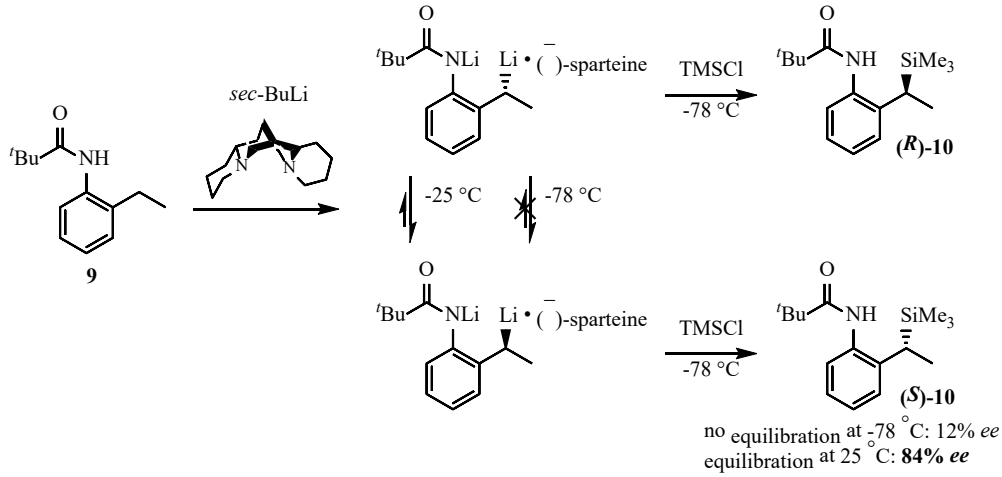


Figure 7. *Energy diagram for a dynamic thermodynamic resolution of a racemate.* ***A****, epi-****A*** *= substrate enantiomers;* ***B**** *= a chiral specie;* ***A•B****, epi-****A•B**** *= diasteroisomeric complexes;* ***C*** *= reagent;* ***D****, epi-****D*** *= enantiomeric products.*

This kind of resolution is a two-stage process: at first, an induced diastereomeric equilibration between the two adducts **A•B*** and *epi*-**A•B*** is established at high temperature; afterwards, lowering the temperature it is locked before the nonequilibrating species react to the enantiomeric products **D** and *epi*-**D**. In contrast to KR and DKR, the rates of stereoisomer interconversion, k_1 and k_{-1}, are smaller than the rates of the successive reaction step, k_2 and k_3, and the difference in the Gibbs free energy, ΔG, of **A•B***/*epi*-**A•B*** determines the final product ratio D/*epi*-D for reactions carried to complete conversion (Figure 7). The most common and successful examples concern electrophilic substitution reactions of organolithium nucleophiles[29]. A representative case is reported by Beak[30] and co-workers in 1997. As illustrated in Scheme 3, *N*-pivaloyl 2-ethylaniline **9** reacts with two equivalents of *sec*-butyllithium to give diastereomeric adducts **10** with (–)-sparteine at -78 °C. At this temperature, these species cannot equilibrate, and the reaction with an excess of trimethylsilyl chloride gives the product with low enantiomeric excess (12%), as a probable consequence of enantiotopic deprotonation of the prochiral substrate by (–)-sparteine. In contrast, high enantioselectivities are achieved by warming the reaction mixture to -25 °C for the time to reach a rapid interconversion and equilibration of the diastereomeric complexes, and then cooling to -78 °C to lock the equilibrium and trap the more populated carbanion with trimethylsilyl chloride. In this way, the product ratio reflects the thermodynamic ratio of diastereoisomeric substrate/ (–)-sparteine complexes and the corresponding (*R*)-silane **10** is afforded in 84% *ee*.



Scheme 3. *Dynamic thermodynamic resolution of N-pivaloyl 2-ethylaniline.*

1.2.2 Chiral Pool

Use of enantiopure building blocks provided by Nature.[31] In most cases, the natural compounds are used "as is" or with only small modifications. These reagents are manipulated through successive reactions to obtain the desired enantiopure product. Nevertheless, this synthetic approach can be very expensive because a stoichiometric amount of a chiral reagent is required and not all the reactions involved give quantitative yield. Moreover, the field of enantiopure compounds derived from natural molecules is limited regard to structure and stereochemistry.

1.2.3 Chiral Auxiliary Approach

Chiral enantiomerically pure compounds temporarily incorporated into the prochiral substrates allowing diastereoselective reactions.[32] This approach is rather unattractive because the chiral auxiliary is used in a stoichiometric amount and additional synthetic steps to append and remove it are required. Moreover, both enantiomers of a chiral auxiliary are usually not readily available and, often, one enantiomer may be far more expensive than the other. However, this strategy gives some advantages such as predictable stereoselectivity and reproducible results and, in some cases, it is the only available way to enter enantiopure products.

1.2.4 Asymmetric Catalysis

Asymmetric catalysis is a type of catalysis in which a small amount of enantiopure catalyst directs the preferred formation of one particular stereoisomer, by being continuously regenerated during the process. While chiral reagents or chiral auxiliaries are used in a stoichiometric amount and are often expensive, chiral catalysts are used in a substoichiometric quantity and not consumed, providing the best “atom economy”.

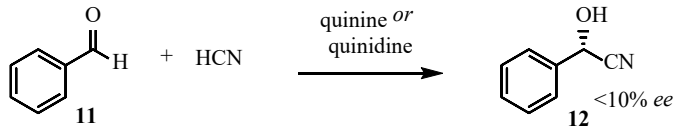
In 2001, the Nobel Prize in Chemistry has been awarded to three scientists: Dr William S. Knowles and Pr. Ryōji Noyori in Japan "*for their work on chirally catalysed hydrogenation reactions*" and Pr. K. Barry Sharpless in the USA "*for his work on chirally catalysed oxidation reactions*".[33]

Nobel Laureates’ pioneering work has inspired many research groups to develop other catalytic asymmetric syntheses. Until about twenty years ago, the enantioselective synthesis of pharmaceutical products, fine chemicals, agrochemicals and synthetic intermediates was based on metal and enzymatic catalysis.[34] Nowadays, the use of small organic molecules as catalysts, the so-called *organocatalysis*, is a relatively new and popular field within the domain of stereoselective synthesis,[35] but, nevertheless, offers many advantages over transition metal and enzymatic catalysis: thanks to the absence of transition metals, the organocatalytic approach is attractive for the pharmaceutical industry when the preparation of compounds does not tolerate metal contamination.[34] Moreover, organocatalysts are usually robust, affordable and readily available, and non-toxic; reactions can be performed under air and, in many cases, can tolerate water, so are easy to perform.

Because of all these features, asymmetric organocatalysis is becoming a powerful synthetic tool in industrial scale processes.[36]

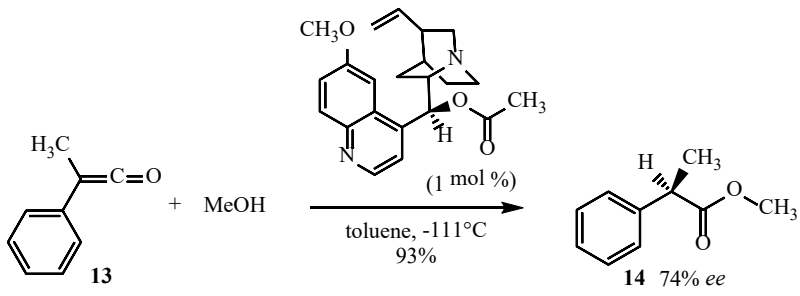
1.2.4.1 Asymmetric Organocatalysis

About 100 years ago, Bredig and Friske reported the first example of an asymmetric organocatalytic approach.[37]



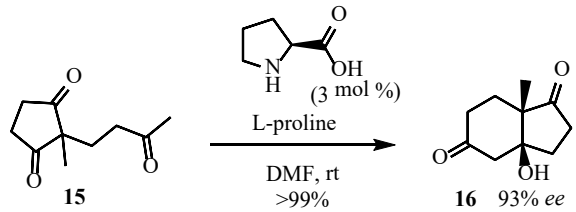
Scheme 4. *Asymmetric addition of HCN to benzaldehyde.*

They found that quinine and quinidine, two pseudoentiomer, accelerate the addition of HCN to benzaldehyde **11** giving chiral cyanohydrins **12** of opposite chirality, but in the range of <10% *ee* (scheme 4). Only after 50 years, Pracejus[38] obtained useful level of enantioselectivity in the addition of methanol to phenylmethylketene **13** using 1 mol % O-acetylquinine as the catalyst (Scheme 5), affording (–)-α-phenylmethylpropionate **14** with 74% of *ee*.



Scheme 5. *Asymmetric addition of methanol to phenylmethylketene **13**.*

Furthermore, in the early 70s, Hajos and Parrish[39] and Eder, Sauer and Wiechert[40] reported the asymmetric version of the Robinson annulation for the synthesis of the Wieland-Miescher ketone **16**, an important intermediate in steroid synthesis. The reaction was catalyzed by a catalytic amount of L-proline to achieve the bicyclic product **16** with 93% *ee* (Scheme 6)



Scheme 6. *The Hajos-Parrish-Eder-Sauer-Wiechert-reaction.*

However, only after two seminal reports by List, Lerner, and Barbas,[41] and MacMillan and co-workers[42] on catalysis by chiral secondary amines that the "organocatalysis gold rush" was triggered.

1.2.4.2 Modes of Activation in Organocatalysis

In the last two decades, asymmetric organocatalysis has become a rapidly growing field and now is one of the main branches of enantioselective synthesis.[35] Many research groups are directing their efforts towards the development of new stereoselective protocols and efficient organocatalysts. In general, organocatalytic methodologies are classified on the basis of the catalyst-substrate interaction as "*covalent"* and "*non-covalent"* catalysis (Figure 8).[19,34,43,44]

In covalent catalysis, the organocatalyst can covalently bind the substrate via imminium ions or via enamine formation, and the energies involved are higher than 15 kcal mol^{-1}. In this category, aminocatalysts[45]and carbenes[46] are included. In non-covalent catalysis, the activation of the substrate by catalyst occurs via *H*-bonding (e.g., thioureas,[47] squaramides[48] and phosphoric acids[49]) or ionic interactions (e.g., chiral bases such as Cinchona alkaloids[50] and phase-transfer catalysts (PTCs)),[51] with energies that usually do not exceed 4 Kcal/mol^{-1}.

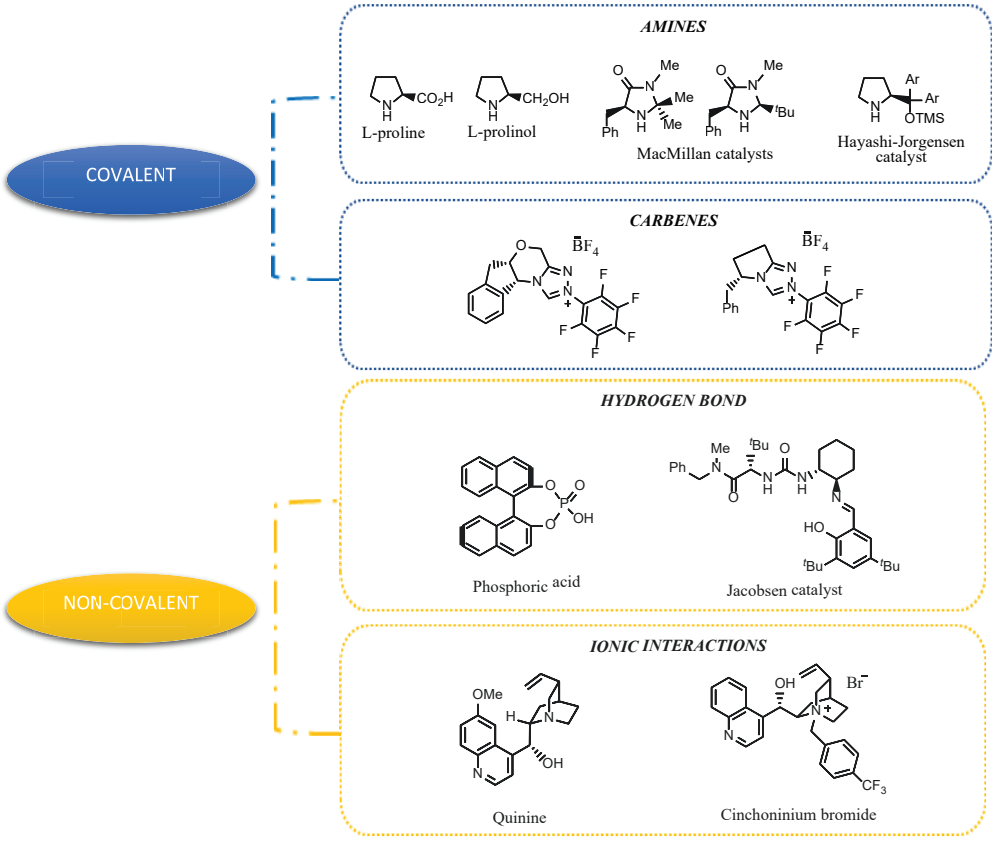
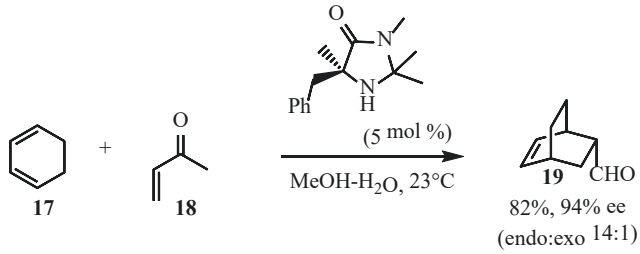


Figure 8. *Classification of Asymmetric Modes of Activation in Organocatalysis.*

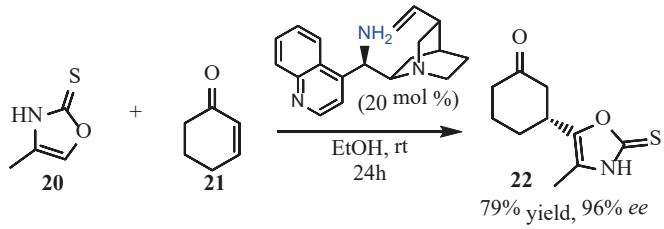
- ***Covalent Catalysis***

Chiral secondary and, to a lesser extent, primary amines are the most used catalysts for this kind of catalysis (e.g., L-proline, MacMillan's imidazolidinones, Cinchona-derived primary amines, etc.). For instance, MacMillan[52] showed that the Diels-Alder reaction of *α,β*-unsaturated aldehydes is efficiently catalyzed by imidazolidinone organocatalyst (Scheme 7).



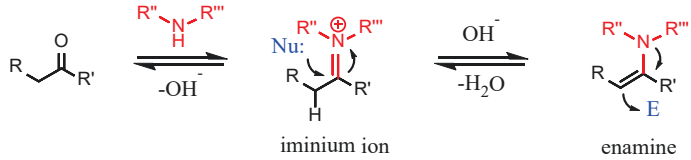
Scheme 7. *The First Highly Enantioselective Organocatalytic Diels-Alder Reaction.*

Furthermore, S. Silva[53] *et al.* have recently reported the asymmetric addition of oxazole-2(3H)-thiones **20** to α,β-unsaturated ketones **21** catalyzed by chiral cinchonine-derived primary amines (Scheme 8).



Scheme 8. *Addition of oxazole-2(3H)-thiones **20** to α,β-unsaturated ketones **21**.*

In this reactions, amine base catalyst activates the substrate to give imminium ions or enamines as intermediates, which are more reactive towards nucleophiles and electrophiles respectively (Scheme 9).



Scheme 9. *Iminium/enamine equilibrium.*

For example, a secondary amine reacts with a ketone or an α,β-unsaturated aldehyde to provide an iminium ion intermediate (Figure 9, intermediate **A**), by lowering the LUMO (Lower Unoccupied Molecular Orbital) energy of the π-system and thus increasing its reactivity toward nucleophiles.

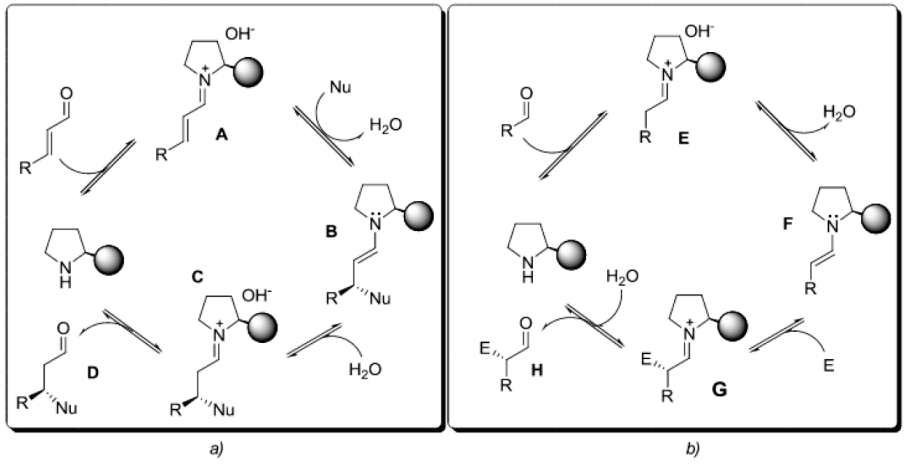
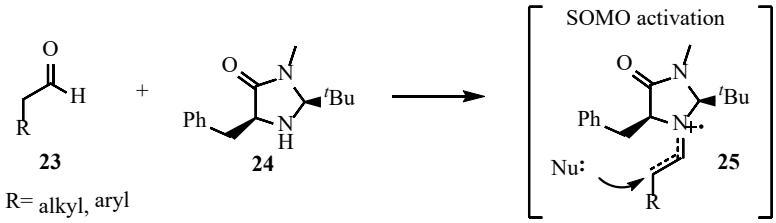


Figure 9. *Catalytic cycle via iminium ion catalysis (a), enamine catalysis (b).*

Instead, for saturated carbonyl systems, the formation of the iminium ion intermediate (Figure 9, intermediate **E**) increases the acidity of the α-proton. The next deprotonation by a base leads to the enamine **F**, whose HOMO (Highest Occupied Molecular Orbital) is enhanced in energy, gaining a more nucleophilic character.

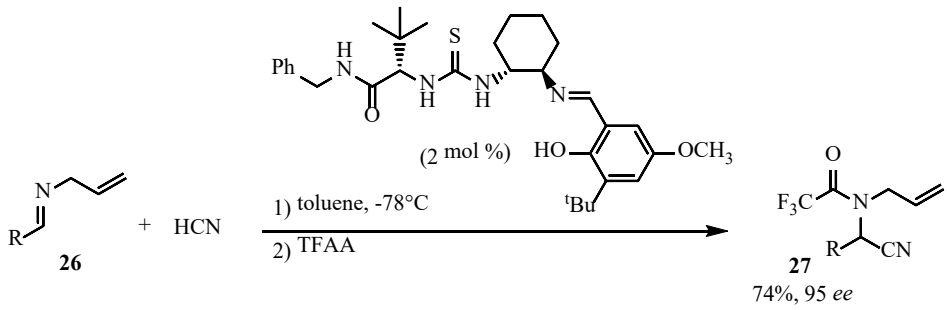
This approach has also been extended to unsaturated carbonyl systems like dienamines,[54] trienamines[55] and tetraenamines.[56] Very recently, MacMillan introduced another type of covalent activation mode, the so-called SOMO (Singly Occupied Molecular Orbital) catalysis (Scheme 10), showing that also radical reactions can achieve reasonable levels of stereocontrol.[57] In this catalysis, electron-rich enamine can undergo one-electron oxidation selectively generating a reactive radical cation with three π-electrons that is activated towards a range of enantioselective catalytic transformations not currently possible using established catalysis concepts.



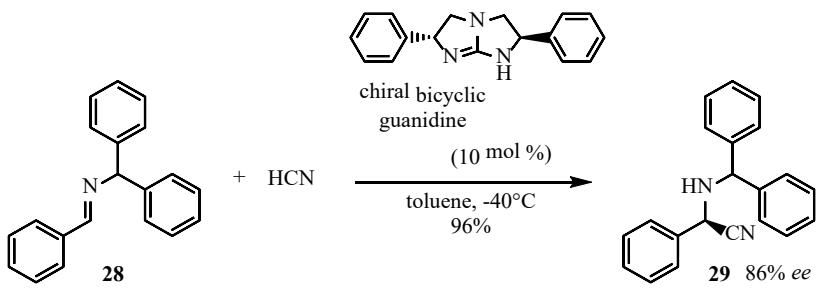
Scheme 10. *SOMO activation.*

- ***Non-covalent catalysis***

This category is characterized by non-covalent interactions (*H*-bonding, ion pair formation, π–π stacking, van der Waals forces) between substrate and catalyst. Up to the years 2000, in asymmetric catalysis the only *H*-bonding interaction was considered insufficient to obtain good enantioselectivity. But thanks to reports published by Jacobsen[58] (Scheme 11) and Corey[59] (Scheme 12), it was demonstrated that chiral thiourea and chiral bicyclic guanidine as catalysts can activate imines in Strecker reaction and allow to obtain high enantioselectivities through a well-defined hydrogen-bonding network.

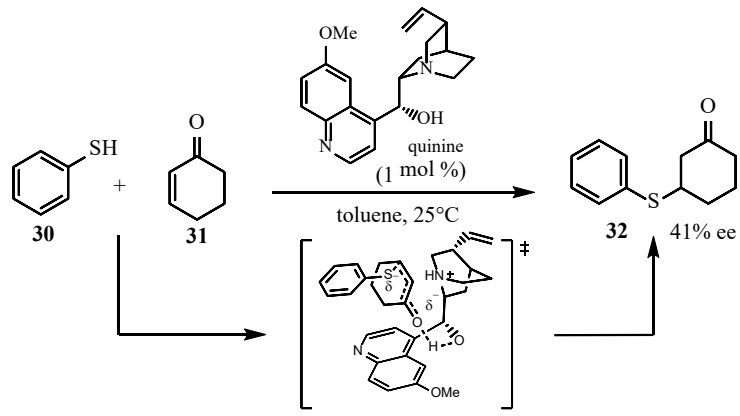


Scheme 11. *Asymmetric Strecker reaction catalyzed by Jacobsen catalyst.*



Scheme 12. *Asymmetric Strecker reaction reported by Corey in 1999.*

Usually, non-covalent interactions are cooperating within the reaction mechanism. For example, Wynberg and Hiemstra[60] reported the addition of aromatic thiols to conjugated cycloalkenones catalyzed by quinine (a Cinchona alkaloid). The mechanistic study of this homogeneous catalytic asymmetric synthesis shows that the reaction proceeds via a tight transition-state complex, involving an electrostatic interaction between the thiol anion and the ammonium cation, a hydrogen bond between the catalyst hydroxyl group and the enone carbonyl group, and a dispersion interaction between the catalyst aromatic ring system and the thiol anion (Scheme 13).



Scheme 13. *Addition of aromatic thiols* ***30*** *to conjugated cycloalkenones* ***31*** *catalyzed by quinine.*

Along with quinine, all the other Cinchona alkaloid derivatives are among the most privileged chiral catalysts in the field of asymmetric organic synthesis because of their large availability and lower cost.[61] In Nature they exist in several pseudoenantiomeric forms such as quinine, quinidine, cinchonine, cinchonidine, and their skeleton is characterized by the presence of the 1,2-aminoalcohol subunit containing the highly basic and bulky quinuclidine, which is mainly responsible for their catalytic activity. Moreover, the secondary 9-hydroxy group can easily be derivatized into ureas, thioureas, amides, and so on; the 6'-methoxy group of quinine and quinidine can also be readily transformed to the free OH group or thiourea moiety and the quinuclidine nitrogen quaternized in ammonium salt for phase-transfer catalysis applications. Thus, because of all these possible active sites, Cinchona alkaloids catalysts can be tunable for diverse types of reactions (Figure 10, 11).

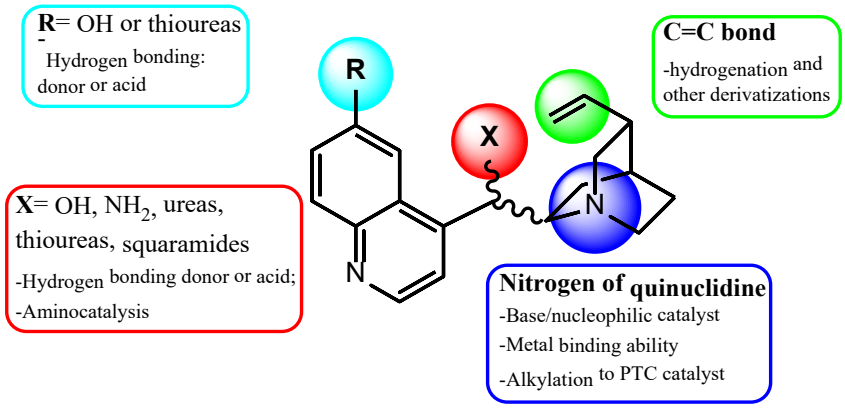


Figure 10. *All possible active sites in Cinchona Alkaloid derivatives.*

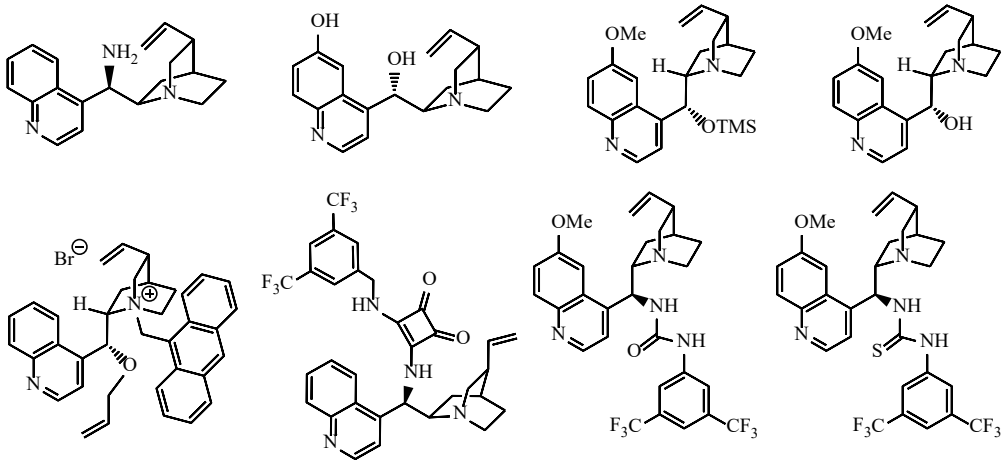
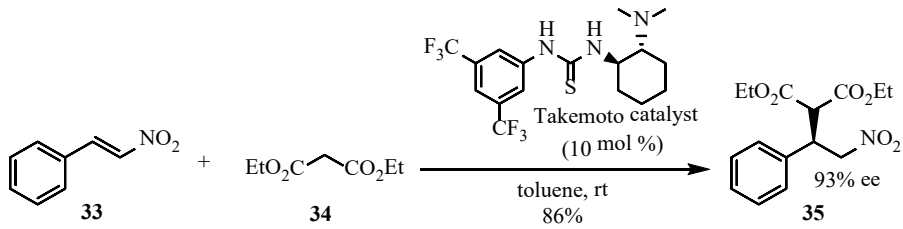


Figure 11. *Representative Cinchona alkaloid catalysts.*

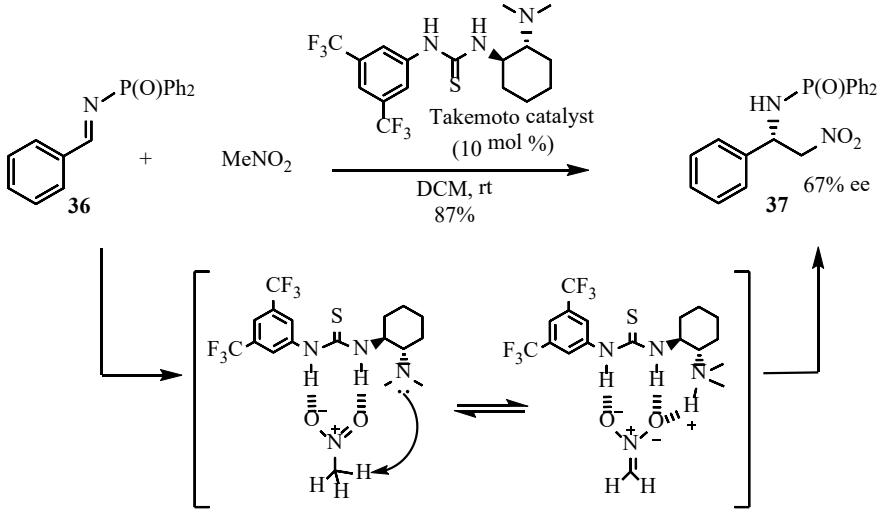
In general, urea, thiourea and, recently, squaramide derivatives represent another privileged class of organocatalysts, often inserted into the skeleton of Cinchona alkaloid compounds (Figure 11). These catalysts can preorganize and activate the reacting partners using cooperative double hydrogen bonds and the tertiary amino group.[62] A first important example of the application of these organocatalysts is reported by Takemoto[63] in 2003 on the enantioselective Michael reaction of malonates to nitroolefins. In this reaction, the nitroolefin **33** and the pro-nucleophile **34** are simultaneously activated by the acidic hydrogens of thiourea and the nucleophile-activating group on the chiral

catalyst (now called Takemoto catalyst), and these synergistic interactions between the functional groups lead to excellent enantioselectivities (Scheme 14).



Scheme 14. *Enantioselective Michael reaction of malonates to nitroolefins.*

Subsequently, the same group[64] reported the first enantioselective aza-Henry reaction catalyzed by a bifunctional organocatalyst. In this approach, the reaction is promoted by synergistic effects of the active groups on the catalyst. The proposed reaction mechanism provides that the thiourea interacts with the nitro group of the nitroolefin enhancing its electrophilicity, and the neighbouring amino group deprotonates the substrate (Scheme 15).



Scheme 15. *The first enantioselective aza-Henry reaction catalyzed by a bifunctional organocatalyst.*

Recently, squaramides has proved to be excellent organocatalysts.[48] Compared to ureas and thioureas, which reveal especially strong anion-binding affinities, these compounds can recognize both anions and cations (Figure 12) by providing a more conformationally

rigid transition state. However, these catalysts show a self-association tendency and so the use of more polar solvents is often required.

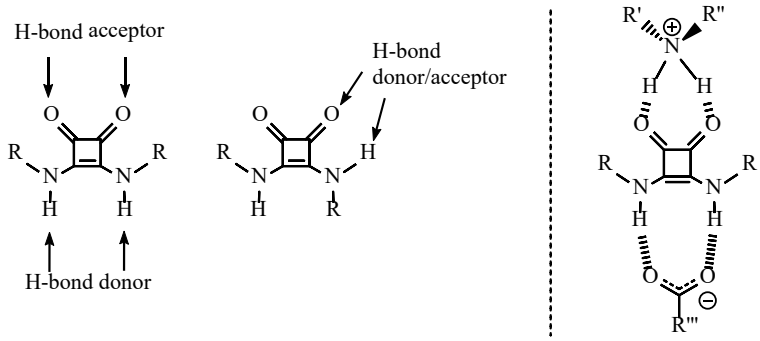
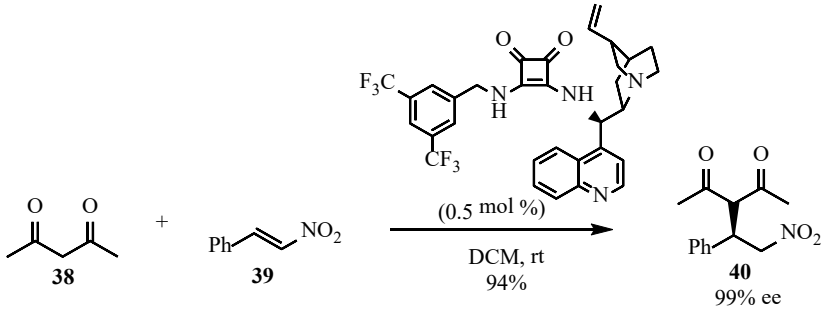


Figure 12. *Squaramides hydrogen bonding networks.*

In 2008, Rawal[65] reported the enantioselective conjugate addition of 2,4-pentanedione **38** to *β*-nitrostyrene **39** using 2 mol % of chiral squaramide Cinchona alkaloid derivative as bifunctional organocatalyst (Scheme 16)



Scheme 16. *The first example of squaramides as bifunctional organocatalyst.*

After this first report, chiral squaramides and their derivatives have been used as organocatalysts in several reactions, e.g in the alfa-hydrazination of 1,3-dicarbonyl compounds with azodicarboxylates,[66] in the enantioselective Michael addition of nitroalkanes to chalcones[67] and in the asymmetric Michael addition of barbituric acids to nitroalkenes.[68] Besides, lately bifunctional organocatalysts having a much stronger Brønsted acid group have been developed. In this case, we talk about specific Brønsted acid catalysis, since proton transfer from the catalyst to the substrate occurs. (*R*)- or (*S*)-BINOL-phosphoric acids are the most used scaffold for this kind of compounds because

aryl or bulky substituents at the 3,3'-positions allow modulating the chiral induction by means of steric and electronic interactions. In addition, the phosphoryl moiety can simultaneously activate both the electrophile and the nucleophile, giving a well-defined transition state (Figure 13).

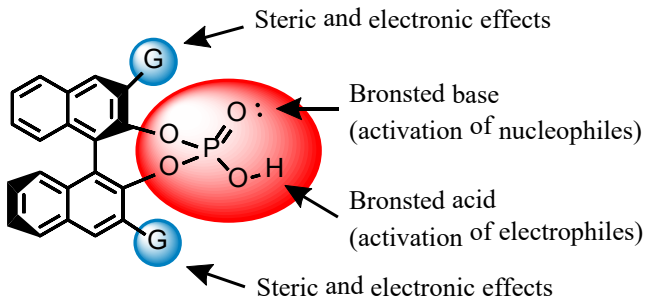
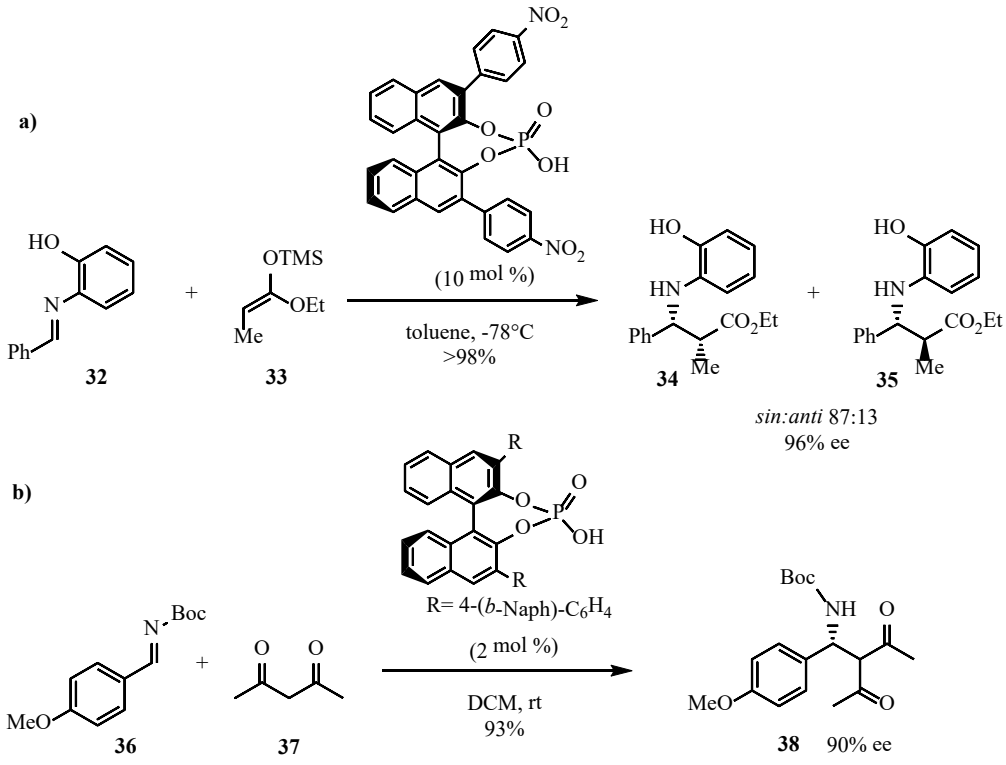


Figure 13. *Key features of chiral phosphoric acids.*

In 2004, Akiyama[69] (Scheme 17, a) and Terada[70] (Scheme 17, b) independently reported the first examples of enantioselective reactions of *N*-aryl and *N*-Boc substituted imines **32** and **36** with silyl ketene acetals **33** and acetylacetone **37**, catalyzed by BINOL derivatives of phosphoric acid.



Scheme 17. *Asymmetric Mannich reaction catalyzed by phosphoric acids. a) reported by Akiyama, b) reported by Terada.*

Finally, I want to describe another important versatile method in non-covalent catalysis, the so-called phase transfer catalysis (PTC). Phase-transfer catalysis is a mechanistically unique non-covalent approach because the phase-transfer catalyst is involved not only in the activation of the substrates but also in a transport phenomenon.[34] This type of organocatalysis was introduced by Starks together with Makosza and Brändström in the late 1960s.[71] Now is a widely applied green methodology in synthetic organic chemistry because of its several advantages. The distinctive benefits of this technique, such as extremely simple protocols and work-ups, mild reaction conditions, the absence of water-sensitive reagents, suitability for large-scale synthesis,[72] make it especially suitable for industrial applications. In phase-transfer catalysis conditions became possible to promote reactions in two-phase immiscible systems since the catalysts are lipophilic species able to facilitate the migration of the anionic reactant from aqueous (liquid-liquid phase-transfer catalysis) or solid phase (solid-liquid phase transfer catalysis) to an organic phase where the reaction with an organic electrophile takes place.

Typically, according to Makosza,[73] reacting anions are generated *in situ* at the interface after deprotonation of a protic precursor by an inorganic base (in the absence of catalyst). Then, the PTC catalyst is involved in the extraction of metal carbanion species from the interface into the organic phase, where it reacts with the electrophile (Figure 14).

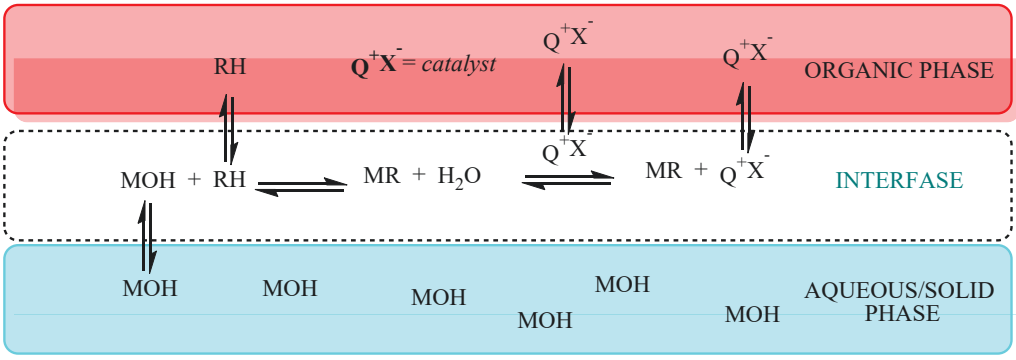
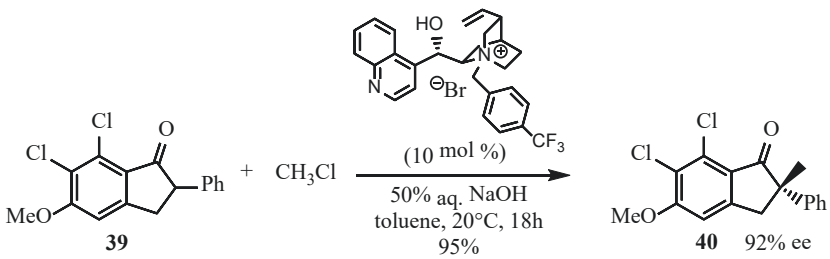


Figure 14. *Proposed mechanism for PTC.*

The most popular chiral phase-transfer catalysts are quaternary onium salts, among them, quaternary ammonium salts are, absolutely, the most broadly studied. The first efficient application was described by researchers at Merk Labs concerning the enantioselective synthesis of (+)-Indacrinone, a potent diuretic, promoted by a Cinchona-alkaloid-derived quaternary ammonium bromide as the chiral phase transfer catalyst (Scheme 18).[74]



Scheme 18. *First example of efficient chiral phase transfer catalysis.*

After this synthetically challenging example of the formation of carbon quaternary stereogenic centre under PTC conditions, there was an enormous progress and development in the design and synthesis of new PTC catalysts.[75]

In Figure 15 are shown some considerable examples of common and new PTC catalysts.

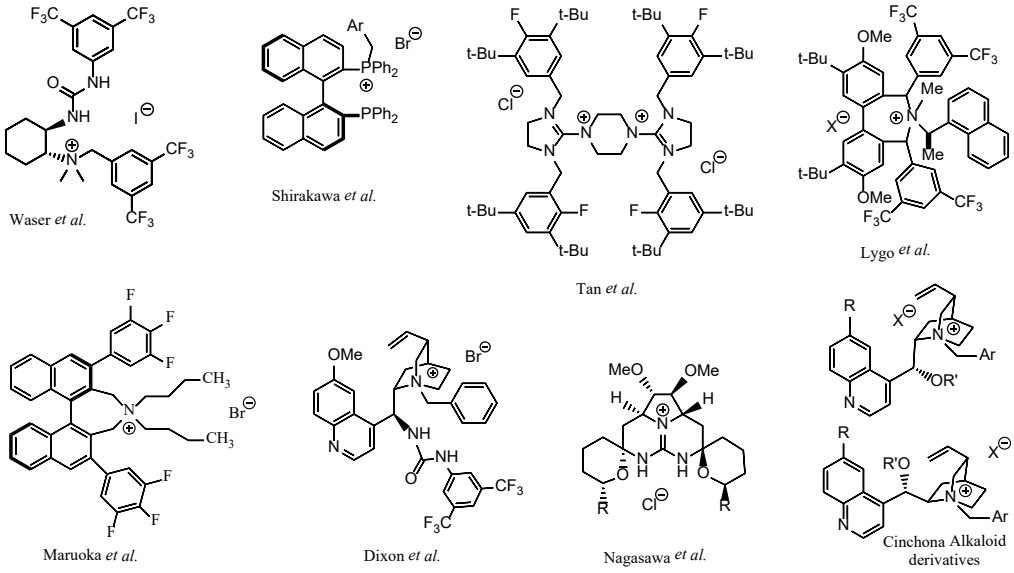


Figure 15. *Representative examples of common and new PTC catalysts.*

CHAPTER 2

OBJECTIVES OF THE THESIS

2.1 Heterocycles

IUPAC defined heterocyclic compounds as "*cyclic compounds having as ring members atoms of at least two different elements*",[76] The most common heteroatoms are nitrogen, oxygen and sulphur[77] but heterocyclic rings containing other heteroatoms are also well known.[78] Heterocyclic compounds are widely present in Nature and are fundamental for the development of life as we know it. Indeed, pyrimidine and purine basis of genetic material DNA and RNA are heterocycles, amino acids like proline, histidine and tryptophan contain a heterocyclic ring, such as chlorophyll and haemoglobin, the oxygen carriers in plants and animals, the vitamins and coenzymes precursors such as thiamine, riboflavin, pyridoxine, folic acid, biotin, B12 and E families of the vitamins and many more.[79]

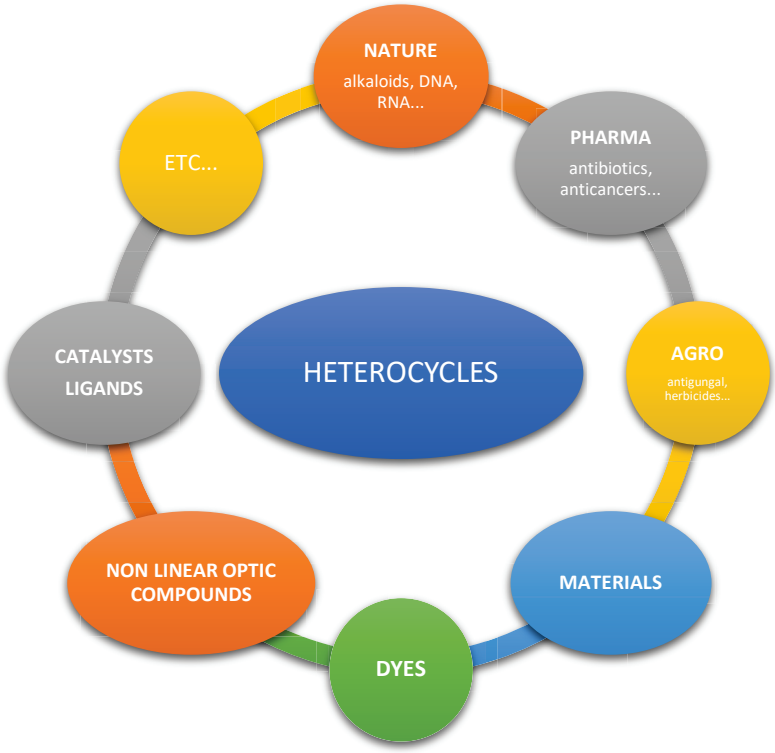


Figure 16. *Heterocycles and their applications.*

Most of the heterocycles are used in materials science as dyestuffs, fluorescent sensors, brightening agents, and in polymer chemistry, especially in conjugated polymers.[79a] They are also used in organic synthesis as protecting groups, chiral auxiliaries, organo-catalysts, and metal ligands;[80] they have a considerable active role as agrochemicals and veterinary products and find applications as sensitizers, developers, antioxidants, as corrosion inhibitors, as copolymers and dyestuff.[81] But, the main application is in the pharmaceutical industry. Indeed, many heterocycles are key scaffolds in anti-bacterial,[82] anti-viral,[83] anti-fungal,[84] anti-inflammatory,[85] and anti-tumour drugs[86] (Figure 17).

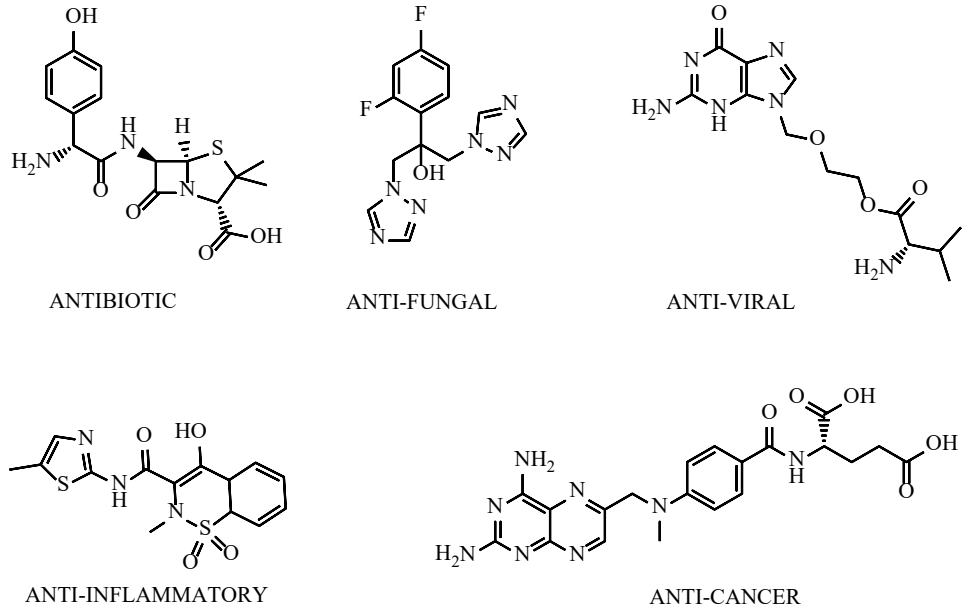
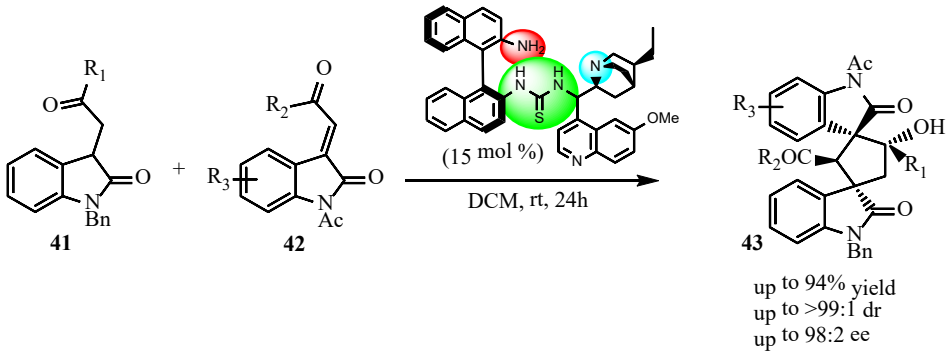


Figure 17. *Some biological active heterocyclic compound.*

Given the importance of this class of compounds, the aim of this PhD project has been the enantioselective construction of new heterocyclic scaffolds via organocatalyzed cascade reactions.

2.2 Organocatalyzed Domino reactions

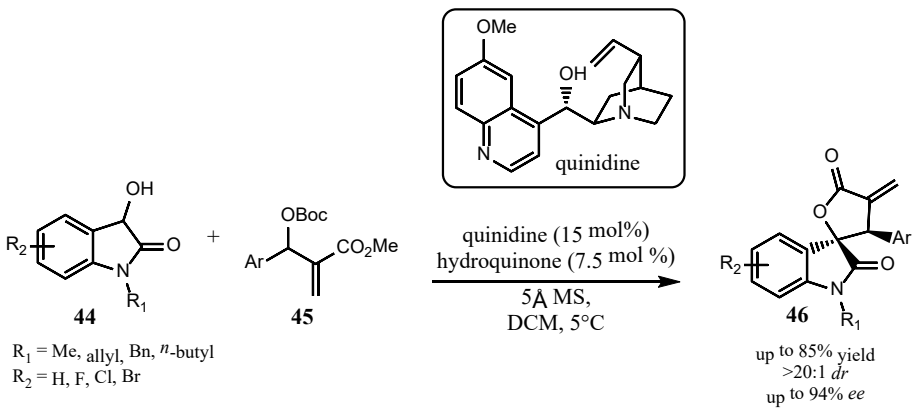
One of the big benefits of this approach over classical synthesis is the rapid construction of complex molecular scaffolds, often in very high stereoselectivities, avoiding time-consuming and protection/deprotection steps as well as the purification of intermediates, because at least two reactions are run in a single operation under the same reaction conditions.[87] In general, the chemical community uses *tandem reaction, cascade reaction* and *domino reaction* as synonyms. In particular, however, Tietze defined a *domino reaction* as "*a process involving two or more bond-forming transformations (usually C-C bonds) which take place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step",*[88] while reactions that involve *"individual transformations of independent functionalities in one molecule, also forming several bonds under the same reaction conditions, are not classified as domino reactions".*[89] Later, Fogg and dos Santos denominated a domino reaction and a tandem in accordance to the mechanism involved and the role of the catalyst: a domino reaction refers to consecutive transformations with the same mechanism, while in tandem processes each step is characterized by different mechanisms. Moreover, both domino and tandem approcaches are one-pot processes in which the catalyst is present from the beginning.[90] Again, a subclass of domino reactions involving at least three substrates is usually referred to as multicomponent reactions (MCRs). MCRs are chemical transformations leading products that include in their structures considerable portions of all the reactants.[91] Ugi reaction,[92] Biginelli reaction,[93] Passerini reaction,[94] Mannich reaction[95] are only a few beautiful examples of MCRs. In recent years, asymmetric organocatalysis has proved to be a powerful tool to carry out cascade transformations. An impressive proof that shows all the potential of this approach is reported by Carlos F. Barbas III[96] in 2011 for the synthesis of bispirooxindoles **43**, containing three quaternary stereocentres. In this beautiful reaction, the enantioselective challenging construction of multiple quaternary carbon stereocentres is accomplished by using a multifunctional organocatalyst that contains tertiary and primary amines and thiourea moieties to activate substrates simultaneously (Scheme 19).



Scheme 19. *Asymmetric synthesis of bispirooxindoles* ***43****.*

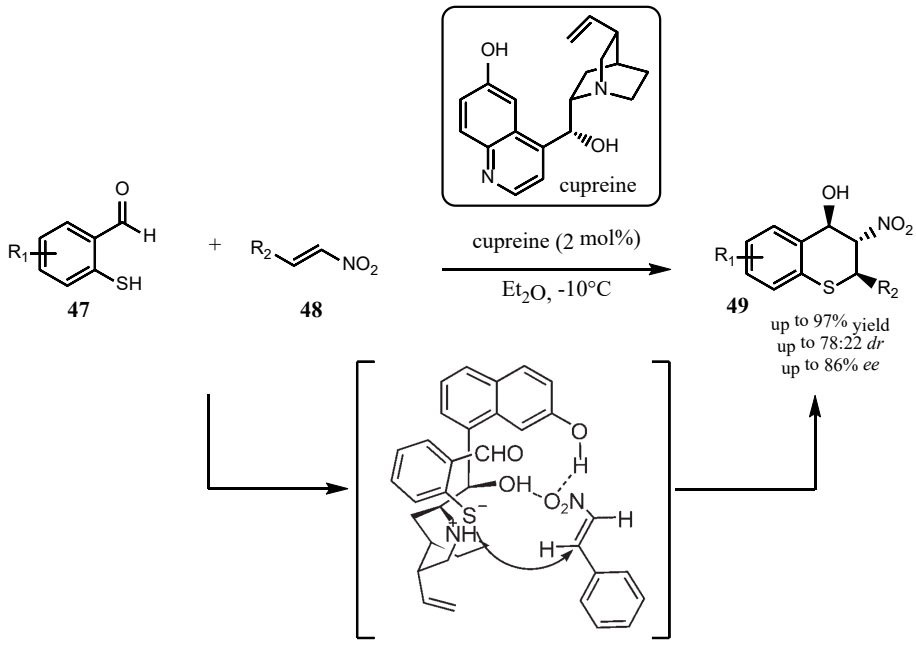
This organocatalytic asymmetric domino Michael-aldol reaction between 3-substituted oxindoles **41** and methyleneindolinones **42** provides facile access to a range of multisubstituted bispirocyclooxindole derivatives **43** with high enantio- and diastereo purity, in one step.

Another relevant example of organocatalyzed domino reaction for the synthesis of heterocycles is described by Wang[97] and co-workers, who developed the first asymmetric allylic alkylation-cyclization of 3-hydroxyoxindoles **44** with Morita-Baylis-Hillman carbonates (MBHc) **45** (Scheme 20). The use of quinidine as organocatalyst led to highly functionalized spirooxindoles **46** bearing α-methylene-γ-butyrolactone motifs in good yields and with excellent diastereo- and enantioselectivities.



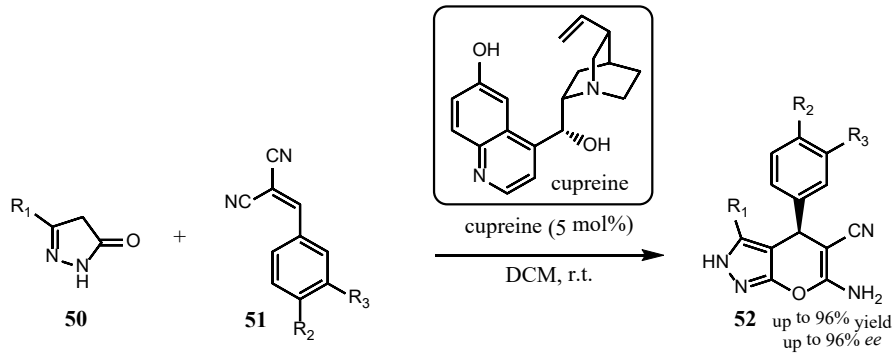
Scheme 20*. Allylic alkylation-cyclization of Morita-Baylis-Hillman carbonates* ***45*** *and 3-hydroxyoxindoles* ***44****.*

In 2007, Zhao[98] and co-workers studied a new synthesis of chiral 2-aryl-3-nitrothiochroman-4-ols **49** by using an organocatalyzed tandem Michael addition-Henry reaction between 2-mercaptobenzaldehydes **47** and β-nitrostyrenes **48** (Scheme 21). In this case the asymmetric induction is ensured thanks to two hydrogen bonds between hydroxy groups of the curpreine and the nitro group of reagent **48** (Scheme 21).



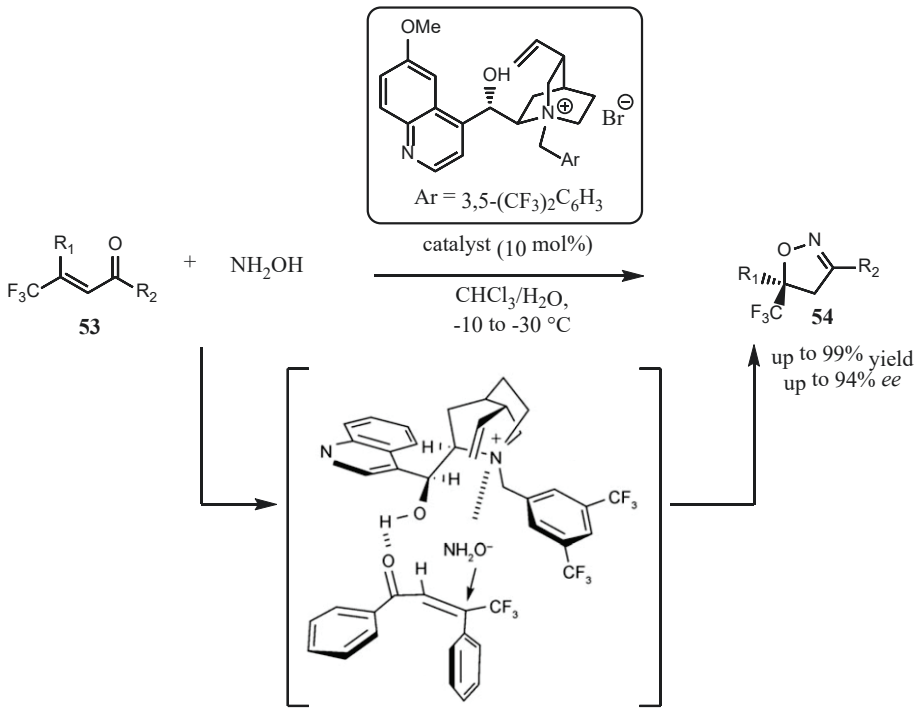
Scheme 21. *Enantioselective tandem Michael–Henry reaction of 2-mercaptobenzaldehydes **47** with β-nitrostyrenes **48**.*

Furthermore, the same author[99] described the first enantioselective synthesis of biologically active 6-amino-5-cyanodihydropyrano[2,3-c]pyrazoles **52** through a Cinchona alkaloid-catalyzed domino Michael-Thorpe-Ziegler-type reaction between 2-pyrazolin-5-ones **50** and benzylidenemalononitriles **51** (Scheme 22). Even in this process, cupreine proved to be the most efficient catalyst, affording the product in excellent yields with mediocre to excellent enantioselectivities.



Scheme 22. *Enantioselective synthesis of pyranopyrazoles* ***52****.*

Instead, Shibata[100] *et al*. disclosed a protocol to achieve a wide range of 5-trifluoromethyl-2-isoxazoline N-oxides **54** by a domino Michael-cyclization-dehydration reaction of hydroxylamine with a range of (*E*)-trifluoromethylated enone derivatives **53** under phase-transfer catalysis conditions. *N*-3,5-bis(trifluoromethylbenzyl) quinidinium bromide, in combination with CsOH as base, provided a series of trifluoromethyl-substituted 2-isoxazolines **54** in high yields and enantioselectivities up to 94% *ee* (Scheme 23). Moreover, the authors proposed a transition state model that affords product **54** in which cooperative interactions between catalyst and substrates are involved. In particular, the free hydroxy group in catalyst captures the prochiral substrate **53** and hydroxylamine anion is associated with the nitrogen cation of the catalyst through a very strong ionic interaction, providing the stereocontrol of the reaction (Scheme 23).



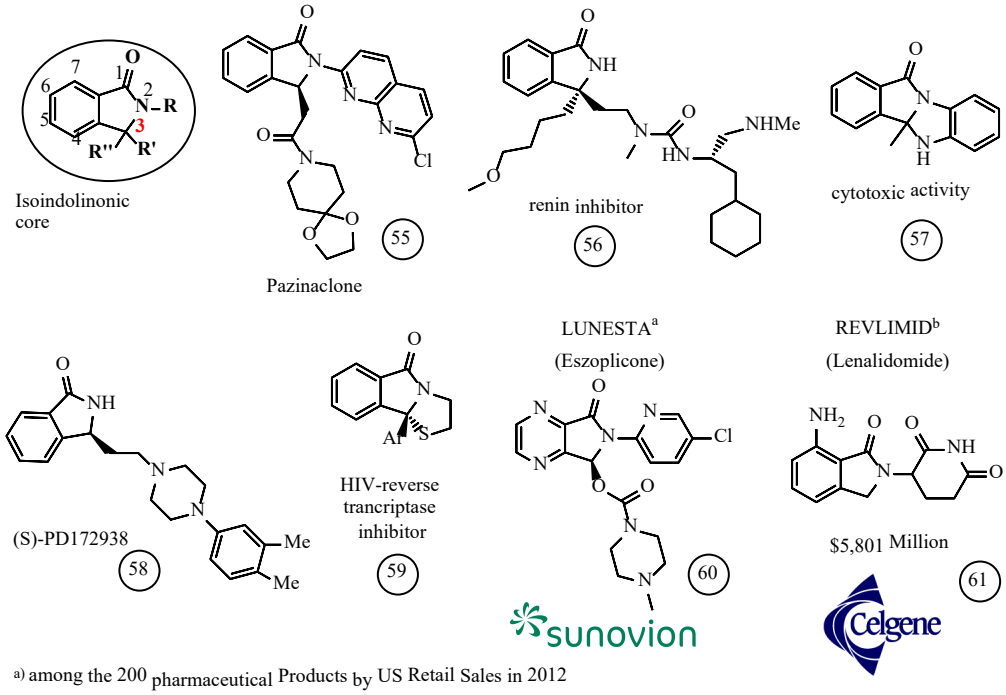
Scheme 23. *Enantioselective synthesis of trifluoromethyl-substituted 2-isoxazolines* ***54*** *by an asymmetric hydroxylamine/enone tandem reaction.*

Taking into account the notable advantages of domino reactions and organocatalytic approach, we decided to develop new organocatalyzed domino strategies for the asymmetric synthesis and derivatization of important heterocycles like isoindolinones and isoxazolidinones, structural motifs found in many biologically active natural products and drug candidates.

CHAPTER 3: THE FIRST ASYMMETRIC SYNTHESIS OF 3-AMINO-SUBSTITUTED ISOINDOLINONES

3.1 Introduction

An important class of heterocyclic compounds is that of isoindolinones. These compounds are found in many natural[101] and pharmaceutical products and show a range of biological activities, such as antiviral,[102] antileukemic,[103] antihypertensive,[104] anxiolytic[105] properties (Figure 18).



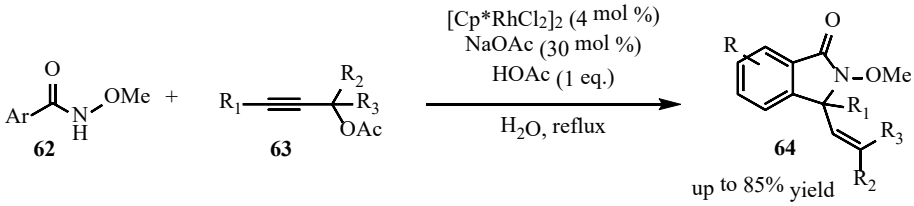
[a] among the 200 pharmaceutical Products by US Retail Sales in 2012
[b] among the 200 pharmaceutical Products by US Retail Sales in 2015

Figure 18. *Biologically active compounds containing isoindolinone nucleus.*

For example, Pazinaclone (**55**) is a non-benzodiazepine anxiolytic compound, belonging to the cyclopyrrolone or isoindolinone family, with relatively mild sedative effects, since it is a partial agonist of the GABA-A receptor;[106] the compound **58**, known as PD172938, is a potent dopamine D4 ligand[107]; Lenalidomide (**61**), marketed by Celgene under the brand-name Revlimid, is efficient against haematological disorders and also used in the treatment for multiple myeloma;[108] some 3-hetero-substituted isoindolinones are

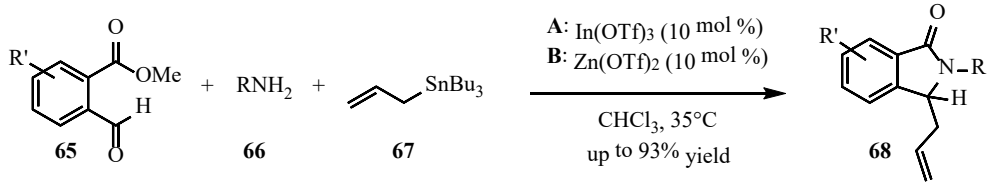
important drugs: Eszopiclone (**60**), marketed by Sunovion under the brand-name Lunesta, is a nonbenzodiazepine hypnotic agent used in the treatment of insomnia and one of the most sold drugs in 2012;[109] the benzoimidazo isoindolone **57** shows cytotoxic activity;[110] the 3-thiosubstituted isoindolinone **59** is an HIV-reverse transcriptase inhibitor.[111]

Given their significance in medicinal chemistry, substantial attention has been paid to the accomplishment of these scaffolds and their related structures, both as racemic and chiral products. Recently, Ma[112] *et al*. introduced a synthesis of isoindolin-1-ones Rhodium-catalyzed (Scheme 24).



Scheme 24. *Synthesis of isoindolin-1-ones* ***64****.*

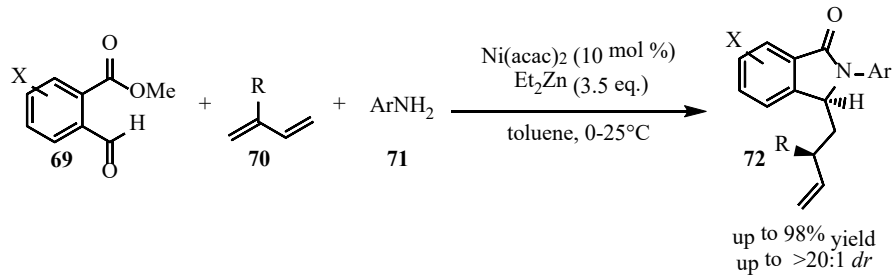
The process involves a reaction between *N*-substituted benzamides **62** and 2-alkynylic acetates **63** via a transition-metal-catalyzed C−H activation/allene formation/cyclization pathway with an excellent regioselectivity. Water was used as the solvent, and potentially useful functional groups such as Br, CO_2Me, and CF_3 were well tolerated. In 2014, Singh[113] *et al*. reported a practical approach to isoindolinones **68** using a Lewis acid catalyzed one-pot three-component allylation-lactamization cascade reaction of *o*-formyl methyl benzoates **65** with primary amines **66** and allyltributylstannane **67** (Scheme 25).



Scheme 25. *Practical approach to isoindolinones* ***68****.*

A variety of primary aromatic amines **66** were tolerated and 10 mol % of Zinc triflate or Indium triflate was used as catalyst in chloroform at 35°C to achieve different substituted

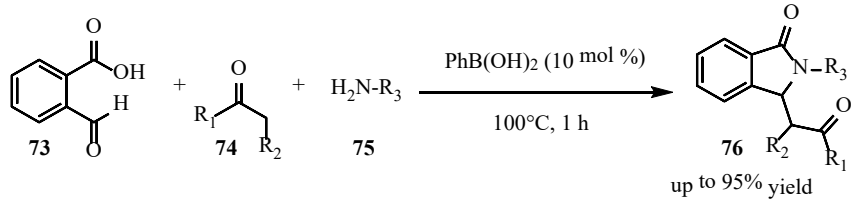
substrates **68**. Again, the same group[114] described an efficient route to isoindolinones **72** via a domino Ni-catalyzed homoallylation/lactamization from *in situ* prepared imines, derived from *o*-formyl benzoates **69**, with conjugated dienes **70** promoted by diethylzinc (Scheme 26).



Scheme 26. *Synthesis of isoindolinones **72** via a domino Ni-catalyzed homoallylation/lactamization.*

The reaction proceeds at room temperature for a variety of aldehydes **69**, amines **71**, and dienes **70**, affording the 1,3-syn product **72** in high regio- and stereoselectivity. Moreover, substrates with an electron-donating and -withdrawing functionality are tolerated, and the reaction can be performed on a gram scale.

Instead, Ordóñez[115] *et al.* illustrated a one-pot synthesis of 3-substituted isoindoline-1-ones **76** under solvent-free conditions (Scheme 27).

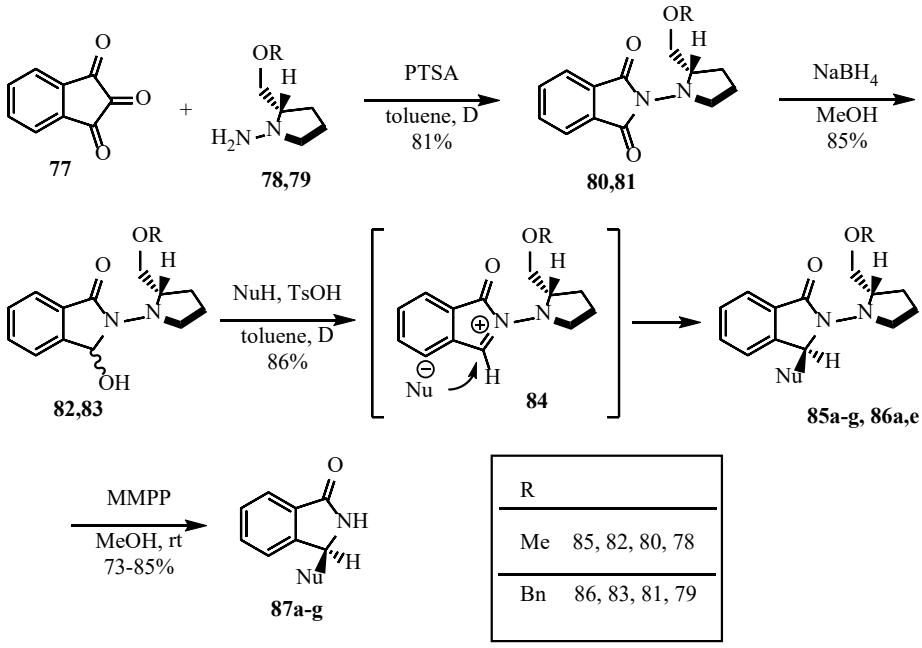


Scheme 27. *Synthesis of 3-substituted isoindoline-1-ones **76** under solvent-free conditions.*

This strategy involves the sequential two-step Mannich/lactamization cascade reaction of 2-formylbenzoic acid **73** with primary amines **75** and a wide variety of ketones **74**, under solvent free-conditions using phenylboronic acid as catalyst.

Regarding the stereoselective approach, the first asymmetric synthesis of isoindolinones was reported by Allin[116] in 1999, and then a relatively high number of methodologies have been developed.[117] Some of that involves the use of chiral auxiliaries. For example,

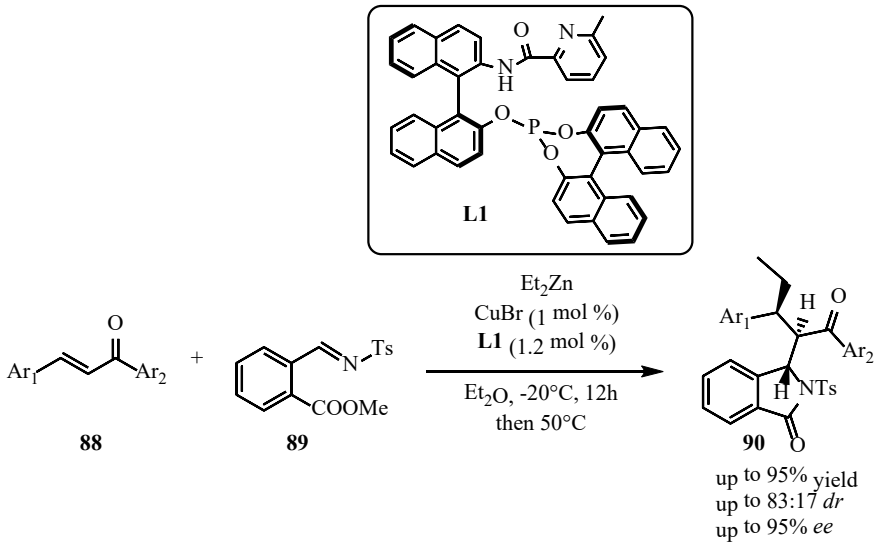
Deniau[110] *et al.* studied the asymmetric synthesis of 3-hetero-substituted 2,3-dihydro-1*H*-isoindol-1-ones **87** (Scheme 28).



Scheme 28. *Synthesis of 3-heterosubstituted isoindolinones **87**.*

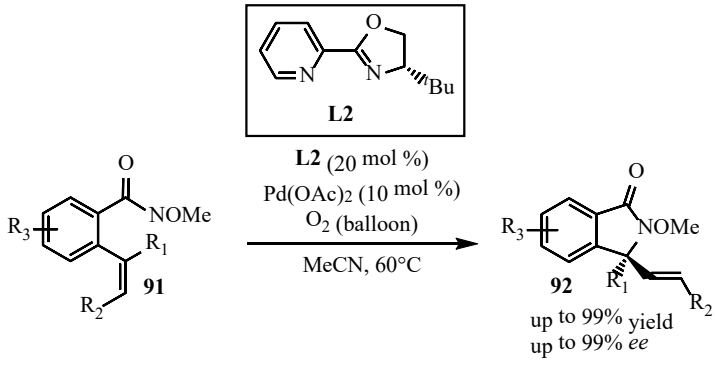
This synthetic route requires the use of the enantiopure phthalhydrazides **80** and **81**, obtained by condensation between phthalic anhydride **77** and (*S*)-1-amino-2-methoxy and 2-benzyloxymethylpyrrolidine **78** and **79**, respectively. Then, the imides **80** and **81** are reduced with sodium borohydride to provide the hemiaminals **82** and **83** that, under acidic conditions, react with an array of hetero-nucleophiles (N, S, P) to afford the 3-hetero-substituted compounds **85** and **86**. Finally, the cleavage of the chiral auxiliary brings to the target enantioenriched isoindolinones **87**.

A stereoselective transition-metal catalyzed reaction was introduced by Huang[118] *et al.*. They exploited a copper-catalyzed tandem conjugate addition/Mannich reaction of diethylzinc reagent and acyclic α,β-unsaturated ketones **88** in the presence of imines **89** to afford chiral isoindolinones **90** (Scheme 29). In this process, the catalytic species is generated *in situ* and the authors found that the stereoselectivity was significantly affected by the nature of the counterion of the copper salts. The best results were obtained using CuBr and the chiral ligand **L1**.



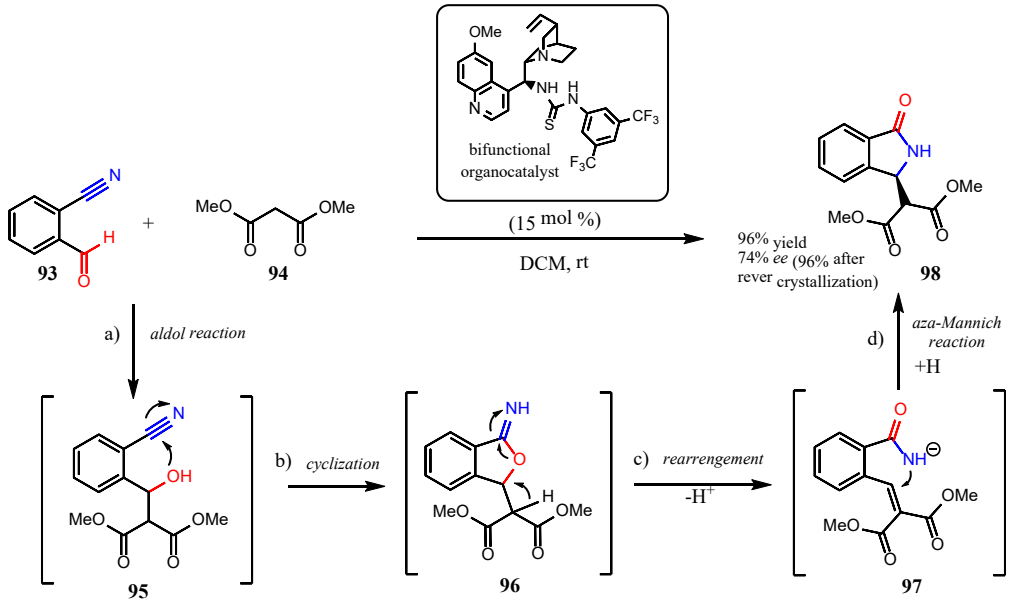
Scheme 29. *Access to isoindolinones* ***90*** *by a transition-metal catalyzed reaction.*

Besides, in 2012 Zhang[119] *et al*. developed an intramolecular aerobic aza-Wacker-type cyclization for the preparation of isoindolinones **92** bearing tetrasubstituted carbon centres (Scheme 30). The highest level of enantioselectivity was achieved using chiral pyridine-oxazoline ligand **L2** and $Pd(OAc)_2$ as the palladium source. Acetonitrile was the best solvent for this reaction, due to its small size and its ability to coordinate strongly through its nitrogen atom.



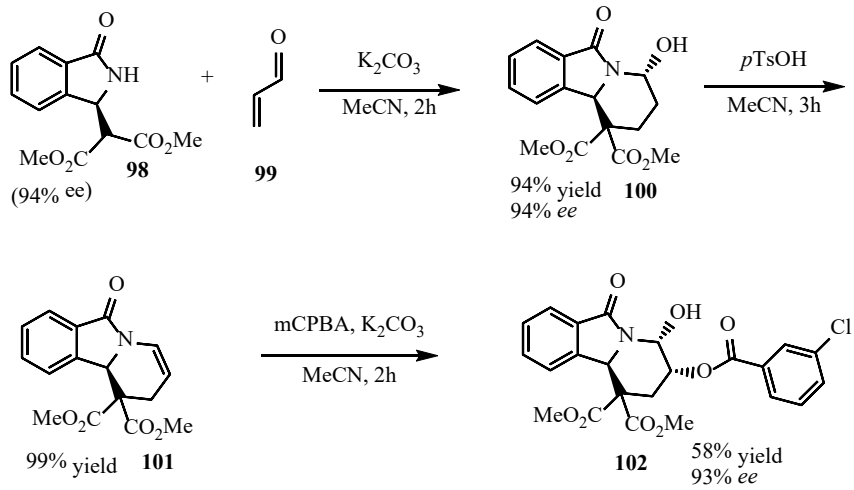
Scheme 30. *Stereoselective synthesis of tetrasubstituted isoindolinones* ***92****.*

In the last years, important organocatalytic methodologies have been also reported.[120] Especially, in 2012 Massa[120c] *et al.* developed in our laboratories an asymmetric organocatalytic cascade reaction for the synthesis of 3-substituted isoindolinones **98** employing 2-formyl benzaldehydes **93** and active methylene compounds **94** (Scheme 31). The reaction is catalyzed by a bifunctional tertiary amine derived from the quinine and bearing a thiourea moiety and, from the mechanistic point of view, takes place through an aldol addition (step **a**), a cyclization via entrapping of the -OH at the 2-cyano group to give the imidate intermediate **96** (step **b**), a rearrangement (step **c**), and an intramolecular aza-Michael reaction (step **d**) to afford the isoindolinonic product **98** in high yields and with enantiomeric excesses from moderate to good (up to 86% *ee*). Then, an efficient process of reverse crystallization led to a further enrichment up to 96% *ee*, in good overall yields (up to 70%).



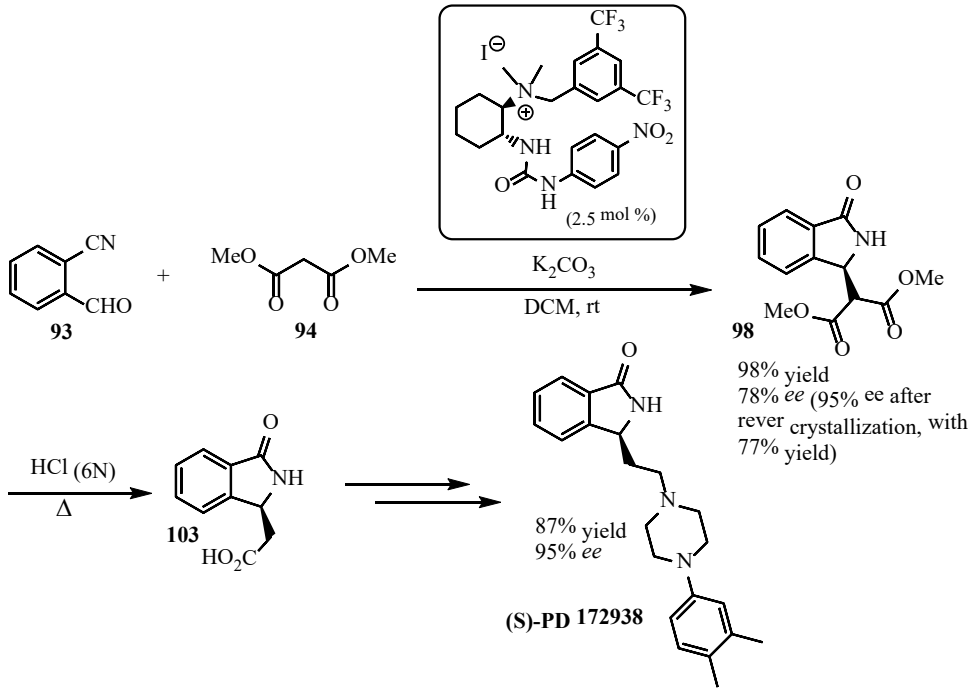
Scheme 31. *Massa approach to chiral 3-substituted isondolinones **98** via bifunctional catalyst.*

Moreover, the obtained enantioenriched isoindolinone **98** can be used as a nucleophile in a further Michael/cyclization cascade transformation with the acrolein **99**, affording fused benzoindolizidinones **100**,**101**,**102** in high yields and unchanged enantiomeric purity (Scheme 32).[117c]



Scheme 32. *Derivatization of isoindolinone* ***98*** *to fused benzoindolizidinones* ***100***, ***101*** *and* ***102***.

Afterwards, this tandem process was exploited under PTC conditions. A new bifunctional chiral ammonium salt was used at 2.5 mol % in combination with potassium carbonate and a high *ee* of **98** (95%) and good yield (77%) were achieved scaling up the reaction to 2 mmol scale. Then, the product was transformed by decarboxylation with HCl 6M into isoindolinone acetic acid **103** used as a key intermediate in the total synthesis of medicinally important isoindolinones such as **(*S*)-PD172938** (Scheme 33).[117b]



Scheme 33. *Massa approach to chiral 3-substituted isondolinones* ***98*** *via phase transfer catalyst.*

Again, recently, our group focused on the synthesis of *N*-Mannich bases of 1-isoindolinones (Figure 19), an important class of products useful in drug synthesis, as well as ligands for catalytic purposes.[121]

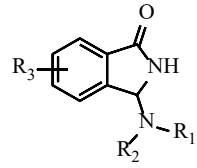
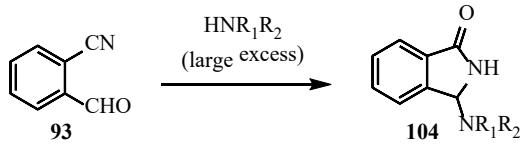


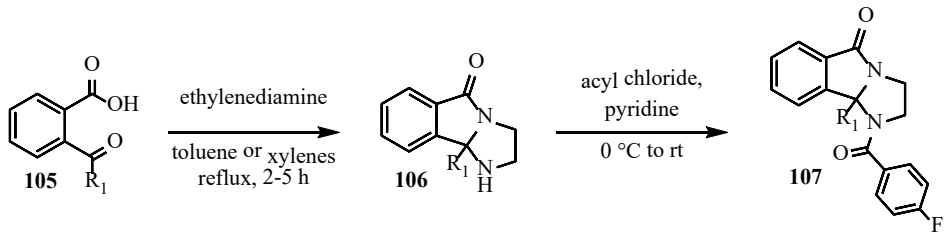
Figure 19. *N-Mannich bases of 1-isoindolinones.*

Despite their potential, in literature there are only a few synthetic examples: the pioneering study by Sato[122] which showed the access to compounds **104** by reaction of 2-cyanobenzaldehyde **93** with a large excess of amines (Scheme 34);



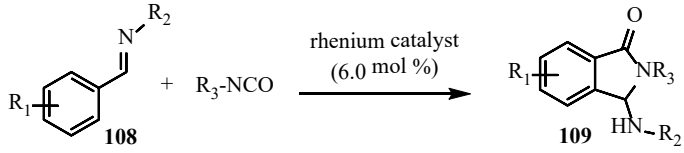
Scheme 34. *Sato's synthesis of 3-amino-substituted isoindolinones* ***104****.*

Bond[123] *et al*. reported the reaction between keto acid compounds **105** with an excess of ethylenediamine in refluxing toluene or xylenes to give cores **106**, and the next acylation affordes the target compounds **107** (Scheme 35);



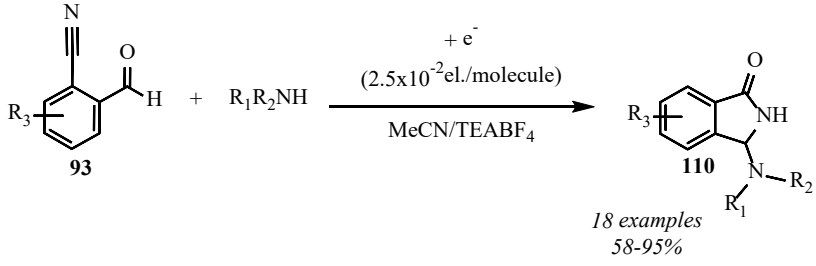
Scheme 35. *Bond's approach to 3-amino-substituted isoindolinones* ***106*** *and* ***107****.*

again, Kuninobu[124] *et al.* proposed a different route using a Rhenium catalyst in the reaction between aldimines **108** and isocyanates (Scheme 36).



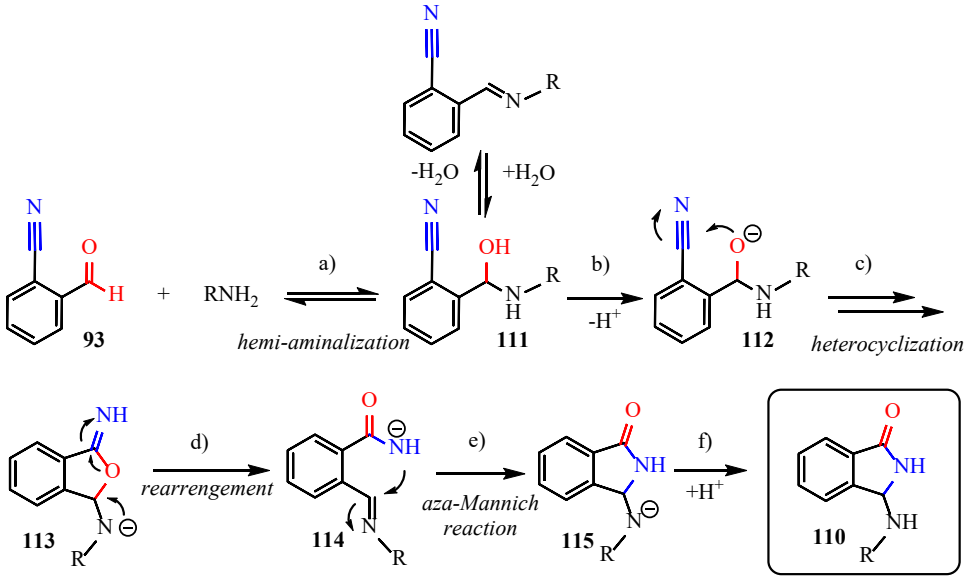
Scheme 36. *Kuninobu's approach to 3-amino-substituted isoindolinones* ***109****.*

Recently, based on Sato's paper, Palombi[125] *et al*. described in our laboratories a quick and easy access to *N*-Mannich bases of 1-isoindolinones **110** by catalytic electroactivation of primary and secondary amines (Scheme 37).



Scheme 37. *Electrochemical catalyzed the synthesis of 3-amino-substituted isoindolinones* ***110****.*

Furthermore, the isoindolinonic product **110** can be also obtained by treatment of the reactants with a stoichiometric amount of K_2CO_3 in acetonitrile. In this case, we can hypothesize a reaction pathway which involves, after the spontaneous hemiaminalization of 2-cyanobenzaldehyde **93** with a primary amine (step **a)**, the deprotonation of the hemiaminal intermediate **111** (step **b**) by the potassium carbonate, and the subsequent tandem heterocyclization-rearrangement-intramolecular aza-Mannich reaction (step **c**, **d**, **e**, **f**) affording 3-amino-substituted isoindolinone **110** (Scheme 38).



Scheme 38. *Reaction pathway for the reaction of 2-formybenzonitriles and primary amines.*

With this data in hand, I started my doctoral project to design an asymmetric approach for the synthesis of 3-amino-substituted isoindolinones by an organocatalytic tandem process between 2-formylbenzonitriles and benzylamines.

3.2 Results and discussion

Taking into account the good results obtained in the reaction of 2-formylbenzonitrile and dimethyl malonate[117b] (Scheme 33), the investigation started using PTC conditions. In a first attempt, benzylamine **116a** and *o*-cyanobenzaldehyde **93a** were reacted in the presence of potassium carbonate, using the ammonium salts listed in Figure 20. According to the data in Table 1, catalyst **IV** gave the best performances in term of selectivity (56% *ee*, entry 15). Many of bifunctional catalyst with an *H*-bonding donor (**II**, **IV**, **VI**, **VII**, **VIII**) showed a better catalytic activity in terms of conversion and reaction times compared to the monofunctional ammonium salts (**III**, **V**), which involved only the ion pair interaction. Furthermore, as the group on the ammonium side becomes bulkier (i.e. 9-anthracenylmethyl group), the degree of asymmetric induction becomes higher (entries 8,15: **IV** vs **VI**; entries 13,14: **VII** vs **VIII)**. Unfortunately, dimeric Cinchona ammonium salts **XVIII** and **XIX** gave very low selectivities, too.

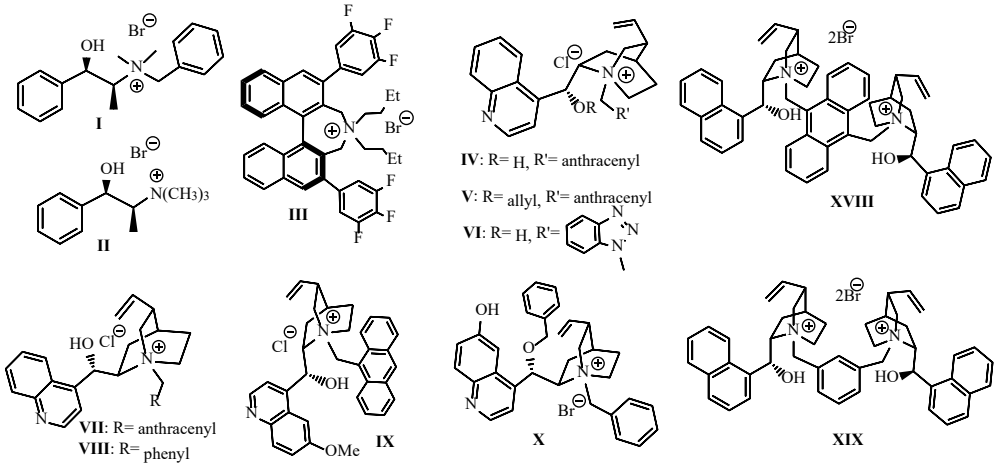
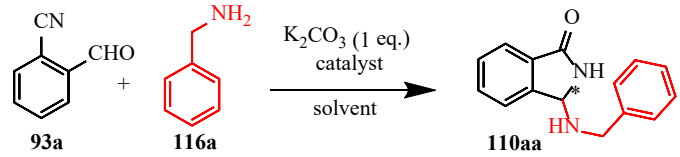


Figure 20. *First screening of chiral ammonium salts tested.*

Table **1**. Tandem reaction of **93a** with **116a** under PTC conditions: initial screening of the common catalysts listed in Figure 20.

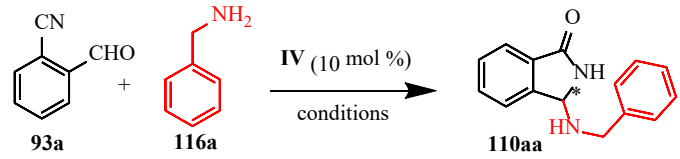


Entry	Cat. (mol %)	Solv.	C (mM)	T (°C)	Time (h)	Yield (%)[a]	*er*[b]
1	**I** (10)	DCM	100	r.t.	3	88	55/45
2	**II** (10)	DCM	100	r.t.	3	88	56/46
3	**IV** (10)	DCM	100	r.t.	3	96	57/43
4	**V** (10)	DCM	100	r.t.	32	71	57/43
5	**X** (10)	DCM	100	r.t.	18	75	51/49
6	**IX** (10)	DCM	100	r.t.	18	85	60/40
7	**VI** (10)	toluene	50	r.t.	1	65	56/44
8	**VI** (10)	toluene	50	-20	3	92	60/40
9	**III** (10)	toluene	50	r.t.	18	92	40/60
10	**IV** (10)	toluene	50	r.t.	1	86	65/35
11	**IV** (5)	toluene	50	r.t.	1	54	72/28
12	**IV** (5)	xylene	50	-20	15	81	64/36
13	**VII** (10)	toluene	50	-20	8	92	32/68
14	**VIII** (10)	toluene	50	-20	18	90	60/40
15	**IV (10)**	**toluene**	**50**	**-20**	**8**	**86**	**78/22**
16	**XVIII** (10)	DCM	100	r.t.	23	67	55/45
17	**XIX** (10)	DCM	100	r.t.	20	74	47/53

[a] Yields refer to isolated products. [b] e.r. determined by HPLC using a chiral stationary phase.

With data so far collected in hand, we investigated the influence of the temperature, base, different biphasic conditions and concentration of the reactants, using the best performing catalyst **IV**. As shown in entry 4 of Table 2, the best enantiomeric excess (56%) was achieved at -20°C using 1 equivalent of potassium carbonate. A lower temperature and a stronger base like potassium hydroxide decreased the selectivity (entries 10,11), as well as, biphasic liquid-liquid conditions (entry 7).

Table **2**. Tandem reaction of **93a** with **116a** with **IV** under different conditions.



93a **116a** **110aa**

Entry	Base (1 eq.)	C (mM)	T (°C)	Time (h)	Yield (%)[a]	*er*[b]
1	K_2CO_3	50	r.t.	1	70	65/35
2	K_2CO_3	50	r.t.	8	71	65/35
3	K_2CO_3	50	-10	3	86	66/34
4	**K_2CO_3**	**50**	**-20**	**8**	**86**	**78/22 (99/1)[c]**
5	K_2CO_3	50	-40	24	84	66/34
6	K_2CO_3	50	-20	8	88	73/27
7[d]	K_2CO_3	50	-20	1	96	70/30
8	Cs_2CO_3	50	-20	4	96	65/35
9	LiOH	50	-20	21	80	74/26
10	KOH	50	-20	0.5	50	62/38
11[e]	KOH	50	-20	0.5	59	67/33
12[f,g]	-	50	20	1	75	58/42
13[f,g]	-	50	-20	72	-	-
14[g,h]	-	20	-20	1	90	57/53
15[g,i]	-	50	-20	1	66	60/40

[a] Yields refer to isolated products. [b] *er* determined on HPLC equipped with a chiral column. [c] In parenthesis e.r. after reverse crystallization. [d] K_2CO_3 has been added as aqueous solution 0.9 M. [e] Catalyst loading 20% mol. [f] Base-free reaction under biphasic conditions (Toluene/H_2O). [g] Toluene/H_2O ratio 1/30. [h] Toluene/H_2O ratio 1/2. [i] Toluene/H_2O ratio 1/20.

At this point, based on the modest enantioselectivity achieved, we considered introducing other hydrogen bonding groups on the catalyst (Figure 21) to get better results, since the multipoint interaction of the catalyst with the substrates could lead to a geometrically well-organized and rigid transition state and improve the stereoselectivity.[51,126,127]

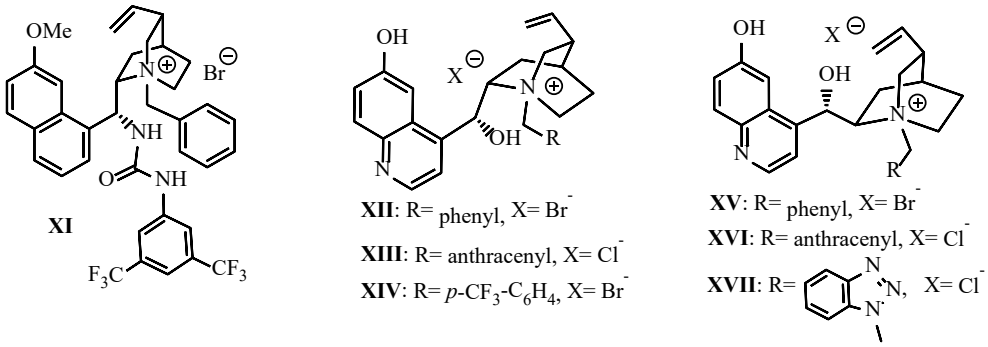
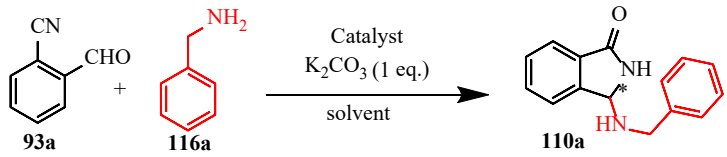


Figure 21. *Multiple H-bonding donors containing chiral ammonium salts.*

So, we started a new screening with Dixon's ammonium salt **XI** and Cinchona alkaloid salts **XII-XVII**, bearing an additional free -OH functionality at C-6' on the quinoline ring. While catalyst **XI** was poorly stereoselective (Table 3, entry 1), catalyst **XII** was identified as the best performing catalyst for this reaction, in DCM at room temperature (entry 15) yielding the product with 86% *ee* (up to 98% after reverse crystallization). Moreover, by comparing data with catalysts **IX** and **X** (Table 1, entries 5,6), it is clear that the structural key-features of the catalyst to obtain high selectivities is to have both the -OH free groups, while different bulky substituents on nitrogen atom of the quinuclidine moiety gave comparable results (Table 3, entries 3,12,13 and 15,16,17). Noteworthy, we can choose the configuration of the product by changing catalyst, because the pseudo-enantiomeric catalysts **XII** and **XV** allowed an inversion of enantioselectivity (Table 3, entries 15 vs 3).

Table **3**. Screening of the catalysts listed in Figure 21.

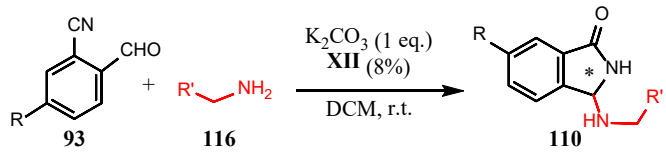


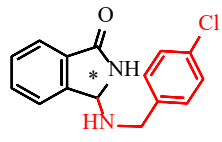
Entry	Cat. (mol %)	Solv.	C (mM)	T (°C)	Time (h)	Yield (%)[a]	*er*[b]
1	**XI** (10)	toluene	56	r.t.	8	92	39/61
2	**XV** (5)	DCM	56	r.t.	42	67	13/87
3	**XV** (8)	DCM	56	r.t.	14	89	15/85
4	**XV** (10)	DCM	56	r.t.	8	89	15/85
5	**XV** (10)	DCM	56	-20	96	67	20/80
6	**XV** (8)	DCM	33	r.t.	19	76	10/90
7	**XV** (8)	1,2-DCE	33	35	16	63	12/88
8	**XV** (8)	1,2-DCE	33	50	5	79	14/86
9	**XV** (6)	toluene	56	r.t.	20	84	24/76
10	**XV** (10)	toluene	56	r.t.	15	84	24/76
11	**XV** (12)	toluene	56	r.t.	10	85	24/76
12	**XVI** (8)	DCM	56	r.t.	24	84	12/88
13	**XVII** (8)	DCM	56	r.t.	18	89	15/85
14	**XII** (8)	toluene	56	r.t.	10	92	87/13
15	**XII (8)**	**DCM**	**56**	**r.t.**	**8**	**92**	**93/7 (99/1)**[c]
16	**XIII** (8)	DCM	56	r.t.	8	92	92/8
17	**XIV** (8)	DCM	56	r.t.	12	92	92/8

[a] Yields refer to isolated products. [b] *er* determined on HPLC equipped with a chiral column. [c] In parenthesis *er* after reverse crystallization.

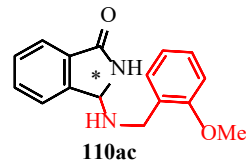
Afterwards, the methodology was expanded to several 2-formylbenzonitriles (**93a-e**) and amines (**116a-d**), under the optimized conditions (Table 3, entry 15). As shown in Table 4, both substituted 2-formylbenzonitriles **93** and primary amines **116** with electron-donating groups and electron-withdrawing groups afforded products in very good yields and high enantiomeric excesses (up to 90%). Finally, an appreciable enantiomeric excess was also obtained with aliphatic amine **116d**.

Table **4**. Scope of the reaction of **93** with **116** under optimized conditions.

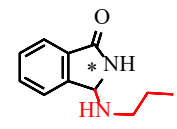




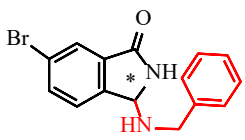
110ab
75%, 95:5 *er*



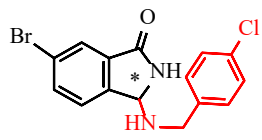
110ac
70%, 88:12 *er*



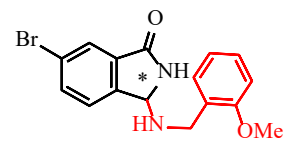
110ad
55%, 87:13 *er*[b]



110ba

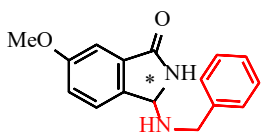


110bb

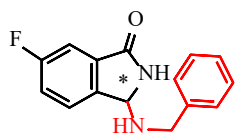


110bc

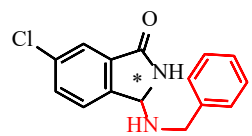
86%, 93:7 *er* (97.5:2.5 *er*)[c] 76% (74%)[d], 95:5 *er* (10:90 *er*)[d] 65%, 85:15 *er*



110ca
83%, 93:7 *er*



110da
65%, 88:12 *er*



110ea
>98% , 90:10 *er*

[a] Experimental conditions: unless otherwise indicated, see entry 15, Table 3. [b] Catalyst loading 10%. Reaction time: 48 h, conversion 60%. [c] In parentheses *er* after reverse crystallization. [d] In parentheses yield and *er* obtained with the catalyst **XV**.

Then, we tried to assign the absolute configuration of the product by *X*-ray crystallography, but several attempts to crystallize product **110aa** failed. Thus, we opted for NMR spectroscopy: (*S*)-α-methylbenzylamine and (*R*)-α-methylbenzylamine were reacted with **93a** under the optimized conditions, yielding the product **110af** with reverse diastereoselectivity (Figure 22) (as shown in the ^{1}H NMR spectra on the crude products). Accordingly, the configuration at the newly created stereogenic centre was the same. In addition, considering the degree of diastereoselectivity, we obtained a similar value to the enantioselectivity produced with achiral benzylamine **116a**, whereas a 1:1 diastereoisomeric mixture was achieved under racemic conditions. Thus, also for chiral amines, the asymmetric induction is completely due to the catalyst and, as a

consequence, the absolute configuration of **110aa** can be confidently assigned on the base of the configurations of **110af**. The relative configurations of the two diastereoisomers **110af** were attributed by comparing ^{1}H NMR experimental spectra with ^{1}H NMR predicted spectra by DFT calculations. The chemical shift of the hydrogen atom in position 3 on the isoindolinonic ring was predicted to be 5.42 ppm for the diastereoisomer (*RR*, *SS*) and 5.05 ppm for the diastereoisomer (*SR*, *RS*). So, knowing the experimental chemical shift of the reference signal (δ= 5.45 ppm and 5.13 ppm, Figure 22) of the two diastereoisomers and the configuration of the chiral starting amines, we could unambiguously say that the newly formed stereocentre possessed *R* configuration, the same applied to the most abundant enantiomer of compound **110aa**.

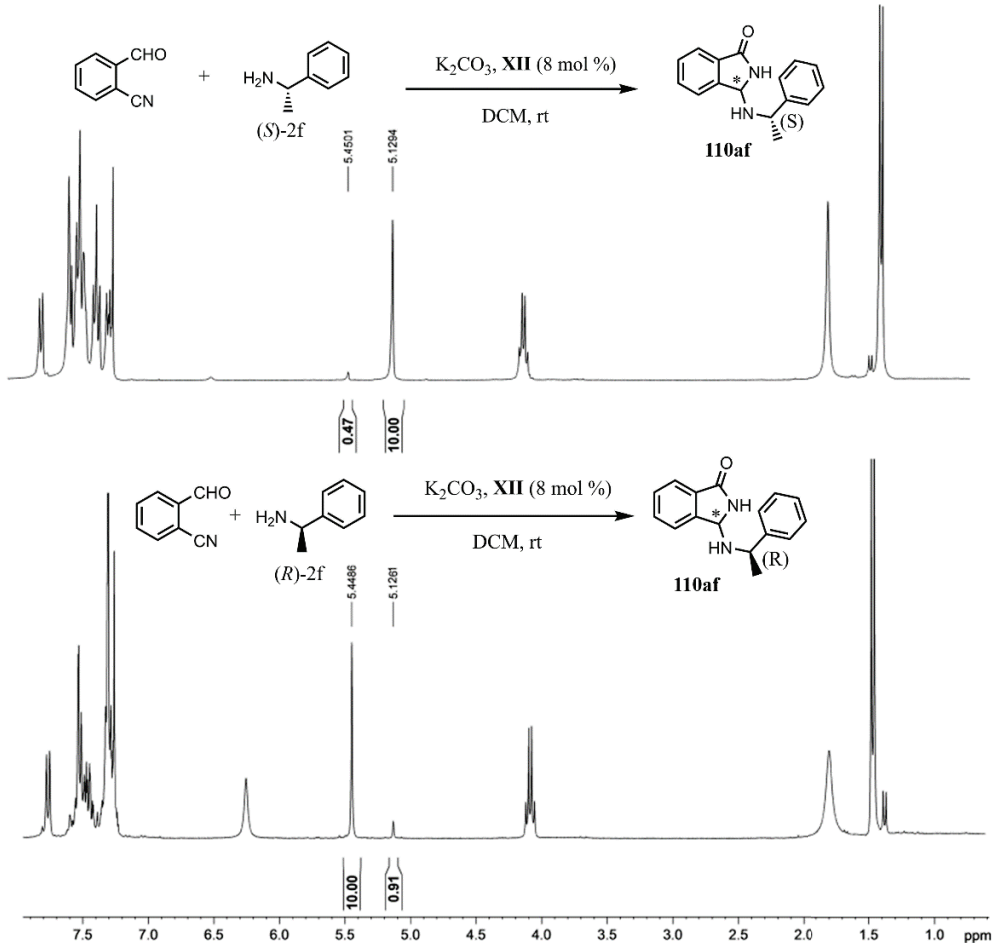
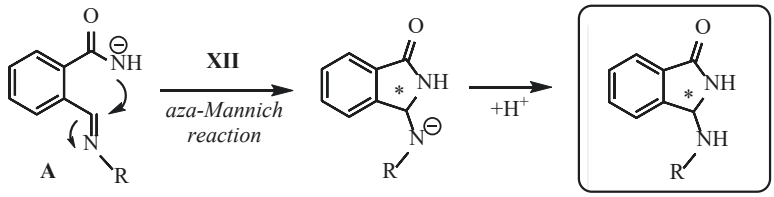


Figure 22. *Reaction of **93a** with chiral amines (S)-2f and (R)-2f under phase transfer conditions and relative ^{1}H-NMR spectra of the diastereomeric mixtures.*

3.2.1 Theoretical study of the reaction mechanism

Thanks to the theoretical studies conducted by Professor Amedeo Capobianco from the Department of Chemistry and Biology of the University of Salerno, it was possible to elucidate the origin of the asymmetric induction. In Scheme 39 is described the last steps of the proposed reaction pathway seen in Scheme 38.



Scheme 39. *Asymmetric intramolecular aza-Mannich reaction.*

The intramolecular aza-Mannich reaction is the enantioselective step of the reaction of **93a** with **116a** (Scheme 39). At first, the conformer distribution of the Cinchona alkaloid-derivative ammonium cation **XII** and the intermediate **A** was investigated. Both because of the highly flexible system and the presence of two hydroxyl donor groups on the catalyst and three acceptor units on the intermediate, numerous binary complexes with different association modes con be obtained. Moreover, the most populated binary reactant complexes include two hydrogen bonds between the ammonium salt **XII** and the intermediate **A** (Figure 23). In ***Ia1*** the nucleophilic nitrogen of intermediate **A** is involved in an *H*-bond with the hydroxyl group at the C^9 of **XII**, while the iminic nitrogen interacts with the hydroxyl group on $C^{6'}$. On the contrary, an opposite coordination arises in ***Ic***. Furthermore, these ion-pairs are stabilized by π–π stacking interactions between the aromatic moiety of the intermediate and the quinoline ring of the catalyst. ***Ia1*** is slightly favoured over ***Ic*** due to a T-shaped CH–π interaction involving the phenyl rings of **A** and **XII**. To generate the actual reactive complexes ***Ib1*** and ***Id*** for the ring closure process, a torsion of 180° about the C–C' bond is necessary. In this way, the nucleophilic nitrogen comes into close contact with the electrophilic carbon and, following the reaction coordinate for the ring-closure, ***Ib1*** and ***Ic*** evolve into ***IIb1-R*** and ***IId-S*** transition states in which an incipient formation of the C–N bond

occurred, as revealed by the shortening of the C–N distance, which amounts to ca. 3 Å in ***Ib1*** and 1.9 Å in ***IIb1-R*** (Figure 24).

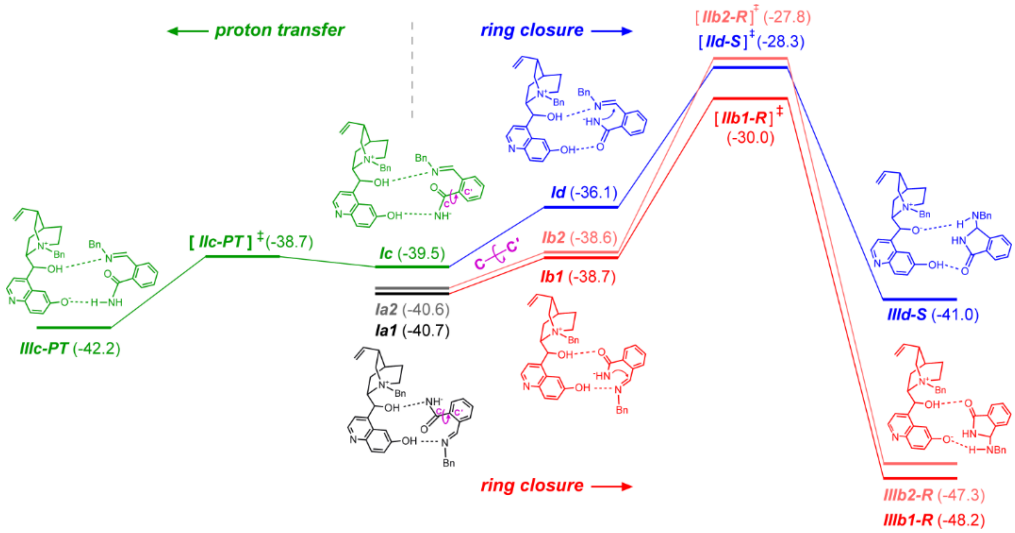


Figure 23. *Schematic energy profile of the enantioselective ring closure step (red and blue) and proton transfer (green). Relative energy (kcal/mol) refers to non-interacting **A** intermediate and **XII** ammonium cation.*

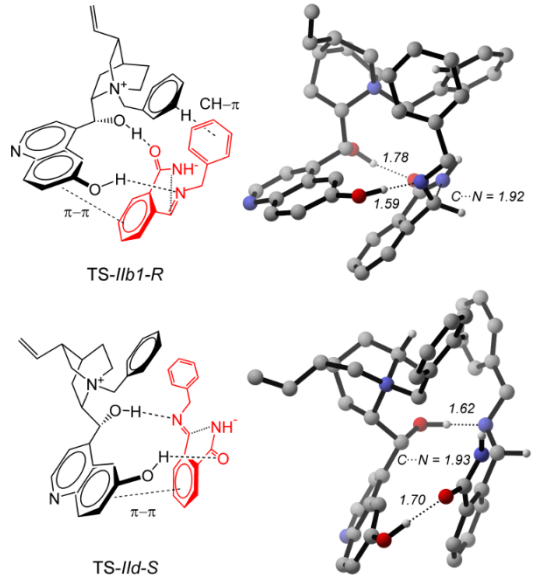


Figure 24. *Energetically most accessible transition states leading to the R and S enantiomers of product **110a**. Noncritical hydrogen atoms omitted for clarity. Distances in Å.*

By DFT calculations, ***IIb1-R*** and ***IId-S*** are the most stable transition states among all pro-*R* and pro-*S* TS, and ***IIb1-R*** is more stable than ***IId-S*** of 1.7 kcal mol^{-1} thanks to an appropriate pattern of hydrogen bonds. This was confirmed by a statistical analysis considering all the transition states which gave an 86% *ee* in favour of the *R* enantiomer, in very good agreement with the observed excess (Table 3, entry 15). The different stability of the transition states depends on the different patterns of hydrogen bonds involved. In fact, in ***IIb1-R*** the quite acidic -OH group at C$^{6'}$ the can hold up the Lewis basicity of the imine moiety of **A**, while a much weaker acidic hydroxyl group (-OH group at C^{9}) is involved in ***IId-S*** TS. Following the intrinsic reaction coordinate, ***IIb1-R*** and ***IId-S*** evolve into ***IIIb1-R*** and ***IIId-S*** product complexes, where the C–N bond is fully formed. Moreover, the cyclization and proton transfer from the ammonium catalyst to the imine nitrogen of the substrate is predicted to be a concerted process, directly affording the final product **110a** and the corresponding betaine of the catalyst (Figure 25).

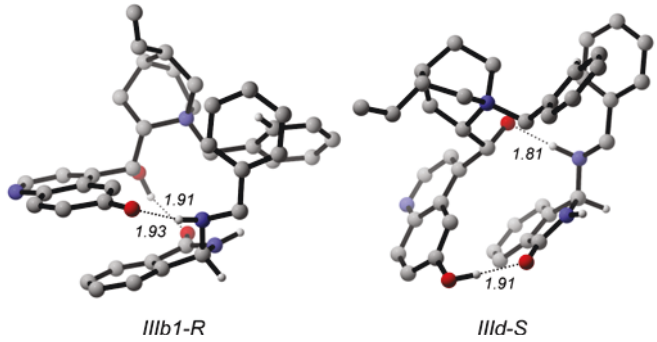
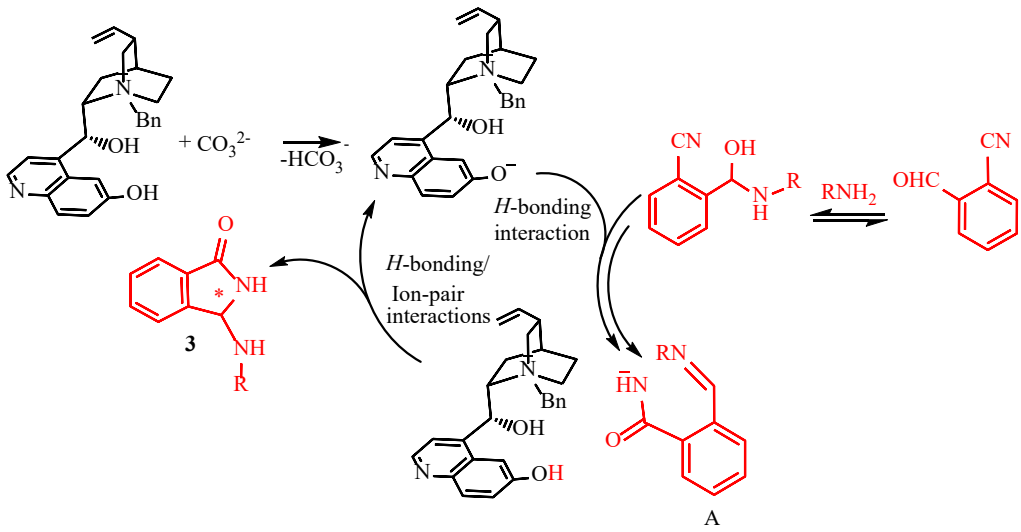


Figure 25. *R and S enantiomers of the final product coordinated to betaine. Noncritical hydrogen atoms omitted for clarity. Distances in Å.*

This strongly suggests that the initial base activator is indeed the betaine specie, whose occurrence can be reasonably expected due to the acidity of **XII** and the presence of carbonate. It was also considered a possible direct acid-base reaction between the rather acidic **XII** cation and intermediate **A** forming the amide represented in Figure 23 (bottom left, green bars). And, although kinetically feasible, this route was predicted to be possible only for ***Ic*** (Figure 23) but would lead to a very modest energy gain (1.5 kcal mol^{-1}) in comparison with the ring closure process (7.5 kcal mol^{-1}, from ***Ib1-R*** to ***IIIb1-R***). Based on available evidence[128] and DFT calculations, it could be supposed that, after

the initial hemi-aminalization, the catalytic cycle should start with an acid-base reaction between the ammonium cation and CO_3^{2-} with the generation of the ammonium betaine assisting the heterocyclization and/or the rearrangement step by *H*-bonding catalysis (Scheme 40). The rearrangement step produces the structured intermediate **A**/ammonium cation ion-pair that undergoes the asymmetric aza-Mannich reaction. The asymmetric step leads to the final product **110** regenerating the betaine catalyst.



Scheme 40. *Comprehensive catalytic cycle.*

In conclusion, it was reported the first asymmetric synthesis of 3-amino-substituted isoindolinones under phase-transfer catalysis conditions. This goal was achieved thanks to an efficient cascade reaction of 2-formylbenzonitriles and primary amines catalyzed by multifunctional Cinchona alkaloid-derivative ammonium salts. The theoretical study showed the establishment of an effective network of hydrogen bonds involved in the asymmetric aza-Mannich rearrangement step, which leads preferentially to one enantiomer.

CHAPTER 4: ASYMMETRIC ACCESS TO A NEW CLASS OF MULTI-HETEROATOMIC CYCLIC COMPOUNDS CONTAINING THE *N,S*-ACETAL FUNCTIONALITY

4.1 Introduction

It is well known that sulfur-containing chiral compounds, as well as their combination with other heteroatoms like nitrogen, are important scaffolds in many synthetic drugs and bioactive natural products.[129] Indeed, *N,S*-acetal moiety is found, for example, within the penicillin family of *β*-lactam antibiotics,[130] the natural product fusaperazine,[131] and the HIV-reverse transcriptase inhibitor[132] (Figure 26), the 3-thiosubstituted isoindolinone already mentioned in Chapter 2.

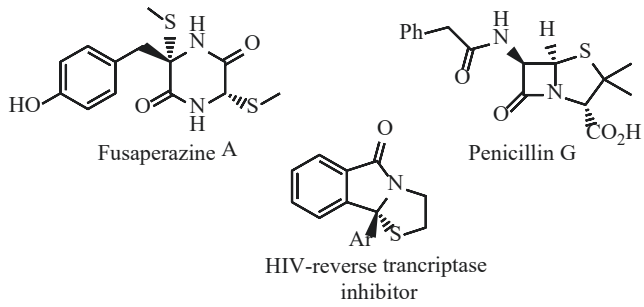


Figure 26. *Useful N,S-acetals.*

Drawing inspiration from the previous work, our attention turned to test thiols as nucleophiles in an asymmetric organocatalytic reaction with 2-formilbenzonitriles and their derivatives (Figure 27), with the primary objective to reach 3-thio-substituted isoindolinones.

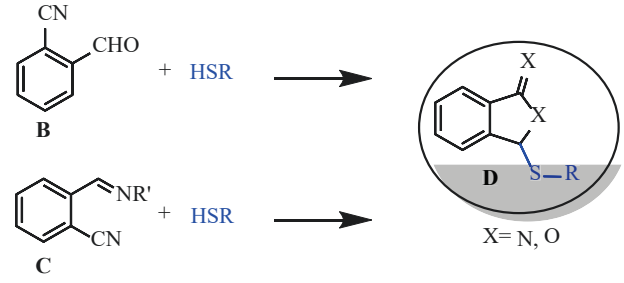
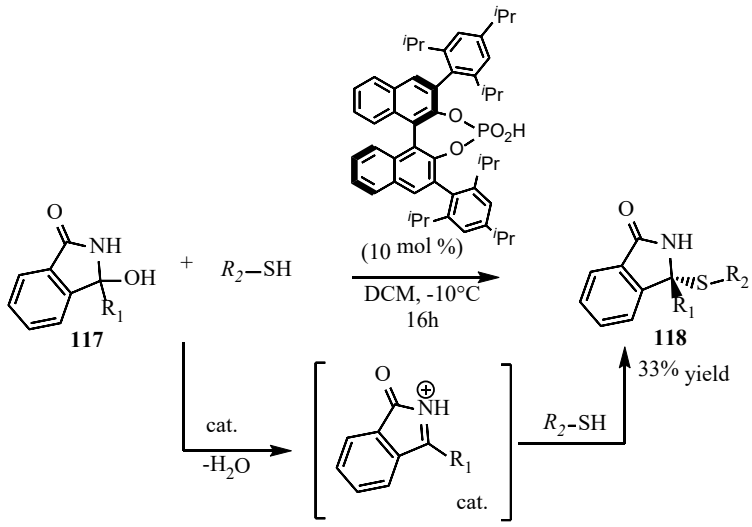


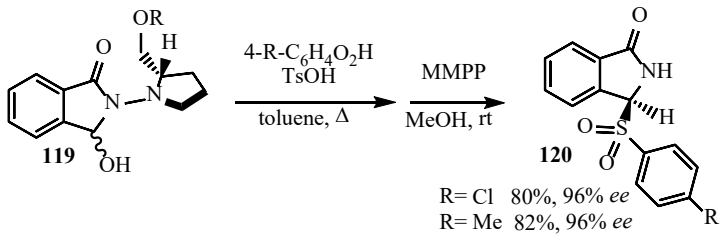
Figure 27. *Model example of heterocyclic architecture with exocyclic heteroatoms at the third position.*

To the best of our knowledge, there are only a few examples in the literature about the stereoselective synthesis of 3-thio-3-substituted isoindolinones and 3-thio-substituted isoindolinones. M. Gredičak[133] *et al.* synthesized isoindolinone-derived *N*(acyl),*S*-acetals **118** by addition of thiols to N-acyl ketimines, which are produced in situ from 3-hydroxy isoindolinones **117** (Scheme 41). This methodology worked with a broad range of ketimines and aromatic and aliphatic thiols using a chiral Brønsted acid catalyst to obtained *N*(acyl),*S*-acetals comprising a tetrasubstituted stereocentre in high yields and enantioselectivities (up to 98.5 : 1.5 *er*).



Scheme 41. *Synthesis of isoindolinone-derived N(acyl),S-acetals.*

Singh[134] and co-workers reported very similar findings on the enantioselective synthesis of isoindolinone-derived *N*(acyl),*S*-acetals. The products were obtained in moderate to excellent yields and enantioselectivities using also a wide variety of thioglycolates and the reaction could be easily scaled up without compromising the asymmetric induction or yield. Finally, Deniau[110] *et al.* reported just two derivatives (**120**) synthesized (Scheme 42) under the reaction conditions already described in Chapter 3, Scheme 28.



Scheme 42. *Deniau approach to isoindolinone-derived N(acyl),S-acetals.*

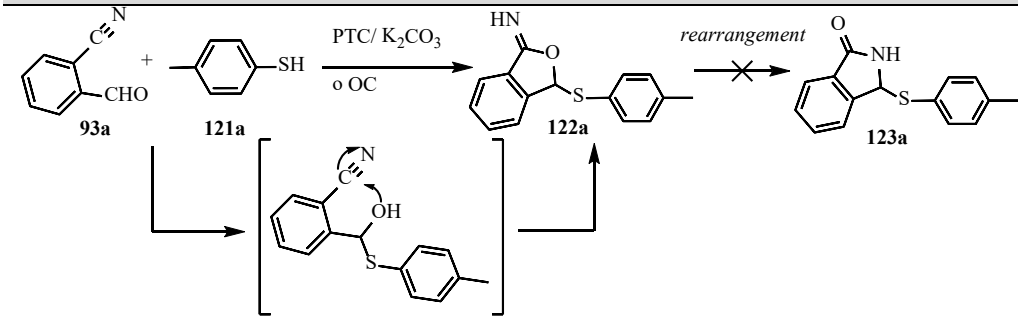
Despite their potential, the synthesis of this class of compounds has been much less investigated to date.

One of our goals was the development of a new asymmetric methodology for the construction and functionalization of multi-heteroatomic cyclic structures.

4.2 Results and discussion

In a preliminary examination of the model reaction between 4-methylbenzenethiol **121a** and 2-formylbenzonitrile **93a**, several different catalytic systems were tried. Under both phase transfer catalysis (PTC) and organocatalytic conditions (OC) (Figure 28), no rearranged isoindolinonic product **123a** was observed, even after long reaction times or by varying catalyst loading, temperature and solvents (Table 5).

Table **5**. Addition of thiol **121a** to 2-formilbenzonitrile **93a**: screening of the catalytic system.



Entry	Cat. (mol %)	Time (h)	**121a** (eq.)	Solvent	T (°C)	Yield (%)[a]	*er*[b]
1	**IV**/K_2CO_3/10	20	1.2	DCM	r.t.	55	48:52
2	**VIII**/K_2CO_3/10	1.5	2.0	DCM	r.t.	71	48:52
3	**VIII**/K_2CO_3/5	28	2.0	Toluene	-20	67	46:54
4	**XII**/K_2CO_3/8	24	2.0	DCM	r.t.	69	47:53
5	**XX**/10	24	1.2	DCM	r.t.	47	50:50
6	**XXI**/5	7	2.0	Toluene	-20	70	58:42
7	**XXI**/5	72	2.0	Toluene	-40	64	57:43
8	**XXII**/10	20	2.0	Toluene	-20	67	52:48

[a)] Yields refer to isolated products. [b)] Determined by chiral stationary phase HPLC analysis.

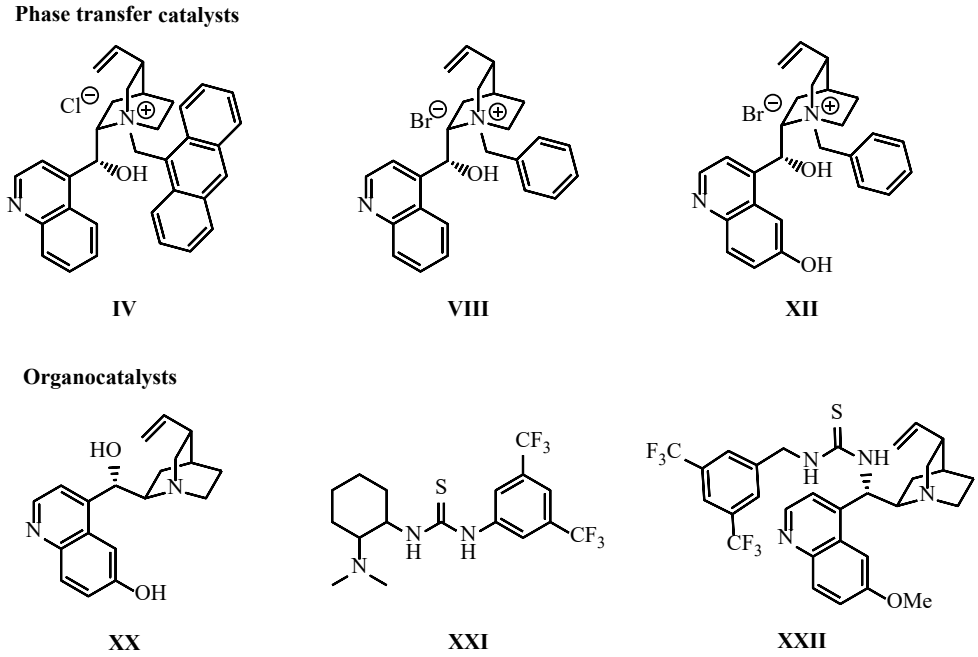
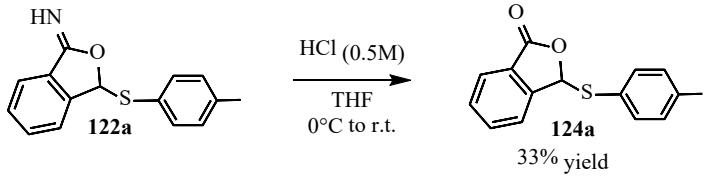


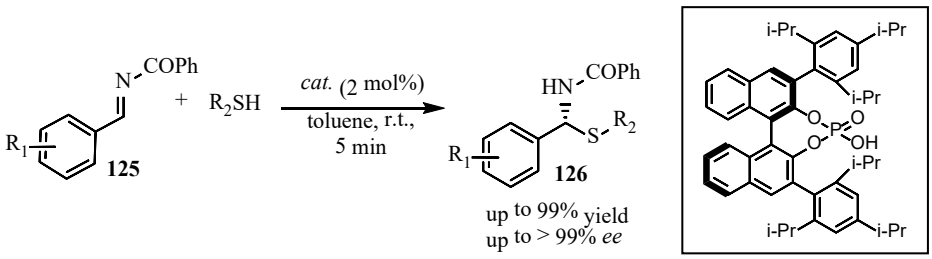
Figure 28. *List of organo- and phase-transfer catalysts.*

Unfortunately, isobenzofuranimine **122a** was just recovered as a nearly racemic mixture (Table 5), and several attempts to synthesize the significant 3-thiophthalides **124a** via hydrolysis[135] of **122a** were disappointing (Scheme 43).



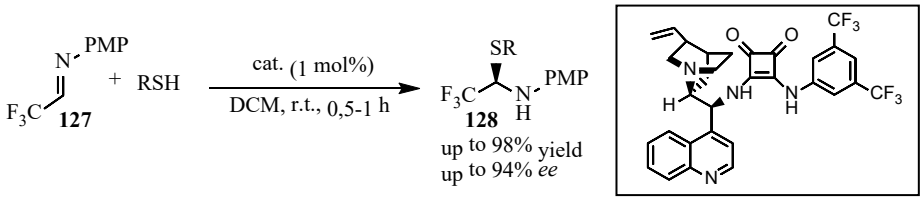
Scheme 43. *Acid hydrolysis of isobenzofuranimine **122a**.*

Thus, we decided to change the electrophile and imines derived from 2-formylbenzonitrile were chosen as possible candidates. Indeed, the pioneering work of Antilla[136] and co-workers reported a catalytic asymmetric 1,2-addition of thiols to *N*-acyl imines **125** for the synthesis of *N,S*-acetals **126** in high enantioselectivities by using a chiral Brønsted acid catalyst (Scheme 44).

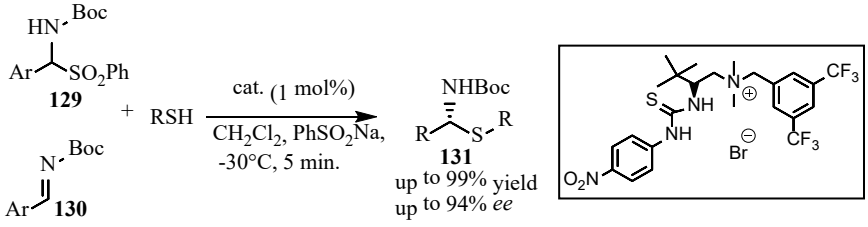


Scheme 44. *Asymmetric 1,2-addition of thiols to N-acyl imines* ***125****.*

Later, Wang[137] *et al*. used Cinchona-derived squaramides to catalyze the asymmetric addition of thiols to fluorinated aldimines **127** (Scheme 45), and Zhao[138] and co-workers described the highly enantioselective addition of thiols to *N*-Boc-protected amidosulfones **129** or imines **130** to provide *N,S*-acetals **131** catalyzed by bifunctional thiourea-ammonium salt catalysts (Scheme 46).

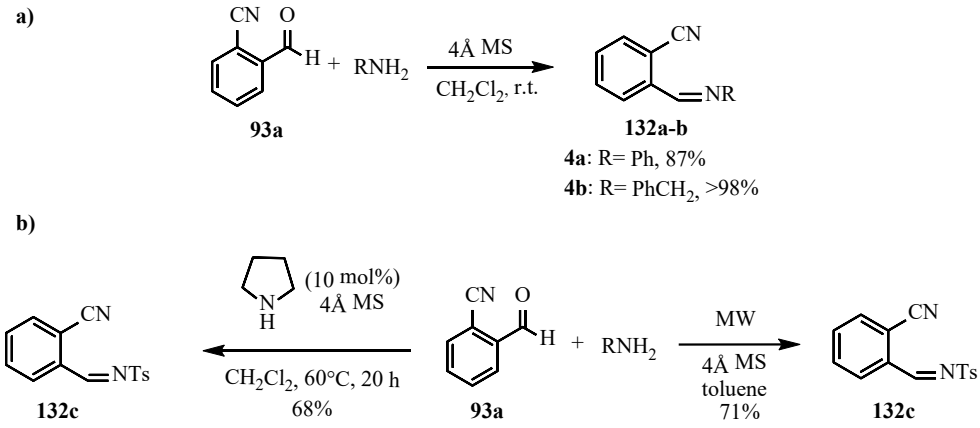


Scheme 45. *Asymmetric addition of thiols to fluorinated aldimines* ***127****.*



Scheme 46. *Enantioselective addition of thiols to N-Boc-protected amidosulfones* ***129*** *or imines* ***130****.*

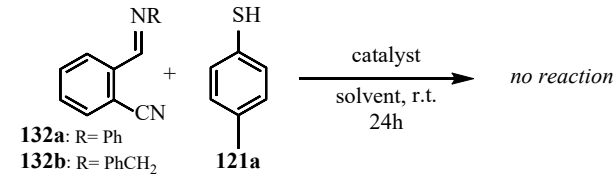
Considering the above literature data, we focused on the synthesis of imine derivatives **132a–c** (Scheme 47) and started our investigation by examining their reactivity with the thiol **121a** under different catalytic systems.



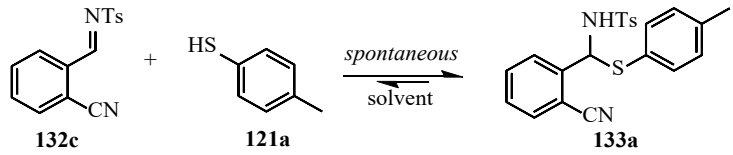
Scheme 47. *Synthesis of imines **132a-c**.*

While imines **132a-b** did not react using both PTC and OC conditions (Table 6), a control experiment showed a fast spontaneous addition of **121a** to the benzylidensulfonylimine **132c**, yielding the acyclic *N,S*-acetal **133a** as single reaction product (Scheme 48).

Table **6**. Addition of thiol **121a** to imines **132a-b**.



Entry	Cat.(mol %)	Substrate	Solvent	Conversion (%)
1	**-**	**132a (o 132b)**	Toluene	-
2	**XXI/10**	**123a**	Toluene	-
3	**IV/K_2CO_3/10**	**123a**	Toluene	-
4	**XXI/10**	**123b**	Toluene	-
5	**IV/K_2CO_3/10**	**123b**	DCM	-



Scheme 48. *Spontaneous addition of thiol **121a** to imine **132c**.*

To find a suitable catalytic system able to promote the heterocyclization on the CN group and a possible Dimroth rearrangement, we followed the reaction of intermediate **133a** with catalyst **XX** (0.5 mol %) in $CDCl_3$ by ^1H NMR analysis.

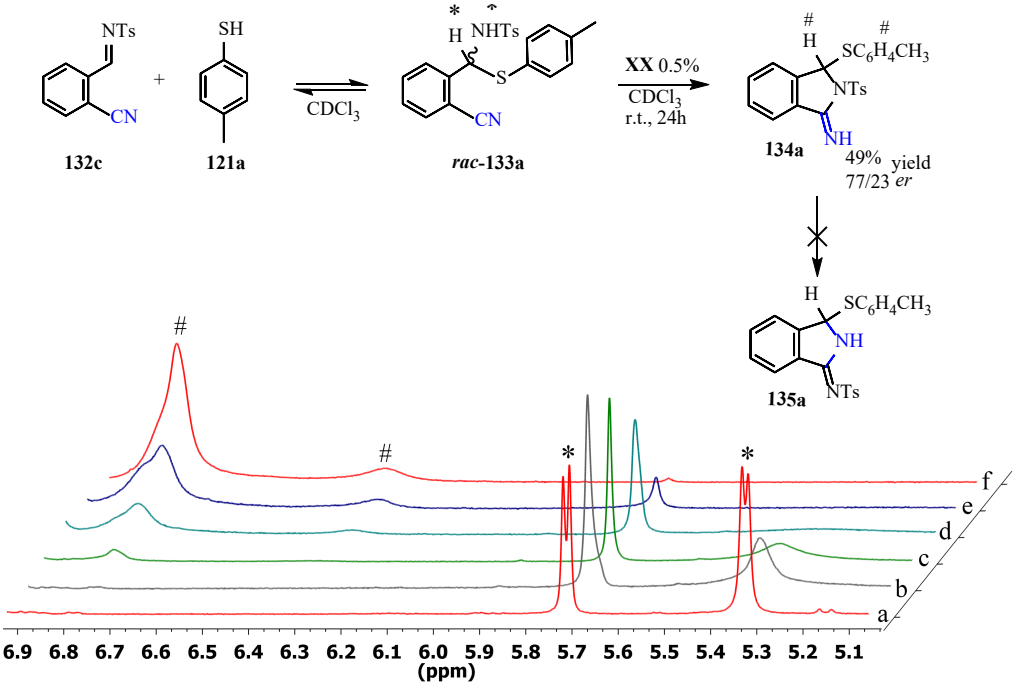


Figure 29. *^1H NMR experiment showing the progression of the reaction of **121a** (1.2 eq.) with **132c** using bifunctional catalyst **XX**. a) A portion of ^1H NMR spectrum recorded after reagents mixing; b–e) Portion of the time depending ^1H NMR spectra collected after 1, 3, 7 h; f) Portion of the ^1H NMR spectrum recorded after 24 h.*

As illustrated in Figure 29, the progressive disappearance of the diagnostic signals at 5.71 and 5.31 ppm for intermediate **133a** (Figure 29, spectrum a) was associated with the occurrence of characteristic picks related to **134a** at 6.78 (4x H_{arom}) and 6.40 ppm (Figure 29, c–f)), which suggested that a process of heterocyclization happened but

excluding the formation of the Dimroth rearrangement product **135a**. This was confirmed by comparison with the theoretical spectra calculated for both the regioisomers. In particular, the chemical shifts of the protons on the asymmetric carbon are predicted to be 6.3 and 5.6 ppm vs TMS, for **134a** and **135a**, respectively, to be compared with the observed shift, 6.40 ppm, thus excluding the Dimroth rearrangement. The above finding was strongly supported by the comparison of the IR spectrum of the final product with the predicted IR spectra of both **134a** and **135a** regioisomers (Figure 30).

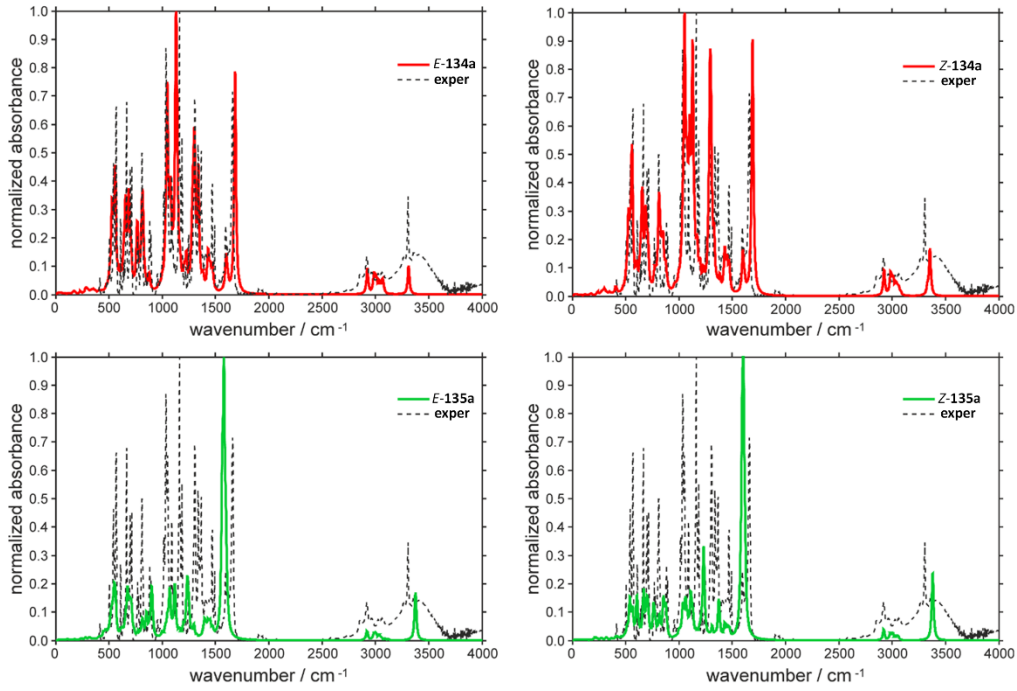


Figure 30. *Observed and predicted IR spectra of regioisomers **134a** (in red) and **135a** (in green). Boltzmann averaged over conformations at 298 K.*

The excellent matching of the observed fingerprint region (500-1500 cm^{-1}) with that predicted for **134a**, proved that the reaction product is indeed **134a**. Apart from the better agreement between the observed intensities in the C─H stretching region (2800 - 3200 cm^{-1}) with the predicted intensities for **134a**, the assignment was further corroborated by the analysis of the signal peaked at 1665 cm^{-1}. An intense absorption 1680 (*E*)/1690 (*Z*) cm^{-1} was predicted for **134a**, corresponding to the N─H stretching, as expected for unsubstituted imines. Instead, for **135a** a very large absorption, far more intense than the

other signals, was predicted to occur at wavenumbers of ca 1580 (*E*)/1600 (*Z*) cm^{-1}, sensibly lower than the observed ones. Such an intense transition, corresponding to a normal coordinate coupling the C=N stretching with the N─H in plane bending, was not observed in the experimental spectrum.

Finally, the slow evaporation of a solution of the racemic derivative of **134m** in dichloromethane/methanol (2:1) produced colourless needle-like single crystals suitable for *X*-ray diffraction analysis (Figure 31). *X*-ray analysis was performed by Dr Giovanni Pierri and Prof. Consiglia Tedesco belonging to Department of Chemistry and Biology "A. Zambelli" of the University of Salerno and confirmed definitively the *X*-ray molecular structure of the product.

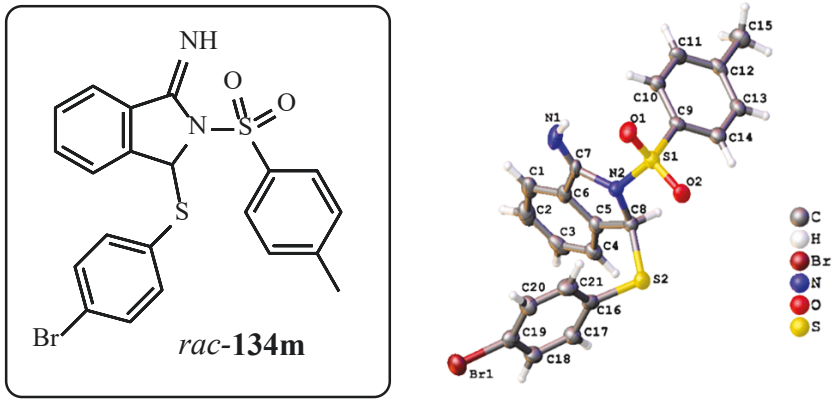


Figure 31. *X-ray molecular structure of rac-**134m**. Atom types: C grey, N blue, O red, S red, Br in purple. Ellipsoids are drawn at 50% probability level.*

As seen above (Scheme 48), the spontaneous addition of thiol **121a** to sulfonylimine **132c**, without the presence of catalyst, gives a racemic mixture of the corresponding acyclic thioaminal **133a**. The introduction of catalyst **XX** promotes the heterocyclization on the CN group affording product **134a** with 54% of enantiomeric excess and 49% yield. But, since the cyclization process of compound **133a** into product **134a** doesn't involve the stereogenic centre, this reaction is driven by a resolution process.[139]

4.2.1 Catalysts screening and hypothesis on the origin of selectivity

Inspired by this result, we carried out a screening of organo- and phase transfer catalysts showed in Figure 32.

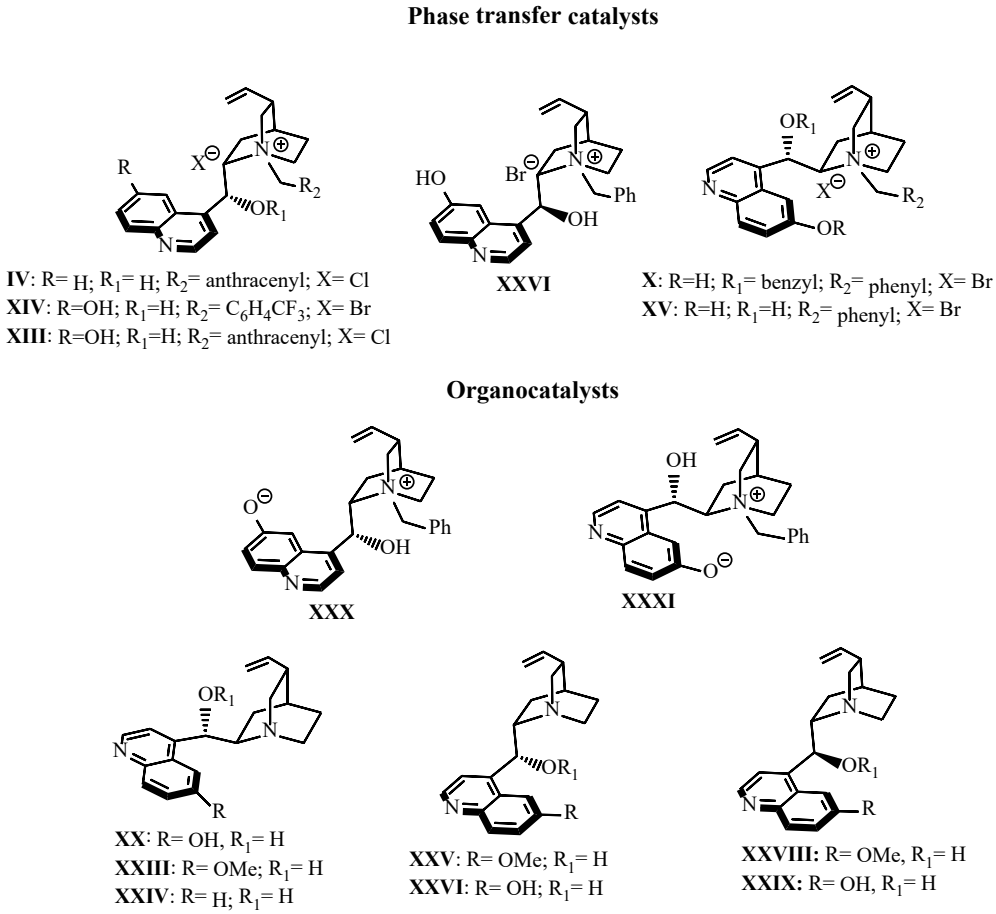
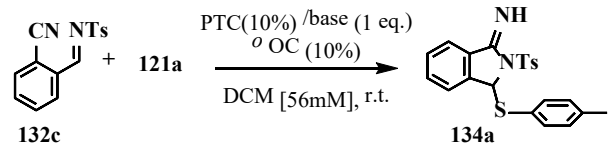


Figure 32. *List of organo- and phase transfer catalysts.*

Table **7**. Addition of thiol **121a** to the sulfonylimine **132c**: screening of the catalytic system.

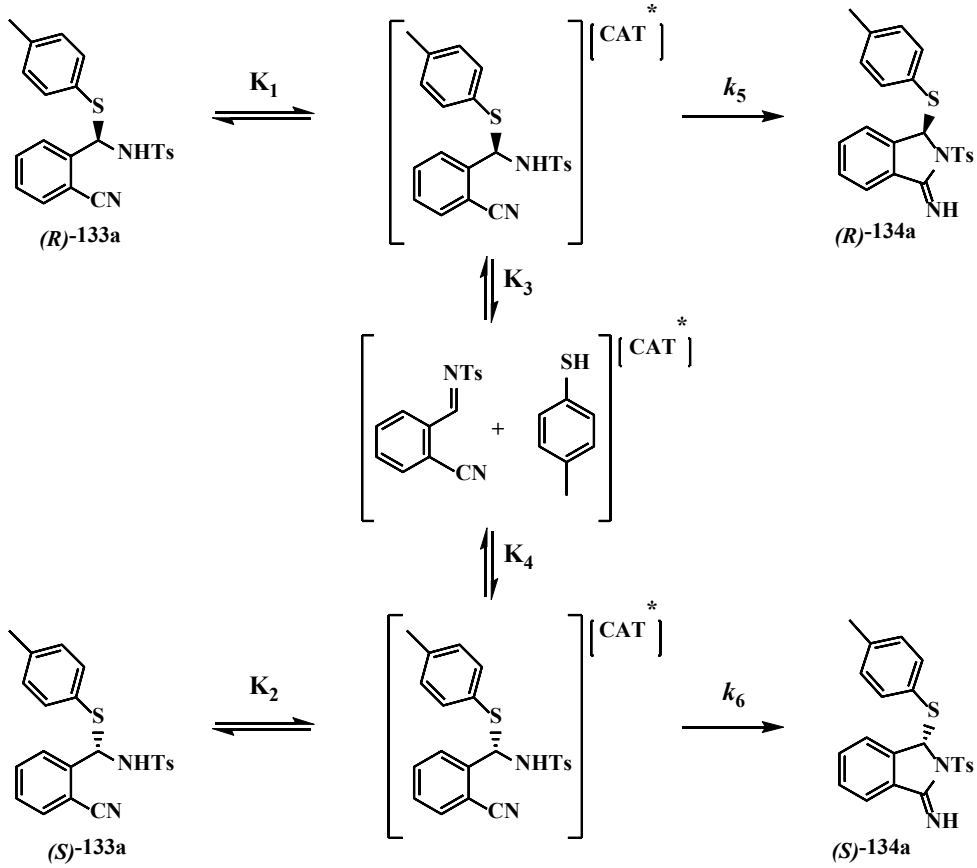


132c **134a**

Entry	Catalyst	Time (h)	Yield (%)[a]	*er*[b]
1	**IV/K_2CO_3**	1	88	46:54
2[c]	**XII/K_2CO_3**	1.2	93	14:86
3[d]	**XII /K_2CO_3**	2	73	22:78
4[e]	**XII /K_2CO_3**	24	83	12:88
5	**XX**	0.20	83	75:25
6[e]	**XXI**	24	93	47:53
7	**XIV/K_2CO_3**	2.5	64	20:80
8	**XIII/K_2CO_3**	1.5	74	22:78
9	**XXVII/K_2CO_3**	24	78	51:49
10	**V/K_2CO_3**	4	64	54:46
11	**XV/K_2CO_3**	0.5	85	76:24
12[d]	**XV/K_2CO_3**	1	85	66:34
13	**XXIII**	0.1	88	40:60
14[e]	**XXIII**	0.25	83	25:75
15	**XXIV**	0.2	83	46:54
16	**XXV**	0.25	78	60:40
17	**XXVI**	0.25	83	20:80
18[e]	**XXVIII**	48	64	53:47
19[f]	**XXIX**	72	83	50:50
20	**XXX**	4	83	22:78
21	**XXXI**	4	83	79:21

[a] Yields refer to isolated products. [b] Determined by chiral stationary phase HPLC analysis. [c] [**132c**]= 28 mM in DCM. [d] Reaction performed with 5 mol % of catalyst. [e] Reaction temperature: -20°C. [f] Reaction in toluene.

The data of Table **7** clearly reflected the dynamic character of the resolution process. In fact, the product **134a** was achieved in high yield and from moderate to good enantiomeric excesses after complete conversion of the intermediate **133a**. In particular, from a preliminary theoretical study, this process seems to be a dynamic thermodynamic resolution, that is the de-symmetrization of the racemic mixture of thioaminal **133a** involves interconverting diastereomeric substrate/catalyst complexes with different energies, then with different equilibration constant K_3 and K_4, but implying similar rate constants of formation of enantiomers of product **134a** (Scheme 49).



Scheme 49. *Proposed dynamic thermodynamic process, in which K_1, K_2 are pre-equilibrium constants for [(R)-**133a**/Catalyst] and [(S)-**133a**/Catalyst] complex formation; K_3, K_4 are equilibration constants of epimerization; k_5, k_6 are rate constant of irreversible formation of product enantiomers; $k_5 \approx k_6$.*

As concerning the catalyst's structure effect, it is clear that:

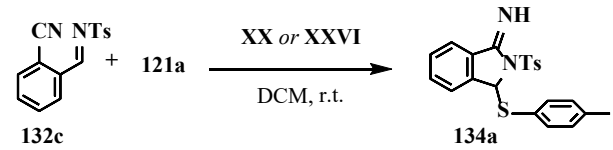
- the presence of multiple *H*-bonding sites, both in organo- and phase transfer catalysts, played a key role in the asymmetric induction catalysts (**XII**, **XX**, **XIV**, **XIII**, **XV**, **XXIII**, **XXVI**, **XXX** and **XXXI** *vs.* **IV**, **XXI**, **V**, **XXIV**);
- the pair of catalysts **XX** and **XXIII**, as well as **XXV** and **XXVI** (which have in turn identical sequence of chiral centres with the same absolute configurations), led to the final product **134a** with reverse configuration, although with different enantioselectivities;
-finally, the right relative configurations C9, C8 was essential to obtain high selectivities, as can be seen by the performance of catalysts **XXVII**, **XXVIII** and **XXIX** (epimers of **XII**, **XXV** and **XXVI**, respectively) which yield the product **134a** in nearly racemic form.

4.2.2 Optimization of reaction conditions and substrate scope

To optimize the reaction conditions we focused on the organocatalytic approach, in particular on the catalyst **XX** and **XXVI** (synthesizable in one step from quinidine and quinine respectively, and more readily available than ammonium salts), since the phase transfer catalysis and organocatalysis provided similar performances. The influence of temperature, solvent and catalyst loading were investigated.

As showed in Table 8, dichloromethane was the best performing solvent for this process and the best enantiomeric excess was achieved at low temperature using 10 mol % of catalysts (entries 6,10). Moreover, further lowering of temperature (entry 9) or the use of an aromatic solvent (entry 14) did not lead to an improvement in selectivity. Finally, it is worth to note that the use of these pseudoenantiomeric catalysts (catalyst **XX** vs **XXVI**) allowed, in general, an effective inversion of enantioselectivity with comparable *er*.

Table **8**. Addition of thiol **121a** to the sulfonylimine **132c** with the OCs **XX** and **XXVI**: screening of the reaction conditions.



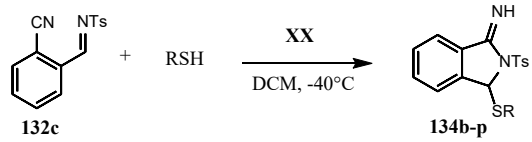
132c **134a**

Entry	Catalyst (%)	T (°C)	Time (h)	Yield (%)[a]	*er*[b]
1	**XX** /0.5	r.t.	3	74	75:25
2	**XX** /0.5	0	5	74	85:15
3	**XX** /10	r.t.	0.25	83	63:37
4	**XX** /10	-20	16	83	87:13
5	**XX** /5	-40	72	83	85:15
6	**XX /10**	**-40**	**29**	**83**	**90:10 (97:3)[c]**
7[d]	**XX** /10	-40	40	60	79:21
8	**XX** /13	-40	20	83	87:13
9	**XX** /10	-50	15	78	90:10
10	**XXVI/10**	**-20**	**24**	**88**	**13:87 (7:93)[c]**
11	**XXVI** /10	0	5	93	15:85
12	**XXVI** /10	-40	42	65	15:85
13[e]	**XXVI** /10	r.t.	0.1	74	24:76
14[f]	**XXVI** /10	r.t.	0.1	93	29:71
15[g]	**XXVI** /10	r.t.	0.3	78	22:78

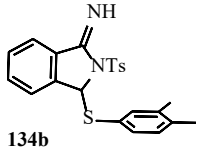
[a] Yields refer to isolated products. [b] Determined by chiral stationary phase HPLC analysis. [c] *er* after reverse crystallization from DCM/hexane solution. [d] 1 eq. of **121a** has been used. [e] Solvent: $CHCl_3$. [f] Solvent: C_6H_5Cl. [g] Solvent: 1,2-DCE.

In according to this results, the methodology was expanded to a series of thiols (Table **9**): substituted aryl thiols bearing electron-donating (**121d**, **121h**, **121i**, **121j**) and relatively electron-neutral groups (**121b**, **121c**, **121e**, **121f**) gave the best enantioselectivities (up to 90% *ee*), while substituted aryl thiols with electron-withdrawing groups led to a decrease in selectivity. Very interesting results were also obtained with thioglycolate and 3-mercaptopropionate (products **134n** and **134o**), compounds with an ester functionality useful for further chemical transformations.

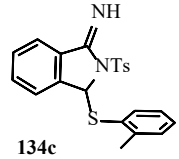
Table **9**. Substrate scope for the enantioselective addition of thiols **121b–p** to the sulfonylimine **132c**.



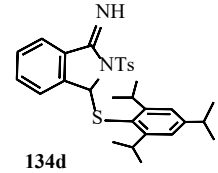
132c **134b-p**



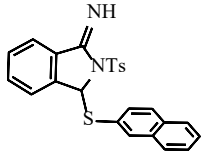
134b
70% yield, 88:12 *er*



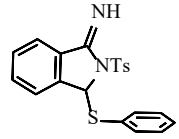
134c
78% yield, 83:17 *er*



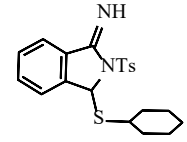
134d
70% yield, 93:7 *er*
(70% yield, 10:90 *er*)[a]



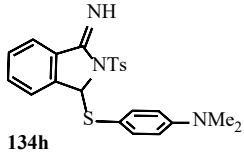
134e
58% yield, 84:16 *er*



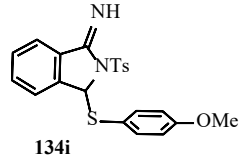
134f
66% yield, 82:18 *er*



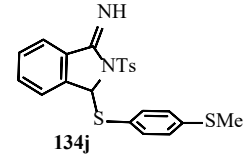
134g
75% yield, 77:23 *er*



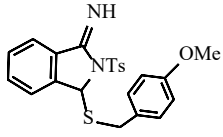
134h
80% yield, 95:5 *er*



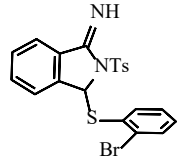
134i
80% yield, 91:9 *er*
(80% yield, 10:90 *er*)[a]



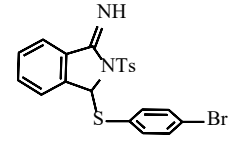
134j
70% yield, 87:13 *er*



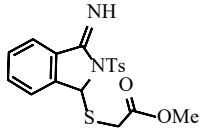
134k
78% yield, 68:32 *er*



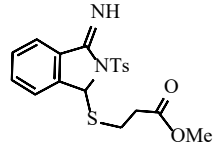
134l
72% yield, 64:36 *er*



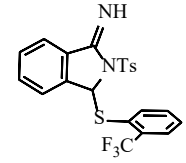
134m
72% yield, 72:28 *er*



134n
97% yield, 92:8 *er*
(81% yield, 10:90 *er*)[a]



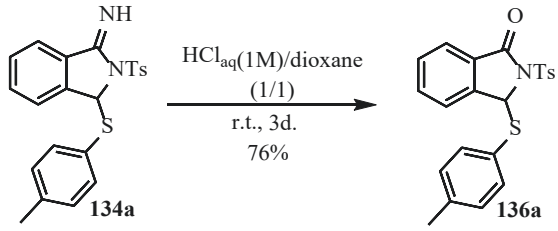
134o
65% yield, 85:15 *er*



134p
39% yield, 60:40 *er*

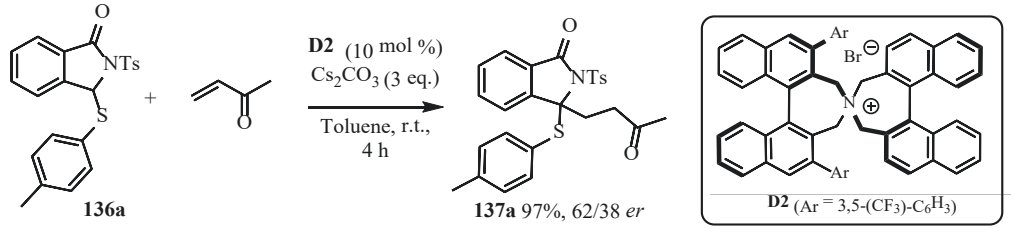
[a] Catalyst **XXVI** was used.

In the final stage of this project, we submitted product **134a** to mild acidic hydrolysis in order to obtain the considerable 3-thio-substituted isoindolinone **136a** (Scheme 50). Although other research efforts are required, a fairly satisfactory yield of 76% was achieved by using a mixture of hydrochloridic acid 1M/ dioxane 1:1.



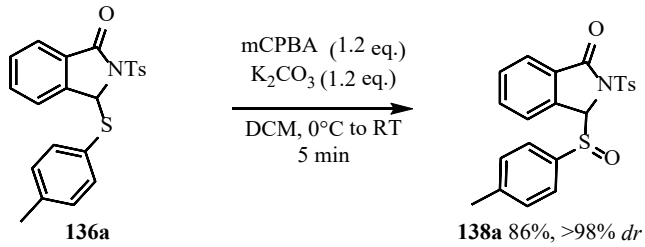
Scheme 50. *Mild hydrolysis of **134a** to give isoindolinone derivative **136a**.*

Furthermore, a preliminary study showed the potential of compound **136a** as a Michael donor in the reaction with methyl vinyl ketone (Scheme 51): 3,3-disubstituted isoindolinone **137a** was obtained in very high yield and with 26% of enantiomeric excess under chiral phase transfer catalysis conditions indicated in Scheme 51.



Scheme 51. *3-thio-substituted isoindolinone **136a** as Michael donor.*

Finally, a completely diastereoselective oxidation of **136a** with meta-Chloroperbenzoicacid (mCPBA) gave the corresponding sulfoxide **138a** in good yield (Scheme 52).



136a **138a** 86%, >98% *dr*

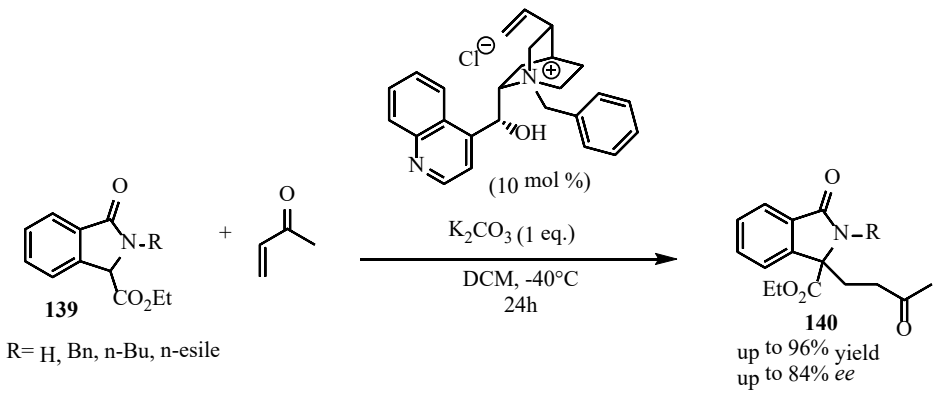
Scheme 52. *Oxidation of compound* ***136a*** *to sulfoxide* ***138a****.*

To sum it up, it was developed, for the first time, an enantioselective cascade reaction of thiols and 2-cyano-N-tosylbenzylidenimine leading to a new class of multi-heteroatomic cyclic scaffolds containing the important *N,S*-acetal functionality. The process was catalyzed by a readily available trifunctional Cinchona alkaloid-based organocatalyst, achieving high yields (up to 97%) and enantiomeric excesses (up to 90%). The scope of the methodology was also expanded to thioglycolate and 3-mercaptopropionate, useful substrates for further derivatizations. Furthermore, submitting these scaffolds to mild acidic hydrolysis, 3-thio-substituted isoindolinones can be obtained and used for more transformations.

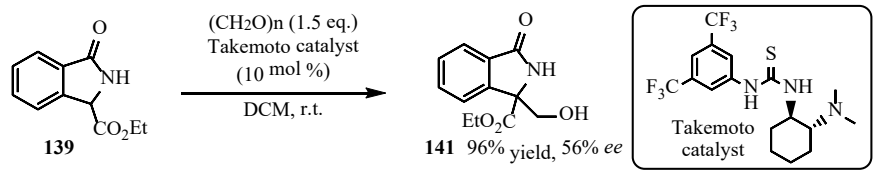
CHAPTER 5: SYNTHESIS OF 2-ACETYLBENZONITRILES AND THEIR REACTIVITY IN TANDEM PROCESSES FOR THE SYNTHESIS OF NEW 3,3-DISUBSTITUTED ISOINDOLINONES

5.1 Introduction

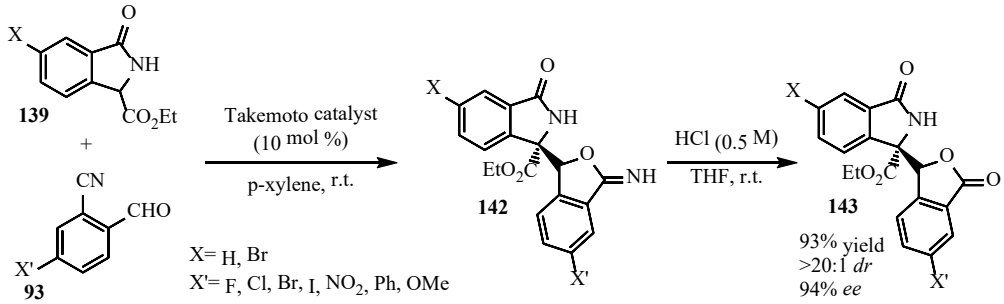
As seen in Chapter 3, many approaches to 3-substituted isoindolinones are well developed. In comparison, the synthesis of 3,3-disubstituted isoindolinones with a tetra-substituted carbon remains underdeveloped[140] and, usually, requires a metallic catalysis and complex, multistep pathways. Recently, our research group reported the asymmetric synthesis of tetrasubstituted derivatives through derivatization of 3-carboxylate substituted isoindolinones. The isoindolinone derivatives **139**, activated in 3-position by an ester group, were used as nucleophiles in asymmetric Michael reaction under phase transfer catalyzed conditions in the synthesis of adducts **140** with tetrasubstituted stereocentres (Scheme 53);[141] in an organocatalytic asymmetric hydroxymethylation of isoindolinones **139** with paraformaldehyde (Scheme 54);[142] and in an asymmetric cascade reaction for the synthesis of new heterocyclic hybrids isoindolinone-imidates **142** and isoindolinonephthalides **143** (Scheme 55).[143]



Scheme 53. *3-carboxylate-substituted isoindolinones **139** as Michael donors.*

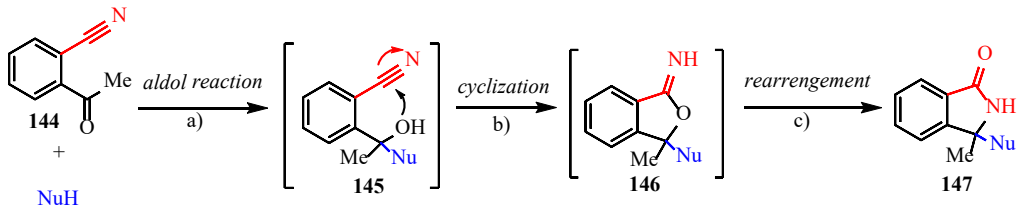


Scheme 54. *Nucleophilic isoindolinones in aldol reactions.*



Scheme 55. *Access to new heterocyclic hybrids isoindolinone-imidates* ***142*** *and isoindolinonephthalides* ***143****.*

Inspired by these and previous reports, we decided to investigate the reactivity of 2-acetylbenzonitriles **144** in tandem reactions according to the proposed mechanism in Scheme 56 (similar to the one proposed in Chapter 3-Scheme 31 for the 2-formylbenzonitriles **93**).



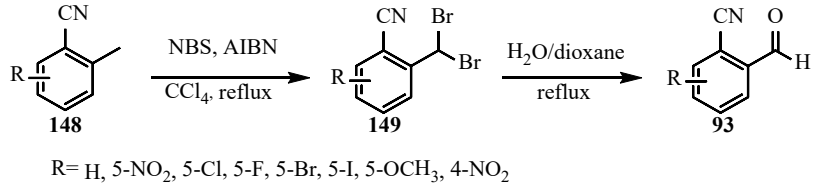
Scheme 56. *Proposed mechanism for the tandem process.*

Although superficially very similar, aldehydes and ketones can exhibit broadly different steric and electronic properties in nucleophilic addition reactions, above all for the poor electrophilic character of the carbonyl group and competitive enolization. However, after the nucleophilic addition (Scheme 56, step a), the *orto*-cyano group should favor the cyclization of the aldol adduct **145** to imidate **146** and, moreover, α-acidic hydrogens on the side chain of the nucleophile could lead to a rearrangement to tetrasubstituted isoindolinones **147**.

5.2 Results and discussion

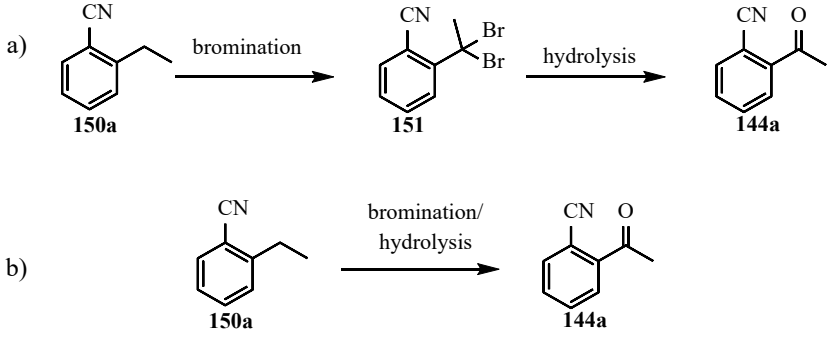
5.2.1 Synthesis of 2-acetyl-benzonitriles

So far as we know, 2-acetyl-benzonitriles are rarely used as substrates. In 2012 and 2016, respectively, Gotor[144] and Romano[145] reported a biocatalytic reduction for the synthesis of benzyl alcohols and methylphthalides. Furthermore, 2-acetylbenzonitrile itself is quite expensive and difficult to synthesize. In fact, some procedures employ cyanating agents like NaCN or CuCN in Sandmeyer reactions[144,146] or a cobalt catalysis but with low yields.[147] Recently, Massa[143,148] and co-workers developed in our laboratories the synthesis in two steps of 2-formylbenzoniriles **93** from 2-methyl-benzonitriles **148** by treatment with N-bromosuccinimide (NBS) and azobis(isobutyronitrile)(AIBN) in CCl_4 and subsequent hydrolysis (Scheme 57).



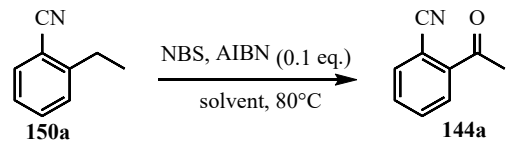
Scheme 57. *Synthesis of 2-formylbenzonitriles **93**.*

Encouraged by these results, we examined the transformation of readily available 2-ethylbenzonitriles **150a** into 2-acetylbenzonitriles **144a**, trying to combine bromination and hydrolysis in a single pot (Scheme 58, b).



Scheme 58. *Synthesis of 2-acetylbenzonitriles **144**. a) two steps synthesis, b) single pot synthesis.*

Table **10**. One-pot bromination/hydrolysis of 2-ethylbenzonitrile **150a**.



150a **144a**

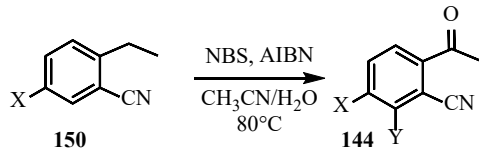
Entry	Solvent (ratio)	NBS (equiv.)	Time (h)	Yield (%)[a]
1	CCl_4	4	48	-
2	CH_3CN	3.5	24	-
3	H_2O	3.5	1.5	58
4	CH_3CN/ H_2O (1:9)	3.5	1.5	69
5	CH_3CN/ H_2O (1:4)	3.5	1.5	62
6	CH_3CN/ H_2O (4:1)	3.5	4	82[b]
7	CH_3CN/ H_2O (4:1)	3.5	3	81[c]
8	CH_3CN/ H_2O (4:1)	3.5	5	55[d]
9	CH_3CN/ H_2O (4:1)	4.5	3.5	83
10[f]	CH_3CN/ H_2O (4:1)	4.5	3.5	83
11	CH_3CN/ H_2O (5:1)	3.5	5	69
12	CH_3CN/ H_2O (4:1)	2.5	3.5	30[g]
13[e]	CH_3CN/ H_2O (4:1)	3.5	3	80

[a] Yields refer to chromatographically pure compounds. [b] α-Bromoethylbenzonitrile and α-bromo ketone were isolated in yields of 5 and 10 %, respectively. [c] α-Bromoethylbenzonitrile and α-bromo ketone were isolated in yields of 12 and 4 %, respectively. [d] α-Bromoethylbenzonitrile and α-bromo ketone were isolated in yields of 5 and 38 %, respectively. [e] The reaction was scaled up to 4 mmol. [f] 0.1 equiv. of dibenzoyl peroxide (BPO) was used instead of AIBN. [g] The main product was α-bromoethylbenzonitrile.

As we can see in Table 10, the treatment of 2-ethylbenzonitrile **150a** with NBS and a catalytic amount of AIBN in CCl_4 or acetonitrile (entry 1,2) did not afford ketone **144a** but led to a mixture of α-bromoethylbenzonitrile and α,α-dibromoethylbenzonitrile, also after a long reaction time. Water proved to be a good solvent for this radical reaction and the final product **144a** was achieved in moderate yield in only 1.5 h, although hydrolysis byproducts were also detected (entry 3). Next, a combination of solvent was examined to minimize the sideproducts and different CH_3CN/H_2O mixtures were used (entries 4-13). The best CH_3CN/H_2O ratio was 4:1 and good yields were obtained in 3-4 h (entries 6 and 7). Anyway, increasing reaction times led to the formation of α-bromo ketone side

product (entry 8). Different amount of NBS and type of radical initiator gave comparable results (entries 9, 12 and 10, respectively). Finally, the process was scaled up to 4 mmol with unchanged efficiency (entry 13). With the optimized one-pot procedure in hand, substantial attention was paid to analyze the scope of the methodology employing substituted ethylbenzonitriles **150a-h** (Table 11). These substrates were obtained following the synthetic pathways showed in scheme 59: by nitration, reduction and acetylation starting from **150a** (pathway a and b) or by Sandmeyer reactions of the substituted aniline **150c** (pathway a). The 5-nitro-2-ethyl benzonitrile **150b** was less reactive and a higher amount of NBS was required (Table 11, entries 2-5). Both 5-chloro-2-ethylbenzonitrile **150d** and 5-Br-2-ethylbenzonitrile **150e** showed a reactivity comparable to **150a**, giving ketones **144c** and **144d**, respectively, in good yields (Table 11, entries 6-8). Again, the acetamide **150f** gave mainly electrophilic bromination on the aromatic ring (compound **150i**) and in less extent the relative ketone **144e**: even after long reaction time, it was poorly reactive for the presence of the free NH group (Scheme 59b; Table 11, Entry 9). On the contrary, the *N*-methylacetamide **150g** reacted smoothly, leading to the desired ketone **144f** in good yield (Scheme 59b and Table 11, entry 10). Moreover, the substrate **150h** bearing a methoxy group led to two new acetylbenzonitriles (**144g**, **144h**), depending on the reaction conditions (Scheme 59, pathway c and Table 11, entries 11 and 12): under the optimized conditions, 2-acetylbenzonitrile **144g** was obtained in poor yield along with 2-bromo-6-ethyl-3-methoxybenzonitrile as the main product, but increasing the amount of NBS and the reaction time, 2-acetylbenzonitrile **144h** was isolated in good yield (Scheme 59 pathway c and Table 11, entry 12).

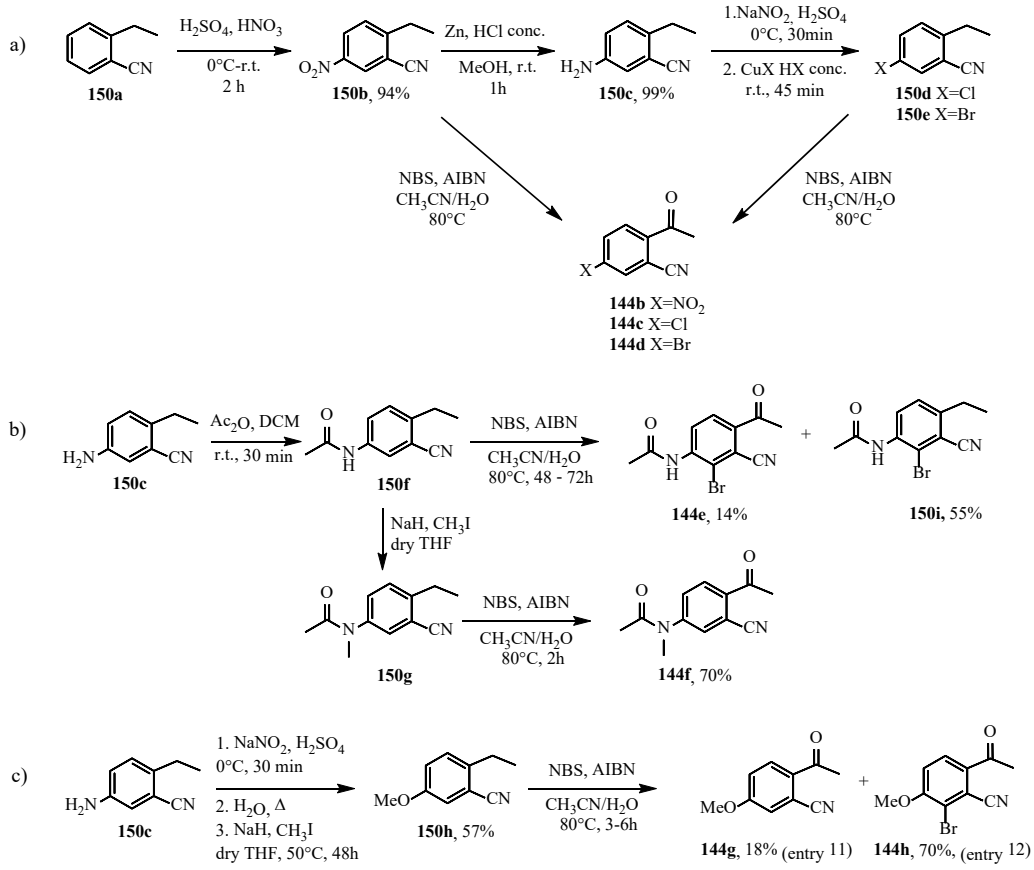
Table **11**. Synthesis of 2-acetylbenzonitriles **144**.



150 **144**

Entry	CH_3CN/ H_2O ratio	**144**	X	Y	NBS (eq.)	t (h)	Yield (%)[a]
1	4:1	**144a**	H	H	3.5	4	82
2	4:1	**144b**	NO_2	H	7.0	36	59
3	4:1	**144b**	NO_2	H	3.5	96	22[b]
4	1:1	**144b**	NO_2	H	4.5	48	19[b]
5	1:4	**144b**	NO_2	H	4.5	48	24[b]
6	4:1	**144c**	Cl	H	3.5	7	67
7	4:1	**144c**	Cl	H	3.5	4	70
8	4:1	**144d**	Br	H	3.5	5.5	72
9	4:1	**144e**	AcNH	Br	7.0	48-72	14
10	4:1	**144f**	AcNMe	H	3.5	2	70
11	4:1	**144g**	MeO	H	3.5	3	18[c]
12	4:1	**144h**	MeO	Br	5.0	6	70

[a)] Yields refer to chromatographically pure compounds. [b)] α-Bromoethylbenzonitrile was the main product. [c)] 2-Bromo-6-ethyl-3-methoxybenzonitrile was the main product.

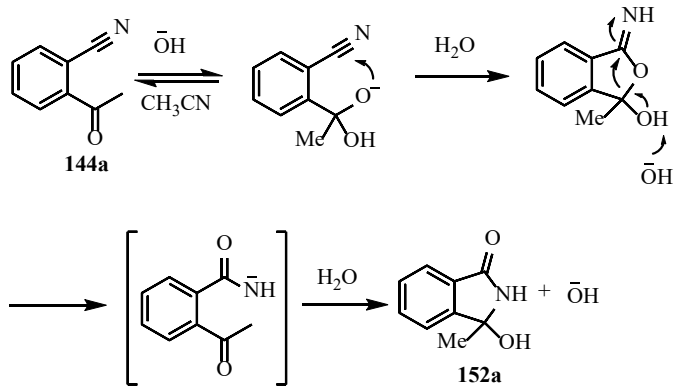


Scheme 59. *Synthesis of substituted 2-ethylbenzonitriles* ***150*** *and corresponding 2-acetylbenzonitriles* ***144****.*

5.2.2 Reactivity of 2-acetylbenzonitriles in tandem reactions with several nucleophiles

2-acetylbenzonitriles **144** were tested in a tandem process with carbon nucleophiles like malonate, nitromethane and malononitrile and hetero-nucleophiles like primary amines. Since ketones could undergo several competitive reactions (enolization as well as deprotonation and addition of the used nucleophile and direct addition of bases like hydroxides), our investigation started by studying the reaction of 2-acetylbenzonitriles **144a** with potassium hydroxide. Interestingly, in a control experiment, 2-acetylbenzonitrile **144a** reacted with potassium hydroxide affording 3-hydroxy-3-methyl isoindolinone **152a** in 80% yield (Scheme 60). The proposed mechanism

includes, after the initial addition of the ion hydroxide to the ketone, a cyclization at cyano group and a final rearrangement process (Scheme 60).

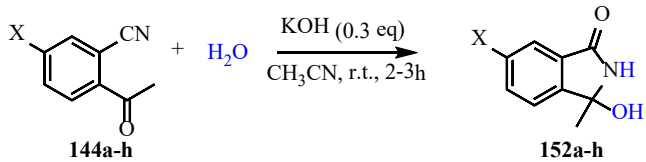


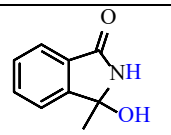
Scheme 60. *Control experiment. Reagents and conditions:* ***144a*** *(0.2 mmol), KOH (1 equiv.), acetonitrile (2 mL), 2 h.*

As seen in Scheme 60, this process involved a formal addition of water to **144a**. Therefore, in a subsequent experiment, a catalytic amount of KOH in CH_3CN/H_2O (9:1) and product **152a** was obtained in an excellent 93 % yield in 3 h (Table 12). Under this conditions, the generality of the reaction was examined using all the previously synthesized 2-acetylbenzonitriles **144a-h**. This process was effective for all substrates bearing both electron-withdrawing and -donating groups, which reacted smoothly to furnish an unprecedented variety of substituted 3-hydroxy-3-methylisoindolin-1-ones **152a-h** (Table 12).

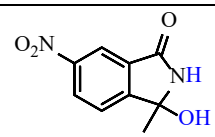
It is worthy to note that 3-hydroxy-3-methylisoindolinones **152** are important substrates for the asymmetric addition of nucleophiles like arylboron reagents or in Friedel–Crafts reactions in the presence of chiral metal complexes or chiral phosphoric acids leading to 3,3-disubstituted isoindolinones, as seen in Chapter 4.[149] Moreover, only a few typical methodologies have been reported for the synthesis of **152a**, by nucleophilic addition of Grignard reagent CH_3MgBr[150] or methyllithium[151] to phthalimide. However, these procedures give mixtures of regioisomeric isoindolinones that are very difficult to separate when a further substituent is present on the aromatic ring of the phthalimide, thereby limiting the applications of these compounds. In comparison, the methodology developed in this work is particularly convenient.

Table **12**. Optimized synthesis of 3-hydroxy-3-methylisoindolinones **152**.

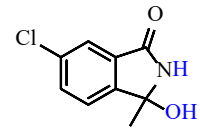




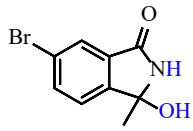
152a, 93%



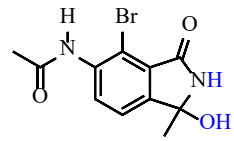
152b, 91%



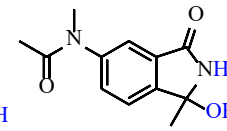
152c, 94%



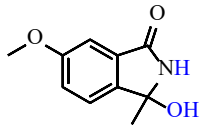
152d, 95%



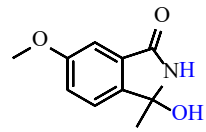
152e, 90%



152f, 87%



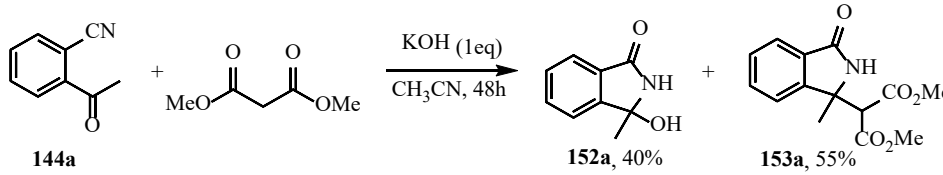
152g, 92%



152h, 96%

Yields refer to chromatographically pure compounds.

Afterwards, the reaction was performed with dimethylmalonate as nucleophile in the presence of 1 equivalent of KOH. Ketone **144a** reacted quantitatively and the product **153a** of the addition of dimethyl malonate was recovered together with **152a** in comparable yields (Scheme 61). The product **153a** was characterized by ^{1}H and ^{13}C NMR spectroscopy as well as by HRMS, and the *X*-ray analysis confirmed definitely the molecular structure of the product (Figure 33). *X*-ray diffraction structure of **152a** was also determined for the first time (Figure 33).



Scheme 61. *Competitive control experiment.*

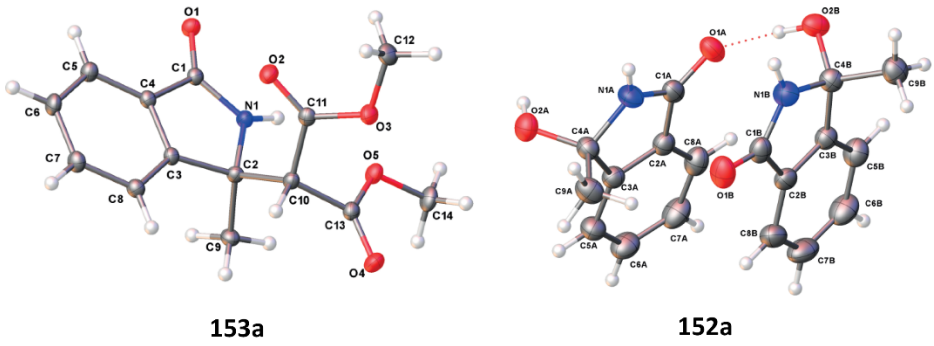
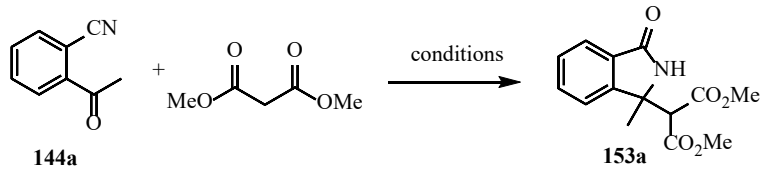


Figure 33. *ORTEP drawings and atom numbering schemes for compounds* ***153a*** *(left) and* ***152a*** *(right). Thermal ellipsoids are drawn at the 30 % probability level.*

Then, the efforts of the research were focused on the improvement of the observed chemoselectivity of the process represented in Scheme 61. As seen above (Scheme 60 and Table 12), the formation of **152a** is favored by the presence of water. Thus, to decrease the amount of the sideproduct **152a**, we carried out the reaction under dry conditions (Table 13).

Table **13**. Optimization of the tandem reaction.



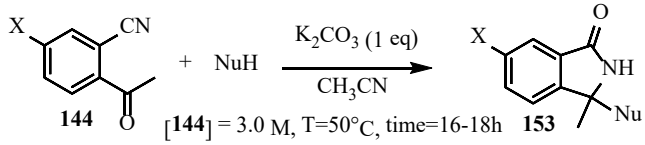
Entry	Base (equiv.)	Solvent ([**144a**] [M])[a]	Time (h)	Yield (%)[b]
1	KOH (1.0)	CH_3CN (0.17)	48	55[c]
2	KOH (1.0)	CH_3CN (0.17)	24	75[e]
3	KOH (0.3)	solvent free	3	80
4	K_2CO_3 (1.0)	CH_3CN (3.0)	48	88
5	K_2CO_3 (1.0)	CH_3CN (3.0)	18	87
6	K_2CO_3 (0.3)	CH_3CN (3.0)	48	82

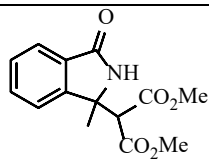
[a] Molar concentration of **144a**. [b] Yields refer to chromatographically pure compounds. [c] **152a** was obtained in 40 % yield. [d] Reaction performed under dry conditions. [e] **152a** was obtained in 17 % yield. [f] Reaction performed at 50 °C.

As reported in entry 2, isoindolinone **153a** was obtained in a good 75% yield. Furthermore, it was possible to increase the minimized again the formation of **152a** using

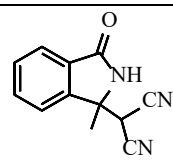
a catalytic amount of KOH under solvent-free and dry conditions (entry 3). The best results were achieved with potassium carbonate, both in stoichiometric or catalytic amounts under quasi solvent-free conditions, affording **153a** in high yields (entries 4-6). In these latter cases, the control of the dryness of the system is not necessary since the presence of OH^- in the system is minimized. With these optimized conditions in hand, the scope of the tandem process was extended to several carbon- and hetero-nucleophiles. As showed in Table 14, the process proved to be robust: a variety of functionalized side-chains and substituents on the aromatic ring were tolerated and new 3,3-disubstituted isoindolinones of high biopharmaceutical potential were obtained in very high yields.

Table **14**. Scope of the tandem reaction.



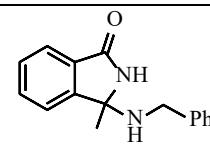


153a, 87%

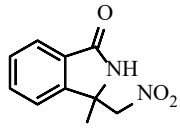


153b, 89%

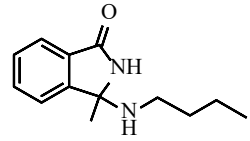
performed at r..t.



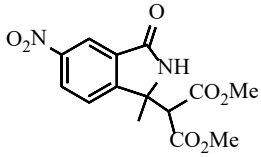
153c, 99%



153d, 94%



153e, 99%



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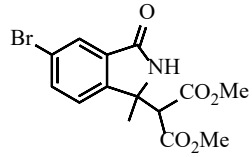
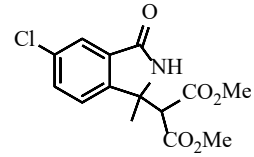
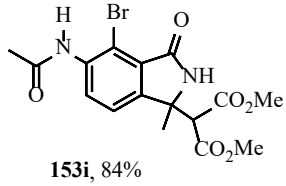


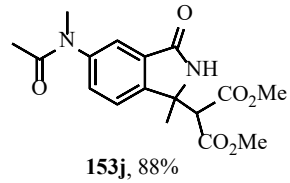
153g 93%



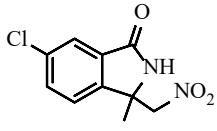
153h, 89%



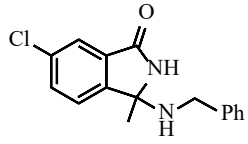
153i, 84%



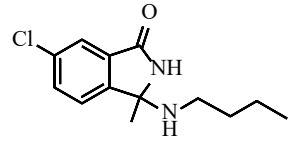
153j, 88%



153k, 85%



153l, 92%



153m, 89%

5.2.3 Preliminary Asymmetric Approach

As seen in paragraph 5.2.2, 2-acetylbenzonitriles **144a** react smoothly with different nucleophiles giving the important 3,3-disubstituted isoindolinones **153** in very good yield. As a central issue of this thesis, we started a preliminary study on an asymmetric version of this reaction under phase-transfer catalysis conditions. In these first attempts, 2-acetylbenzonitrile **144a** was reacted with dimethylmalonate by using chiral ammonium salts drawn in Figure 34 and several catalytic conditions shown in Table 15.

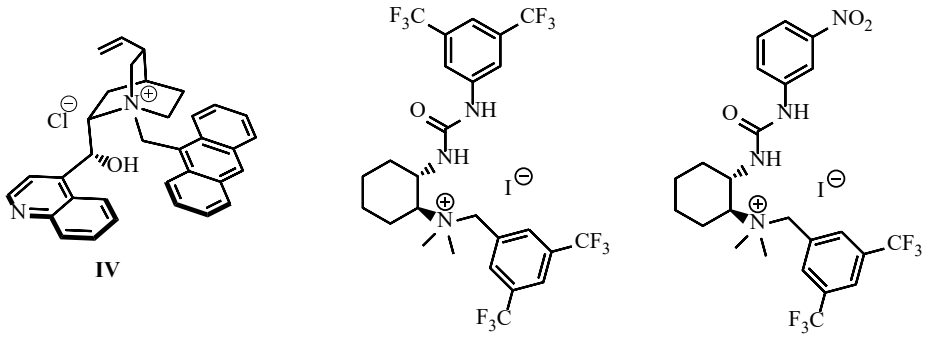
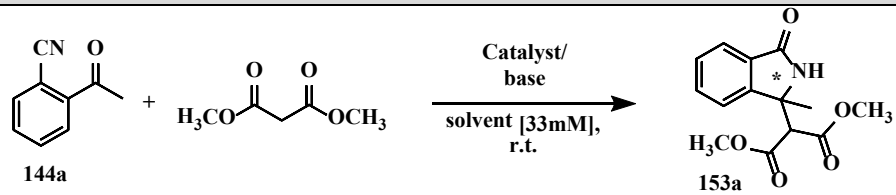


Figure 34. *Chiral catalysts for the preliminary screening.*

While the Cinchona alkaloid derived ammonium salt **IV** led to a very low enantioselectivity (entry 1), Waser catalyst **XXXII** in combination with 1.2 equivalent of potassium carbonate increased the enantiomeric excess up to 48%, although with very low conversion of the starting material (entry 2). A different base like cesium carbonate improved dramatically the conversion, but with significant lowering of selectivity (entry 3). Afterwards, several bases were tested (entry 4-10) and the best results were obtained by using potassium phosphate tribasic (entry 4). We also studied the influence of solvent, and halogenated solvents proved to be the best performing solvents for this process (compare entry 8 and entries 11-13). Moreover, the use of **XXXIII** did not affect the selectivity (compare entry 4 and 14). Although these are preliminary results, they are very encouraging considering the particular domino reaction mechanism involved and the direct formation of a quaternary stereogenic centre. Moreover, it is important to note that the enantioselectivity can be further improved after a reverse crystallization process (entry 4).

Table **15**. Asymmetric domino addition of dimethyl malonate to 2-acetyl benzonitrile **144a**.



Entry	Catalyst/%	Base/ eq.	Solvent	t (h)	Conv./ %	Yield[a]/ %	e.r.[b]
1	**IV**/ 20	K_2CO_3/ 1.2	DCM	96	83	78	55/45
2	**XXXII**/ 10	K_2CO_3/ 1.2	DCM	62	14	11	26/74
3	**XXXII**/ 10	Cs_2CO_3/ 1.2	DCM	20	97	95	36/64
4	**XXXII/ 10**	**K_3PO_4/ 1.2**	**DCM**	**44**	**82**	**80**	**24/76 (2/98)[c]**
5	**XXXII**/ 10	K_2CO_3/aq.50%	DCM	60	12	9	25/75
6	**XXXII**/ 10	K_2CO_3/ 1.0	DCM	60	86	83	25/75
7	**XXXII**/ 5	K_2CO_3/ 1.2	DCM	60	18	15	25/75
8	**XXXII**/ 5	K_3PO_4/ 2.0	DCM	20	89	85	25/75
9	**XXXII**/ 5	K_2HPO_4/ 2.0	DCM	20	No react.	-	-
10	**XXXII**/ 5	KH_2PO_4/ 2.0	DCM	20	No react.	-	-
11	**XXXII**/ 5	K_3PO_4/ 2.0	Toluene	20	70	66	39/61
12	**XXXII**/ 5	K_3PO_4/ 2.0	MtBE	20	80	78	33/67
13	**XXXII**/ 5	K_3PO_4/ 2.0	DCE	20	79	75	25/75
14	**XXXIII**/ 5	K_3PO_4/ 1.2	DCM	72	85	83	24/76

[a)] Yields refer to isolated products. [b)] Determined by chiral stationary phase HPLC analysis. [c)] After reverse crystallization from DCM/ hexane at -20°C

In conclusion, a useful one-pot approach to the synthesis of 2-acetylbenzonitriles was developed by the treatment of readily available 2-ethylbenzonitriles with NBS and a catalytic amount of AIBN in acetonitrile/water as solvent. The obtained substrates were successfully used as electrophiles in a new tandem methodology for the access to 3,3-disubstituted isoindolinones under very mild conditions. Furthermore, a preliminary study demonstrated the applicability of these ketones in an asymmetric reaction with dimethylmalonate leading to very encouraging results.

CHAPTER 6: *β*-ADDITION OF ISOXAZOLIDIN-5-ONES TO MORITA-BAYLIS-HILLMAN CARBONATES CATALYZED BY ASYMMETRIC PHASE-TRANSFER CATALYSIS

6.1 Introduction

During a six months internship in Prof. Mario Waser laboratories (Johannes Kepler University Linz, Austria), I investigated the reaction between Morita-Bayliss-Hillman carbonates and α-substituted *N*-Boc isoxazolidin-5-ones in order to obtain highly functionalized $\beta^{2,2}$-amino acid derivatives.

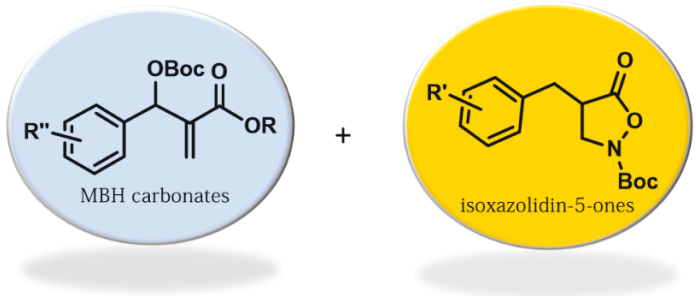
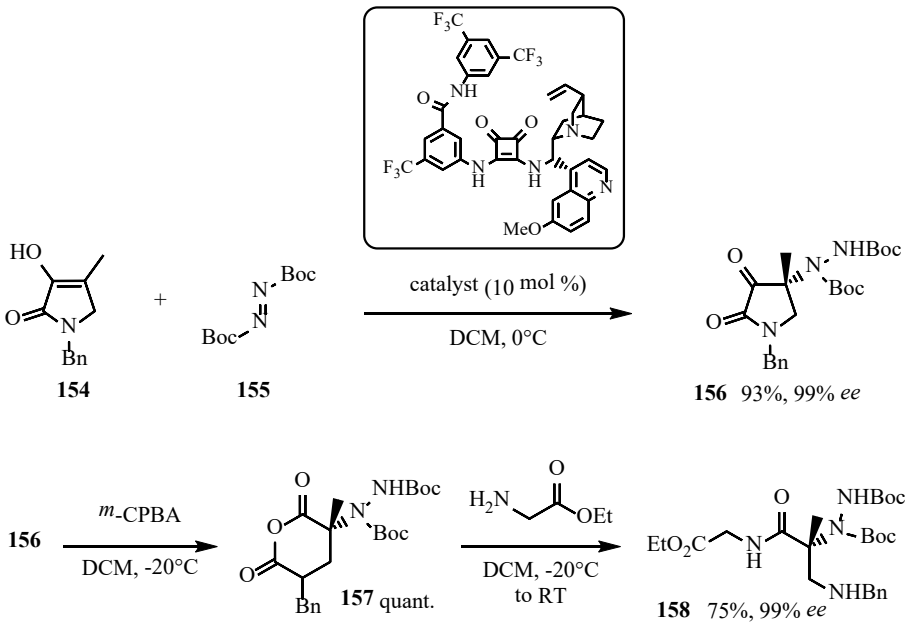


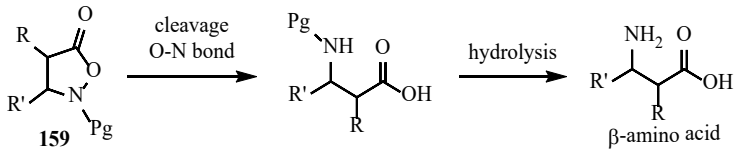
***Figure 35**. MBH carbonates (left) and α-benzyl substituted isoxazolidin-5-ones (right).*

While the asymmetric synthesis of α-amino acid has been a very thoroughly investigated topic, the number of available asymmetric approaches for *β*-amino acids and, in particular, $\beta^{2,2}$-amino acids remain limited. In this context, Palomo *et al.* reported a catalytic asymmetric reaction of pyrrolidin-2,3-diones or their enolic form **154** with different electrophiles, followed by regioselective Bayer-Villiger oxidation and a coupling with appropriate nucleophiles, e.g. glycine ethyl ester, affording the *α*-tetra-substituted *β*-amino *α*-hydrazino acid derived peptide **158** (Scheme 62).

Recently, a different approach to provide a straightforward access to $\beta^{2,2}$-amino acids was described by Briere[152] and co-workers by employing isoxazolidin-5-ones, useful precursors of beta-amino acid through the reductive cleavage of the N–O bond (Scheme 63).

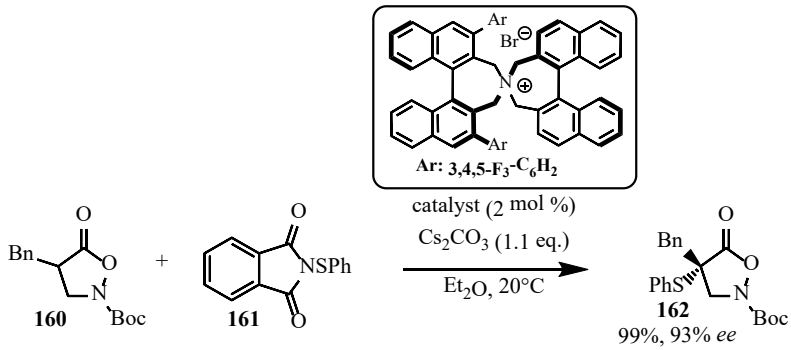


Scheme 62. *Catalytic α-amination of enols **154** with tert-butylazadicarboxylate **155** followed by a regioselective Bayer-Villiger oxidation and a coupling with glycine ethyl ester.*

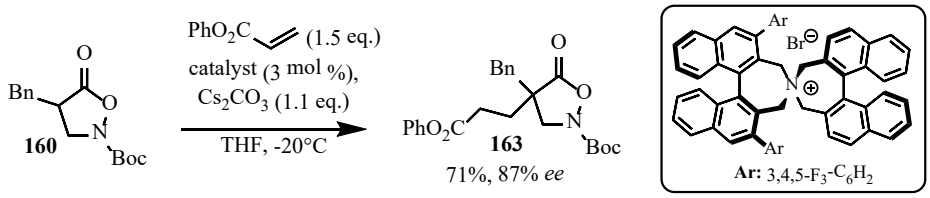


Scheme 63*. Synthesis of β-amino acid from isoxazolidin-5-ones **159** through the cleavage of O-N bond and deprotection of the amino group.*

In this case, the enantioselective phase-transfer catalyzed *α*-Sulfanylation of isoxazolidin-5-one **160** was carried out by using the *N*-sulfanylphthalimide **161** as electrophile and only 2 mol % of a commercial Maruoka *N*-spiro quaternary chiral ammonium catalyst (Scheme 64). Furthermore, the same group[153] described an efficient enantioselective Michael reaction of **160** under similar phase-transfer conditions affording the enantioenriched *α*,*α*-disubstituted isoxazolidin-5-one **163** in good yield and high enantioselectivity (Scheme 65).

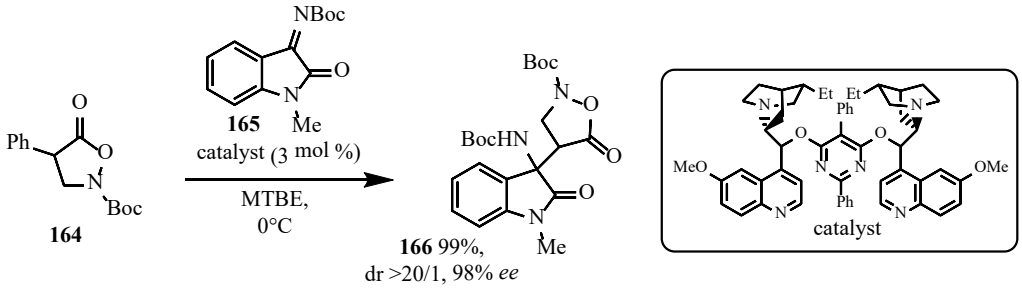


***Scheme 64**. α-functionalization of isoxazolidin-5-one **160** with N-sulfanylphthalimide **161** under PTC conditions.*

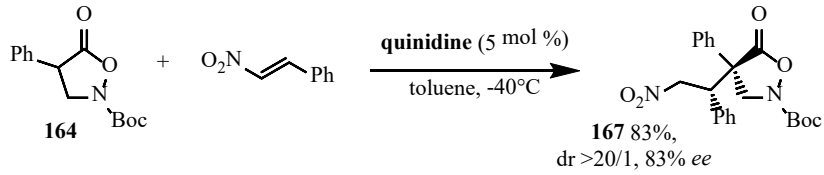


***Scheme 65.** Conjugate addition of isoxazolidin-5-one **160** to phenyl acrylate mediated by asymmetric phase-transfer catalysis.*

Shibasaki[154] *et al.*, instead, demonstrated that the pronucleophile **164** undergo organocatalytic direct Mannich reactions to isatin derived imines **165**, constructing two contiguous stereogenic centres with high stereoselectivities (Scheme 66). Moreover, because of a slight modification of catalytic conditions, the conjugate addition of **164** to trans-*β*-nitrostyrene also proceeded with high diastereoselectivity (Scheme 67).

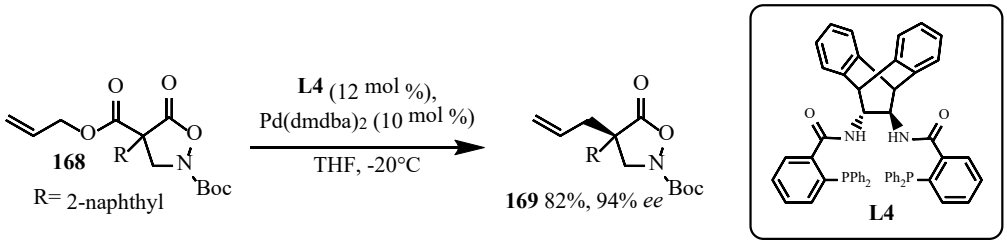


***Scheme 66.** Direct Mannich reaction of **164** to imine **165**.*



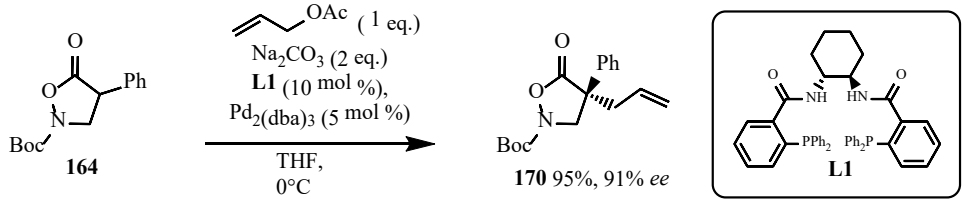
Scheme 67. *Catalytic diastereo- and enantioselective conjugate addition of* ***164*** *to trans-β-nitrostyrene.*

Furthermore, the same group[155] developed a palladium-catalyzed decarboxylative allylation of 4-substituted isoxazolidin-5-ones **168** for the asymmetric synthesis of quaternary $\beta^{2,2}$-amino acid derivatives **169** (Scheme 68).



Scheme 68. *Decarboxylative allylation of 4-substituted isoxazolin-5-ones* ***168****.*

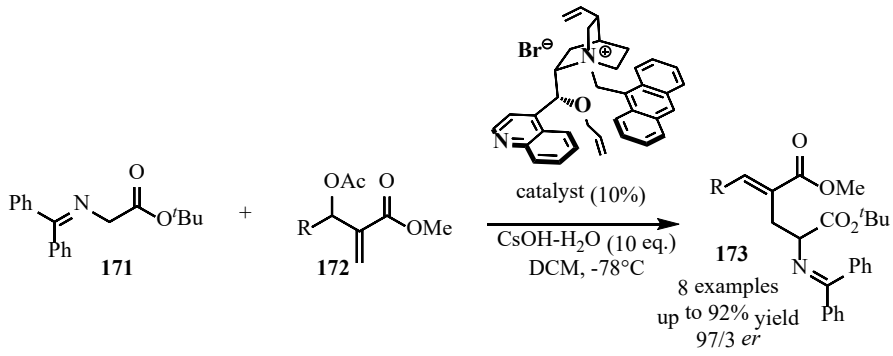
Independently, Cossy[156] and co-workers described the reaction of 4-substituted isoxazolidin-5-one **164** with allyl acetate by employing transition metal-catalysis, leading to the corresponding α,α-disubstituted isoxazolidin-5-ones **170**, bearing an all-carbon a-quaternary stereogenic centre in high yield and enantiomeric excess (Scheme 69).



Scheme 69. *Palladium-catalyzed asymmetric allylic alkylation of α-substituted isoxazolidin-5-ones* ***164****.*

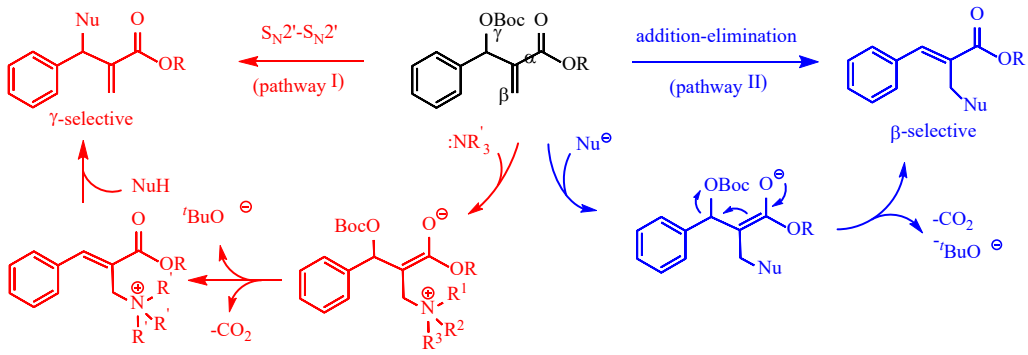
In general, also the easily available Morita-Baylis-Hillman acetates or carbonate promote highly stereoselective allylation reactions under asymmetric organocatalysis, thus resulting in a complementary strategy to transition metal-catalysed allylation approaches.[157] A beautiful example was reported by O'Donnell's group regarding the

highly enantioselective *β*-addition of glycine Schiff base **171** to allylic acetates **172** catalyzed by chiral Cinchona alkaloid ammonium salts (Scheme 70).[158]



Scheme 70. *Enantioselective allylic alkylation of the benzophenone imine of glycine tert-butyl ester **171** using MBH acetates **172**.*

In addition to this pioneering report, it was also impressively shown that the MBH adducts can react with a nucleophile mainly through two different ways, based on the nature of the employed catalyst[159]: through the pathway I, where a catalyst (a tertiary amine or a phosphine) attacks on the beta position with the subsequent ionization of the leaving group. Next, the leaving group deprotonates the pronucleophile, which attacks the intermediate on the gamma position, leading to the *γ*-regioisomer (Scheme 71, pathway I); otherwise, the nucleophile can attack the beta position directly (pathway II), affording the *β*-regioisomer by a tandem addition-elimination reaction (Scheme 71, pathway II).

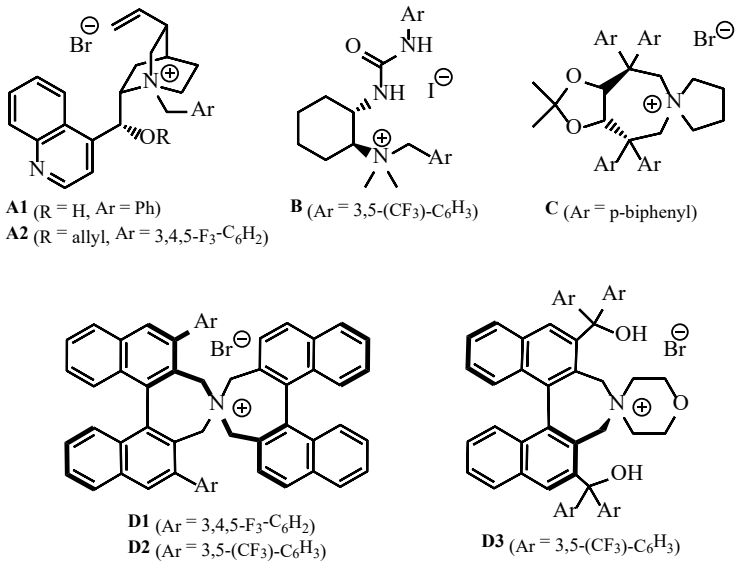


Scheme 71. *Regioselective Allylic Alkylation Reactions of the MBH Adducts.*

In this scenario, we were interested in the development of the first stereoselective *α*-allylation of 4-benzyl isoxazolidin-5-ones by using MBH-carbonates under asymmetric phase-transfer conditions.

6.2 Results and discussion

Our investigation started with the reaction between the benzyl-substituted isoxazolidin-5-one **160a** and the MBH carbonate **174a** under phase-transfer catalysis (Table 16). As proof-of-principle, in a first reaction tetrabutylammonium bromide (TBAB) was used as an achiral catalyst. In these conditions, the addition of **160a** to the conjugated acceptor **174a** occurs exclusively to the *β*-position, giving the (*E*)-configurated product **175a** as the main product (entry 1). Afterwards, several chiral catalysts were tested, including the easily available Cinchona derivatives **A**,[160] the Waser catalysts derived from cyclohexyldiamine **B**[161] and the tartaric acid-based ammonium salt **C**,[162] and the commercially available Maruoka *N*-spiro ammonium catalysts **D**[163] (Figure 36).



A1 (R = H, Ar = Ph)
A2 (R = allyl, Ar = 3,4,5-F_3-C_6H_2)

B (Ar = 3,5-(CF_3)-C_6H_3)

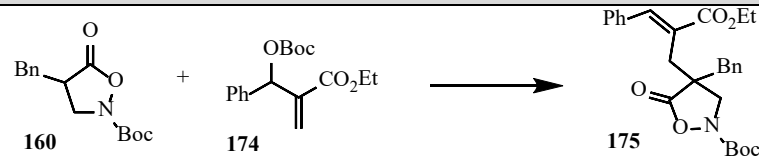
C (Ar = p-biphenyl)

D1 (Ar = 3,4,5-F_3-C_6H_2)
D2 (Ar = 3,5-(CF_3)-C_6H_3)

D3 (Ar = 3,5-(CF_3)-C_6H_3)

Figure 36. *Chiral ammonium salts used in this study.*

Table **16**. Identification of the most selective catalyst and the optimum reaction conditions.



Es[a]	Cat./ %	Solvent	Base/ equiv.	T (°C)	t (h)	Yield[b] (%)	E/Z[c]	*er*[d]
1	TBAB/ 10	THF	Cs_2CO_3/ 20	25	16	94	5:1	--
2	**A2**/ 5	THF	Cs_2CO_3/ 20	25	16	84	6:1	48:52
3	**A2**/ 5	CH_2Cl_2	Cs_2CO_3/ 20	25	16	39	5:1	49:51
4	**A2**/ 5	CH_2Cl_2	K_3PO_4/ 20	25	16	43	3:1	46:54
5	**A2**/ 5	THF	Cs_2CO_3/ 1.1	25	16	<5	--	--
6	**A1**/ 5	THF	Cs_2CO_3/ 1.1	25	72	54	4:1	51:49
7	**B**/ 5	THF	Cs_2CO_3/ 1.1	25	48	75	5:1	50:50
8	**C**/ 5	THF	Cs_2CO_3/ 3.0	25	24	60	6:1	49:51
9	**D1**/ 5	THF	Cs_2CO_3/ 3.0	25	24	86	6:1	74:26
10	**D1**/ 2	THF	Cs_2CO_3/ 3.0	25	72	73	6:1	71:29
11	**D1**/ 10	THF	Cs_2CO_3/ 3.0	25	24	95	7:1	75:25
12	**D2**/ 5	THF	Cs_2CO_3/ 3.0	25	24	82	5:1	85:15
13	**D3**/ 5	THF	Cs_2CO_3/ 3.0	25	24	26	5:1	50:50
14	**D2**/ 5	THF	Cs_2CO_3/ 1.1	25	24	<5	--	--
15	**D2**/ 5	CH_2Cl_2	Cs_2CO_3/ 1.1	25	96	60	3:1	78:22
16	**D2**/ 5	THF	K_2CO_3/3.0	25	24	<5	--	--
17	**D2**/ 5	MTBE	Cs_2CO_3/ 3.0	25	72	86	7:1	83:17
18	**D2**/ 5	*i*Pr_2O	Cs_2CO_3/ 3.0	25	48	90	7:1	87:13
19	**D2/ 5**	***i*Pr$_2$O**	**Cs_2CO_3/ 3.0**	**-20**	**96**	**90**	**10:1**	**94:6**
20	**D2**/ 5	*i*Pr_2O	Cs_2CO_3/ 3.0	-30	96	50	12:1	94:6
21	**D2**/ 5	THF	Cs_2CO_3/ 3.0	-40	96	23	7:1	96:4
22	**D1**/ 5	THF	Cs_2CO_3/ 3.0	-40	96	39	7:1	85:15
23[e]	**D1**/ 5	THF	Cs_2CO_3/ 3.0	25	24	94	6:1	74:26
24[f]	**D1**/ 5	THF	Cs_2CO_3/ 3.0	25	24	98	6:1	74:26

[a)] Using 0.1 mmol **160a** and 0.15 mmol **174a** (c = 0.05 M). [b)] Isolated Yield. [c)] Determined by ^{1}H NMR. [d)] Determined by HPLC using a chiral stationary phase. [e)] Using 0.1 mmol **160a** and 0.3 mmol **174a** (c = 0.05 M). [f)] Using 0.2 mmol **160a** and 0.1 mmol **174a** (c = 0.05 M).

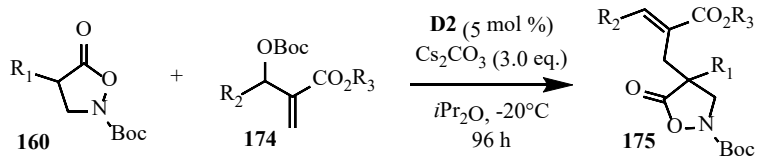
As shown in Table 16, Cinchona alkaloid catalysts didn't lead to an enantioenriched product, also changing the solvent and/or the nature/amount of the base (entries 2-6). In addition, the amount of base has a crucial effect on the conversion (compare entries 2 and 5). Similar disappointing results were obtained using catalysts **B** and **C** and the product was recovered as a nearly racemic mixture (entries 7 and 8).

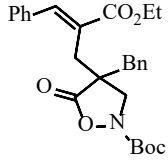
As seen in the introduction of this Chapter (Scheme 65), Briere and co-workers reached the best results for the conjugated addition of pronucleophile **160** to acrylates by employing the rigid Maruoka catalysts **D**. Thus, we tested the commercially available derivatives **D**1-3 next and in the first experiment carried out with catalyst **D**1, the product **175a** was achieved in high yield and with a promising initial *er* of 74:26 (entry 9). Subsequently, we changed several parameters, such as the amount of catalyst (entries 9-11) as well as the stoichiometric ratios of the reagents (entries 23 and 24) but no pronounced effects were observed. So, we used 5 mol% of catalyst and 1.5 equivalents of MBHc **174a** for the further optimization. In these conditions, catalyst **D**2 and **D**3 were examined and, while bifunctional catalyst **D**3 did not give any asymmetric induction at all (entry 13), *N*-spiro bis-binaphthyl ammonium salt **D**2 led to an increase in the stereoselectivity (entry 12). Moreover, we noted that at least 3 equivalents of Cs_2CO_3 in an ether solvent are necessary to achieve reasonable yields and selectivities with catalyst **D**2 (compare entry 12 with entries 14-16). Then, we screened several ethers and diisopropylether (iPr$_2$O) turned out to be the best performing solvent for this process (entry 18). Testing the influence of the temperature, we found that the selectivity could be further improved by lowering the temperature from -20 to -40 °C (entries 19-22), although no product formation in iPr$_2$O at -40 °C and only a very slow reaction in THF at -40 °C.

In according to this extensive screening, we expanded the scope of the reaction to MBH carbonates **174** and 4-benzyl substituted isoxazolidin-5-ones **160** under the optimized experimental conditions given in entry 19 (5 mol% of **D**2 in iPr$_2$O at -20 °C) (Table 16). As shown in Table 17, ethyl ester-based MBH-carbonates (compare products **175a-c**) gave the best enantioselectivities. Substitutions on the benzyl group of the nucleophile **160** were relatively well tolerated (see products **175d-m**), although some reduced enantioselectivities were observed when accessing the halide- and CF_3-substituted

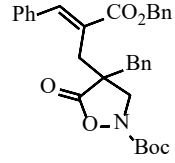
products **175h**, **175i**, **175j**, **175l**. The aryl moieties in the MBH carbonates **174** had a rather minor effect only, regardless of their electronic nature and substitution pattern (products **175n-w**). The only real limitation was observed using a *β*-*i*-propyl containing isoxazolidin-5-one, which did not result in any product formation at all (under the racemic as well as the asymmetric reaction conditions). So, all things considered, our protocol has proved satisfyingly robust affording novel highly functionalized *β*-amino acid derivatives with reasonable yields and high diastereo- and enantioselectivities.

Table **17**. Application scope for the asymmetric reaction of β-amino acid-based compounds **160** with MBH carbonates **174**.

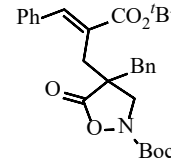




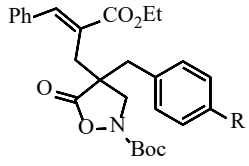
175a (90%)
E:Z = 10:1, e.r. = 94:6



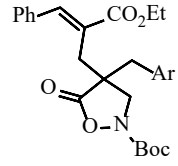
175b (68%)
E:Z = 8:1, e.r. = 78:22



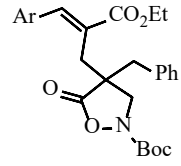
175c (53%)
E:Z = 8:1, e.r. = 91:9



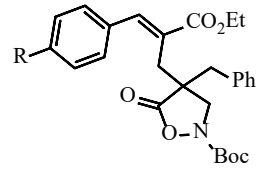
175d (R = Me; 92%)
E:Z = 8:1, e.r. = 92:8
175e (R = ^{t}Bu; 77%)
E:Z = 11:1, e.r. = 95:5
175f (R = Ph; 74%)
E:Z = 9:1, e.r. = 92:8
175g (R = OMe; 77%)
E:Z = 10:1, e.r. = 93:7
175h (R = Cl; 80%)
E:Z = 6:1, e.r. = 88:12
175i (R = Br; 70%)
E:Z = 10:1, e.r. = 84:16
175j (R = CF_3; 82%)
E:Z = 10:1, e.r. = 85:15



175k (Ar = 2,5-Me_2-C_6H_3; 65%)
E:Z = 8:1, e.r. = 89:11
175l (Ar = 2,4-Cl_2-C_6H_3; 75%)
E:Z = 9:1, e.r. = 84:16
175m (Ar = β-Np; 78%)
E:Z = 9:1, e.r. = 91:9



175v (Ar = 2,3-Cl_2-C_6H_3; 90%)
E:Z = 4:1, e.r. = 93:7
175w (Ar = β-Np; 62%)
E:Z = 7:1, e.r. = 91:9



175n (R = Me; 83%)
E:Z = 7:1, e.r. = 92:8
175o (R = *i*Pr; 67%)
E:Z = 6:1, e.r. = 91:9
175p (R = ^{t}Bu; 77%)
E:Z = 8:1, e.r. = 91:9
175q (R = Ph; 92%)
E:Z = 8:1, e.r. = 92:8
175r (R = OMe; 81%)
E:Z = 11:1, e.r. = 92:8
175s (R = Cl; 78%)
E:Z = 5:1, e.r. = 92:8
175t (R = Br; 81%)
E:Z = 5:1, e.r. = 91:9
175u (R = NO_2; 55%)
E:Z = 5:1, e.r. = 93:7

The E/Z ratios were determined by NMR of the crude product mixture; the enantiomeric ratios are given for the major diastereomer and were measured by HPLC using a chiral stationary phase.

Moreover, the *X*-ray diffraction analysis carried out on racemic product **175f** confirmed the (*E*)-double bond configuration, which is in accordance with NMR investigations (Figure 37). Concerning the absolute configuration, unfortunately we were not able to obtain crystals of satisfying quality of the enantioenriched products.

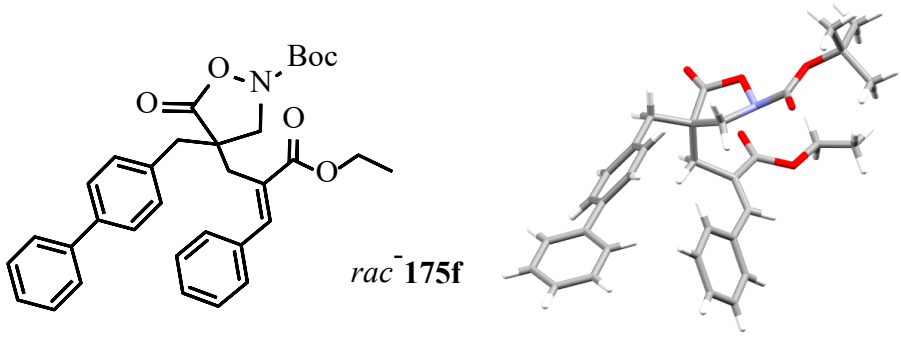
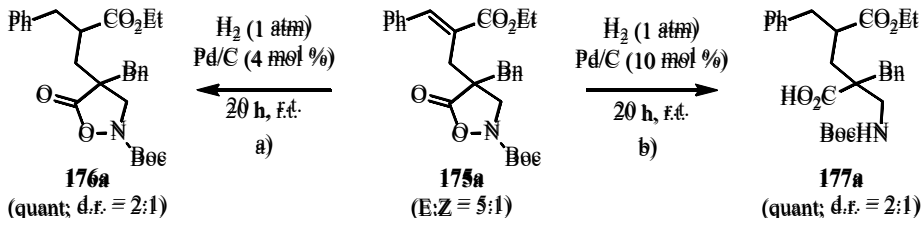


Figure 37. *X-ray molecular structure of racemic compound **175f**. Atom types: C grey, N blue, O red, H white.*

Finally, to further expand the synthetic utility of this transformation for the synthesis of *β*-amino acid, we performed the atmospheric pressure hydrogenation of compound **175a** under heterogeneous conditions (using Pd/C, Scheme 72) and found that double bond reduction occurs easily (step a), albeit with some erosion of *dr*, followed by N–O cleavage to **177a** when using a slightly larger amount of hydrogenation catalyst (step b).

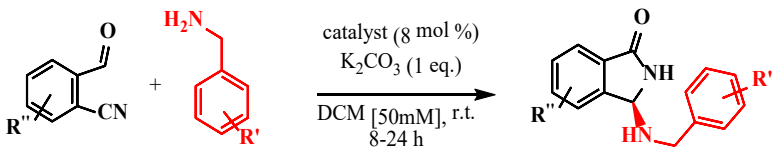


Scheme 72. *Heterogenous hydrogenation of compound **175a**. a) reduction of the double bond; b) cleavage of N–O bond after reduction of double bond.*

To sum it up, 4-substituted isoxazolidin-5-ones **160** were used as pronucleophiles in the asymmetric organocatalytic conjugated addition to MBH carbonates **174**, affording novel highly functionalized β-amino acid derivatives **175**. The scope and generality of this catalytic system were expanded to many substrates bearing both electro-donating and -withdrawing substituents and good results in terms of yield and stereoselectivity were obtained.

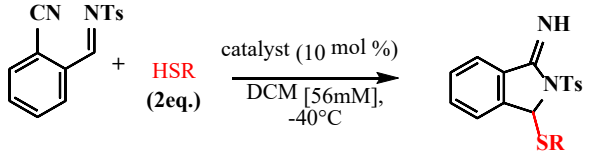
SUMMARY

Chirality has very strong repercussions on our daily life regarding the use of chiral bioactive compounds such as pharmaceuticals, agrochemicals or flavours and fragrances. The development of new catalytic approaches for the synthesis of important products is constantly growing and the organocatalysis has proved to be a useful tool for achieving this goal. In this doctoral project, several enantioselective organocatalyzed methodologies for the synthesis of heterocyclic compounds were developed. Since isoindolinonic core is an important scaffold in medicinal chemistry, a significant part of the PhD work was spent to develop new methodologies to produce enantioenriched functionalized isoindolinones. New 3-amino-substituted isoindolinones were obtained by a tandem reaction of 2-formyl benzonitriles with primary amines catalyzed by trifunctional Cinchona alkaloid ammonium salts. This synthetic approach proved to be robust, and both electro-withdrawing and donating groups on the reagents were tolerated, giving high selectivities and yields.



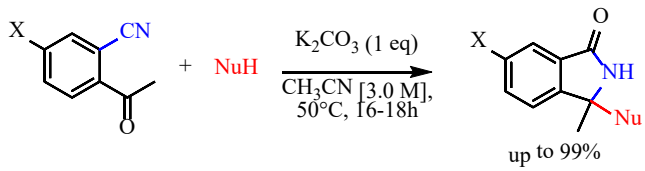
up to 98%, 95:5 *er*

Again, 2-cyano-N-tosylbenzylidenimine were reacted with thiols by an enantioselective cascade process by leading to a new class of multi-heteroatomic cyclic scaffolds containing the important *N,S*-acetal functionality. The reaction was catalyzed by a readily available trifunctional Cinchona alkaloid-based organocatalyst, achieving high yields and enantiomeric excesses. Moreover, the scope of the methodology was expanded to thioglycolate and 3-mercaptopropionate, useful substrates for further derivatizations.

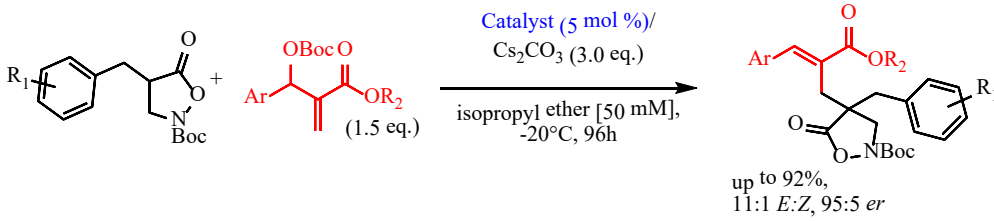


up to 97%, 95:5 *er*

Furthermore, a new tandem methodology for the access to 3,3-disubstituted isoindolinones under very mild conditions was developed. This goal was achieved by developing a useful one-pot approach to the synthesis of 2-acetylbenzonitriles through the treatment of readily available 2-ethylbenzonitriles with NBS and a catalytic amount of AIBN in acetonitrile/water as solvent.



Finally, the stereoselective addition of 4-substituted isoxazolidin-5-ones to MBH carbonates, organocatalyzed by a commercially available Maruoka *N*-spiro quaternary chiral ammonium catalyst, was realized. This protocol enables a facile access to new *α*-allylated highly functionalised *β*-amino acid derivatives bearing a quaternary stereocentre.



EXPERIMENTAL SECTION

General information

Reactions were performed using commercially available compounds without further purification and analytical grade solvents. All reactions requiring dry or inert conditions were conducted in flame dried glassware under a positive pressure of nitrogen. Molecular sieves (Aldrich Molecular Sieves 4 Å) were activated under vacuum at 200 °C overnight. All the reactions were monitored by thin layer chromatography (TLC) on precoated silica gel plates (0.25 mm) and visualized by fluorescence quenching at 254 nm. Flash chromatography was carried out using silica gel 60 (70–230 mesh, Merck). The NMR spectra were recorded on Bruker Avance 600, 400, 300, 250 spectrometers (600 MHz, 400 MHz, 300 MHz, 250 MHz, ^{1}H; 150 MHz,100 MHz, 75 MHz, 62,5 MHz ^{13}C). Spectra were referenced to residual $CHCl_3$ (7.26 ppm, ^{1}H; 77.00 ppm, ^{13}C), CD_3OD (3.33 ppm, ^{1}H; 49.0 ppm, ^{13}C) or $(CH_3)_2SO$ (2.50 ppm, ^{1}H;39.52 ppm, ^{13}C) when indicated. The following abbreviations are used to indicate the multiplicity in NMR spectra: s - singlet; d - doublet; t - triplet; q - quartet; dd – double doublet; ddd - doublet of doublet of doublet; m - multiplet; bs - broad signal. Coupling constants (J) are quoted in hertz. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. FTIR spectra were recorded as thin films on KBr plates using Bruker VERTEX 70 spectrometer and absorption maxima are reported in wavenumber (cm^{-1}). ESI-MS were carried out using a Bio-Q triple quadrupole mass spectrometer (Micromass, Manchester, UK) equipped with an electrospray ion source. High-resolution mass spectra (HRMS) were acquired using a Bruker solariX XR Fourier transform ion cyclotron resonance mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany) equipped with a 7 T refrigerated actively-shielded superconducting magnet. The samples were ionized in positive ion mode using an electrospray (ESI) ionization source or the MALDI ion source. Optical rotation of compounds was performed on a Jasco P-2000 digital polarimeter and a Schmidt + Haensch Polarimeter Model UniPol L 1000. HPLC analyses were performed using a Waters-Breeze 2487, UV dual λ absorbance detector and 1525 Binary HPLC Pump and a Thermo Scientific Dionex

Ultimate 3000 system with diode array detector, using a Chiralpak AD-H (250 x 4.6 mm, 5 µm), IC (250 x 4.6 mm, 5 µm), IA-3 (250 x 4.6 mm, 5 µm) or a YMC Cellulose-SB (250 x 4.6 mm, 5 µm) chiral stationary phase.

7.1 THE FIRST ASYMMETRIC SYNTHESIS OF 3-AMINO-SUBSTITUTED ISOINDOLINONES

Catalysts **I**, **II, III, IV, V** and **VII** are commercially available. Catalysts **VI**,[164] **IX**,[165] **X**[166] and **XI**[167] have been prepared in accordance with the literature and gave spectral and analytical data as reported.

General procedure for the synthesis of bifunctional chiral phase transfer catalysts XV, XVI, XII, XIII, XIV

All the ammonium salts were prepared by following the reported procedure for the quaternisation of tertiary amines[151] from 6'-demethylated quinine (catalyst **XII, XIII, XIV**) and 6'-demethylated quinidine (catalyst **XV, XVI, XVII**) which were prepared as reported in the literature.[168]

Catalyst XII: by following the general procedure, starting from 6'-demethylated quinine (316 mg, 0.98 mmol) and benzyl bromide (128 µl, 184 mg, 0.98 mmol). Beige solid, (350 mg, 0.73 mmol, 74%). mp > 200 °C; $[\alpha]_D$ = -206.6° (c = 1.0, MeOH, 23°C); ^{1}H NMR (600 MHz, CD_3OD, 298.0 K): δ 1.45-1.52 (m, 1H), 1.84-1.92 (m, 1H), 2.06-2.10 (m, 1H), 2.23-2.29 (m, 1H), 2.29-2.36 (m, 1H), 2.68-2.75 (m, 1H), 3.35-3.43 (m, 1H), 3.46-3.53 (m, 1H), 3.56-3.62 (m, 1H), 3.92-3.98 (m, 1H), 4.37-4.45 (m, 1H), 4.92 (d, J = 12.3 Hz, 1H), 5.04 (dd, J_{AC} = 10.5 Hz, J_{AB} = 1.2 Hz, 1H), 5.17 (dd, J_{BC} = 17.1 Hz, J_{AB} = 1.2 Hz, 1H), 5.22 (d, J = 12.3 Hz, 1H), 5.72 (ddd, J_{BC} = 17.1 Hz, J_{AC} = 10.5 Hz, J_{CX} = 6.9 Hz, 1H), 6.49 (s, 1H), 7.43 (dd, J = 2.5 Hz, J = 9.1 Hz, 1H), 7.47 (d, J = 2.4 Hz, 1H), 7.58-7.62 (m, 3H), 7.70-7.75 (m, 2H), 7.85 (d, J = 4.6 Hz, 1H), 7.99 (d, J = 9.1 Hz, 1H), 8.73 (d, J = 4.6 Hz, 1H); ^{13}C NMR (125 MHz, MeOD, 298.0 K): δ 22.9, 26.6, 28.8, 39.9, 53.3, 62.6, 66.2, 66.8, 70.5, 105.5, 118.2, 121.9, 124.0, 128.2, 129.3, 131.1 (2C), 132.5,

132.7, 135.6 (2C), 139.4, 144.7, 146.1, 148.4, 158.7; IR (ATR): 3217, 1620, 1530, 1465, 1216, 925, 861, 832, 766, 719, 706 cm^{-1}; HRMS (API) calcd for [$C_{26}H_{29}N_2O_2^+$] 401.2224, found 401.2216.

Catalyst XIII: by following the general procedure, starting from 6'-demethylated quinine (334 mg, 1.08 mmol) and 4-(trifluoromethyl)benzyl bromide (184 µl, 284 mg, 1.19 mmol). Beige solid (462 mg, 0.84 mmol, 78%). mp > 200 °C; $[\alpha]_D$ = -48.4° (c = 0.5, MeOH, 23°C); ^{1}H NMR (600 MHz, MeOD, 298.0 K): δ 1.43-1.51 (m, 1H), 1.83-1.91 (m, 1H), 2.06-2.10 (m, 1H), 2.22-2.28 (m, 1H), 2.28-2.35 (m, 1H), 2.68-2.74 (m, 1H), 3.29-3.31 (m, 1H), 3.45-3.51 (m, 1H), 3.62-3.68 (m, 1H), 3.94-4.00 (m, 1H), 4.41-4.49 (m, 1H), 5.03 (d, J = 12.4 Hz, 1H), 5.04 (dd, J_{AC} = 10.3 Hz, J_{AB} = 1.2 Hz, 1H), 5.17 (dd, J_{BC} = 17.2 Hz, J_{AB} = 1.2 Hz, 1H), 5.29 (d, J = 12.4 Hz, 1H), 5.72 (ddd, J_{BC} = 17.1 Hz, J_{AC} = 10.5 Hz, J_{CX} = 6.9 Hz, 1H), 6.48 (s, 1H), 7.41 (dd, J = 2.5 Hz, J = 9.1 Hz, 1H), 7.45-7.47 (m, 1H), 7.84 (d, J = 4.6 Hz, 1H), 7.89 (d, J = 8.2 Hz, 2H), 7.95 (d, J = 8.2 Hz, 2H), 7.98 (d, J = 9.1 Hz, 1H), 8.72 (d, J = 4.6 Hz, 1H); ^{13}C NMR (125 MHz, MeOD, 298.0 K): δ 23.1, 26.7, 28.8, 40.0, 53.8, 63.0, 65.3, 67.1, 71.0, 105.7, 118.5, 122.1, 124.2, 126.2 (q, J = 269.9 Hz, 1C), 128.1 (q, J = 2.5 Hz, 2C), 128.4, 132.8, 133.9, 134.4 (q, J = 32.3 Hz, 1H), 136.6 (2C), 139.5, 144.9, 146.2, 148.6, 158.9; IR (ATR): 3182, 1620, 1323, 1116, 1066, 897, 863 cm^{-1}; HRMS (API) calcd for [$C_{27}H_{28}F_3N_2O_2^+$] 469.2097, found 401.2090.

Catalyst XIV: by following the general procedure, starting from 6'-demethylated quinine (334 mg, 1.08 mmol) and 9-(chloromethyl) anthracene (267 mg, 1.18 mmol) as yellow solid (523 mg, 0.97 mmol, 90%). mp = 186-190 °C; $[\alpha]_D$ = -89.3° (c = 1.0, MeOH, 23°C); ^{1}H NMR (600 MHz, MeOD, 298.0 K): δ 1.49-1.65 (m, 2H), 1.93-1.98 (m, 1H), 2.14-2.23 (m, 1H), 2.14-2.23 (m, 1H), 2.31-2.37 (m, 1H), 2.43-2.50 (m, 1H), 2.79-2.88 (m, 1H), 3.22-3.29 (m, 1H), 3.80-3.87 (m, 1H), 4.40-4.47 (m, 1H), 4.64-4.72 (m, 1H), 5.03 (dd, J_{AC} = 10.5 Hz, J_{AB} = 1.2 Hz, 1H), 5.08 (dd, J_{BC} = 17.2 Hz, J_{AB} = 1.2 Hz, 1H), 5.75 (ddd, J_{BC} = 17.2 Hz, J_{AC} = 10.5 Hz, J_{CX} = 7.1 Hz, 1H), 5.92 (d, J = 14.0 Hz, 1H), 6.49 (d, J = 14.0 Hz, 1H), 6.95 (s, 1H), 7.49 (dd, J = 2.2 Hz, J = 9.2 Hz, 1H), 7.63-7.68 (m, 2H), 6.78 (d, J = 2.2 Hz, 1H), 7.79-7.85 (m, 2H), 7.98 (d, J = 4.5 Hz, 1H), 8.05 (d, J = 9.1 Hz, 1H), 8.24 (d, J = 8.4 Hz, 2H), 8.62 (d, J = 9.1 Hz, 1H), 8.78-8.83

(m, 2H), 8.56 (s, 1H); ^{13}C NMR (125 MHz, MeOD, 298.0 K): δ 23.6, 27.1, 28.2, 40.6, 54.3, 57.8, 64.4, 67.9, 70.9, 106.0, 118.5, 120.0, 122.3, 124.3, 125.9, 126.4, 127.4, 127.5, 128.5, 130.1, 130.2, 132.0, 132.0, 132.8, 133.9, 133.9, 134.6, 135.5, 135.6, 139.6, 144.9, 146.4, 148.6, 159.0; IR (ATR): 3077, 2362, 1619, 1464, 1224, 858, 738 cm^{-1}; HRMS (API) calcd for [$C_{34}H_{33}N_2O_2^+$] 501.2537, found 501.2528.

Catalyst XV: by following the general procedure, starting from 6'-demethylated quinidine (100 mg, 0.32 mmol) and benzyl bromide (40 µl, 57,5 mg, 0.34 mmol). Beige solid (108 mg, 0.22 mmol, 70%). mp > 200 °C; $[\alpha]_D$ = +169.2° (c = 0.5, MeOH, 15°C); ^{1}H NMR (300 MHz, CD_3OD, 298.0 K): δ 1.13–1.17 (m, 1H), 1.88-1.96 (m, 3H), 2.45-2.67 (m, 2H), 3.04-3.16 (m, 1H), 3.58-3.67 (m, 1H), 3.88-4.04 (m, 2H), 4.66 (bs, 1H), 5.24-5.30 (m, 2H), 6.00-6.14 (m, 1H), 6.46 (bs, 2H), 7.40 (d, J= 7.5 Hz, 1H), 7.59-7.99 (m, 9H), 8.72 (d, J= 5.0 Hz, 1H). ^{13}C NMR (60MHz, CD_3OD, 298.0 K): δ 20.7; 23.3; 27.1; 37.5; 54.3; 56.8; 63.4; 65.4; 67.6; 103.7; 116.6; 119.7; 122.0; 126.1; 127.2; 129.1 (2C); 130.4 (2C); 133.5 (2C); 136.3; 142.5; 146.3; 156.6.

Catalyst XVI: Spectra and analytical data as reported.[151]

Catalyst XVII: by following the general procedure, starting from 6'-demethylated quinidine (93 mg, 0.3 mmol) and 1-(Chloromethyl) benzotriazole (54 mg, 0.32 mmol). Beige solid (75 mg, 63%) mp > 200 °C; $[\alpha]_D$ = +213.9° (c = 0.5, MeOH, 15°C); ^{1}H NMR (300 MHz, $CDCl_3$, 298.0 K): δ 0.86–1.00 (m, 1H), 1.60-1.98 (m, 3H), 2.09-2.39 (m, 2H), 2.59-2.86 (m, 1H), 3.12-3.49 (m, 1H), 4.06-4.46 (m, 2H), 4.59-4.79 (m, 1H), 5.06-5.30 (m, 2H), 5.74-5.93 (m, 1H), 6.43 (bs, 2H), 6.81 (d, J= 9.2 Hz, 1H), 7.13-7.25 (m, 3H), 7.31-7.45 (m, 1H), 7.46-7.74 (m, 4H), 7.91 (s, 1H), 8.48 (d, J= 8.5 Hz, 1H), 8.64 (d, J= 4.5 Hz, 1H). ^{13}C NMR (75MHz, $CDCl_3$, 298.0 K): δ 21.2; 23.6; 26.6; 37.8; 54.1; 57.0; 65.8; 66.6; 67.7; 103.2; 110.6; 118.6; 119.2; 119.8; 121.2; 124.3; 125.0; 129.8; 131.2; 133.7; 134.5; 140.7; 142.5; 144.7; 146.6; 156.1.

General procedure for the synthesis of isoindolinones 110 under phase transfer catalyzed conditions

In a round-bottom flask, amine **116** (0.11 eq., 0.11 mmol) was added at room temperature to a stirred solution of 2-formylbenzonitrile **93** (0.10 mmol), K_2CO_3 (1 eq., 0.1 mmol) and phase transfer catalyst **XII** (8% mol) in CH_2Cl_2 (1.8 mL). The mixture was stirred until starting material disappeared (8-18h), then the solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel with hexane–ethyl acetate 1:1 mixtures.

3-(benzylamino)isoindolin-1-one (110aa): $[\alpha]_D$ = -63.7° (e.r.= 99:1, c = 0.5, $CHCl_3$, 22°C). Spectra and analytical data as reported.[125] HPLC: Chiral pack AD column, hexane–*i*PrOH 8:2, 0.6 mL/min, λ = 254 nm (t_{minor} = 12.5 min, t_{major} = 15.7 min).

3-((4-chlorobenzyl)amino)isoindolin-1-one (110ab): $[\alpha]_D$ = -55.2° (e.r.= 95:5, c = 0.5, $CHCl_3$, 17°C). Spectra and analytical data as reported.[125] HPLC: Chiralpack AD column, hexane–*i*PrOH 8:2, 0.6 mL/min, λ = 254 nm (t_{minor} = 15.5 min, t_{major} = 16.6 min).

3-((2-methoxybenzyl)amino)isoindolin-1-one (110ac): white amorphous solid; ^{1}H NMR (250 MHz, $CDCl_3$, 298.0 K): δ 7.81 (1H, d, J = 7.5 Hz); 7.59-7.46 (3H, m); 7.28-7.25 (2H, m); 6.97-6.87 (2H, m); 6.36 (1H, s); 5.47 (1H, s); 4.02 (1H, d, J= 12.5 Hz); 3.84 (3H, s); 3.72 (1H, d, J= 12.5 Hz); 1.76 (1H, bs). ^{13}C NMR (60 MHz, $CDCl_3$, 298.0 K): δ 169.8; 157.5; 145.7; 132.1; 132.0; 129.7; 129.1; 128.9; 128.0; 123.8; 123.3; 120.9; 110.5; 70.7; 55.3.3; 43.3. MS (ESI): m/z = 291 ($M + Na^+$). Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44; O, 11.93. Found: C, 71.65; H, 6.03; N, 10.41. HPLC: Chiralpack AD column, hexane–*i*PrOH 8:2, 0.6 mL/min, λ = 254 nm (t_{minor} = 13.0 min, t_{major} = 15.7 min).

3-(propylamino)isoindolin-1-one (110ad): white amorphous solid; ^{1}H NMR (250 MHz, $CDCl_3$, 298.0 K): δ 7.81 (1H, d, J = 5.0 Hz); 7.59-7.50 (3H, m); 6.92 (1H, bs); 5.49 (1H, bd); 2.67-2.60 (1H, m); 2.60-2.49 (1H, m); 1.69 (1H, bs) 1.53-1.45 (2H, m), 0.91 (3H, t, J= 7.5 Hz). ^{13}C NMR (60 MHz, $CDCl_3$, 298.0 K): δ 170.1; 145.6; 132.2; 132.0; 129.1; 123.6; 123.4; 70.5; 46.3; 23.6; 11.6. MS (ESI): m/z = 191 ($M + H^+$). Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.73; O, 8.41. Found: C, 69.48; H, 7.44; N,

14.70. HPLC: Chiralpack AD column, hexane–^{i}PrOH 8:2, 0.6 mL/min, λ = 254 nm (t_{minor} = 9.0 min, t_{major} = 11.3 min).

3-(benzylamino)-6-bromoisoindolin-1-one (110ba): $[\alpha]_D$ = -31.5° (e.r.= 98:2, c = 0.4, $CHCl_3$, 19°C). Spectra and analytical data as reported.[155] HPLC: Chiralpack AD column, hexane–^{i}PrOH 8:2, 0.6 mL/min, λ = 254 nm (t_{minor} = 13.0 min, t_{major} = 15.7 min).

6-bromo-3-((4-chlorobenzyl)amino)isoindolin-1-one(110bb): $[\alpha]_D$=-64.4° (e.r.= 93:7, c = 0. 8, $CHCl_3$, 19°C). pale yellow amorphous solid; ^{1}H NMR (300 MHz, $CDCl_3$, 298.0 K): *δ* 7.94 (1H, s); 7.72-7.68 (1H, m); 7.52-7.46 (2H, m); 7.28-7.26 (3H, m); 5.49 (1H, s); 4.03 (1H, bs); 3.85 (1H, d, *J* = 13.3 Hz); 3.71 (1H, d, *J* = 13.3 Hz); 2.28 (1H, bs). ^{13}C NMR (75 MHz, $CDCl_3$, 298.0 K): *δ* 143.9; 137.7; 135.3; 134.1; 133.1; 129.4; 128.7; 126.7; 125.4; 123.5; 69.8; 47.8. MS (ESI): *m*/*z* = 273 ($M + H^+$). Anal. Calcd for $C_{15}H_{13}ClN_2O$: C, 66.06; H, 4.80; Cl, 13.00; N, 10.27; O, 5.87. HPLC: Chiralpack AD column, hexane–^{i}PrOH 8:2, 0.6 mL/min, λ = 254 nm (t_{major} = 18.3 min, t_{minor} = 23.4 min).

6-bromo-3-((2-methoxybenzyl)amino)isoindolin-1-one (110bc): White amorphous solid; ^{1}H NMR (250 MHz, $CDCl_3$, 298.0 K): *δ* 7.92 (1H, s); 7.70-7.66 (1H, m); 7.46-7.43 (1H, m); 7.28-7.23 (2H, m); 6.98-6.87 (2H, m); 6.39 (1H, bs); 5.42 (1H, s); 4.01 (1H, d, J= 12.5 Hz); 3.83 (3H, s); 3.70 (1H, d, *J* = 12.5 Hz); 1.70 (1H, bs). ^{13}C NMR (75 MHz, $CDCl_3$, 298.0 K): *δ* 168.2; 157.4; 144.3; 135.1; 134.0; 129.7; 129.0; 127.8; 126.5; 125.5; 123.2; 120.9; 110.6; 70.5; 55.3; 45.2. MS (ESI): *m*/*z* = 385 ($M + K^+$). Anal. Calcd for $C_{16}H_{15}BrN_2O_2$: C, 55.35; H, 4.35; Br, 23.01; N, 8.07; O, 9.22. Found: C, 55.38; H, 4.35; Br, 22.09; N, 8.05. HPLC: Chiralpack AD column, hexane–^{i}PrOH 8:2, 0.6 mL/min, λ = 254 nm (t_{minor} = 12.7 min, t_{major} = 17.0 min).

3-(benzylamino)-6-methoxyisoindolin-1-one (110ca): White amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$, 298.0 K): *δ* 7.50 (1H, d, J= 8 Hz); 7.34-7.14 (6H, m); 7.12 (1H, d, J= 4.0 Hz); 6.52 (1H, s); 5.49 (1H, s); 3.89 (1H, d, J= 12 Hz); 3.87 (3H, s); 3.75 (1H, d, *J* = 12 Hz); 1.61 (1H, bs). ^{13}C NMR (100 MHz, $CDCl_3$, 298.0 K): *δ* 170.1; 160.9; 139.6; 137.5; 133.5; 128.6 (2C); 128.1 (2C); 127.4; 124.6; 120.3; 106.3; 69.9; 55.7; 48.7. MS (ESI): *m*/*z* = 307 ($M + K^+$). Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44;

O, 11.93. Found: C, 71.64; H, 6.04; N, 10.42; HPLC: Chiralpack AD column, hexane–^{i}PrOH 8:2, 0.6 mL/min, λ = 254 nm (t_{minor} = 14.4 min, t_{major} = 19.7 min).

3-(benzylamino)-6-fluoroisoindolin-1-one (110da): White amorphous solid; ^{1}H NMR (300 MHz, $CDCl_3$, 298.0 K): δ 7.59 (1H, dd, J_{AC} = 9.0 Hz, J_{AB} = 3.0 Hz); 7.49-7.47 (1H, m); 7.35-7.25 (6H, m); 6.90 (1H, s); 5.50 (1H, s); 3.90 (1H, d, J= 12 Hz); 3.75 (1H, d, J= 12 Hz); 1.96 (1H, bs). ^{13}C NMR (75 MHz, $CDCl_3$, 298.0 K): δ 168.8; 163.5 (1C, d, J'_{FC}= 246 Hz); 140.7; 139.3; 134.1 (1C, d, J'''_{FC}= 9 Hz); 128.7 (2C); 128.1(2C); 127.5; 125.4 (1C, d, J'''_{FC}= 8 Hz) ; 119.7 (1C, d, J''_{FC}= 23 Hz); 110.3 (1C, d, J''_{FC}= 23 Hz); 69.8; 48.8. MS (ESI): *m*/*z* = 257 ($M + H^+$). Anal. Calcd for $C_{15}H_{13}FN_2O$: C, 70.30; H, 5.11; F, 7.41; N, 10.93; O, 6.24. Found: C, 70.32; H, 5.10; F, 7.39; N, 10.91. HPLC: Chiralpack AD column, hexane–^{i}PrOH 8:2, 0.6 mL/min, λ = 254 nm (t_{minor} = 11.0 min, t_{major} = 12.7 min).

3-(benzylamino)-6-chloroisoindolin-1-one (110ea): $[\alpha]_D$ = -103.9° (e.r.= 90:10, c = 0.5, $CHCl_3$, 17°C). White amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$, 298.0 K): δ 7.79 (1H, s); 7.56 (2H, bs); 7.34-7.28 (5H, m); 5.53 (1H, s); 3.90 (1H, d, J= 13.0 Hz); 3.75 (1H, d, J= 13.0 Hz); 1.98 (1H, bs). ^{13}C NMR (100 MHz, $CDCl_3$, 298.0 K): δ 168.9; 143.6; 139.3; 135.6; 133.9; 132.5; 128.6 (2C); 128.1 (2C); 127.5; 125.1; 123.7; 69.8; 48.8 MS (ESI): *m*/*z* = 295 ($M + Na^+$). Anal. Calcd for $C_{15}H_{13}ClN_2O$: C, 66.06; H, 4.80; Cl, 13.00; N, 10.27; O, 5.87. Found: C, 66.09; H, 4.82; Cl, 12.96; N, 10.25. HPLC: Chiralpack AD column, hexane–^{i}PrOH 8:2, 0.6 mL/min, λ = 254 nm (t_{minor} = 13.9 min, t_{major} = 16.4 min).

(*R*)-3-(((*S*)-1-phenylethyl)amino)isoindolin-1-one (110af): $[\alpha]_D$ = -137.0° (c = 0.5, $CHCl_3$, 17°C). Spectra and analytical data as reported.[155]

(*R*)-3-(((*R*)-1-phenylethyl)amino)isoindolin-1-one (110af): $[\alpha]_D$ = -57.1° (c = 0.5, $CHCl_3$, 17°C). Spectra and analytical data as reported.[155]

Computational procedure

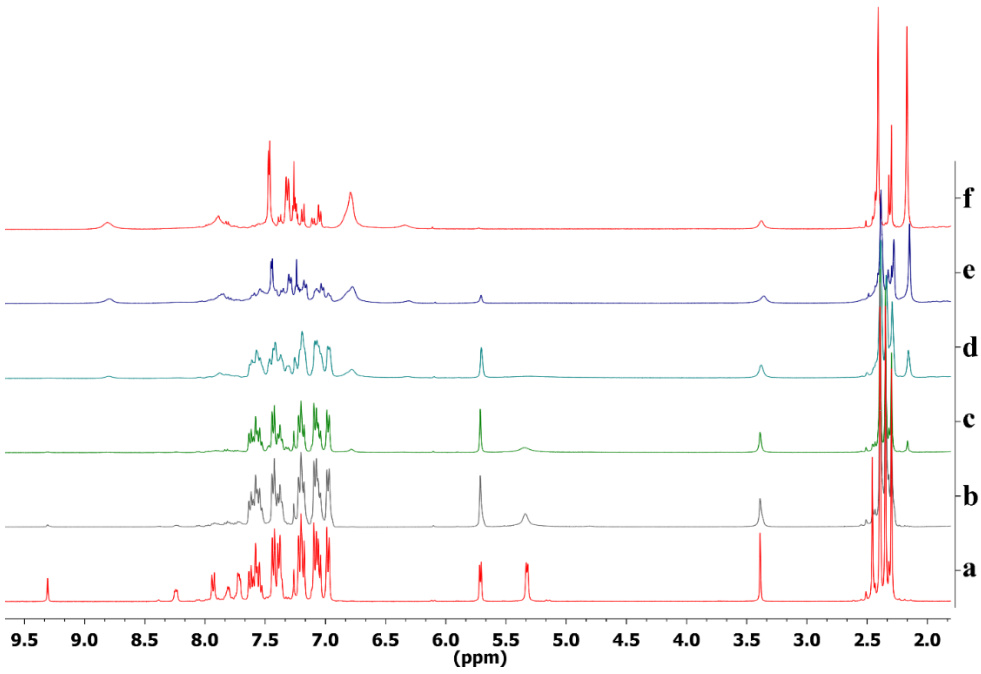
Conformer search for the **XII** ammonium cation, intermediate **A** and **110af** (*RR* and *RS* diastereoisomers) was carried out by using the MMFF94 force field as implemented in Spartan.[169] Different starting structures were considered for each system and both the systematic and the Montecarlo based algorithms were employed. All the conformers up to 10 kcal/mol with respect to minimum energy structures were then optimized by quantum chemical computations using density functional theory (DFT). Guess structures of the ion pair consisting of catalyst **XII** and intermediate **A** were obtained by docking simulations employing a homemade program; the starting geometries of the catalyst and the ligand were initially optimized at the MMFF94 level. Geometry optimizations and Hessian computations needed to ascertain the nature of the stationary points were carried out by using the M06-2X functional which is known to provide reliable geometries and barrier heights, especially for large systems.[170] The 6-31G(d) basis set was used in optimizations; single point computations with the 6-311+G(d,p) basis set were carried out to obtain accurate energies. Intrinsic reaction coordinate (IRC) calculations were performed to check the connectivity of all the TS with their corresponding minima. All the TS's exhibit only one large imaginary frequency corresponding to the stretching coordinate of the forming bond, while the minimum energy structures have only positive eigenvalues of the Hessian matrix. Solvent effects were taken into account by means of the polarizable continuum model (PCM) which was included in all computations.[171] All the quoted energies refer to 6-311+G(d,p) basis set; they include zero point vibrational corrections (computed at the 6-31G(d) level) and the solvent polarization contribution. Atomic charges were estimated by the atomic polar tensor approach (APT).[172] DFT computations were carried out by using the Gaussian program.[173]

Although entropic contributions are expected to be significant for association processes, their effects should elide in differences, the quantities that really matter. Therefore our discussion has been based on internal energies, following the same arguments given in ref.s.[174]

NMR computations for the RS/RR diastereomers of **110af** were carried out by following the procedure of ref[175]: the minimum energy configurations and the energetics needed for the Boltzmann weighting of the shielding tensors were taken from PCM($CHCl_3$)/M06-2X/6-31+G(d,p) calculations, while shielding tensors were calculated at the PCM($CHCl_3$)/B3LYP/6-311+G(2d,p) level.

7.2 ASYMMETRIC ACCESS TO A NEW CLASS OF MULTI-HETEROATOMIC CYCLIC COMPOUNDS CONTAINING THE *N,S*-ACETAL FUNCTIONALITY.

^{1}H-NMR experiment: entire spectra



^{1}H-NMR experiment showing the progression of the reaction of **121a** (1.2 eq.) with **132c** using catalyst **XX**. a) ^{1}H-NMR spectrum recorded after reagents mixing; b-e) time depending ^{1}H-NMR spectra collected after the addition of catalyst **XX** (0.2% mol); f) ^{1}H-NMR spectrum recorded after 24h from the addition of 0.5 mol catalyst **XX**.

Typical procedure for the synthesis of catalyst I-XIX

Catalysts **IV**, **XXI**, **XXII**, **XXIII**, **XXIV**, **XXV** and **XXVIII** are commercially available. Catalysts **VIII**,[126] **XII**,[176] **XX**,[177] **XIV-XIII**,[176] **X**,[178] **XV**,[176] **XXVI**,[177] **XXIX**,[178] **XXX-XXXI**[180] have been prepared in accordance with the literature. Catalyst **IX** has been prepared starting from **XXIX** by following the reported procedure for the quaternization of tertiary amines.[126]

Typical procedure for the reaction of 132c with 121a-o under PTC conditions

In a round-bottom flask, phase transfer catalyst (10% mol) was added at indicated temperature to a stirred solution of **132c** (0.1 mmol, 28 mg), thiol **121a** (2 eq., 0.2 mmol), K_2CO_3 (1 eq., 0.1 mmol) in CH_2Cl_2 (1.8 mL). The mixture was stirred until starting material disappeared (0.5–30 h), then the mixture was directly purified by flash chromatography on silica gel with hexane/ethyl acetate 2/1.

Typical procedure for the reaction of 132c with 121a-p under organocatalyzed conditions

In a round-bottom flask, **132c** (0.1 mmol, 28 mg) and thiol **121a-p** (2 eq., 0.2 mmol) were stirred at r.t. in CH_2Cl_2 (1.8 mL). After 10 min, the mixture was cooled at -40°C and organocatalyst **XX** (10% mol) was added. The mixture was stirred until starting material disappeared (2–65 h), then the crude was directly purified by flash chromatography on silica gel with hexane/ethyl acetate 2/1.

Computational details

Quantum chemical computations were carried out at the density functional level of theory (DFT) by using the Gaussian program.[173] Solvent ($CHCl_3$) effects were included via the polarizable continuum model.[171] The M06-2X functional with 6-31+G(d,p) basis set was adopted for geometry optimizations and for the calculation of Hessian matrices. Shielding tensors were evaluated at the B3LYP/6-311+G(2d,p) level.[176] To take anharmonic effects into account, predicted frequencies were scaled as in ref.[181]

***X*-ray crystallography**

Colourless needle-like single crystals of the compound *rac*-**134m** suitable for *X*-ray diffraction analysis were obtained by slow evaporation of a solution of dichloromethane/methanol (2:1) dissolving 4 mg of the compound in 0.4 ml of dichloromethane.

A crystal of 0.36 x 0.21 x 0.18 mm was selected and mounted on a cryoloop with paratone oil and measured at 100 K with a Rigaku AFC7S diffractometer equipped with a Mercury CCD detector using graphite monochromated MoKα radiation (λ = 0.71069 Å). Data reduction was performed with the crystallographic package CrystalClear.[182] Data have been corrected for Lorentz, polarization and absorption. The structure was solved by direct methods using the program SIR2014[183] and refined by means of full matrix least-squares based on F using the program SHELXL.[184] Non-hydrogen atoms were refined anisotropically, the imine hydrogen atom was located from the difference Fourier map and only its position refined, all other hydrogen atoms were positioned geometrically and included in structure factors calculations but not refined.

A total of 257 refinable parameters were finally considered, final disagreement indices: $R1$ = 0.0601 for 2398 reflections with $I > 2\sigma_I$, ${}_wR2$ = 0.1489 for all 4428 reflections. Maximum and minimum residual density were respectively 0.57 and -0.73 e Å^{-3}.

ORTEP diagram was drawn using OLEX^2.[185]

Crystal data: Formula $C_{21}H_{17}BrN_2O_2S_2$, FW=473.39, triclinic, P-1, a = 6.4438(18) Å, b = 8.602(2) Å, c = 18.909(5) Å, α = 92.026(4)°, β = 98.483(6)°, γ = 108.435(6)°, V = 979.7(4) Å^3, Z = 2, D_x = 1.605 g cm^{-3}, μ= 2.331 mm^{-1}.

CCDC-1543494 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Typical procedure for the synthesis of 122 under phase transfer catalyzed conditions

In a round-bottom flask, phase transfer catalyst **IV, VIII, XII** (5-10% mol) was added at indicated temperature to a stirred solution of 2-formylbenzonitrile **93a** (0.10 mmol), thiol **121a** (2 eq., 0.2 mmol), K_2CO_3 (1 eq., 0.1 mmol) in CH_2Cl_2 (1.8 mL). The mixture was stirred until starting material disappeared (1.5–28 h), then the crude was directly purified by flash chromatography on silica gel with hexane : ethyl acetate 2 : 1 mixture.

Typical procedure for the reaction of 122 under organocatalyzed conditions

In a round-bottom flask, organocatalyst **XX, XXI, XXII** (1-10% mol) was added at indicated temperature to a stirred solution of 2-formylbenzonitrile **93a** (0.10 mmol), thiol **121a** (2 eq., 0.2 mmol) in CH_2Cl_2 (1.8 mL). The mixture was stirred until starting material disappeared (0.5–20 h), then the mixture was directly purified by flash chromatography on silica gel with hexane:ethyl acetate 2: 1 mixtures.

3-(p-tolylthio)isobenzofuran-1(3H)-imine (122): brown oil, ^{1}H NMR (250 MHz, $CDCl_3$, 298.0 K) δ 7.74 (d, *J* = 7.6 Hz, 1H), 7.63 – 7.50 (m, 2H), 7.48 – 7.41 (m, 1H), 7.37 (d, *J* = 7.9 Hz, 2H), 7.06 (d, *J* = 7.9 Hz, 2H), 6.70 (s, 1H), 2.30 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$, 298.0 K) 143.5, 138.9, 133.8 (2C), 132.2, 129.8, 129.7 (2C), 129.6, 127.3, 123.6, 123.0, 89.0, 21.2. **HRMS (MALDI-FT ICR)** exact mass calculated $[M+H]^+$ for $C_{15}H_{14}NOS$: 256.0791 found: 256.0788.

Synthesis of imine derivatives 132a-c

2-((phenylimino)methyl)benzonitrile (132a): was prepared according to the reported procedures[186] and gave spectral and analytical data as reported.

2-((benzylimino)methyl)benzonitrile (132b): was prepared according to the reported procedures[187] and gave spectral and analytical data as reported.

N-(2-cyanobenzylidene)-4-methylbenzenesulfonamide(132c): was prepared according to the reported procedures[188] and purified as follows: crude was dissolved in hot toluene and cooled at r.t. to precipitate the excess of *p*-Toluenesulfonamide. Mater liquor was separated by filtration and toluene evaporated under reduced pressure. The imine was then precipitated in $CHCl_3$/hexane, filtered and washed with Et_2O.

Typical Procedure for the Reaction of 132c with 121a–p under PTC Conditions

In a round-bottom flask, phase transfer catalyst **I–III** and **VII–XI** (10% mol) was added at indicated temperature to a stirred solution of **132c** (0.1 mmol, 28 mg), thiol **121a–p** (2 eq., 0.2 mmol), K_2CO_3 (1 eq., 0.1 mmol) in CH_2Cl_2 (1.8 mL). The mixture was stirred

until starting material disappeared (0.5– 30 h), then the mixture was directly purified by flash chromatography on silica gel with hexane/ethyl acetate 2/1.

Typical Procedure for the Reaction of 132c with 121a–p Under Organocatalyzed Conditions

In a round-bottom flask, **132c** (0.1 mmol, 28 mg) and thiol **121a–p** (2 eq., 0.2 mmol) was stirred at r.t. in CH_2Cl_2 (1.8 mL). After 10 min, the mixture was cooled at -40 °C and organocatalyst **IV** (0.1 eq., 0.01 mmol, 3.2 mg) was added. The mixture was stirred until starting material disappeared (2–65 h), then the mixture was directly purified by flash chromatography on silica gel with hexane/ethyl acetate 2/1.

Compounds characterization

4-methyl-N-(3-(p-tolylthio)isoindolin-1-ylidene)benzenesulfonamide (134a): pink oil, $[\alpha]_D$= +115.2 (e.r.= 90 : 10, c= 0.8, $CHCl_3$, 25°C). ^{1}H NMR (250 MHz, $CDCl_3$, 298.0 K) δ 8.07 – 7.87 (m, 2H), 7.53 – 7.36 (m, 3H), 7.36 – 7.17 (m, 3H), 6.78 (s, 4H), 6.40 (s, 1H), 2.40 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$, 298.0 K) δ 157.3, 145.0, 140.4, 139.4, 136.0 (2C), 135.8, 132.1 (2C), 129.8 (2C), 129.2 (2C), 128.8, 127.9, 126.4, 124.1, 123.8, 122.6, 70.0, 21.6, 21.1. HPLC analysis with Chiralpak AD column, 70:30 *n*-hexane:^{i}PrOH, 0.8 mL/min, λ= 254 nm; (t_{major} = 17.9 min, t_{minor} = 26.9 min)**. HRMS (MALDI-FT ICR)** exact mass calculated $[M+H]^+$ for $C_{22}H_{21}N_2O_2S_2$: 409.1039 found: 409.1040.

N-(3-((3,4-dimethylphenyl)thio)isoindolin-1-ylidene)-4-methylbenzenesulfonamide (134b): pink oil, ^{1}H NMR (400 MHz, $CDCl_3$, 298.0 K) δ 8.00 (s br, 2H), 7.47 (d, J = 4.0 Hz, 2H), 7.45 – 7.39 (m, 1H), 7.33 (d, J = 8.2 Hz, 2H), 7.28 – 7.20 (m, 2H), 6.70 (d, J = 7.8 Hz, 1H), 6.60 (d, J = 7.6 Hz, 1H), 6.55 (s, 1H), 6.42 (s, 1H), 2.41 (s, 3H), 2.06 (s, 3H), 1.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 298.0 K) δ 157.2, 145.0, 140.4, 137.9, 137.0, 136.7, 136.1, 133.4 (2C), 132.0, 129.8 (2C), 129.6 (2C), 128.8, 128.1, 124.2, 123.9, 122.5, 70.1, 21.6, 19.4, 19.2. HPLC analysis with Chiralpak AD column, 70:30 *n*-hexane:^{i}PrOH, 0.8 mL/min, λ= 254 nm; (t_{major} = 14.5 min, t_{minor} = 34.6 min)**. HRMS**

(MALDI-FT ICR) exact mass calculated $[M+H]^+$ for $C_{23}H_{23}N_2O_2S_2$: 423.1200 found: 423.1193.

4-methyl-N-(3-(o-tolylthio)isoindolin-1-ylidene)benzenesulfonamide (134c): pink oil, ^{1}H NMR (300 MHz, $CDCl_3$, 298.0 K) δ 7.88 (d, *J* = 7.9 Hz, 2H), 7.52 (d, *J* = 7.3 Hz, 1H), 7.44 – 7.31 (m, 2H), 7.30 – 7.21 (m, 3H), 7.07 – 6.96 (m, 3H), 6.89 – 6.79 (m, 1H), 6.43 (s, 1H), 2.41 – 2.34 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, 298.0 K) δ 145.5, 143.1, 140.9, 136.7, 135.9, 132.4 (2C), 130.7, 130.3 (2C), 129.6, 129.4, 128.7, 128.1 (2C), 126.3, 124.0, 123.2, 70.3, 22.0, 21.6. HPLC analysis with Chiralpak AD column, 70:30 *n*-hexane:^{i}PrOH, 0.8 mL/min, λ= 254 nm; (t_{major} = 16.5 min, t_{minor} = 20.7 min)**. HRMS (MALDI-FT ICR)** exact mass calculated $[M+H]^+$ for $C_{22}H_{21}N_2O_2S_2$: 409.1039 found: 409.1038.

4-methyl-N-(3-((2,4,6-triisopropylphenyl)thio)isoindolin-1-ylidene)benzenesulfonamide (134d): pink oil, ^{1}H NMR (250 MHz, $CDCl_3$, 298.0 K) δ 7.89 (d, *J* = 7.8 Hz, 2H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.38 – 7.23 (m, 3H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.00 (s, 2H), 6.27 (d, *J* = 7.7 Hz, 1H), 6.13 (s, 1H), 3.65 (s br, 2H), 2.89 (p, *J* = 7.0 Hz, 1H), 2.38 (s, 3H), 1.25 (d, *J* = 6.9 Hz, 6H), 1.21 – 1.10 (m, 6H), 1.06 (d, *J* = 6.0 Hz, 6H). ^{13}C NMR (63 MHz, $CDCl_3$, 298.0 K) δ 157.6, 154.1, 151.1, 145.0, 141.1, 135.6, 131.4 (2C), 129.8 (2C), 128.9, 127.6 (2C), 124.3, 123.5 (2C), 122.9, 121.7 (2C), 67.7, 34.3, 31.6, 24.7, 24.0, 21.6. HPLC analysis with Chiralpak AD column,90:10 *n*-hexane:^{i}PrOH, 0.6 mL/min, λ= 254 nm; (t_{minor} = 10.2 min, t_{major} = 11.2 min)**. HRMS (MALDI-FT ICR)** exact mass calculated $[M+H]^+$ for $C_{30}H_{37}N_2O_2S_2$: 521.2291 found: 521.2290.

4-methyl-N-(3-(naphthalen-2-ylthio)isoindolin-1-ylidene)benzenesulfonamide (134e): pink oil, ^{1}H NMR (250 MHz, $CDCl_3$, 298.0 K) δ 8.14 – 7.96 (m, 2H), 7.69 – 7.60 (m, 1H), 7.57 – 7.27 (m, 10H), 7.23 – 7.12 (m, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.55 (s, 1H), 2.43 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$, 298.0 K) δ 157.1, 145.1, 140.1, 136.0, 136.0, 132.9, 132.9, 132.1 (2C), 131.8, 129.8 (2C), 128.9, 128.1 (2C), 127.8, 127.7, 127.4, 126.9, 126.2, 125.2, 123.8, 122.5, 70.0, 21.7. HPLC analysis with Chiralpak AD column,70:30 *n*-hexane:^{i}PrOH, 0.8 mL/min, λ= 254 nm; (t_{major} = 20.2 min, t_{minor} = 42.0

min)**. HRMS (MALDI-FT ICR)** exact mass calculated $[M+H]^+$ for $C_{25}H_{21}N_2O_2S_2$: 445.1039 found: 445.1037.

4-methyl-N-(3-(phenylthio)isoindolin-1-ylidene)benzenesulfonamide (134f): pink oil, ^{1}H NMR (250 MHz, $CDCl_3$, 298.0 K) δ 8.02 (d, *J* = 8.3 Hz, 2H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.60 – 7.47 (m, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 7.3 Hz, 1H), 7.13 (t, *J* = 8.0 Hz, 1H), 6.97 (t, *J* = 7.6 Hz, 2H), 6.90 – 6.78 (m, 2H), 6.47 (s, 1H), 2.43 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$, 298.0 K) δ 159.3, 146.4, 140.8, 135.8 (2C), 134.6, 133.9, 130.3 (2C), 129.7, 129.7, 129.0 (2C), 128.7, 128.3 (2C), 126.7, 126.5, 125.1, 123.8, 71.2, 21.8. HPLC analysis with Chiralpak AD column,70:30 *n*-hexane:^{i}PrOH, 0.8 mL/min, λ= 254 nm; (t_{major} = 15.5 min, t_{minor} =30.7 min). **HRMS (MALDI-FT ICR)** exact mass calculated $[M+H]^+$ for $C_{21}H_{19}N_2O_2S_2$: 395.0882 found: 395.0880.

N-(3-(cyclohexylthio)isoindolin-1-ylidene)-4-methylbenzenesulfonamide (134g): pink oil, ^{1}H NMR (300 MHz, $CDCl_3$, 298.0 K) δ 8.07 (d, *J* = 7.5 Hz, 1H), 7.94 (d, *J* = 8.3 Hz, 2H), 7.64 – 7.56 (m, 1H), 7.55 – 7.46 (m, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 6.33 (s, 1H), 2.41 (s, 3H), 1.69 – 0.94 (m, 11H). ^{13}C NMR (75 MHz, $CDCl_3$, 298.0 K) δ 158.8, 145.9, 141.9, 136.2, 133.8, 130.6, 130.3 (2C), 130.0, 128.3 (2C), 124.6, 124.4, 69.1, 43.0, 35.1, 33.6, 26.2, 26.0, 25.8, 22.1. HPLC analysis with Chiralpak AD column,70:30 *n*-hexane:^{i}PrOH, 0.8 mL/min, λ= 254 nm; (t_{major} = 11.1 min, t_{minor} = 16.6 min)**. HRMS (MALDI-FT ICR)** exact mass calculated $[M+H]^+$ for $C_{21}H_{25}N_2O_2S_2$: 401.1352 found: 401.1351.

N-(3-((4-(dimethylamino)phenyl)thio)isoindolin-1-ylidene)-4-methylbenzenesulfonamide (134h): pink oil, ^{1}H NMR (250 MHz, $CDCl_3$, 298.0 K) δ 8.16 (d, *J* = 7.9 Hz, 1H), 8.01 (d, *J* = 8.3 Hz, 2H), 7.67 – 7.51 (m, 2H), 7.45 – 7.30 (m, 3H), 6.57 (d, *J* = 8.9 Hz, 2H), 6.32 (s, 1H), 6.21 (d, *J* = 9.0 Hz, 2H), 2.84 (s, 6H), 2.45 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$, 298.0 K) δ 159.8, 151.0, 146.5, 141.6, 137.4 (2C), 134.6, 134.0, 130.3 (2C), 129.6, 128.4 (2C), 125.5, 123.8, 111.7 (2C), 109.8, 72.0, 39.9 (2C), 21.8. HPLC analysis with Chiralpak AD column,70:30 *n*-hexane:^{i}PrOH, 0.8 mL/min, λ= 254 nm; (t_{major} = 18.4 min, t_{minor} = 47.0 min)**. HRMS (MALDI-FT ICR)** exact mass calculated $[M+H]^+$ for $C_{23}H_{24}N_3O_2S_2$: 438.1304 found: 438.1303.

N-(3-((4-methoxyphenyl)thio)isoindolin-1-ylidene)-4-methylbenzenesulfonamide (134i): pink oil, ^{1}H NMR (250 MHz, $CDCl_3$, 298.0 K) δ 7.96 (s br, 2H), 7.53 – 7.36 (m, 3H), 7.35 – 7.18 (m, 3H), 6.82 (d, *J* = 8.1 Hz, 2H), 6.49 (d, *J* = 8.6 Hz, 2H), 6.36 (s, 1H), 3.66 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$, 298.0 K) δ 160.5, 157.3, 145.0, 140.4, 137.9 (2C), 135.9, 132.0, 129.8 (2C), 128.8 (2C), 127.9 (2C), 123.8, 122.6, 118.0, 113.9 (2C), 70.11, 55.1, 21.6. HPLC analysis with Chiralpak AD column,70:30 *n*-hexane:^{i}PrOH, 0.8 mL/min, λ= 254 nm; (t_{major} = 24.6 min, t_{minor} = 40.0 min)**. HRMS (MALDI-FT ICR)** exact mass calculated $[M+H]^+$ for $C_{22}H_{21}N_2O_3S_2$: 425.0988 found: 425.0989.

4-methyl-N-(3-((4-(methylthio)phenyl)thio)isoindolin-1-ylidene)benzenesulfonamide (134j): pink oil, ^{1}H NMR (400 MHz, $CDCl_3$, 298.0 K) δ 7.97 (s br, 2H), 7.52 – 7.40 (m, 3H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.29 – 7.22 (m, 1H), 6.81 (s, 4H), 6.41 (s, 1H), 2.41 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 298.0 K) δ 145.1, 140.8, 140.1, 136.3 (2C), 135.6, 132.2 (2C), 129.8 (82C), 129.0, 127.9 (2C), 125.4 (2C), 123.8, 123.2, 122.7, 69.9, 21.7, 15.0. HPLC analysis with Chiralpak AD column,70:30 *n*-hexane:^{i}PrOH, 0.8 mL/min, λ= 254 nm; (t_{major} = 30.6 min, t_{minor} = 64.9 min)**. HRMS (MALDI-FT ICR)** exact mass calculated $[M+H]^+$ for $C_{22}H_{21}N_2O_2S_3$: 441.0760 found: 441.0758.

N-(3-((4-methoxybenzyl)thio)isoindolin-1-ylidene)-4-methylbenzenesulfonamide (134k): pink oil, ^{1}H NMR (250 MHz, $CDCl_3$, 298.0 K) δ 7.99 (d, *J* = 8.1 Hz, 2H), 7.81 – 7.73 (m, 1H), 7.54 – 7.48 (m, 1H), 7.47 – 7.35 (m, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 6.71 (d, *J* = 8.5 Hz, 2H), 6.26 (s, 1H), 3.76 (s, 3H), 3.29 (d, *J* = 12.3 Hz, 1H), 3.11 (d, *J* = 12.4 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$, 298.0 K) δ 158.7, 157.1, 144.9, 140.5, 136.4, 132.7 (2C), 130.1 (2C), 129.7 (2C), 129.3, 128.2, 127.8, 126.5, 123.7, 122.9, 113.8 (2C), 68.0, 55.2, 32.5, 21.6. HPLC analysis with Chiralpak AD column,80:20 *n*-hexane:^{i}PrOH, 0.6 mL/min, λ= 254 nm; (t_{minor} = 53.1 min, t_{major} = 56.5 min). **HRMS (ESI-FT ICR)** exact mass calculated $[M+H]^+$ for $C_{23}H_{23}N_2O_3S_2$: 439.1145 found: 439.1142.

N-(3-((2-bromophenyl)thio)isoindolin-1-ylidene)-4-methylbenzenesulfonamide (134l): pink oil, ^{1}H NMR (400 MHz, $CDCl_3$, 298.0 K) δ 8.12 – 8.05 (m, 1H), 7.93 (d, *J* = 8.0 Hz, 2H), 7.57 – 7.47 (m, 2H), 7.46 – 7.40 (m, 1H), 7.37 (d, *J* = 7.3 Hz, 1H), 7.32 (d, *J* = 7.9 Hz, 2H), 7.05 – 6.98 (m, 3H), 6.62 (s, 1H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 298.0 K) δ 159.2, 146.3, 139.8, 136.0, 134.4, 133.8, 133.4, 130.6, 130.3 (2C), 130.0, 129.5, 128.0 (2C), 127.7, 126.5, 124.8 (2C), 124.1, 71.0, 21.8. HPLC analysis with Chiralpak AD column,70:30 *n*-hexane:^{i}PrOH, 0.8 mL/min, λ= 254 nm; (t_{major} = 21.5 min, t_{minor} = 32.8 min). **HRMS (MALDI-FT ICR)** exact mass calculated $[M+H]^+$ for $C_{21}H_{18}BrN_2O_2S_2$: 472.9986 found: 472.9987.

N-(3-((4-bromophenyl)thio)isoindolin-1-ylidene)-4-methylbenzenesulfonamide (134m):pink oil, ^{1}H NMR (400 MHz, $CDCl_3$, 298.0 K) δ 8.00 (d, *J* = 8.0 Hz, 2H), 7.88 (d, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.40 – 7.33 (m, 3H), 7.10 (d, *J* = 8.2 Hz, 2H), 6.69 (d, *J* = 8.1 Hz, 2H), 6.45 (s, 1H), 2.43 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$, 298.0 K) δ 158.5, 146.1, 140.2, 137.2 (2C), 134.9, 133.5, 131.8 (2C), 130.2 (2C), 129.7 (2C), 128.2 (2C), 126.2, 124.5, 123.7, 70.6, 21.8. HPLC analysis with Chiralpak AD column,70:30 *n*-hexane:^{i}PrOH, 0.8 mL/min, λ= 254 nm; (t_{major} = 20.8 min, t_{minor} = 23.8 min). **HRMS (ESI-FT ICR)** exact mass calculated $[M+H]^+$ for $C_{21}H_{18}BrN_2O_2S_2$: 472.9988 found: 472.9985.

methyl-2-((3-(tosylimino)isoindolin-1-yl)thio)acetate (134n): pink oil, ^{1}H NMR (250 MHz, $CDCl_3$, 298.0 K) δ 7.91 (d, *J* = 8.2 Hz, 2H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.59 – 7.50 (m, 2H), 7.50 – 7.40 (m, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 6.43 (s, 1H), 3.56 (s, 3H), 3.24 (d, *J* = 15.6 Hz, 1H), 2.89 (d, *J* = 15.6 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$, 298.0 K) δ 170.1, 157.2, 145.1, 139.8, 135.6, 132.8 (2C), 129.9 (2C), 129.7, 127.7 (2C), 124.2, 123.1, 67.8, 52.5, 31.0, 21.6. HPLC analysis with Chiralpak AD column,70:30 *n*-hexane:^{i}PrOH, 1.0 mL/min, λ= 254 nm; (t_{major} = 30.3 min, t_{minor} = 44.2 min). **HRMS (MALDI-FT ICR)** exact mass calculated $[M+H]^+$ for $C_{18}H_{19}N_2O_4S_2$: 391.0781 found: 391.0780.

methyl-3-((3-(tosylimino)isoindolin-1-yl)thio)propanoate (134o): pink oil, ^{1}H NMR (250 MHz, $CDCl_3$, 298.0 K) δ 7.95 (d, *J* = 8.3 Hz, 2H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.56

(d, 1H), 7.53 – 7.41 (m, 2H), 7.31 (d, J = 8.1 Hz, 2H), 6.30 (s, 1H), 3.60 (s, 3H), 2.40 (s, 3H), 2.28 – 2.07 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$, 298.0 K) δ 171.7, 157.2, 145.1, 140.2, 136.0, 132.7, 131.5, 129.7 (2C), 129.5, 127.7 (2C), 123.7, 123.2, 67.9, 51.8, 33.6, 22.9, 21.6. HPLC analysis with Chiralpak AD column,70:30 *n*-hexane:^{i}PrOH, 1.0 mL/min, λ= 254 nm; (t_{major} = 18.0 min, t_{minor} = 23.1 min)**. HRMS (MALDI-FT ICR)** exact mass calculated $[M+H]^+$ for $C_{19}H_{21}N_2O_4S_2$: 405.0937 found: 405.0937.

2-tosyl-3-((2-(trifluoromethyl)phenyl)thio)isoindolin-1-imine (134p): pink oil, ^{1}H NMR (300 MHz, $CDCl_3$, 298.0 K) δ 7.91 (d, J = 7.6 Hz, 2H), 7.61 (d, J = 7.7 Hz, 1H), 7.57 – 7.49 (m, 1H), 7.42 – 7.13 (m, 8H), 6.58 (s, 1H), 2.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 298.0 K) δ 145.21, 138.96, 135.94, 135.20, 132.36, 131.56, 129.88 (2C), 129.33, 128.38, 127.76 (2C), 126.69, 126.62, 123.97, 122.66, 70.22, 21.60. HPLC analysis with Chiralpak AD column,70:30 *n*-hexane:^{i}PrOH, 0.8 mL/min, λ= 254 nm; (t_{major} = 14.3 min, t_{minor} = 20.5 min). **HRMS (MALDI-FT ICR)** exact mass calculated $[M+H]^+$ for $C_{22}H_{18}F_3N_2O_2S_2$: 463.0756 found: 463.0756.

Typical procedure for the hydrolysis of 134a:

In a round-bottom flask, compound **134a** (0.05 mmol, 20 mg), dioxane (1.0 mL), HCl (1 M, 1.0 mL) were added. The mixture was stirred at room temperature until starting material disappeared, then neutralized with a saturated $NaHCO_3$ solution and extracted with DCM. The combined organic phases dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, petroleum hexane : ethyl acetate, 3:1) to afford a white solid.

3-(p-tolylthio)-2-tosylisoindolin-1-one 136a: White solid, p.f. 115 – 118 °C. ^{1}H NMR (250 MHz, $CDCl_3$, 298.0 K) δ 8.25 (d, J = 8.2 Hz, 2H), 7.63 – 7.50 (m, 2H), 7.48 – 7.34 (m, 3H), 7.32 – 7.21 (m, 1H), 6.66 (d, J = 7.9 Hz, 2H), 6.53 (s, 1H), 6.49 (d, J = 7.9 Hz, 2H), 2.46 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$, 298.0 K) δ 165.0, 145.3, 142.9, 139.5, 136.0, 135.8 (2C), 133.7, 129.5 (2C), 129.2 (2C), 129.0 (2C), 124.2, 124.1, 123.5, 67.2, 21.8, 21.0. **HRMS (MALDI-FT ICR)** exact mass calculated $[M+Na]^+$ for $C_{22}H_{19}NNaO_3S_2$: 432.0698 found: 432.0698.

Typical procedure for the Michael addition of 137a to methyl vinyl ketone:

In a round-bottom flask, compound **136a** (0.05 mmol, 20 mg), catalyst **D2** (10 mol %) and methyl vinyl ketone (1.5 eq., 0.075 mmol, 6.1 μL) were added in toluene (0.8 mL). Then Cs_2CO_3 (3.0 eq., 0.15 mmol, 48 mg) was added and the mixture stirred at room temperature for 4 hours. The crude product was directly purified by flash chromatography (silica gel, petroleum hexane : ethyl acetate, 3:1) to afford the product in 97% of yield.

3-(3-oxobutyl)-3-(p-tolylthio)-2-tosylisoindolin-1-one 137a: White solid, p.f. 138 – 141 °C.^{1}H NMR (250 MHz, $CDCl_3$, 298.0 K) δ 8.33 (d, *J* = 8.4 Hz, 2H), 7.55 – 7.31 (m, 5H), 7.25 – 7.16 (m, 1H), 6.58 (d, *J* = 8.0 Hz, 2H), 6.40 (d, *J* = 8.0 Hz, 2H), 3.37 (ddd, *J* = 14.3, 11.2, 4.8 Hz, 1H), 2.84 (ddd, *J* = 14.3, 11.2, 4.8 Hz, 1H), 2.61 (ddd, *J* = 14.3, 11.2, 4.8 Hz, 1H), 2.45 (s, 3H), 2.07 (s, 3H), 1.99 (s, 3H), 1.83 (ddd, *J* = 14.3, 11.2, 4.8 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$, 298.0 K) δ 206.3, 165.8, 145.8, 145.5, 139.3, 136.1, 135.6 (2C), 134.1, 129.7 (2C), 129.4 (2C), 129.1 (3C), 128.4, 125.8, 123.9, 122.83, 81.3, 38.5, 32.7, 30.0, 21.7, 21.0. HPLC analysis with Chiralpak AD column,70:30 *n*-hexane:^{i}PrOH, 0.8 mL/min, λ= 254 nm; (t_{major} = 12.7 min, t_{minor} = 15.8 min). **HRMS (MALDI-FT ICR)** exact mass calculated $[M+H]^+$ for $C_{26}H_{25}NO_4S_2$: 479.1225 found: 479.1211.

Typical procedure for the synthesis of 138a:

In a round-bottom flask, compound **136a** (0.03 mmol, 12 mg), DCM (0.8 mL), K_2CO_3 (1.2 eq., 0.036 mmol, 5.0 mg) were added. The the mixture was cooled at 0 °C and, after 10 min, mCPBA (1.2 eq., 0.036 mmol, 6.0 mg) was added and the mixture stirred for 5 min. The crude product was directly purified by flash chromatography (silica gel, petroleum hexane : ethyl acetate, 3:1) to afford a white solid in 86% of yield.

3-(p-tolylsulfinyl)-2-tosylisoindolin-1-one 138a: White solid, p.f. 152 – 155°C. ^{1}H NMR (400 MHz, $CDCl_3$, 298.0 K) δ 8.09 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 7.7 Hz, 1H), 7.66 – 7.55 (m, 1H), 7.41 – 7.30 (m, 4H), 6.85 (d, J = 8.0 Hz, 2H), 6.71 (d, J = 8.0 Hz, 2H), 6.21 (s, 1H), 2.44 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 298.0 K) δ

164.5, 146.0, 142.6, 136.0, 135.0, 133.4, 132.0, 130.0, 129.9 (2C), 129.2, 128.8 (2C), 128.6 (2C), 125.2 (2C), 124.6, 124.4, 74.6, 21.7, 21.3. **HRMS (MALDI-FT ICR)** exact mass calculated $[M+H]^+$ for $C_{26}H_{25}NO_4S_2$: 425.0756 found: 425.0768.

7.3 SYNTHESIS OF 2-ACETYLBENZONITRILES AND THEIR REACTIVITY IN TANDEM PROCESSES FOR THE SYNTHESIS OF NEW 3,3-DISUBSTITUTED ISOINDOLINONES

Compounds **144a, 144c** and **152a** were identified comparing their spectral data with the those reported in the literature.[133,144,150] Spectroscopic data are given only for compounds never previously described.

2-ethyl-5-nitrobenzonitrile (150b). A mixture of fuming HNO_3 (400 µL) and concentrated H_2SO_4 (800 µL) was stirred at room temperature for 1 h. Then, 2-ethylbenzonitrile (400 mg, 408 µL, 3.05 mmol) was added slowly at 0°C and the solution stirred at room temperature 1h. The crude mixture was poured into ice/water and extracted twice with CH_2Cl_2. The combined organic phases were washed with a saturated $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated in vacuo. The product was obtained quantitatively (530 mg, 99% yield) as a yellow solid without further purification. Mp: 77-78°C (lit. 77-78°C). ^{1}H NMR (250 MHz, $CDCl_3$, 298.0 K) δ 8.41 (d, *J* = 2.4 Hz, 1H), 8.32 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.55 (d, *J* = 8.6 Hz, 1H), 2.95 (q, *J* = 7.6 Hz, 2H), 1.30 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (65 MHz, $CDCl_3$, 298.0 K) δ 155.2, 137.3, 130.3, 128.0, 127.7, 116.0, 113.6, 28.1, 14.7. HRMS (ESI) *m/z:* calcd for $C_9H_9N_2O_2$ ($[M+ H]^+$) 177.06585; found 177.06571.

5-amino-2-ethylbenzonitrile (150c). To a solution of 2-ethyl-5-nitrobenzonitrile (1.2 g, 6.82 mmol) in methanol (40 mL), zinc powder (4 eq., 1.762 g, 27.2 mmol) and concentrated HCl (6 mL) were added. The mixture was stirred at room temperature for 2 h. Subsequently, NaOH 1 M was added to basify and the mixture was extracted with ethyl acetate (three times). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, hexane−ethyl acetate 70/30) to give the desired product (1.0 g, 99%) quantitatively as a yellow oil. ^{1}H NMR (300 MHz, MeOD, 298.0 K) δ 7.07 (d, *J* = 7.8 Hz, 1H), 6.95 – 6.82 (m, 2H), 2.67 (q, *J* = 7.5 Hz, 5H), 1.18 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz,

MeOD, 298.0 K) δ 146.0, 136.4, 129.3, 119.9, 118.1, 117.4, 111.1, 26.3, 14.6. HRMS (ESI) *m/z:* calcd for $C_9H_{11}N_2$ ([M+ H]$^+$) 147.0917; found 147.0928.

General Procedure for the Synthesis of 5-halogeno 2-ethylbenzonitriles 150d-e

A solution of $NaNO_2$ (1.5 eq., 2.03 mmol, 138 mg) in H_2O (500 µL) was added at 0°C to a solution of 5-amino-2-ethylbenzonitrile (200 mg, 1.37 mmol) in acetic acid (2.6 mL). Then, concentrated H_2SO_4 (500 µL) was added and the mixture was stirred for 0.5 h. The mixture was warmed to room temperature and a solution of CuX (2.2 eq., 1.5 mmol) in HX (HCl 37% or HBr 48%) (2.5 mL) was added under an inert atmosphere. After 45 minutes, the mixture was extracted with ethyl acetate twice. The combined organic phases were washed with a saturated $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, petroleum ether-ethyl acetate, 99:1) to afford a colorless liquid.

5-chloro-2-ethylbenzonitrile (150d). Colorless liquid (149 mg, 66%). ^{1}H NMR (250 MHz, $CDCl_3$, 298.0 K) δ 7.54 (bs, 1H), 7.47 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.27 (d, *J* = 8.2 Hz, 1H), 2.83 (q, *J* = 7.5 Hz, 2H), 1.26 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (65 MHz, $CDCl_3$, 298.0 K) δ 146.7, 133.4, 132.3, 130.4, 117.0, 113.7, 27.4, 15.2. HRMS (ESI) *m/z:* calcd for $C_9H_9ClN_2$ ([M+ H]$^+$) 166.0418; found 166.0402.

5-bromo-2-ethylbenzonitrile (150e). Colorless liquid (224 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$, 298.0 K) δ 7.72 (d, *J* = 2.2 Hz, 1H), 7.63 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 2.84 (q, *J* = 7.6 Hz, 2H), 1.29 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 298.0 K) δ 146.9, 136.0, 134.9, 130.3, 119.4, 116.5, 113.8, 27.2, 14.8. HRMS (ESI) *m/z:* calcd for $C_9H_9BrN_2$ ([M+ H]$^+$) 209.9913; found 209.9928.

***N*-(3-cyano-4-ethylphenyl)acetamide (150f).** Acetic anydride (260 µL, 2.74 mmol) was added at room temperature to a solution of 5-amino-2-ethylbenzonitrile (200 mg, 1.37 mmol) in dichloromethane (2.0 mL) and the mixture was stirred for 0.5 h. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (silica gel, petroleum ether-ethyl acetate 1:1) to afford the desidered product as a white solid (237 mg, 92%). Mp: 115-116°C. ^{1}H NMR (400 MHz, $CDCl_3$,

298.0 K) δ 8.58 (bs, 1H), 7.90 (s, 1H), 7.64 (d, *J* = 8.3 Hz, 1H), 7.26 (d, *J* = 8.3 Hz, 1H), 2.80 (q, *J* = 7.6 Hz, 2H), 2.19 (s, 3H), 1.26 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 298.0 K) δ 169.3, 143.6, 136.6, 129.3, 124.6, 123.6, 117.9, 111.9, 27.1, 24.2, 15.0. HRMS (ESI) calcd for $C_{11}H_{13}N_2O$ *m/z:* ([M+ H]$^+$) 189.1022; found 189.1034.

***N*-(3-cyano-4-ethylphenyl)-*N*-methylacetamide (150g).** Under nitrogen atmosphere, CH_3I (322 µL, 5.22 mmol) was added to a solution of *N*-(3-cyano-4-ethylphenyl)acetamide (98 mg, 0.52 mmol) in THF dry (2.0 mL) and sodium hydride 60% (64 mg, 1.58 mmol). The mixture was stirred overnight at room temperature. Then, water was added, the solvent removed under reduced pressure and the mixture was extracted with dichloromethane twice. The combined organic phases were combined, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, petroleum ether-ethyl acetate, 60:40) to afford the product as a white solid (91 mg, 85%). Mp: 95-96°C. ^{1}H NMR (300 MHz, $CDCl_3$, 298.0 K) δ 7.46 (s, 1H), 7.43 – 7.32 (m, 2H), 3.24 (s, 3H), 2.90 (q, *J* = 7.6 Hz, 2H), 1.87 (s, 3H), 1.32 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 298.0 K) δ 170.04, 147.52, 142.68, 131.77, 130.95, 130.34, 116.81, 113.34, 37.04, 27.27, 22.37, 14.80. HRMS (ESI) *m/z:* calcd for $C_{11}H_{15}N_2O$ ([M+ H]$^+$) 203.1179; found 203.1166.

General Procedure for the Synthesis of 2-acetylbenzonitriles 144a-e

A mixture of benzonitriles **150a-g** (0.76 mmol), *N*-Bromosuccinimide (3.5 eq., 2.7 mmol, 478 mg) and AIBN (0.1 eq., 0.076 mmol, 12 mg) in CH_3CN/H_2O 4/1 (3.5 mL) was heated at 80°C under stirring for the indicated time. After cooling to room temperature, the solvent was removed under reduced pressure and the residue taken up with dichloromethane was washed with water. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography.

2-acetylbenzonitrile (144a). Purified by flash chromatography (silica gel, hexane-ethyl acetate, 80/20). White solid (92 mg, 82%). Mp: 47-48 °C (lit. 47-49 °C)[9a]. HRMS (ESI) *m/z:* calcd for C_9H_7NNaO [(M+Na)$^+$] 168.0425; found: 168.0419. IR and NMR data are in agreement with the literature.[182]

2-acetyl-5-nitrobenzonitrile (144b). Prepared using 7 eq. of *N*-Bromosuccinimide. Purified by flash chromatography (silica gel, dichlorometane-petroleum ether, 60/30). White solid (85 mg, 59%). Mp: 78-80°C. ^{1}H NMR (250 MHz, $CDCl_3$, 298.0 K) δ 8.65 (d, *J* = 2.3 Hz, 1H), 8.53 (dd, *J* = 8.6, 2.3 Hz, 1H), 8.12 (d, *J* = 8.6 Hz, 1H), 2.78 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 298.0 K) δ 194.6, 149.2, 144.2, 130.8, 129.8, 127.4, 115.8, 112.6, 28.2. **FTIR** (KBr):ν_{max} = 3365, 2231, 1703, 1665, 1521 cm-1. HRMS (ESI) *m/z:* calcd for $C_9H_6NNaO_3$ [$(M+Na)^+$] 213.0271; found: 213.0265.

2-acetyl-5-chlorobenzonitrile (144c). Purified by flash chromatography (silica gel, hexane-ethyl acetate 80/20). White solid (95 mg, 70%). Mp: 86-87°C (lit. 85-87°C).[182] HRMS (ESI) *m/z:* calcd for $C_9H_6ClNNaO$ [$(M+Na)^+$] 202.0030; found: 202.0038. IR and NMR data are in agreement with the literature.[182]

2-acetyl-5-bromobenzonitrile (144d). Purified by flash chromatography (silica gel, hexane-ethyl acetate, from 85/15). White solid (122 mg, 72%). Mp: 117-118°C. ^{1}H NMR (300 MHz, $CDCl_3$, 298.0 K) δ 7.99 – 7.92 (m, 1H), 7.89 – 7.80 (m, 2H), 2.69 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 298.0 K) δ 194.9, 138.3, 137.7, 135.8, 131.0, 127.0, 116.6, 112.6, 27.7. **FTIR** (KBr):ν_{max} = 2924, 2224, 1685. HRMS (ESI) *m/z:* calcd for $C_9H_6BrNNaO$ [$(M+Na)^+$] 245.9525; found: 245.9534.

***N*-(4-acetyl-2-bromo-3-cyanophenyl)acetamide (144e)**

Purified by flash chromatography (silica gel, ethyl acetate/hexane, 50:50). White solid (30 mg, 14 %). M.p.: 203–204 °C. ^{1}H NMR (250 MHz, $CDCl_3$, 298.0 K): δ = 8.78 (d, *J* = 8.8 Hz, 1 H), 7.90 (d, *J* = 8.8 Hz, 1 H), 2.67 (s, 3 H), 2.32 (s, 3 H) ppm. ^{13}C NMR (250 MHz, $CDCl_3$, 298.0 K): δ = 194.3, 168.8, 140.3, 136.7, 130.2, 123.5, 119.2, 116.2, 114.9, 27.9, 25.4 ppm. **FTIR** (KBr):ν_{max} = 3291, 2232, 1704, 1690, 1526 cm^{-1}. HRMS (ESI): calcd. For $C_{11}H_9BrN_2NaO_2$ $[M + Na]^+$ 302.9739; found 302.9740.

***N*-(4-acetyl-3-cyanophenyl)-*N*-methylacetamide (144f).** Purified by flash chromatography (silica gel, hexane-ethyl acetate, 70/30). Pale yellow solid (113 mg, 70%). Mp:105-106°C. ^{1}H NMR (250 MHz, $CDCl_3$, 298.0 K) δ 8.01 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 1.8 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 3.37 (s, 3H), 2.72 (s, 3H), 2.09 (s, 3H).

^{13}C NMR (65 MHz, $CDCl_3$, 298.0 K) δ 195.20, 170.16, 148.03, 137.79, 132.87, 131.45, 130.62, 117.46, 112.63, 37.67, 28.01, 22.97. **FTIR** (KBr):ν_{max} = 2230, 1690, 1662. HRMS (ESI) *m/z:* calcd for $C_{12}H_{12}N_2NaO_2$ [(M+ Na)$^+$] 239.0791; found 239.0782.

General procedure for the tandem reaction of 2-acetyl benzonitriles with the hydroxide anion.

To a solution of 2-acetylbenzonitriles **144a-f** (0.2 mmol) in acetonitrile (2 mL), KOH (0.3 eq) in water (200 µL) was added and the mixture was stirred at room temperature until disappearance of the starting material (TLC hexane-acetyl acetate 3:7). After 1-3h, the solution was diluted with dichloromethane, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash chromatography.

3-hydroxy-3-methylisoindolin-1-one (152a). Purified by flash chromatography (silica gel, hexane−ethyl acetate, 40/60). White solid (31 mg, 93%). Mp: 113-115°C. HRMS (ESI) *m/z:* calcd for $C_9H_{10}NO_2$ [(M+ H)$^+$] 164.0706; found: 164.0713. NMR data are in accordance with the literature.[184]

3-hydroxy-3-methyl-6-nitroisoindolin-1-one (152b). Purified by flash chromatography (silica gel, hexane−ethyl acetate, 50/60). White solid (38 mg, 91%). Mp: 197°C (dec.). ^{1}H NMR (250 MHz, DMSO-d_6, 298.0 K): δ = 9.28 (s, 1 H), 8.47 (dd, J = 8.3, 2.1 Hz, 1 H), 8.25 (d, J = 2.0 Hz, 1 H), 7.87 (d, J = 8.2 Hz, 1 H), 6.45 (s, 1 H), 1.66 (s, 3 H) ppm. ^{13}C NMR (150 MHz, DMSO-d_6, 298.0 K): δ = 165.6, 156.5, 149.1, 133.1, 127.9, 124.2, 117.9, 85.4, 26.5 ppm. **FTIR** (KBr):ν_{max} = 3369, 3200, 1717, 1547. HRMS (ESI) *m/z:* calcd for $C_9H_9N_2O_4$ [(M+ H)$^+$] 209.0557; found: 209.0563.

6-chloro-3-hydroxy-3-methylisoindolin-1-one (152c). Purified by (silica gel, hexane−ethyl acetate, 50/50). White solid (38 mg, 94%). Mp: 134-135°C. ^{1}H NMR (400 MHz, $CDCl_3$, 298.0 K) δ 7.56 (dd, J = 8.0, 1.9 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 1.9 Hz, 1H), 7.29 (bs, 1H), 1.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 298.0 K) δ 167.6, 147.4, 135.8, 133.2, 131.5, 123.5, 123.1, 85.9, 25.8; **FTIR** (KBr):ν_{max} = 3363, 3206, 1717, 1665. HRMS (ESI) *m/z*: calcd for $C_9H_9ClNO_2$ [(M+H)$^+$] 198.0132; found: 198.0137.

6-bromo-3-hydroxy-3-methylisoindolin-1-one (152d). Purified by flash chromatography (silica gel, hexane−ethyl acetate, 40/60). White solid (46 mg, 95%). Mp: 180°C (dec.). ^{1}H NMR (300 MHz, DMSO-d_6, 298.0 K) δ 8.99 (s, 1H), 7.78 (dd, J = 8.0, 1.9 Hz, 1H), 7.69 (d, J = 1.8 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 6.21 (s, 1H), 1.60 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6, 298.0 K) δ 166.19, 149.82, 135.16, 133.81, 125.44, 124.61, 122.23, 85.17, 26.62. **FTIR** (KBr):ν_{max} = 3346, 3207, 1718, 1664. HRMS (ESI) *m/z:* calcd for $C_9H_9BrNO_2$ [(M+H)$^+$] 241.9811; found: 241.9816.

***N*-(4-Bromo-1-hydroxy-1-methyl-3-oxoisoindolin-5-yl)acetamide (152e):** Purified by flash chromatography (silica gel, ethyl acetate). White solid (53 mg, 90 % yield). M.p. 241–242 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 298.0 K): δ = 9.59 (s, 1 H), 9.00 (s, 1 H), 7.73 (d, J = 7.9 Hz, 1 H), 7.53 (d, J = 8.0 Hz, 1 H), 6.14 (s, 1 H), 2.10 (s, 3 H), 1.59 (s, 3 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6, 298.0 K): δ = 169.1, 165.7, 150.0, 137.9, 131.3, 129.2, 121.4, 113.9, 83.1, 26.7, 23.6 ppm. **FTIR** (KBr):ν_{max} = 3340, 3200, 1714, 1668 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{12}BrN_2O_3$ [M + H]$^+$ 299.0026; found 299.0034.

***N*-(1-hydroxy-1-methyl-3-oxoisoindolin-5-yl)-*N*-methylacetamide (152f).** Purified by flash chromatography (silica gel, dichloromethane-methanol, 95/5). White solid (41 mg, 87%). M.p.: 110-112 °C. ^{1}H NMR (250 MHz, $CDCl_3$, 298.0 K) δ 7.64 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 1.9 Hz, 1H), 7.44 (dd, J = 8.0, 1.9 Hz, 1H), 7.18 (s, 1H), 3.28 (s, 3H), 1.88 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (65 MHz, $CDCl_3$, 298.0 K) δ 170.54, 167.70, 148.52, 146.11, 132.21, 131.90, 123.52, 122.29, 86.00, 37.49, 26.21, 22.71; **FTIR** (KBr):ν_{max} = 3260, 1712, 1608. HRMS (ESI) *m/z:* calcd for $C_{12}H_{15}N_2O_3$ [(M+ H)$^+$] 235.1077; found: 235.1069.

General Procedure for Tandem Reaction of 2-acetyl benzonitriles with carbon- and hetero-nucleophiles

2-acetylbenzonitriles **144a-f** (0.24 mmol) were added to a solution of dimethyl malonate (3 eq., 0.72 mmol, 82 μL) and K_2CO_3 (1eq.,0.24 mmol) in acetonitrile (80 μL) and the mixture was stirred at 50°C until disappearance of the starting material (TLC hexane-acetyl acetate 3:7). After 18 h, dichloromethane was added and the mixture was filtered

and the solvent evaporated in vacuo. The crude product was purified by flash chromatography (silica gel, hexane-ethyl acetate, 60/40-ethyl acetate).

dimethyl 2-(1-methyl-3-oxoisoindolin-1-yl)malonate (153a). White solid (58 mg, 87%). Mp: 123-125°C. ^{1}H NMR (400 MHz, $CDCl_3$, 298.0 K) δ 7.83 (d, *J* = 7.7 Hz, 1H), 7.63 – 7.54 (m, 1H), 7.51 – 7.46 (m, 1H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.11 (bs, 1H), 3.85 (s, 1H), 3.82 (s, 3H), 3.45 (s, 3H), 1.70 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 298.0 K) δ 168.9, 167.9, 166.1, 148.6, 132.0, 130.9, 128.9, 124.0, 121.7, 60.7, 58.8, 52.9, 52.7, 24.8. **FTIR** (KBr):ν_{max} = 3208, 1767, 1740, 1682. HRMS (ESI) *m/z:* calcd for $C_{14}H_{16}NO_5$ [(M+ H)$^+$] 278.1023; found: 278.1028.

2-(1-methyl-3-oxoisoindolin-1-yl)malononitrile (153b). The reaction was carried out at room temperature. After 3 h, acetic acid (15 μL) diluted in dichloromethane (1 mL) was added and the solution was filtered. Purified by flash chromatography (silica gel, hexane/ ethyl acetate, 60:40). White solid (45 mg, 89%). Mp: 134-136°C. ^{1}H NMR (250 MHz, $CDCl_3$, 298.0 K) δ 7.99 – 7.85 (m, 1H), 7.80 – 7.57 (m, 3H), 4.21 (s, 1H), 1.93 (s, 3H). ^{13}C NMR (65 MHz, $CDCl_3$, 298.0 K) δ 169.7, 145.5, 133.8, 131.1, 130.9, 125.0, 122.0, 111.0, 110.7, 61.9, 35.0, 23.2; **FTIR** (KBr):ν_{max} = 32381 2224, 2206, 1728, 1704, 1693. HRMS (ESI) *m/z:* calcd for $C_{12}H_{10}N_3O$ [(M+H)$^+$] 212.0818; found 212.0823.

3-(benzylamino)-3-methylisoindolin-1-one (153c). White solid (60 mg, 99%). Mp: 136-138°C. ^{1}H NMR (300 MHz, $CDCl_3$, 298.0 K) δ 7.85 (dd, *J* = 7.5, 0.8 Hz, 1H), 7.71 – 7.58 (m, 2H), 7.54 (dt, *J* = 8.4, 4.3 Hz, 1H), 7.32 – 7.13 (m, 5H), 7.02 (bs, 1H), 3.67 (d, *J* = 12.6 Hz, 1H), 3.22 (d, *J* = 12.6 Hz, 1H), 1.80 (s, 3H). ^{13}C NMR (65 MHz, $CDCl_3$, 298.0 K) δ 169.6, 148.9, 139.4, 132.8, 131.9, 129.4, 128.6, 128.4, 127.4, 123.9, 122.3, 76.1, 46.7, 27.9. **FTIR** (KBr):ν_{max} = 3272, 1692, 1691. HRMS (ESI) *m/z:* calcd for $C_{16}H_{17}N_2O$ [(M+H)$^+$] 253.1335; found: 253.1322.

3-methyl-3-(nitromethyl)isoindolin-1-one (153d). Acetic acid (15 μL) diluted in dichloromethane (1 mL) was added and the solution was filtered. Purified by flash chromatography (silica gel, hexane/ ethyl acetate, 60:40). White solid (47 mg, 94%). Mp: 135-136°C. ^{1}H NMR (250 MHz, $CDCl_3$, 298.0 K) δ 7.89 (d, *J* = 7.4 Hz, 1H), 7.73

– 7.50 (m, 2H), 7.43 (d, *J* = 7.4 Hz, 1H), 7.24 (bs, 1H), 4.86 (d, *J* = 12.8 Hz, 1H), 4.41 (d, *J* = 12.8 Hz, 1H), 1.68 (s, 3H). ^{13}C NMR (65 MHz, $CDCl_3$, 298.0 K) δ 168.7, 146.6, 132.8, 130.9, 129.8, 124.8, 121.3, 82.7, 59.4, 23.2; **FTIR** (KBr):ν_{max} = 3412, 1714, 1542. HRMS (ESI) *m/z:* calcd for $C_{10}H_{11}N_2O_3$ [(M+H)$^+$] 207.0764; found: 207.0769.

3-(butylamino)-3-methylisoindolin-1-one (153e). White solid (52 mg, 99%). Mp: 112-114 °C. ^{1}H NMR (250 MHz, $CDCl_3$, 298.0 K) δ 7.83 – 7.75 (m, 1H), 7.65 – 7.53 (m, 1H), 7.51 – 7.41 (m, 2H), 6.28 (bs, 1H), 2.47 (dt, *J* = 11.2, 6.9 Hz, 1H), 1.99 (dt, *J* = 11.2, 6.9 Hz, 1H), 1.68 (s, 3H), 1.39 – 1.16 (m, 4H), 0.80 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 298.0 K) δ 169.4, 149.6, 132.5, 131.8, 129.0, 123.7, 121.0, 76.0, 41.9, 32.6, 28.0, 20.4, 14.0; **FTIR** (KBr):ν_{max} = 3285, 1686. HRMS (ESI) calcd for $C_{13}H_{19}N_2O$ [(M+ H)$^+$] 219.1492; found: 219.1487.

dimethyl 2-(1-methyl-5-nitro-3-oxoisoindolin-1-yl)malonate (153f). White solid (62 mg, 80%). Mp: 151-153°C. ^{1}H NMR (250 MHz, $CDCl_3$, 298.0 K) δ 8.65 (d, *J* = 2.1 Hz, 1H), 8.45 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.60 (d, *J* = 8.7 Hz, 1H), 7.28 (bs, 1H), 3.90 (s, 1H), 3.84 (s, 3H), 3.50 (s, 3H), 1.72 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 298.0 K) δ 167.8, 166.2, 165.9, 154.6, 149.1, 133.2, 127.3, 123.3, 119.9, 61.2, 58.6, 53.4, 53.2, 25.2. **FTIR** (KBr):ν_{max} = 3218, 1765, 1742, 1689, 1549. HRMS (ESI) *m/z:* calcd for $C_{14}H_{15}N_2O_7$ [(M+ H)$^+$] 323.0874; found: 323.0871.

dimethyl 2-(5-bromo-1-methyl-3-oxoisoindolin-1-yl)malonate (153g). White solid (80 mg, 93%). Mp: 138-140 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 298.0 K) δ 7.96 (d, *J* = 2.0 Hz, 1H), 7.70 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.20 (bs, 1H), 3.84 (s, 1H), 3.82 (s, 3H), 3.51 (s, 3H), 1.70 (s, 3H). ^{13}C NMR (65 MHz, $CDCl_3$, 298.0 K) δ 168.0, 167.6, 166.3, 147.6, 135.3, 133.4, 127.4, 123.8, 123.3, 60.9, 58.8, 53.2, 53.0, 25.0; **FTIR** (KBr):ν_{max} = 3224, 1763, 1741, 1685. HRMS (ESI) *m/z:* calcd for $C_{14}H_{15}BrNO_5$ [(M+ H)$^+$] 356.0128; found: 356.0134.

dimethyl 2-(5-chloro-1-methyl-3-oxoisoindolin-1-yl)malonate (153h). White solid (67 mg, 89%); Mp: 138-140°C. ^{1}H NMR (300 MHz, $CDCl_3$, 298.0 K) δ 7.80 (d, *J* = 2.0 Hz, 1H), 7.55 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.16 (bs, 1H), 3.89 –

3.77 (m, 4H), 3.51 (s, 3H), 1.69 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 298.0 K) δ 167.8, 167.5, 166.1, 146.8, 135.3, 132.9, 132.3, 124.3, 123.2, 60.6, 58.7, 53.0, 52.9, 24.9. **FTIR** (KBr):ν_{max} = 3216, 1764, 1742, 1685. HRMS (ESI) *m/z:* calcd for $C_{14}H_{15}ClNO_5$ [(M+ H)$^+$] 312.0633; found: 312.0637.

Dimethyl 2-(5-Acetamido-4-bromo-1-methyl-3-oxoisoindolin-1-yl)malonate (153i): Waxy solid (83 mg, 84 %). ^{1}H NMR (300 MHz, $CDCl_3$, 298.0 K): δ = 8.64 (d, J = 8.3 Hz, 1 H), 7.97 (br. s, 1 H), 7.34 (d, J = 8.4 Hz, 1 H), 7.22 (br. s, 1 H), 3.84 (s, 3 H), 3.82 (s, 1 H), 3.53 (s, 3 H), 2.30 (s, 3 H), 1.68 (s, 3 H) ppm. ^{13}C NMR (65 MHz, $CDCl_3$, 298.0 K): δ = 168.7, 168.1, 166.9, 166.3, 145.9, 137.0, 128.8, 125.0, 121.6, 109.4, 59.0, 58.9, 53.2, 53.1, 25.2, 25.2 ppm. **FTIR** (KBr):ν_{max} = 3216, 1764, 1742, 1724, 1685 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{18}BrN_2O_6$ [M + H]$^+$ 413.0343; found 413.0338.

Dimethyl 2-[1-Methyl-5-(*N*-methylacetamido)-3-oxoisoindolin- 1-yl]malonate (153j): White solid (73 mg, 88 %). M.p.: 138-140 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 298.0 K): δ = 7.69–7.63 (m, 1 H), 7.55–7.37 (m, 2 H), 7.26 (br. s, 1 H), 3.88 (s, 1 H), 3.84 (s, 3 H), 3.50 (s, 3 H), 3.30 (s, 3 H), 1.89 (s, 3 H), 1.73 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 298.0 K): δ = 170.1, 167.7, 166.0, 147.7, 145.3, 132.8, 130.8, 123.3, 122.4, 60.7, 58.6, 52.9, 52.7, 37.2, 24.8, 22.4 ppm. **FTIR** (KBr):ν_{max} = 3210, 1760, 1747, 1721, 1686 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{21}N_2O_6$ [M + H]$^+$ 349.1394; found 349.1387.

6-chloro-3-methyl-3-(nitromethyl)isoindolin-1-on (153k). White solid (49 mg, 85%). Mp. 140-141°C. ^{1}H NMR (400 MHz, $CDCl_3$, 298.0 K) δ 7.85 (s, 1H), 7.61 (d, J = 8.1 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.05 (bs, 1H), 4.82 (d, J = 12.9 Hz, 1H), 4.40 (d, J = 12.9 Hz, 1H), 1.67 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 298.0 K) δ 167.4, 144.8, 136.5, 133.2, 133.0, 125.2, 122.9, 82.5, 59.5, 23.4. **FTIR** (KBr):ν_{max} = 3392, 1717, 1552. HRMS (ESI) *m/z:* calcd for $C_{10}H_{10}ClN_2O_3$ [(M+ H)$^+$] 241.0374; found: 241.0368.

3-(benzylamino)-6-chloro-3-methylisoindolin-1-one (153l). White solid (63 mg, 92%). Mp: 140-142°C. ^{1}H NMR (250 MHz, $CDCl_3$, 298.0 K) δ 7.78 (d, J = 1.9 Hz, 1H), 7.53 (dd, J = 8.1, 1.9 Hz, 1H), 7.43 (d, J = 8.1 Hz, 1H), 7.35 – 7.11 (m, 5H), 6.43 (bs, 1H), 3.62 (d, J = 12.7 Hz, 1H), 3.19 (d, J = 12.7 Hz, 1H), 1.73 (s, 3H). ^{13}C NMR (65

MHz, $CDCl_3$, 298.0 K) δ 168.1, 147.5, 139.8, 135.4, 133.7, 132.8, 128.6, 128.2, 127.4, 124.0, 123.6, 76.0, 46.8, 28.1. **FTIR** (KBr):ν_{max} = 3316, 1698, 1656. HRMS (ESI) *m/z:* calcd for $C_{16}H_{16}ClN_2O$ [(M+ H)$^+$] 287.0946; found: 287.0931.

3-(butylamino)-6-chloro-3-methylisoindolin-1-one (153m). White solid (54 mg, 89%). Mp: 130-132°C. ^{1}H NMR (300 MHz, $CDCl_3$, 298.0 K) δ 7.76 (d, *J* = 2.0 Hz, 1H), 7.55 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.40 (d, *J* = 8.1 Hz, 1H), 6.77 (bs, 1H), 2.48 (dt, *J* = 11.2, 6.7 Hz, 1H), 1.99 (dt, *J* = 11.2, 6.7 Hz, 1H), 1.69 (s, 3H), 1.40 – 1.14 (m, 4H), 0.82 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 298.0 K) δ 168.0, 147.8, 135.2, 133.6, 132.6, 123.9, 123.4, 75.9, 41.9, 32.6, 28.0, 20.4, 14.0. **FTIR** (KBr):ν_{max} = 3285, 1691. HRMS (ESI) *m/z:* calcd for $C_{13}H_{18}ClN_2O$ [(M+ H)$^+$] 253.1102; found: 253.1097.

General Procedure for Asymmetric Tandem Reaction of 2-acetyl benzonitrile 144a with Dimethyl malonate

2-acetylbenzonitriles **144a** (0.070 mmol, 10.2 mg) were added to a mixture of and K_3PO_4 (1.2 eq., 0.084 mmol, 17.8 mg) in DCM (2.0 mL). Then dimethyl malonate (2 eq., 0.17 mmol, 19 μL) was added and the mixture was stirred at room temperature for 44h. After, dichloromethane was added and the mixture was filtered and the solvent evaporated in vacuo. The crude product was purified by flash chromatography (silica gel, hexane-ethyl acetate, 60/40-ethyl acetate). HPLC analysis: Chiralpack IA-3 column, hexane–^{i}PrOH 80:20, 0.6 mL/min, λ = 254 nm (t_{minor} = 20.6 min, t_{major} = 24.7 min).

CCDC 1587578 (for **152a**), and 1587579 (for **153a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

7.4 β-ADDITION OF ISOXAZOLIDIN-5-ONES TO MORITA-BAYLIS-HILLMAN CARBONATES CATALYSED BY ASYMMETRIC PHASE-TRANSFER CATALYSIS

Catalysts **A1-2**, **B**, **C**, **D1-3** were either commercial or prepared as described previously.[75k,162a,190,191.]

General procedure for the synthesis of racemic compounds 175:

In a Schlenk tube, under argon atmosphere, the Baylis-Hillman carbonate **174** (1.5 eq., 0.15 mmol), benzyl-substituted isoxazolidin-5-one **160** (1.0 eq., 0.10 mmol) and tetrabutylammonium bromide (0.20 eq., 0.020 mmol, 6.4 mg) were dissolved in THF (2 ml). Then, Cs_2CO_3 (3.0 eq., 0.30 mmol, 98 mg) was added and the resulting heterogeneous solution was stirred (1000 rpm) at room temperature for 24 h. Then, the mixture was filtered over a pad of Na_2SO_4, the solvent evaporated and the residue dried in vacuo. The resulting crude product was purified by chromatography (silica gel, heptane-ethyl acetate, 15/1 to 10/1) to afford racemic products **175.**

General procedure for the asymmetric *β*-addition of isoxazolidin-5-ones 160 to MBH carbonates 174 to obtain enantioenriched products 175a-w:

In a Schlenk tube, under argon atmosphere, the Baylis-Hillman carbonate **174a-m** (1.5 eq., 0.15 mmol), benzyl-substituted isoxazolidin-5-one **160a-k** (1.0 eq., 0.10 mmol) and catalyst **D2** (0.05 eq., 0.005 mmol, 5.4 mg) were charged and dissolved in 2.0 ml of isopropyl ether, and the mixture cooled at -20°C. After 20 minutes, Cs_2CO_3 (3.0 eq., 0.30 mmol, 97.7 mg) was quickly added and the mixture was stirred (1000 rpm) for 96 h. Then, the mixture was filtered over a pad of Na_2SO_4, washed with DCM, the solvent evaporated, and the residue dried in vacuo. The resulting crude product was purified by chromatography (silica gel, heptane-ethyl acetate, 15/1 to 10/1) to afford enantioenriched products **175a-w**.

tert-butyl (E)-4-benzyl-4-(2-(ethoxycarbonyl)-3-phenylallyl)-5-oxoisoxazolidine-2-carboxylate (**175a)**: Following the general procedure with tert-butyl 4-benzyl-5-oxoisoxazolidine-2-carboxylate **160a** (27.7 mg, 0.10 mmol, 1.0 eq.) and ethyl 2-(((tert-butoxycarbonyl)oxy)(phenyl)methyl)acrylate **174a** (46.0 mg, 0.15 mmol, 1.5 eq.), the title compound **175a** was obtained as a colorless oil (41.9 mg, 90%, E/Z= 10:1, e.r.= 94:6 (major diastereomer)). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$= 43.9° (c = 0.41, $CHCl_3$). **^{1}H NMR** (300 MHz, Chloroform-d, 298 K) δ 7.83 (s, 1H), 7.30 – 7.06 (m, 8H), 7.04 – 6.94 (m, 2H), 4.21 (q, J = 7.1 Hz, 2H), 3.82 – 3.70 (m, 2H), 3.06 (s, 2H), 2.96 (d, J = 13.9 Hz, 1H), 2.58 (d, J = 13.9 Hz, 1H), 1.40 (s, 9H), 1.28 (t, J = 7.1 Hz, 3H) ppm; **^{13}C NMR** (75 MHz, Chloroform-d, 298 K) δ 175.5, 167.7, 154.9, 143.5, 134.9, 134.9, 130.4, 128.9, 128.8, 128.7, 128.7, 128.0, 127.4, 83.6, 61.4, 54.4, 49.8, 40.8, 31.7, 28.1, 14.1 ppm; **IR** (film): ν (cm-1) 2977, 2938, 1794, 1712, 1454, 1369, 1254, 1202, 1146, 1095, 1022, 848, 754, 701; **HRMS (MALDI-FT ICR)**: *m/z* calcd for $C_{27}H_{31}NNaO_6$ $[M+Na]^+$= 488.20456, found: 488.20359; The enantioselectivity was determined by **HPLC** (Chiralpak AD-H column, n-hexane:i-PrOH = 95:5, 0.5 mL/min, 10 °C, t_{major} = 46.8 min, t_{minor} = 61.4 min).

tert-butyl (E)-4-benzyl-4-(2-((benzyloxy)carbonyl)-3-phenylallyl)-5-oxoisoxazolidine-2-carboxylate (175b): Following the general procedure with tert-butyl 4-benzyl-5-oxoisoxazolidine-2-carboxylate **160a** (27.7 mg, 0.10 mmol, 1.0 eq.) and benzyl 2-(((tert-butoxycarbonyl)oxy)(phenyl)methyl)acrylate **174b** (55.2 mg, 0.15 mmol, 1.5 eq.), the title compound **175b** was obtained as a colorless oil (35.9 mg, 68%, E/Z= 8:1, e.r.= 78:22 (major diastereomer)). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$= 22.3° (c = 0.22, $CHCl_3$). **^{1}H NMR** (300 MHz, Chloroform-d, 298 K) δ 7.85 (s, 1H), 7.46 – 7.04 (m, 13H), 7.04 – 6.89 (m, 2H), 5.22 (d, J = 12.3 Hz, 1H), 5.15 (d, J = 12.3 Hz, 1H), 3.79 (d, J = 11.1 Hz, 1H), 3.73 (d, J = 11.1 Hz, 1H), 3.08 (s, 2H), 2.95 (d, J = 13.9 Hz, 1H), 2.57 (d, J = 13.9 Hz, 1H), 1.38 (s, 9H) ppm; **^{13}C NMR** (75 MHz, Chloroform-d, 298 K) δ 175.4, 167.6, 154.9, 143.8, 135.8, 134.8, 134.8, 130.4, 128.9, 128.8, 128.7, 128.6, 128.6, 128.3, 127.8, 127.4, 83.6, 67.1, 54.5, 49.9, 40.7, 31.8, 28.1 ppm; **IR** (film): ν (cm-1) 2920, 2852, 1794, 1713, 1633, 1497, 1456, 1369, 1253, 1146, 1030, 848, 753, 700; **HRMS (MALDI-FT ICR)**: *m/z* calcd for $C_{32}H_{33}NNaO_6$ $[M+Na]^+$= 550.22001, found: 550.21909; The

enantioselectivity was determined by **HPLC** (YMC Cellulose-SB column, n-hexane:i-PrOH = 80:20, 0.5 mL/min, 10 °C, t_{minor} = 21.1 min, t_{major} = 26.7 min).

tert-butyl (E)-4-benzyl-4-(2-(tert-butoxycarbonyl)-3-phenylallyl)-5-oxoisoxazolidine-2-carboxylate (5c): Following the general procedure with tert-butyl 4-benzyl-5-oxoisoxazolidine-2- carboxylate **160a** (27.7 mg, 0.10 mmol, 1.0 eq.) and tert-butyl 2-(((tert-butoxycarbonyl)oxy)(phenyl)methyl)acrylate **174c** (50.2 mg, 0.15 mmol, 1.5 eq.), the title compound **175c** was obtained as a colorless oil (26.2 mg, 53%, E/Z= 8:1, e.r.= 91:9 (major diastereomer)). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$= 33.0° (c = 1.00, $CHCl_3$). **^{1}H NMR** (300 MHz, Chloroform-d, 298 K) δ 7.82 (s, 1H), 7.40 – 7.14 (m, 8H), 7.10 – 7.00 (m, 2H), 3.83 (d, J = 10.9 Hz, 1H), 3.76 (d, J = 10.9 Hz, 1H), 3.11 (s, 2H), 3.02 (d, J = 13.9 Hz, 1H), 2.63 (d, J = 13.9 Hz, 1H), 1.54 (s, 9H), 1.46 (s, 9H) ppm; **^{13}C NMR** (75 MHz, Chloroform-d, 298 K) δ 175.2, 166.8, 154.9, 142.5, 135.3, 135.0, 130.4, 129.5, 128.8, 128.7, 128.7, 128.4, 127.4, 83.6, 81.9, 54.6, 50.0, 40.7, 31.5, 28.1, 28.0 ppm; **IR** (film): ν (cm-1) 2976, 2933, 1798, 1711, 1495, 1477, 1455, 1394, 1369, 1255, 1147, 1017, 850, 758, 701; **HRMS (MALDI-FT ICR)**: *m/z* calcd for $C_{29}H_{35}NNaO_6$ $[M+Na]^+$= 516.23566, found: 516.23499; The enantioselectivity was determined by **HPLC** (Chiralpak IA-3 column, n-hexane:i-PrOH = 80:20, 0.8 mL/min, t_{major} = 6.4 min, t_{minor} = 8.6 min).

tert-butyl (E)-4-(2-(ethoxycarbonyl)-3-phenylallyl)-4-(4-methylbenzyl)-5-oxoisoxazolidine-2-carboxylate (175d): Following the general procedure with tert-butyl 4-(4-methylbenzyl)-5-oxoisoxazolidine-2-carboxylate **160b** (29.1 mg, 0.10 mmol, 1.0 eq.) and ethyl 2-(((tert-butoxycarbonyl)oxy)(phenyl)methyl)acrylate **174a** (46.0 mg, 0.15 mmol, 1.5 eq.), the title compound **175d** was obtained as a colorless oil (44.1 mg, 92%, E/Z= 8:1, e.r.= 92:8 (major diastereomer)). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$= 30.9° (c = 0.80, $CHCl_3$). **^{1}H NMR** (300 MHz, Chloroform-d, 298 K) δ 7.82 (s, 1H), 7.30 – 7.15 (m, 3H), 7.14 – 7.06 (m, 2H), 6.97 (d, J = 7.8 Hz, 2H), 6.87 (d, J = 7.8 Hz, 2H), 4.20 (q, J = 7.2 Hz, 2H), 3.76 (s, 2H), 3.04 (s, 2H), 2.91 (d, J = 14.0 Hz, 1H), 2.54 (d, J = 14.0 Hz, 1H), 2.24 (s, 3H), 1.39 (s, 9H), 1.28 (d, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, Chloroform-d, 298 K) δ 175.7, 167.7, 154.9, 143.5, 137.0, 134.9, 131.7, 130.2, 129.4, 128.9, 128.7, 128.6, 128.0,

83.6, 61.4, 54.4, 49.8, 40.5, 31.7, 28.1, 21.0, 14.1 ppm; **IR** (film): ν (cm-1) 2978, 2937, 1197, 1715, 1629, 1446, 1369, 1254, 1202, 1147, 1023, 848, 813, 763, 700; **HRMS (MALDI-FT ICR)**: *m/z* calcd for $C_{28}H_{33}NNaO_6$ $[M+Na]^+$= 502.22001, found: 502.21955; The enantioselectivity was determined by **HPLC** (Chiralpak AD-H column, n-hexane:i-PrOH = 80:20, 0.5 mL/min, t_{major} = 11.9 min, t_{minor} = 16.0 min).

tert-butyl (E)-4-(4-(tert-butyl)benzyl)-4-(2-(ethoxycarbonyl)-3-phenylallyl)-5-oxoisoxazolidine-2-carboxylate (**175e)**: Following the general procedure with tert-butyl 4-(4-(tert-butyl)benzyl)-5-oxoisoxazolidine-2-carboxylate **160c** (33.3 mg, 0.10 mmol, 1.0 eq.) and ethyl 2-(((tert-butoxycarbonyl)oxy)(phenyl)methyl)acrylate **174a** (46.0 mg, 0.15 mmol, 1.5 eq.), the title compound **175e** was obtained as a colorless oil (40.2 mg, 77%, E/Z= 11:1, e.r.= 95:5 (major diastereomer)). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$= 41.8° (c = 1.00, $CHCl_3$). **^{1}H NMR** (300 MHz, Chloroform-d, 298 K) δ 7.82 (s, 1H), 7.25 – 7.16 (m, 5H), 7.16 – 7.09 (m, 2H), 6.92 (d, J = 7.9 Hz, 2H), 4.20 (d, J = 7.2 Hz, 2H), 3.77 (s, 2H), 3.06 (s, 2H), 2.91 (d, J = 14.0 Hz, 1H), 2.54 (d, J = 14.0 Hz, 1H), 1.41 (s, 9H), 1.27 (t, J = 7.2 Hz, 3H), 1.22 (s, 9H) ppm; **^{13}C NMR** (75 MHz, Chloroform-d, 298 K) δ 175.6, 167.7, 155.0, 150.2, 143.5, 135.0, 131.7, 130.2, 129.0, 128.7, 128.6, 128.0, 125.6, 83.6, 61.4, 54.4, 49.7, 40.2, 34.4, 31.6, 31.3, 28.1, 14.1 ppm; **IR** (film): ν (cm-1) 2968, 2869, 1797, 1745, 1714, 1629, 1494, 1477, 1394, 1446, 1369, 1318, 1254, 1202, 1147, 1099, 1020, 850, 757, 701; **HRMS (MALDI-FT ICR)**: *m/z* calcd for $C_{31}H_{39}NNaO_6$ $[M+Na]^+$= 544.26696, found: 544.26614; The enantioselectivity was determined by **HPLC** (Chiralpak IC column, n-hexane:i-PrOH = 80:20, 1.0 mL/min, t_{minor} = 11.0 min, t_{major} = 17.7 min).

tert-butyl (E)-4-([1,1'-biphenyl]-4-ylmethyl)-4-(2-(ethoxycarbonyl)-3-phenylallyl)-5-oxoisoxazolidine-2-carboxylate (**175f)**: Following the general procedure with tert-butyl 4-([1,1'-biphenyl]-4-ylmethyl)-5-oxoisoxazolidine-2-carboxylate **160d** (35.3 mg, 0.10 mmol, 1.0 eq.) and ethyl 2-(((tert-butoxycarbonyl)oxy)(phenyl)methyl)acrylate **174a** (46.0 mg, 0.15 mmol, 1.5 eq.), the title compound **175f** was obtained as a colorless oil (40.1 mg, 74%, E/Z= 9:1, e.r.= 92:8 (major diastereomer)). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = 19.8° (c = 0.36, $CHCl_3$). **^{1}H NMR** (300 MHz, Chloroform-d, 298 K) δ 7.91 (s, 1H), 7.56 (d, J = 7.8 Hz,

2H), 7.50 – 7.41 (m, 4H), 7.39 – 7.34 (m, 1H), 7.31 – 7.23 (m, 3H), 7.19 (s, 2H), 7.14 (d, J = 7.8 Hz, 2H), 4.29 (q, J = 7.1 Hz, 2H), 3.88 (s, 2H), 3.16 (s, 2H), 3.06 (d, J = 13.9 Hz, 1H), 2.71 (d, J = 13.9 Hz, 1H), 1.47 (s, 9H), 1.36 (t, J = 7.1 Hz, 3H) ppm; **^{13}C NMR** (75 MHz, Chloroform-d, 298 K) δ 175.6, 167.7, 155.0, 143.6, 140.5, 140.3, 134.9, 133.9, 130.8, 128.8, 128.8, 128.6, 128.0, 127.4, 127.4, 127.0, 83.7, 61.5, 54.4, 49.8, 40.5, 31.6, 28.1, 14.1 ppm; **IR** (film): ν (cm-1) 2979, 2935, 1796, 1713, 1636, 1488, 1447, 1369, 1253, 1202, 1149, 1008, 848, 754, 698; **HRMS (MALDI-FT ICR)**: *m/z* calcd for $C_{33}H_{35}NNaO_6$ $[M+Na]^+$= 564.23566, found: 564.23488; The enantioselectivity was determined by **HPLC** (YMC Cellulose-SB column, n-hexane:i-PrOH = 80:20, 0.5 mL/min, t_{minor} = 25.5 min, t_{major} = 29.1 min).

tert-butyl (E)-4-(2-(ethoxycarbonyl)-3-phenylallyl)-4-(4-methoxybenzyl)-5-oxoisoxazolidine-2-carboxylate (**175g)**: Following the general procedure with tert-butyl 4-(4-methoxybenzyl)-5-oxoisoxazolidine-2-carboxylate **160e** (30.7 mg, 0.10 mmol, 1.0 eq.) and ethyl 2-(((tert-butoxycarbonyl)oxy)(phenyl)methyl)acrylate **174a** (46.0 mg, 0.15 mmol, 1.5 eq.), the title compound **175g** was obtained as a colorless oil (38.1 mg, 77%, E/Z= 10:1, e.r.= 93:7 (major diastereomer)). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$= 23.1° (c = 0.30, $CHCl_3$). **^{1}H NMR** (300 MHz, Chloroform-d, 298 K) δ 7.89 (s, 1H), 7.35 – 7.27 (m, 3H), 7.21 – 7.14 (m, 2H), 6.98 (d, J = 8.2 Hz, 2H), 6.77 (d, J = 8.2 Hz, 2H), 4.28 (q, J = 7.1 Hz, 2H), 3.83 (s, 2H), 3.78 (s, 3H), 3.11 (s, 2H), 2.97 (d, J = 14.1 Hz, 1H), 2.59 (d, J = 14.1 Hz, 1H), 1.46 (s, 9H), 1.35 (t, J = 7.1 Hz, 3H) ppm; **^{13}C NMR** (75 MHz, Chloroform-d, 298 K) δ 175.7, 167.7, 158.9, 154.9, 143.5, 143.4, 134.9, 131.4, 128.9, 128.7, 128.6, 128.0, 126.7, 114.1, 83.6, 61.4, 55.2, 54.3, 49.9, 40.1, 31.7, 28.1, 14.1 ppm; **IR** (film): ν (cm-1) 2979, 2930, 1797, 1715, 1612, 1514, 1458, 1369, 1303, 1252, 1202, 1181, 1146, 1034, 847, 763, 700; **HRMS (MALDI-FT ICR)**: *m/z* calcd for $C_{28}H_{33}NNaO_7$ $[M+Na]^+$= 518.21492, found: 518.21471; The enantioselectivity was determined by **HPLC** (Chiralpak AD-H column, n-hexane:i-PrOH = 80:20, 0.5 mL/min, 10 °C, t_{major} = 23.0 min, t_{minor} = 31.3 min).

tert-butyl (E)-4-(4-chlorobenzyl)-4-(2-(ethoxycarbonyl)-3-phenylallyl)-5-oxoisoxazolidine-2-carboxylate (175h): Following the general procedure with tert-butyl 4-(4-chlorobenzyl)-5-oxoisoxazolidine-2-carboxylate **160f** (31.2 mg, 0.10 mmol, 1.0 eq.) and ethyl 2-(((tert-butoxycarbonyl)oxy)(phenyl)methyl)acrylate **174a** (46.0 mg, 0.15 mmol, 1.5 eq.), the title compound **175h** was obtained as a colorless oil (40.0 mg, 80%, E/Z= 6:1, e.r.= 88/12 (major diastereomer)). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$= 19.0° (c = 0.37, $CHCl_3$). **^{1}H NMR** (300 MHz, Chloroform-d, 298 K) δ 7.91 (s, 1H), 7.38 – 7.27 (m, 3H), 7.24 – 7.14 (m, 4H), 6.97 (d, J = 8.0 Hz, 2H), 4.28 (q, J = 7.1 Hz, 2H), 3.84 (d, J = 11.1 Hz, 1H), 3.76 (d, J = 11.1 Hz, 1H), 3.09 (s, 2H), 2.97 (d, J = 14.0 Hz, 1H), 2.61 (d, J = 14.0 Hz, 1H), 1.47 (s, 9H), 1.35 (t, J = 7.1 Hz, 3H) ppm; **^{13}C NMR** (75 MHz, Chloroform-d, 298 K) δ 175.4, 167.6, 154.8, 143.7, 134.9, 133.5, 133.3, 131.6, 128.9, 128.8, 128.7, 128.7, 127.9, 83.8, 61.5, 54.4, 49.7, 40.1, 31.6, 28.1, 14.1 ppm; **IR** (film): ν (cm-1) 2983, 2936, 1795, 1714, 1632, 1494, 1446, 1369, 1253, 1202, 1146, 1095, 1016, 847, 756, 701; **HRMS (MALDI-FT ICR)**: *m/z* calcd for $C_{27}H_{30}ClKNNaO_6$ $[M+Na]^+$= 538.13932, found: 538.13875; The enantioselectivity was determined by **HPLC** (YMC Cellulose-SB column, n-hexane:i-PrOH = 90:10, 0.5 mL/min, 10 °C, t_{minor} = 22.7 min, t_{major} = 31.0 min).

tert-butyl (E)-4-(4-bromobenzyl)-4-(2-(ethoxycarbonyl)-3-phenylallyl)-5-oxoisoxazolidine-2-carboxylate (175i): Following the general procedure with tert-butyl 4-(4-bromobenzyl)-5-oxoisoxazolidine-2-carboxylate **160g** (35.6 mg, 0.10 mmol, 1.0 eq.) and ethyl 2-(((tert-butoxycarbonyl)oxy)(phenyl)methyl)acrylate **174a** (46.0 mg, 0.15 mmol, 1.5 eq.), the title compound **175i** was obtained as a colorless oil (38.1 mg, 70%, E/Z= 10:1, e.r.= 84:16 (major diastereomer)). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$= 24.4° (c= 1.00, $CHCl_3$). **^{1}H NMR** (300 MHz, Chloroform-d, 298 K) δ 7.91 (s, 1H), 7.40 – 7.28 (m, 5H), 7.21 – 7.13 (m, 2H), 6.91 (d, J = 8.0 Hz, 2H), 4.28 (q, J = 7.1 Hz, 2H), 3.84 (d, J = 11.1 Hz, 1H), 3.76 (d, J = 11.1 Hz, 1H), 3.09 (s, 2H), 2.95 (d, J = 14.0 Hz, 1H), 2.60 (d, J = 14.0 Hz, 1H), 1.47 (s, 9H), 1.35 (t, J = 7.1 Hz, 3H) ppm; **^{13}C NMR** (75 MHz, Chloroform-d, 298 K) δ 175.3, 167.6, 154.8, 143.7, 134.9, 133.8, 132.0, 131.8, 128.8, 128.7, 127.9, 121.7, 83.8, 61.5, 54.4, 49.6, 40.12, 31.6, 28.1, 14.1 ppm; **IR** (film): ν (cm-1) 2980, 2937, 1795, 1712, 1490, 1369, 1253, 1146, 1074, 1012, 846, 755, 701; **HRMS (MALDI-FT ICR)**:

m/z calcd for $C_{27}H_{30}BrNNaO_6$ $[M+Na]^+$= 566.11487, found: 566.11407; The enantioselectivity was determined by **HPLC** (Chiralpak IC column, n-hexane:i-PrOH = 80:20, 1.0 mL/min, t_{minor} = 12.7 min, t_{major} = 24.8 min).

tert-butyl (E)-4-(2-(ethoxycarbonyl)-3-phenylallyl)-5-oxo-4-(4-(trifluoromethyl)benzyl)isoxazolidine-2-carboxylate (**175j)**: Following the general procedure with tert-butyl 5-oxo-4-(4-(trifluoromethyl)benzyl)isoxazolidine-2-carboxylate **160h** (34.5 mg, 0.10 mmol, 1.0 eq.) and ethyl 2-(((tert-butoxycarbonyl)oxy)(phenyl)methyl)acrylate **174a** (46.0 mg, 0.15 mmol, 1.5 eq.), the title compound **175j** was obtained as a colorless oil (43.8 mg, 82%, E/Z= 10:1, e.r.= 85:15 (major diastereomer)). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{26}}$= 25.2° (c = 0.50, $CHCl_3$). **^{1}H NMR** (300 MHz, Chloroform-d, 298 K) δ 7.93 (s, 1H), 7.48 (d, J = 7.9 Hz, 2H), 7.34 – 7.27 (m, 3H), 7.23 – 7.11 (m, 4H), 4.28 (q, J = 7.1 Hz, 2H), 3.87 (d, J = 11.1 Hz, 1H), 3.74 (d, J = 11.1 Hz, 1H), 3.11 (s, 2H), 3.04 (d, J = 13.9 Hz, 1H), 2.70 (d, J = 13.9 Hz, 1H), 1.47 (s, 9H), 1.36 (t, J = 7.1 Hz, 3H) ppm; **^{13}C NMR** (75 MHz, Chloroform-d, 298 K) δ 175.1, 167.5, 154.8, 143.8, 139.0, 134.9, 130.6, 129.7 (q, J= 32.6 Hz), 128.8, 128.7, 128.7, 127.8, 125.6 (q, J= 3.7 Hz), 124.0 (q, J= 272.0 Hz), 83.9, 61.5, 54.6, 49.7, 40.4, 31.6, 28.0, 14.1 ppm; **IR** (film): ν (cm-1) 2919, 2849, 1798, 1714, 1634, 1447, 1370, 1326, 1255, 1203, 1163, 1125, 1068, 1019, 850, 764, 701; **HRMS (MALDI-FT ICR)**: *m/z* calcd for $C_{28}H_{30}F_3NNaO_6$ $[M+Na]^+$= 556.19174, found: 556.19087; The enantioselectivity was determined by **HPLC** (Chiralpak AD-H column, n-hexane:i-PrOH = 80:20, 0.5 mL/min, t_{major} = 14.3 min, t_{minor} = 25.6 min).

tert-butyl (E)-4-(2,5-dimethylbenzyl)-4-(2-(ethoxycarbonyl)-3-phenylallyl)-5-oxoisoxazolidine-2-carboxylate (**175k)**: Following the general procedure with t tert-butyl 4-(2,5-dimethylbenzyl)-5-oxoisoxazolidine-2-carboxylate **160i** (30.5 mg, 0.10 mmol, 1.0 eq.) and ethyl 2-(((tert-butoxycarbonyl)oxy)(phenyl)methyl)acrylate **174a** (46.0 mg, 0.15 mmol, 1.5 eq.), the title compound **175k** was obtained as a colorless oil (32.1 mg, 65%, E/Z= 8:1, e.r.= 89:11 (major diastereomer)). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{24}}$= 66.9° (c= 1.00, $CHCl_3$). **^{1}H NMR** (300 MHz, Chloroform-d, 298 K) δ 7.93 (s, 1H), 7.37 – 7.28 (m, 3H), 7.28 – 7.19 (m, 2H), 7.00 (d, J = 7.5 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.86 (s, 1H), 4.37

– 4.21 (m, 2H), 3.94 (d, J = 10.9 Hz, 1H), 3.56 (d, J = 10.9 Hz, 1H), 3.23 – 3.08 (m, 2H), 2.96 (d, J = 14.4 Hz, 1H), 2.73 (d, J = 14.4 Hz, 1H), 2.21 (s, 3H), 2.07 (s, 3H), 1.47 (s, 9H), 1.37 (t, J = 7.1 Hz, 3H) ppm; **^{13}C NMR** (75 MHz, Chloroform-d, 298 K) δ 175.7, 167.6, 154.8, 143.5, 136.0, 135.1, 133.8, 133.6, 130.8, 130.6, 128.9, 128.8, 128.6, 128.3, 128.0, 83.6, 61.4, 54.2, 50.3, 36.3, 32.2, 28.1, 20.9, 19.5, 14.1 ppm; **IR** (film): ν (cm-1) 2981, 2932, 1796, 1714, 1629, 1504, 1447, 1369, 1257, 1201, 1147, 1099, 1022, 848, 813, 755, 701; **HRMS (MALDI-FT ICR)**: *m/z* calcd for $C_{29}H_{35}NNaO_6$ $[M+Na]^+$= 516.23566, found: 516.23513; The enantioselectivity was determined by **HPLC** (Chiralpak IC column, n-hexane:i-PrOH = 90:10, 0.5 mL/min, t_{minor} = 31.4 min, t_{major} = 46.0 min).

tert-butyl (E)-4-(2,4-dichlorobenzyl)-4-(2-(ethoxycarbonyl)-3-phenylallyl)-5-oxoisoxazolidine-2-carboxylate (**175l)**: Following the general procedure with tert-butyl 4-(2,4-dichlorobenzyl)-5-oxoisoxazolidine-2-carboxylate **160j** (34.6 mg, 0.10 mmol, 1.0 eq.) and ethyl 2-(((tert-butoxycarbonyl)oxy)(phenyl)methyl)acrylate **174a** (46.0 mg, 0.15 mmol, 1.5 eq.), the title compound **175l** was obtained as a colorless oil (40.1 mg, 75%, E/Z= 9:1, e.r.= 84:16 (major diastereomer)). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{26}}$= 37.4° (c= 0.80, $CHCl_3$). **^{1}H NMR** (300 MHz, Chloroform-d, 298 K) δ 7.96 (s, 1H), 7.45 – 7.27 (m, 6H), 7.12 (s, 2H), 4.29 (q, J = 7.2 Hz, 2H), 3.98 (d, J = 11.2 Hz, 1H), 3.55 (d, J = 11.2 Hz, 1H), 3.25 – 3.10 (m, 2H), 3.02 – 2.95 (m, 2H), 1.46 (s, 9H), 1.36 (d, J = 7.2 Hz, 3H) ppm; **^{13}C NMR** (75 MHz, Chloroform-d, 298 K) δ 175.1, 167.5, 154.7, 143.8, 135.8, 135.0, 134.1, 132.6, 131.9, 129.5, 128.8, 128.8, 128.3, 127.8, 127.7, 83.8, 61.5, 54.4, 50.4, 36.0, 32.3, 28.0, 14.1 ppm; **IR** (film): ν (cm-1) 2979, 1796, 1717, 1475, 1370, 1255, 1202, 1146, 1020, 849, 759, 700; **HRMS (MALDI-FT ICR)**: *m/z* calcd for $C_{27}H_{29}Cl_2NNaO_6$ $[M+Na]^+$= 556.12641, found: 556.12767; The enantioselectivity was determined by **HPLC** (Chiralpak AD-H column, n-hexane:i-PrOH = 80:20, 0.5 mL/min, t_{minor} = 13.7 min, t_{major}= 15.8 min).

tert-butyl (E)-4-(2-(ethoxycarbonyl)-3-phenylallyl)-4-(naphthalen-2-ylmethyl)-5-oxoisoxazolidine-2-carboxylate (**175m)**: Following the general procedure with tert-butyl 4-(naphthalen-2-ylmethyl)-5-oxoisoxazolidine-2-carboxylate **160k** (32.7 mg, 0.10

mmol, 1.0 eq.) and ethyl 2-(((tert-butoxycarbonyl)oxy)(phenyl)methyl)acrylate **174a** (46.0 mg, 0.15 mmol, 1.5 eq), the title compound **175m** was obtained as a colorless oil (40.2 mg, 78%, E/Z= 9:1, e.r.= 91:9 (major diastereomer)). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$= 22.0° (c = 0.37, $CHCl_3$). **^{1}H NMR** (300 MHz, Chloroform-d, 298 K) δ 7.91 (s, 1H), 7.87 – 7.78 (m, 1H), 7.78 – 7.70 (m, 2H), 7.54 (s, 1H), 7.52 – 7.43 (m, 2H), 7.22 – 7.08 (m, 6H), 4.29 (q, J = 6.8 Hz, 2H), 3.96 – 3.83 (m, 2H), 3.26 – 3.14 (m, 3H), 2.83 (d, J = 13.9 Hz, 1H), 1.39 (d, J = 16.1 Hz, 12H) ppm; **^{13}C NMR** (75 MHz, Chloroform-d, 298 K) δ 175.7, 167.7, 154.8, 143.6, 134.8, 133.4, 132.6, 132.4, 129.3, 128.7, 128.6, 128.6, 128.4, 128.2, 128.0, 127.8, 127.6, 126.8, 126.1, 83.6, 61.5, 54.4, 50.0, 41.0, 31.8, 28.0, 14.1 ppm; **IR** (film): ν (cm-1) 2981, 2936, 1796, 1711, 1631, 1369, 1251, 1202, 1147, 1099, 1020, 849, 757, 700; **HRMS (MALDI-FT ICR)**: *m/z* calcd for $C_{31}H_{32}NNaO_6$ $[M+Na]^+$= 538.22001, found: 53821925; The enantioselectivity was determined by **HPLC** (YMC Cellulose-SB column, n-hexane:i-PrOH = 80:20, 0.5 mL/min, 10 °C, t_{minor} = 19.2 min, t_{major} = 25.6 min).

tert-butyl (E)-4-benzyl-4-(2-(ethoxycarbonyl)-3-(p-tolyl)allyl)-5-oxoisoxazolidine-2-carboxylate (**175n)**: Following the general procedure with tert-butyl 4-benzyl-5-oxoisoxazolidine-2-carboxylate **160a** (27.7 mg, 0.10 mmol, 1.0 eq.) and ethyl 2-(((tert-butoxycarbonyl)oxy)(p-tolyl)methyl)acrylate**174d** (48.0 mg, 0.15 mmol, 1.5 eq.), the title compound **175n** was obtained as a colorless oil (39.8 mg, 83%, E/Z= 7:1, e.r.= 92:8 (major diastereomer)). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$= 48.8° (c= 0.80, $CHCl_3$). **^{1}H NMR** (300 MHz, Chloroform-d, 298 K) δ 7.87 (s, 1H), 7.30 – 7.23 (m, 3H), 7.13 – 7.03 (m, 6H), 4.27 (q, J = 7.1 Hz, 2H), 3.90 – 3.77 (m, 2H), 3.15 (s, 2H), 3.04 (d, J = 14.0 Hz, 1H), 2.68 (d, J = 14.0 Hz, 1H), 2.35 (s, 3H), 1.46 (s, 9H), 1.35 (t, J = 7.1 Hz, 3H) ppm; **^{13}C NMR** (75 MHz, Chloroform-d, 298 K) δ 175.7, 167.8, 154.9, 143.6, 138.9, 134.9, 131.9, 130.4, 129.5, 129.0, 128.7, 127.4, 127.0, 83.6, 61.4, 54.4, 49.8, 40.9, 31.8, 28.1, 21.3, 14.1 ppm; **IR** (film): ν (cm-1) 2979, 2928, 1797, 1715, 1629, 1497, 1369, 1292, 1147, 1021, 848, 813, 759, 703; **HRMS (MALDI-FT ICR)**: *m/z* calcd for $C_{28}H_{33}NNaO_6$ $[M+Na]^+$= 502.22001, found: 502.21964; The enantioselectivity was determined by **HPLC** (Chiralpak IC column, n-hexane:i-PrOH = 80:20, 1.0 mL/min, t_{minor} = 15.8 min, t_{major} = 25.2 min).

tert-butyl (E)-4-benzyl-4-(2-(ethoxycarbonyl)-3-(4-isopropylphenyl)allyl)-5-oxoisoxazolidine-2-carboxylate (**175o)**: Following the general procedure A with tert-butyl 4-benzyl-5-oxoisoxazolidine-2-carboxylate **160a** (27.7 mg, 0.10 mmol, 1.0 eq.) and ethyl 2-(((tert-butoxycarbonyl)oxy)(4-isopropylphenyl)methyl)acrylate **174e** (52.3 mg, 0.15 mmol, 1.5 eq.), the title compound **175o** was obtained as a colorless oil (34.0 mg, 67%, E/Z= 6:1, e.r.= 91:9 (major diastereomer)). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$= 45.7° (c = 1.00, $CHCl_3$). **^{1}H NMR** (300 MHz, Chloroform-d, 298 K) δ 7.85 (s, 1H), 7.29 – 7.22 (m, 3H), 7.15 – 7.05 (m, 6H), 4.27 (q, J = 7.1 Hz, 2H), 3.86 (s, 2H), 3.22 – 3.09 (m, 2H), 3.05 (d, J = 14.0 Hz, 1H), 2.96 – 2.83 (m, 1H), 2.71 (d, J = 14.0 Hz, 1H), 1.46 (s, 9H), 1.35 (t, J = 7.1 Hz, 3H), 1.26 (s, 3H), 1.24 (s, 3H). ppm; **^{13}C NMR** (75 MHz, Chloroform-d, 298 K) δ 175.8, 167.9, 154.9, 149.8, 143.6, 134.9, 132.2, 130.5, 129.2, 128.8, 128.7, 127.4, 126.9, 83.6, 61.4, 54.4, 49.7, 41.1, 33.9, 31.8, 28.1, 23.8, 23.8, 14.1 ppm; **IR** (film): ν (cm-1) 2979, 1797, 1714, 1635, 1455, 1369, 1253, 1146, 1017, 848, 703; **HRMS (MALDI-FT ICR)**: *m/z* calcd for $C_{30}H_{37}NNaO_6$ $[M+Na]^+$= 530.25131, found: 530.25046; The enantioselectivity was determined by **HPLC** (Chiralpak AD-H column, n-hexane:i-PrOH = 80:20, 0.5 mL/min, t_{major}= 14.2 min, t_{minor} = 15.6 min).

tert-butyl (E)-4-benzyl-4-(3-(4-(tert-butyl)phenyl)-2-(ethoxycarbonyl)allyl)-5-oxoisoxazolidine-2-carboxylate (**175p)**: Following the general procedure with tert-butyl 4-benzyl-5-oxoisoxazolidine-2-carboxylate **160a** (27.7 mg, 0.10 mmol, 1.0 eq.) and ethyl 2-(((tert-butoxycarbonyl)oxy)(4-(tert-butyl)phenyl)methyl)acrylate **174f** (54.4 mg, 0.15 mmol, 1.5 eq.), the title compound **175p** was obtained as a colorless oil (40.2 mg, 77%, E/Z= 8:1, e.r.= 91:9 (major diastereomer)). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26}}$= 63.4° (c = 0.80, $CHCl_3$). **^{1}H NMR** (400 MHz, Chloroform-d, 298 K) δ 7.84 (s, 1H), 7.32 – 7.22 (m, 5H), 7.11 (d, J = 7.8 Hz, 4H), 4.33 – 4.21 (m, 2H), 3.91 – 3.83 (m, 2H), 3.23 – 3.10 (m, 2H), 3.05 (d, J = 13.9 Hz, 1H), 2.73 (d, J = 13.9 Hz, 1H), 1.47 (s, 9H), 1.38 – 1.29 (m, 12H) ppm; **^{13}C NMR** (100 MHz, Chloroform-d, 298 K) δ 175.8, 167.8, 154.8, 152.0, 143.4, 134.9, 131.7, 130.4, 128.9, 128.6, 127.3, 126.8, 125.6, 83.5, 61.3, 54.4, 49.5, 40.9, 34.6, 31.7, 31.1, 28.0, 14.0 ppm; **IR** (film): ν (cm-1) 3023, 2966, 2929, 2856, 1798, 1713, 1456, 1394, 1319, 1295, 1255, 1216, 1192, 1147, 1023, 849, 758, 703, 667; **HRMS (MALDI-FT ICR)**: *m/z* calcd for $C_{31}H_{39}NNaO_6$ $[M+Na]^+$= 544.26696, found: 544.26616; The

enantioselectivity was determined by **HPLC** (Chiralpak IC column, n-hexane:i-PrOH = 80:20, 1.0 mL/min, t_{minor} = 12.2 min, t_{major} = 19.9 min).

tert-butyl (E)-4-(3-([1,1'-biphenyl]-4-yl)-2-(ethoxycarbonyl)allyl)-4-benzyl-5-oxoisoxazolidine-2-carboxylate (**175q)**: Following the general procedure with tert-butyl 4-benzyl-5-oxoisoxazolidine-2-carboxylate **160a** (27.7 mg, 0.10 mmol, 1.0 eq.) and ethyl 2-([1,1'-biphenyl]-4-yl((tert-butoxycarbonyl)oxy)methyl)acrylate **174g** (57.4 mg, 0.15 mmol, 1.5 eq.), the title compound **175q** was obtained as a colorless oil (49.8 mg, 92%, E/Z= 8:1, e.r.= 92:8 (major diastereomer)). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{23}}$= 44.1° (c= 1.00, $CHCl_3$). **^{1}H NMR** (300 MHz, Chloroform-d, 298 K) δ 7.92 (s, 1H), 7.61 (d, J = 7.7 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 7.7 Hz, 2H), 7.40 (d, J = 7.4 Hz, 1H), 7.34 (d, J = 8.3 Hz, 1H), 7.25 (d, J = 6.3 Hz, 4H), 7.15 – 7.04 (m, 2H), 4.30 (q, J = 7.1 Hz, 2H), 3.89 (s, 2H), 3.27 – 3.13 (m, 2H), 3.07 (d, J = 13.9 Hz, 1H), 2.74 (d, J = 13.9 Hz, 1H), 1.47 (s, 9H), 1.37 (t, J = 7.1 Hz, 3H). ppm; **^{13}C NMR** (75 MHz, Chloroform-d, 298 K) δ 175.7, 167.7, 154.9, 143.1, 141.4, 140.1, 134.9, 133.7, 130.4, 129.6, 128.9, 128.8, 127.8, 127.5, 127.4, 127.0, 127.0, 83.7, 61.5, 54.5, 49.8, 40.9, 31.8, 28.1, 14.1 ppm; **IR** (film): ν (cm-1) 2978, 2924, 2849, 1797, 1713, 1628, 1604, 1488, 1455, 1369, 1291, 1253, 1146, 1097, 1007, 848, 763, 700; **HRMS (MALDI-FT ICR)**: *m/z* calcd for $C_{33}H_{35}NNaO_6$ $[M+Na]^+$= 564.23566, found: 564.23490; The enantioselectivity was determined by **HPLC** (Chiralpak IC column, n-hexane:i-PrOH = 80:20, 1.0 mL/min, t_{minor} = 17.1 min, t_{major} = 25.6 min).

tert-butyl (E)-4-benzyl-4-(2-(ethoxycarbonyl)-3-(4-methoxyphenyl)allyl)-5-oxoisoxazolidine-2-carboxylate (**175r)**: Following the general procedure with tert-butyl 4-benzyl-5-oxoisoxazolidine-2-carboxylate **160a** (27.7 mg, 0.10 mmol, 1.0 eq.) and ethyl 2-(((tert-butoxycarbonyl)oxy)(4-methoxyphenyl)methyl)acrylate **174h** (50.4 mg, 0.15 mmol, 1.5 eq.), the title compound **175r** was obtained as a colorless oil (40.1 mg, 81%, E/Z= 11:1, e.r.= 92:8 (major diastereomer)). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{24}}$= 39.6° (c = 1.00, $CHCl_3$). **^{1}H NMR** (400 MHz, Chloroform-d, 298 K) δ 7.82 (s, 1H), 7.31 – 7.26 (m, 3H), 7.17 – 7.08 (m, 4H), 6.79 (d, J = 8.8 Hz, 2H), 4.26 (m, 2H), 3.87 (s, 2H), 3.82 (s, 3H), 3.16 (s, 2H), 3.06 (d, J = 13.9 Hz, 1H), 2.74 (d, J = 13.9 Hz, 1H), 1.46 (s, 9H), 1.34 (t, J = 7.1

Hz, 3H) ppm; **^{13}C NMR** (150 MHz, Chloroform-d, 298 K) δ 175.8, 168.0, 160.0, 154.9, 143.2, 135.0, 130.9, 130.5, 128.7, 127.4, 127.2, 125.6, 114.2, 83.6, 61.3, 55.3, 54.4, 49.8, 41.0, 31.7, 28.1, 14.1 ppm; **IR** (film): ν (cm-1) 2981, 2921, 2850, 1796, 1709, 1605, 1512, 1456, 1369, 1303, 1255, 1176, 1146, 1030, 847, 759, 700; **HRMS (MALDI-FT ICR)**: *m/z* calcd for $C_{28}H_{33}NNaO_6$ $[M+Na]^+$= 518.21492, found: 518.21503; The enantioselectivity was determined by **HPLC** (Chiralpak IC column, n-hexane:i-PrOH = 80:20, 1.0 mL/min, t_{minor} = 21.8 min, t_{major} = 32.6 min).

tert-butyl (E)-4-benzyl-4-(3-(4-chlorophenyl)-2-(ethoxycarbonyl)allyl)-5-oxoisoxazolidine-2-carboxylate (**175s)**: Following the general procedure with tert-butyl 4-benzyl-5-oxoisoxazolidine-2-carboxylate **160a** (27.7 mg, 0.10 mmol, 1.0 eq.) and ethyl 2-(((tert-butoxycarbonyl)oxy)(4-chlorophenyl)methyl)acrylate **174i** (51.1 mg, 0.15 mmol, 1.5 eq.), the title compound **175s** was obtained as a colorless oil (39.0 mg, 78%, E/Z= 5:1, e.r.= 92:8 (major diastereomer)). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$= 37.9° (c = 1.00, $CHCl_3$). **^{1}H NMR** (300 MHz, Chloroform-d, 298 K) δ 7.81 (s, 1H), 7.33 – 7.19 (m, 5H), 7.14 – 7.01 (m, 4H), 4.27 (q, J = 7.1 Hz, 2H), 3.88 – 3.75 (m, 2H), 3.07 (s, 2H), 3.02 (d, J = 14.0 Hz, 1H), 2.69 (d, J = 14.0 Hz, 1H), 1.47 (s, 9H), 1.35 (t, J = 7.1 Hz, 3H) ppm; **^{13}C NMR** (75 MHz, Chloroform-d, 298 K) δ 175.5, 167.4, 154.9, 142.1, 134.7, 134.6, 133.2, 130.4, 130.1, 129.0, 128.8, 128.6, 127.5, 83.8, 61.6, 54.4, 49.8, 40.8, 31.4, 28.1, 14.1 ppm; **IR** (film): ν (cm-1) 2981, 1798, 1713, 1634, 1490, 1369, 1253, 1146, 1093, 1013, 762, 703; **HRMS (MALDI-FT ICR)**: *m/z* calcd for $C_{27}H_{30}ClNNaO_6$ $[M+Na]^+$= 522.16539, found: 522.16470; The enantioselectivity was determined by **HPLC** (Chiralpak AD-H column, n-hexane:i-PrOH = 80:20, 0.5 mL/min, t_{major}= 15.1 min, t_{minor} = 17.9 min).

tert-butyl (E)-4-benzyl-4-(3-(4-bromophenyl)-2-(ethoxycarbonyl)allyl)-5-oxoisoxazolidine-2-carboxylate (**175t)**: Following the general procedure with tert-butyl 4-benzyl-5-oxoisoxazolidine-2-carboxylate **160a** (27.7 mg, 0.10 mmol, 1.0 eq.) and ethyl 2-((4-bromophenyl)((tert-butoxycarbonyl)oxy)methyl)acrylate **174j** (57.8 mg, 0.15 mmol, 1.5 eq.), the title compound **175t** was obtained as a colorless oil (44.1 mg, 81%, E/Z= 5:1, e.r.= 91:9 (major diastereomer)). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26}}$= 27.0° (c = 0.80, $CHCl_3$). **^{1}H NMR** (300 MHz, Chloroform-d, 298 K) δ 7.78 (s, 1H), 7.40 (d, J = 8.2 Hz, 2H), 7.30 –

7.22 (m, 3H), 7.08 – 7.04 (m, 2H), 7.01 (d, J = 8.2 Hz, 2H), 4.27 (q, J = 7.1 Hz, 2H), 3.87 – 3.74 (m, 2H), 3.06 (s, 2H), 3.01 (d, J = 13.9 Hz, 1H), 2.68 (d, J = 13.9 Hz, 1H), 1.47 (s, 9H), 1.34 (t, J = 7.1 Hz, 3H) ppm; **^{13}C NMR** (75 MHz, Chloroform-d, 298 K) δ 175.5, 167.4, 154.9, 142.2, 134.7, 133.7, 132.0, 130.3, 128.8, 128.7, 127.5, 122.8, 83.8, 61.6, 54.4, 49.8, 40.8, 31.4, 28.1, 14.1 ppm; **IR** (film): ν (cm-1) 2978, 1797, 1712, 1636, 1487, 1456, 1393, 1369, 1308, 1252, 1146, 1074, 1010, 847, 811, 762, 703; **HRMS (MALDI-FT ICR)**: *m/z* calcd for $C_{27}H_{30}BrNNaO_6$ $[M+Na]^+$= 566.11487, found: 566.11408; The enantioselectivity was determined by **HPLC** (Chiralpak AD-H column, n-hexane:i-PrOH = 80:20, 0.5 mL/min, t_{major}= 15.1 min, t_{minor} = 18.8 min).

tert-butyl (E)-4-benzyl-4-(2-(ethoxycarbonyl)-3-(4-nitrophenyl)allyl)-5-oxoisoxazolidine-2-carboxylate (175u): Following the general procedure with tert-butyl 4-benzyl-5-oxoisoxazolidine-2-carboxylate **160a** (27.7 mg, 0.10 mmol, 1.0 eq.) and ethyl 2-(((tert-butoxycarbonyl)oxy)(4-nitrophenyl)methyl)acrylate **174k** (52.7 mg, 0.15 mmol, 1.5 eq.), the title compound **175u** was obtained as a colorless oil (28.1 mg, 55%, E/Z= 5:1, e.r.= 93:7 (major diastereomer)). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26}}$= 19.5° (c = 0.80, $CHCl_3$). **^{1}H NMR** (400 MHz, Chloroform-d, 298 K) δ 8.11 (d, J = 8.5 Hz, 2H), 7.86 (s, 1H), 7.28 (d, J = 8.5 Hz, 2H), 7.27 – 7.20 (m, 3H), 7.04 (d, J = 7.3 Hz, 2H), 4.37 – 4.22 (m, 2H), 3.82 (d, J = 11.0 Hz, 1H), 3.79 (d, J = 11.0 Hz, 1H), 3.03 (s, 2H), 2.99 (d, J = 14.0 Hz, 1H), 2.70 (d, J = 14.0 Hz, 1H), 1.48 (s, 9H), 1.35 (t, J = 7.1 Hz, 3H) ppm; **^{13}C NMR** (100 MHz, Chloroform-d, 298 K) δ 175.1, 166.8, 154.8, 147.3, 141.4, 140.7, 134.5, 131.1, 130.2, 129.4, 128.7, 127.5, 123.8, 83.9, 61.8, 54.4, 49.7, 40.8, 31.2, 28.0, 13.9 ppm; **IR** (film): ν (cm-1) 2983, 2933, 2850, 1794, 1719, 1710, 1600, 1476, 1456, 1394, 1370, 1347, 1302, 1254, 1205, 1146, 1110, 1015, 852, 756, 703; **HRMS (MALDI-FT ICR)**: *m/z* calcd for $C_{27}H_{32}N_2NaO_8$ $[M+2H+Na]^+$= 535.20509, found: 535.20425; The enantioselectivity was determined by **HPLC** (Chiralpak AD-H column, n-hexane:i-PrOH = 80:20, 0.5 mL/min, t_{major}= 26.3 min, t_{minor} = 30.0 min).

tert-butyl (E)-4-benzyl-4-(3-(2,3-dichlorophenyl)-2-(ethoxycarbonyl)allyl)-5-oxoisoxazolidine-2-carboxylate (175v): Following the general procedure with tert-butyl 4-benzyl-5-oxoisoxazolidine-2-carboxylate **160a** (27.7 mg, 0.10 mmol, 1.0 eq.)

and ethyl 2-(((tert-butoxycarbonyl)oxy)(2,3-dichlorophenyl)methyl)acrylate **174l** (56.3 mg, 0.15 mmol, 1.5 eq.), the title compound **175v** was obtained as a colorless oil (41.9 mg, 90%, E/Z= 4:1, e.r.= 93:7 (major diastereomer)). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26}}$= 25.3° (c= 0.80, $CHCl_3$). **^{1}H NMR** (400 MHz, Chloroform-d, 298 K) δ 7.81 (s, 1H), 7.41 (d, J = 7.9 Hz, 1H), 7.23 – 7.17 (m, 3H), 7.14 (t, J = 7.9 Hz, 1H), 7.04 – 6.96 (m, 3H), 4.36 – 4.21 (m, 2H), 3.82 (d, J = 11.0 Hz, 1H), 3.77 (d, J = 11.0 Hz, 1H), 2.99 – 2.92 (m, 3H), 2.59 (d, J = 13.9 Hz, 1H), 1.47 (s, 9H), 1.35 (t, J = 7.1 Hz, 3H). ppm; **^{13}C NMR** (100 MHz, Chloroform-d, 298 K) δ 175.2, 166.8, 154.9, 140.2, 135.8, 134.6, 133.6, 131.6, 130.7, 130.3, 130.1, 128.5, 127.7, 127.4, 127.3, 83.7, 61.6, 54.4, 49.7, 40.4, 31.6, 28.0, 14.0. ppm; **IR** (film): ν (cm-1) 3017, 2928 2856, 1795, 1717, 1641, 1559, 1456, 1411, 1395, 1371, 1216, 1184, 1149, 1098, 1049, 1024, 848, 760, 702, 668; **HRMS (MALDI-FT ICR)**: *m/z* calcd for $C_{27}H_{29}Cl_2NNaO_6$ $[M+Na]^+$= 556.12641, found: 556.12582; The enantioselectivity was determined by **HPLC** (Chiralpak IC column, n-hexane:i-PrOH = 80:20, 1.0 mL/min, t_{minor} = 13.0 min, t_{major} = 17.2 min).

tert-butyl (E)-4-benzyl-4-(2-(ethoxycarbonyl)-3-(naphthalen-2-yl)allyl)-5-oxoisoxazolidine-2-carboxylate (**175w)**: Following the general procedure A with tert-butyl 4-benzyl-5-oxoisoxazolidine-2-carboxylate**160a** (27.7 mg, 0.10 mmol, 1.0 eq.) and ethyl 2-(((tert-butoxycarbonyl)oxy)(naphthalen-2-yl)methyl)acrylate **174m** (53.5 mg, 0.15 mmol, 1.5 eq.), the title compound **175w** was obtained as a colorless oil (32.0 mg, 62%, E/Z= 7:1, e.r.= 91:9 (major diastereomer)). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$= 45.3° (c = 0.80, $CHCl_3$). **^{1}H NMR** (300 MHz, Chloroform-d, 298 K) δ 8.06 (s, 1H), 7.89 – 7.68 (m, 4H), 7.59 – 7.47 (m, 2H), 7.40 – 7.20 (m, 2H), 7.16 – 7.07 (m, 2H), 7.05 – 6.92 (m, 2H), 4.31 (q, J = 7.1 Hz, 2H), 3.89 (d, J = 11.0 Hz, 1H), 3.80 (d, J = 11.0 Hz, 1H), 3.22 (s, 2H), 3.05 (d, J = 13.9 Hz, 1H), 2.65 (d, J = 13.9 Hz, 1H), 1.45 (s, 9H), 1.38 (t, J = 7.1 Hz, 3H) ppm; **^{13}C NMR** (75 MHz, Chloroform-d, 298 K) δ 175.5, 167.7, 154.9, 143.6, 134.8, 133.1, 133.0, 132.4, 130.2, 128.8, 128.6, 128.5, 128.4, 128.2, 127.7, 127.4, 126.9, 126.6, 125.9, 83.63, 61.49, 54.60, 49.93, 40.79, 31.96, 28.05, 14.13. ppm; **IR** (film): ν (cm-1) 3017, 2928, 2856, 1795, 1717, 1641, 1456, 1411, 1395, 1371, 1216, 1184, 1149, 1098, 1049, 1024, 848, 760, 702, 668; **HRMS (MALDI-FT ICR)**: *m/z* calcd for $C_{31}H_{33}NNaO_6$ $[M+Na]^+$= 538.22001, found: 538.21934; The enantioselectivity was determined by **HPLC**

(Chiralpak AD-H column, n-hexane:i-PrOH = 80:20, 0.5 mL/min, t_{major}= 18.6 min, t_{minor} = 21.4 min).

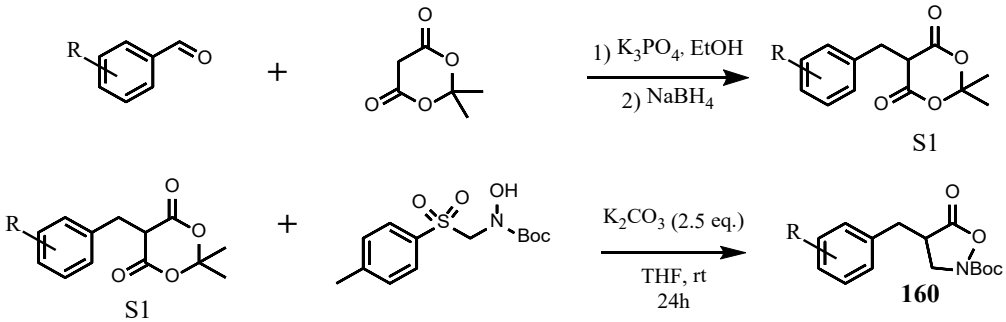
tert-butyl 4-benzyl-4-(2-benzyl-3-ethoxy-3-oxopropyl)-5-oxoisoxazolidine-2-carboxylate (176a): 175a (22.7 mg, 0.05 mmol, 1 eq.) was dissolved in MeOH and Pd/C (10%w/w, 2.1 mg, 0.002 mmol, 0.04 eq.) was added followed by three freeze-pump-thaw cycles to remove any remaining oxygen. The reaction mixture was flushed with hydrogen, and then vigorously stirred under a hydrogen atmosphere (balloon) over night at room temperature. The catalyst was filtered off over a pad of Celite® and washed 3 times with DCM. The filtrate was concentrated to give **(176a)** as a colourless oil (22.4 mg, 0.05 mmol, quant., d.r.=2:1). **^{1}H NMR** (700 MHz, δ, $CDCl_3$, 298 K): *Major:* 1.12 (t, *J* = 7.1 Hz, 3H), 1.46 (s, 9H), 1.77 (dd, *J* = 14.6, 1.8 Hz, 1H), 2.19-2.26 (m, 1H), 2.68-2.72 (m, 1H), 2.73 (d, *J* = 13.9 Hz, 1H), 2.84-2.91 (m, 1H), 2.92-2.96 (m, 1H), 2.95 (d, *J* = 13.9 Hz, 1H), 3.71 (d, *J* = 11.1 Hz, 1H), 3.88 (d, *J* = 11.1 Hz, 1H), 4.00-4.08 (m, 2H), 6.98-7.00 (m, 1H), 7.08 (d, *J* = 11.1 Hz 1H), 7.13-7.15 (m, 1H), 7.22-7.31 (m, 7H). *Minor:* 1.15 (t, *J* = 7.1 Hz, 3H), 1.48 (s, 9H), 1.86 (dd, *J* = 14.8, 2.6 Hz, 1H), 2.19-2.26 (m, 1H), 2.68-2.72 (m, 1H), 2.80 (d, *J* = 13.9 Hz, 1H), 2.84-2.91 (m, 1H), 2.92-2.96 (m, 1H), 3,00 (d, *J* = 13.9 Hz, 1H), 3.75 (d, *J* = 11.0 Hz, 1H), 3.90 (d, *J* = 11.0 Hz, 1H), 4.00-4.08 (m, 2H), 6.98-7.00 (m, 1H), 7.12-7.15 (m, 2H), 7.22-7.31 (m, 7H). **^{13}C NMR** (176 MHz, δ, $CDCl_3$, 298 K): *Major:* 14.1, 28.2, 35.4, 40.0, 40.5, 43.5, 48.9, 56.0, 61.0, 84.0, 127.0, 127.6, 128.7, 128.9, 129.3, 130.2, 134.7, 138.0, 155.7, 174.7, 175.7. *Minor:* 14.1, 28.2, 29.8, 36.3, 39.7, 40.1, 43.1, 48.8, 55.3, 61.1, 84.0, 126.9, 127.7, 128.7, 128.8, 129.1, 130.3, 134.7, 138.1, 155.5, 174.8, 175.4. **IR** (film): ν (cm-1) 3326, 3030, 2979, 2926, 2853, 1792, 1719, 1455, 1369, 1275, 1146, 1029, 847, 747, 700. **HRMS** (ESI): m/z calcd for $C_{27}H_{33}NO_6$: 468.2381$[M+H]^+$; found: 468.2370.

2,4-dibenzyl-2-(((tert-butoxycarbonyl)amino)methyl)-5-ethoxy-5-oxopentanoic acid (177a): 175a (57.6 mg, 0.12 mmol, 1 eq.) was dissolved in MeOH and Pd/C (10%w/w, 13.2 mg, 0.012 mmol, 0.1 eq.) was added followed by three freeze-pump-thaw cycles to remove any remaining oxygen. The reaction mixture was flushed with hydrogen, and then vigorously stirred under a hydrogen atmosphere (balloon) over night at room temperature. The catalyst was filtered off over a pad of Celite® and washed 3

times with DCM. The filtrate was concentrated to give **(177a)** as a colourless oil (57.1 mg, 0.12 mmol, quant., d.r.=2:1). Mixture of diastereomers (ratio 2:1): **^{1}H NMR** (300 MHz, δ, $CDCl_3$, 298 K): 0.88-0.98 (m, 3H), 1.48 (s, 9H), 1.66-1.84 (m, 1H), 2.23-2.34 (m, 1H), 2.67-2.99 (m, 6H), 3.33-3.55 (m, 1H), 3.88-3.99 (m, 2H), 7.10-7.27 (m, 10H). **^{13}C NMR** (75 MHz, δ, $CDCl_3$, 298 K): 13.9, 28.4, 35.8, 40.7, 41.1, 43.4, 43.7, 51.4, 60.6, 79.5, 126.6, 126.8, 128.3, 128.4, 129.1, 130.1, 130.2, 136.1, 138.3, 138.4, 156.2, 176.1, 180.5. **IR** (film): ν (cm-1) 3370, 2978, 2927, 2854, 1712, 1497, 1454, 1392, 1366, 1325, 1248, 1163, 1046, 1023, 990, 851, 700. **HRMS** (ESI): m/z calcd for $C_{27}H_{33}NO_6$: 470.2537$[M+H]^+$; found: 470.2528.

General procedure for the synthesis of benzyl-substituted isoxazolidin-5-one 160a-k:

The benzyl-substituted isoxazolidin-5-one **160** were prepared according to literature.[152,192.]



To a stirred solution of Meldrum's acid (1.0 eq., 2.08 mmol) in ethanol (10 ml) was added potassium phosphate (0.20 eq., 0.416 mmol) and the appropriate substituted benzaldehyde (1.0 eq., 2.08 mmol). After 24-48 h the temperature of the reaction mixture was cooled at 0 °C and sodium borohydride (1.05 eq., 2.18 mmol) was added and the mixture was stirred overnight at room temperature. Afterward, 1 M aqueous HCl was added drop by drop until the pH value to 7 (or 6-5). Ethanol was removed by using a rotary evaporator and the crude product was extracted with ethyl acetate (3x60 mL). The combined organic phases washed with brine and dried over Na_2SO_4, the solvent evaporated and the residue dried in vacuo to yield derivatives of meldrum's acid **S1**.

To a solution of crude **S1** in THF (0.1 M) were added *tert*-butyl hydroxy(tosylmethyl)carbamate (1.0 eq.) and K_2CO_3(2.5 eq.) at 25 °C. After 24h, the reaction mixture was filtered through a pad of sodium sulphate, washed with DCM and the filtrates were evaporated under reduced pressure to give the crude residue that was purified by chromatography (silica gel, heptane-ethyl acetate, 25/1 to 15/1) to yield benzyl-substituted isoxazolidin-5-one **160** as a oil or a white/yellow solid.

tert-butyl 4-benzyl-5-oxoisoxazolidine-2-carboxylate (160a):

Known compound[193]

tert-butyl 4-(4-methylbenzyl)-5-oxoisoxazolidine-2-carboxylate (160b):

^{1}H NMR (300 MHz, Chloroform-d, 298 K) δ 7.14 (d, J = 7.8 Hz, 2H), 7.08 (d, J = 7.8 Hz, 2H), 4.24 – 4.03 (m, 1H), 3.81 – 3.60 (m, 1H), 3.31 – 3.04 (m, 2H), 2.76 (dd, J = 13.7, 9.4 Hz, 1H), 2.33 (s, 3H), 1.51 (s, 9H) ppm;

^{13}C NMR (75 MHz, Chloroform-d, 298 K): δ 174.3, 156.0, 136.9, 133.8, 129.6, 128.6, 84.1, 52.9, 42.2, 34.0, 28.0, 21.0 ppm.

tert-butyl 4-(4-(tert-butyl)benzyl)-5-oxoisoxazolidine-2-carboxylate (160c):

^{1}H NMR (300 MHz, Chloroform-d, 298 K) δ 7.35 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 4.16 (dd, J = 11.0, 8.3 Hz, 1H), 3.82 – 3.62 (m, 1H), 3.33 – 3.03 (m, 2H), 2.76 (dd, J = 13.7, 9.6 Hz, 1H), 1.52 (s, 9H), 1.31 (s, 9H) ppm;

^{13}C NMR (75 MHz, Chloroform-d, 298 K) δ 174.4, 156.0, 150.2, 133.9, 128.4, 125.9, 84.1, 53.0, 42.2, 34.5, 34.0, 31.3, 28.1 ppm.

tert-butyl 4-([1,1'-biphenyl]-4-ylmethyl)-5-oxoisoxazolidine-2-carboxylate (160d):

^{1}H NMR (300 MHz, Chloroform-d, 298 K) δ 7.64 – 7.52 (m, 4H), 7.45 (t, J = 7.4 Hz, 2H), 7.37 (d, J = 7.4 Hz, 1H), 7.27 (d, J = 7.9 Hz, 2H), 4.20 (dd, J = 11.1, 8.2 Hz, 1H),

3.85 – 3.66 (m, 1H), 3.36 – 3.12 (m, 2H), 2.86 (dd, J = 13.7, 9.4 Hz, 1H), 1.53 (s, 9H) ppm;

^{13}C NMR (75 MHz, Chloroform-d, 298 K) δ 174.2, 156.0, 140.5, 140.2, 136.0, 129.2, 128.9, 127.7, 127.5, 127.0, 84.2, 53.0, 42.2, 34.1, 28.1 ppm.

tert-butyl 4-(4-methoxybenzyl)-5-oxoisoxazolidine-2-carboxylate (160e):

Known compound[193]

tert-butyl 4-(4-chlorobenzyl)-5-oxoisoxazolidine-2-carboxylate (160f):

Known compound[155]

tert-butyl 4-(4-bromobenzyl)-5-oxoisoxazolidine-2-carboxylate (160g):

Known compound[155]

tert-butyl 5-oxo-4-(4-(trifluoromethyl)benzyl)isoxazolidine-2-carboxylate (160h):

^{1}H NMR (300 MHz, Chloroform-d, 298 K) δ 7.60 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 4.17 (dd, J = 11.1, 8.4 Hz, 1H), 3.77 – 3.59 (m, 1H), 3.37 – 3.11 (m, 2H), 2.89 (dd, J = 13.9, 9.2 Hz, 1H), 1.51 (s, 9H) ppm;

^{13}C NMR (75 MHz, Chloroform-d, 298 K) δ 173.8, 155.8, 140.9, 129.7 (q, J= 32.6 Hz), 129.2, 126.0 (q, J= 3.7 Hz), 124.0 (q, J= 272.0 Hz), 84.4, 52.8, 41.8, 34.2, 28.0 ppm.

tert-butyl 4-(2,5-dimethylbenzyl)-5-oxoisoxazolidine-2-carboxylate (160i):

^{1}H NMR (300 MHz, Chloroform-d, 298 K) δ 7.07 (d, J = 7.7 Hz, 1H), 6.99 (d, J = 7.7 Hz, 1H), 6.92 (s, 1H), 4.15 (dd, J = 11.1, 8.3 Hz, 1H), 3.79 – 3.67 (m, 1H), 3.28 (dd, J = 14.3, 4.3 Hz, 2H), 3.21 – 3.05 (m, 1H), 2.72 (dd, J = 14.3, 10.4 Hz, 1H), 2.31 (s, 3H), 2.29 (s, 3H), 1.53 (s, 9H) ppm;

^{13}C NMR (75 MHz, Chloroform-d, 298 K) δ 174.4, 156.0, 136.0, 135.1, 132.9, 130.7, 129.8, 128.1, 84.2, 53.3, 41.1, 31.9, 28.1, 21.0, 18.9 ppm.

tert-butyl 4-(2,4-dichlorobenzyl)-5-oxoisoxazolidine-2-carboxylate (160j):

^{1}H NMR (300 MHz, Chloroform-d, 298 K) δ 7.40 (s, 1H), 7.21 (s, 2H), 4.17 (dd, J = 11.1, 8.2 Hz, 1H), 3.77 – 3.63 (m, 1H), 3.45 – 3.14 (m, 2H), 2.90 (dd, J = 13.6, 8.2 Hz, 1H), 1.50 (s, 9H) ppm;

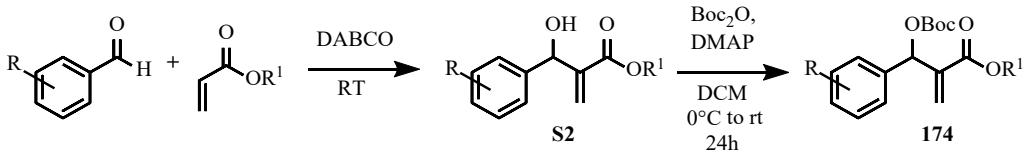
^{13}C NMR (75 MHz, Chloroform-d, 298 K) δ 173.8, 155.8, 134.7, 134.0, 133.3, 131.9, 129.7, 127.7, 84.4, 52.9, 40.4, 31.5, 28.0 ppm.

tert-butyl 4-(naphthalen-2-ylmethyl)-5-oxoisoxazolidine-2-carboxylate (160k):

Known compound[193]

Preparation of Morita-Baylis-Hillman Carbonates 174a-m:

The Morita-Baylis-Hillman carbonates **174** were prepared according to the literature.[194,195.]



A mixture of aldehyde (1.0 eq, 4.41 mmol), acrylate (2.0 eq., 8.81 mmol) and DABCO (0.40 eq., 1.76 mmol) was stirred for 3-7 days at rt. Then, the mixture was diluted with Et_2O (30 mL) and washed with water (2x20 mL), 1M HCl (1x20 mL) and brine (10 mL). The organic phase was dried with sodium solphate and evaporated in vacuo to yield alcohols **S2**.

Then, alcohols **S2** were converted to the corresponding carbonates **174a-m:** alcohol S1 (1.0 eq., 1.0 mmol) and Boc_2O (1.1 eq., 1.1 mmol) were dissolved in DCM (2.0 mL) and the solution was cooled to 0°C. Afterward, DMAP (0.10 eq., 0.10 mmol) was added and the reaction mixture stirred at room temperature for 24h. After 24h, the reaction mixture was diluted with CH_2Cl_2. The combined organic phase was washed with 4 N aq. HCl solution, saturated aq. $NaHCO_3$ and brine. The organic layer, dried over anhydrous

Na_2SO_4, filtered and vacuum at rotary evaporator to obtain an oil. The crude product was purified by chromatography (silica gel, heptane-ethyl acetate, 50/1 to 20/1) to afford an oil or a white/pale yellow solid.

ethyl 2-(((tert-butoxycarbonyl)oxy)(phenyl)methyl)acrylate (174a):

Known compound[195]

benzyl 2-(((tert-butoxycarbonyl)oxy)(phenyl)methyl)acrylate (174b):

Known compound[196]

tert-butyl 2-(((tert-butoxycarbonyl)oxy)(phenyl)methyl)acrylate (174c):

Known compound[197]

ethyl 2-(((tert-butoxycarbonyl)oxy)(p-tolyl)methyl)acrylate (174d):

Known compound[198]

ethyl 2-(((tert-butoxycarbonyl)oxy)(4-isopropylphenyl)methyl)acrylate (174e):

Known compound[198]

ethyl 2-(((tert-butoxycarbonyl)oxy)(4-(tert-butyl)phenyl)methyl)acrylate (174f):

^{1}H NMR (300 MHz, Chloroform-d, 298 K) δ 7.39 – 7.27 (m, 4H), 6.47 (s, 1H), 6.39 (s, 1H), 5.89 (s, 1H), 4.23 – 4.10 (m, 2H), 1.46 (s, 9H), 1.30 (s, 9H), 1.23 (t, J = 7.1, 3H) ppm.

ethyl 2-([1,1'-biphenyl]-4-yl((tert-butoxycarbonyl)oxy)methyl)acrylate (174g):

^{1}H NMR (300 MHz, Chloroform-d, 298 K) δ 7.57 – 7.49 (m, 4H), 7.45 (d, J = 8.0 Hz, 2H), 7.38 (t, J = 7.5 Hz, 2H), 7.30 (d, J = 7.1 Hz, 1H), 6.52 (s, 1H), 6.40 (s, 1H), 5.92 (s, 1H), 4.14 (d, J = 7.2 Hz, 2H), 1.44 (s, 9H), 1.20 (t, J = 7.2 Hz, 3H) ppm.

ethyl 2-(((tert-butoxycarbonyl)oxy)(4-methoxyphenyl)methyl)acrylate (174h):

Known compound[198]

ethyl 2-(((tert-butoxycarbonyl)oxy)(4-chlorophenyl)methyl)acrylate (174i):

Known compound[198]

ethyl 2-((4-bromophenyl)((tert-butoxycarbonyl)oxy)methyl)acrylate (174j):

Known compound[198]

ethyl 2-(((tert-butoxycarbonyl)oxy)(4-nitrophenyl)methyl)acrylate (174k):
^{1}H NMR (300 MHz, Chloroform-d, 298 K) δ 8.18 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 8.3 Hz, 2H), 6.51 (s, 1H), 6.45 (s, 1H), 5.98 (s, 1H), 4.15 (q, J = 7.1 Hz, 2H), 1.44 (s, 9H), 1.22 (t, J = 7.1 Hz, 3H) ppm.

ethyl 2-(((tert-butoxycarbonyl)oxy)(2,3-dichlorophenyl)methyl)acrylate (174l):

^{1}H NMR (300 MHz, Chloroform-d, 298 K) δ 7.44 (d, J = 7.8 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.21 (t, J = 7.8 Hz, 1H), 6.89 (s, 1H), 6.47 (s, 1H), 5.63 (s, 1H), 4.20 (q, J = 7.1 Hz, 2H), 1.47 (s, 9H), 1.24 (t, J = 7.1 Hz, 3H) ppm.

ethyl 2-(((tert-butoxycarbonyl)oxy)(naphthalen-2-yl)methyl)acrylate (174m):

Known compound195

_X_-Ray Analysis of 175f

_X_-ray quality crystals were selected in Fomblin® Y H-VAC 140/13 perfluoropolyether at ambient temperature. The data was collected at 296(2) K on a *Bruker* ***D8 Quest Eco*** diffractometer using graphite monochromated Mo K_α radiation ($\lambda = 0.71073$ Å). The data was processed using APEX3,[199] the structures were solved by intrinsic phasing (SHELXT, Version 2014/5),[200] and refined by full matrix least squares procedures on F^2 (SHELXL, Version 2014/7)[201] using the graphical interface Shelxle[202] within the SHELXTL suite of programs by Bruker. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were calculated geometrically, and a riding model was applied in the refinement process.

Due to the absence of heavy atoms, compound **175f** is a weak anomalous scatterer, rendering the Flack parameter meaningless. Detailed crystallographic and refinement data can be found in Table S1.

1870182 contains the supplementary crystallographic data for **175f**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk.

Table S1: Crystal data, data collection and structure refinement details for compounds **175f**.

Compound	**175f**
Empirical formula	$C_{33}H_{35}NO_6$
Formula weight [g/mol]	541.62
Color	colorless
Crystal size [mm]	0.70 × 0.53 × 0.07
Crystal system	monoclinic
Space group	*Cc*
a [Å]	9.900(3)
b [Å]	34.441(10)
c [Å]	9.602(3)
α [°]	90

β [°]	116.727(10)
γ [°]	90
V [Å^3]	2924.2(15)
Z	4
D_{calc} [g/cm^3]	1.230
μ [mm^{-1}]	0.08
T [K]	296
θ range [°]	2.5-23.3
No. of reflections measured	30621
No. of independent reflections	4190
Obs. Reflections with $I > 2\sigma(I)$	2414
No. of Parameters refined/restraints	365/2
Absorption correction	Multi-scan
T_{min}, T_{max}	0.77, 0.99
$\Delta\rho_{min}/\Delta\rho_{max}$ [e Å^{-3}]	−0.24/0.20
F(000)	1152
R_{int}	0.172
R_1 ($R[F^2 \geq 2\sigma(F^{2)})]$)	0.086
wR_2 ($wR(F^2)$)	0.174
GooF	1.12
CCDC no.	1870182

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